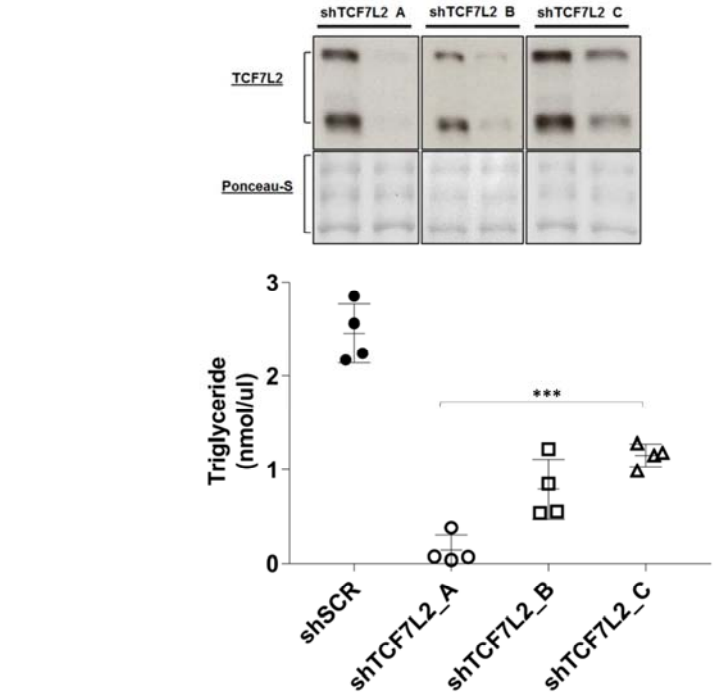
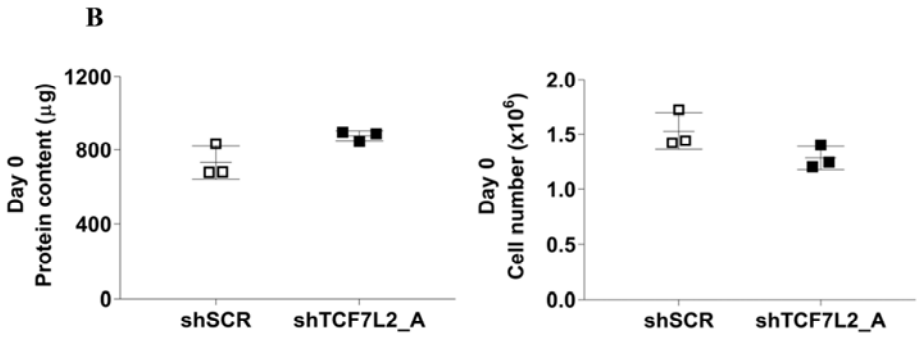
SUPPLEMENTARY DATA

Supplementary Figure 1. (A) Multiple shRNA sequences targeting various regions of *Tcf7l2* mRNA were used to confirm that silencing of TCF7L2 inhibited adipogenesis, as shown by triglyceride accumulation in multiple clones of shTCF7L2 3T3-L1 cells **(B)** (n = 4 independent experiments for each stable clone; $^{***}P < 0.001$ one-way ANOVA Holm-Sidak multiple comparison t-test versus shSCR control**). (C)** Protein content and cell number at the induction of adipogenesis on D0 was not different between shSCR and shTCF7L2 (shown is data for shTCF7L2_A).

A

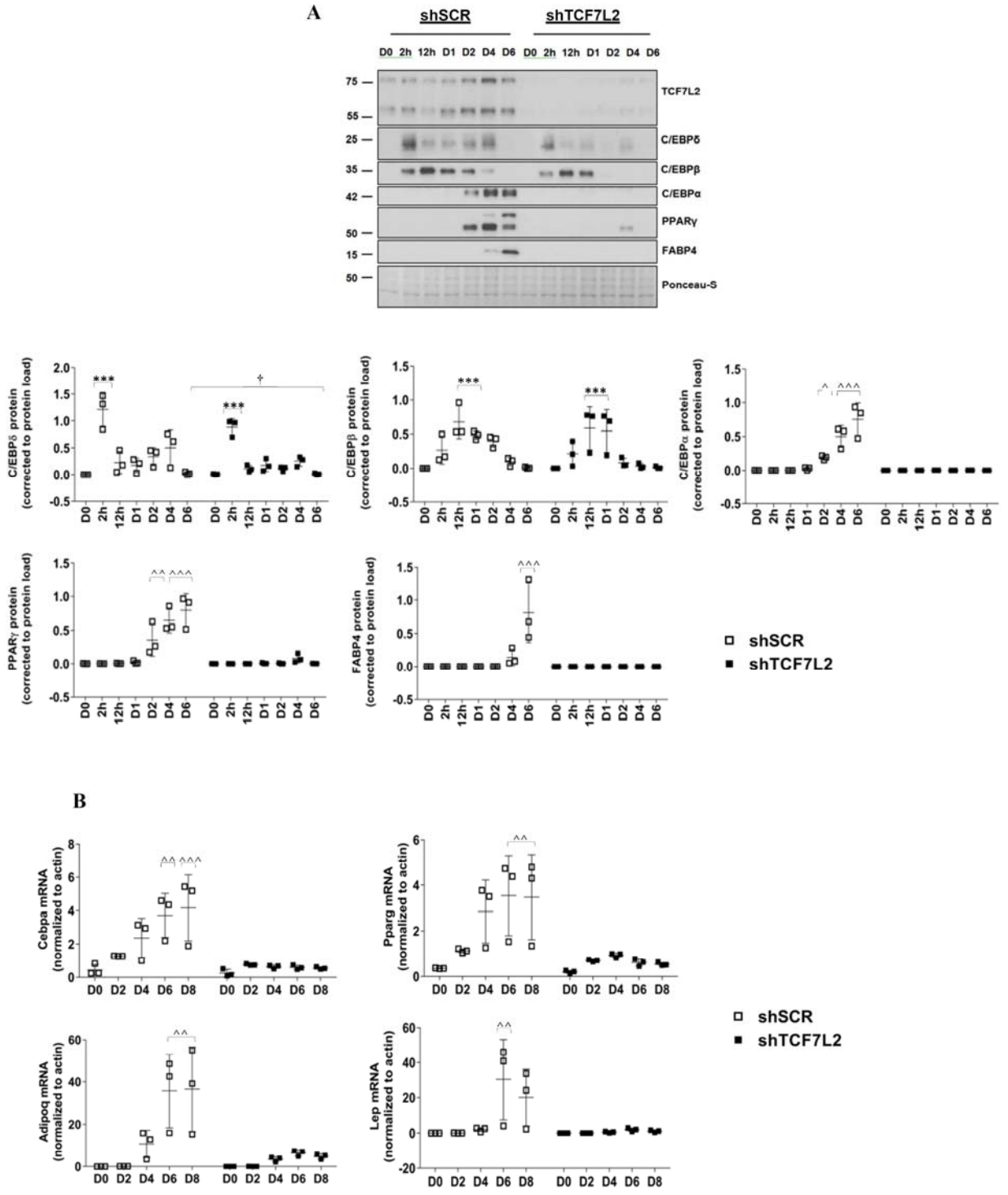
	Supplier	Plasmid	Clone ID	Position	Target Sequence
shRNA_A	Dharmacon	SMARTvector	SH01-058892-01	1062	TCACGCCTCTCATCACGTA
shRNA_B	Sigma	pLKO_TRC005	TRCN0000416397	579	ACGAGCTGATCTCCTTCAAAG
shRNA_C	Sigma	pLKO.1	TRCN0000012180	1312	GCTGACAGTCAACGCATCTAT





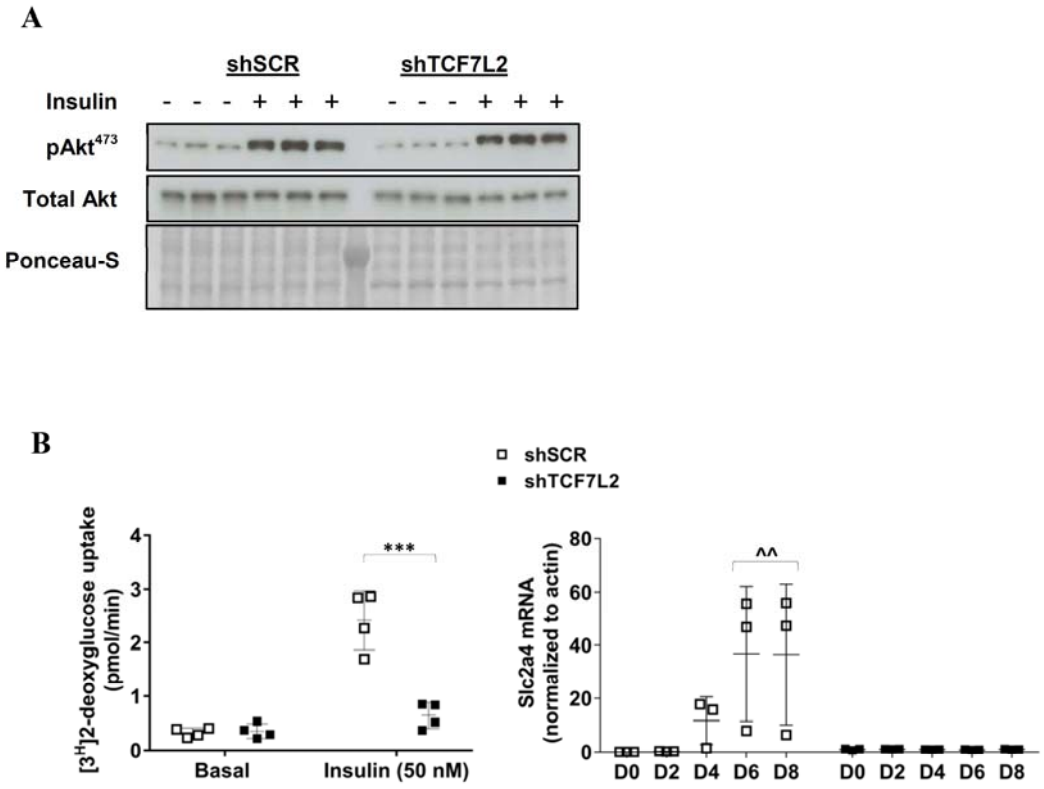
SUPPLEMENTARY DATA

Supplementary Figure 2. (A) Representative Western blots and corresponding quantitation for adipogenic transcription factor protein levels during adipogenesis in shSCR and shTCF7L2 3T3-L1 cells. **(B)** mRNA expression of adipogenic transcription factors during adipogenesis in shSCR and shTCF7L2 3T3-L1 cells (n = 3 independent experiments; $^{***}P < 0.001$ two-way ANOVA Holm-Sidak multiple comparison t-test versus D0; $^{\dagger}P < 0.05$ two-way ANOVA main effect of shTCF7L2; $^{\wedge}P < 0.05$, $^{\wedge\wedge}P < 0.01$, $^{\wedge\wedge\wedge}P < 0.001$ two-way ANOVA time x shTCF7L2 interaction Holm-Sidak multiple comparison t-test versus corresponding shSCR time point).



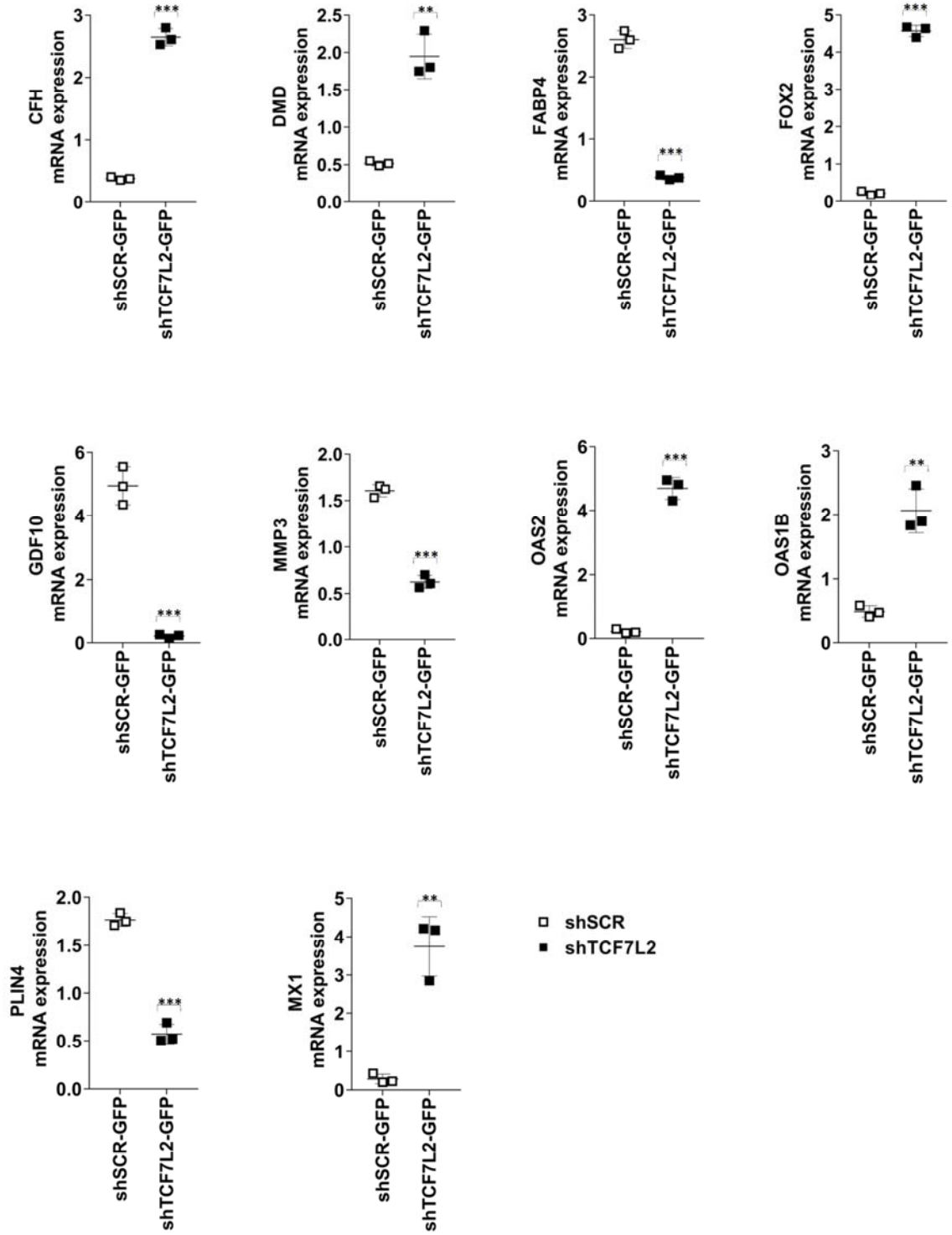
SUPPLEMENTARY DATA

Supplementary Figure 3. (A) Representative Western blot of insulin stimulated phosphorylation of Akt in shSCR and shTCF7L2 cells. **(B)** Insulin-stimulated glucose uptake (n = 4 independent experiments; $^{***}P < 0.001$ t-test versus shSCR) and *Slc2a4* mRNA expression (n = 3 independent experiments; $^{\wedge\wedge}P < 0.01$ two-way ANOVA time x shTCF7L2 interaction Holm-Sidak multiple comparison t-test versus corresponding shSCR time point).



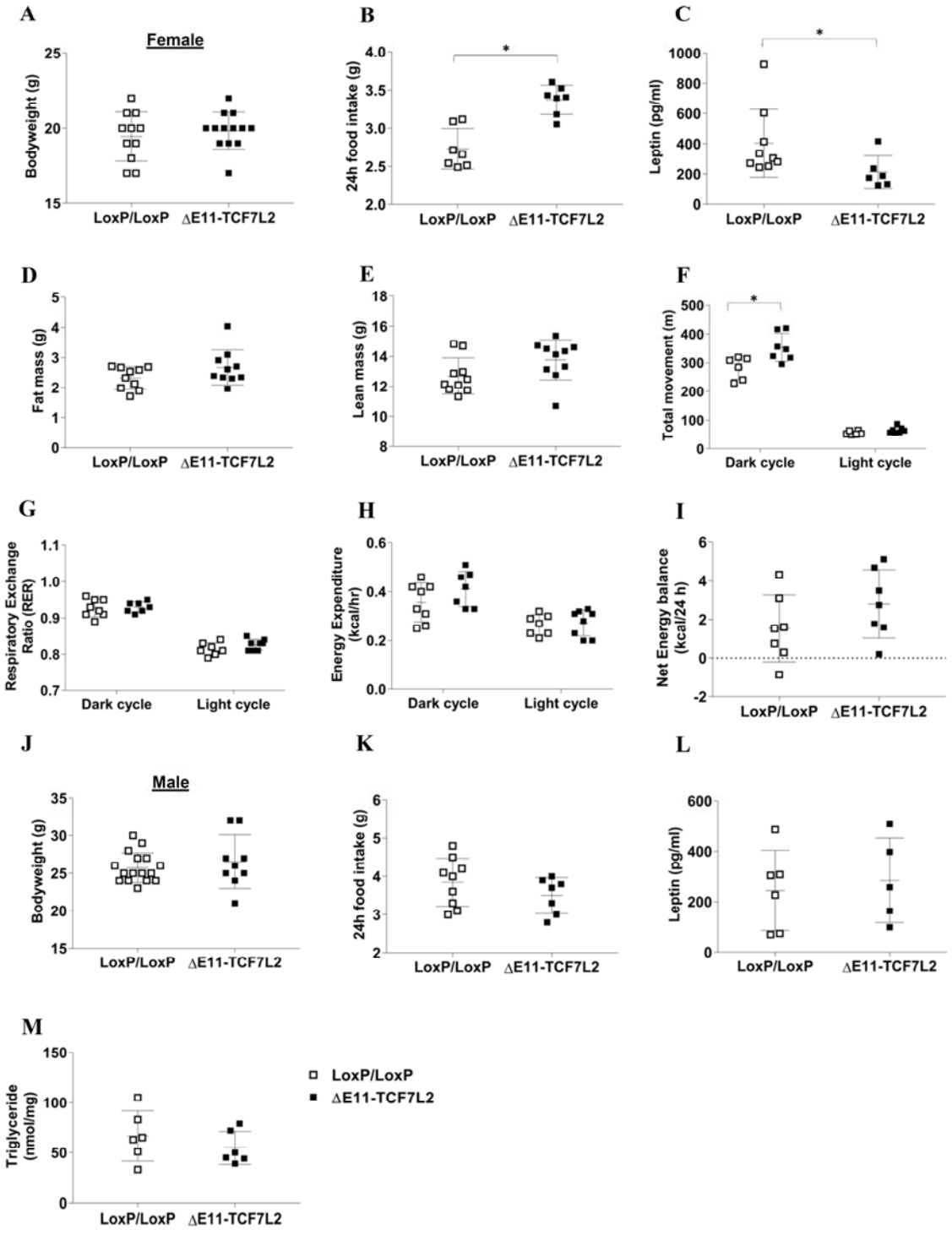
SUPPLEMENTARY DATA

Supplementary Figure 4. mRNA expression of key inflammatory and metabolic genes in shTCF7L2 cells. The RNA-Seq data was generated in clone A and the above qRT-PCR data was generated in clone B (see Supplementary Fig 1). Analysis was performed using Biogazelle Qbase+. (n = 3 independent experiments; $^{**}P < 0.01$, $^{***}P < 0.001$ t-test versus shSCR).



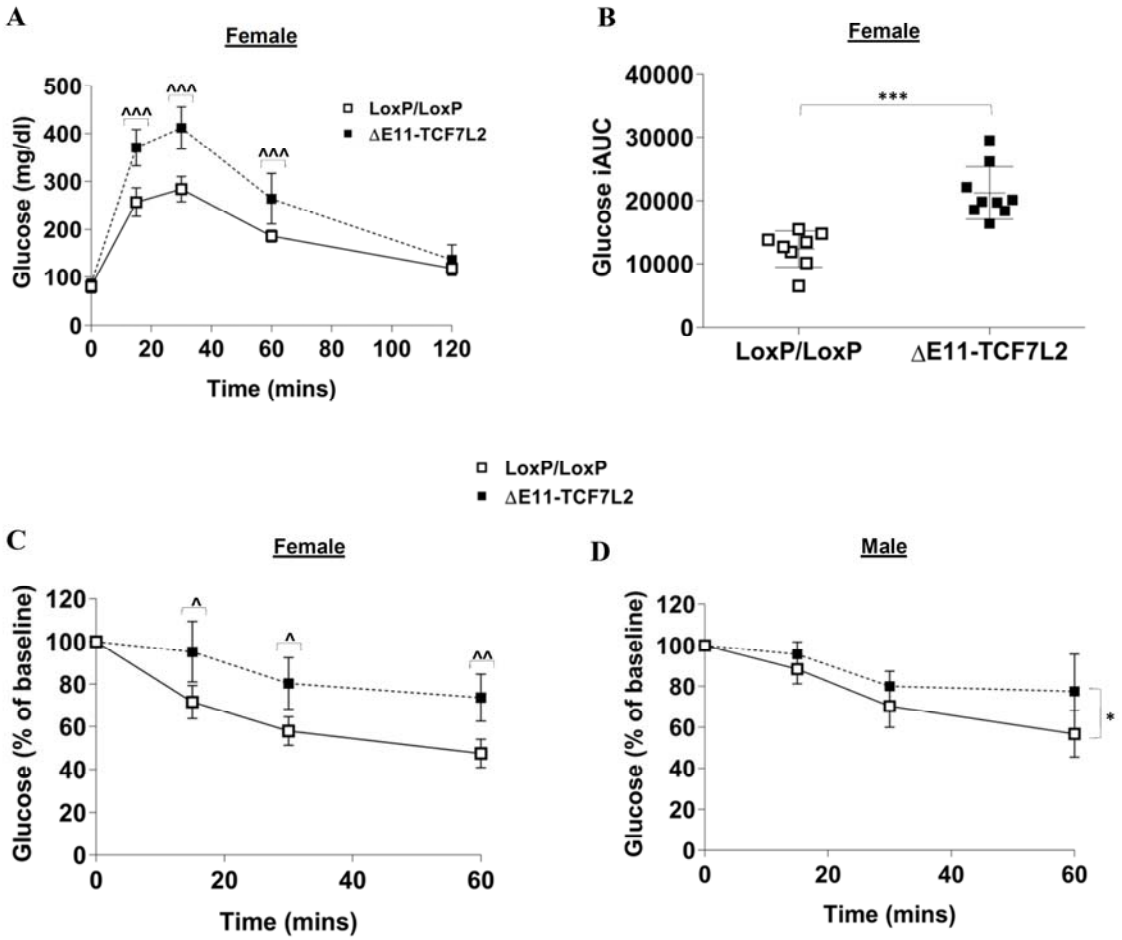
SUPPLEMENTARY DATA

Supplementary Figure 5. Bodyweight **[A** (rounded to nearest number) **and J]**, food intake **(B and K)** and Leptin levels **(C and L)** for 3 month old female and male mice. **(D and E)** NMR analysis of total lean and fat mass, and **(F – H)** metabolic cage analysis is shown for female mice and includes assessment of total movement, respiratory exchange ratio (RER) and energy expenditure during dark and light cycles. **(I)** Net energy balance is calculated for female mice. **(M)** Liver triglyceride quantification of shown for male 3 month old mice (n = 5 – 12 ΔE11-TCF7L2, n = 6 – 11 LoxP controls; $^{*}P < 0.05$ t-test versus control mice).



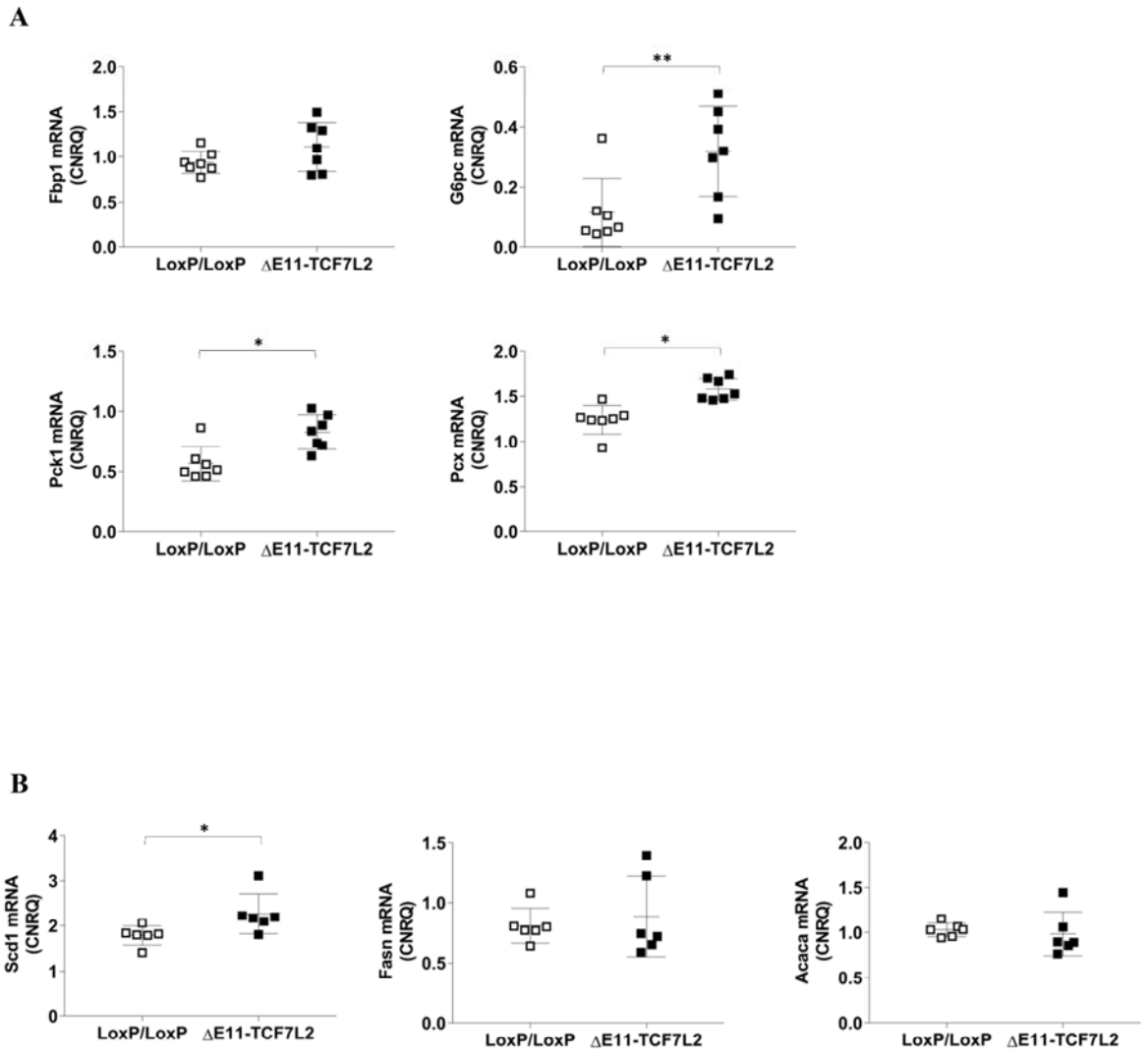
SUPPLEMENTARY DATA

Supplementary Figure 6. (A) Intraperitoneal glucose tolerance tests (IPGTT, n = 9 ΔE11-TCF7L2, n = 8 LoxP controls; $^{\wedge\wedge\wedge}P < 0.001$ two-way ANOVA time x *Tcf7l2* genotype interaction Holm-Sidak multiple comparison t-test versus corresponding control time point). **(B)** Incremental area under the IPGTT curve (iAUC; $^{***}P < 0.001$ t-test). **(C and D)** Insulin tolerance tests (ITT) for female (n = 8 ΔE11-TCF7L2, n = 12 LoxP controls) and male (n = 8 ΔE11-TCF7L2, n = 7 LoxP controls) mice ($^{\wedge}P < 0.05$, $^{\wedge\wedge}P < 0.01$ two-way ANOVA time x *Tcf7l2* genotype interaction Holm-Sidak multiple comparison t-test versus corresponding control time point; $^{*}P < 0.05$ two-way ANONA main effect of *Tcf7l2* genotype)



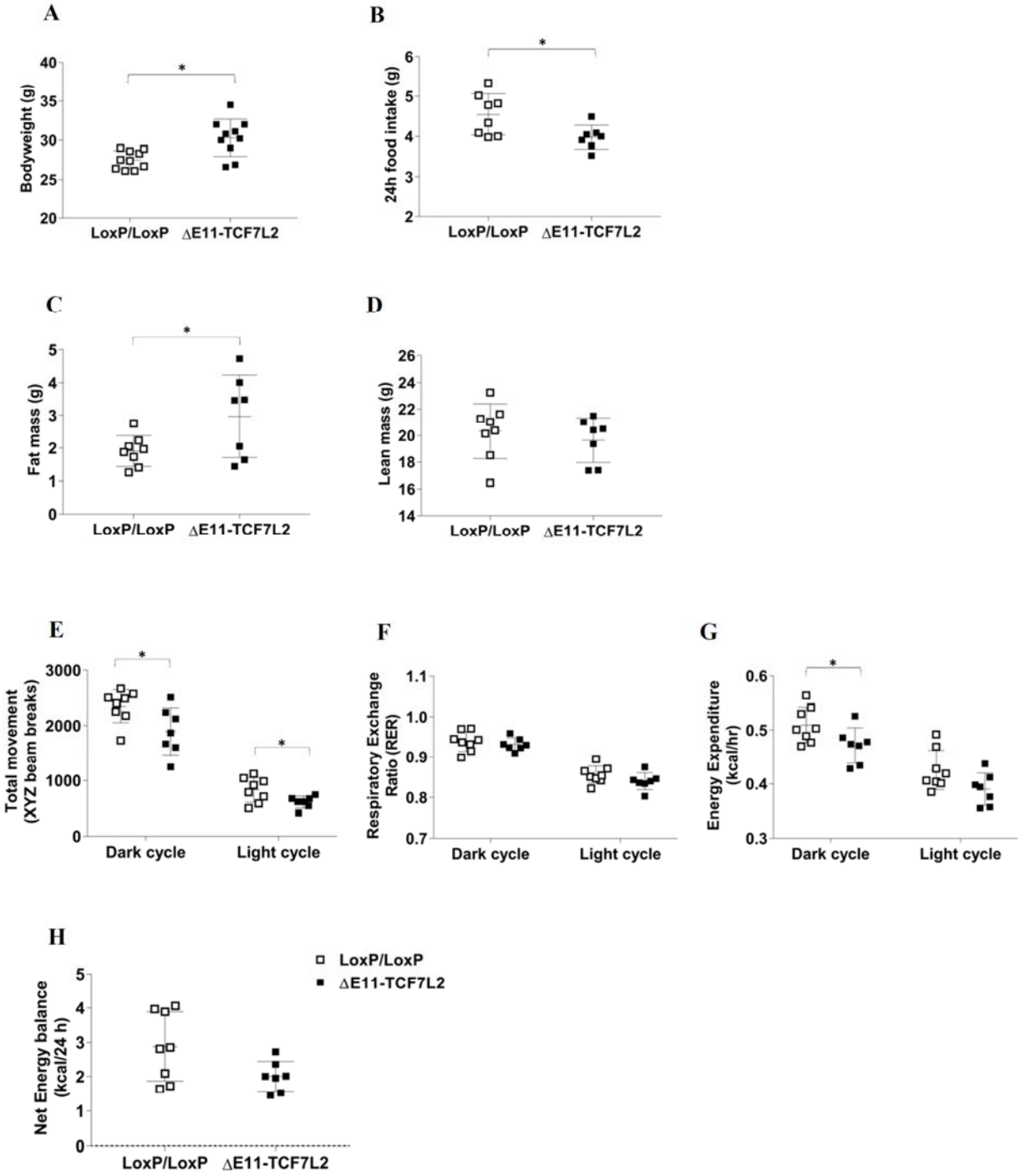
SUPPLEMENTARY DATA

Supplementary Figure 7. (A) Gene expression of hepatic gluconeogenic genes at the end of insulin clamp experiments, and **(B)** gene expression of hepatic lipogenic genes in the fasted state. Both were from 3 month old chow fed mice ($^{*}P < 0.05$, $^{**}P < 0.01$ t-test versus control mice, corrected for multiple comparisons using Holm-Sidak method)



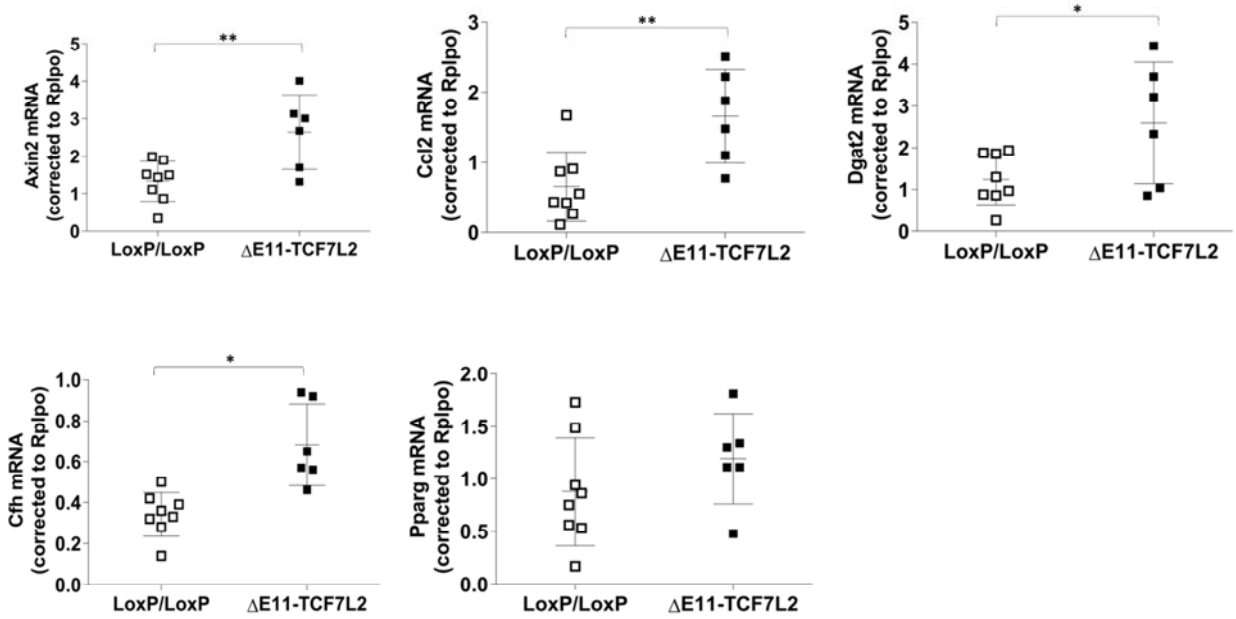
SUPPLEMENTARY DATA

Supplementary Figure 8. Bodyweight **(A)** and food intake **(B)** in 6 month old male mice. **(C and D)** NMR analysis of total lean and fat mass. **(E – H)** Metabolic cage analysis and net energy expenditure is shown for 6 month old male mice. (I) (n = 7 – 10 ΔE11-TCF7L2, n = 8 – 10 LoxP controls). *P < 0.05 t-test versus control mice.



SUPPLEMENTARY DATA

Supplementary Figure 9. Gene expression of *Axin2*, *Ccl2*, *Dgat2*, *Cfh* and *Pparg* in isolated adipocytes from male iWAT following HFD (n = 6 ΔE11-TCF7L2, n = 8 control mice; $^{*}P < 0.05$, $^{**}P < 0.01$ t-test versus control)



SUPPLEMENTARY DATA

Supplementary Table 1. Clinical characteristics of human patients used in the present study (corresponds to Figure 7)

	NGT	**IGT**	***p***
n	21	22	
Sex (M/F)	4/17	8/14	
Age (years)	47 ± 2	49 ± 2	0.42
BMI (kg/m^2)	31.3 ± 1.6	33.7 ± 1.5	0.26
Fasting Glucose (mg/dL)	92.6 ± 1.4	103.7 ± 1.6	< 0.001
2h Glucose (mg/dL)	107.7 ± 5.8	160.9 ± 4	< 0.001
Fasting Insulin (mU/L)	5.0 ± 0.7	6.6 ± 0.6	0.09
2h Insulin (mU/L)	42.2 ± 7.4	81.8 ± 11.3	< 0.01
Fasting FFA (mmol/L)	0.49 ± 0.03	0.56 ± 0.04	0.18
1h FFA (mmol/L)	0.13 ± 0.02	0.20 ± 0.02	< 0.05