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Comparative Analysis of Healthy Gut Microbiota in German and Korean Populations: Insights from Large-Scale Cohort Studies

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Abstract: Healthy individuals often have different gut microbiota, and these differences can be influenced by their country of origin or their race. This study aimed to compare the gut microbiota compositions of healthy Germans and Koreans using 16S rRNA sequencing data extracted from public sources. Two cohorts, comprising 1592 samples (804 Germans and 788 Koreans), were analyzed for alpha and beta diversity, core microbiome, and abundances of specific taxa. The *Prevotella* enterotype was more prevalent in Koreans, and significant diversity differences were observed depending on cohorts and enterotypes. The core microbiomes across all enterotypes and cohorts included *Bacteroides*, *Faecalibacterium*, *Parabacteroides*, and *Lachnospira*. Several common core microbiomes were also found depending on enterotype. Koreans exhibited higher abundances of *Faecalibacterium*, *Prevotella*, and *Bacteroides*, while Germans had higher abundances of *Blautia*, *Subdoligranulum*, and *Agathobacter*. Distinctive microbiomes were identified by enterotype. The study enhances comprehension of gut microbiome variations linked to enterotype and geographical factors, and emphasizes the need for additional research to establish correlations between specific microbial properties and individual health status.

Keywords: gut microbiome; healthy population; Korean; German; 16S rRNA; enterotype

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1. Introduction

Understanding the healthy gut microbiome and the complex community of microorganisms that reside in the gastrointestinal tract is essential for maintaining overall health. The human gut microbiome consists of at least 2300 genera and 15,000–36,000 species of bacteria [1,2] and plays many critical roles, including educating the immune system [3], providing protection against pathogens [4], enabling energy biogenesis [5], and producing vitamins, enzymes, and other compounds not synthesized by human cells [5]. Furthermore, detailed knowledge could be used to develop new therapies and interventions to treat diseases that are linked to imbalances or disruptions in the gut microbiome, such as inflammatory bowel disease [6], obesity [7], and metabolic disorders [8].

Studying the healthy gut microbiome can provide insights into its broader role in human health and disease, and thus, it is important to understand the nature of gut microbiota compositions and microbiomes in healthy populations [9]. Gut microbiota may exhibit unique country- and race-dependent compositions [10–12]. In addition, endogenous and exogeneous factors, such as age [13], ethnicity, geography [14,15], diet [16], and medications [17,18], can influence the composition and function of the gut microbiome. The majority of the studies conducted to date have been on European and American populations [19], and relatively little is known about the healthy gut microbiome in Asian populations [10].

Recently, the use of next-generation sequencing (NGS) of bacterial 16S rRNA genes has expanded understanding of the complexity of microbial communities. This technique allows comprehensive, detailed examinations of microbial communities and provides a more thorough understanding of the microbiome diversities and compositions. Additionally, NGS has greater sensitivity and accuracy for detecting low-abundance micro-organisms and provides a more comprehensive and nuanced analysis of microbial populations [20–22].

In the present study, the data of two large cohorts was retrieved from the European Bioinformatics Institute database and analyzed to determine the compositions of healthy gut microbiomes in Korean and German populations.

2. Materials and Methods

2.1. Dataset

We searched for human gut microbiome data in the European Bioinformatics Institute dataset repository (EBI data set; https://www.ebi.uk.ac, accessed on 16 November 2023). The selection criteria were: (1) sample size over 500, (2) same target site, (3) same sequencing platform, and (4) healthy subjects. Two of 1063 studies were finally selected, that is, PRJEB33905, submitted by the Korean Food Research Institute, which involved a study of the gut microbiomes of members of the general Korean population residing in or near Seoul [10], and PRJNA701859, submitted by the Technical University Munich, which studied gut microbiomes in a healthy southern German population [11]. Both cohort studies collected samples from the general population and included more than 800 samples targeting the V3–V4 region.

2.2. Microbiome Analysis and Statistical Analysis

Basic microbiome analysis was performed using QIIME2 (version 2020.11) [23] and its associated plugins. The Choa1 index and Shannon index methods were used to measure alpha diversities. Beta diversity was assessed by calculating distance matrices based on Bray-Curtis distances and visualized by principal coordinates analysis (PCoA). The Kruskal–Wallis test and non-parametric permutation multivariate analysis of variance (PERMANOVA) were used to assess the statistical significances of alpha and beta diversities, respectively. A pre-trained Naive Bayes classifier using the EzBioCloud 16S Database as a reference [24] was used to assign taxonomy to unique representative sequences. The core microbiome was determined at the genus level using adjustable parameters for relative abundance and prevalence [25]. Linear discriminant analysis effect size (LEfSe) [26] was applied with default settings to test for differential abundance of bacterial species in the two cohorts. Spearman's correlation coefficients with p-value between two species were calculated to visualize internal interactions and further measurement of the microbial community. Statistical significance was accepted for p-value < 0.05. The network was visualized using Cytoscape [27]; nodes represented species and connections. Clusters of nodes that formed coherent structural subsystems of interacting units were measured with the function *cluster_louvain* in the graph package [28].

3. Results

3.1. Data Preprocessing Summary

The data of 815 German and 890 Korean samples were uploaded. Uploaded files of <2 Mb and broken files were excluded from the study. Thus, 804 and 788 samples were included in the analysis. The average input read counts for the German and Korean cohorts were 34,184 ± 10,067 (79,178–13,802) and 134,103 ± 111,787 (1,076,815–24,859), respectively. After trimming, pairing, and chimera removal, non-chimeric read counts for the German and Korean cohorts were 16,783 ± 5229 (39,184–3873) and 60,943 ± 46,978 (460,695–8075), respectively. The number of total operational taxonomic units (OTUs) for the German and Korean cohorts were 24,182 and 62,472, respectively. Since the input read count of the Korean cohort was much larger, this cohort produced a much larger number of OTU counts (Table 1).

Table 1. Summary of OTU* and sequence read counts during data pre-processing.

	German Cohort (PRJNA701859)	Korean Coort (PRJEB33905)
Sample number	804	788
Input read count	34,184 ± 10,067 (79,178–13,802)	134,103 ± 111,787 (1,076,815–24,859)
Filtered read count	24,448 ± 7640	94,568 ± 73,972
Denoised read count	23,548 ± 7449	92,642 ± 73,051
Merged read count	21,364 ± 6924	88,912 ± 71,105
Non-chimeric read count	16,783 ± 5229 (39,184–3873)	60,943 ± 46,978 (460,695–8075)
Percentage of input non-chimeric (%)	49.1 ± 5.5	66.3 ± 12.4
Total OTU count	24,182	62,472
Paired read length	432.1 ± 12.5	432.6 ± 17.3

OTU*: Operational taxonomic unit.

3.2. Diversity and Abundance of Microbiota

Following taxonomic classification, relative abundances were calculated, and enterotypes were determined for the samples based on the abundances of *Bacteroides*, *Prevotella*, and *Ruminococcus*. In both cohorts, the *Bacteroides* enterotype was the most abundant, followed by *Prevotella* (Figure 1A). Alpha diversities of microbiota were estimated using the Chao1 and Shannon indices. The Korean cohort had larger Chao1 indices, which represent community richness (Figure 1B), whereas the German cohort had larger Shannon indices, which represents both microbial community richness and evenness (Figure 1C). For beta diversity analysis, Bray-Curtis distance was used to analyze the structure of the microbiota. The PERMANOVA test showed that microbiome compositions were significantly dependent on cohort and enterotype. In both cohorts, *Ruminococcus* enterotype were mostly observed among the *Bacteroides* enterotype relatively near the *Prevotella* enterotype (Figure 1D).

Next, average relative abundances were analyzed at various levels. The five most abundant phyla at the phylum level were Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Verrucomicrobia. In both cohorts, the relative abundances of the phyla showed similar abundance depending on the enterotype. The *Prevotella* enterotype had the highest abundance of Bacteroidetes, while the *Ruminococcus* enterotype had the highest abundance of Firmicutes. The abundance of Proteobacteria was higher in the Korean cohort. Interestingly, the Fusobacteria was only noted for the *Ruminococcus* enterotype in the Korean cohort (Figure 2A). At the order level, the most abundant were *Clostridiales*, *Bacteroidales*, *Burkholderiales*, *Acidaminococcales*, and *Bifidobacteriales*, which accounted for more than 95% of the total sequences in both cohorts. The relative abundance of *Bacteoidales* was highest in the *Prevotella* enterotype and lowest in the *Ruminococcus* enterotype in both cohorts, while abundance of *Clostidiales* was highest in the *Ruminococcus* enterotype and lowest in the *Prevotella* enterotype. The abundance of *Enterobacterales* was greater in the Korean cohort (Figure 2B). At the family level, the most abundant family were *Bacteroideceae*, *Lachnospiraceae*, *Prevotellaceae*, and *Ruminococcaceae* (Figure 2C), and at the genus level, the top four most abundant genera were *Bacteroides*, *Faecalibacterium*, *Prevotella*, and *Ruminococcus* in both cohorts. For the *Bacteroides* enterotype, *Bacteroides* was most abundant followed by *Feacalibacterium* and *Ruminococcus*. For the *Prevotella* enterotype, *Prevotella* was the most abundant, followed by *Faecalibacterium* and *Bacteroides*, and for the *Ruminococcus* enterotype, *Ruminococcus* and *Faecalibacterium* were the most abundant, followed by *Bacteroides* and *Prevotella*. *Faecalibacterium* was more abundant in the Korean cohort, and the abundances of *Clostridium*, *Escherichia*, and *Fusobacterium* were prominent in the *Ruminococcus* enterotype of the Korean cohort (Figure 2D).

Next, the core microbiome was characterized at the genus level (Figure 3). Compared to relative abundance, the core microbiome provides the proportion of samples that share a set of microbial taxa and the relative abundances of shared taxa across the samples. The

core microbiome was determined as the minimum detection threshold of 1% and minimum prevalence threshold of 50%. The German cohort had more of the core microbiomes assigned in all the enterotypes. Also, the *Ruminococcus* enterotype had more core microbiomes assigned than other enterotypes in both cohorts (Figure 3). In the *Bacteroides* enterotype, *Bacteroides*, *Faecalibacterium*, *Parabacteroides*, *Oscillibacter*, *Alistipes*, *Lachnospira*, *Bifidobacterium*, *Subdoligranulum*, and *Roseburia* were found as the core microbiomes (Figure 3A,B). For the *Prevotella* enterotype, *Prevotella*, *Bacteroides*, *Faecalibacterium*, *Oscillibacter*, *Lachnospira*, *Sutterella*, *Sporobacter*, *Subdoligranulum*, and *Parabacteroides* composed the core microbiome (Figure 3C,D), and for *Ruminococcus* enterotype, *Bacteroides*, *Faecalibacterium*, *Ruminococcus*, *Lachnospira*, *Bifidobacterium*, *Parabacteroides*, *Blautia*, and *Roreburia* composed the core microbiome (Figure 3E,F).

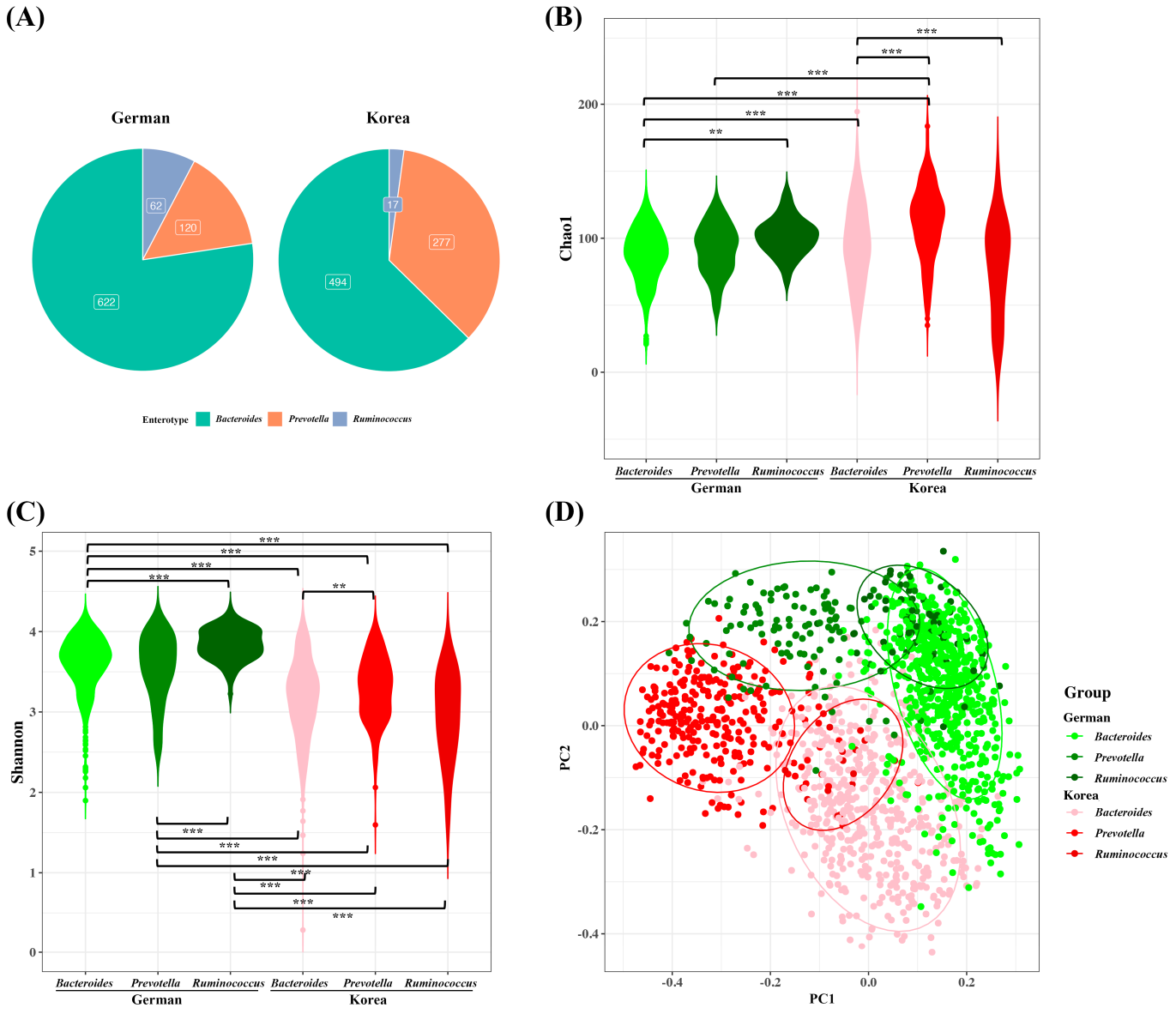

Figure 1. Bacterial community comparisons between the two cohorts. (**A**) Pie charts showing sample numbers of the different enterotypes in the two cohorts. (**B**,**C**) Alpha diversity. (**B**) Chao1 and (**C**) Shannon indices. (**D**) Beta diversity of the microbiome. Principal coordinates analysis (PCoA) was performed based on OTU abundances. ** $p < 0.01$, *** $p < 0.001$.

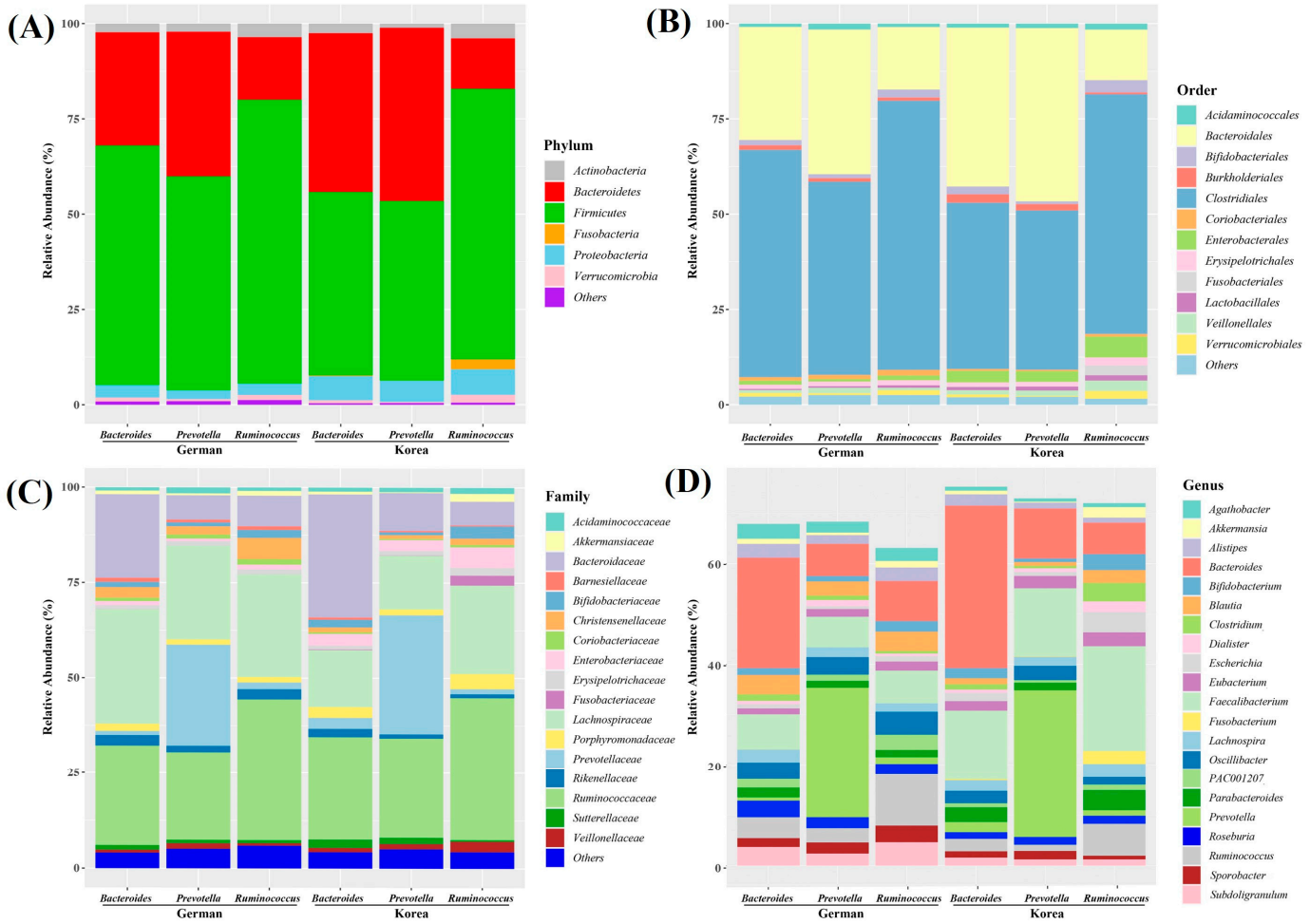

Figure 2. Relative microbiome abundances by enterotype in the German and Korean cohorts at (**A**) phylum, (**B**) order, (**C**) family, and (**D**) genus levels.

3.3. Species Taxa Comparison

Next, LEfSe was applied to evaluate the differences in relative abundances between the German and Korean cohorts. When the genus abundances were compared, *Blautia*, *Subdoligranulum*, *Agathobacter*, *Roseburia*, and *Fusicatenibacter* were the top 5 taxa in the German cohort, while *Faecalibacterium*, *Prevotella*, *Bacteroides*, *Parabacteroides*, and *Escherichia* were the top 5 in the Korean cohort (Figure 4A). For the *Bacteroides* enterotype, *Blautia*, *Subdoligranulum*, *Agathobacter*, and *Roseburia* were the most abundant taxa in the German cohort, while *Bacteroides*, *Faecalibacterium*, *Parabacteroides*, and *Escherichia* were the most abundant in the Korean cohort (Figure 4B). For the *Prevotella* enterotype, *Blautia*, *Agathobacter*, *Subdoligranulum*, and *Dorea* were the most abundant in the German cohort, while *Faecalibacterium*, *Prevotella*, *Bacteroides*, *Klebsiella*, and *Alloprevotella* were the most abundant in the Korean cohort (Figure 4C). For the *Ruminococcus* enterotype, *Ruminococcus*, *Subdoligranulum*, *Oscillibacter*, and *Sporobacter* were the most abundant in the German cohort, while *Faecalibacterium*, *Clostridium*, *Escherichia*, *Parabacteroides*, and *Dialister* were the most abundant in the Korean cohort (Figure 4D).

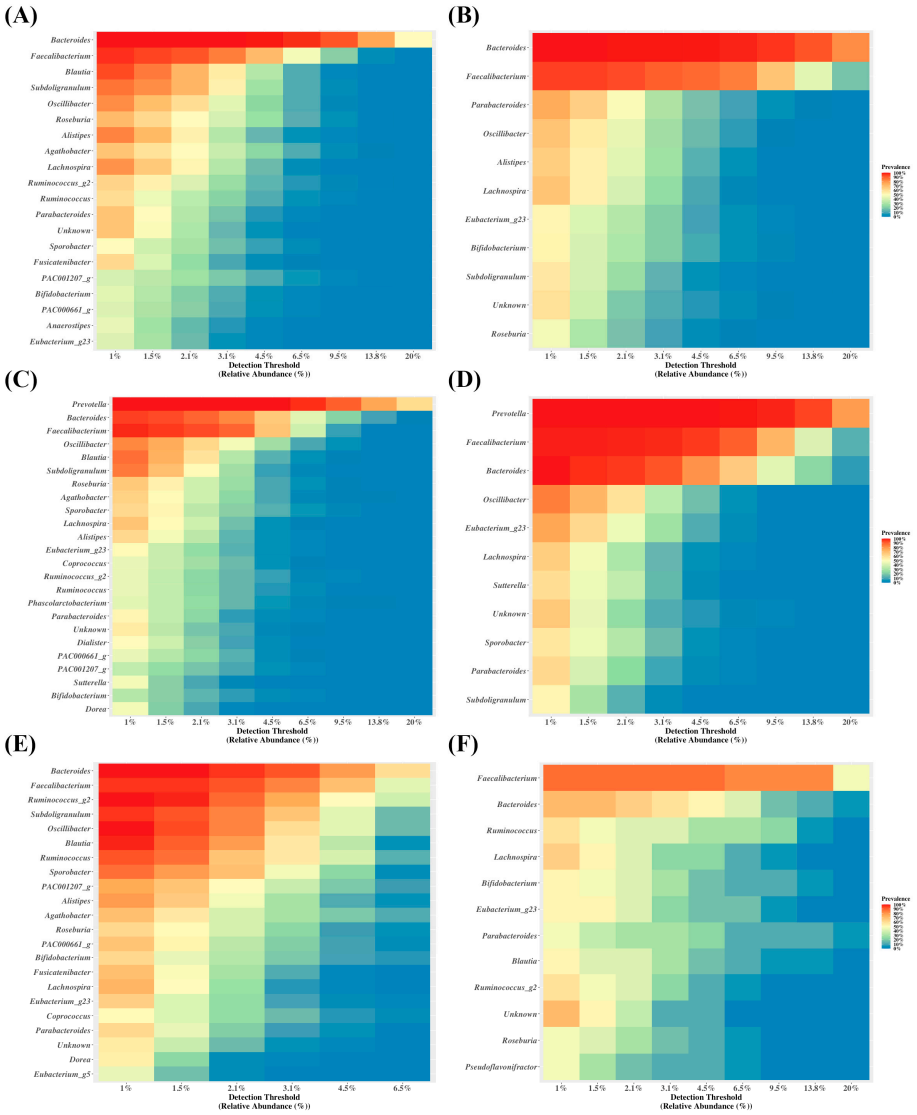

Figure 3. Heat map of the core microbiome by enterotype at the genus level. (**A**) German *Bacteroides* enterotype, (**B**) Korean *Bacteroides* enterotype, (**C**) German *Prevotella* enterotype, (**D**) Korean *Prevotella* enterotype, (**E**) German *Ruminococcus* enterotype, and (**F**) Korean *Ruminococcus* enterotype.

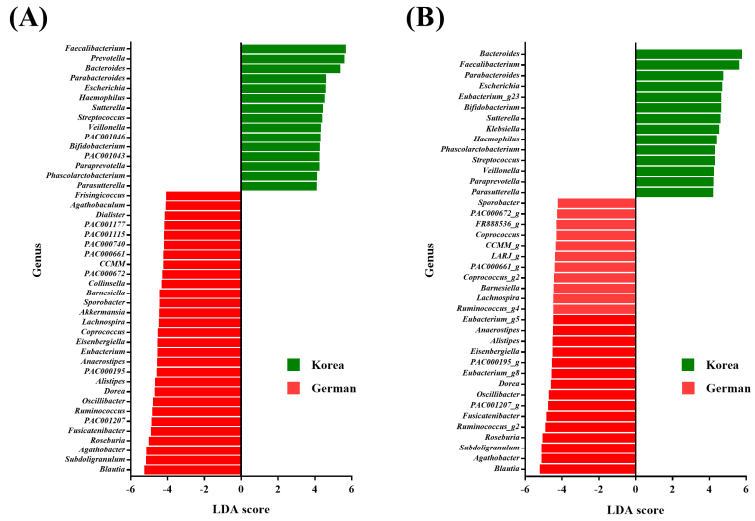

Figure 4. *Cont.*

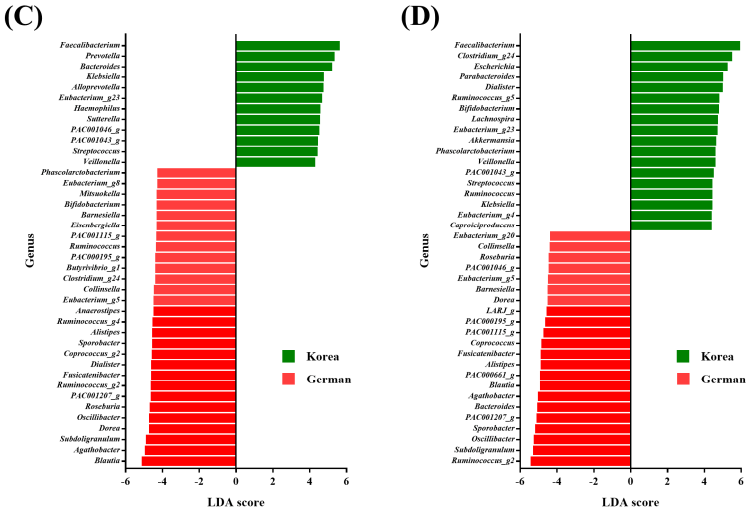

Figure 4. Comparisons of the LDA scores of microbiota and significant taxa in the German and the Korean cohort (**A**) Total, (**B**) *Bacteroides* enterotype, (**C**) *Prevotella* enterotype, and (**D**) *Ruminococcus* enterotype. The analysis has been performed using linear discriminant analysis effect size (LefSe) method.

3.4. Network Analysis

We also investigated microbial interaction networks to discern potential patterns of interaction. The *Bacteroides* enterotype network was the simplest, and the *Ruminococcus* enterotype network was the most complex network in both cohorts (Figure 5). In the *Bacteroides* enterotype network, *Bacteroides* was positively correlated with those of *Blautia* and *Anaerostipes* (Figure 5A,D). In the *Prevotella* enterotype network, *Prevotella* was positively correlated with those of *Blautia*, *Bacteroides*, and *Faecalibacterium* (Figure 5B,E). In the *Ruminococcus* enterotype network, a highly complex microbial interaction was observed in both cohorts (Figure 5C,F).

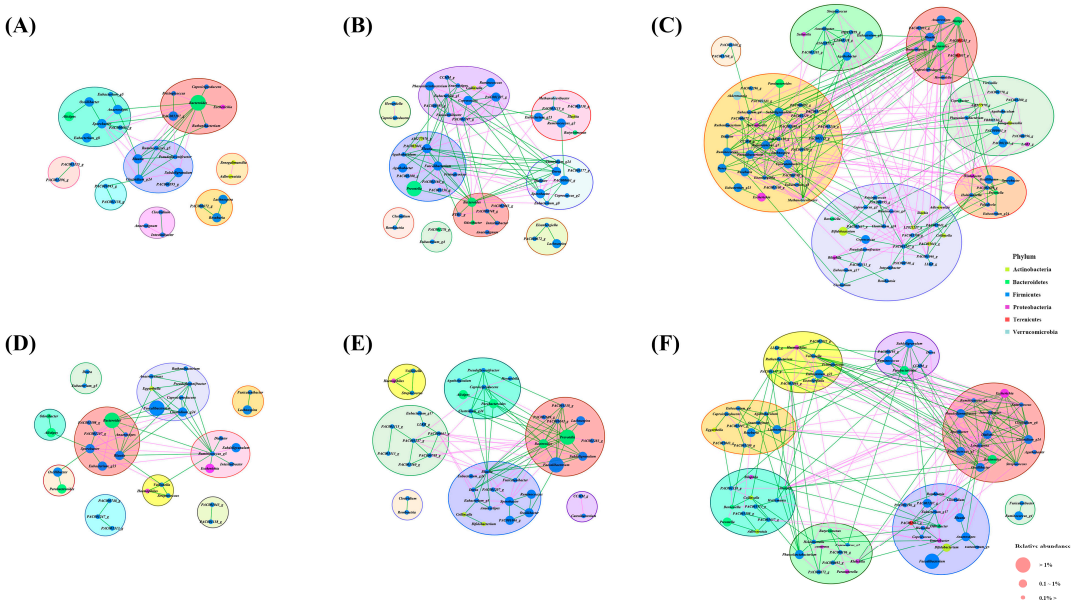

Figure 5. Gut microbiome network analysis by enterotype at the genus level. (**A**) German *Bacteroides* enterotype, (**B**) German *Prevotella* enterotype, (**C**) German *Ruminococcus* enterotype, (**D**) Korean *Bacteroides* enterotype, (**E**) Korean *Prevotella* enterotype, and (**F**) Korean *Ruminococcus* enterotype. Bubbles represent a genus whose color varied with phylum according to the legend. A connection between two bubbles indicates the existence of a correlation between the corresponding genera. Green and red lines represent positive and negative correlations. Clusters of nodes that form coherent structural subsystems of interacting units are represented as distinct modules.

4. Discussion

A key objective in human microbiome research is to pinpoint and characterize bacterial taxa that significantly contribute to different diseases compared to individuals in good health. In the present study, relative abundances were calculated, and enterotypes were determined for each sample. Arumugam et al. found that gut microbiome samples can be stratified into three distinct robust clusters including the *Bacteroides*, *Prevotella*, and *Ruminococcus* enterotypes [29]. We found that the *Bacteroides* enterotype was the most abundant, followed by the *Prevotella* enterotype in both cohorts. Interestingly, the *Prevotella* enterotype was more abundant in the Korean cohort (35.1% vs. 14.9%). Enterotypes have been suggested to be strongly associated with diet; for example, a protein- and animal-fat-rich diet has been associated with the *Bacteroides* enterotype, while a carbohydrate-rich diet has been linked to the *Prevotella* enterotype [29]. Thus, the higher abundance of the *Prevotella* enterotype in the Korean cohort is consistent with a previous report [10].

Alpha diversity was estimated to evaluate the richness and evenness of the microbiome. The Korean cohort had a higher Chao1 index, which represents community richness. Since the Korean cohort had much greater input read and OTU counts, its higher Chao1 index may have been due to more input data. Regarding the Shannon index, which represents microbial community richness and evenness, the German cohort had the higher index [30]. A comparison of the structures of the microbiomes revealed that the cohort microbiome compositions were significantly different and that this was significantly dependent on enterotype. The *Ruminococcus* enterotype was mostly clustered within the *Bacteroides* enterotype. Wu et al. also reported that the *Bacteroides* enterotype is fused with the less well-distinguished *Ruminococcus* enterotype [31]. However, we found the *Ruminococcus* enterotype mainly clustered near the *Prevotella* enterotype, suggesting that these two enterotypes have features distinguishing them from the *Bacteroides* enterotype. Thus, we maintained three enterotypes during subsequent analysis.

When we analyzed the average relative abundance, the five most abundant phyla were Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Verrucomicrobia. At the genus level, the top four most abundant genera in both cohorts were *Bacteroides*, *Faecalibacterium*, *Prevotella*, and *Ruminococcus*. Interestingly, the overall abundance of *Faecalibacterium* was higher in the Korean cohort compared to the German cohort. *Faecalibacterium* is a probiotic isolated from healthy human microbiota and has anti-inflammatory properties attributed to the production of butyrate [32,33]. Interestingly, *Feacalibacterium* has low abundances in Crohn's disease and colon cancer [34,35].

Core microbiota include specific keystone species that are important for maintaining an efficiently functioning ecosystem [36]. Although the criteria used for quantifying the core microbiome vary, it is generally defined as the proportion of samples that share a set of microbial taxa, the relative abundances of shared taxa, or a combination of the two [37]. In this study, the core microbiome contained *Bacteroides*, *Faecalibacterium*, *Parabacteroides*, and *Lachnospira.* A mixture of bacteria, including *Bacteroides* and *Parabacteroides*, have been reported to suppress inflammatory responses induced by *E. coli* and to enhance epithelial tight junction barrier function [38]. *Bacteroides*, *Faecalibacterium*, and *Lachnospira* are member of butyrate producing bacteria in the gut microbiome [39]. Furthermore, butyrate is the primary source of energy for gut epithelial cells, and it also reduces inflammation and oxidative stress. Butyrate is also involved in cell growth, cell differentiation, intestinal motility, ion absorption, cholesterol synthesis, and energy expenditure [40].

Next, LEfSe was applied to evaluate the enterotype differences between the two cohorts. It has been established that gut microbiota composition depends on various factors, including age [41], geography, ethnicity [15], and lifestyle factors such as dietary habits [42] and exercise [43]. The *Bacteroides* enterotype exhibits a significant interaction with the Western-style diet [44], and persons with the *Bacteroides* enterotype have been reported to have consumed diets rich in animal protein and fat over long periods [45]. In 2015, average meat consumptions per capita in Germany and Korea were 88 and 67 kg, respectively (http://ourworlddata.org, accessed on 16 November 2023). On the other

hand, the *Prevotella* enterotype has been strongly associated with a carbohydrate-rich diet. The Western-style carbohydrate-rich diet is characterized by high levels of refined carbohydrates, including sucrose, starch, fructose syrup, and white bread [46]. In contrast, traditional Korean diets are characterized by higher intakes of fermented vegetables and legumes such as kimchi and fermented soybean [47]. Thus, although the development of each enterotype might be dependent on overall protein or carbohydrate consumption, carbohydrate diet composition might also influence the composition of the gut microbiome.

Finally, microbial networks were analyzed to understand how microbiota interact within the community. Distinctive network complexities were observed in each enterotype group. The co-abundance of correlations in networks indicates strong community symbiosis. Furthermore, the gut is colonized by a complex community of indigenous microorganisms that interact to shape a reticular system that maintains the microbial composition [48–50]. However, these network maps represent patterns, not direct interactions, and many of the observed interactions may be due to microbes sharing a similar ecological niche. Further studies are required to reveal causal relationships between gut microbiota, related metabolic activity, and long-term health.

The limitation of this study is that only geographical background was considered for the analysis. More detailed analysis that addresses causal relationships between gut microbiota and clinical metadata is needed. Also, prospective observational or interventional studies should be conducted to improve understanding of the healthy gut microbiome. Furthermore, random sampling of larger sample sizes by an international consortium would be essential to define healthy gut microbiomes.

In conclusion, we investigated and compared the gut microbiome structures of healthy German and Korean subjects. Enterotype proportions different in the two cohorts and the richness and compositions of the gut microbiomes were found to depend significantly on enterotype and cohort. Based on the analysis of enterotype, we identified several common core microbiome and interaction networks, which suggests the existence of common ecological conditions. Our results expand understanding of the relationships between the gut microbiome and enterotype and geographic distribution. However, further investigations are needed to determine the nature of the relations between microbial properties and individual health statuses. We anticipate that precise enterotypes driven by age, gender, ethnicity, nutritional habits, and medication might be used to define healthy gut microbiomes and predict the health statuses of individuals.

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Conflicts of Interest: The authors declare no conflicts of interest.

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