**Supplemental Figure 1.** Generation of Sfrp4−/− mice. (A) Sfrp4−/− mice were generated by homologous recombination using Regeneron’s VelociGene technology, as described in the Method section. Cassette insertion deleted a 8.9 Kb segment containing all six murine Sfrp4 exons with the LacZ fused in frame just after Sfrp4’s ATG. (B) Relative mRNA expression of Sfrp4 in visceral (epididymal) white adipose tissue (WAT) and bone (femur) from wildtype (WT) and Sfrp4−/− (KO) mice (n=8 per group). (C) mRNA expression of Sfrp1-3 and 5 genes in the hypothalamus of WT and KO mice at 36 weeks of age and after 19 weeks on a high-fat diet. Results expressed in RPKM (n=8 per group). (D) Epdr1 mRNA expression in tissues from C57BL/6 mice (n=6 per group, except spleen which had 5 mice). (E) Expression of Epdr1 in the hypothalamus of the same cohort as (C). Values are mean ± SEM. ****p < 0.0001.

**Supplemental Figure 2.** Histology and LacZ staining in femur from Sfrp4−/− mouse. (A) Whole femur from 12-week-old male Sfrp4−/− mouse on regular chow diet showing cortical bone staining in osteoblasts and periosteum. (B) 5X magnification of the staining in (A). (C) LacZ staining suggesting Sfrp4 expression in areas of the bone marrow. Images are representative of 5 animals.

**Supplemental Figure 3.** Energy expenditure, food intake and locomotor activity in chow-fed Sfrp4−/− mice. Energy expenditure (A), food intake (B) and locomotor activity (C) of male Sfrp4−/− mice on regular chow diet at 9 weeks of age. Energy expenditure was normalized to body weight. All groups had 8 animals.

**Supplemental Figure 4.** Energy expenditure of male Sfrp4−/− mice on chow diet (A-D) and after 12 weeks of high-fat diet feeding (E-H) was correlated with body weight, lean mass, fat mass and bone mass by ANCOVA. While there was no significant difference in the contribution of any tissue, the Sfrp4−/− mice showed decreased energy expenditure on a high-fat diet when correlated to both body weight and all three individual tissues. All groups had 8 animals.
Supplemental Figure 5. Hypothalamic expression of WNT ligands and receptors in Sfrp4^−/− mice. Wnt ligand (A) or Wnt receptor or binding protein (B) mRNA expression in hypothalami from wildtype (WT) or Sfrp4^−/− (KO) mice at 36 weeks of age and on a high-fat diet for 19 weeks (n=8 per group). Results are expressed in reads per kilobase per million (RPKM). Values are mean ± SEM.
A: Energy Expenditure

B: Food Intake

C: Locomotor Activity

**Energy Expenditure**

- KCal/kg/hr vs. Time (hr)
- WT vs. KO

**Food Intake**

- Grams vs. Time (hr)
- WT vs. KO

**Locomotor Activity**

- Counts vs. Time (hr)
- WT vs. KO

**Body Weight (g)**

- kJ/hr vs. Body Weight (g)
- WT vs. KO

**Light vs. Dark**

- Grams
- Counts (x 10^3)
A) Body Weight
B) Lean Mass
C) Fat Mass
D) Bone Mass

Chow

Time (hr) vs. kCal/kg/hr

WT vs. KO

E) Body Weight
F) Lean Mass
G) Fat Mass
H) Bone Mass

High Fat Diet

Time (hr) vs. kCal/kg/hr

WT vs. KO

Body Weight (g) vs. kJ/hr

Lean Mass (g) vs. kJ/hr

Fat Mass (g) vs. kJ/hr

Bone Mass (g) vs. kJ/hr