

***Bifidobacterium adolescentis* is effective in relieving type 2 diabetes and may be related to its dominant core genome and gut microbiota modulation capacity**

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1 Supplementary Methods

1.1 Feed and gavage formulations

Low-fat diet: energy: 3.6 kcal g⁻¹; 10% kcal from fat, 71% kcal from carbohydrate, and 19% kcal from protein. High-fat diet: energy: 5.1 kcal g⁻¹; 60% kcal from fat, 21% kcal from carbohydrate, and 19% kcal from protein. Gavage formulation of Control or Model group: 0.2 mL 3% sucrose solution. Gavage formulation of Metformin group: 200 mg per kg·bw metformin dissolved in 3% sucrose solution. Gavage formulation of Treatment group: 0.2 mL 2 × 10⁸ CFU per mL bacterial suspension resuspended in 3% sucrose solution

1.2 Bioinformatical analysis of gut microbiota

Bioinformatical analysis was performed as previously described (Molecular Nutrition & Food Research, 2021, 65(8): 2000704). The raw data of sequencing was processed using Quantitative Insights into Microbial Ecology (QIIME) wrapper and software (Caporaso, J, et al. Nature methods 2010, 7, 335). The operational taxonomic unit (OTU) was picked using a criterion of 97% nucleotide identity and the taxonomy was assigned using the SILVA database. The Shannon and Chao 1 indices were measured from the rarefied OTU. β -diversity was estimated using compositional data analysis by PCA using Aitchison distance (Gloor, G. B, et al. Front. Microbiol. 2017, 8, 2224), following a PERMANOVA test to assess differences. LEfSe was used to differentiate microbial taxa (Wilcoxon rank-sum test, $\alpha < 0.05$ and log LDA > 2.0 were used as the threshold). GBMs analysis was performed as previously described (Valles-Colomer, M, J, et al.

Nature microbiology 2019, 4, 623). Briefly, the metagenomic composition was predicted from 16S rRNA sequences using PICRUST2 (Nature Biotechnology, 2020, 38(6): 685-688). The identified KEGG Orthogroups (KOs) abundance was normalized and mapped to 56 GBMs using the Omixer-RPM V1.0. The GBMs enrichment differences were calculated by Welch's t-test, $P < 0.015$ adjusted by the Benjamini & Hochberg method were considered significantly different.

1.3 Bioinformatical analysis of genome

Reads were assembled with SOAPdenovo. Overall, for each strain, Prodigal (v2.6.3), Glimmer (v3.02) and GeneMarkS-2 (web-server) were run on their default settings to generate sets of predicted genes. The predicted genes were annotated in public databases including the Non-redundant (NR, download in 12/31/2021), Kyoto Encyclopedia of Genes and Genomes (KEGG, <http://www.genome.jp/kegg>), Clusters of Orthologous Groups (COG, <http://www.ncbi.nlm.nih.gov/COG>). Additionally, the eggNOG-mapper v2.1.6 (<https://github.com/eggnogdb/eggno-mapper>) was also used for further annotation. Pan-Genome Analysis Pipeline was used to analyze the pan-genome and Orthologous gene families were analyzed using OrthoMCL (version v2.0.9) and OrthoFinder. The orthologous genes of all *Bifidobacterium* genomes were aligned using MAFFT v7.3.

2 Supplementary Figures and Tables

Table S1. Genome data used in this study

| <i>B. adolescentis</i> | | | | <i>B. bifidum</i> | | | |
|------------------------|-----------------|----------|-----------------|-------------------|-----------------|--------|-----------------|
| Genome | Accession | Genome | Accession | Genome | Accession | Genome | Accession |
| ID | number | ID | number | ID | number | ID | number |
| QCNCBI1 | GCF_000010425.1 | QCNCBI46 | GCF_003856735.1 | NCBI1 | GCF_000155395.1 | NCBI46 | GCF_003465425.1 |
| QCNCBI2 | GCF_000154085.1 | QCNCBI47 | GCF_004167585.1 | NCBI2 | GCF_000164965.1 | NCBI47 | GCF_003466365.1 |
| QCNCBI3 | GCF_000702865.1 | QCNCBI48 | GCF_005845205.1 | NCBI3 | GCF_000165905.1 | NCBI48 | GCF_003466395.1 |
| QCNCBI4 | GCF_000737885.1 | QCNCBI49 | GCF_009832825.1 | NCBI4 | GCF_000265095.1 | NCBI49 | GCF_003466485.1 |
| QCNCBI5 | GCF_000741415.1 | QCNCBI50 | GCF_013249115.1 | NCBI5 | GCF_000273525.1 | NCBI50 | GCF_003467985.1 |
| QCNCBI6 | GCF_000771705.1 | QCNCBI51 | GCF_014524935.1 | NCBI6 | GCF_000299595.1 | NCBI51 | GCF_003468415.1 |
| QCNCBI7 | GCF_000817995.1 | QCNCBI52 | GCF_015547885.1 | NCBI7 | GCF_000300215.1 | NCBI52 | GCF_003470585.1 |
| QCNCBI8 | GCF_001010915.1 | QCNCBI53 | GCF_015548665.1 | NCBI8 | GCF_000466525.1 | NCBI53 | GCF_003470615.1 |
| QCNCBI9 | GCF_001406215.1 | QCNCBI54 | GCF_015548755.1 | NCBI9 | GCF_000741085.1 | NCBI54 | GCF_003471555.1 |
| QCNCBI10 | GCF_001406455.1 | QCNCBI55 | GCF_015548985.1 | NCBI10 | GCF_000771485.1 | NCBI55 | GCF_003471595.1 |
| QCNCBI11 | GCF_001406735.1 | QCNCBI56 | GCF_015549865.1 | NCBI11 | GCF_001020245.1 | NCBI56 | GCF_003472345.1 |
| QCNCBI12 | GCF_001756865.1 | QCNCBI57 | GCF_015552825.1 | NCBI12 | GCF_001020255.1 | NCBI57 | GCF_003473145.1 |
| QCNCBI13 | GCF_002075965.1 | QCNCBI58 | GCF_015553845.1 | NCBI13 | GCF_001020265.1 | NCBI58 | GCF_003573895.1 |
| QCNCBI14 | GCF_002107925.1 | QCNCBI59 | GCF_015553925.1 | NCBI14 | GCF_001020275.1 | NCBI59 | GCF_003790385.1 |
| QCNCBI15 | GCF_002107955.1 | QCNCBI60 | GCF_015553955.1 | NCBI15 | GCF_001020325.1 | NCBI60 | GCF_004167365.1 |
| QCNCBI16 | GCF_002107975.1 | QCNCBI61 | GCF_015554265.1 | NCBI16 | GCF_001020335.1 | NCBI61 | GCF_004799295.1 |
| QCNCBI17 | GCF_002107995.1 | QCNCBI62 | GCF_015555595.1 | NCBI17 | GCF_001020355.1 | NCBI62 | GCF_005844205.1 |
| QCNCBI18 | GCF_002108015.1 | QCNCBI63 | GCF_015557595.1 | NCBI18 | GCF_001020375.1 | NCBI63 | GCF_005844365.1 |
| QCNCBI19 | GCF_002108035.1 | QCNCBI64 | GCF_015557685.1 | NCBI19 | GCF_001020405.1 | NCBI64 | GCF_008868415.1 |
| QCNCBI20 | GCF_002108045.1 | QCNCBI65 | GCF_015558085.1 | NCBI20 | GCF_001020415.1 | NCBI65 | GCF_009075765.1 |
| QCNCBI21 | GCF_002108075.1 | QCNCBI66 | GCF_015558415.1 | NCBI21 | GCF_001025135.1 | NCBI66 | GCF_009075785.1 |
| QCNCBI22 | GCF_002108095.1 | QCNCBI67 | GCF_015558565.1 | NCBI22 | GCF_001281345.1 | NCBI67 | GCF_009077915.1 |
| QCNCBI23 | GCF_002108135.1 | QCNCBI68 | GCF_015558575.1 | NCBI23 | GCF_001405355.1 | NCBI68 | GCF_009077955.1 |
| QCNCBI24 | GCF_002108155.1 | QCNCBI69 | GCF_015558745.1 | NCBI24 | GCF_001546225.1 | NCBI69 | GCF_009077975.1 |
| QCNCBI25 | GCF_002108165.1 | QCNCBI70 | GCF_015559505.1 | NCBI25 | GCF_001595435.1 | NCBI70 | GCF_009078005.1 |
| QCNCBI26 | GCF_003030905.1 | QCNCBI71 | GCF_015560095.1 | NCBI26 | GCF_001685685.1 | NCBI71 | GCF_009078015.1 |
| QCNCBI27 | GCF_003429385.1 | QCNCBI72 | GCF_016069975.1 | NCBI27 | GCF_002076105.1 | NCBI72 | GCF_009078055.1 |
| QCNCBI28 | GCF_003436185.1 | QCNCBI73 | GCF_017815835.1 | NCBI28 | GCF_002114145.1 | NCBI73 | GCF_009078065.1 |
| QCNCBI29 | GCF_003437735.1 | QCNCBI74 | GCF_018785705.1 | NCBI29 | GCF_002845845.1 | NCBI74 | GCF_009078095.1 |
| QCNCBI30 | GCF_003437755.1 | QCNCBI75 | GCF_018785715.1 | NCBI30 | GCF_003094645.1 | NCBI75 | GCF_009078115.1 |
| QCNCBI31 | GCF_003437775.1 | QCNCBI76 | GCF_019041695.1 | NCBI31 | GCF_003094715.1 | NCBI76 | GCF_009159095.1 |
| QCNCBI32 | GCF_003457765.1 | QCNCBI77 | GCF_019041975.1 | NCBI32 | GCF_003094735.1 | NCBI77 | GCF_009159495.1 |
| QCNCBI33 | GCF_003458805.1 | QCNCBI78 | GCF_019042035.1 | NCBI33 | GCF_003094755.1 | NCBI78 | GCF_009159505.1 |
| QCNCBI34 | GCF_003462885.1 | QCNCBI79 | GCF_019042045.1 | NCBI34 | GCF_003094795.1 | NCBI79 | GCF_009159555.1 |
| QCNCBI35 | GCF_003462895.1 | QCNCBI80 | GCF_019127685.1 | NCBI35 | GCF_003095035.1 | NCBI80 | GCF_009160775.1 |
| QCNCBI36 | GCF_003464325.1 | QCNCBI81 | GCF_019127775.1 | NCBI36 | GCF_003390735.1 | NCBI81 | GCF_009160825.1 |
| QCNCBI37 | GCF_003465205.1 | QCNCBI82 | GCF_019127835.1 | NCBI37 | GCF_003436135.1 | NCBI82 | GCF_009160845.1 |
| QCNCBI38 | GCF_003466335.1 | QCNCBI83 | GCF_019128025.1 | NCBI38 | GCF_003436575.1 | NCBI83 | GCF_009160865.1 |
| QCNCBI39 | GCF_003467335.1 | QCNCBI84 | GCF_019129365.1 | NCBI39 | GCF_003436635.1 | NCBI84 | GCF_009160885.1 |
| QCNCBI40 | GCF_003468385.1 | QCNCBI85 | GCF_019131675.1 | NCBI40 | GCF_003436655.1 | NCBI85 | GCF_009160905.1 |
| QCNCBI41 | GCF_003469145.1 | QCNCBI86 | GCF_019734235.1 | NCBI41 | GCF_003437175.1 | NCBI86 | GCF_009160915.1 |
| QCNCBI42 | GCF_003472095.1 | QCNCBI87 | GCF_019734295.1 | NCBI42 | GCF_003437325.1 | NCBI87 | GCF_009160945.1 |
| QCNCBI43 | GCF_003472245.1 | QCNCBI88 | GCF_019972965.1 | NCBI43 | GCF_003437345.1 | NCBI88 | GCF_011029205.1 |
| QCNCBI44 | GCF_003472265.1 | QCNCBI89 | GCF_022133115.1 | NCBI44 | GCF_003437785.1 | NCBI89 | GCF_013867495.1 |
| QCNCBI45 | GCF_003473105.1 | QCNCBI90 | GCF_022135325.1 | NCBI45 | GCF_003437945.1 | NCBI90 | GCF_015549125.1 |

Genome ID: The ID used in this study.

Accession number: The number used to obtain genomic data in RefSeq database.

Table S2. Effects of *Bifidobacterium* on body weight and organ quality

| Group | Fasting body (g) | Liver (g) | Kidney (g) |
|------------------|---------------------------|---------------------------|--------------------------|
| Control | 25.47 ± 1.10 ^a | 0.89 ± 0.04 ^a | 0.30 ± 0.03 ^a |
| Model | 25.10 ± 1.20 ^a | 1.23 ± 0.09 ^b | 0.33 ± 0.01 ^a |
| Metformin | 25.19 ± 1.63 ^a | 1.16 ± 0.15 ^b | 0.34 ± 0.05 ^a |
| 3M10 | 24.87 ± 1.11 ^a | 1.06 ± 0.07 ^{ab} | 0.32 ± 0.03 ^a |
| 8M4 | 25.14 ± 1.39 ^a | 1.02 ± 0.19 ^{ab} | 0.33 ± 0.04 ^a |
| 26M1 | 23.60 ± 2.18 ^a | 1.01 ± 0.17 ^{ab} | 0.31 ± 0.03 ^a |
| 30M5 | 24.93 ± 1.33 ^a | 1.14 ± 0.06 ^b | 0.33 ± 0.03 ^a |
| 34M4 | 25.25 ± 1.28 ^a | 1.18 ± 0.13 ^b | 0.35 ± 0.21 ^a |
| 41M3 | 25.38 ± 1.25 ^a | 1.13 ± 0.06 ^b | 0.34 ± 0.03 ^a |
| 50M3 | 25.09 ± 1.38 ^a | 1.12 ± 0.07 ^b | 0.33 ± 0.03 ^a |
| 2016 | 25.41 ± 1.61 ^a | 1.04 ± 0.14 ^{ab} | 0.33 ± 0.04 ^a |
| 5M8 | 25.69 ± 1.72 ^a | 1.16 ± 0.08 ^b | 0.33 ± 0.07 ^a |
| 7-05 | 25.45 ± 0.98 ^a | 1.10 ± 0.07 ^b | 0.32 ± 0.03 ^a |
| 9M10 | 26.10 ± 1.08 ^a | 1.17 ± 0.07 ^b | 0.35 ± 0.03 ^a |
| 19M10 | 26.01 ± 2.12 ^a | 1.19 ± 0.19 ^b | 0.35 ± 0.06 ^a |
| 21M3 | 24.28 ± 1.89 ^a | 1.09 ± 0.07 ^b | 0.34 ± 0.04 ^a |
| 23M2 | 25.22 ± 2.07 ^a | 1.11 ± 0.09 ^b | 0.34 ± 0.04 ^a |
| 26M7 | 25.48 ± 1.22 ^a | 1.10 ± 0.09 ^b | 0.34 ± 0.02 ^a |
| 26-7 | 24.38 ± 1.22 ^a | 1.13 ± 0.12 ^b | 0.33 ± 0.03 ^a |

Different letters a/b indicate significant differences ($P < 0.05$).

Table S3. Effect of *Bifidobacterium* on organ index

| Group | Liver / body weight (%) | Kidney / body weight (%) |
|------------------|--------------------------------|---------------------------------|
| Control | 3.52 ± 0.16 ^a | 1.19 ± 0.08 ^a |
| Model | 4.89 ± 0.21 ^c | 1.30 ± 0.04 ^a |
| Metformin | 4.59 ± 0.36 ^{bc} | 1.34 ± 0.12 ^a |
| 3M10 | 4.25 ± 0.24 ^{bc} | 1.29 ± 0.07 ^a |
| 8M4 | 4.08 ± 0.61 ^{ab} | 1.32 ± 0.12 ^a |
| 26M1 | 4.25 ± 0.38 ^{bc} | 1.32 ± 0.07 ^a |
| 30M5 | 4.58 ± 0.17 ^{bc} | 1.32 ± 0.06 ^a |
| 34M4 | 4.66 ± 0.38 ^{bc} | 1.37 ± 0.07 ^a |
| 41M3 | 4.44 ± 0.18 ^{bc} | 1.34 ± 0.07 ^a |
| 50M3 | 4.47 ± 0.23 ^{bc} | 1.30 ± 0.07 ^a |
| 2016 | 4.08 ± 0.44 ^{ab} | 1.29 ± 0.10 ^a |
| 5M8 | 4.50 ± 0.20 ^{bc} | 1.26 ± 0.24 ^a |
| 7-05 | 4.32 ± 0.23 ^{bc} | 1.26 ± 0.09 ^a |
| 9M10 | 4.47 ± 0.30 ^{bc} | 1.33 ± 0.07 ^a |
| 19M10 | 4.55 ± 0.48 ^{bc} | 1.34 ± 0.12 ^a |
| 21M3 | 4.51 ± 0.26 ^{bc} | 1.40 ± 0.14 ^a |
| 23M2 | 4.43 ± 0.40 ^{bc} | 1.35 ± 0.10 ^a |
| 26M7 | 4.33 ± 0.24 ^{bc} | 1.32 ± 0.05 ^a |
| 26-7 | 4.63 ± 0.31 ^{bc} | 1.29 ± 0.08 ^a |

Different letters a/b indicate significant differences ($P < 0.05$).

Table S4. Pathway statistics of unique core genes in two *Bifidobacterium* species

| Pathway | B.ad | B.bi | Pathway | B.ad | B.bi |
|---|----------|----------|---|----------|----------|
| Glycolysis / Gluconeogenesis | 2 | 1 | Riboflavin metabolism | 1 | 0 |
| Citrate cycle (TCA cycle) | 1 | 0 | Vitamin B6 metabolism | 1 | 1 |
| Pentose phosphate pathway | 4 | 0 | Nicotinate and nicotinamide metabolism | 2 | 4 |
| Pentose and glucuronate interconversions | 5 | 0 | Pantothenate and CoA biosynthesis | 3 | 4 |
| Fructose and mannose metabolism | 1 | 0 | Folate biosynthesis | 1 | 2 |
| Galactose metabolism | 2 | 4 | Zeatin biosynthesis | 1 | 0 |
| Ascorbate and aldarate metabolism | 1 | 3 | Nitrogen metabolism | 1 | 1 |
| Oxidative phosphorylation | 2 | 0 | Aminoacyl-tRNA biosynthesis | 2 | 0 |
| Arginine biosynthesis | 2 | 0 | Vancomycin resistance | 1 | 0 |
| Ubiquinone and other terpenoid-quinone biosynthesis | 0 | 1 | Cationic antimicrobial peptide (CAMP) resistance | 1 | 0 |
| Purine metabolism | 10 | 5 | Antifolate resistance | 1 | 0 |
| Pyrimidine metabolism | 13 | 3 | Drug metabolism - other enzymes | 0 | 1 |
| Alanine, aspartate and glutamate metabolism | 4 | 1 | beta-Lactam resistance | 0 | 2 |
| Glycine, serine and threonine metabolism | 4 | 0 | ABC transporters | 9 | 1 |
| Monobactam biosynthesis | 3 | 0 | Two-component system | 3 | 0 |
| Cysteine and methionine metabolism | 2 | 1 | Quorum sensing | 3 | 2 |
| Valine, leucine and isoleucine biosynthesis | 1 | 3 | Biofilm formation - Escherichia coli | 2 | 1 |
| Lysine biosynthesis | 6 | 0 | Phosphotransferase system (PTS) | 1 | 4 |
| Arginine and proline metabolism | 3 | 0 | Ribosome biogenesis in eukaryotes | 1 | 0 |
| Histidine metabolism | 1 | 0 | Ribosome | 3 | 1 |
| Penicillin and cephalosporin biosynthesis | 0 | 2 | RNA degradation | 3 | 0 |
| Phenylalanine, tyrosine and tryptophan biosynthesis | 1 | 2 | RNA polymerase | 2 | 0 |
| Taurine and hypotaurine metabolism | 1 | 0 | DNA replication | 3 | 0 |
| Cyanoamino acid metabolism | 2 | 0 | Protein export | 2 | 0 |
| D-Alanine metabolism | 1 | 0 | Bacterial secretion system | 1 | 0 |
| Starch and sucrose metabolism | 4 | 0 | Base excision repair | 2 | 1 |
| Novobiocin biosynthesis | 0 | 1 | Nucleotide excision repair | 2 | 0 |
| Phenazine biosynthesis | 0 | 1 | Mismatch repair | 3 | 0 |
| Amino sugar and nucleotide sugar metabolism | 2 | 7 | Homologous recombination | 5 | 0 |
| Inositol phosphate metabolism | 1 | 0 | HIF-1 signaling pathway | 1 | 0 |
| Glycerophospholipid metabolism | 3 | 1 | Phosphatidylinositol signaling system | 1 | 0 |
| Pyruvate metabolism | 3 | 1 | Cell cycle - Caulobacter | 2 | 0 |
| Glyoxylate and dicarboxylate metabolism | 3 | 0 | Peroxisome | 1 | 0 |
| Propanoate metabolism | 3 | 0 | Necroptosis | 2 | 0 |
| Aminobenzoate degradation | 0 | 1 | Insulin signaling pathway | 1 | 0 |
| Butanoate metabolism | 1 | 1 | Glucagon signaling pathway | 1 | 0 |
| C5-Branched dibasic acid metabolism | 1 | 1 | Insulin resistance | 1 | 0 |
| One carbon pool by folate | 2 | 0 | Alzheimer disease | 1 | 0 |
| Methane metabolism | 2 | 0 | Chagas disease (American trypanosomiasis) | 1 | 0 |
| Carbon fixation in photosynthetic organisms | 3 | 0 | African trypanosomiasis | 1 | 0 |
| Carbon fixation pathways in prokaryotes | 3 | 0 | Tuberculosis | 1 | 0 |
| Thiamine metabolism | 3 | 1 | Proteoglycans in cancer | 1 | 0 |
| cGMP-PKG signaling pathway | 0 | 1 | Aldosterone-regulated sodium reabsorption | 0 | 1 |
| cAMP signaling pathway | 0 | 1 | Endocrine and other factor-regulated calcium reabsorption | 0 | 1 |
| Sulfur relay system | 0 | 1 | Proximal tubule bicarbonate reclamation | 0 | 1 |
| Autophagy - yeast | 0 | 1 | Salivary secretion | 0 | 1 |
| Cardiac muscle contraction | 0 | 1 | Gastric acid secretion | 0 | 1 |
| Adrenergic signaling in cardiomyocytes | 0 | 1 | Pancreatic secretion | 0 | 1 |
| Prolactin signaling pathway | 0 | 1 | Carbohydrate digestion and absorption | 0 | 1 |
| Thyroid hormone synthesis | 0 | 1 | Protein digestion and absorption | 0 | 1 |
| Thyroid hormone signaling pathway | 0 | 1 | Bile secretion | 0 | 1 |
| Aldosterone synthesis and secretion | 0 | 1 | Mineral absorption | 0 | 1 |

B.ad: Number of unique core genes in *B. adolescentis*.**B.bi:** Number of unique core genes in *B. bifidum*.

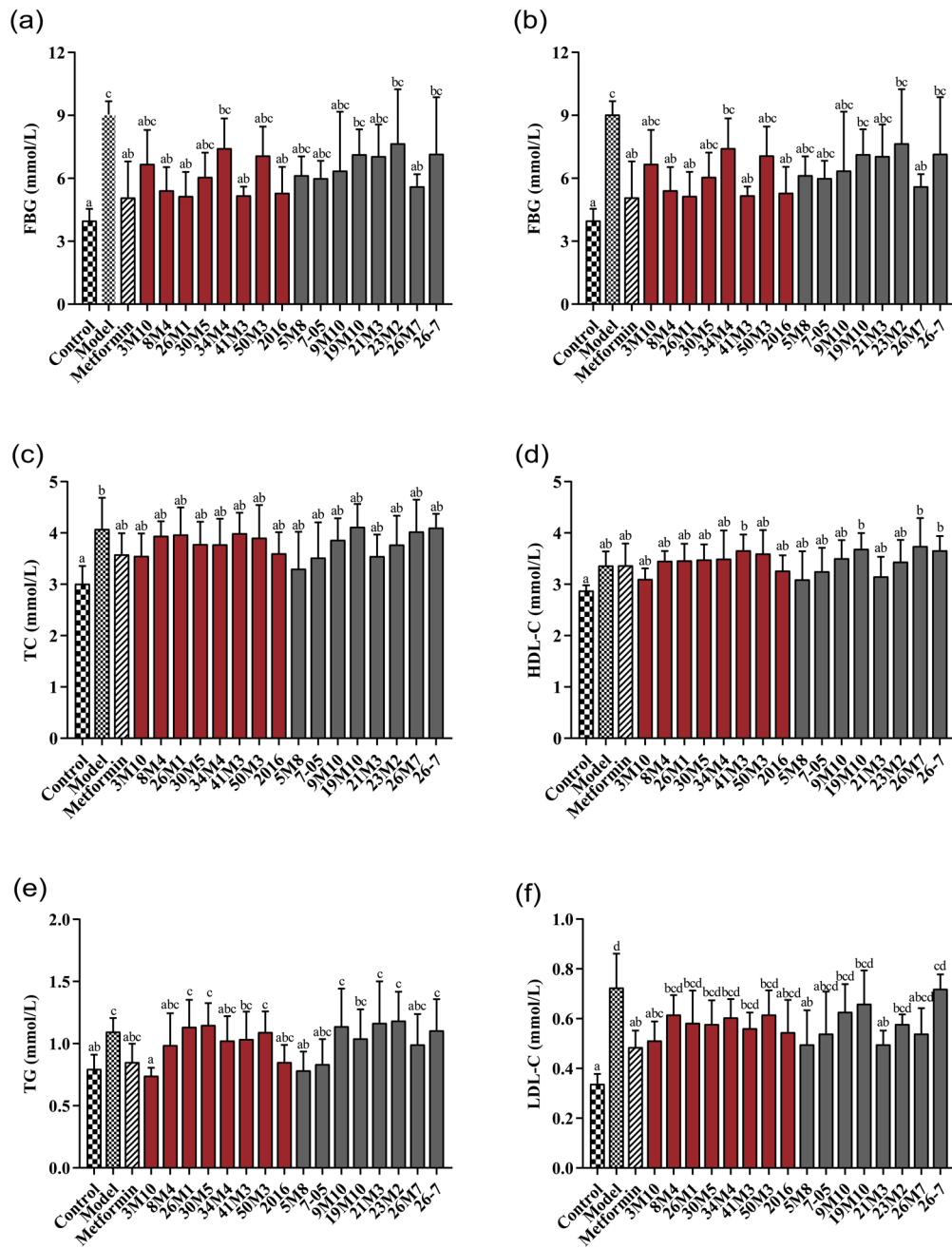


Figure S1. Effects of different *Bifidobacterium* on the regulation of glucose and lipid metabolism in T2D mice. (a, b) FBG at 1 or 5 weeks after STZ injection, respectively; (c-f) TC, TG, HDL-C and LDL-C level. Different letters represent statistically significant differences between different groups ($P < 0.05$), $n = 6$.

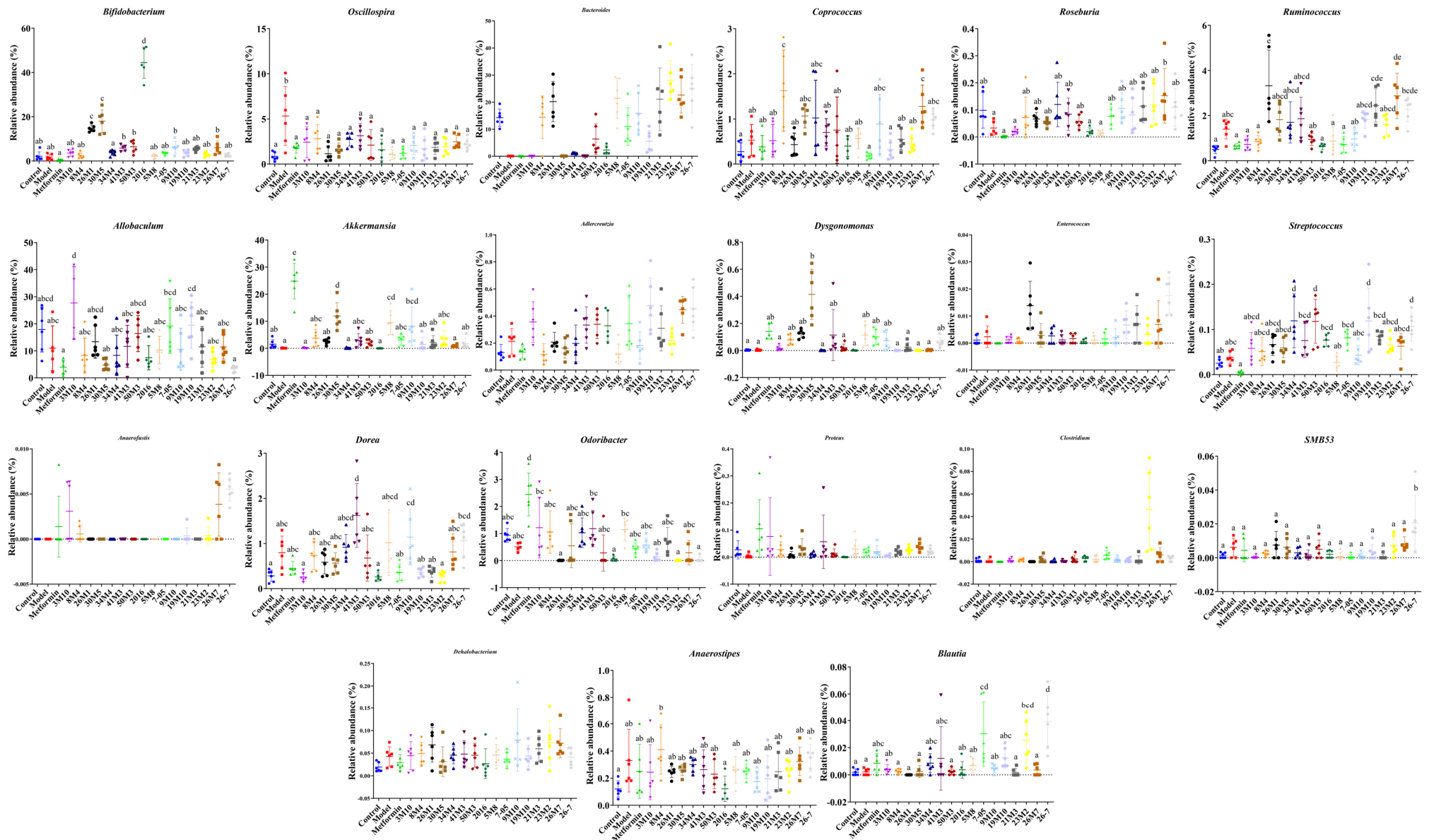


Figure S2. *Bifidobacterium* treatment alters the diversity and the structure at the species level of the gut microbiota.

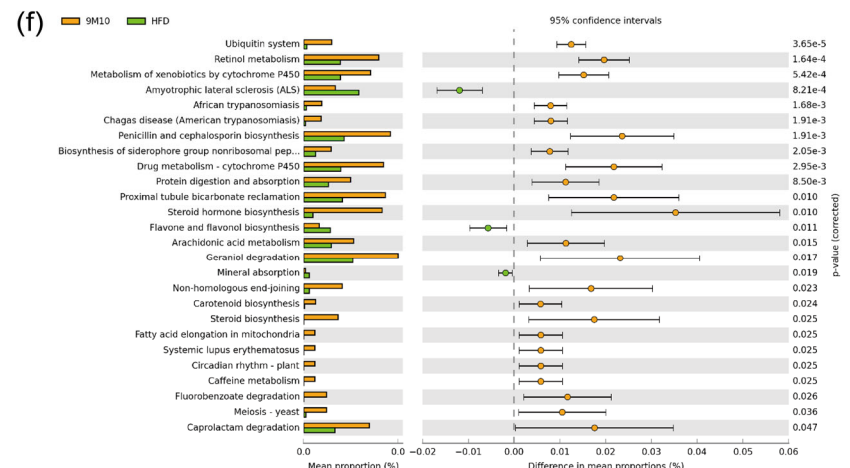
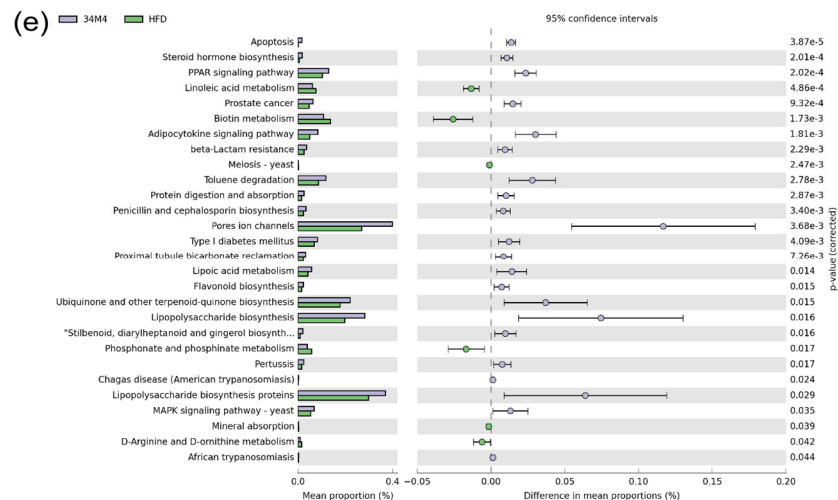
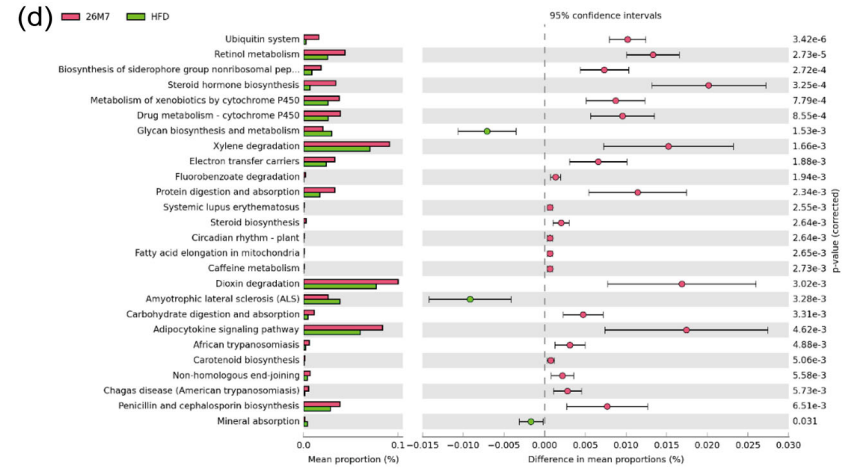
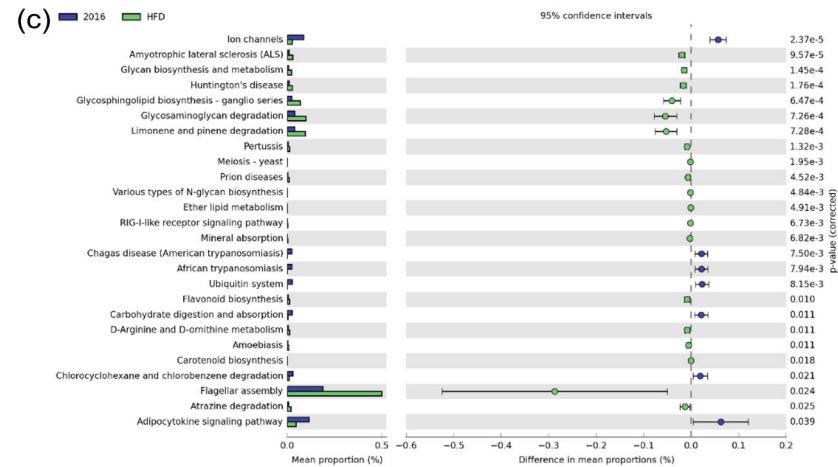
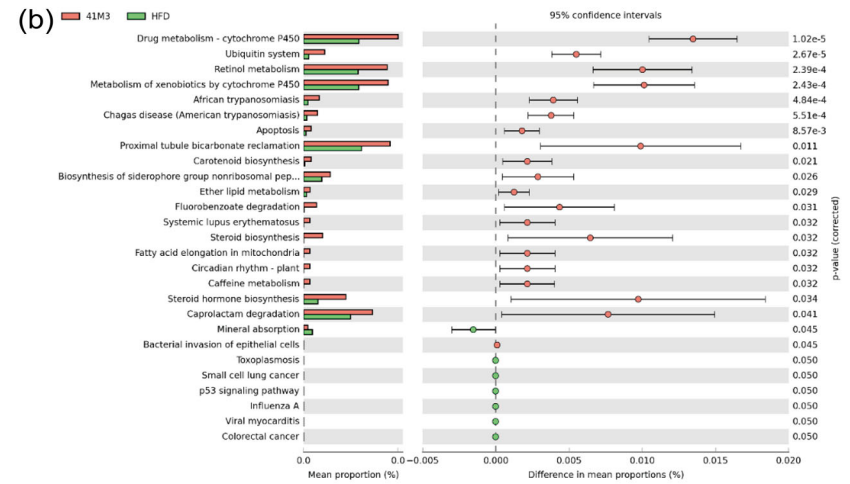
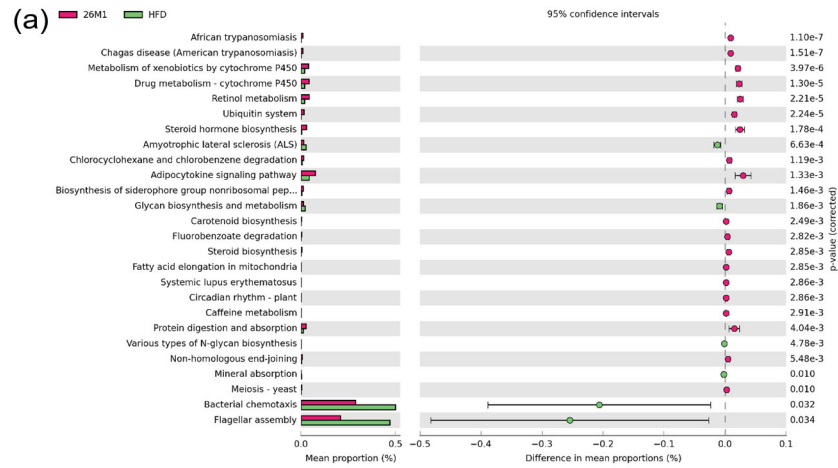


Figure S3. Prediction of gut microbiota function in T2D mice after *Bifidobacterium* intervention. (a) *B. adolescentis* 26M1; (b) *B. adolescentis* 41M3; (c) *B. adolescentis* 2016; (d) *B. bifidum* 26M7 (e) *B. adolescentis* 34M4; (f) *B. bifidum* 9M10. All results were compared with T2D Model group.

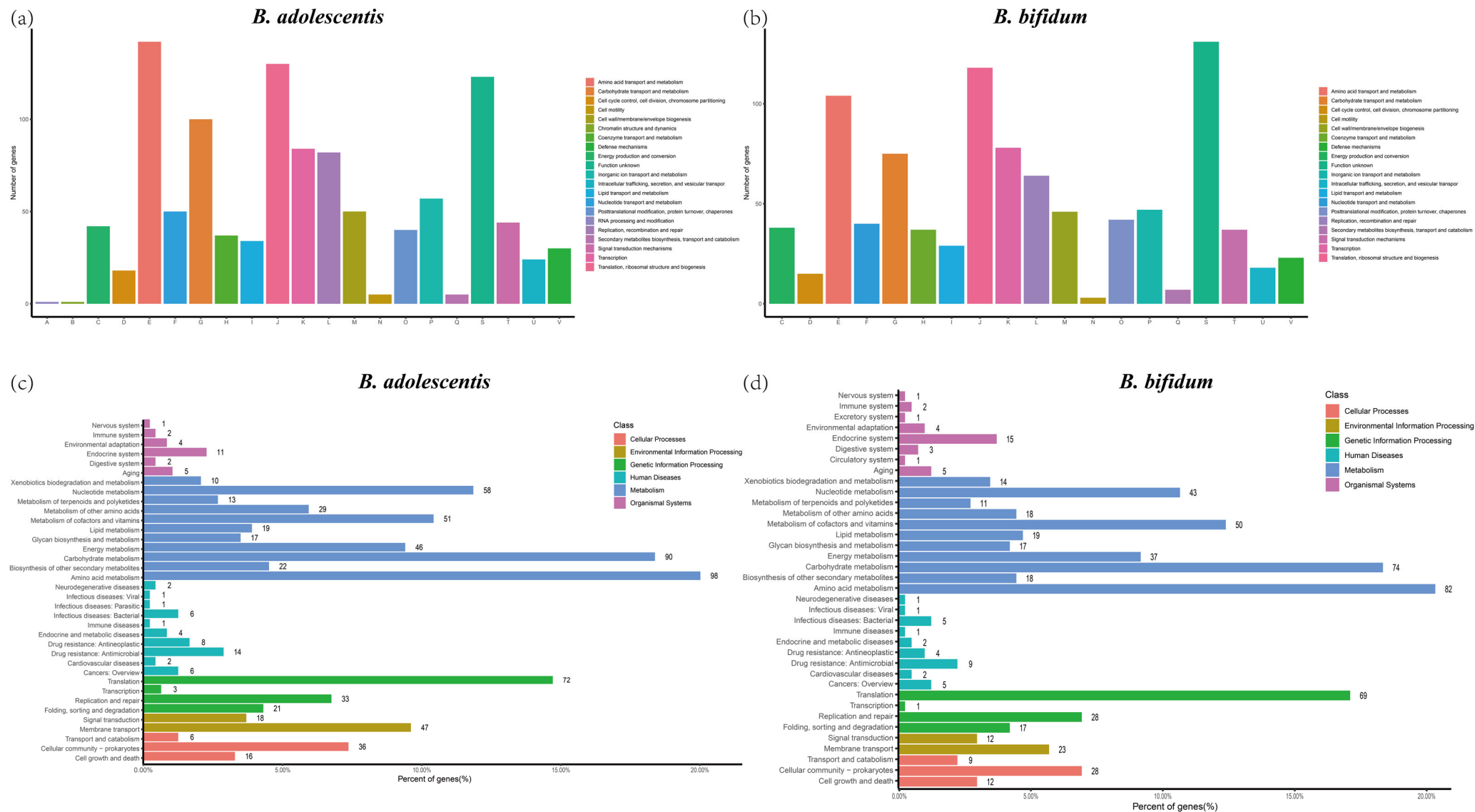


Figure S4. Functional clustering of core genes of *B. adolescentis* and *B. bifidum*. (a, b) Based on COG database; (c-d) Based on KEGG pathway database.