Supplementary Table 1. Organ weight and hepatic lipid content

| Diet       | Genotype | SD        | Ptpn6<sup>fl</sup> | Ptpn6<sup>fl-KO</sup> | Ptpn6<sup>fl</sup> | Ptpn6<sup>fl-KO</sup> |
|------------|----------|-----------|---------------------|----------------------|---------------------|----------------------|
|            |          |           |                     |                      |                     |                      |
| PCAT (g)   | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | 0.014    | 0.011     | 0.035               | 0.021                | ±                   | ±                    |
|            | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
| IWAT (g)   | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | 0.004    | 0.005     | 0.010<sup>^</sup>    | 0.007<sup>^</sup>    | ±                   | ±                    |
|            | 0.23     | 0.27      | 0.79                | 0.85                 | ±                   | ±                    |
| PWAT (g)   | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | 0.03     | 0.04      | 0.12<sup>^</sup>     | 0.09<sup>^</sup>     | ±                   | ±                    |
| EWAT (g)   | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | 0.37     | 0.52      | 2.30                | 2.57                 | ±                   | ±                    |
| Gastroc (g)| ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | 0.25     | 0.27      | 0.27                | 0.26                 | ±                   | ±                    |
| BAT (g)    | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | 0.07     | 0.07      | 0.15                | 0.14                 | ±                   | ±                    |
| Liver (g)  | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | 0.89     | 0.96      | 1.55                | 1.76                 | ±                   | ±                    |
| Triglyceride| ±       | ±         | ±                   | ±                    | ±                   | ±                    |
| (mg/g liver)| 9.18    | 12.75     | 36.15               | 42.18                | ±                   | ±                    |
| Total      | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
| Cholesterol| ±       | ±         | ±                   | ±                    | ±                   | ±                    |
| (mg/g liver)| 1.19    | 1.37      | 3.22                | 3.95                 | ±                   | ±                    |
|            | ±        | ±         | ±                   | ±                    | ±                   | ±                    |
|            | ±        | ±         | ±                   | ±                    | ±                   | ±                    |

SD − Standard diet; HFD − High fat diet
PCAT − Pericardiac adipose tissue; IWAT − Inguinal white adipose tissue
PWAT − Perirenal white adipose tissue; EWAT − Epididymal white adipose tissue
Gastroc − Gastrocnemius skeletal muscles; BAT − Brown adipose tissue

Data presented as Mean ± SEM, n = 6/genotype and diet group

Genotype Difference: * P < 0.05 and *** P < 0.005

Diet Effect: * P < 0.05 and ** P < 0.005
Supplementary Figure 1. Production scheme of Ptpn6/f/f and Ptpn6H-KO mice
1) Homozygous Ptpn6-floxed mice (Ptpn6/f/f) were bred with homozygous Alb-Cre mice to yield hemizygous mice for both Ptpn6-LoxP and Alb-Cre; 2) hemizygous mice were mated with siblings to produce 8 possible mouse genotypes at approximately 12.5% each, including homozygous Ptpn6-floxed mice with no Alb-Cre (Ptpn6/f/f) and Ptpn6H-KO mice with either homo- or hemizygous Alb-Cre; 3) Ptpn6/f/f and hemizygous Alb-Cre Ptpn6H-KO mice were finally bred to generate exclusively half Ptpn6/f/f and half hemizygous Alb-Cre Ptpn6H-KO offsprings used for all diet studies.
Supplementary Figure 2. Glucose turnover rates during HIEG clamp studies
Ra (rate of appearance) and Rd (rate of disappearance) glucose turnover rates during the hyperinsulinemic-euglycemic clamp studies were assessed for both Ptpn6f/f and Ptpn6H-KO mice fed SD or HFD for 8 weeks (n = 6-10/genotype and diet group, ^^ P < 0.01 and ^^^ p < 0.005 diet effect, *** p < 0.005 genotype difference)

Supplementary Figure 3. Insulin signaling through IRS-1 and IRS-1
Whole liver lysate was immunoprecipitated for IRS-1 and IRS-2 followed by western blot analysis of phosphorylation on tyrosine residues (pY), total IRS-1 and IRS-2, and associated p85 subunit of PI3K (n = 2/insulin-stimulated genotype or diet group)