**Supplementary Table 1. Evidence for *Fto* in the regulation of emotional responses and behaviors**

| Reference | Model | Disease/Phenotype | Effects |
|---|---|---|---|
| Br J Psychiatry, 2017[1] | rs9939609 | Obesity and depression | Depression increases the effect of *Fto* on BMI |
| J Neurosci, 2016[2] | Lentiviral-mediated knockdown of *Fto* in the mPFC | Memory processes | Associates with memory processes in mice |
| Neuron,2018[3] | Conditional knockout in forebrain excitatory neurons | fear memory | Associates with memory processes after acute stress |
| J Affect Disord, 2016[4] | rs9939609 | *Fto* and MDD | SNP rs9939609 within *Fto* is not associated with MDD |
| J Clin Psychiatry, 2015[5] | rs9939609 | Obesity and MDD | SNP rs9939609 within *Fto* is not associated with depression status |
| Nutrients, 2014[6] | *Fto* polymorphisms | *Fto* and psychological health | The risk alleles of the *Fto* polymorphisms are associated with poorer psychological health |
| Mol Psychiatry, 2012[7] | *Fto* variants | *Fto* for mood disorders and obesity | Having a history of depression mediates the effect of *Fto* on BMI |
| Mol Psychiatry, 2013[8] | rs9939609 | *Fto* and depression | *Fto* rs9939609 A variant may be associated with a lower risk of depression |
| Nat Neurosci, 2013[9] | *Fto*-deficient mice | Dopaminergic midbrain circuitry | *Fto* impairs D2R and D3R-dependent control of neuronal activity and behavioral responses |

Abbreviations: BMI: body mass index; MDD: major depressive disorder; SNP: single nucleotide polymorphism

**References:**


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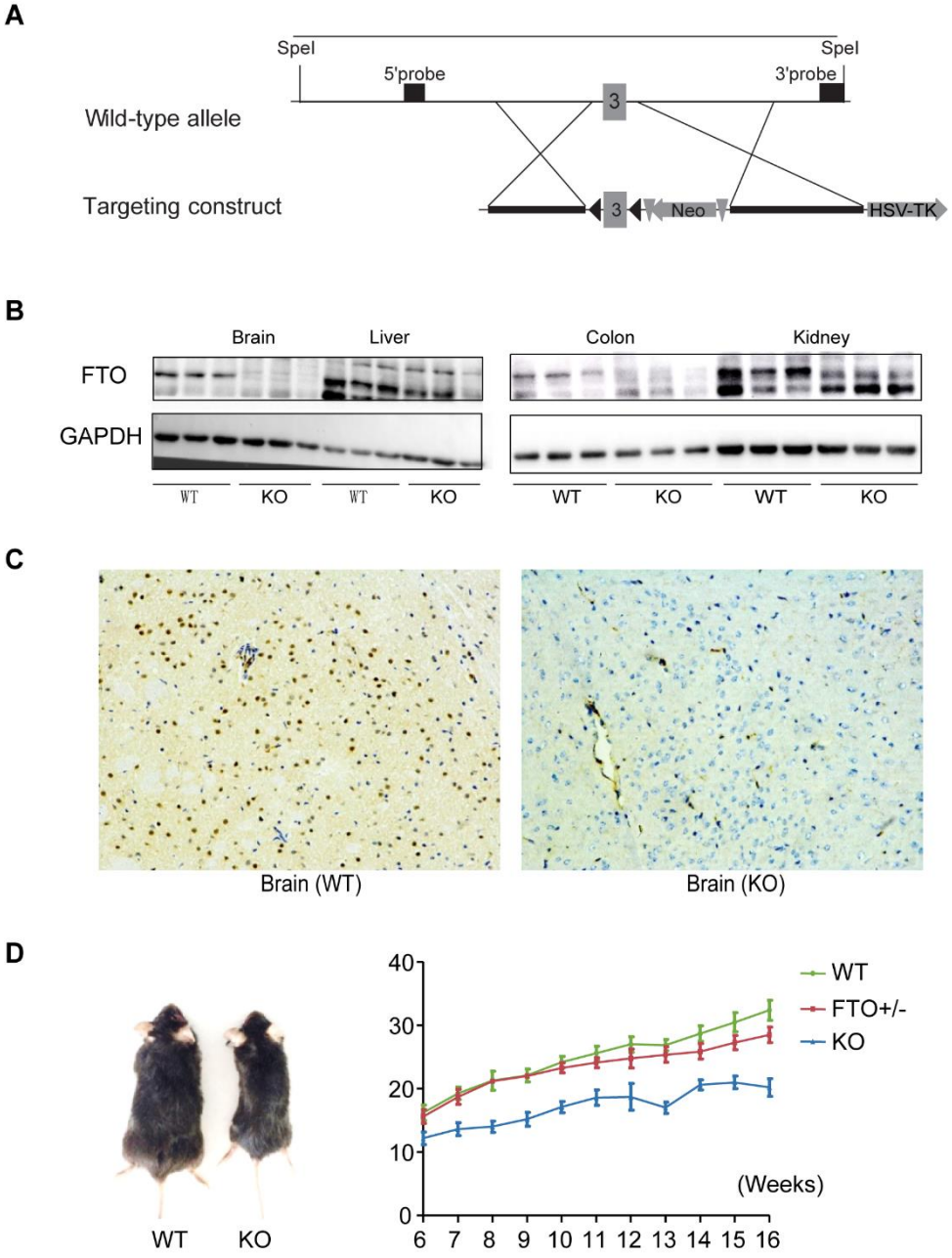


**Figure S1. Global knockout of *Fto* affects growth and causes weight loss.**

(A) Strategy for global knockout of *Fto* in mice. (B) Western blotting results. (C) Immunohistochemical staining for *Fto* in the hypothalamus of WT and KO mice. (D) Global knockout of *Fto* affects growth and causes weight loss. KO: knockout; WT: wild-type.

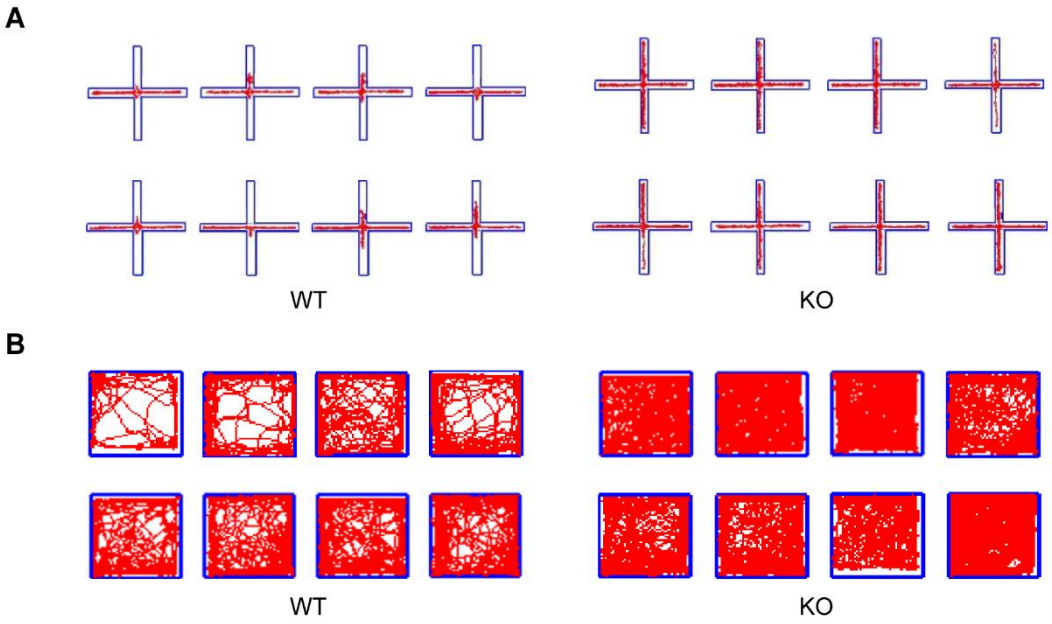


**Figure S2. *Fto* regulates mouse behavior.**

(A). Motion tracks in the EPM test. (B) Motion tracks in the OFT. EPM: elevated plus maze; OFT: open-field test. KO: knockout; WT: wild-type

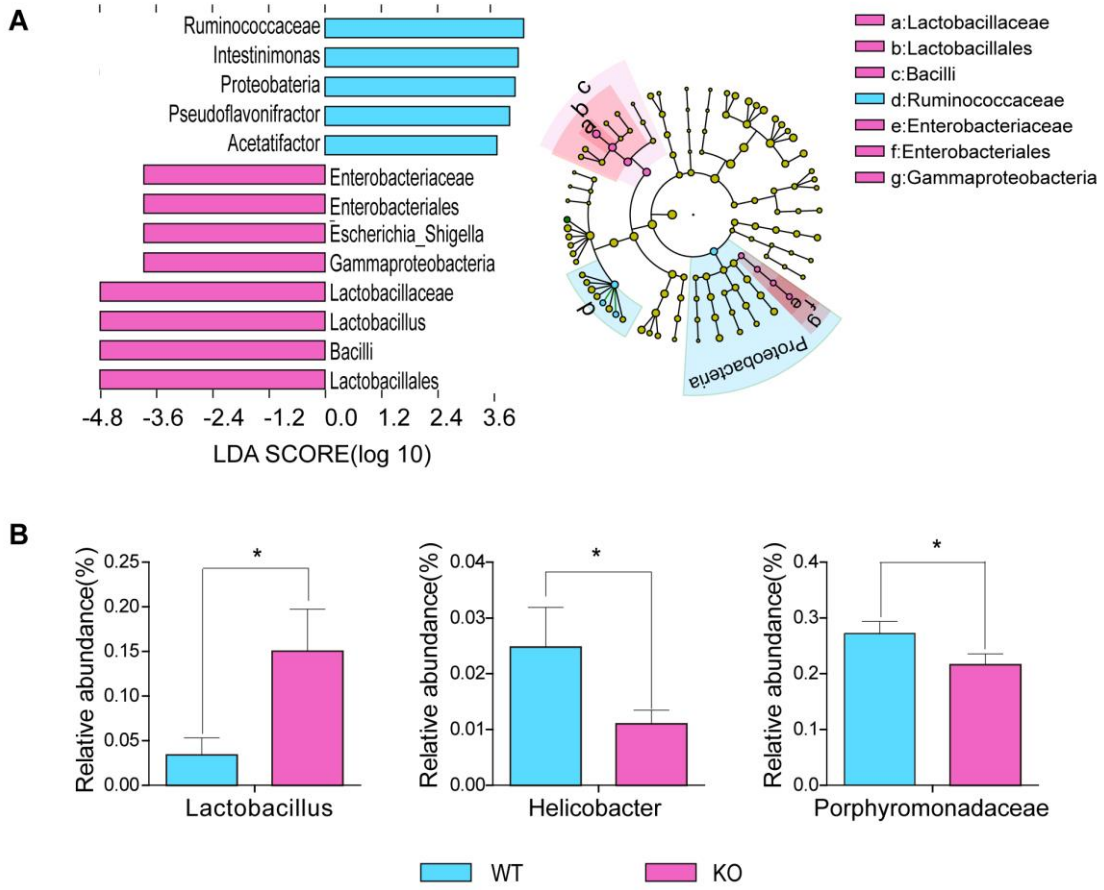


**Figure S3. Lefse analysis of microbiomes.**

(A)The LDA score represents log changes in relative bacterial family representation. (B) Comparison of *Lactobacillus*, *Helicobacter* and Porphyromonadaceae. LDA: linear discriminant analysis; KO: knockout; WT: wild-type.

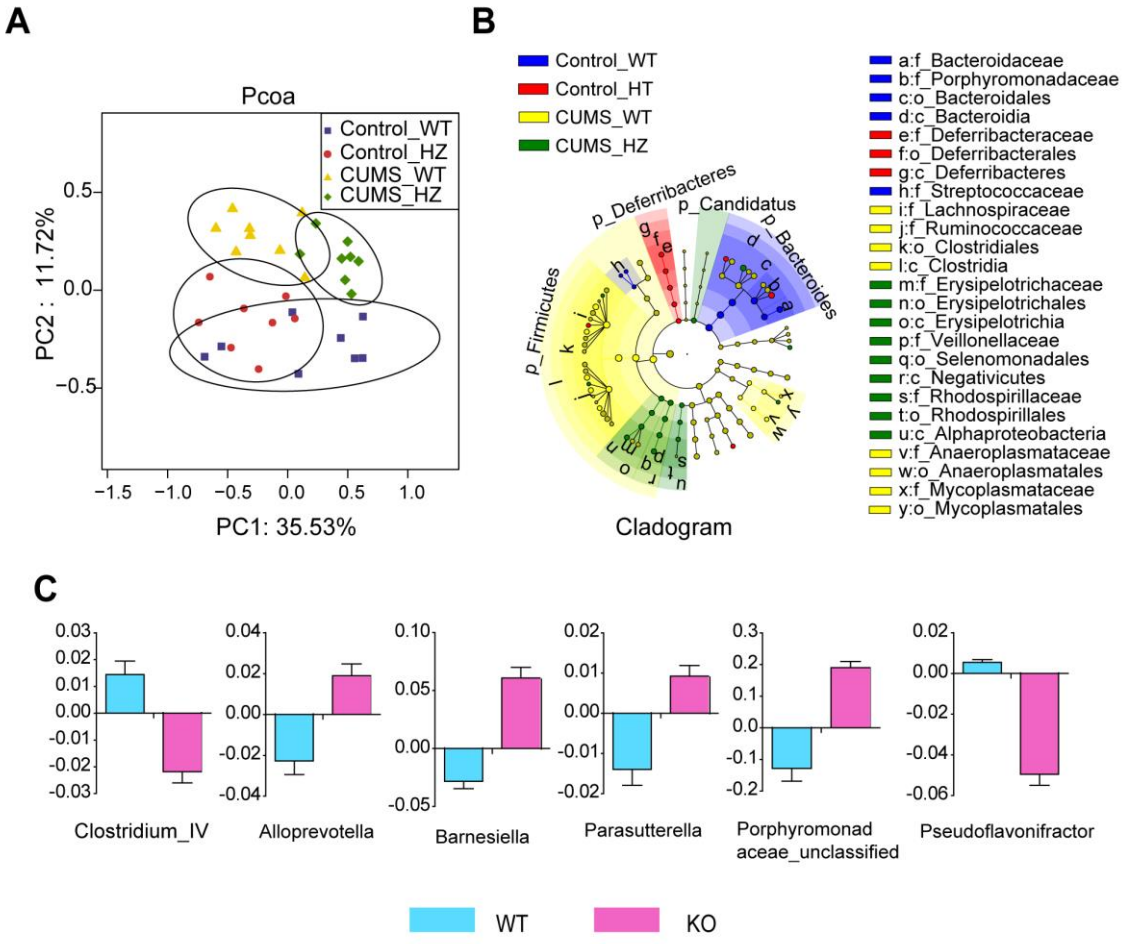


**Figure S4. *Fto* deficiency against CUMS-induced dysbiosis of intestinal microbiota.**
(A) PCoA plots based on the Fast UniFrac distance metric were used to compare the changes in microbiota composition between WT and HZ mice before and after CUMS. Microbiota communities were altered in all four animal groups (WT, n=8; HZ, n=8; WT+CUMS, n=8; HZ+CUMS, n=8). (B) Lefse analysis of microbiome among the four groups. (C) Taxonomic shifts at the genus level before and after CUMS in the two main groups. Taxonomic in C presented a significant different abundance before and after CUMS in WT group according to the paired two-tailed Student's *t*-test ($P<0.05$). The bar above X axis represented rise in taxonomic after CUMS, on the contrary, bar below X axis represented down in taxonomic after CUMS. In addition, we showed the variation trend in HZ group. CUMS: chronic unpredictable mild stress; HZ: heterozygous; PCoA: principal correlation analysis; WT: wild-type.