Supplementary Material

**Table S1.** Characteristics of gut microbiota profiles studied in PKU.

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| **Reference** | **Cohort** | **Mean Age (years)** | **Methods and Platforms** | **Results****(PKU vs Controls)** |
| Mancilla et al., 2021 | 11PKU21 HCa | 33.0 ± 1.9829.0 ± 3.07 | 16S rRNA sequencing: V4 hypervariable region; MiSeq Illumina platform; VSEARCH v2.8.1 and EzBiocloud | ↑ *Clostridium* spp.↓ *Faecalibacterium* and *Blautia* spp. |
| Bassanini et al., 2019 | 21 PKU21 MHPd | 8.0 ± 3.410.0 ± 3.5 | 16S rRNA sequencing: V3-V4 hypervariable regions; MiSeq Illumina platform; Version 13.8  | ↓α-diversitybβ- diversityc (*p*≤ 0.05)↑*Lachnospiraceae (other), Blautia* and *Clostridium* spp.↓*Ruminococcaceae (other), Faecalibacterium* and *Dialister* spp. |
|  |  |  | SCFAe quantification: Gas chromatography  | ↓Total SCFA and butyrate (in feces) |
|  |  |  |  |  |
| Pinheiro de Oliveira et al., 2016 | 8 PKU10 HCa | 4.24 ± 1.746.06 ± 1.78 | 16S rRNA sequencing: V4 hypervariable regions; IonTorrent platform; Version 13.8 | ↓α-diversitybβ- diversityc (*p*≤ 0.003)↑ Bacteroidetes, Verrucomicrobia↓ Firmicutes↑ Peptostreptococcaceae, *Akkermansia,Prevotella* spp.↓*Coprococcus, Dorea, Lachnospira, Odoribacter, Ruminococcus* and *Veillonella* |

aHC, healthy controls; bα-diversity, the diversity in the bacterial composition within each sample; cβ- diversity, the diversity between sample groups; dMHP, mild hyperphenylalaninemia patients as controls; eSCFA, short-chain fatty acids.

**Table S2.** Characteristics of gut microbiota profiles studied in GSD.

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| **Reference** | **Cohort** | **Mean Age (years)** | **Methods and Platforms** |  **Results** **(GSD vs HCa)**  |
| Ceccarini et al., 2020 | 9 GSD(Ia=4, Ib=5)12 HCa | 27.7 ± 12.5 4.7 ± 7.9 | 16S rRNA sequencing: V3-V4 hypervariable region; MiSeq Illumina platform; Greengenes Version 13.8SCFAd quantification:Gas chromatography | ↓α-diversitybβ- diversityc (*p*≤ 0.004)↑ Proteobacteria↑*Enterobacteriaceae* and *Veillonellaceae*↓*Ruminococcaceae*↑*Escherichia* spp.↓*Ruminococcus*, *Faecalibacterium* and *Oscillospira* spp.↑ Total SCFA, acetate and propionate (in feces) |
| Colonetti et al., 2019 | 24 GSD(Ia=15, Ib=5, III=1, IXα=3) 16 HCa | 1212.5 | 16S rRNA sequencing: V4 hypervariable regions; IonTorrent platform; Version 13.8  | ↓α-diversitybβ- diversityc (*p*≤ 0.003)↑ Proteobacteria and Actinobacteria↑*Lactobacillus* and *Escherichia/Shigella* ↓*Alistipes, Faecalibacterium* and *Roseburia* |

aHC, healthy controls; bα-diversity, the diversity in the bacterial composition within each sample; cβ- diversity, the diversity between sample groups; dSCFA, short-chain fatty acids.