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Research article

Composition of the bacterial community in the gastrointestinal tract of Kunming mice

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ABSTRACT

Background: The intestinal bacterial community has an important role in maintaining human health. Dysbiosis is a key inducer of many chronic diseases including obesity and diabetes. Kunming mice are frequently used as a model of human disease and yet little is known about the bacterial microbiome resident to the gastrointestinal tract.

Results: We undertook metagenomic sequencing of the luminal contents of the stomach, duodenum, jejunum, ileum, cecum, colon, and rectum of Kunming mice. Firmicutes was the dominant bacterial phylum of each intestinal tract and *Lactobacillus* the dominant genus. However, the bacterial composition differed among the seven intestinal tracts of Kunming mice. Compared with the small intestine, the large intestine bacterial community of Kunming mice is more stable and diverse.

Conclusions: To our knowledge, ours is the first study to systematically describe the gastrointestinal bacterial composition of Kunming mice. Our findings provide a better understanding of the bacterial composition of Kunming mice and serves as a foundation for the study of precision medicine.

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1. Introduction

The human intestinal bacterial community is a complex symbiotic microbial ecosystem of an estimated 10^{14} cells [1]. There are over 500 types of anaerobic bacteria in the intestine [2], which is 10 times the number of human cells. Moreover, the amount of genetic material in these bacteria is approximately 100 times that of human genes [1]. The bacteria community that colonizes the host intestine is closely associated with various physiological functions of the host, including digestion, nutrient metabolism and immunity, and may even affect the host's adaptation to the environment and evolution [1,3,4,5]. The intestinal bacterial community thus has an important role in maintaining human life and health [6]. Recent studies have associated intestinal microorganisms with intestinal diseases, cancer and obesity [7,8,9]. Hence, the study of the relationship between the bacterial community and human health and disease, and furthering our understanding of the role of bacterial changes in disease development and progression may provide new strategies for diagnosing and treating diseases.

Mice are the most frequently studied and best understood of animal models. Owing to long-term selective breeding, mouse models have many advantages over other experimental animals, such as stable genetic backgrounds, ease of handling and maintenance, feasibility of genetic manipulations and so on [10]. In addition, because of the diversity of species and the specific distribution of intestinal bacteria in the host, the bacterial composition is slightly different between each host [11,12,13,14]. Therefore, it is necessary to explore the microbial composition of the gastrointestinal tract of various mice.

Kunming mice were derived in 1944 from a pair of Swiss mice that had been introduced from Hoffline Institution of Hindustan into Kunming of China [15]. Since the mice were originally introduced into Kunming, they were called Kunming mice. After more than half a century of breeding and reproduction, there were distinct genetic differences between KM mice and Swiss mice [16]. At present,

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Kunming mice are unique to China, and are also the most widely used and produced strain of outbred mice in China [17]. And Kunming mice are widely used in pharmacology and toxicology due to their high reproductive and survival rates, resistance to disease, and high adaptability [15]. Therefore, Kunming mice are very important in China. However, the intestinal bacterial community of Kunming mice has not been examined in detail. The present study analyzes and compares the species, distribution and correlation of bacteria in different intestinal segments of Kunming mice using metagenomics sequencing. The aim is to facilitate subsequent studies using Kunming mice as the animal model.

2. Material and methods

2.1. Animals and sample collection

Ten female Kunming mice aged 8 weeks were purchased from the Laboratory Animal Center at the Xuzhou Medical University. Experimental mice were maintained on the same mouse diet for 20 d in a barrier system according to the feeding standards of a specific-pathogen-free grade laboratory. Mice were fasted for 8 h before euthanasia by cervical dislocation. The intestinal luminal contents of the stomach, duodenum, jejunum, ileum, cecum, colon, and rectum were harvested from mice under sterile conditions. After adding 500 μL sterilized water, an equal weight (20 mg) of luminal contents from the same intestinal segment of each mouse was mixed thoroughly by vortex instrument, and then stored at -80°C.

All procedures involving animals were approved by the Laboratory Animal Ethics Committee of Xuzhou Medical University. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

2.2. DNA extraction and PCR amplification

Microbial DNA was extracted from mice samples using the E.Z.N.A.® soil DNA Kit (Omega Bio-tek, Norcross, GA, U.S.) according to manufacturer's protocols. The final DNA concentration and purification were determined by NanoDrop 2000 UV–vis spectrophotometer (Thermo Scientific, Wilmington, USA), and DNA quality was checked by 1% agarose gel electrophoresis. The V3-V4 hypervariable regions of the bacteria 16S rRNA gene were amplified with primers 338F (5′-ACTCCTACGGGAGGCAGCAG-3′) and 806R (5′-GGACTACHVGGGTWTCTAAT-3′) [18] by thermocycler PCR system (GeneAmp 9700, ABI, USA). The PCR reactions were conducted using the following program: 3 min of denaturation at 95°C, 27 cycles of 30 s at 95°C, 30 s for annealing at 55°C, and 45 s for elongation at 72°C, and a final extension at 72°C for 10 min. PCR reactions were performed in triplicate 20 μL mixture containing 4 μL of 5 × FastPfu Buffer, 2 μL of 2.5 mM dNTPs, 0.8 μL of each primer (5 μM), 0.4 μL of FastPfu Polymerase and 10 ng of template DNA. The resulted PCR products were extracted from a 2% agarose gel and further purified using the AxyPrep DNA Gel Extraction Kit (Axygen Biosciences, Union City, CA, USA) and quantified using QuantiFluor™-ST (Promega, USA) according to the manufacturer's protocol.

2.3. Illumina MiSeq sequencing

Purified amplicons were pooled in equimolar and paired-end sequenced (2 × 300) on an Illumina MiSeq platform (Illumina, San Diego,USA) according to the standard protocols by Majorbio Bio-Pharm Technology Co. Ltd. (Shanghai, China).

2.4. Processing of sequencing data

Raw fastq files were quality-filtered by Trimmomatic and merged by FLASH with the following criteria: (i) The reads were truncated at any site receiving an average qualityscore <20 over a 50 bp sliding window. (ii) Sequences whose overlap being longer than 10 bp were merged according to their overlap with mismatch no more than 2 bp. (iii) Sequences of each sample were separated according to barcodes (exactly matching) and Primers (allowing 2 nucleotide mismatching), and reads containing ambiguous bases were removed.

Operational taxonomic units (OTUs) were clustered with 97% similarity cutoff using UPARSE (version 7.1 http://drive5.com/uparse/) with a novel 'greedy' algorithm that performs chimera filtering and OTU clustering simultaneously. The taxonomy of each 16S rRNA gene sequence was analyzed by RDP Classifier algorithm (http://rdp.cme.msu.edu/) against the SILVA database [19] using confidence threshold of 70% [20]. Heatmaps of microbiota composition in different gastrointestinal regions were created using the 'gplots' package [21].

3. Results

A total of 393,377 optimized sequences were obtained from 7 mouse intestinal samples (Table 1). The majority of these were from the stomach (64,060) and the least from the jejunum (48,911). The mean sequence length was 444 bp. A total of 174,831,717 bases were sequenced from the seven gastrointestinal segments; most of which were from the colon (28,304,051) and the least from the jejunum (21,829,781).

Next, we performed an alpha diversity analysis on all samples. Alpha diversity refers to the diversity of a specific region or ecosystem, and the commonly used metrics are Sobs, Chao, Shannon, Simpson and coverage. The diversity and abundance of species can be determined by the various index values. Coverage of each sample was ≥0.99 (Table 1), thereby suggesting that the sample size we have sequenced is representative of the bacterial microbiota. The Sobs and Shannon indices reflect the abundance and diversity of the bacterial communities sequenced. The bacterial community was largest and most diverse in the duodenum and least small and least diverse in the ileum (Table 1). The abundance and diversity of the bacterial community were more stable in the large intestine than in the small intestine (Table 1).

We undertook a taxonomic analysis of representative OTU sequences with 97% similarity using the RDP classifier (Bayesian algorithm) and identified 15 Phyla. Firmicutes (64–96%), Bacteroidetes (0.19–24.40%), Actinobacteria (1.13–8.60%), Proteobacteria (0.13–4.17%), and Deferribacteres (0.01–1.32%) were the most abundant phyla in each mouse intestinal segment (Fig. 1). Of these phyla, Firmicutes was most abundant in the ileum and least abundant in the rectum; Bacteroidetes was most abundant in the colon and least abundant in the ileum; Actinobacteria was most abundant in the rectum and least abundant in the stomach; and Proteobacteria was most abundant in the duodenum and least abundant in the ileum. The relative abundance of other phyla

Table 1
The trimmed sequences and Alpha diversity of each gastrointestinal region.

Sample	Reads	Base (bp)	Mean length	Sobs	Shannon	Coverage
Stomach	51,997	23,320,537	448.49	366	2.17	0.996
Duodenum	52,809	23,504,288	445.08	571	4.11	0.998
Jejunum	48,911	21,829,781	446.31	368	2.53	0.997
Ileum	53,815	24,023,367	446.40	157	1.79	0.997
Cecum	59,330	26,064,048	439.30	351	4.05	0.999
Colon	64,060	28,304,051	441.83	346	3.91	0.999
Rectum	62,455	27,785,645	444.89	306	3.16	0.999

Note: The richness estimators (Sobs) and diversity indices (Shannon) were calculated.

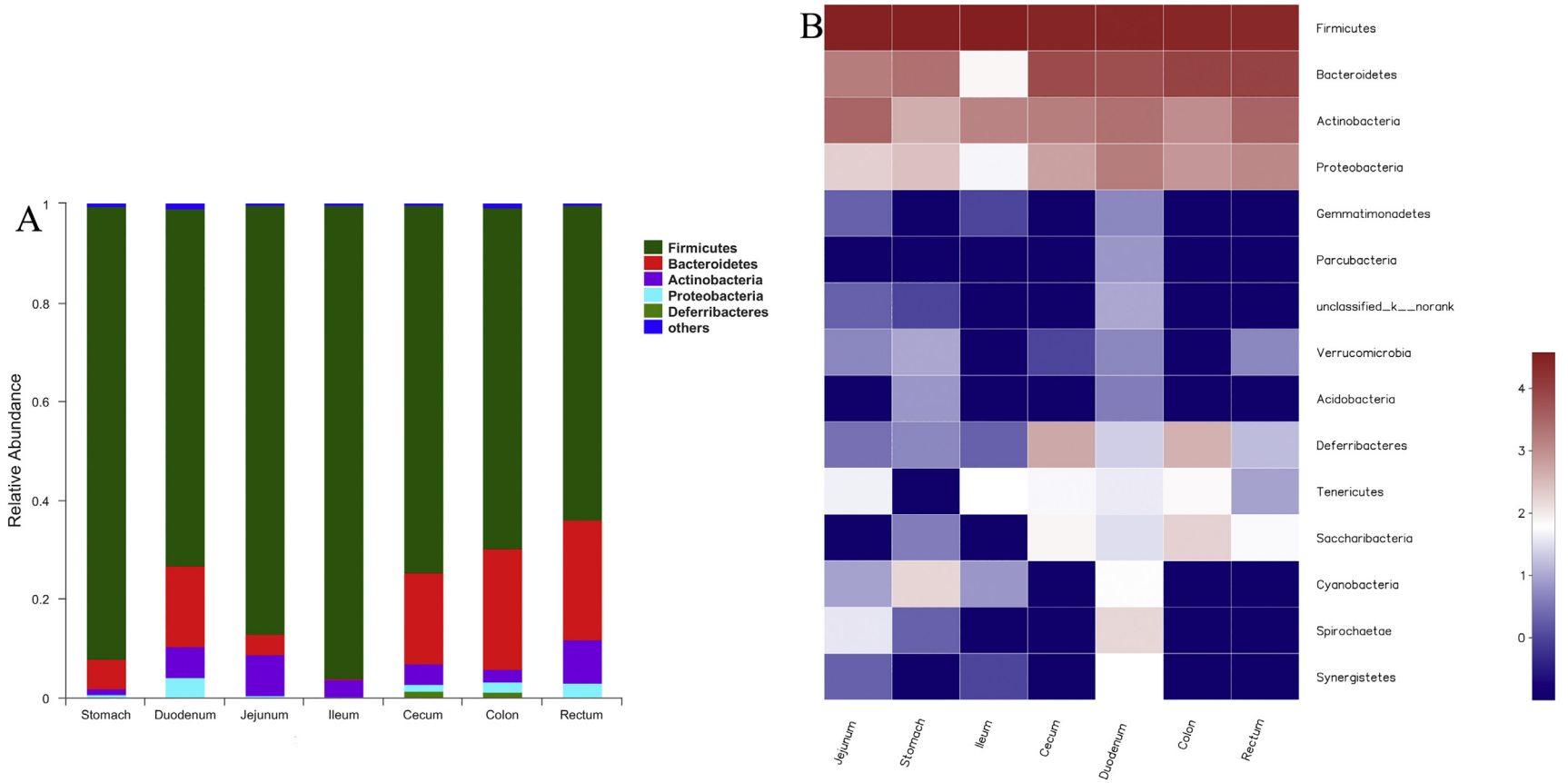

Fig. 1. Bacterial composition of different regions of the gastrointestinal tract in Kunming mice at Phylum level. (A) Bar chart. Each bar represents the relative abundance of each bacterial taxon within a region of the gastrointestinal tract. Bacteria taxon with the relative abundance less than 0.01 in all samples were classified as "others". (B) Heatmap. The lg values of the sequence number for bacterial taxon are depicted by color intensity with the legend indicated at the right side of the figure.

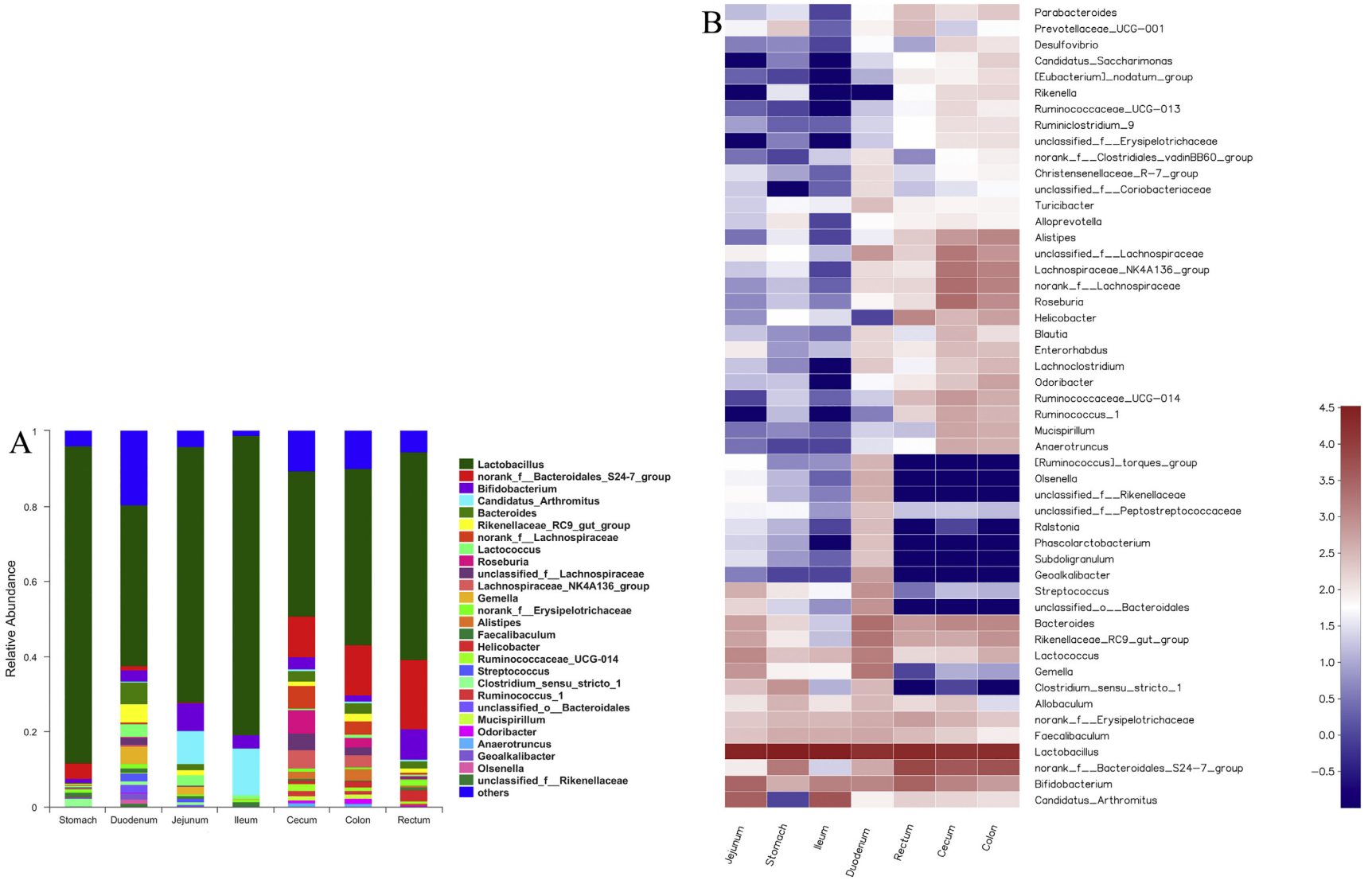

Fig. 2. Bacterial composition of different regions of the gastrointestinal tract in Kunming mice at Genus level. (A) Bar chart. Each bar represents the relative abundance of each bacterial taxon within a region of the gastrointestinal tract. Bacteria taxon with the relative abundance less than 0.01 in all samples were classified as "others". (B) Heatmap. The lg values of the sequence number for bacterial taxon are depicted by color intensity with the legend indicated at the right side of the figure.

was relatively low, with the most abundant phylum being less than 1% of the duodenum microbiota.

To further explore the intestinal bacterial composition of the mice, we analyzed the composition and changes in the bacterial community at the genus level and identified 247 genera by sequence alignment. *Lactobacillus* was the dominant genus in each intestinal segment, although its abundance differed in each segment (Fig. 2). *Lactobacillus* was most abundant in the stomach and least abundant in the cecum. Genera accounting for >1% of the stomach microbiota were *Lactobacillus* (84.33%), *S24–7* (4.20%), *Bifidobacterium* (1.04%), *Faecalibaculum* (1.10%), and *Clostridium_sensu_stricto_1* (2.04%). The genera that were found at >2% in the duodenum were *Lactobacillus* (42.75%), *Bacteroides* (5.75%), *RC9* (4.88%), *Gemella* (4.55%), *Lactococcus* (3.67%), *Bifidobacterium* (3.05%), *Streptococcus* (2.25%), and *unclassified_o__Bacteroidales* (2.09%). Genera that were found at >1% in the ileum were *Lactobacillus* (67.68%), *Candidatus_Arthromitus* (8.88%), *Bifidobacterium* (7.53%), *Lactococcus* (2.82%), *Gemella* (1.94%), *Bacteroides* (1.50%), and *RC9* (1.40). Genera that were found at >1% in the jejunum were *Lactobacillus* (79.67%), *Candidatus_Arthromitus* (12.52%), *Bifidobacterium* (3.31%), and *Faecalibaculum* (1.04%). Genera that were found at >5% in the cecum include *Lactobacillus* (38.62%), *S24-7* (10.89%), *Roseburia* (6.17%), and *Lachnospiraceae* (6.01%). Genera that were found at >5% in the colon were *Lactobacillus* (46.86%) and *S24-79* (13.37%). Finally, genera that were found at >5% in the rectum were *Lactobacillus* (55.10%), *S24-7* (18.52%), and *Bifidobacterium* (8.23%).

Thereafter we analyzed the Beta diversity for each gastrointestinal segment. Beta diversity is a useful tool for comparing the composition between bacterial communities. The bacterial composition was similar among the stomach & duodenum, ileum & jejunum, and cecum & colon & rectum (Fig. 3A and Fig. 3B). Bacterial communities within the large intestine were more similar, abundant and diverse than within the small intestine (Fig. 2A and Fig. 3C).

4. Discussion

The human gut contains many bacterial communities which are collectively referred to as the intestinal bacterial community. Intestinal microbes are a complex and dynamic ecosystem that co-evolves with their host [22]. Although the composition of the intestinal microbes is extremely complex with over 500 species, the relative abundance of a few species accounts for 99% of the abundance of the intestinal bacterial community. Metagenomic studies of the bacterial community indicated that Firmicutes and Bacteroidetes are the dominant phyla in mammals [23,24,25,26]. Similarly, our results showed that each gastrointestinal region was dominated by Firmicutes, which accounted for 96% of the bacterial species in the ileum, followed by Bacteroidetes and Actinobacteria.

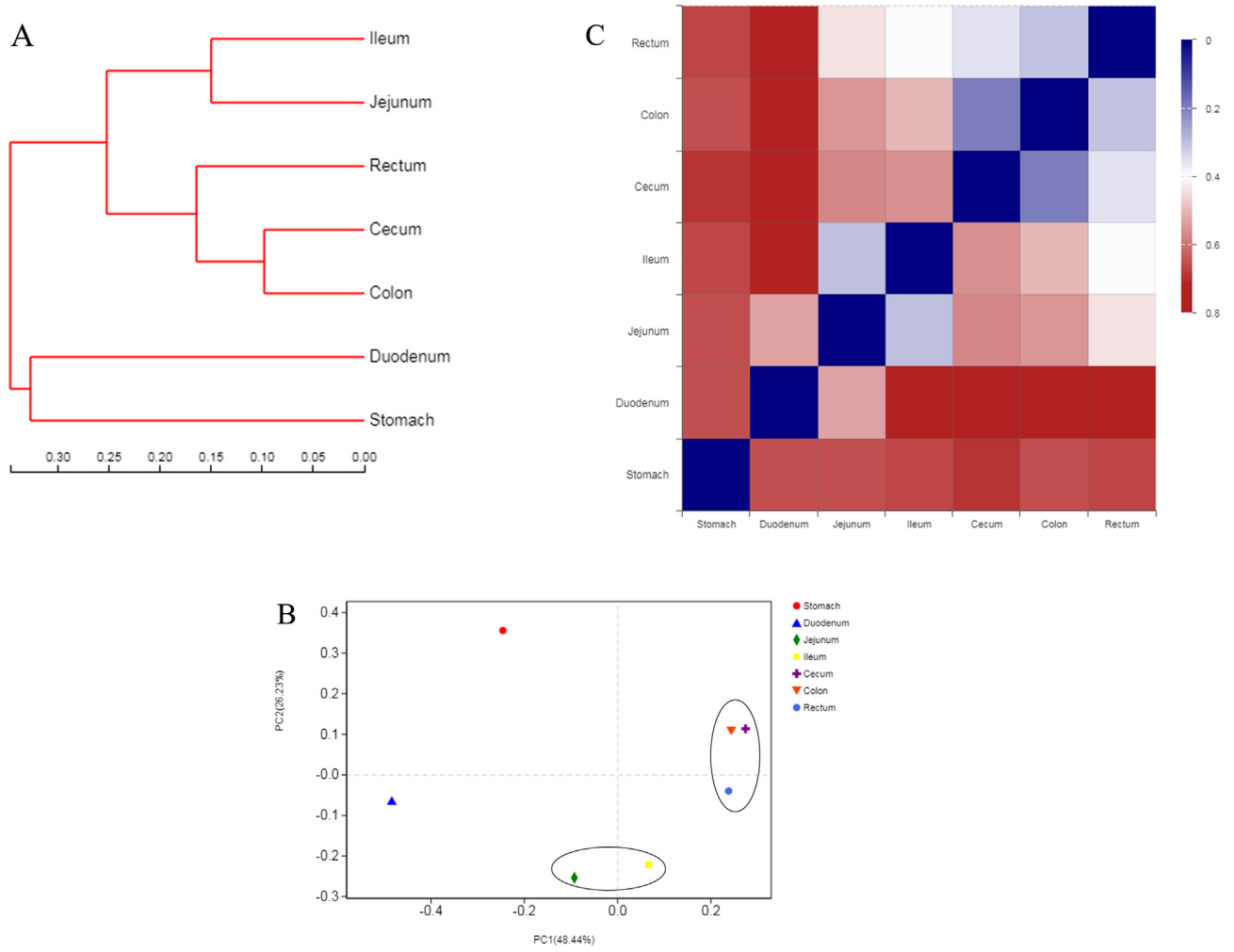

Fig. 3. Differences in bacterial composition and relationship between all of different regions of the gastrointestinal tract. (A) The Hierarchical clustering tree analysis. Branch length represents the distance between samples. (B) Principal Coordinate Analysis (PCoA). Points of different colors or shapes represent sample of different regions of the gastrointestinal tract. The closer the two sample points are, the more similar the bacterial composition of the two samples is. (C) Samples distances heatmap. Different color gradients represent the distance between samples with the legend indicated at the right side of the figure.

Our study found that the intestinal bacterial structure in Kunming mice was different from those in other mouse strains [27,28,29]. These results indicate that both environment and genetics of the host can influence microbial populations. Zoetendal et al. [30] compared the intestinal bacterial structure among different individuals, including twins, couples, and unrelated individuals, and found that the bacterial community was highly similar between individuals with the same genetic background, such as twins. Jussi et al. [31] analyzed the intestinal bacterial structure of two mouse strains and showed that the intestinal bacterial community was differed significantly between BALB/c and C57BL/6J mice. Ley et al. [32] also compared the intestinal bacterial structure of different mouse genotypes and demonstrated that genetic alteration can also affect the diversity of bacterial communities. For example, the relative abundance of Firmicutes and Bacteroidetes was significantly altered when leptin-knockout mice (ob/ob) became obese.

The large and small intestines are functionally distinct, and this distinction determines the difference in the bacterial community between these two intestinal segments. Our study found that the types and distribution of bacteria were different among the various intestinal segments, which is consistent with previous studies [33,34]. There was greater similarity, both at the phylum and genus levels, among the large intestinal segments than among the small intestinal segments. This is likely attributable to the fact that the small intestine is the primary site for digestion and nutrient absorption, and there are many factors that affect the distribution of bacteria such as pH, digestive juices, secretions and hormones. In contrast, the large intestine is the site of bacterial fermentation and the environment is relatively stable, which may be the reason for the observed stability in bacterial community in the large intestine and relative instability in the small intestine [33]. We also found that the bacterial abundance and diversity were higher in the duodenum than in other intestinal segments, which is inconsistent with the traditional notion that the diversity and abundance of intestinal bacteria gradually increase from the duodenum to the distal colon. Furthermore, we observed that the diversity and abundance of intestinal bacteria first decreased and then increased, with the lowest diversity and richness in the ileum. A possible reason may be that the mechanical and structural differences in the gut. The forestomach and small intestine are related to digestion and absorption, while the large intestine is mainly responsible for microbial fermentation. In the small intestine, the transient bacteria have to face the harsh environment of the small intestine such as the competitive advantage of commensals, the impact of host immune defense, the anaerobic conditions inhibition and so on [35], which leads to the gradual decrease of bacteria in the small intestine. However, once these bacteria reach the optimal environment (more neutral pH, slow intestinal transit, and/or low oxidation–reduction potential) of the large intestine, they begin to substantially multiply and establish a rich and diverse bacterial community.

Although our findings are similar to those of the above two studies [33,34], where the intestinal bacterial community is different among various intestinal segments, we also found that each intestinal segment is dominated by different bacterial species. Gu et al. [33] examined the intestinal bacterial community of C57BL/6 J mice and showed that the bacterial communities in the small intestine and stomach were different from those in the large intestine and feces. The proportion of *Lactobacillus* was higher in the stomach and small intestine, while the proportions of anaerobic bacteria including Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae, and Ruminococcaceae were higher in the large intestine and feces. Suzuki and Nachman [34] analyzed the bacterial communities at ten points along the alimentary canal of wild mice (mouth, esophagus, stomach, duodenum, ileum, proximal cecum, distal cecum, colon, rectum and feces) and found high heterogeneity among the segments of the gastrointestinal tract. Lactobacilaceae was the predominant family in the stomach of wild mice, while Mycoplasmataceae was predominant in the duodenum and ileum. On the other hand, the large intestine was rich in anaerobic bacteria. Our study showed that, although the various intestinal segments had different bacterial communities, they were all dominated by *Lactobacillus*, which is inconsistent with the results of the previous two studies and may be related to the strain of mice used. Therefore, understanding the structure and changes in the intestinal bacterial community is important for studying the experiments about the bacterial community-host relationship because every animal's intestinal bacterial community is different.

5. Conclusions

In summary, we compared the species and distribution of bacteria in different intestinal segments and analyzed their distribution in Kunming mice by metagenomic sequencing. We found that different intestinal segments have different bacterial communities. *Lactobacillus* is the most-abundant genus throughout the gastrointestinal tract of Kunming mice. The bacterial community is more similar in the large intestine than in the small intestine in Kunming mice. Our findings provide insights into structure of the bacterial populations of different regions of the gastrointestinal tract in Kunming mice.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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