

## Research Article

# Bacterial Atlas of Mouse Gut Microbiota

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**Background.** Mouse model is one of the most widely used animal models for exploring the roles of human gut microbiota, a complex system involving in human immunity and metabolism. However, the structure of mouse gut bacterial community has not been explored at a large scale. To address this concern, the diversity and composition of the gut bacteria of 600 mice were characterized in this study. **Results.** The results showed that the bacteria belonging to 8 genera were found in the gut microbiota of all mouse individuals, indicating that the 8 bacteria were the core bacteria of mouse gut microbiota. The dominant genera of the mouse gut bacteria contained 15 bacterial genera. It was found that the bacteria in the gut microbiota were mainly involved in host's metabolisms via the collaborations between the gut bacteria. The further analysis demonstrated that the composition of mouse gut microbiota was similar to that of human gut microbiota. **Conclusion.** Our study presented a bacterial atlas of mouse gut microbiota, providing a solid basis for investing the bacterial communities of mouse gut microbiota.

## 1. Background

The human gut microbiota plays key roles in human homeostasis, thus largely affecting human health [1]. The composition of gut microbiota develops dynamically in the first 2-3 years of life, which can affect risk factors related to adult health [2]. Increasing evidence has linked the human gut microbiota to diseases. The altered microbial communities are associated with obesity [3], gastrointestinal cancer [4], and type 2 diabetes [5]. To characterize human gut microbiota, murine models have been widely used, due to the extensive similarities in anatomy, physiology, and genetics [6]. In mice, the dysbiosis of gut microbiota leads to severe diseases. Cognitive dysfunction is associated with the abnormal composition of the gut microbiota of mice [7]. The gut microbiota of mice influences the pathogenesis of malaria [8] and is identified as an important mediator of acute pancreatitis [9]. There are numerous lines of evidence suggesting that the gut microbiota of mice takes great effects on major depressive disorder [10] and type 1 diabetes [11]. In the gut microbiota of mice, *Bacteroides thetaiotaomicron* can affect the immune system because it is able

to recapitulate the effects of the entire conventional microbiota and notably induces Treg pathways [12]. *Chryseomonas*, *Veillonella*, and *Streptococcus* may be the initial source of the atherosclerotic [13], while *Akkermansia muciniphila*, a mucin-degrading bacterium, elicits beneficial effects on metabolism and reduces atherosclerotic lesion formation [14]. As reported, type 2 diabetes is associated with a reduced abundance of butyrate producing bacteria and an increased abundance of *Lactobacillus* sp. [15]. Although the gut microbiota of mice plays very important roles in health, the structure of gut microbiota of mice has not been extensively explored.

The colonization of the gut is influenced by many complex environmental factors, such as host genetics, age, diet, lifestyle, diseases, and antibiotic use [16]. Based on microbial metagenome sequencing of some mice fed with low-fat or high-fat diets, the dominate genera in mice gut microbiota are *Faecalibacterium*, *Coprococcus*, *Odoribacter*, *Anaerotruncus*, *Desulfovibrio*, *Enterococcus*, *Marvinbryantia*, *Pseudoflavonifractor*, *Coprococcus*, *Parabacteroides*, *Blautia*, *Eubacterium*, *Ruminococcus*, *Roseburia*, *Lactobacillus*, *Alistipes*, *Prevotella*, *Butyrivibrio*, *Clostridium*, and *Bacteroides* [17]. An increased ratio of

the major phyla *Firmicutes* and *Bacteroidetes* (FIR/BAC ratio) and depletion of several bacterial species such as *Akkermansia muciniphila* can promote the development of obesity in mice [18]. Generally, the mouse gut microbiota can be divided into two enterotypes, including *Ruminococcus* enterotype and *Bacteroides* enterotype, a reproducible pattern of variation in the microbiota, according to their composition and community structure properties [19, 20]. At present, however, the diversity and abundance of the gut bacteria in healthy mice have not been characterized at a large scale.

To address this issue, the composition of the gut microbiota of 600 healthy mice was explored in the present investigation. The results revealed that at the genus level, the core bacteria of mouse gut microbiota contained 8 bacteria, and the dominant bacteria consisted of 15 bacteria. There was a similarity between mouse and human gut bacterial communities.

## 2. Methods

**2.1. Sample Collection.** A total of 300 ICR (Institute of Cancer Research) female and 300 ICR male mice (8 weeks old) purchased from Zhejiang Academy of Medical Sciences were raised in a sterilized condition for 3 days to stabilize the composition of gut microbiome. The mice were raised for another 7 days in the same sterilized condition. On day 3 and day 10, the feces of each mouse were collected for later use.

**2.2. Sequencing and Sequence Analysis of Bacterial 16S rRNA.** The bacterial genomic DNA was extracted directly from the fecal samples with FastDNA® SPIN Kit (MP Biomedicals, USA) according to the manufacturer's manuals. Subsequently, the bacterial 16S rRNA gene was amplified by PCR using gene-specific primers (515F, 5'-GTGCCAGCMGCCGCGG-3'; 907R, 5'-CCGTCAA TTCMTTTRAGTTT-3') (M = A/C; R = A/G). The libraries of bacterial 16S rRNA gene were generated using NEB Next®Ultra™DNA Library Prep Kit for Illumina (NEB, USA) following the manufacturer's recommendation. The libraries were sequenced on an Illumina MiSeq platform.

Sequence analysis was performed by the UPARSE software package using the UPARSE-OTU and UPARSE-OTUref algorithms. All primers, spacers, low-quality fragments, and the sequences shorter than 50 bp were removed. The remaining sequences were further processed with the pre.cluster command and chimera.uchime command in Mothur. All sequences were denoised and screened for chimeric sequences. Then, the sequences were assigned to the same operational taxonomic units (OTUs) by 97% sequence similarity. The uclust was used to annotate taxonomic information for each OTU. Mothur was used to analyze the community richness, community diversity, and rarefaction curve.

**2.3. Principal Coordinate Analysis.** To compare two or more microbial communities, principal coordinate analysis (PCoA) was performed. The Bray-Curtis dissimilarity algorithm was applied for PCoA. The vegan of package R (version 3.4.4) (<https://www.r-project.org/>) was used.

**2.4. KEGG (Kyoto Encyclopedia of Genes and Genomes) Pathway Analysis.** The bacterial 16S gene sequencing data were clustered with Greengenes database ([.secondgenome.com\) using closed reference OTU picking. The internal standardization was conducted to obtain the normalized species abundance. Subsequently, the abundance of three levels of KEGG Orthology and pathway was obtained according to the relationship between the Greengenes database and the copy number of KEGG Orthology.](http://greengenes</a></p>
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**2.5. Correlation Analysis.** Correlation analysis was performed using the OmicStudio tools at <https://www.omicstudio.cn/tool/62>. Correlation plots were generated using the corrplot R package (version 3.6.1).

## 3. Results

**3.1. Bacterial Communities in Mice.** To determine the composition of microbiota in the gut of mice, a total of 600 ICR (Institute of Cancer Research) mice (300 female and 300 male mice), one of the most commonly used laboratory mice, were subjected to the analysis of bacterial community (Figure 1(a)). On day 3 and day 10 after mouse raise, the bacterial 16S rRNA sequencing of mouse feces was performed (Figure 1(a)). The results of transmission electron microscopy showed that the bacteria of mouse gut were rod-shaped, short rod-shaped, and spherical-shaped (Figure 1(b)). The sequencing analysis of bacterial 16S rRNA gene of 1,200 mice yielded a total of 33,390,144 reads (Table S1). Based on these reads, 2478 operational taxonomic units (OTUs) were identified (GenBank accession no. PRJNA721276) (Table S1). All OTUs were defined by 97% similarity. The rarefaction curves of all samples approached plateaus (Figure 1(c)), indicating that the sequencing data represented the gut microbiome of mice.

In total, 29 phyla, 70 classes, 134 orders, 252 families, 624 genera, and 828 species were classified (Figure 1(d) and Table S2). At the genus level, among 624 OTUs, only 19 OTUs could not be classified (3.04%), while the remaining 605 OTUs were matched to the known bacteria (96.96%) (Figure 1(e) and Table S3).

**3.2. The Dominant Bacteria and Core Bacteria in the Gut Microbiota of Mice.** To determine the dominant bacteria and the core bacteria in the gut microbiota of mice, the composition of the gut microbiota of 600 ICR mice was characterized. The results of the principal coordinate analysis of mouse gut microbiota showed that there was no significant difference of gut microbiota composition on day 3 and day 10 (Figure 2(a)), indicating that the gut microbiota was stable and the data were reliable. However, the dots representing the gut microbiota of 600 mice were scattered in different locations (Figure 2(a)), showing the existence of individual differences of gut microbiota.

To determine the dominant bacteria in the gut microbiota of mice, the bacteria of 600 mice were analyzed. The results revealed that at the phylum level, dominant bacteria in the gut microbiota of mice mainly included *Firmicutes* (55.75%), *Bacteroidetes* (37.02%), *Proteobacteria* (4.05%), *Actinobacteria* (1.98%), and *Tenericutes* (1.09%), while the abundance of other bacteria was less than 1% (Figure 2(b)). The most dominant genus was *Bacteroidales* S24-7 group\_norank (23.89%), followed by *Lactobacillus* (22.98%), *Faecalibaculum* (11.17%),

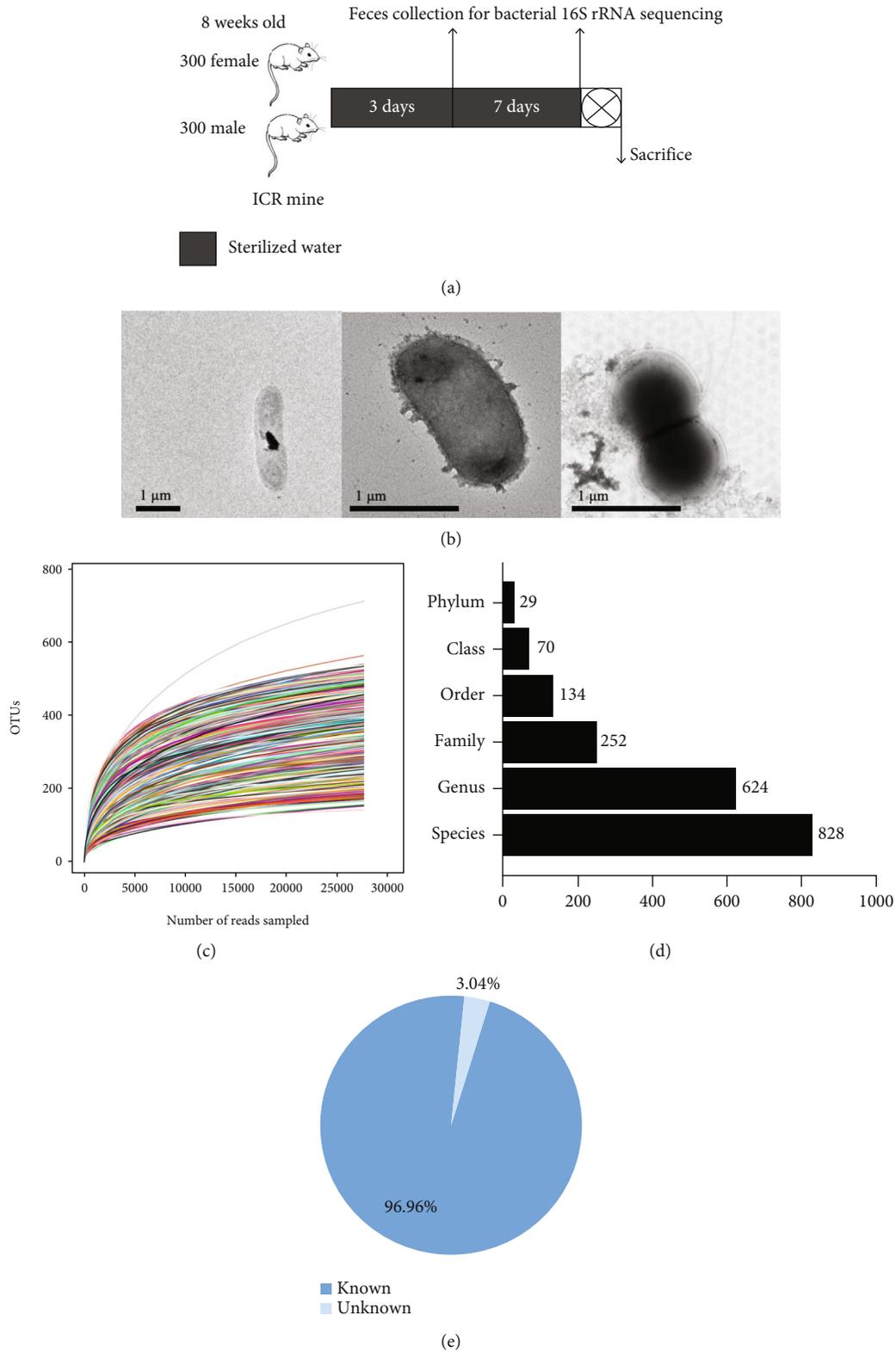
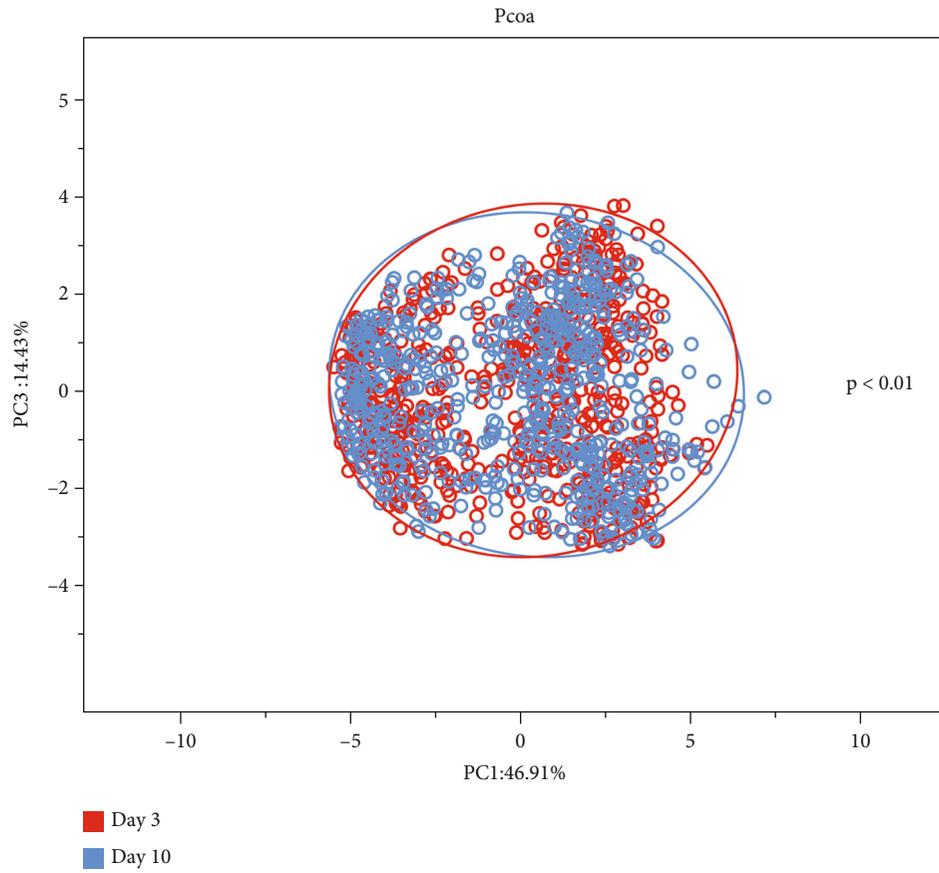
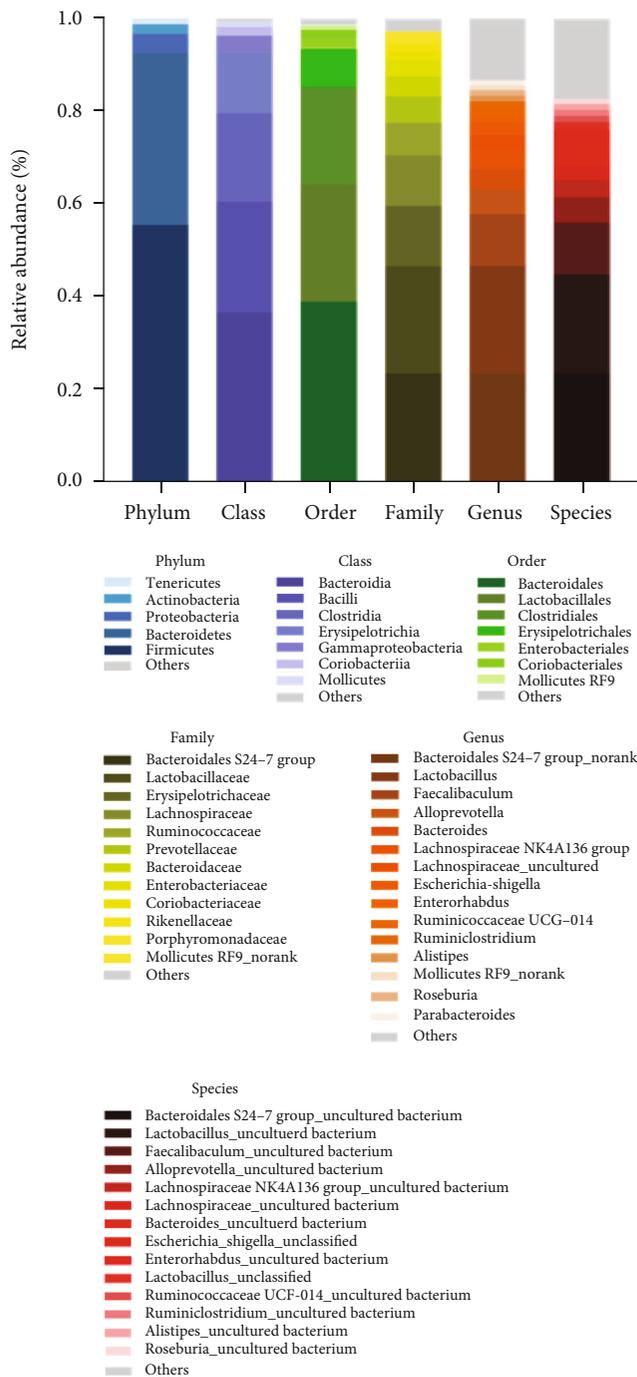


FIGURE 1: Bacterial communities in mice. (a) A flow diagram of the experiment. A total of 300 female and 300 male mice were fed sterilized water. Fecal samples were collected on day 3 and day 7 for bacteria 16S rRNA sequencing. At day 7, the blood and intestinal tissues of mice were subjected to the detection of physiological parameters. (b) Observation of microbes isolated from fecal samples of mice using transmission electron microscopy. The representative images were presented. Scale bar, 1 μm. (c) Rarefaction curves of the bacterial 16S rRNA genes of the feces of 600 mice. (d) Numbers of OTUs homologous to the known bacteria in mouse gut microbiota at each classification level. (e) Pie diagram of the known and unknown OTUs in all samples at the genus level.



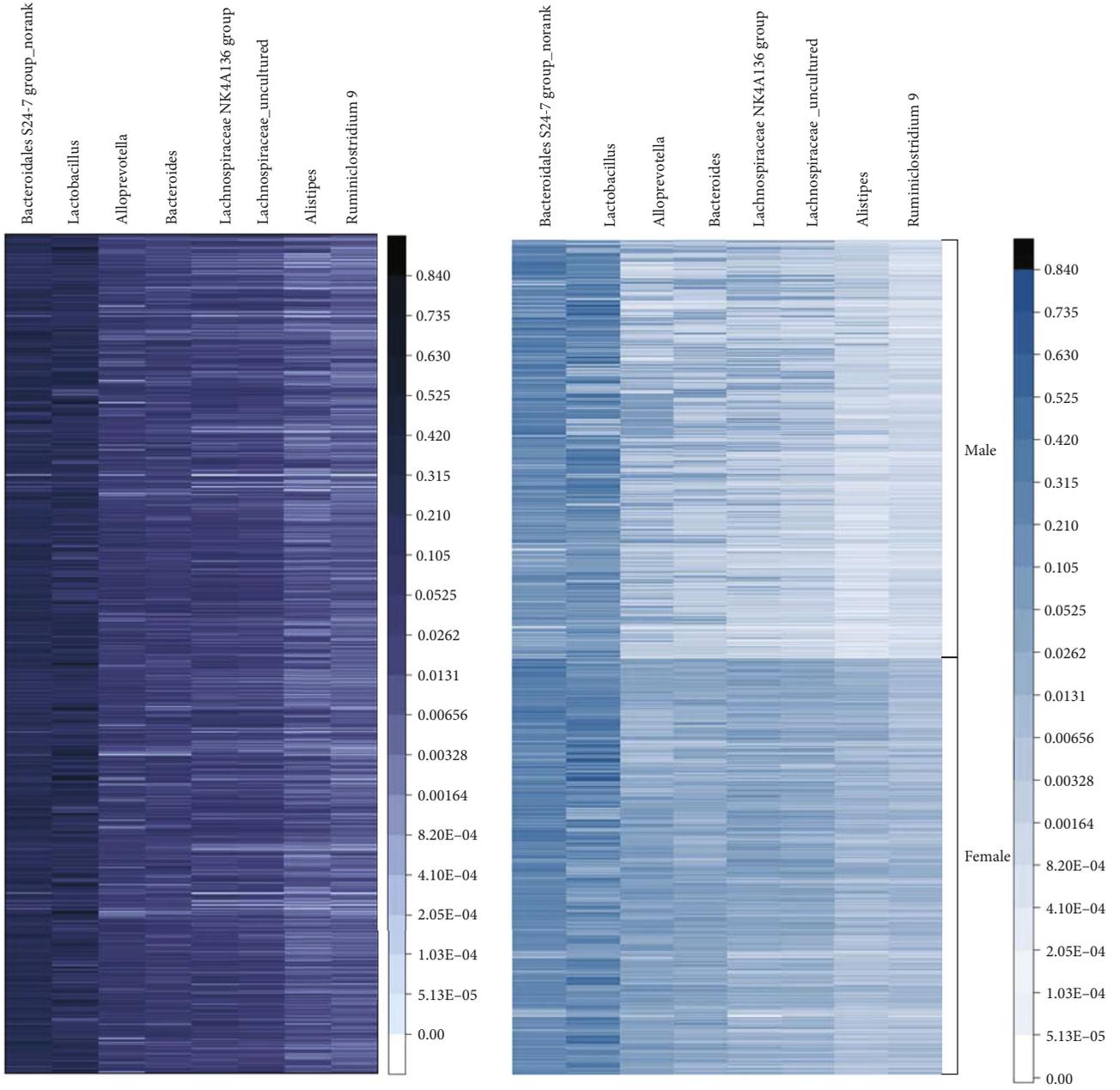
(a)

FIGURE 2: Continued.



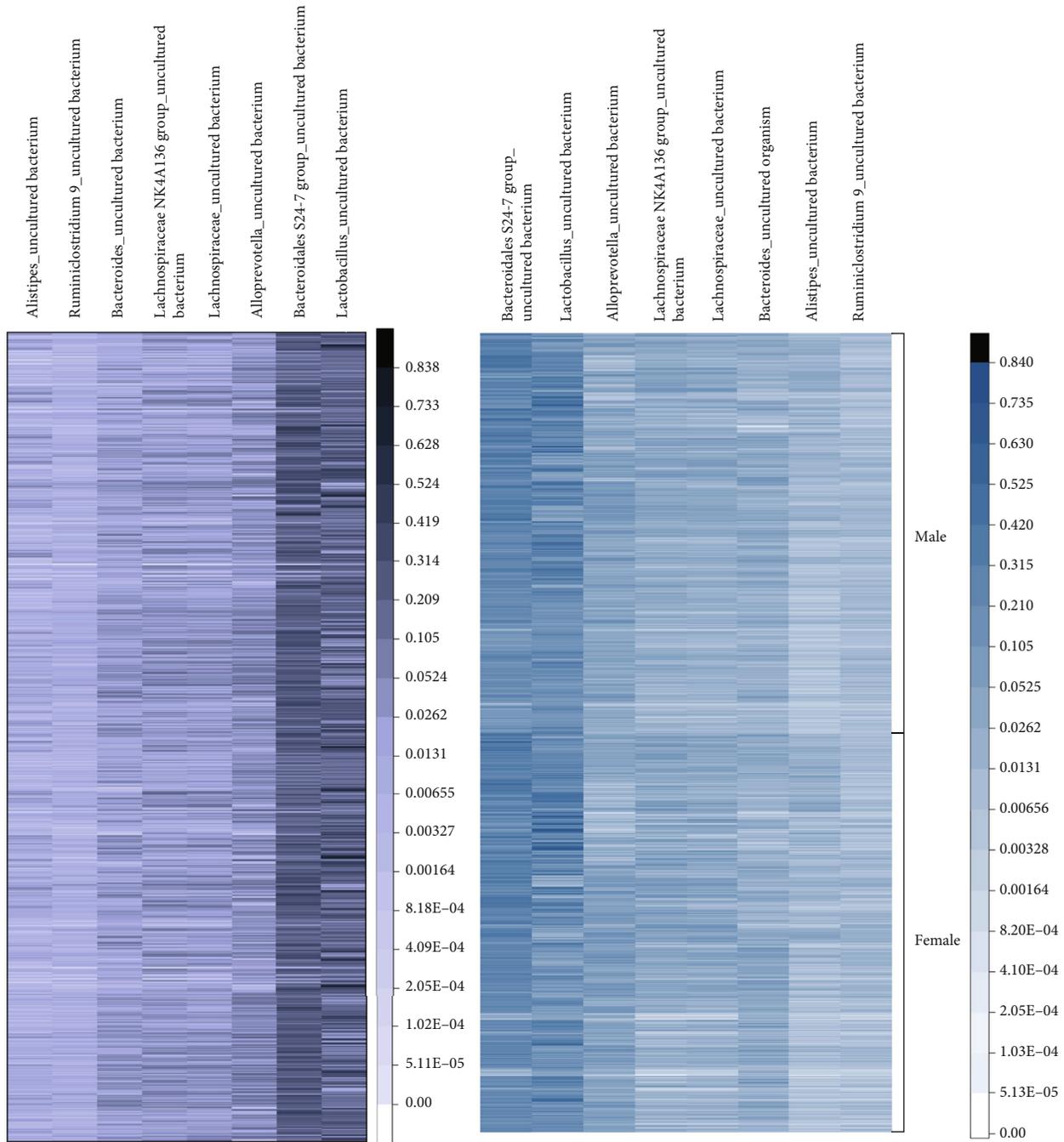
(b)

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(c)

FIGURE 2: Continued.

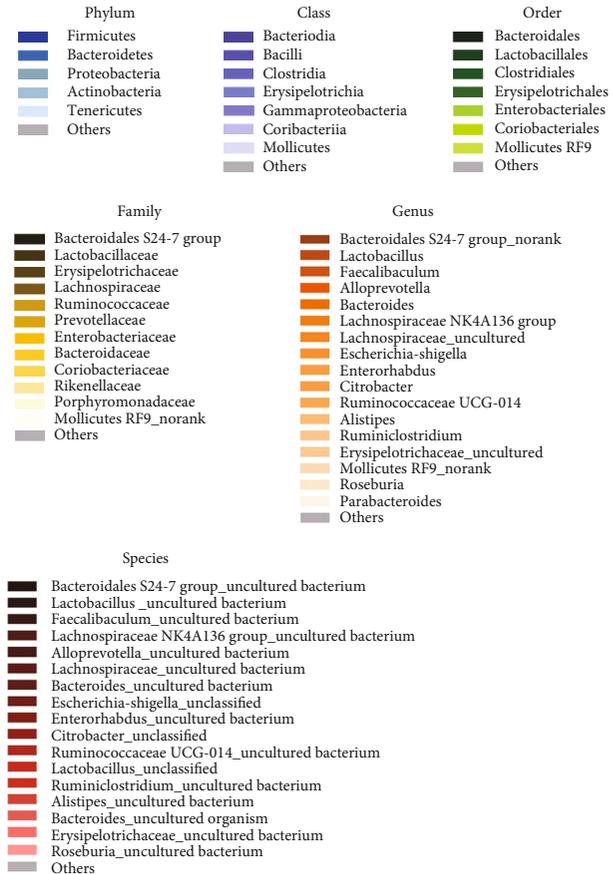
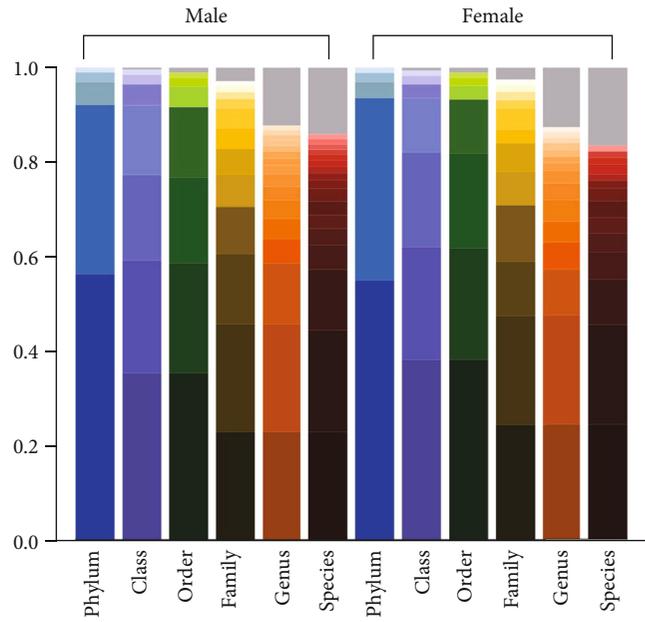
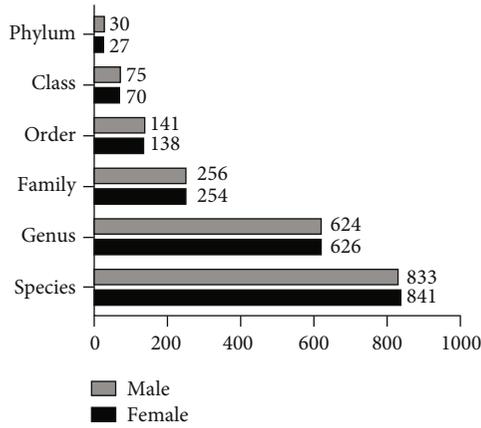


(d)

FIGURE 2: The dominant bacteria and core bacteria in the gut microbiota of mice. (a) Principal coordinate analysis (PCoA) of the bacterial communities of mouse fecal samples. Each dot represented the structure of gut microbiota of mice on day 3 (blue) or day 10 (red). There was no statistically significant difference of gut microbiota composition on day 3 and day 10 ( $p < 0.01$ ). (b) Relative abundance of gut bacteria of mice. “Uncultured” represented the bacteria that could not be cultured. “Unclassified” indicated the sequences that could not be classified. “Norank” represented that there was no classification information or classification name. Bacteria with a relative abundance of less than 1% were classified as “Others.” (c) The core bacteria of mouse gut microbiota at the genus level. (d) The core bacteria of mouse gut microbiota at the species level. “Uncultured” represented the bacteria that could not be cultured.

*Alloprevotella* (5.44%), *Bacteroides* (4.31%), *Lachnospiraceae NK4A136 group* (4.17%), *Lachnospiraceae\_ uncultured* (3.20%), *Escherichia-Shigella* (2.68%) and *Enterorhabdus* (1.73%), *Ruminococcaceae UCG-014* (1.37%), *Ruminiclostridium* (1.31%), *Alistipes* (1.30%), *Roseburia* (1.11%), *Mollicutes*

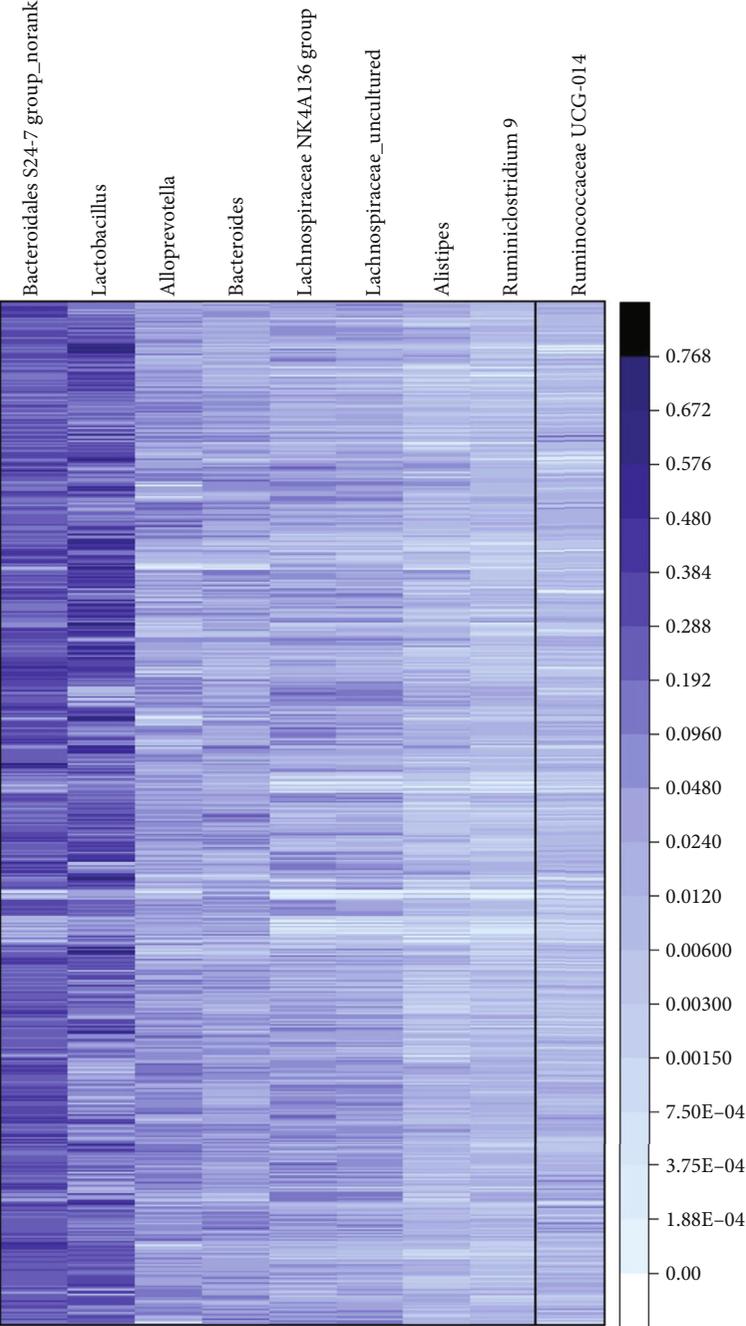
*RF9\_norank* (1.07%), and *Parabacteroides* (1.03%) (Figure 2(b)). At the species level, the dominant bacteria in the gut microbiota of mice were *Bacteroidales S24-7 group\_ uncultured bacterium* (23.89%), *Lactobacillus\_ uncultured bacterium* (21.23%), *Faecalibaculum\_ uncultured bacterium*



(a)

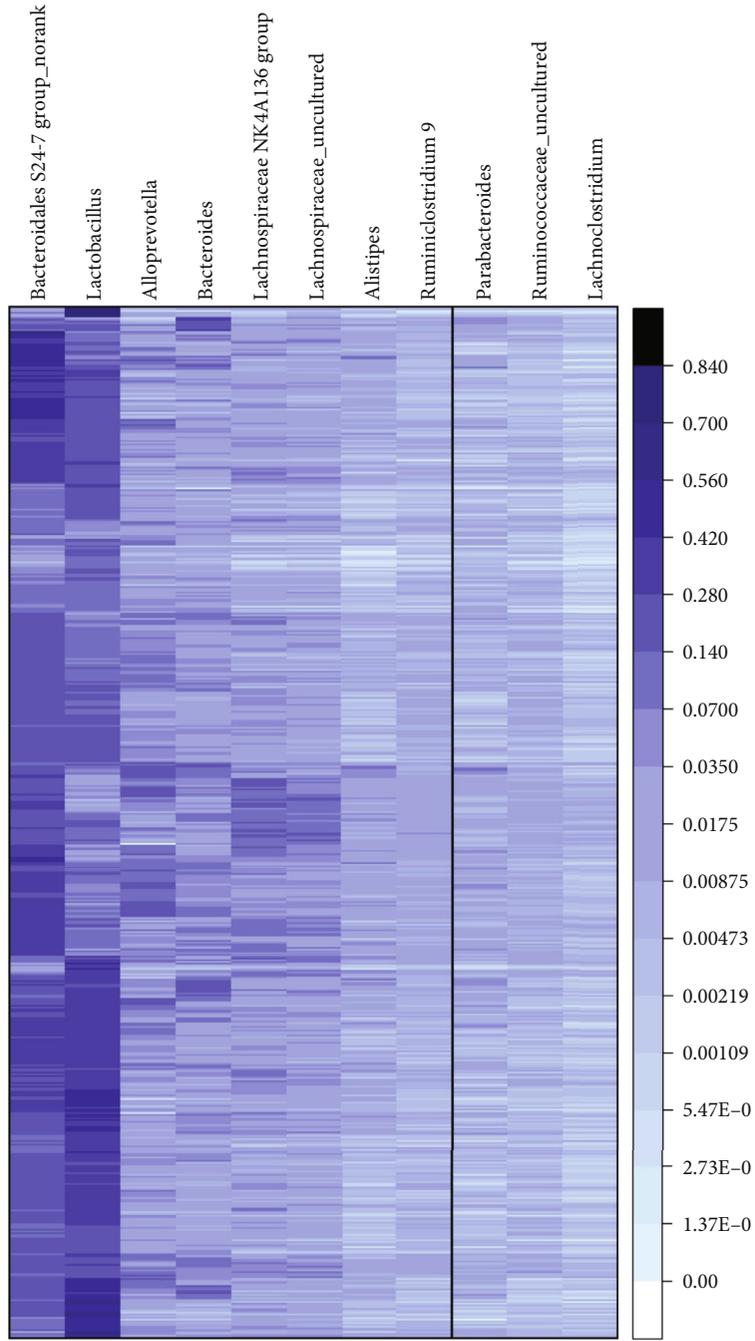
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FIGURE 3: Continued.



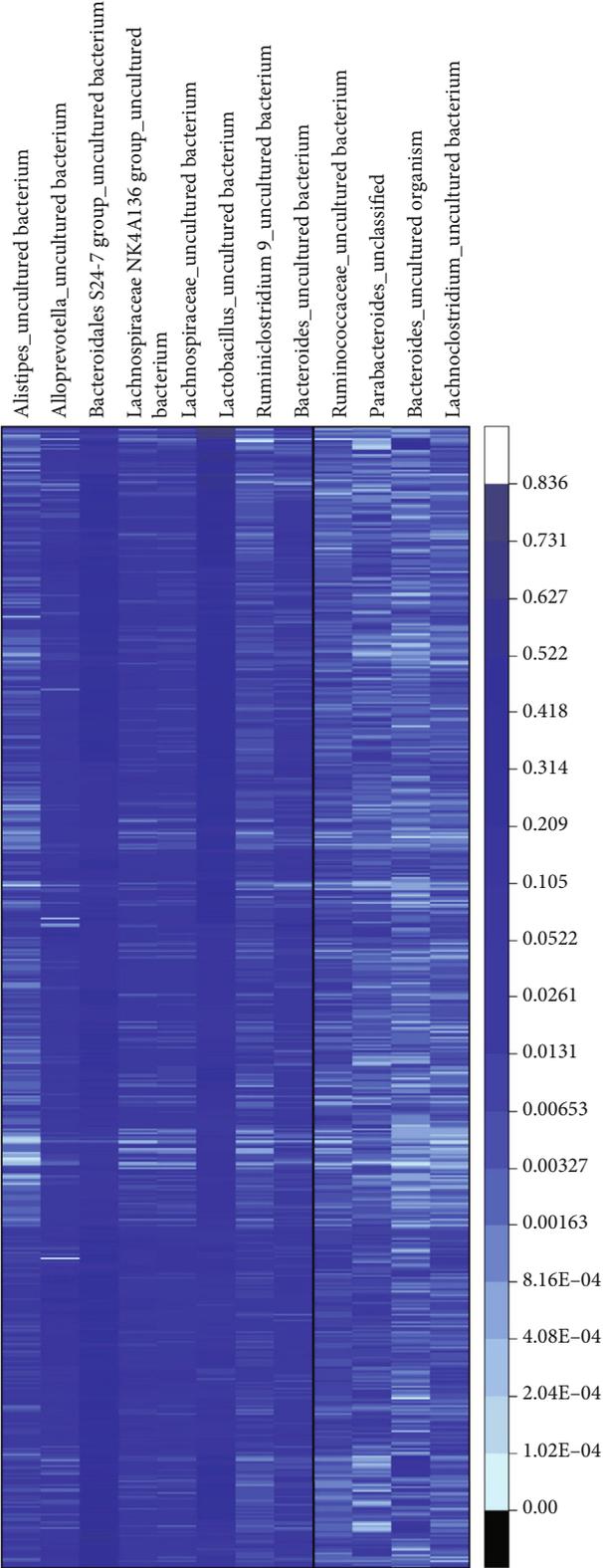
(c)

FIGURE 3: Continued.



(d)

FIGURE 3: Continued.



(e)

FIGURE 3: Continued.

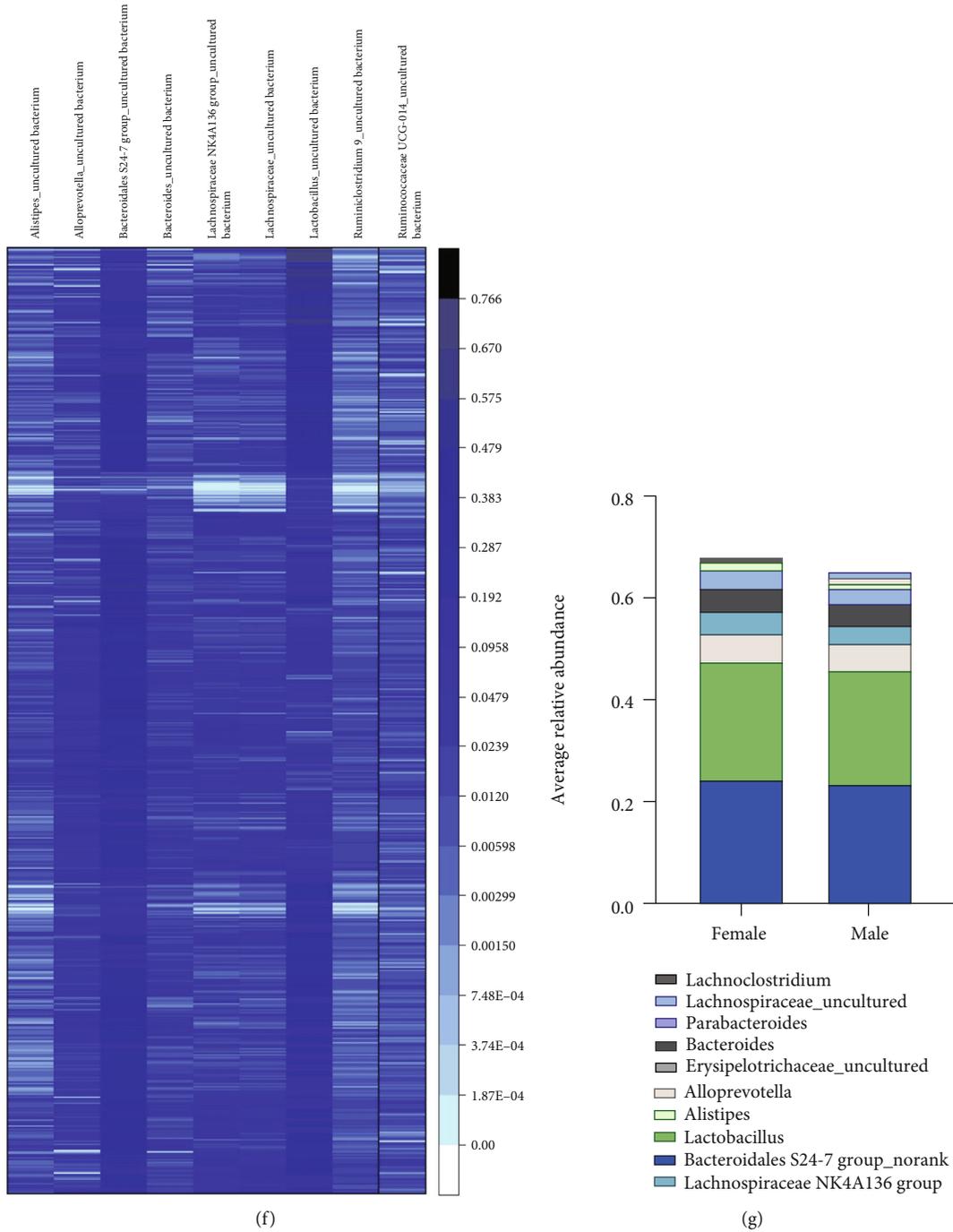


FIGURE 3: Bacterial composition in the gut microbiota of male and female mice. (a) Number of the bacteria in male and female mouse gut microbiota at each classification level. (b) Relative abundance of gut bacteria in male and female mice. “Uncultured” represented the bacteria that could not be cultured. “Unclassified” indicated the sequences that could not be classified. “Norank” represented that there was no classification information or classification name. Bacteria with a relative abundance of less than 1% were classified as “Others.” (c) Core bacteria in the gut microbiota of female mice at the genus level. The left side of the black line represented the core bacterium shared by male and female mice, while the right side of the black line indicated the core bacteria different from male mice. (d) Core bacteria in the gut microbiota of male mice at the genus level. The left side of the black line indicated the core bacteria shared by male and female mice. (e) Core bacteria in the gut microbiota of female mice at the species level. The left side of the black line represented the core bacterium shared by male and female mice, while the right side of the black line indicated the core bacteria different from male mice. (f) Core bacteria in the gut microbiota of male mice at the species level. The left side of the black line represented the core bacteria shared by male and female mice. (g) Relative abundance of the core bacteria in the gut microbiota of female and male mice at the genus level. “Uncultured” indicated the bacteria that could not be cultured. “Unclassified” showed the sequences that could not be classified. “Norank” represented that there was no classification information or classification name. Only the bacteria with a relative abundance of more than 1% were listed.

(11.17%), *Alloprevotella\_uncultured bacterium* (5.44%), *Lachnospiraceae NK4A136 group\_ uncultured bacterium* (3.71%), *Lachnospiraceae\_ uncultured bacterium* (3.16%), *Bacteroides\_ uncultured bacterium* (3.10%), *Escherichia-Shigella\_ Unclassified* (2.68%), *Enterorhabdus\_ uncultured bacterium* (1.73%), *Lactobacillus\_ unclassified* (1.73%), *Ruminococcaceae UCG-014\_ uncultured bacterium* (1.34%), *Ruminiclostridium\_ uncultured bacterium* (1.31%), *Alistipes\_ uncultured bacterium* (1.25%), and *Roseburia\_ uncultured bacterium* (1.09%) (Figure 2(b)).

To reveal the core bacteria (the bacteria existing in all individuals) of the gut microbiota of mice, the gut microbiota of 600 mice were compared. The results showed that among the 624 known bacterial genera, 8 genera existed in all mouse individuals (Figure 2(c)), indicating that these bacteria were the core bacteria of mice. The 8 bacterial genera were *Bacteroidales S24-7 group\_norank*, *Lactobacillus*, *Alloprevotella*, *Bacteroides*, *Lachnospiraceae NK4A136 group*, *Lachnospiraceae\_ uncultured*, *Alistipes*, and *Ruminiclostridium* 9, accounting for 23.91%, 22.99%, 5.44%, 4.31%, 4.17%, 3.39%, 1.30%, and 0.89%, respectively. At the species level, the core microbiota contained 8 bacterial species, including *Alistipes\_ uncultured bacterium*, *Alloprevotella\_ uncultured bacterium*, *Bacteroidales S24-7 group\_ uncultured bacterium*, *Bacteroides\_ uncultured bacterium*, *Lachnospiraceae NK4A136 group\_ uncultured bacterium*, *Lachnospiraceae\_ uncultured bacterium*, *Lactobacillus\_ uncultured bacterium*, and *Ruminiclostridium 9\_ uncultured bacterium*, accounting for 1.25%, 5.44%, 23.91%, 2.97%, 3.61%, 3.34%, 21.22%, and 0.89%, respectively (Figure 2(d)). However, the bacteria belonging to the 8 species could not be cultured.

Among the core bacteria, 7 out of 8 genera belonged to the dominant bacteria of mouse gut microbiota, including *Bacteroidales S24-7 group\_norank* (23.91%), *Lactobacillus* (22.99%), *Alloprevotella* (5.44%), *Bacteroides* (4.31%), *Lachnospiraceae NK4A136 group* (4.17%), *Lachnospiraceae\_ uncultured* (3.39%), and *Alistipes* (1.30%). At the species level, 7 species of the core bacteria were the dominant bacteria, including *Bacteroidales S24-7 group\_ uncultured bacterium* (23.91%), *Lactobacillus\_ uncultured bacterium* (21.22%), *Alloprevotella\_ uncultured bacterium* (5.44%), *Lachnospiraceae NK4A136 group\_ uncultured bacterium* (3.61%), *Lachnospiraceae\_ uncultured bacterium* (3.34%), *Bacteroides\_ uncultured bacterium* (2.97%), and *Alistipes\_ uncultured bacterium* (1.25%).

Collectively, these results revealed that the bacteria belonging to 8 genera were the core bacteria of the mouse gut microbiota. The dominant genera of the mouse gut bacteria contained 15 bacterial genera.

**3.3. Bacterial Composition in the Gut Microbiota of Male and Female Mice.** To compare the bacterial composition of male and female mice, the gut microbiota of mice were analyzed. The results showed that the female mice had a total of 1,041 OTUs, which could be classified into 27 phyla, 70 classes, 138 orders, 254 families, 626 genera, and 841 species (Figure 3(a)). The male mice contained a total of 1038 OTUs, which were classified into 30 phyla, 75 classes, 141 orders, 256 families, 624 genera, and 833 species (Figure 3(a)).

At the genus level, the dominant bacteria in the gut microbiota of male mice were *Bacteroidales S24-7 group\_*

*norank* (23.12%), *Lactobacillus* (22.85%), *Faecalibaculum* (12.81%), *Alloprevotella* (5.14%), *Bacteroides* (4.23%), *Lachnospiraceae NK4A136 group* (3.81%), *Lachnospiraceae\_ uncultured* (2.84%), *Escherichia-Shigella* (2.69%), *Enterorhabdus* (1.81%), *Citrobacter* (1.47%), *Ruminococcaceae UCG-014* (1.43%), *Alistipes* (1.19%), *Ruminiclostridium* (1.17%), *Erysipelotrichaceae\_ uncultured* (1.08%), *Mollicutes RF9\_norank* (1.06%), and *Roseburia* (1.02%), while the most dominant bacteria in the gut microbiota of female mice included *Bacteroidales S24-7 group\_norank* (24.60%), *Lactobacillus* (23.11%), *Faecalibaculum* (9.62%), *Alloprevotella* (5.72%), *Bacteroides* (4.39%), *Lachnospiraceae NK4A136 group* (4.51%), *Lachnospiraceae\_ uncultured* (3.53%), *Escherichia-Shigella* (2.66%), *Enterorhabdus* (1.67%), *Ruminococcaceae UCG-014* (1.31%), *Alistipes* (1.40%), *Ruminiclostridium* (1.44%), *Mollicutes RF9\_norank* (1.08%), *Roseburia* (1.20%), and *Parabacteroides* (1.05%) (Figure 3(b)). Among these bacteria, 2 genera (*Citrobacter* and *Erysipelotrichaceae\_ uncultured*) were dominant only in male mice, and *Parabacteroides* was dominant only in female mice. At the species level, the dominant bacteria in the gut microbiota of male mice contained *Bacteroidales S24-7 group\_ uncultured bacterium* (23.12%), *Lactobacillus\_ uncultured bacterium* (21.51%), *Faecalibaculum\_ uncultured bacterium* (12.81%), *Alloprevotella\_ uncultured bacterium* (5.14%), *Lachnospiraceae NK4A136 group\_ uncultured bacterium* (3.41%), *Bacteroides\_ uncultured bacterium* (2.86%), *Lachnospiraceae\_ uncultured bacterium* (2.81%), *Escherichia-Shigella\_ Unclassified* (2.69%), *Enterorhabdus\_ uncultured bacterium* (1.81%), *Citrobacter\_ Unclassified* (1.47%), *Ruminococcaceae UCG-014\_ uncultured bacterium* (1.40%), *Lactobacillus\_ Unclassified* (1.32%), *Ruminiclostridium\_ uncultured bacterium* (1.17%), *Alistipes\_ uncultured bacterium* (1.12%), *Bacteroides\_ uncultured organism* (1.09%), *Erysipelotrichaceae\_ uncultured bacterium* (1.08%), and *Roseburia\_ uncultured bacterium* (1.00%) (Figure 3(b)). The most dominant species in female mice was *Bacteroidales S24-7 group\_ uncultured bacterium* (24.60%), followed by *Lactobacillus\_ uncultured bacterium* (20.98%), *Faecalibaculum\_ uncultured bacterium* (9.62%), *Alloprevotella\_ uncultured bacterium* (5.72%), *Lachnospiraceae NK4A136 group\_ uncultured bacterium* (3.99%), *Bacteroides\_ uncultured bacterium* (3.32%), *Lachnospiraceae\_ uncultured bacterium* (3.48%), *Escherichia-Shigella\_ Unclassified* (2.66%), *Enterorhabdus\_ uncultured bacterium* (1.67%), *Ruminococcaceae UCG-014\_ uncultured bacterium* (1.28%), *Lactobacillus\_ Unclassified* (2.12%), *Ruminiclostridium\_ uncultured bacterium* (1.44%), *Alistipes\_ uncultured bacterium* (1.37%), and *Roseburia\_ uncultured bacterium* (1.17%) (Figure 3(b)). Among these bacteria, 3 species (*Citrobacter\_ Unclassified*, *Bacteroides\_ uncultured organism*, and *Erysipelotrichaceae\_ uncultured bacterium*) were dominant only in male mice.

At the genus level, the core bacteria of female mouse gut microbiota included *Bacteroidales S24-7 group\_norank*, *Lactobacillus*, *Alloprevotella*, *Bacteroides*, *Lachnospiraceae NK4A136 group*, *Lachnospiraceae\_ uncultured*, *Alistipes*, *Ruminiclostridium* 9, and *Ruminococcaceae UCG-014* (Figure 3(c)). The core bacteria of male mice were *Bacteroidales S24-7 group\_norank*, *Lactobacillus*, *Alloprevotella*, *Bacteroides*, *Lachnospiraceae NK4A136 group*, *Lachnospiraceae\_ uncultured*, *Alistipes*,

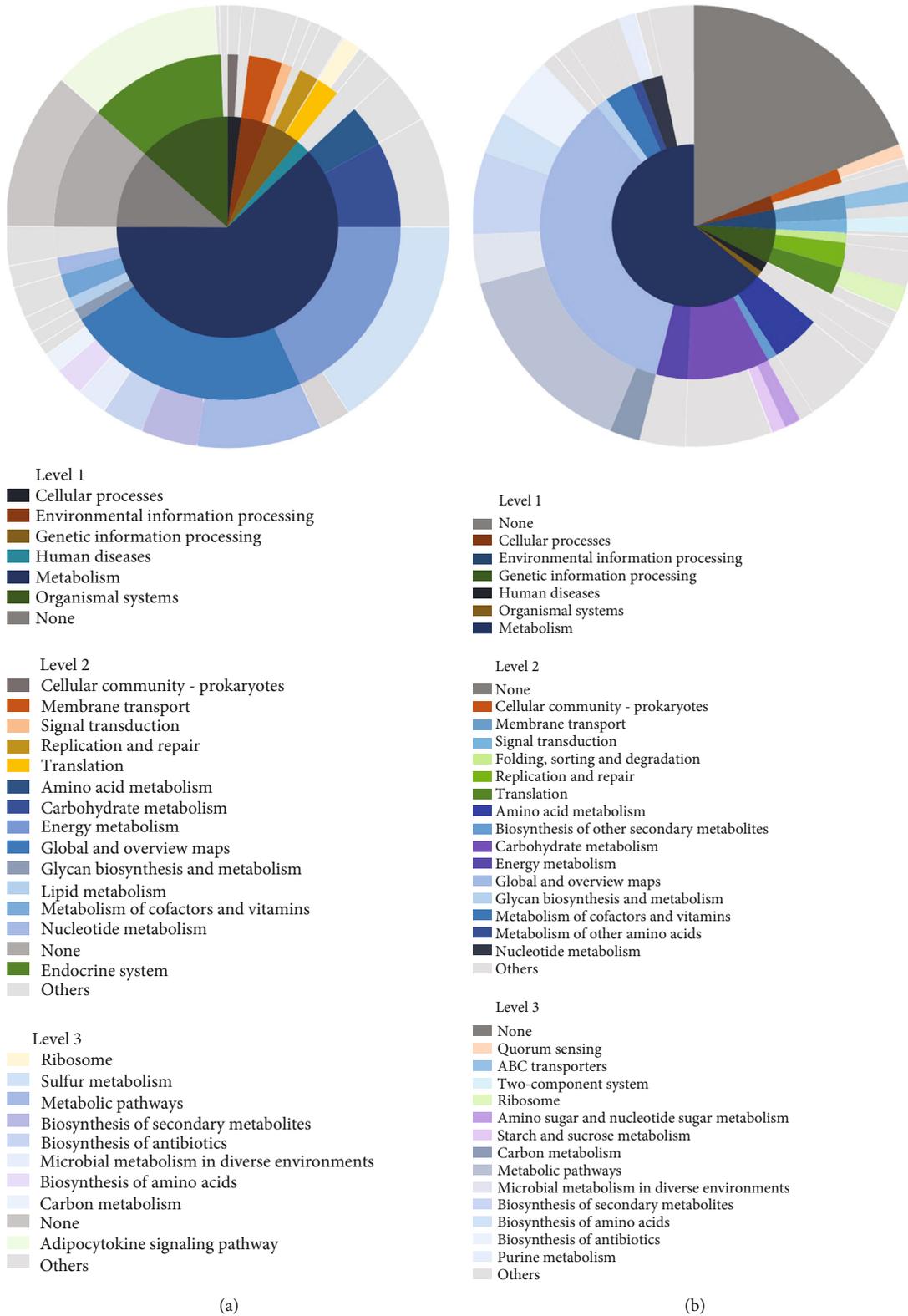
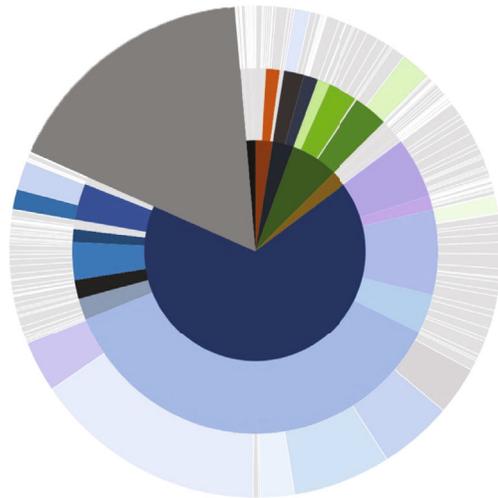


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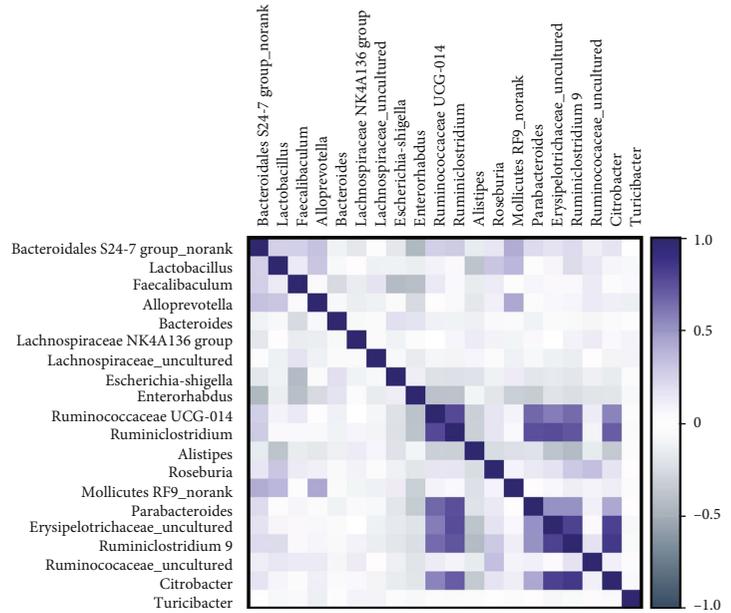


- Level 1
- Cellular processes
  - Environmental information processing
  - Genetic information processing
  - Human diseases
  - Metabolism
  - None
  - Organismal systems

- Level 2
- Cellular community - prokaryotes
  - Membrane transport
  - Signal transduction
  - Folding, sorting and degradation
  - Replication and repair
  - Translation
  - Amino acid metabolism
  - Biosynthesis of other secondary metabolites
  - Carbohydrate metabolism
  - Energy metabolism
  - Global and overview maps
  - Glycan biosynthesis and metabolism
  - Lipid metabolism
  - Metabolism of cofactors and vitamins
  - Metabolism of other amino acids
  - Nucleotide metabolism
  - None
  - Others

- Level 3
- ABC transporters
  - Ribosome
  - Amino sugar and nucleotide sugar metabolism
  - Biosynthesis of amino acids
  - Biosynthesis of antibiotics
  - Biosynthesis of secondary metabolites
  - Carbon metabolism
  - Metabolic pathways
  - Microbial metabolism in diverse environments
  - Purine metabolism
  - Pyrimidine metabolism
  - None
  - Others

(c)



(d)

FIGURE 4: Functional profiles of the bacteria in the gut microbiota of mice. (a) The functional profiles of the bacteria in the gut microbiota of mice. The functions of the gut bacteria of mice were analyzed using KEGG. The KEGG pathways in level 1 (inner layer), level 2 (middle layer), and level 3 (outer layer) were indicated. Only pathways with a percentage more than 1% were shown, and the remaining was labeled as “Others.” (b) The functions of the dominant bacteria in the gut microbiota of mice. The KEGG pathways involved by the gut bacteria were indicated. (c) The pathways involved by the core bacteria in the mouse gut microbiota. Based on the KEGG analysis, the pathways involved by the gut core bacteria were obtained. (d) Correlation analysis of the bacteria in mouse gut microbiota. The top 20 abundant bacteria were analyzed.

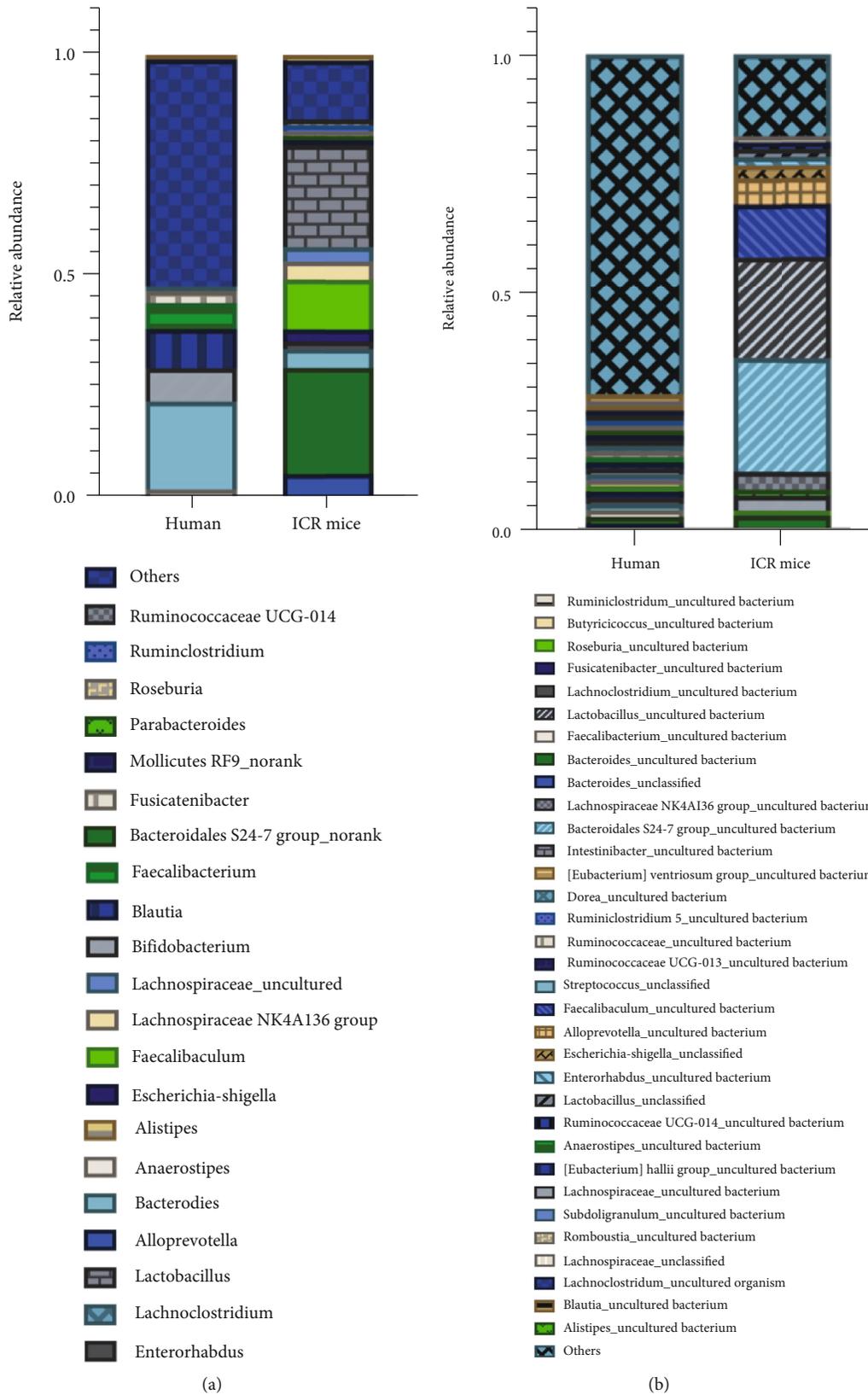


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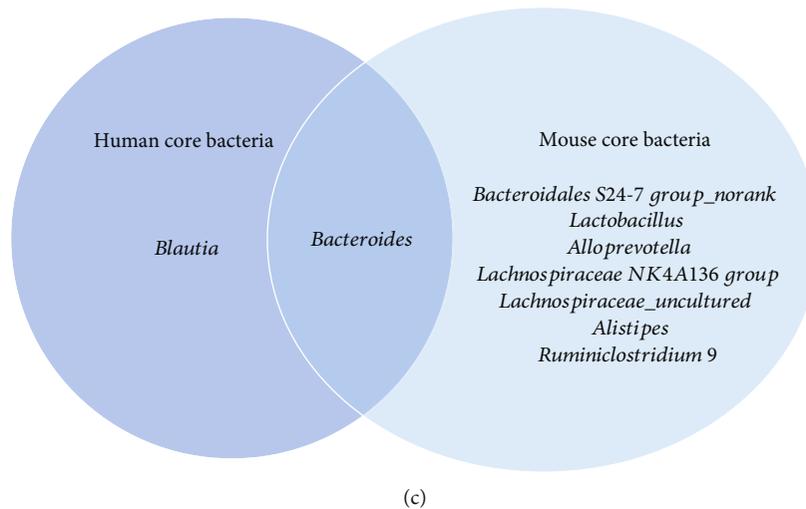


FIGURE 5: Similarity between human and mouse gut microbiota. (a) The dominant bacteria of mouse and human gut microbiota at the genus level. “uncultured” represented the bacteria that could not be cultured. “unclassified” indicated the bacteria that could not be classified. “norank” represented that there was no classification information or classification name. Bacteria with a relative abundance of less than 1% were classified as “others.” (b) The dominant bacteria of mouse and human gut microbiota at the species level. (c) Comparison of the core bacteria in human and mouse gut microbiota.

*Ruminiclostridium 9*, *Parabacteroides*, *Ruminococcaceae\_ uncultured*, and *Lachnoclostridium* (Figure 3(d)). Among these core bacteria, the bacteria of 8 genera coexisted in male and female mice, including *Bacteroidales S24-7 group\_ norank*, *Lactobacillus*, *Alloprevotella*, *Bacteroides*, *Lachnospiraceae NK4A136 group*, *Lachnospiraceae\_ uncultured*, *Alistipes*, and *Ruminiclostridium 9*.

At the species level, the core bacteria of female mice contained *Alistipes\_ uncultured* bacterium, *Alloprevotella\_ uncultured* bacterium, *Bacteroidales S24-7 group\_ uncultured* bacterium, *Bacteroides\_ uncultured* bacterium, *Lachnospiraceae NK4A136 group\_ uncultured* bacterium, *Lachnospiraceae\_ uncultured* bacterium, *Lactobacillus\_ uncultured* bacterium, *Ruminiclostridium 9\_ uncultured* bacterium, and *Ruminococcaceae UCG-014\_ uncultured* bacterium (Figure 3(e)), while the core bacteria of male mice included *Alistipes\_ uncultured* bacterium, *Alloprevotella\_ uncultured* bacterium, *Bacteroidales S24-7 group\_ uncultured* bacterium, *Bacteroides\_ uncultured* bacterium, *Lachnospiraceae NK4A136 group\_ uncultured* bacterium, *Lachnospiraceae\_ uncultured* bacterium, *Lactobacillus\_ uncultured* bacterium, *Ruminiclostridium 9\_ uncultured* bacterium, *Bacteroides\_ uncultured* bacterium, *Lachnoclostridium\_ uncultured* bacterium, *Parabacteroides\_ unclassified*, and *Ruminococcaceae\_ uncultured* bacterium (Figure 3(f)). Except for *Ruminococcaceae UCG-014\_ uncultured* bacterium only in the core bacteria of female mice and *Bacteroides\_ uncultured* organism, *Lachnoclostridium\_ uncultured* bacterium, *Parabacteroides\_ unclassified*, and *Ruminococcaceae\_ uncultured* bacterium in the core bacteria of male mice, the remaining bacteria of 8 species existed in the core microbiota of both male and female mice.

To determine whether the core bacteria in the gut microbiota of male and female mice were dominant, the relative abundance of core bacteria was further analyzed. The results revealed that among the core bacteria, 8 out of 9 genera

belonged to the dominant bacteria in the gut microbiota of female mice, including *Bacteroidales S24-7 group\_ norank* (24.62%), *Lactobacillus* (23.12%), *Alloprevotella* (5.72%), *Lachnospiraceae NK4A136 group* (4.52%), *Bacteroides* (4.39%), *Lachnospiraceae\_ uncultured* (3.73%), *Alistipes* (1.41%), and *Ruminococcaceae UCG-014* (1.34%). Among the core bacteria of male mice, 8 out of 11 genera were dominant, including *Bacteroidales S24-7 group\_ norank* (23.15%), *Lactobacillus* (22.85%), *Alloprevotella* (5.14%), *Bacteroides* (4.24%), *Lachnospiraceae NK4A136 group* (3.81%), *Lachnospiraceae\_ uncultured* (3.02%), *Alistipes* (1.19%), and *Parabacteroides* (1.00%) (Figure 3(g)).

Taken together, these findings revealed that the dominant bacteria in the gut microbiota of male and female mice contained 16 and 15 genera of bacteria, respectively. The core bacteria in the gut microbiota of male and female mice consisted of 11 and 9 genera, respectively.

**3.4. Functional Profiles of the Bacteria in the Gut Microbiota of Mice.** To characterize the functions of the bacteria in the gut microbiota of mice, KEGG analysis was performed. The results exhibited that at level 1, the bacteria in gut microbiota of mice involved in metabolism (61.99%), none (11.51%), organismal systems (13.45%), genetic information processing (4.80%), environmental information processing (4.12%), human diseases (2.14%), and cellular processes (1.99%), indicating that the bacteria in the gut microbiota of mice mainly functioned in host’s metabolism (Figure 4(a)).

At level 2, the gut bacteria of mice played important roles in global and overview maps (22.94%), energy metabolism (18.08%), endocrine system (12.85%), carbohydrate metabolism (8.08%), amino acid metabolism (3.89%), membrane transport (3.12%), metabolism of cofactors and vitamins (2.27%), translation (2.11%), replication and repair (1.79%), nucleotide metabolism (1.61%), lipid metabolism (1.16%),

glycan biosynthesis and metabolism (1.09%), cellular community-prokaryotes (1.01%), and signal transduction (1.00%) (Figure 4(a)). At level 3, the main functions of mouse gut bacteria included sulfur metabolism (15.81%), adipocytokine signaling pathway (12.52%), metabolic pathways (9.09%), biosynthesis of secondary metabolites (4.11%), biosynthesis of antibiotics (3.09%), microbial metabolism in diverse environments (2.22%), biosynthesis of amino acids (2.13%), carbon metabolism (1.47%), and ribosome (1.34%) (Figure 4(a)). These data showed that the main functions of the bacteria in the gut microbiota of mice were associated with metabolisms.

To explore the functions of the dominant bacteria and the core bacteria in mouse gut microbiota, the dominant and the core bacteria were subjected to the KEGG analysis. The results showed that the dominant bacteria were mainly involved in the metabolisms, including carbohydrate metabolism, amino acid metabolism, energy metabolism, nucleotide metabolism, metabolism of cofactors and vitamins, lipid metabolism, glycan biosynthesis and metabolism, xenobiotic biodegradation and metabolism and metabolism of terpenoids and polyketides (Figure 4(b)). At the same time, the analysis indicated that the core bacteria in the mouse gut microbiota mainly took part in the metabolisms, including carbohydrate metabolism, amino acid metabolism, energy metabolism, nucleotide metabolism, metabolism of cofactors and vitamins, glycan biosynthesis and metabolism, lipid metabolism, metabolism of terpenoids and polyketides, and xenobiotic biodegradation and metabolism (Figure 4(c)). These data revealed that the involvement of metabolisms was the major role of gut bacteria.

To reveal the relationship between the gut bacteria, the correlation analysis of the top 20 abundant bacterial genera of mouse gut microbiota was performed. The results indicated that *Citrobacter* was positively correlated with *Erysipelotrichaceae\_ uncultured*, *Ruminiclostridium*, and *Ruminiclostridium* 9, while *Ruminiclostridium* was positively correlated with *Parabacteroides*, *Erysipelotrichaceae\_ uncultured*, and *Ruminiclostridium* 9, showing the interactions between these gut bacteria (Figure 4(d)). There were also positive correlations between *Parabacteroides* and *Ruminococcaceae* UCG-014, as well as *Ruminiclostridium* 9 and *Ruminococcaceae* UCG-014 (Figure 4(d)). Negative correlation was found between *Escherichia-Shigella* and *Ruminococcaceae* UCG-014, *Escherichia-Shigella*, and *Ruminiclostridium* (Figure 4(d)). In addition, *Alistipes* appeared to be negatively correlated with *Roseburia*, *Mollicutes* RF9\_norank, *Erysipelotrichaceae\_ uncultured*, and *Citrobacter* (Figure 4(d)). These interacted gut bacteria were associated with the metabolisms (Figures 4(a)–4(c)).

Taken together, these findings presented that the bacteria in the gut microbiota mainly took part in the metabolisms by the collaborations between the gut bacteria.

**3.5. Similarity between Human and Mouse Gut Microbiota.** To explore the similarity and difference between mouse and human gut microbiota, the dominant and core bacteria in human and mouse gut microbiota were compared. The sequencing data of human gut microbiota were obtained from the NCBI database (Table S4), including 1,053 human fecal samples. At the genus level, the dominant bacteria in the human gut microbiota contained *Bacteroides* (19.73%),

*Blautia* (8.81%), *Bifidobacterium* (7.56%), *Faecalibacterium* (5.85%), *Fusicatenibacter* (2.65%), *Anaerostipes* (2.00%), *Lachnoclostridium* (1.08%), and *Alistipes* (1.05%) (Figure 5(a)). Among these bacteria, *Alistipes* and *Bacteroides* were the dominant bacteria in the gut microbiota of mice, while the remaining bacteria were the dominant bacterium unique in human gut microbiota. At the genus level, the human gut microbiota was partially similar to that of mouse gut microbiota.

At the species level, the dominant bacteria in the human gut microbiota included *Blautia\_ uncultured bacterium* (1.48%), *Bacteroides\_ Unclassified* (1.45%), *Bacteroides\_ uncultured bacterium* (1.43%), *Faecalibacterium\_ uncultured bacterium* (1.40%), *Streptococcus\_ Unclassified* (1.34%), *Lachnoclostridium\_ uncultured bacterium* (1.27%), *Fusicatenibacter\_ uncultured bacterium* (1.26%), *Roseburia\_ uncultured bacterium* (1.22%), *Butyricoccus\_ uncultured bacterium* (1.21%), *Subdoligranulum\_ uncultured bacterium* (1.21%), *Lachnospiraceae\_ uncultured bacterium* (1.21%), (*Eubacterium*) *hallii* group\_ *uncultured bacterium* (1.21%), *Anaerostipes\_ uncultured bacterium* (1.20%), *Ruminococcaceae\_ uncultured bacterium* (1.18%), *Dorea\_ uncultured bacterium* (1.10%), *Intestinibacter\_ uncultured bacterium* (1.08%), *Ruminococcaceae* UCG-013\_ *uncultured bacterium* (1.08%), *Alistipes\_ uncultured bacterium* (1.06%), *Romboutsia\_ uncultured bacterium* (1.06%), *Ruminiclostridium* 5\_ *uncultured bacterium* (1.04%), *Lachnospiraceae* NK4A136 group\_ *uncultured bacterium* (1.04%), *Lachnoclostridium\_ uncultured organism* (1.03%), (*Eubacterium*) *ventriosum* group\_ *uncultured bacterium* (1.01%), and *Lachnospiraceae\_ Unclassified* (1.00%). Among these bacteria, *Bacteroides\_ uncultured bacterium*, *Roseburia\_ uncultured bacterium*, *Lachnospiraceae\_ uncultured bacterium*, *Alistipes\_ uncultured bacterium*, and *Lachnospiraceae* NK4A136 group\_ *uncultured bacterium* were the dominant bacteria in the gut microbiota of mice, while the remaining were the dominant bacterium unique in human gut microbiota (Figure 5(b)). However, all of these bacteria are uncultured or not classified.

Based on the NCBI database (Table S4), the human gut microbiota analysis showed that only two genera of bacteria were present in all human fecal samples. The bacteria were *Bacteroides* and *Blautia*, accounting for 19.73% and 8.81%, respectively. *Bacteroides* belonged to the core bacteria of mouse gut microbiota, while *Blautia* was unique in the human gut microbiota (Figure 5(c)). At the species level, there was no core species of bacteria in human gut microbiota.

Taken together, the findings indicated that the structure of mouse gut microbiota was similar to that of human gut microbiota.

## 4. Discussion

It is well known that the gut microbiota plays important roles in human health by affecting metabolisms. The gut microbiota participates in energy metabolism via inducing the expression of genes related to lipid and carbohydrate metabolism, whose dysbiosis can lead to obesity [21]. The structure of gut microbiota is always changed in patients with inflammatory bowel disease [22]. The gut microbiota is able to promote dysbiosis, barrier failure, colorectal cancer, and inflammation [23]. Multiple neurological diseases, such as autism spectrum disorder, are related to gut microbiota, which regulates behaviors

through production of neuroactive metabolites [24]. Many investigations demonstrate that the functions of gut microbiota depend on the structure of gut bacteria [25, 26]. The dysbiosis of gut microbiota can promote or boost susceptibility to metabolic disorders [26]. Therefore, the gut microbiota has attracted more and more attentions. As mammalian models, rodents, especially mouse, are widely to explore the roles of gut microbiota [27]. For the better genetic and physiological similarities to humans, mouse model is most commonly employed. The mouse model has the ability to control environmental factors more easily in experiments to minimize changes in baseline gut microbiota between individuals. Although many investigations focus on mouse gut microbiota, the structure of gut microbiota of mouse has not been explored at a large scale [28]. Based on the analysis of mouse gut bacteria at a large scale, our findings revealed that the core bacteria of the mouse gut microbiota included 8 bacteria at the genus level, while the dominant genera of the mouse gut bacteria contained 15 bacteria. Compared with the previous study [29], 4 of 8 genera of core bacteria (*Bacteroidales S24-7 group\_norank*, *Lachnospiraceae NK4A136 group*, *Lachnospiraceae\_uncultured*, and *Ruminiclostridium* 9) and 10 of 15 genera of dominant bacteria (*Bacteroidales S24-7 group\_norank*, *Faecalibaculum*, *Lachnospiraceae NK4A136 group*, *Lachnospiraceae\_uncultured*, *Escherichia-Shigella*, *Enterorhabdus*, *Ruminococcaceae UCG-014*, *Ruminiclostridium*, *Roseburia*, and *Mollicutes RF9\_norank*) revealed in this study were novel. The remaining core and dominant bacteria of this investigation were consistent with the previous data [29]. In this study, the results revealed that the exclusive core genera in female mice was *Ruminococcaceae UCG-014*, while *Parabacteroides*, *Ruminococcaceae\_uncultured*, and *Lachnoclostridium* were the exclusive core genera in male mice. The dominant bacteria in the gut microbiota of male and female mice contained of 16 and 15 genera of bacteria, respectively. These data indicated that there were differences of the core and dominant microbiota between male and female mice. The structure of the gut microbiota of mice, including the core bacteria and the dominant bacteria, was similar to that of human being. Therefore, our study provided a solid basis for the investigations of gut microbiota.

Our findings revealed that two bacteria at the genus level, *Alistipes* and *Bacteroides*, were shared by mouse and human microbiota, suggesting the importance of *Alistipes* and *Bacteroides* in mammalian gut microbiota. *Alistipes*, one of the genus members of the *Bacteroidetes* phylum, is highly relevant to dysbiosis and metabolic diseases [30]. Various species of gut bacteria belonging to the genus *Alistipes* have been isolated from patients with appendicitis and abdominal and rectal abscess [31]. It is found that *Alistipes* is pathogenic in patients with colorectal cancer or depression [32, 33]. However, *Alistipes* also has protective effects against some diseases, such as liver fibrosis, colitis, cancer immunotherapy, and cardiovascular disease [30]. These data demonstrate that *Alistipes* in gut microbiota plays important regulatory roles in metabolic diseases. *Bacteroides*, a dominant bacterial genus in gut microbiota of mouse and human being, can product sphingolipid, which is essential for the maintenance of the symbiotic relationship between gut microbiota and mammalian hosts [34]. Evidences indicate that *Bacteroides* is related to host-

and diet-derived glycans and has tremendous capability to utilize complex recalcitrant glycans to sustaining gut microbial symbiosis [35]. These findings show that *Bacteroides* can confer health benefit to the host, therefore helping prevent or delay diseases. Nevertheless, some species of *Bacteroides* are pathogenic. *B. fragilis* and *B. thetaiotaomicron* are commonly isolated anaerobic pathogens, which are often found in the patients with gangrenous and perforated appendicitis [36, 37]. In this context, *Alistipes* and *Bacteroides* might be biomarker bacteria for metabolic diseases as well as bacterial indicators for human health.

## Data Availability

Sequencing data was stored at NCBI database (PRJNA721276).

## Conflicts of Interest

The authors declare that they have no competing interests.

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## Supplementary Materials

*Supplementary 1.* Table S1: diversities of bacterial communities of mouse gut microbiota. A total of 300 female and 300 male mice (8 weeks old) were kept in a sterilized environment for 10 days. Mice were fed with sterilized water. At day 3 and day 10, fecal samples were collected. In the sample ID, 0/7 represented the fecal samples taken at day 3/day 10, C/X indicated female/male mice, and the number represented the number of mice in the same group.

*Supplementary 2.* Table S2: the identified operational taxonomic units (OTUs) of mouse gut microbiota at each classification level.

*Supplementary 3.* Table S3: the known operational taxonomic units (OTUs) of mouse gut microbiota at the genus level.

*Supplementary 4.* Table S4: sequencing data of human gut microbiota.

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