

<Supplementary data for *Experimental & Molecular Medicine*>

## **Linking visceral fat accumulation to gut microbiota: Key bacterial taxa and their roles in the glycogen synthesis pathway**

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## **Supplementary material**

**Supplementary Fig. 1. Comparison of bacterial taxa composition between 16S rRNA and shotgun metagenome data.**

**Supplementary Fig. 2. Network analysis of the prevalent Korean gut microbiota and related host metabolites.**

**Supplementary Fig. 3. Contribution plot illustrating significantly correlated pathways with *Dorea longicatena*.**

**Supplementary Fig. 4. Scatter plot of *Dorea longicatena* and GLYCOGENSYNTH-PWY.**

**Supplementary Fig. 5. KEGG pathway map (ko00500 - Starch and sucrose metabolism) matched with GLYCOGENSYNTH-PWY from MetaCyc.**

**Supplementary Fig. 6. Linear discriminant analysis (LDA) of microbial taxa associated with clinical metabolic traits.**

**Supplementary Table 1. Baseline characteristics of clinical variables.**

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**Supplementary Table 3. Comparison of median values of clinical variables among the four Enterotypes.**

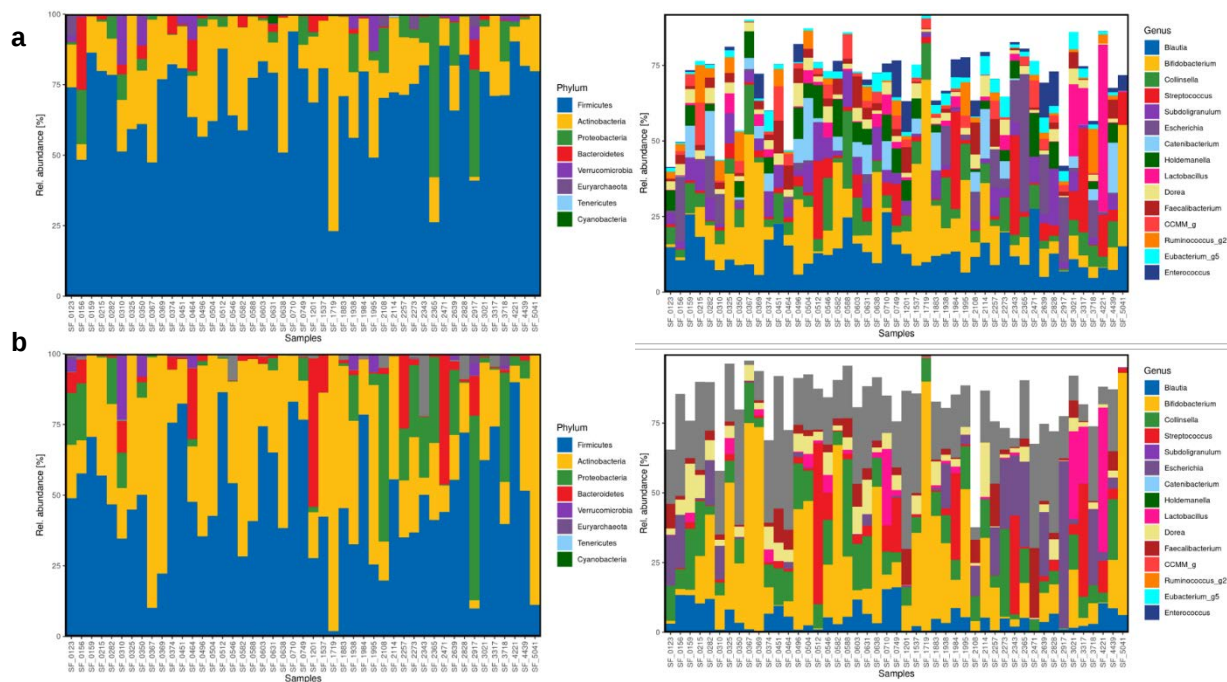
**Supplementary Table 4. Association test using TMAP between principal components (PCs) and 16S rRNA bacterial taxa.**

**Supplementary Table 5. Comparison of median values of 16S rRNA bacterial taxa among the four Enterotypes.**

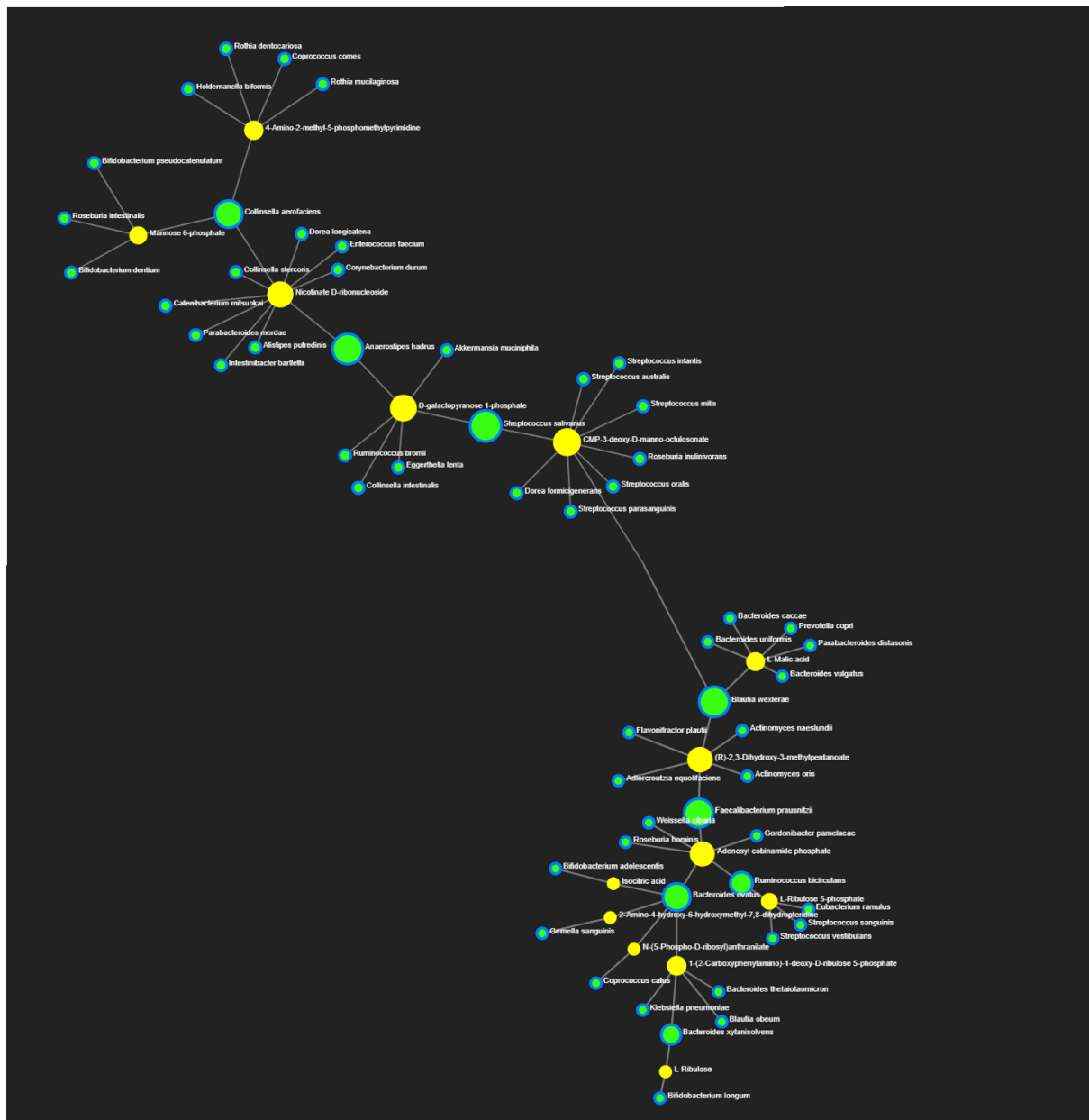
**Supplementary Table 6. Association analyses between *Dorea longicatena* and pathways by linear regression with clinical variables.**

**Supplementary Table 7. Association test using linear regression between clinical variables and pathways.**

**Supplementary Table 8. Association analyses by linear regression with clinical variables.**

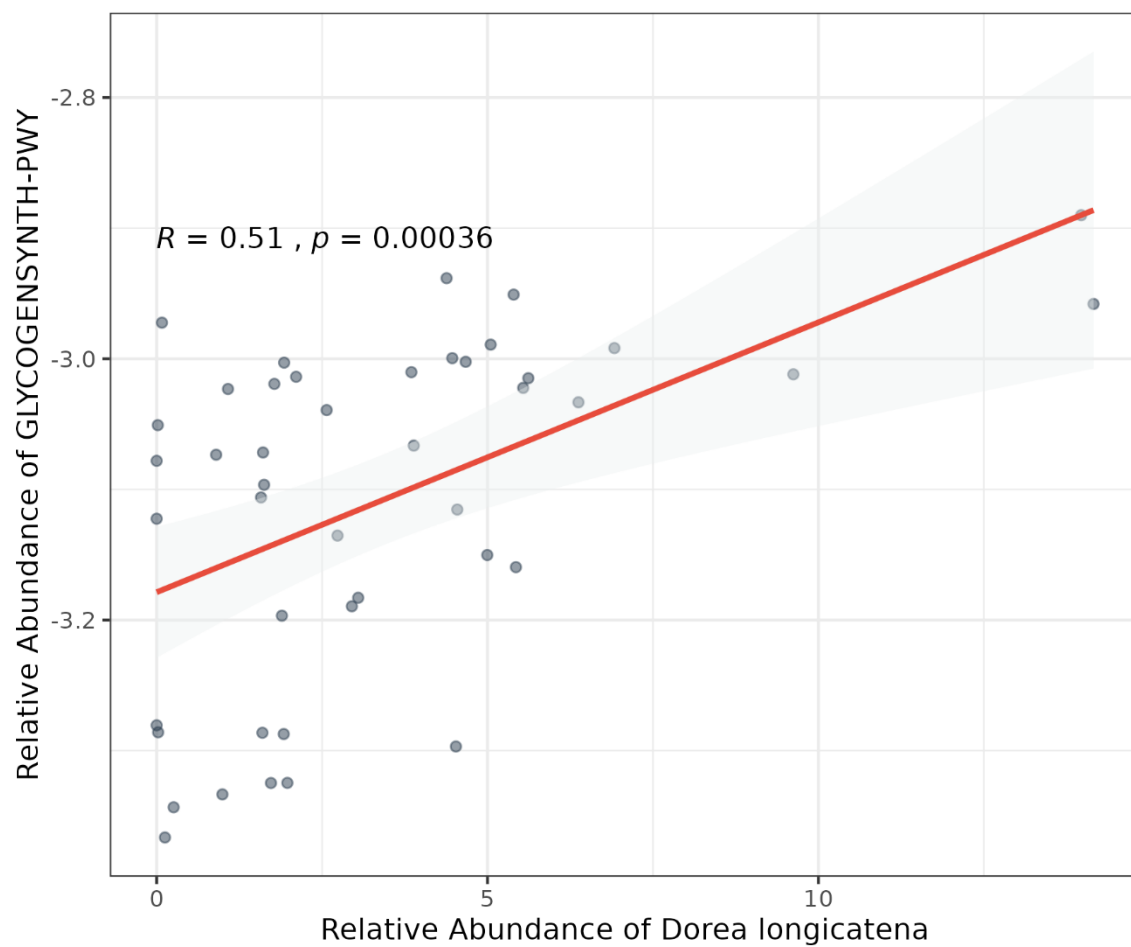


**Supplementary Fig. 1. Comparison of bacterial taxa composition between 16S rRNA and shotgun metagenome data.** **a** Phylum-level composition. **b** Genus-level composition. The upper and lower plots represent the 16S rRNA composition and the metagenome composition, respectively.

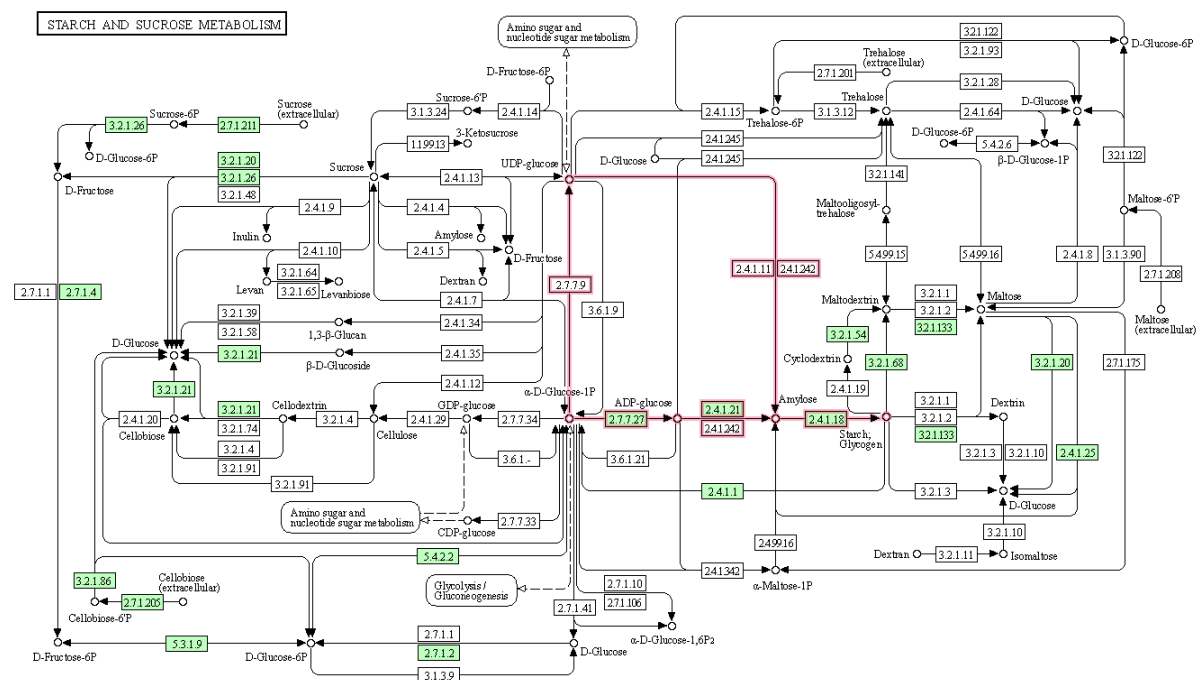


**Supplementary Fig. 2. Network analysis of the prevalent Korean gut microbiota and related host metabolites.** The network illustrates the functional connections among a subset of the 91 prevalent species that show significant metabolic potential (potential score < 0.8) using AGORA GEMS and OmicsNet.





**Supplementary Fig. 4. Scatter plot of *Dorea longicatena* and GLYCOGENSYNTH-PWY.** Correlation between the relative abundance of *D. longicatena* and its metagenomic contribution to the GLYCOGENSYNTH-PWY.



**Supplementary Fig. 5. KEGG pathway map (ko00500 - Starch and sucrose metabolism) matched with GLYCOGENSYNTH-PWY from MetaCyc. The pathway highlighted using pink lines corresponds to KEGG module M00854-dlo00500 (Glycogen biosynthesis, glucose-1 P → glycogen/starch) of the *Dorea longicatena* VE303-06.**



**Supplementary Fig. 6. Linear discriminant analysis (LDA) of microbial taxa associated with clinical metabolic traits. a-g** LDA effect size (LEfSe) plot showing microbial taxa enriched in high-risk versus low-risk groups for various clinical metabolic parameters: waist circumference (**a**), body mass index (**b**), cholesterol (**c**), high density lipoprotein (HDL; **d**), low density lipoprotein (LDL; **e**), glucose (**f**), and triglyceride (**g**).

| Level                            | Overall        |
|----------------------------------|----------------|
| n                                | 1771           |
| Age (mean (SD))                  | 58.05 (11.43)  |
| Sex (%) F                        | 800 (45.2)     |
| Sex (%) M                        | 971 (54.8)     |
| BMI (mean (SD))                  | 23.85 (3.09)   |
| Waist circumference (mean (SD))  | 85.42 (9.25)   |
| Heart rate (mean (SD))           | 72.19 (11.38)  |
| Diastolic BP (mean (SD))         | 74.38 (10.32)  |
| Systolic BP (mean (SD))          | 123.23 (15.62) |
| Percent body fat (mean (SD))     | 26.08 (6.28)   |
| Eye press (Right) (mean (SD))    | 15.54 (2.42)   |
| Eye press (Left) (mean (SD))     | 15.99 (2.38)   |
| Mean DEXA (L1–L4) (mean (SD))    | -0.07 (1.08)   |
| DEXA (Femur neck) (mean (SD))    | -0.29 (0.78)   |
| Total fat (mean (SD))            | 287.82 (68.11) |
| Visceral fat (mean (SD))         | 126.64 (49.32) |
| Calcium (mean (SD))              | 9.34 (0.36)    |
| Phosphorus (mean (SD))           | 3.45 (0.48)    |
| Glucose (mean (SD))              | 99.23 (21.62)  |
| BUN (mean (SD))                  | 14.21 (3.82)   |
| Uric acid (mean (SD))            | 5.53 (1.34)    |
| Cholesterol (mean (SD))          | 196.89 (38.72) |
| Total protein (mean (SD))        | 7.36 (0.39)    |
| Albumin (mean (SD))              | 4.43 (0.26)    |
| Total bilirubin (mean (SD))      | 1.03 (0.40)    |
| Alkaline phosphatase (mean (SD)) | 63.13 (20.10)  |
| AST (mean (SD))                  | 25.19 (10.43)  |
| ALT (mean (SD))                  | 26.12 (17.84)  |
| GGT (mean (SD))                  | 34.94 (38.24)  |
| TFT (free T4) (mean (SD))        | 1.18 (0.16)    |
| TFTTSH (mean (SD))               | 1.99 (4.25)    |
| OH-Vitamin D3 (mean (SD))        | 25.04 (8.78)   |
| Creatinine (mean (SD))           | 0.83 (0.18)    |
| Na (mean (SD))                   | 141.88 (1.87)  |
| K (mean (SD))                    | 4.08 (0.30)    |
| Cl (mean (SD))                   | 104.74 (3.32)  |
| Total CO2 (mean (SD))            | 28.09 (2.74)   |

|                             |                |
|-----------------------------|----------------|
| Triglyceride (mean (SD))    | 110.71 (64.64) |
| HDL cholesterol (mean (SD)) | 60.22 (16.36)  |
| LDL cholesterol (mean (SD)) | 116.85 (35.48) |
| hsCRP (mean (SD))           | 0.12 (0.36)    |
| ESR (mean (SD))             | 14.22 (12.21)  |
| WBC (mean (SD))             | 5.70 (1.66)    |
| RBC (mean (SD))             | 4.72 (0.50)    |
| Hemoglobin (mean (SD))      | 14.44 (1.55)   |
| Hematocrit (mean (SD))      | 43.58 (4.21)   |
| MCV (mean (SD))             | 92.45 (4.05)   |
| RDW (mean (SD))             | 12.64 (0.81)   |
| Platelet (mean (SD))        | 242.90 (57.19) |
| HbA1c (mean (SD))           | 5.88 (0.76)    |
| Insulin (mean (SD))         | 7.94 (2.43)    |
| AFP (mean (SD))             | 3.50 (3.98)    |
| CEA (mean (SD))             | 1.71 (1.15)    |
| PSA (mean (SD))             | 1.42 (1.10)    |
| CA 19-9 (mean (SD))         | 8.47 (10.47)   |
| CA 125 (mean (SD))          | 14.61 (22.31)  |

**Supplementary Table 1. Baseline characteristics of clinical variables.**

| Clinical variables   | P        | Adjusted P |
|----------------------|----------|------------|
| GGT                  | 3.25E-08 | 1.82E-06   |
| Triglyceride         | 2.30E-05 | 0.001      |
| Insulin              | 2.70E-05 | 0.001      |
| Systolic BP          | 4.10E-05 | 0.002      |
| Visceral fat         | 1.42E-04 | 0.007      |
| WBC                  | 0.001    | 0.028      |
| Alkaline phosphatase | 0.002    | 0.077      |
| Glucose              | 0.002    | 0.093      |
| Diastolic BP         | 0.002    | 0.099      |
| Uric acid            | 0.002    | 0.099      |
| BMI                  | 0.003    | 0.130      |
| hsCRP                | 0.004    | 0.167      |
| Total fat            | 0.004    | 0.187      |
| Percent body fat     | 0.004    | 0.188      |
| Heart rate           | 0.006    | 0.233      |
| Albumin              | 0.007    | 0.291      |
| RBC                  | 0.008    | 0.33       |
| Waist circumference  | 0.01     | 0.368      |
| Calcium              | 0.011    | 0.384      |
| ALT                  | 0.01     | 0.384      |
| CA 125               | 0.012    | 0.412      |
| HbA1c                | 0.014    | 0.489      |
| DEXA (Femur neck)    | 0.016    | 0.519      |
| CA 19-9              | 0.016    | 0.522      |
| Hemoglobin           | 0.021    | 0.652      |
| Phosphorus           | 0.033    | 0.964      |
| Eye press (Right)    | 0.558    | 1          |
| Eye press (Left)     | 0.165    | 1          |
| Mean DEXA (L1~L4)    | 0.529    | 1          |
| BUN                  | 0.478    | 1          |
| Cholesterol          | 0.473    | 1          |
| Total protein        | 0.083    | 1          |
| Total bilirubin      | 0.173    | 1          |
| AST                  | 0.254    | 1          |
| TFT (free T4)        | 0.36     | 1          |
| TFTTSH               | 0.911    | 1          |
| OH-Vitamin D3        | 0.988    | 1          |
| Creatinine           | 0.09     | 1          |
| Na                   | 0.457    | 1          |
| K                    | 0.324    | 1          |
| Cl                   | 0.755    | 1          |
| Total CO2            | 0.519    | 1          |
| HDL cholesterol      | 0.597    | 1          |
| LDL cholesterol      | 0.041    | 1          |
| ESR                  | 0.183    | 1          |
| Hematocrit           | 0.051    | 1          |
| MCV                  | 0.284    | 1          |
| RDW                  | 0.204    | 1          |
| Platelet             | 0.805    | 1          |
| AFP                  | 0.536    | 1          |
| CEA                  | 0.234    | 1          |
| PSA                  | 0.12     | 1          |

**Supplementary Table 2. Results of statistical analysis evaluating the impact of Enterotypes on clinical variables.**

|                            | Enterotype 1                    | Enterotype 2                    | Enterotype 3                    | Enterotype 4                    | ANOVA    |          |
|----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|----------|----------|
| n                          | 633                             | 478                             | 348                             | 312                             | P        | FDR      |
| <b>Waist circumference</b> | 4.44 [4.37;4.52]                | 4.45 [4.37;4.51]                | 4.43 [4.35;4.49]                | 4.48 [4.42;4.54]                | 2.41E-08 | 1.28E-06 |
| <b>Heart rate</b>          | 2.05 [2.03;2.06]                | 2.05 [2.03;2.07]                | 2.05 [2.03;2.06]                | 2.05 [2.03;2.06]                | 0.000303 | 0.011214 |
| <b>Diastolic BP</b>        | 27.91 [26.25;29.53]             | 28.18 [25.97;30.07]             | 27.36 [25.40;29.27]             | 28.46 [26.53;30.33]             | 3.84E-05 | 0.001638 |
| <b>Systolic BP</b>         | 4.81 [4.72;4.90]                | 4.81 [4.72;4.89]                | 4.78 [4.69;4.87]                | 4.85 [4.74;4.92]                | 1.96E-06 | 9.78E-05 |
| Percent body fat           | 32.94 [27.56;39.95]             | 33.57 [27.84;39.95]             | 33.50 [27.43;39.24]             | 32.39 [27.22;38.19]             | 0.49649  | 1        |
| Eye press (Right)          | 15.34 [14.00;17.00]             | 15.00 [14.00;17.00]             | 15.00 [14.00;17.00]             | 15.48 [14.00;17.00]             | 0.73642  | 1        |
| Eye press (Left)           | 2.77 [2.64;2.85]                | 2.77 [2.64;2.83]                | 2.77 [2.64;2.83]                | 2.77 [2.67;2.89]                | 0.48536  | 1        |
| Mean Dexa (L1–L4)          | -0.86 [-1.71;-0.02]             | -1.05 [-1.61;-0.31]             | -0.84 [-1.79;0.10]              | -0.97 [-1.65;-0.22]             | 0.303    | 1        |
| DEXA (Femur neck)          | -0.20 [-0.64;0.11]              | -0.22 [-0.72;0.09]              | -0.25 [-0.72;0.00]              | -0.20 [-0.64;0.07]              | 0.27695  | 1        |
| <b>Total fat</b>           | 280.95<br>[248.27;320.28]       | 282.72<br>[247.30;322.58]       | 277.47<br>[237.48;310.91]       | 299.68<br>[257.34;335.11]       | 1.49E-05 | 0.000687 |
| <b>Visceral fat</b>        | 14.44 [12.77;16.37]             | 14.56 [12.71;16.39]             | 13.84 [12.08;15.67]             | 15.61 [13.40;17.12]             | 1.01E-09 | 5.46E-08 |
| Calcium                    | 2.98 [2.94;3.02]                | 2.99 [2.96;3.02]                | 2.97 [2.94;3.00]                | 2.97 [2.94;3.00]                | 0.000229 | 0.008708 |
| Phosphorus                 | 3.40 [3.20;3.80]                | 3.45 [3.10;3.80]                | 3.40 [3.10;3.70]                | 3.40 [3.10;3.70]                | 0.13157  | 1        |
| <b>Glucose</b>             | 4.55 [4.48;4.64]                | 4.54 [4.48;4.65]                | 4.54 [4.47;4.62]                | 4.58 [4.51;4.70]                | 0.000215 | 0.008374 |
| BUN                        | 2.71 [2.48;2.83]                | 2.70 [2.48;2.83]                | 2.71 [2.56;2.89]                | 2.71 [2.56;2.89]                | 0.004256 | 0.127674 |
| <b>Uric acid</b>           | 2.51 [2.26;2.72]                | 2.54 [2.29;2.77]                | 2.40 [2.18;2.64]                | 2.52 [2.29;2.72]                | 1.68E-05 | 0.000757 |
| Cholesterol                | 5.27 [5.12;5.41]                | 5.26 [5.12;5.41]                | 5.27 [5.12;5.39]                | 5.27 [5.14;5.39]                | 0.96966  | 1        |
| Total protein              | 2.00 [1.96;2.03]                | 2.00 [1.96;2.03]                | 1.99 [1.95;2.03]                | 2.00 [1.96;2.03]                | 0.015994 | 0.430056 |
| <b>Albumin</b>             | 6.12 [5.95;6.45]                | 6.29 [5.95;6.62]                | 6.12 [5.79;6.29]                | 6.12 [5.87;6.29]                | 1.20E-05 | 0.000576 |
| Total bilirubin            | 0.47 [0.42;0.51]                | 0.45 [0.42;0.51]                | 0.47 [0.42;0.51]                | 0.45 [0.42;0.51]                | 0.94031  | 1        |
| Alkaline phosphatase       | 4.11 [3.91;4.29]                | 4.14 [3.97;4.29]                | 4.06 [3.89;4.26]                | 4.13 [3.93;4.26]                | 0.006191 | 0.173345 |
| AST                        | 1.15 [1.14;1.16]                | 1.15 [1.14;1.17]                | 1.15 [1.14;1.16]                | 1.15 [1.14;1.17]                | 0.21967  | 1        |
| ALT                        | 3.09 [2.77;3.40]                | 3.14 [2.77;3.47]                | 3.00 [2.64;3.30]                | 3.04 [2.80;3.40]                | 0.00267  | 0.082782 |
| <b>GGT</b>                 | 3.14 [2.83;3.61]                | 3.22 [2.89;3.74]                | 3.00 [2.71;3.33]                | 3.26 [2.94;3.66]                | 1.55E-11 | 8.54E-10 |
| TFT (free T4)              | 0.15 [0.08;0.22]                | 0.17 [0.06;0.24]                | 0.16 [0.08;0.23]                | 0.17 [0.09;0.25]                | 0.36042  | 1        |
| TFTTSH                     | 0.45 [0.19;0.83]                | 0.43 [0.09;0.78]                | 0.43 [0.18;0.71]                | 0.41 [0.19;0.73]                | 0.46153  | 1        |
| OH-Vitamin D3              | 3.18 [2.92;3.38]                | 3.18 [3.00;3.35]                | 3.22 [2.98;3.41]                | 3.16 [2.92;3.34]                | 0.42693  | 1        |
| Creatinine                 | -0.21 [-0.36;-0.06]             | -0.21 [-0.37;-0.04]             | -0.25 [-0.39;-0.09]             | -0.16 [-0.30;-0.06]             | 0.005157 | 0.149565 |
| Na                         | 10224.00<br>[10081.50;10367.50] | 10224.00<br>[10081.50;10367.50] | 10224.00<br>[10081.50;10367.50] | 10224.00<br>[10081.50;10367.50] | 0.87829  | 1        |
| K                          | 4.10 [3.90;4.30]                | 4.10 [3.90;4.30]                | 4.10 [3.90;4.20]                | 4.10 [3.90;4.30]                | 0.53136  | 1        |
| Cl                         | 5617.50<br>[5407.50;5831.50]    | 5617.50<br>[5407.50;5831.50]    | 5617.50<br>[5407.50;5831.50]    | 5617.50<br>[5407.50;5831.50]    | 0.5861   | 1        |
| Total CO2                  | 315.56<br>[275.43;358.26]       | 315.56<br>[275.43;358.26]       | 315.56<br>[295.17;358.26]       | 315.56<br>[289.38;358.26]       | 0.66764  | 1        |
| <b>Triglyceride</b>        | 95.00 [69.00;131.00]            | 102.00<br>[75.00;144.00]        | 84.00 [62.50;115.50]            | 97.50 [72.00;141.50]            | 1.15E-07 | 5.87E-06 |
| HDL cholesterol            | 4.06 [3.89;4.25]                | 4.08 [3.89;4.23]                | 4.09 [3.91;4.28]                | 4.01 [3.85;4.20]                | 0.015928 | 0.430056 |
| LDL cholesterol            | 4.74 [4.52;4.94]                | 4.72 [4.48;4.91]                | 4.75 [4.54;4.93]                | 4.73 [4.52;4.96]                | 0.55604  | 1        |
| hsCRP                      | 0.04 [0.01;0.09]                | 0.05 [0.01;0.11]                | 0.02 [0.01;0.08]                | 0.05 [0.01;0.10]                | 0.002355 | 0.077718 |
| ESR                        | 2.20 [1.77;2.55]                | 2.13 [1.77;2.59]                | 2.20 [1.77;2.59]                | 2.20 [1.88;2.51]                | 0.97956  | 1        |

|                   |                              |                              |                              |                              |          |          |
|-------------------|------------------------------|------------------------------|------------------------------|------------------------------|----------|----------|
| <b>WBC</b>        | 1.67 [1.51;1.85]             | 1.72 [1.56;1.91]             | 1.65 [1.49;1.80]             | 1.71 [1.55;1.87]             | 6.02E-05 | 0.00247  |
| <b>RBC</b>        | 4.70 [4.40;5.07]             | 4.74 [4.39;5.12]             | 4.58 [4.27;4.96]             | 4.79 [4.49;5.07]             | 1.29E-05 | 0.000607 |
| <b>Hemoglobin</b> | 26.14 [23.89;28.89]          | 26.14 [23.89;28.89]          | 25.23 [23.22;28.20]          | 26.82 [24.56;28.89]          | 3.81E-05 | 0.001638 |
| <b>Hematocrit</b> | 43.40 [40.70;46.70]          | 43.50 [40.70;46.90]          | 42.70 [39.65;45.80]          | 44.25 [41.70;46.75]          | 0.000134 | 0.005379 |
| MCV               | 4333.30<br>[4112.74;4588.32] | 4351.94<br>[4140.00;4588.32] | 4398.72<br>[4185.62;4612.30] | 4342.62<br>[4149.10;4550.08] | 0.074023 | 1        |
| RDW               | 0.50 [0.50;0.50]             | 0.50 [0.50;0.50]             | 0.50 [0.50;0.50]             | 0.50 [0.50;0.50]             | 0.058927 | 1        |
| Platelet          | 5.46 [5.33;5.63]             | 5.49 [5.33;5.64]             | 5.46 [5.32;5.61]             | 5.46 [5.31;5.60]             | 0.44322  | 1        |
| <b>HbA1c</b>      | 0.49 [0.49;0.49]             | 0.49 [0.49;0.49]             | 0.49 [0.49;0.49]             | 0.49 [0.49;0.49]             | 0.000676 | 0.024336 |
| <b>Insulin</b>    | 2.02 [1.89;2.17]             | 2.04 [1.93;2.19]             | 1.97 [1.86;2.11]             | 2.07 [1.92;2.22]             | 9.93E-08 | 5.16E-06 |
| AFP               | 0.89 [0.81;0.95]             | 0.89 [0.82;0.95]             | 0.89 [0.81;0.96]             | 0.90 [0.82;0.97]             | 0.62151  | 1        |
| CEA               | 1.50 [0.90;2.10]             | 1.60 [1.00;2.30]             | 1.50 [0.90;2.20]             | 1.50 [1.00;2.30]             | 0.23074  | 1        |
| PSA               | 1.39 [0.93;1.69]             | 1.33 [0.87;1.67]             | 1.48 [1.04;1.81]             | 1.35 [0.69;1.73]             | 0.002019 | 0.068643 |
| CA 19-9           | 4.30 [1.90;10.70]            | 5.15 [2.30;12.30]            | 5.20 [2.20;13.95]            | 4.30 [1.80;8.90]             | 0.017391 | 0.434775 |
| CA 125            | 2.54 [2.23;2.83]             | 2.62 [2.25;2.93]             | 2.46 [2.16;2.74]             | 2.51 [2.29;2.83]             | 0.002559 | 0.081888 |
| BMI               | 3.16 [3.08;3.25]             | 3.16 [3.08;3.25]             | 3.15 [3.06;3.23]             | 3.20 [3.13;3.27]             | 1.55E-06 | 7.88E-05 |

**Supplementary Table 3. Comparison of median values of clinical variables among the four Enterotypes.**

| Phenotype | Taxa                                    | Beta     | FDR_TMAT_F16 |
|-----------|-----------------------------------------|----------|--------------|
| PC1       | <i>Dorea_longicatena</i>                | 0.045004 | 0.000443     |
| PC1       | <i>Clostridium_glycyrrhizinilyticum</i> | 0.038008 | 0.001873     |
| PC1       | <i>Ruminococcus_gnavus</i>              | 0.02934  | 0.019669     |
| PC1       | <i>Dorea_formicigenerans</i>            | 0.029287 | 0.022893     |
| PC1       | <i>Ruminococcus_faecis</i>              | 0.028765 | 0.024726     |
| PC1       | <i>Blautia_wexlerae</i>                 | 0.026248 | 0.041047     |
| PC1       | <i>Holdemanella_biformis</i>            | 0.025713 | 0.041047     |
| PC1       | <i>Lactococcus_lactis</i>               | -0.02701 | 0.029664     |
| PC1       | <i>Akkermansia_muciniphila</i>          | -0.02787 | 0.024726     |
| PC1       | <i>Intestinibacter_bartlettii</i>       | -0.03019 | 0.013833     |
| PC1       | <i>Ruminococcus_bromii</i>              | -0.03296 | 0.012977     |
| PC1       | <i>Bacteroides_uniformis</i>            | -0.03539 | 0.007136     |
| PC1       | <i>Ruminococcus_lactaris</i>            | -0.03548 | 0.007778     |
| PC1       | <i>Anaerostipes_hadrus</i>              | -0.0535  | 9.80E-06     |
| PC4       | <i>Ruminococcus_gnavus</i>              | -0.08865 | 0.024152     |
| PC4       | <i>Eggerthella_lenta</i>                | -0.10639 | 0.007052     |
| PC5       | <i>Blautia_faecis</i>                   | 0.139343 | 0.003968     |
| PC5       | <i>Turicibacter_sanguinis</i>           | 0.101649 | 0.031565     |
| PC5       | <i>Eggerthella_lenta</i>                | -0.09409 | 0.048332     |
| PC5       | <i>Clostridium_glycyrrhizinilyticum</i> | -0.1105  | 0.019669     |

**Supplementary Table 4. Association test using TMAT between principal components (PCs) and 16S rRNA bacterial taxa.**