**Supplementary material**

**Fig S1. Relationship between body weight and daily food consumption in female and male DO mice.**

**Fig S2. Pairwise correlation among all physiological traits.**

Pearson’s correlation is shown between physiological traits for female (**A**) and male (**B**) DO mice. Circle color (blue, positive; red, negative) and diameter denote correlation strength.

**Fig S3. Motif for Hnf4a is enriched in transcripts mapping to Chr 2 eQTL hotspot.**

PSCAN (<http://159.149.160.88/pscan/>) was used to determine if a motif was enriched in the promoter region of the 206 transcripts that map to the Chr 2 hotspot. A position weight matrix (PWM) associated with Hnf4a binding is illustrated.

**Fig S4. Mediation predicts *Il6st* as a driver at the Chr 13 eQTL hotspot.**

**A**) Genome-wide LOD profile for the PC1 of the eQTL hotspot at ~112 Mbp on Chr 13. **B**) Allele dependence of Chr 13 hotspot, showing B6, 129 and A/J, versus NZO and PWK are the low, and high alleles respectively. **C**) LOD score for Chr 13 eQTL hotspot after conditioning, one at a time, on the expression of 800 genes that were located on Chr 13. Conditioning on *Il6st* local-eQTL resulted in the LOD profile for the PC1 hotspot being reduced essentially to zero. **D**) LOD profile for *Il6st* local-eQTL with a peak at 112.5 Mbp on Chr 13. **E**) Allele dependence for *Il6st* local-eQTL demonstrates a similar genetic architecture as the eQTL hotspot.

**Fig S5. Mediation predicts *Pdx1* as a driver at the Chr 5 eQTL hotspot.**

**A**) Genome-wide LOD profile for the PC1 of the eQTL hotspot at ~146 Mbp on Chr 5. **B**) Allele dependence of Chr 5 hotspot, showing B6 and 129 are the low alleles, and NOD as the high allele. **C**) LOD score for Chr 5 eQTL hotspot after conditioning, one at a time, on the expression of 1306 genes that were located on Chr 5. Conditioning on *Pdx1* local-eQTL resulted in a significant drop in the LOD profile for the hotspot. **D**) LOD profile for *Pdx1* local-eQTL with a peak at 147.2 Mbp on Chr 5. **E**) Allele dependence for *Pdx1* local-eQTL demonstrates a similar genetic architecture as the eQTL hotspot.

**Fig S6. Mediation predicts *Fam83e* as a driver at the Chr 7 eQTL hotspot.**

**A**) Genome-wide LOD profile for the PC1 of the eQTL hotspot at ~46 Mbp on Chr 7. **B**) Allele dependence of Chr 7 hotspot; NZO (high) and PWK, CAST (low) alleles. **C**) LOD score for Chr 7 eQTL hotspot after conditioning, one at a time, on the expression of 1602 genes that were located on Chr 7. Conditioning on *Fam83e* local-eQTL resulted in the largest drop in the LOD profile for hotspot. **D**) LOD profile for *Fam83e* local-eQTL with a peak at 45.7 Mbp on Chr 7. **E**) Allele dependence for *Fam83e* local-eQTL demonstrates similar genetic architecture as the eQTL hotspot; strongly driven by NZO allele.

**Fig S7. Mediation predicts *Sat2* as a driver at the Chr 11 eQTL hotspot.**

**A**) Genome-wide LOD profile for the PC1 of the eQTL hotspot at ~71 Mbp on Chr 11. **B**) Allele dependence of Chr 11 hotspot, showing PWK and CAST, versus WSB and NOD as the high and low alleles, respectively. **C**) LOD score for Chr 11 eQTL hotspot after conditioning, one at a time, on the expression of 1810 genes that were located on Chr 11. Conditioning on *Sat2* local-eQTL resulted in the largest drop in the LOD profile for hotspot. **D**) LOD profile for *Sat2* local-eQTL with a peak at 69.7 Mbp on Chr 11. **E**) Allele dependence for *Sat2* local-eQTL demonstrates the same genetic architecture as the eQTL hotspot.

**Fig S8. Module color code key.**

Modules are arranged alphabetically based on color name. The top GO and KEGG terms are listed for each module. Some modules did not show significant enrichment for one or both categories; NA.

**Fig S9. Islet modules that were most strongly influenced by sex.**

Module eigengenes (ME) for islet modules showing the most significant differences between female and male DO mice. **A**) MEs where transcript abundance was higher in females than males; **B**) MEs where transcript abundance was higher in males than females. P-values for the difference between females vs. males is shown for each module. Module names are shown along the bottom, and the top-enriched GO category (Z-score > 5) is shown along the top. MEs for all modules are included in **Table S5**, along with *p*-values for sex-dependent differences.

**Fig S10. Genome-wide LOD profile for *Tcf7l2* expression in DO islets.**

A distal- and local-eQTL was identified on chromosomes 13 and 19, respectively (*p* < 0.05).

**Fig S11. Allele dependences for *Tcf7l2* eQTL.**

Allele dependence for *Tcf7l2* eQTL on Chr 19 (**A**) and Chr 13 (**B**).

**Fig S12. Mediation analysis to predict candidate drivers of *Tcf7l2* expression.**

Conditional analysis identifies *Tcf7l2* and *Il6st* as drivers for local- (**A**) and distal-eQTL (**B**), respectively.

**Fig S13. SNP associations for *Tcf7l2* eQTL.**

SNP association for Tcf7l2 expression at local- (**A**) and distal-eQTL (**B**), respectively.

**Supplementary Table 1. eQTL hotspots.**

**Supplementary Table 2. Module memberships.**

**Supplementary Table 3. GO/KEGG enrichment for all modules.**

**Supplementary Table 4. Percent variance explained by module eigengenes (ME).**

**Supplementary Table 5. Sex effects for module transcripts.**

**Supplementary Table 6. Physiological QTL and their syntenic positions in human.**

**Supplementary Table 7. Module-QTL and their syntenic positions in human.**

**Supplementary Table 8. List of T1D and T2D associated SNPs obtained from GWAS Central.**

**File S1. R markdown file detailing the analyses for all physiological phenotypes.**

**File S2. R markdown file detailing the analyses for eQTL hotspots.**

**File S3. R markdown file detailing the analyses for co-expression module eigengenes.**

**File S4. Guide to R markdown files (Files S1 – 3) for QTL analysis.**

**File S5. R markdown file for integration of mouse QTL with human GWAS.**

**File S6. Data files used for GWAS integration R markdown file.**

**File S7. Guide to R markdown file for GWAS integration.**