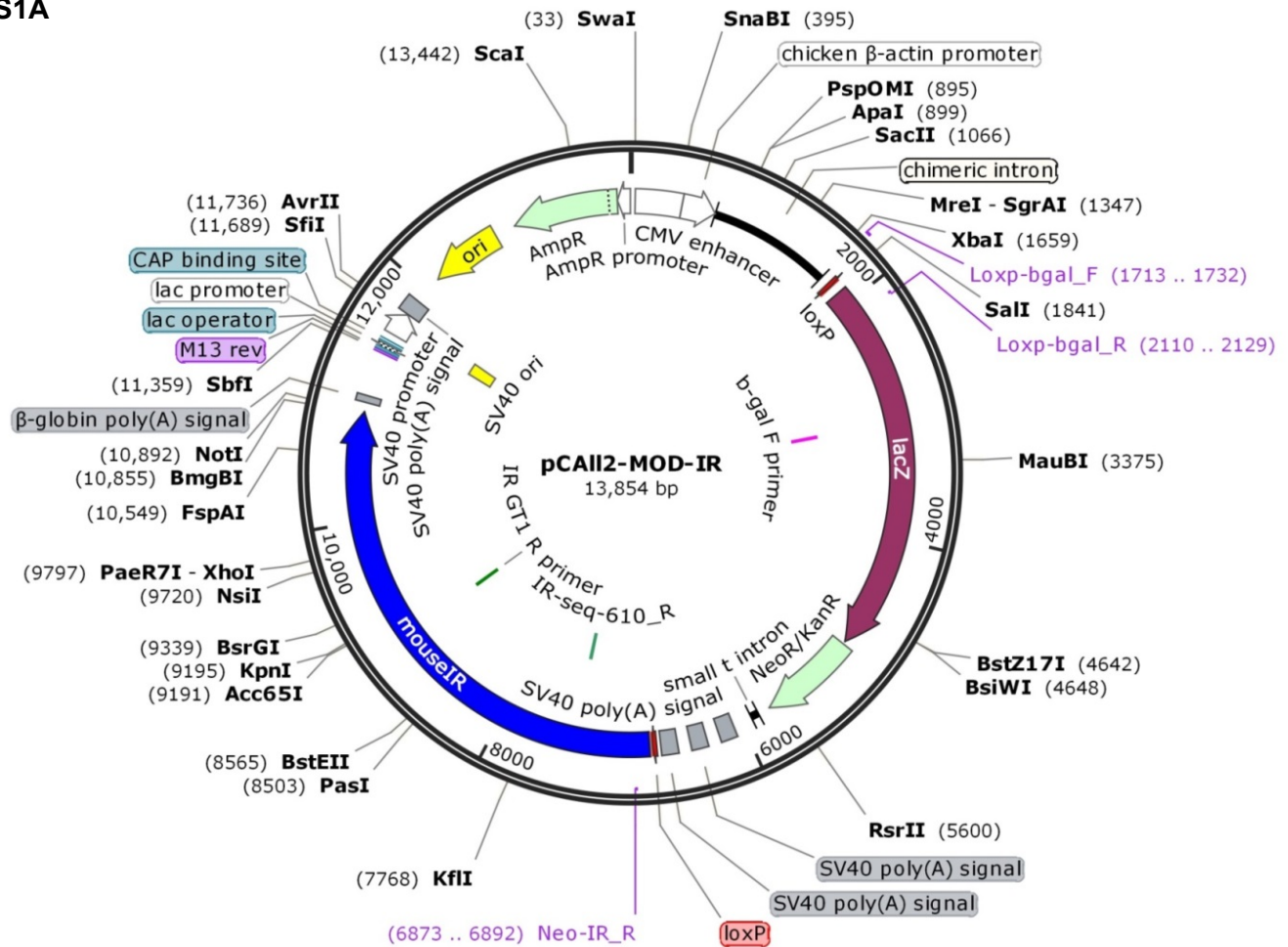
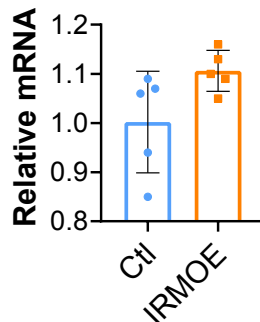


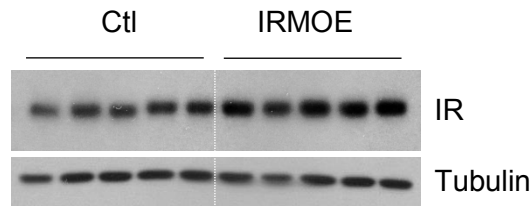
S1A



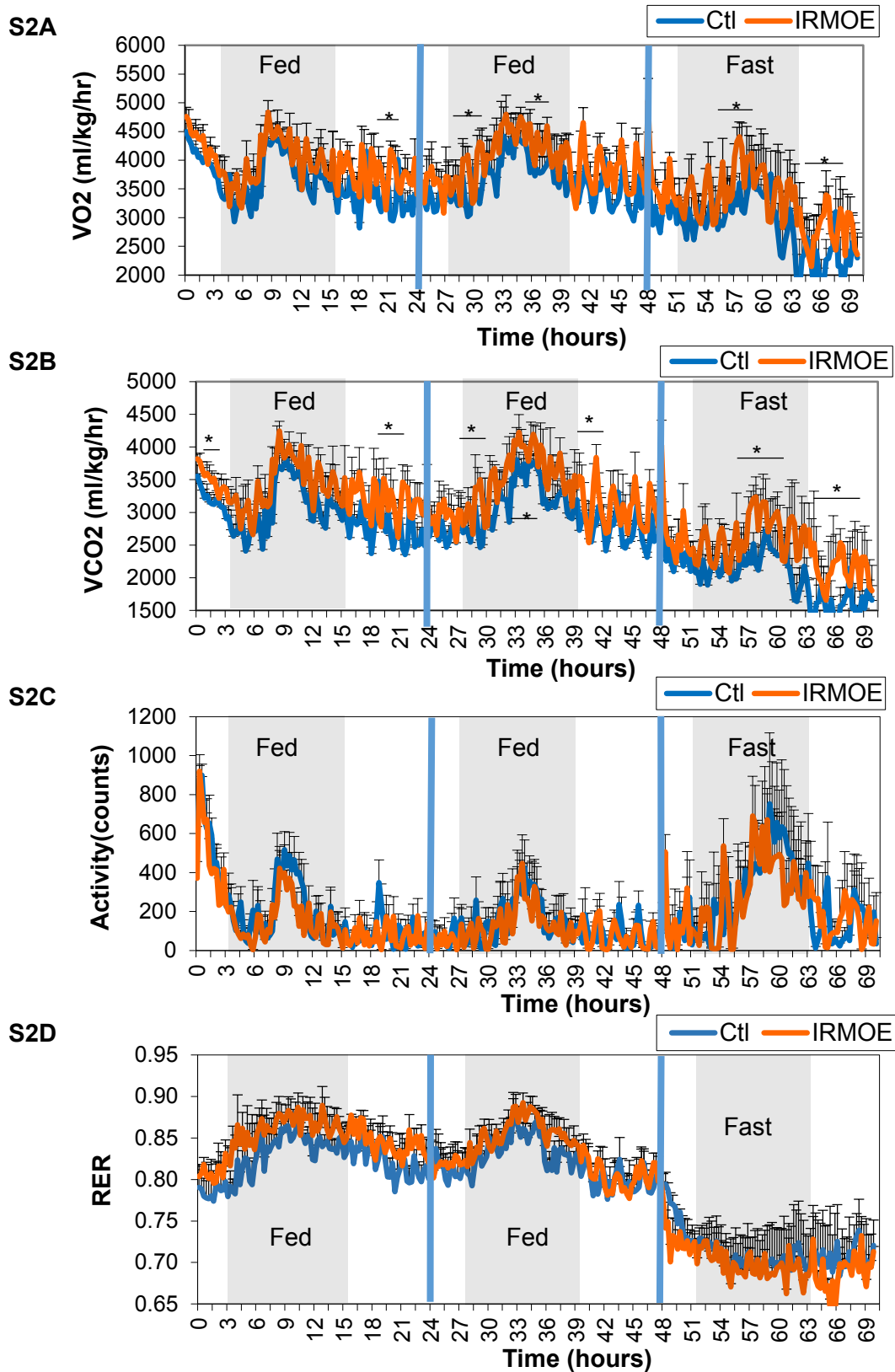
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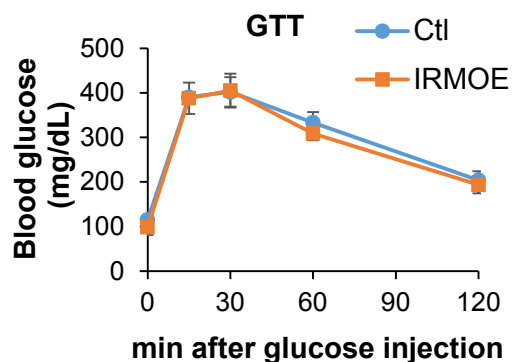
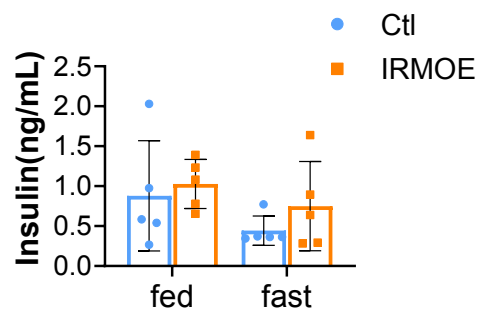
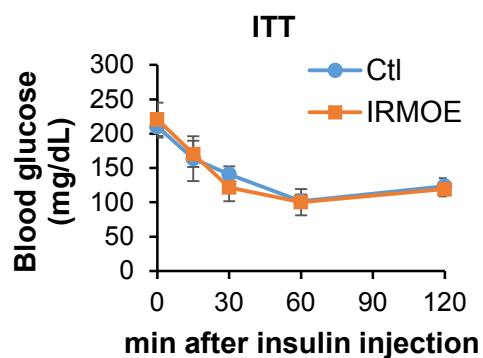
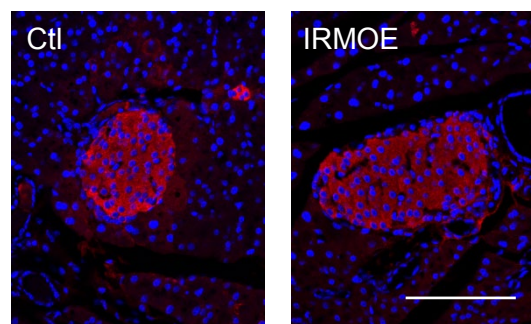
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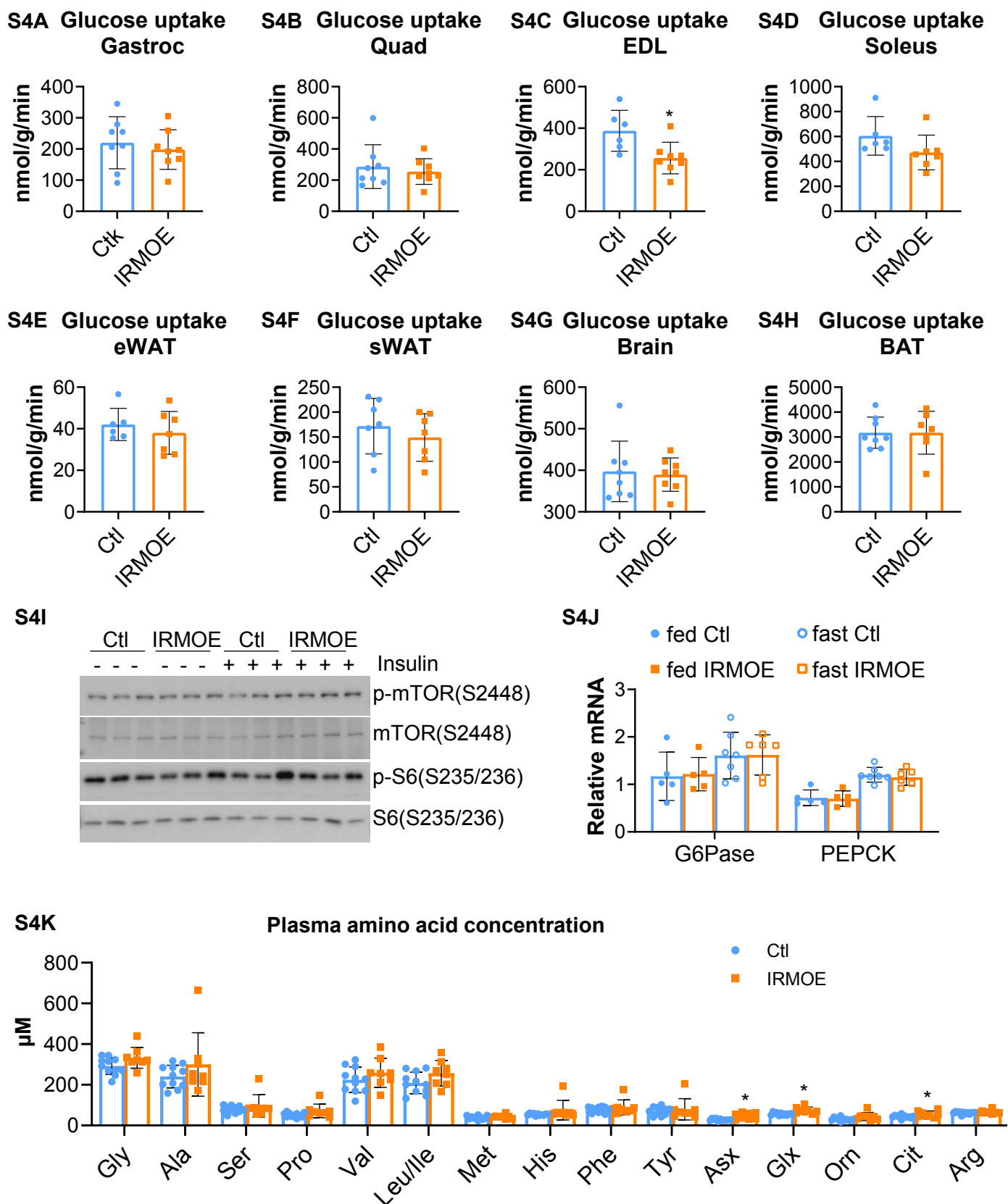
**Figure S1. (A)** Map of the plasmid harboring the “CAG-loxp-bgal-stop-loxp-IR” cassette for pro-nuclear injection. **(B)** IR mRNA expression measured by qPCR in heart from control and IRMOE mice (n=5). **(C)** Western blot showing IR protein level in heart from control and IRMOE mice (n=5). Data represent mean  $\pm$  SD, Student's *t*-test.



**Figure S2. (A)** O<sub>2</sub> consumption rate, **(B)** CO<sub>2</sub> production rate, **(C)** Activity and **(D)** Respiration exchange ratio in control and IRMOE mice on chow diet (n=5). Data represent mean  $\pm$  SEM, \*p<0.05.

**S3A****S3B****S3C****S3D**

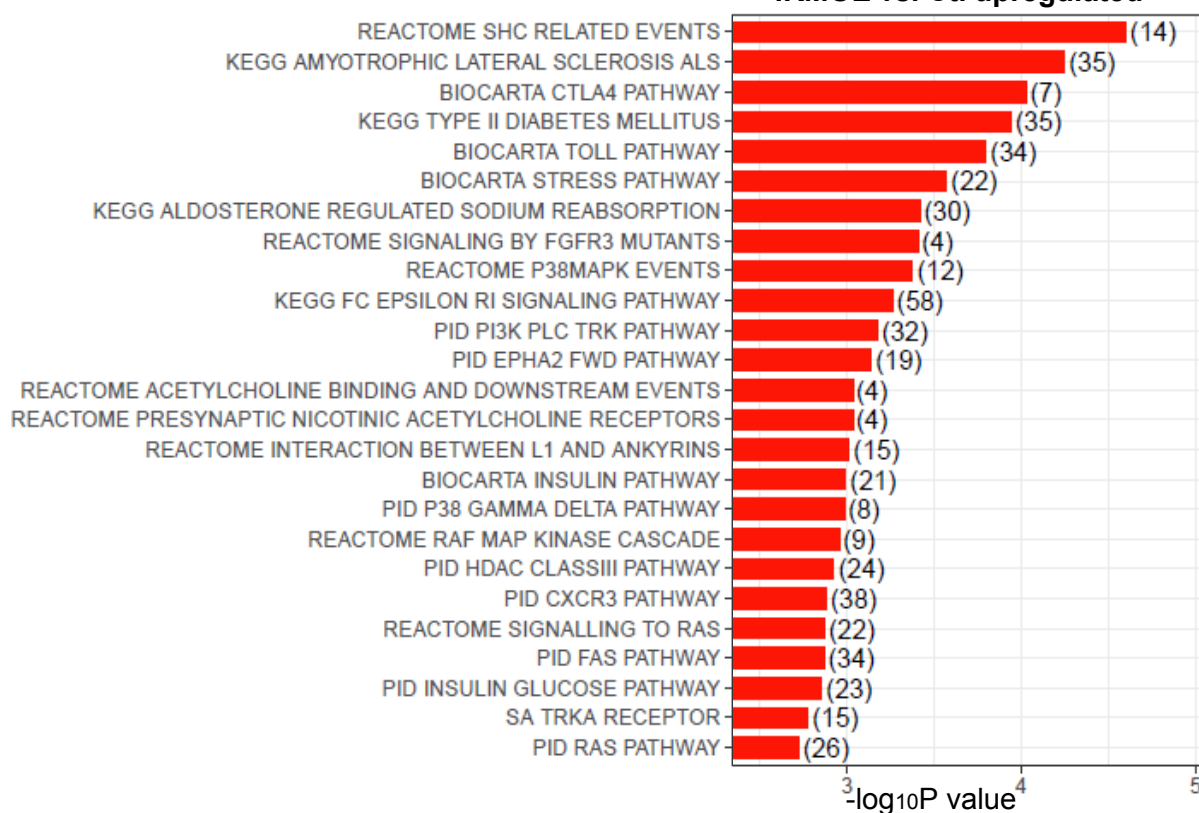
**Figure S3.** (A) Glucose tolerance test in 2.5 months old control and IRMOE mice on chow diet (n=5). (B) Plasma insulin levels in 5-month-old Ctl and IRMOE mice on chow diet (n = 5). (C) Insulin tolerance tests in 5-month-old Ctl and IRMOE mice on chow diet (n = 5). (D) Representative Insulin staining of pancreas paraffin section in 3.5 months old Ctl and IRMOE mice on chow diet (n=3), scale bar = 100 $\mu$ m. Data represent mean  $\pm$  SD.



**Figure S4.** Glucose uptake in **(A)** Gastrocnemius **(B)** Quadriceps **(C)** EDL **(D)** Soleus muscles and **(E)** Epididymal white fat **(F)** Subcutaneous white fat **(G)** Brain and **(H)** Brown fat in 7 months old male mice measured after euglycemic-hyperinsulinemic clamps (n=8). **(I)** Western blot showing insulin signaling in tibialis anterior muscles under basal conditions and after vena cava injection of insulin (n = 3). **(J)** Gluconeogenic gene expression in liver measured by qPCR in fed and fasted control and IRMOE mice (n=5-7). **(K)** Plasma amino acids levels in control and IRMOE mice after overnight fast (n=8-11). Data represent mean $\pm$ SD, \*p<0.05.

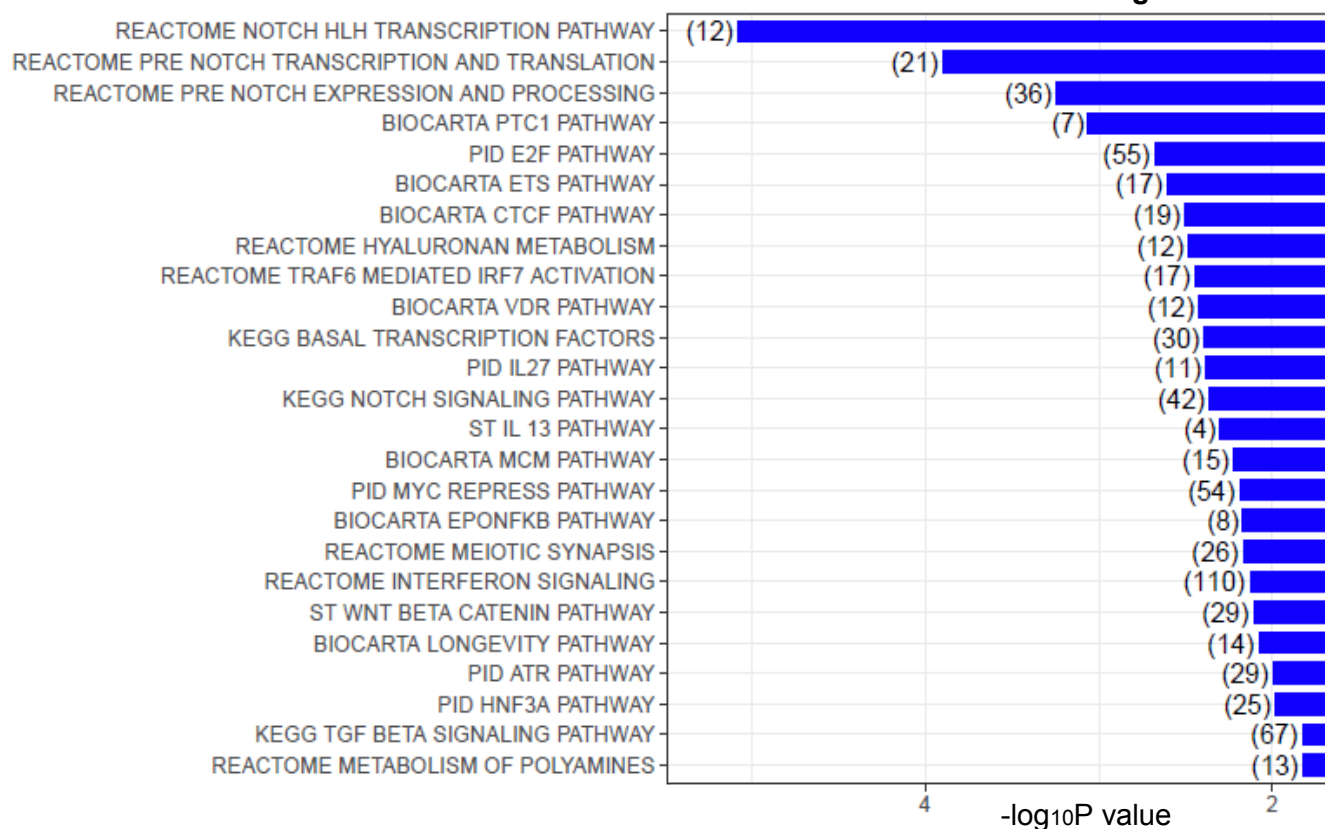
**S5A**

**IRMOE vs. Ctl upregulated**



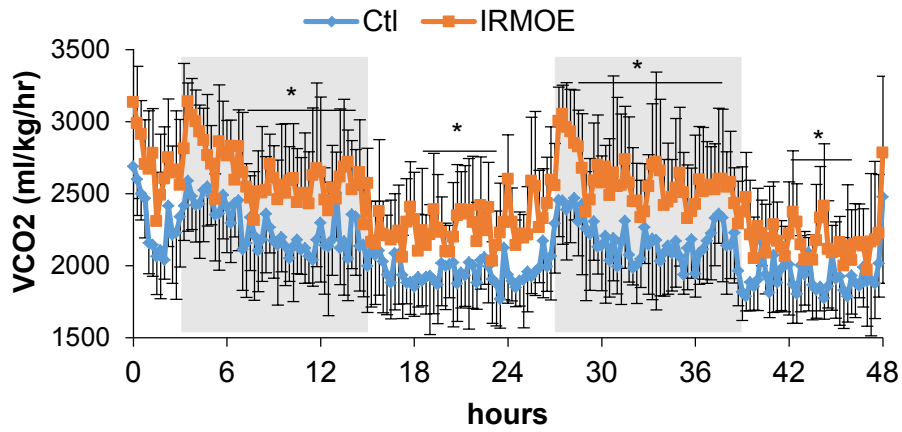
**S5B**

**IRMOE vs. Ctl downregulated**

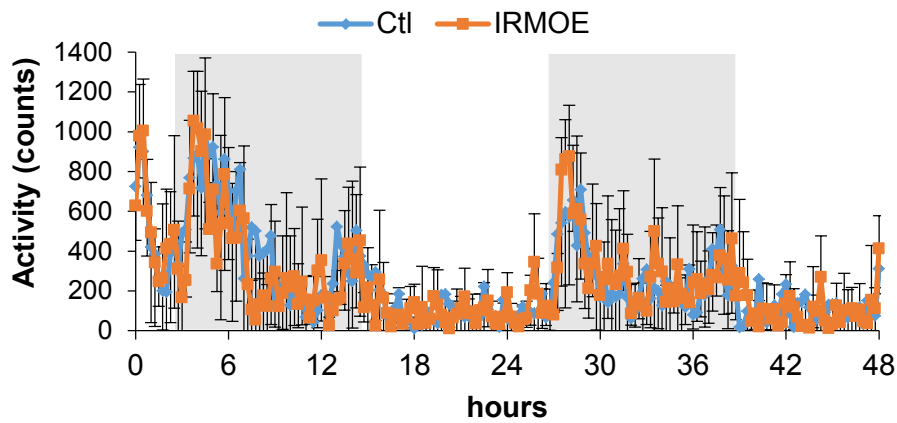


**Figure S5.** Top ranked pathways (A) up-regulated and (B) down-regulated in quadriceps muscle in IRMOE mice compared to control

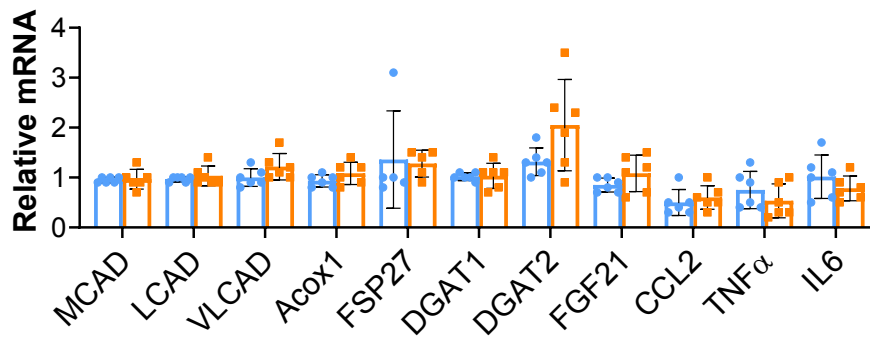
S6A



S6B



S6C



**Figure S6.** (A) CO<sub>2</sub> production rate and (B) activity in control and IRMOE mice after 11 weeks on HFD (n=5-6). (C) Q-PCR of quadriceps muscles from 24hr fasted chow fed control and IRMOE mice (n=5-6). Data represent mean  $\pm$  SD, \*p<0.05.