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ORIGINAL ARTICLE

Effects of host identity on the gut microbiota: A comparative study on three microtinae species

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Abstract

Background: Gut microbiota exert an immense effect on host health and host environmental adaptation. Furthermore, the composition and structure of gut microbiota are determined by the environment and host genetic factors. However, the relative contribution of the environment and host genetic factors toward shaping the structure of gut microbiota has been poorly understood.

Methods: In this study, we characterized the fecal microbial communities of the closely related voles *Neodon fuscus*, *Lasiopodomys brandtii*, and *L. mandarinus* after caged feeding in the laboratory for 6 months, through high-throughput sequencing and bioinformatics analysis.

Results: The results of pairwise comparisons of *N. fuscus* vs. *L. brandtii* and *L. mandarinus* vs. *L. brandtii* revealed significant differences in bacterial diversity and composition after domestication. While 991 same operational taxonomic units (OTUs) were shared in three voles, there were 362, 291, and 303 species-specific OTUs in *N. fuscus*, *L. brandtii*, and *L. mandarinus*, respectively. The relative abundances of Proteobacteria and *Prevotella*, which are reported to be enriched in high-altitude populations, were significantly higher in high-altitude *N. fuscus* than in low-altitude *L. brandtii* after domestication. Firmicutes, which produce various digestive enzymes for energy metabolism, and Spirochaetes, which can degrade cellulose, were found in higher abundance in subterranean *L. mandarinus* than that in *L. brandtii* which dwells on the earth surface.

Conclusion: Our findings showed that some components of gut microbiota still maintained dominance even when different host species are reared under the same environmental conditions, suggesting that these bacteria are substantially influenced by host factors.

KEYWORDS
gut microbiota, high-altitude, *Lasiopodomys brandtii*, *Neodon fuscus*

1 | INTRODUCTION

The mammalian intestine is inhabited by trillions of microbes termed gut microbiota, which play an integral role in nutrient intake,[1] behavior, metabolism, immune function, and development of the host.[2] Increasing evidence has shown that gut microbiota have essential metabolic and immunological functions in the adaptation of their host to complex, variable environments. For instance, the dynamic gut microbiota in Mongolian gerbils (*Meriones unguiculatus*) confer host plasticity in thermoregulation in response to intermittent temperature fluctuations.[3] Some unique gut bacteriomes, including *Acinetobacter* spp. and *Pseudomonas* spp., are found to be enriched in Tibetans and Tibetan pigs, and their functions might facilitate adaptation by their host to high-altitude environments.[4] Furthermore, gut microbiome assessments from 315 mammals and 491 birds have suggested that host–gut microbiome symbiosis is potentially associated with physiological adaptations to flight.[5]

The gut microbiome, which primarily consists of bacteria, archaea, and fungi, is complex and dynamic. The development and composition of mammalian gut microbiota are influenced by environmental and host genetic factors. Environmental factors such as the season, altitude, diet, and photoperiod affect the diversity of gut microbial communities in mammals. For instance, it was observed that two herbivorous panda species share more similarities in their gut microbiota structure than they do with their carnivorous relatives,[6] implying that, within Arctoidea, the specialized herbivorous diet rather than host phylogeny is the dominant driver of gut microbiome convergence. Furthermore, the gut microbial community of high-altitude rhesus macaques was found to be markedly distinct from that of low-altitude populations in terms of diversity, composition, and function.[7] Another study showed that high-altitude yaks and Tibetan sheep have more short-chain fatty acid (SCFA)-producing gut bacteria than low-altitude animals, which confers stronger fermentation ability and provides energy for the epithelial cells of the host.[8]

In addition to host genetics, gender, age, and other host factors influence the composition and diversity of the gut microbiome.[9–11] Studies have shown that the gut microbiota in the cecum of inbred mice with different genetic backgrounds is different,[12] and the similarity in gut microbiota between monozygotic twins is significantly higher than that between dizygotic twins.[13] It has also been reported that host genetics, especially from the paternal genome, significantly contribute to the structure of the gut microbiota of preweaning calves at the age of 3 months, suggesting that host genotype influences the colonization of certain microbiota.[14]

Although there is extensive evidence on the respective effects of environmental and host genetic factors on gut microbiota, there is no clear information on the relative contribution of the environment and host genetics toward shaping the structure of gut microbiota. In particular, it is not clear which component of gut microbiota will be maintained and which component will be changed when one factor is changed. To investigate this issue, we reared wild *Neodon fuscus*, *Lasiopodomys brandtii*, and *L. mandarinus* in the laboratory for 6 months to explore the contribution of host genetics to the structure of gut microbiota. These three species of voles living in different wild surroundings provide an excellent model to investigate mammalian adaptation. *L. mandarinus* is a type of subterranean rodent living in plain areas (average altitude of 100 m), whereas both *L. brandtii* and *N. fuscus* are ground-dwelling voles living at different altitudes.[15,16] In our study, we performed 16S rRNA gene high-throughput sequencing to compare the changes in bacteria in the fecal samples of these wild voles after breeding under the same laboratory conditions to elucidate the effects of host genetic background on gut microbiota. Our findings will hopefully contribute to a deeper understanding of the effects of the host genetics on gut microbiota.

2 | METHODS

2.1 | Sample collection

This study was designed and conducted according to the Guide for the Care and Use of Laboratory Animals of China. All experiments involving animals were approved by the Animal Care and Use Committee of Zhengzhou University.

Ten wild *L. brandtii* was collected in Xilinhot, Inner Mongolia Autonomous Region, China, approximately 1200 m above sea level (N45°52′, E116°97′). Ten wild *N. fuscus* were collected in Tibetan Autonomous Prefecture of Golog, Qinghai Province, China, approximately 4300 m above sea level (N34°15′, E100°20′). Ten wild *L. mandarinus* were captured from cropland in Xinzheng, Henan, China (N34°52′, E113°85′). These animals were subsequently housed in polycarbonate cages, fed with commercial rat and rabbit pellets mixed in a 1:1 ratio (Laboratory Animal Center of Henan Province), and water was provided freely for 6 months in our laboratory at a lower altitude. Fresh fecal samples were collected from these three voles and stored at −80°C for sequencing.

2.2 | DNA extraction and high-throughput sequencing

Total DNA was extracted from each fecal sample using the HiPure Stool DNA Kit (Magen, Guangzhou, China) according to the manufacturer's protocol. The V3–V4 region of 16S rRNA was amplified by PCR using barcoded primers.[17,18] The barcoded PCR products were purified using a DNA gel extraction kit (Axygen Biosciences, Union City, CA, USA) and quantified using the ABI StepOnePlus Real-Time PCR System (Life Technologies, Foster City, USA).[19] The purified amplicons were pooled in equimolar amounts and paired-end sequenced (2×250) on Illumina HiSeq 2500 at Gene Denovo Biotechnology Co., Ltd (Guangzhou, China).

2.3 | Bioinformatics and statistical analysis

After sequencing, the raw reads were deposited into the NCBI Sequence Read Archive database (accession number:

PRJNA664869). To obtain high-quality sequences, all raw 16S sequences were filtered using FASTP.[20] Then paired-end clean reads were merged as raw tags using Flash[21] (version 1.2.11) with a minimum overlap of 10 bp and mismatch error rates of 2%. Raw tags were filtered using the QIIME[22] (version 1.9.1) pipeline, and the UCHIME algorithm[23] was used to cut off chimeric tags to obtain effective tags. These high-quality sequences were clustered into operational taxonomic units (OTUs) with 97% similarity using UPARSE,[24] and the highest abundance of each cluster was selected as the representative sequence. Moreover, the 16S representative sequences were classified into organisms using the Greengene database.[25]

Alpha diversity indices (Chao1 and Shannon) calculated using QIIME were used to measure the diversity of microbial communities. Alpha index comparison between groups was performed using Welch's *t* test in R project. OTU rarefaction curve was plotted in the R project ggplot2 package. Differences between samples were evaluated using the principal coordinates analysis (PCoA) of unweighted unifrac distances and the analysis of similarities (ANOSIM) and plotted in R project. The stacked bar plot of the community composition was visualized in the R project ggplot2 package. We focused on those microbial taxa that had an average relative abundance of ≥0.1% across all samples. Bacterial genera with an average relative abundance of ≥0.01 in samples were considered to be major genera. At the phylum level, OTU network-based visualization was applied to identify unique and common OTUs. The diagram was generated using CYTOSCAPE[26] (version 3.6.0), and indicator taxa were identified using the indicator value analysis.

Gene annotation was performed by aligning sequences to the GreenGene (version gg_13_5) database. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and modules were predicted by BLAST analysis of OTUs against the KEGG database via PICRUST (version 2.1.4).

3 | RESULTS

3.1 | Illumina sequencing and OTU cluster

A total of 5 151 613 raw reads were obtained using the Illumina Hiseq sequencing platform from the fecal bacteria of *N. fuscus* ($N=10$), *L. brandtii* ($N=10$), and *L. mandarinus* ($N=10$) housed in the laboratory. After quality filtering and data processing, an average of 1540 OTUs were identified in each species at a threshold of 97% sequence identity. The rarefaction curves of 16S sequences, which were used to evaluate the sampling depth, tended to be saturated, indicating that most bacteria were identified in this study.

Compared to the total number of OTUs, the analysis of the core community revealed a high number of OTUs in a tight association after rearing under the same conditions, and 991 OTUs were shared among all three voles. In addition, there were 362, 303, and 291 species-specific OTUs in *N. fuscus*, *L. mandarinus* and *L. brandtii*, respectively (Figure 1).

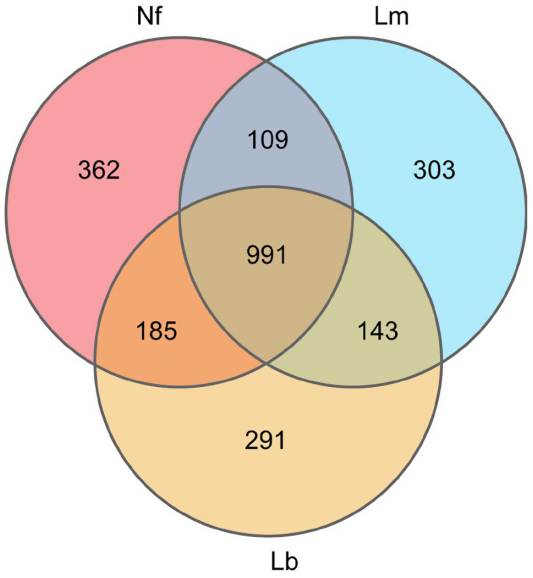

FIGURE 1 Venn diagram based on OUTs shows that the three species of voles share some of the same gut bacteria. Nf: *Neodon fuscus*; Lb: *Lasiopodomys brandtii*; Lm: *L. mandarinus*.

3.2 | Comparison of fecal bacteria between *N. fuscus* and *L. brandtii*

α-Diversity and β-diversity analyses were performed to evaluate the diversity of gut microbiota in *N. fuscus* and *L. brandtii* after housing in the same environments. The intestinal microbial richness was evaluated using the Chao1 index, which revealed significant differences between *N. fuscus* and *L. brandtii* ($t=-4.486$, $df=18$, $p=2.850\text{E-}04$) (Figure 2A). The diversity was estimated using the Shannon index, which revealed no notable differences between the two voles ($t=-1.361$, $df=18$, $p=0.190$) (Figure 2B), suggesting that the richness rather than the diversity of the gut microbiome in the voles remained different after rearing in the laboratory. The results of PCoA showed that the microbial communities of *N. fuscus* and *L. brandtii* clustered in PCoA space, respectively ($R=0.782$, $p=0.01$) (Figure 2C), but they were more closely related to each other in *N. fuscus* than in *L. brandtii*. Overall, these results indicate that the fecal bacteria of *N. fuscus* differed significantly from those of *L. brandtii* even when the two species were reared in the same environment.

The 16S rDNA sequencing revealed a total of 17 phyla and 89 genera in the gut bacterial community from both *N. fuscus* and *L. brandtii*. The top five dominant phyla, accounting for approximately 97% of the relative abundance, were Bacteroidetes, Firmicutes, Spirochaetes, Proteobacteria, and Cyanobacteria (Figure 3A). A high proportion of Bacteroidetes was detected in both groups (*N. fuscus* 63.37%, *L. brandtii* 54.75%), with no significant differences between them ($p=0.09$). However, the relative abundance of Firmicutes was lower in *N. fuscus* than in *L. brandtii* ($p<0.05$), implying a lower Firmicutes/Bacteroidetes ratio in *N. fuscus*. As depicted in Figure 3C, the proportion of Proteobacteria was significantly higher in *N. fuscus* than in *L. brandtii* ($p<0.05$). At the genus level, the

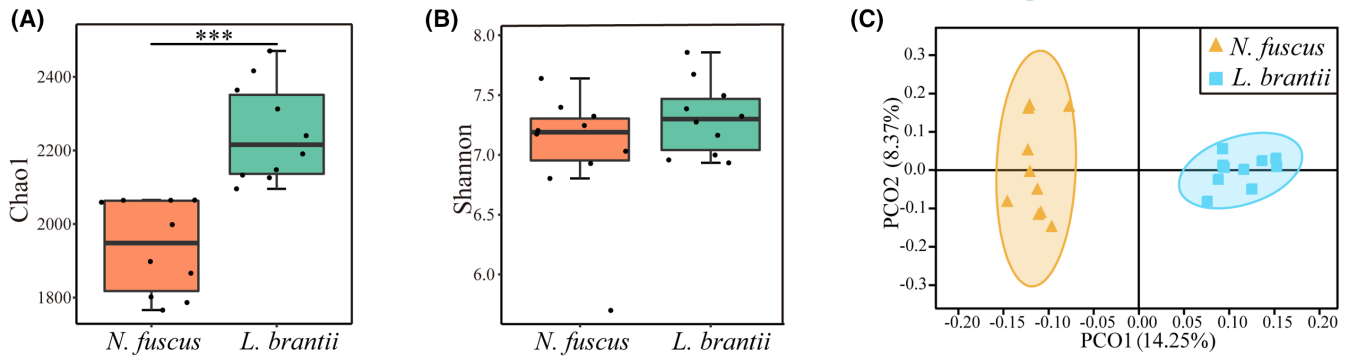

FIGURE 2 α-Diversity and β-diversity analysis between *N. fuscus* and *L. brantii*. (A), The Chao1 index indicating the difference in species richness of gut microbiota between the two species. (B), Shannon index showed no significant difference between the two species. (C), PCoA analysis of unweighted Unifrac distance showed a significant difference in gut bacterial structure between *N. fuscus* and *L. brantii*. Statistical significance was assessed by Student's *t* test. *N. fuscus*: *Neodon fuscus*; *L. breantii*: *Lasiopodomys brandtii*. ***$p < 0.001$.

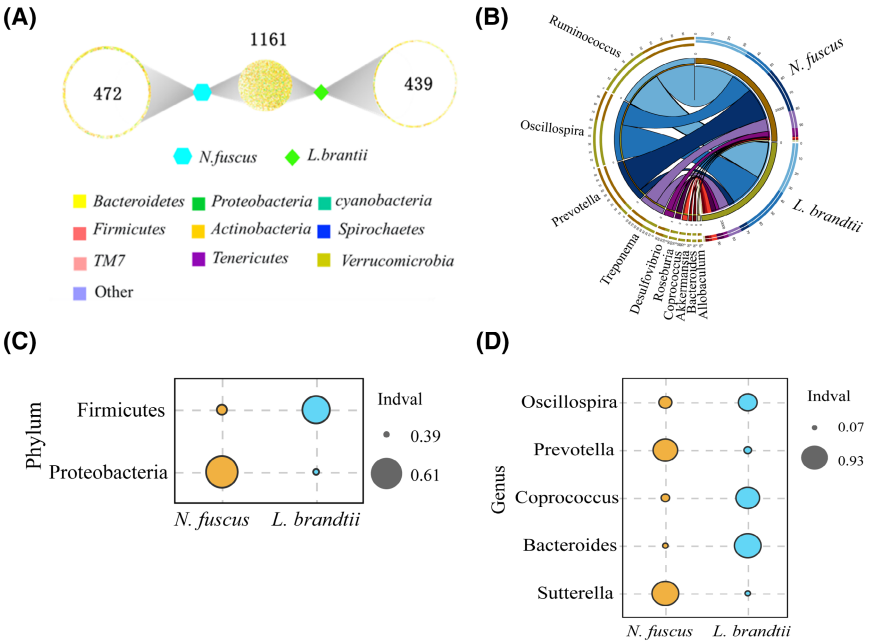

FIGURE 3 The gut bacterial communities comparision between *N. fuscus* and *L. brantii*. (A), The results of 16S rDNA sequencing showed that there are 1161 OTUs in the gut bacterial communities of *N. fuscus* and *L. brantii*. (B), At the genus level, the gut bacterial communities of both groups were dominated by *Ruminococcus*, etc. (C), Species analysis showed that *Firmicutes* were more enriched in the gut tract of *L. brantii* at the phylum level. However, Proteobacteria were more abundant in the gut tract of *N. fuscus*, and the difference was significant. (D), At the generic level, *Prevotella* and *Sutterella were* more enriched in the gut tract of *N. fuscus*. *Oscillospira* and others were more enriched in the gut tract of *L. brantii*, and the difference was significant. Statistical significance was assessed by Student's *t* test. *N. fuscus*: *Neodon fuscus*; *L. breantii*: *Lasiopodomys brandtii*.

predominant bacteria in *N. fuscus* and *L. brandtii* were *Ruminococcus*, *Oscillospira*, *Treponema*, and *Prevotella* (Figure 3B), whereas *Prevotella* ($Indval_{Nf}=0.840$, $Indval_{Lb}=0.160$, $p=0.001$) and *Sutterella* ($Indval_{Nf}=0.930$, $Indval_{Lb}=0.070$, $p=0.003$) were remarkably enriched in *N. fuscus*, and *Oscillospira* ($Indval_{Nf}=0.384$, $Indval_{Lb}=0.616$, $p=0.010$), *Coprococcus* ($Indval_{Nf}=0.195$, $Indval_{Lb}=0.805$, $p=0.013$), and *Bacteroides* ($Indval_{Nf}=0.070$, $Indval_{Lb}=0.930$, $p=0.001$) were significantly enriched in *L. brandtii* (Figure 3D).

Based on the abundant metadata for KEGG genes, 20 KEGG orthologs at level 2 were identified, with no difference between *N. fuscus* and *L. brandtii*. Of these, the top five orthologs were 'Carbohydrate metabolism,' 'Amino acid metabolism,' 'Replication and repair,' 'Membrane transport,' and 'Translation'. Interestingly, more genes were enriched in the 'Digestive system' category in *N. fuscus* microbiomes than in *L. brandtii* microbiomes, illustrating that the high-altitude *N. fuscus* has a more active digestive system than the low-altitude *L. brandtii*.

3.3 | Comparison of gut microbiome between *L. mandarinus* and *L. brandtii*

Based on the above-described interesting results, we further explored the differences in bacteria between *L. mandarinus* and *L. brandtii*. First, we evaluated the richness and diversity of gut microbiomes in these voles. The α-diversity analysis indicated that Chao1 ($t = -3.937$, $df = 18$, $p = 0.002$) indexes were noticeably lower in *L. mandarinus* than in *L. brandtii*. However, the Shannon index showed no significant difference between these voles (Figure 4). As shown in Figure 4, PCoA of the gut bacteria of *L. mandarinus* and *L. brandtii* revealed that the two voles still presented a distinct clustering of microbiota composition after rearing under laboratory conditions.

After annotation, 15 phyla and 95 genera were detected in *L. mandarinus* and *L. brandtii*. The most relatively abundant phyla were Bacteroidetes, Firmicutes, and Proteobacteria, accounting for 94%–98% collectively (Figure 5A). The dominant genera of gut microbiota in *L. mandarinus* were Oscillospira, Prevotella and Akkermansia; the dominant gut genera of *L. brantii* were *Ruminococcus*, *Oscillospir*, and *Treponema* (Figure 5B). A comparative analysis between *L. mandarinus* and *L. brandtii* revealed that, at the phylum level, the abundances of Firmicutes ($t = -2.400$, $df = 18$, $p = 0.027$) and Spirochaetes ($t = -6.403$, $df = 18$, $p = 5.000\text{E-}06$) were obviously greater in *L. brandtii* than in *L. mandarinus*, but the abundance of Cyanobacteria ($t = 2.178$, $df = 18$, $p = 0.043$) was lower in wild *L. brandtii* (Figure 5C). At the genus level, the relative abundances of *Ruminococcus* ($t = -4.206$, $df = 18$, $p = 0.001$), *Treponema* ($t = -6.404$, $df = 18$, $p = 5.000\text{E-}06$), and *Bacteroides* ($t = -2.857$, $df = 18$, $p = 0.010$) were higher in *L. brandtii*, and that of *Desulfovibrio* ($t = 2.599$, $df = 18$, $p = 0.018$) was lower than that in *L. mandarinus* (Figure 5D).

Furthermore, 11 KEGG categories were observed to be significantly different between *L. mandarinus* and *L. brandtii*, including 'Carbohydrate metabolism', 'Replication and repair', 'Translation', 'Nucleotide metabolism', and 'Transcription' and 'Enzyme families'.

4 | DISCUSSION

Accumulating evidence indicates that gut microorganisms have essential metabolic and immunological functions for the physiological adaptation of the host,[27] and both the environment and host genetic background can impact the structure of gut microbiomes in return. In the present study, we conducted pairwise comparisons of high-altitude *N. fuscus* vs. low-altitude *L. brandtii* and subterranean *L. mandarinus* vs. ground-dwelling *L. brandtii* to determine which bacteria in intestinal microorganisms were influenced by the host genetic background. Our results showed that these voles shared some bacteria in the gut after living under the same laboratory conditions. However, some gut microorganisms that might help host adaptation to their environment were still different even when the environmental conditions were significantly altered.

To survive under different conditions, voles and their gut microbiomes have evolved physiological adaptations to various challenges, such as extreme cold, limited food availability, and hypoxia. The community structure of gut microbiota might reassemble in response to food availability. In both *N. fuscus* and *L. brandtii*, the gut microbes were dominated by Bacteroidetes and Firmicutes. It has been reported that the ratio of Firmicutes to Bacteroidetes in a microbial community is associated with the capacity for energy harvest.[28] High-altitude mammals generally have a higher ratio of Firmicutes to Bacteroidetes,[29,30] which is beneficial to the host through gut microbiota-mediated energy harvest and further helps the plateau animals to maintain a balance between metabolism and body temperature at low temperatures.[29] However, in our study, the ratio of Firmicutes to Bacteroidetes in *N. fuscus* was lower than that in *L. brandtii*, which might be attributed to the environmental changes caused by being fed in the laboratory.

Nevertheless, studies have also reported that intestinal microbial communities are resilient and difficult to change through dietary interventions. Microbial enterotypes are clustered by microbiota composition, principally represented by *Bacteroides*, *Prevotella*, and *Ruminococcus*.[31] The predominance of *Bacteroides* in individuals

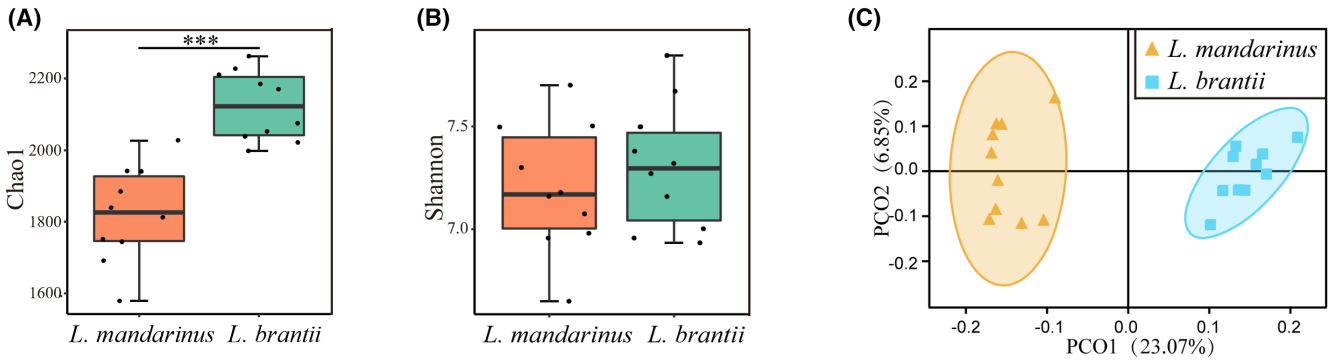

FIGURE 4 Diversity analysis of *L. mandarinus* and *L. brantii*. (A), The Chao1 index indicating that the species richness of gut bacteria of *L. mandarinus* was lower than that of *L. brantii*. (B), There was no significant difference in the Shannon index of gut bacteria between *L. mandarinus* and *L. brantii*. (C), Beta diversity analysis showed that there were differences in gut bacterial structure between *L. mandarinus* and *L. brantii*. *L. brantii*: *Lasiopodomys brandtii*. Statistical significance was assessed by Student's *t* test. ***$p < 0.001$.

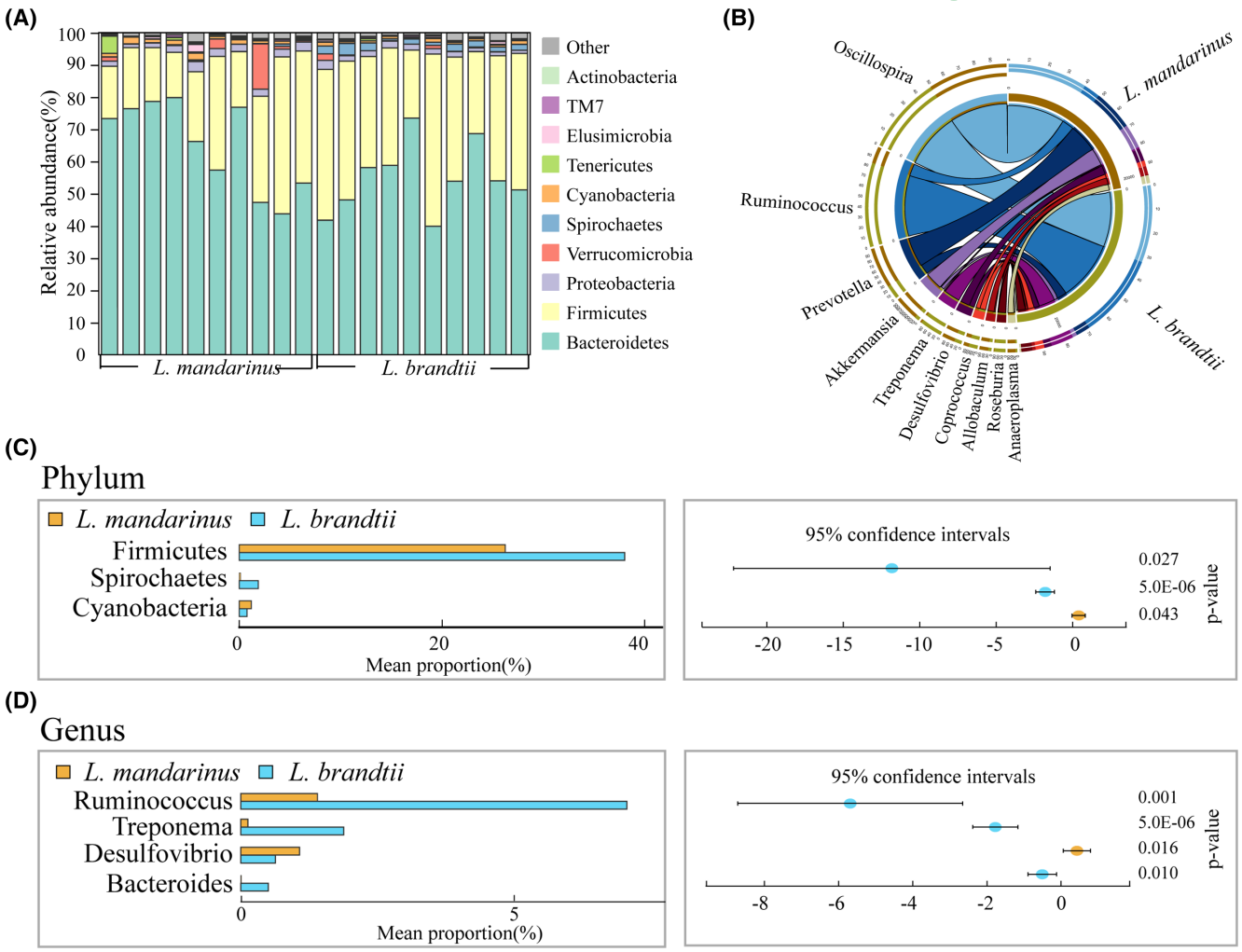

FIGURE 5 Species composition of gut bacteria in *L. mandarinus* and *L. brantii*. (A), The top three dominant phyla Bacteroidetes, Firmicutes and Proteobacter account for 94% of the relative abundance in the two species. (B), At the genus level, the dominant genera of gut microbiota in *L. mandarinus* and *L. brantii is Oscillospira, etc*. (C), At the phylum level, Firmicutes and Spirochaetes were more abundant in the gut tract of *L. brantii*. However, Cyanobacteria had a higher abundance in the intestine of *L. mandarinus*, and the difference was significant. (D), At the genus level, *Desulfovibrio* is more abundant in the intestines of *L. mandarinus*, and *Treponema* and *Bacteroides* were more abundant in the gut tract of *L. brantii*, and the difference was significant. *L. brantii*: *Lasiopodomys brandtii*. Statistical significance was assessed by Student's *t* test.

reflects a high intake of protein and animal fat, whereas the predominance of *Prevotella* reflects the intake of diets rich in carbohydrate and fiber.[32,33]

Recent studies have shown that a high *Prevotella*: *Bacteroides* ratio indicates a high-fiber, plant-rich diet.[34] In our study, this ratio in *N. fuscus* was higher than that in *L. brandtii*, indicating that the capacity to digest cellulose-rich plant was still maintained in wild *N. fuscus* when its diet was changed. Moreover, Proteobacteria were significantly enriched in the high-altitude *N. fuscus*. Proteobacteria are associated with the digestion of lignin components, and previous studies have also demonstrated a high abundance of Proteobacteria in the high-altitude mouflon sheep and blue sheep,[29] which can assist the host to more effectively degrade food to obtain more nutrition and energy.[35,36] *Prevotella*, which has been observed in high abundance in the house mouse, pika, yak, and Tibetan sheep at high elevations,[8,37,38] is associated with the production of SCFAs that help mammals to adapt to pulmonary hypertension.[39,40] It is worth mentioning that *N. fuscus* primarily consumes plant stems as its diet at high elevations and low temperatures. Hence, it needs some bacteria to help digest cellulose and lignin to produce more energy. The high abundances of Proteobacteria and *Prevotella* in the intestinal tract of the high-altitude *N. fuscus* indicate that some characteristic microorganisms are affected by the host itself rather than the environment.

Similarly, we detected a higher proportion of Firmicutes and Spirochaetes, as well as *Ruminococcus*, *Treponema*, and *Bacteroides*, in *L. mandarinus* than in *L. brandtii*. Firmicutes are believed to encode energy metabolism-related enzymes that can produce various digestive enzymes to decompose various substances. Spirochaetes are primarily associated with the degradation of cellulose, and *Bacteroides* spp. primarily degrade carbohydrates and proteins.[28] *Ruminococcus* belongs to the Firmicutes phylum and produces SCFAs to enhance the protective function of the intestinal barrier

and reduce the colonization of pathogenic bacteria in the intestine. *Ruminococcus* plays a pivotal role in the degradation of cellulose. Through microbial fermentation, cellulose can be converted into SCFAs, which are an important energy source for epithelial cells and can provide approximately 10% of energy for humans.[7] In black howler monkeys, the abundance of *Ruminococcus* increases during periods of energy deficiency, which compensates for the decrease in energy intake.[41] *Treponema* belongs to the Spirochaetes group and helps the host to digest and extract valuable nutrients, such as acetic acid and propionic acid,[42] from fibrous natural plants by degrading pectin in plant cell walls, and provides SCFAs to animals.[43] The proportions of *Ruminococcus* and *Treponema* in the subterranean *L. mandarinus* and ground-dwelling *L. brandtii* were still strikingly different after rearing both species under the same environmental conditions, suggesting that the flora that was the characteristic of the adaptation in response to extreme environments was primarily determined by the host itself.

In conclusion, some intestinal microbe populations can be altered by changes in environments, including diet and temperature, but some microbial populations that are involved in host energy metabolism and homeostasis may be substantially affected by host factors. We speculate that mammals have a relatively stable internal environment that helps their intestinal microorganisms maintain a relatively stable state, which facilitates an optimum adaptation to environmental demands.

AUTHOR CONTRIBUTIONS

Zhen Yao performed the data analysis; Qinghua Li performed the formal analysis; Baohong Tang, Zhenlong Wang performed the validation; Qinghua Li, Zhen Yao wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared that they have no competing interests.

ETHICS STATEMENT

This study passed an ethical review: ZZUIRB2024-32.

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