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Supplementary Information for

Nuclear receptor REVERBα is a state-dependent regulator of liver energy metabolism

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Supplementary Text

Reverbα$^{Flox2-6}$ CRISPR generation strategy

No single exon of *Reverbα* (*Nr1d1*) displays suitable criteria for conditional removal (i.e. no unequal splicing phase, small flanking intron sizes for loxP integration). We integrated loxP sites at intron 2 and intron 6 in a two-step process, first achieving a precise integration of the 5’ loxP in intron 2, and bred a homozygote colony of this genotype, which were then used as a genetic background to integrate the second 3’ loxP. A founder mouse with both 5’ and 3’ loxP was identified and bred forward for crossing with Cre drivers.

sgRNA were designed using stringent criteria for off-target predictions (guides with mismatch (MM) of 0, 1 or 2 for elsewhere in the genome were discounted, and MM3 were tolerated if predicted off-targets were not exonic). sgRNA were then purchased as crRNA oligos, which were annealed with tracrRNA (both oligos supplied by Sigma-Merck) in sterile, RNase-free injection buffer (TrisHCl 1mM, pH 7.5, EDTA 0.1mM) by combining 2.5 μg crRNA with 5 μg tracrRNA and heating to 95°C, which was allowed to slowly cool to room temperature.

For 5’ loxP integration, the sgRNA CAGCTAGGGTCTTAGTTACA-*AGG* was used, along with the ssDNA repair template TTTTTTTGTGTGTGTGTGTATGAATAACTGTCAGCTGTCCATCTCCTTCCCAAGTCTACCCataacttcgtatagcatacattatacgaagttat*ggtacc*AGACCCTAGCTGCTGTCAGTACTCCCCAGGAAGCAGCTAGCTCAGGGGTTCCCATGTATGAGATG, where capitals denote the 60bp homology arms, and lowercase bases indicate the loxP site and a KpnI (in italics) for screening purposes. For integration of the 3’ loxP in intron 6, the sgRNA AACTCTCCTCTACTCTAGGC-*CGG* was used along with ssDNA2 GGGAAGTCTATCCTCTAGGCTGGTGTTGCCTCCAAACTCAGTGCATCAGAGTAACCAAAGAGACAACTCTCataacttcgtatagcatacattatacgaagttat*ggtacc*CGGAGCTGGTGACCTTCGGTTAAATTACATTCCAGAAGTGGCGGGCACTCCCACCTGCATCC. For embryo microinjection, the annealed sgRNA was complexed with Cas9 protein (New England Biolabs) at room temperature for 10 minutes, before addition of ssDNA donor (final concentrations; sgRNA 20 ng/μl, Cas9 protein 20 ng/μl, ssDNA 50 ng/μl). CRISPR reagents were directly microinjected into B6D2F1 (Envigo) zygote pronuclei using standard protocols. Zygotes were cultured overnight and the resulting 2-cell embryos surgically implanted into the oviduct of day 0.5 post-coitum pseudopregnant mice. PCR and Sanger sequencing was used to determine correct integration of donor template. The 5' loxP integrated precisely and the full loxP sequence integrated at the 3' site, along with an additional 5bp immediately upstream which has no impact on the mouse model. LoxP sites transmitted to the germline, and a colony was established.

HaloReverbα CRISPR generation strategy

We used CRISPR-Cas9 to generate NR1D1 (REVERBα) N-terminally tagged with a HaloTag fusion protein. As the 3' sequences of *Nr1d1* (*Reverbα*) overlap with the *Thra* gene on the antisense strand, a C-terminal fusion was not possible. 2 sgRNA targeting the ATG region of the *Nr1d1* gene were selected that adhered to our criteria for off-target predictions (as above). The donor repair template, employing the EASI-CRISPR long-ssDNA strategy, comprised the HaloTag gene with linker flanked by 101 and 96nt homology arms. Of note the homology arms contained single nucleotide synonymous nucleotide changes to prevent re-cutting of correctly repaired genomic DNA.

sgRNA sequences (ATGTCTTCACCAGCTGAAAG-CGG and CTCAGTACCTGTGTTGTTAT-TGG) were purchased as crRNA oligos, which were annealed with tracrRNA (Sigma-Merck) in sterile, RNase free injection buffer (TrisHCl 1mM, pH 7.5, EDTA 0.1mM) by combining 2.5 μg crRNA with 5 μg tracrRNA and heating to 95^{o}C, which was allowed to slowly cool to room temperature.

For embryo microinjection the annealed sgRNA was complexed with Cas9 protein (New England Biolabs) at room temperature for 10 minutes, before addition of long ssDNA donor (final concentrations; sgRNA 20 ng/μl, Cas9 protein 20 ng/μl, lssDNA 10 ng/μl). CRISPR reagents were directly microinjected into C57BL6/J (Envigo) zygote pronuclei using standard protocols. Zygotes were cultured overnight and the resulting 2 cell embryos surgically implanted into the oviduct of day 0.5 post-coitum pseudopregnant mice. Potential founder mice were screened by PCR, first using primers that flank the sgRNA sites (Cut test F atcctgattgcgaactgcgg, Cut test R gttctcggactgaggggaac), which both identifies editing activity in the form of InDels from NHEJ repair in almost every pup, and can also detect larger products implying HDR. Secondary PCRs used the same homology flanking Cut test primers PCRs in combination with HaloTag primers (HaloTag

R gtaggaggaggtcgggttac, HaloTag F gctgtcgacgctcgagattt). Pups which gave positive products in all three PCR reactions, were sequenced by amplifying again with the cut test F/R primers using high fidelity Phusion polymerase (NEB), gel extracted and subcloned into pCRblunt (Invitrogen) and Sanger sequenced with M13 Forward and Reverse primers. Pups showing perfect sequence integration were bred with C57BL6/J mice to confirm germline transmission. *HaloReverbα* mice were subsequently bred to homozygosity.

Protein extraction and Western blotting

Tissue was disrupted in T-PER (Thermo Fisher Scientific), supplemented with Protease Inhibitor Cocktail (Promega), with the FastPrep Lysing Matrix D system (MP Biomedicals). Lysates were benzonase-treated (EMD Millipore) before being spun down (8 minutes at 10,000g, at 4ºC) and the supernatants reserved. Equal masses of protein (75µg for REVERBα detection) were mixed with 4x NuPAGE LDS sample buffer (Invitrogen), NuPAGE sample reducing agent (dithiothreitol) (Invitrogen) and water, then denatured. Proteins were separated on 4-20% Mini-PROTEAN TGX Precast Protein Gels (Bio-Rad), and transferred to nitrocellulose membranes, before membranes were blocked with Protein-Free Blot Blocking Buffer (Azure Biosystems). Membranes were incubated with primary (1:1000 dilution) then secondary antibodies (1:10,000 dilution), with the antibodies being used as follows: rabbit polyclonal anti-REVERBα (NR1D1) (ProteinTech, Cat#14506-1-AP, lot 5745); mouse monoclonal anti-β-ACTIN (ACTB) (ProteinTech, Cat#60008-1, lot 0001084); goat polyclonal anti-Mouse IgG (H+L), CF680R Conjugated (Biotium, Cat#20192-1, lot 11C0414); goat polyclonal anti-Rabbit IgG (H+L), CF770 Conjugated (Biotium. Cat#20078, lot 17C1121); goat polyclonal anti-Rabbit IgG (H+L), DyLight 680 Conjugate, (Cell Signaling Technology, Cat#5366P, lot 7). The LI-COR Odyssey system was used to image blots. Uncropped blot images can be provided by the corresponding authors.

RNA extraction

Total RNA was extracted from frozen tissue lysates using TRIzol Reagent (Invitrogen), according to manufacturer's instructions. For RNA-seq, the isopropanol phase of TRIzol extraction was transferred to Reliaprep Tissue Miniprep columns (Promega, USA) and then RNA clean-up and DNase treatment continued as per Reliaprep manufacturer's protocol.

RT-qPCR

RNA was DNase treated (RQ1 RNase-Free DNase, Promega, USA) then converted to cDNA using the High Capacity RNA-to-cDNA kit (Applied Biosystems). GoTaq qPCR Master Mix (Promega, USA) and primers listed in SI Appendix, Table S8 were then used to perform qPCR, using the Step One Plus (Applied Biosystems) qPCR system. The ΔΔCT method was used to calculate relative gene expression, normalised using the geometric mean of the housekeeping genes *Hprt, Ppib* and *Actb*, and then calculating fold difference of expression relative to control groups.

HaloChIP-seq sample preparation

Frozen liver tissue was first homogenised in 2mM disuccinimidyl glutarate (DSG) (20593, Thermo Fisher Scientific) using a handheld TissueRuptor (Qiagen) and rotated at room temperature for 15 minutes. After being spun down, the cell pellet was resuspended in 1% formaldehyde-PBS, rotated for a further 15 minutes, before glycine quenching with Stop Solution (Active Motif ChIP-IT High Sensitivity kit 53040). The cell pellet was washed and dounce-homogenised as per the standard Active Motif ChIP-IT kit instructions. It was then resuspended in 650µl of Mammalian Cell Lysis Buffer (Promega HaloChIP kit G9410) supplemented with Protease Inhibitor Cocktail (G6521, Promega) and incubated on ice for 15 minutes before sonication at 20% amplitude for 8 cycles (30s on, 30s off, with 2 minutes of 'on' time per cycle), using the Active Motif EpiShear Probe Sonicator. Chromatin concentration was quantified with the Qubit BR dsDNA assay (Q32850, Thermo Fisher Scientific) and shearing efficacy checked with TapeStation electrophoresis (Agilent Technologies). For the pull-down step, 100µg chromatin, in a volume of 650µl Mammalian Cell Lysis Buffer, was rotated at room temperature with prepared HaloLink Resin (Promega) as per the Promega HaloChIP kit protocol. Wash and elution steps were also carried out as per the same manufacturer’s protocol, incorporating the recommended LiCl buffer wash step. ChIP DNA was cleaned up with the MinElute PCR Purification Kit (28004, Qiagen) and quantified with the Qubit HS dsDNA assay (Q32854, Thermo Fisher Scientific).

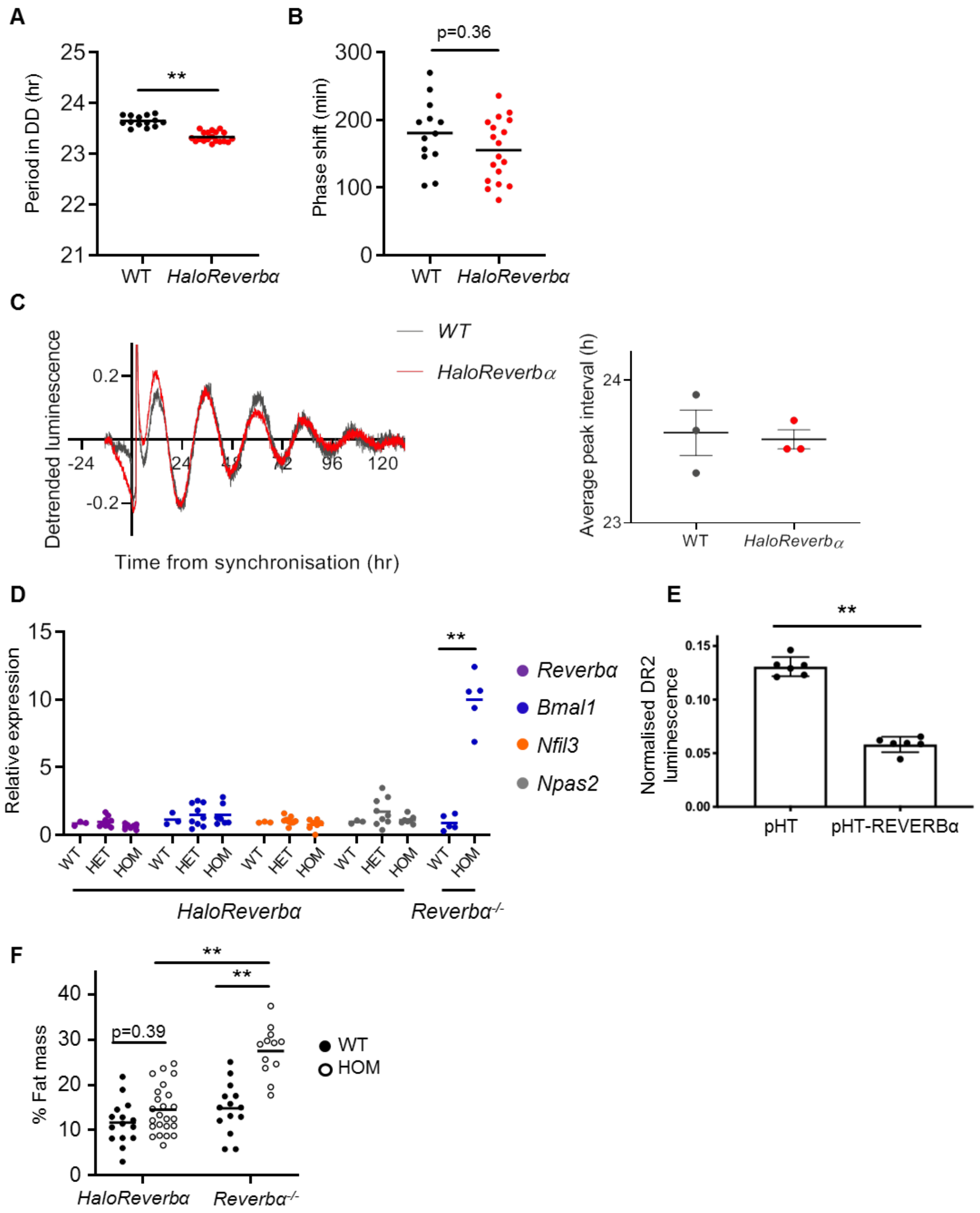


Fig. S1. A. Length of free-running period for WT and *HaloReverbα* mice in constant darkness (DD). **B.** Shift response to a 1hr light pulse delivered at CT14 in WT and *HaloReverbα* mice. n=13-17 per group. **C.** Representative bioluminescence recordings (left) collected from primary lung fibroblasts transduced with a PER2::LUC lentiviral reporter. Time zero indicates synchronisation with dexamethasone treatment. Right-hand plot shows circadian period of PER2::LUC bioluminescence, in WT and *HaloReverbα* primary cells. Each point represents individual animals, each multiple (>3) replicates. **D.** Relative expression (as measured by qPCR) of clock genes *Reverbα*, *Bmal1*, *Nfil3*, *Npas2* in liver tissue from WT, heterozygous and homozygous *HaloReverbα* mice at ZT8. Liver *Bmal1* expression from WT and *Reverbα*$^{-/-}$ mice shown for comparison. Relative expression calculated separately for each gene. n=3-9 per group. **E.** HaloREVERBα-mediated repression of DR2 element-driven reporter activity. Expression of HaloREVERBα (pHT-REVERBα) in HEK293 cells causes a significant repression of DR2-site reporter activity, relative to expression of HaloTag (pHT) alone. n=6 per group (biological replicates). **F.** Percentage fat mass (of total body mass) of 13-week old *HaloReverbα* and *Reverbα*$^{-/-}$ male mice (empty circles) and their respective WT littermate controls (filled circles). n=12-24 per group.

Data displayed as individual data points plus mean (A,B,D,F) +/- SEM (C,E); unpaired t-tests (A-E), two-way ANOVA with Tukey's multiple comparisons tests (F). **P<0.01.

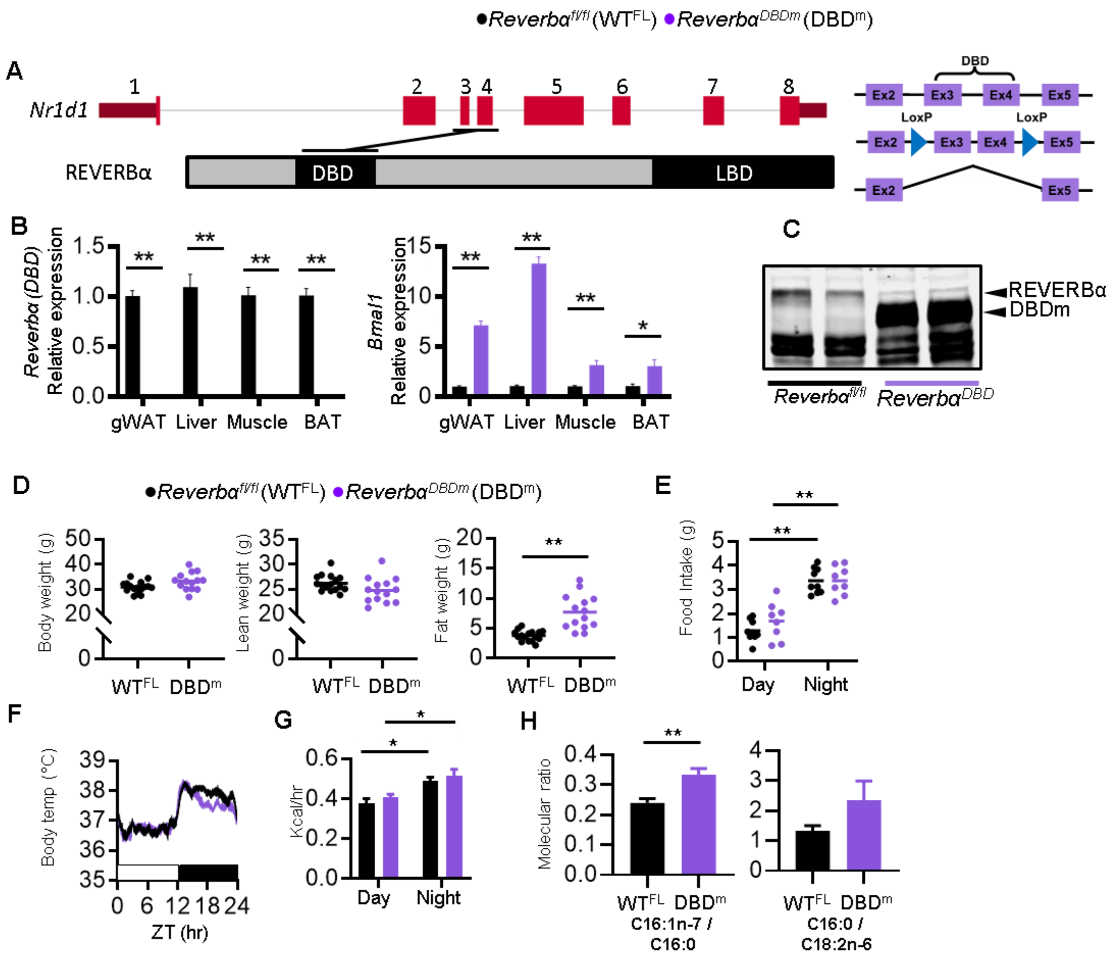


Fig. S2. A. Schematic of the *Nr1d1/Reverbα* gene and protein, showing targeting of DNA-binding domain (*Reverbα*^{DBDm}). **B.** qPCR validation of *Reverbα*^{DBDm} targeting leading to a loss of *Reverbα* expression and up-regulation of *Bmal1* (qPCR primers target the DNA binding domain region of *Reverbα*). (n=6 per group) **C.** As previously reported (20), *Reverbα*^{DBDm} produces an over-expressed hypomorph of REVERBα shown here by Western blot analysis of liver tissue. **D.** Despite similar body weights, *Reverbα*^{DBD} mice exhibit a significant increase in fat mass relative to littermate controls (13 week-old males, n = 14-16 per group). **E-G.** This adiposity phenotype was not accompanied by altered daily food intake (**E**), body temperature (**F**), or energy expenditure (**G**). All mice showed robust diurnal rhythms in physiological parameters. n=8-9 per group). **H.** Analyses of fatty acid (FA) composition in livers of *Reverbα*^{DBD} mice and littermate controls. FA desaturation is reflected by C16:1n-7/C16:0 ratio, *de novo* lipogenesis by C16:0/C18:2n ratio. n=5-6 per group.

Data displayed as individual data points with line at mean (D, E) or mean +/- SEM (B, G, H); two-way ANOVA with Tukey's multiple comparisons tests (E, G) or unpaired t-tests (B, D, H) with correction for multiple testing (B). *P<0.05, **P<0.01.

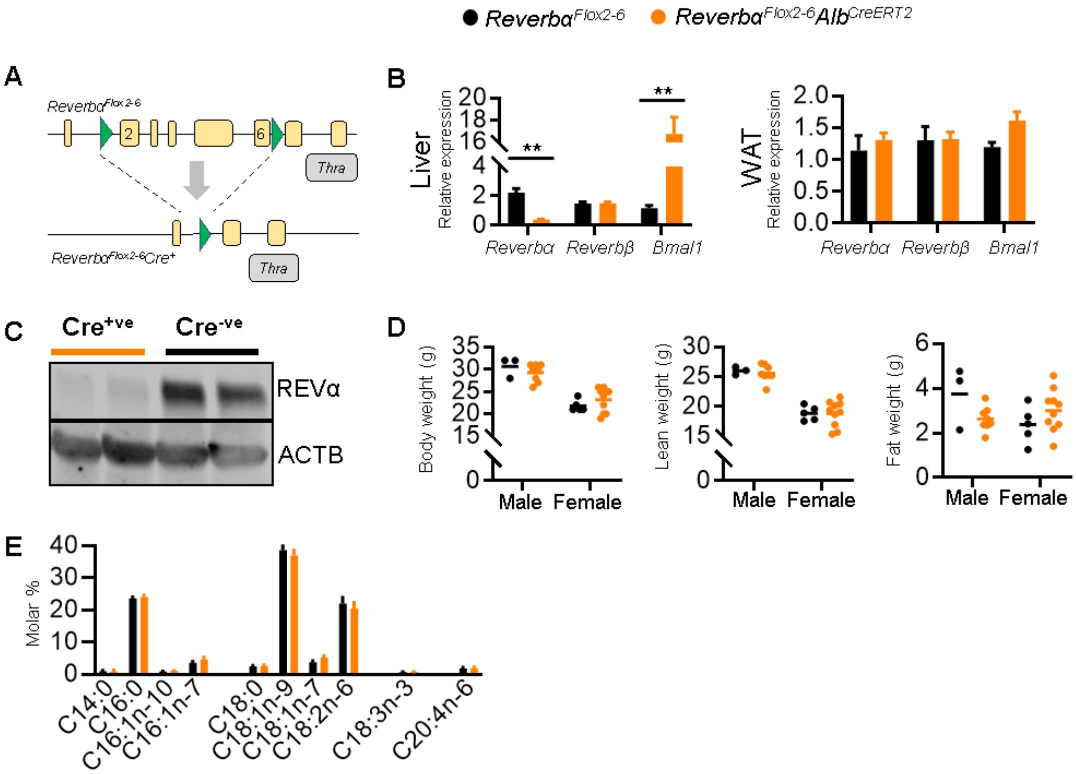


Fig. S3. A. Targeting strategy for LoxP site integration flanking exons 2 to 6 of the *Nr1d1* (*Reverbα*) locus. **B-C.** Liver-specific deletion of REVERBα achieved with tamoxifen-treatment of *Reverbα*$^{Flox2\text{-}6}$*Alb*^{CreERT2} mice, as confirmed by *Reverbα, Reverbβ* and *Bmal1* gene expression in liver and WAT (**B**; n=8-16 per group), and Western blot analysis of liver REVERBα (**C**). **D.** Body weight and body composition of male and female *Reverbα*$^{Flox2\text{-}6}$*Alb*^{CreERT2} mice and *Reverbα*$^{Flox2\text{-}6}$ littermate controls (12-14 week-old animals, n = 3-10 per group, profiled on day 25 after the start of tamoxifen treatment). **E.** Fatty acid composition analysis (molar percentages) of *Reverbα*$^{Flox2\text{-}6}$*Alb*^{CreERT2} liver and *Reverbα*$^{Flox2\text{-}6}$ littermate controls (n=6-8 per group, 12-14 week-old males and females, 15 days after the start of tamoxifen treatment).

Data shown as mean +/-SEM (B,E), or as individual data points with line at mean (D), **P<0.01, unpaired t-tests with correction for multiple testing (B,E); two-way ANOVA with Tukey's multiple comparisons tests (D).

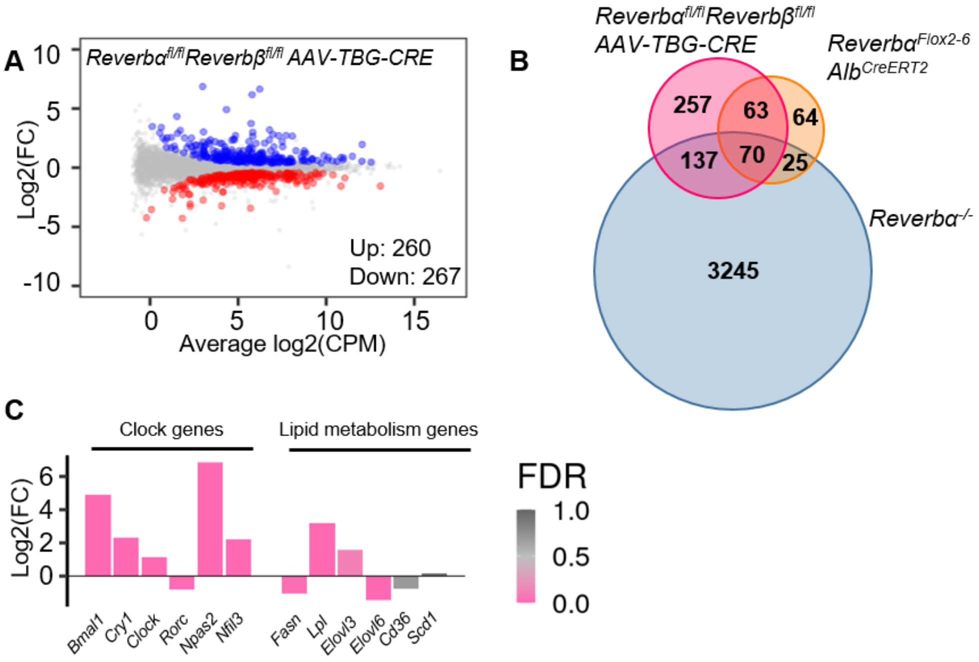


Fig. S4. A. Mean difference (MD) plot of ZT10 liver RNA-seq from *Reverbα*$^{fl/fl}$*Reverbβ*$^{fl/fl}$ *AAV-TBG-CRE* mice (relative to *Reverbα*$^{fl/fl}$*Reverbβ*$^{fl/fl}$ *AAV-TBG-GFP* controls); genes with significant differential expression (FDR<0.05) highlighted in colour (up-regulated in blue, down-regulated in red). Raw data from Guan et al. 2020 (37). **B.** Venn diagram showing overlap of significantly differentially expressed genes in liver RNA-seq from the three models: *Reverbα*$^{fl/fl}$*Reverbβ*$^{fl/fl}$ *AAV-TBG-CRE*, *Reverbα*$^{Flox2-6}$*Alb*^{CreERT2}, *Reverbα*$^{-/-}$. **C.** Fold-change (FC) and false discovery rate (FDR) of selected circadian clock and lipid metabolism genes from RNA-seq experiment in **A**.

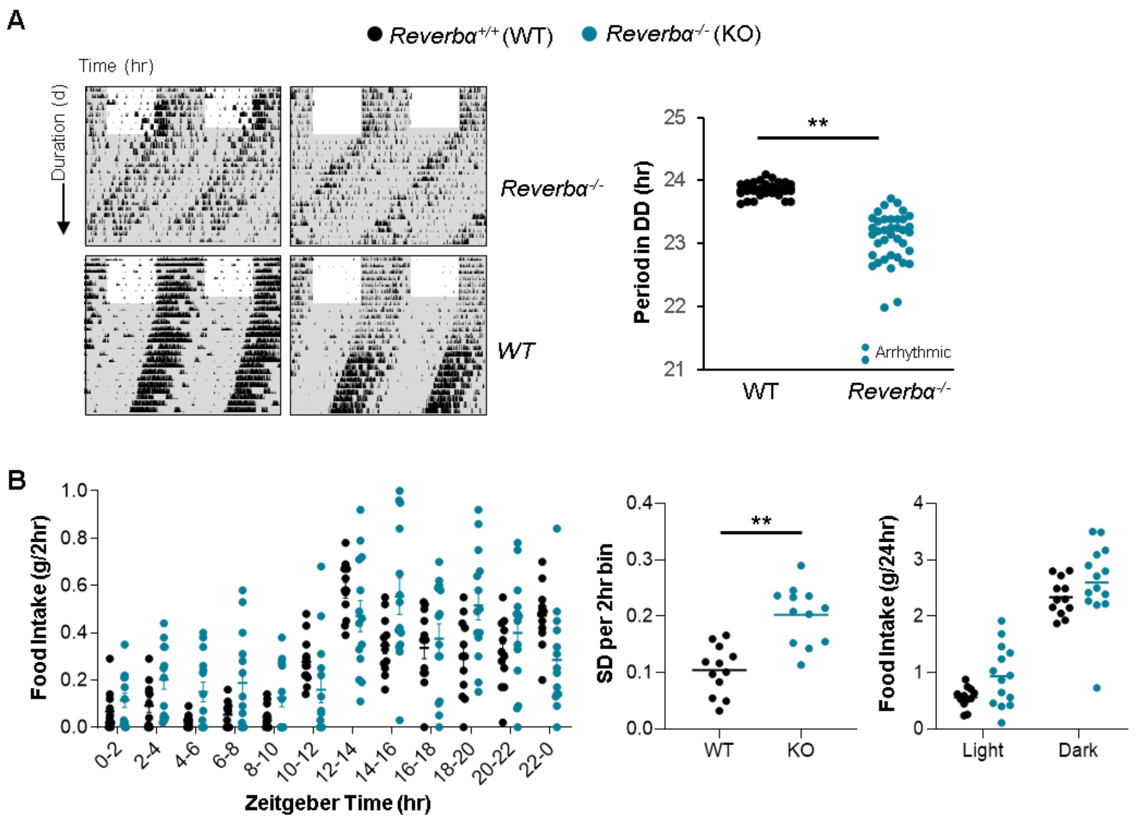
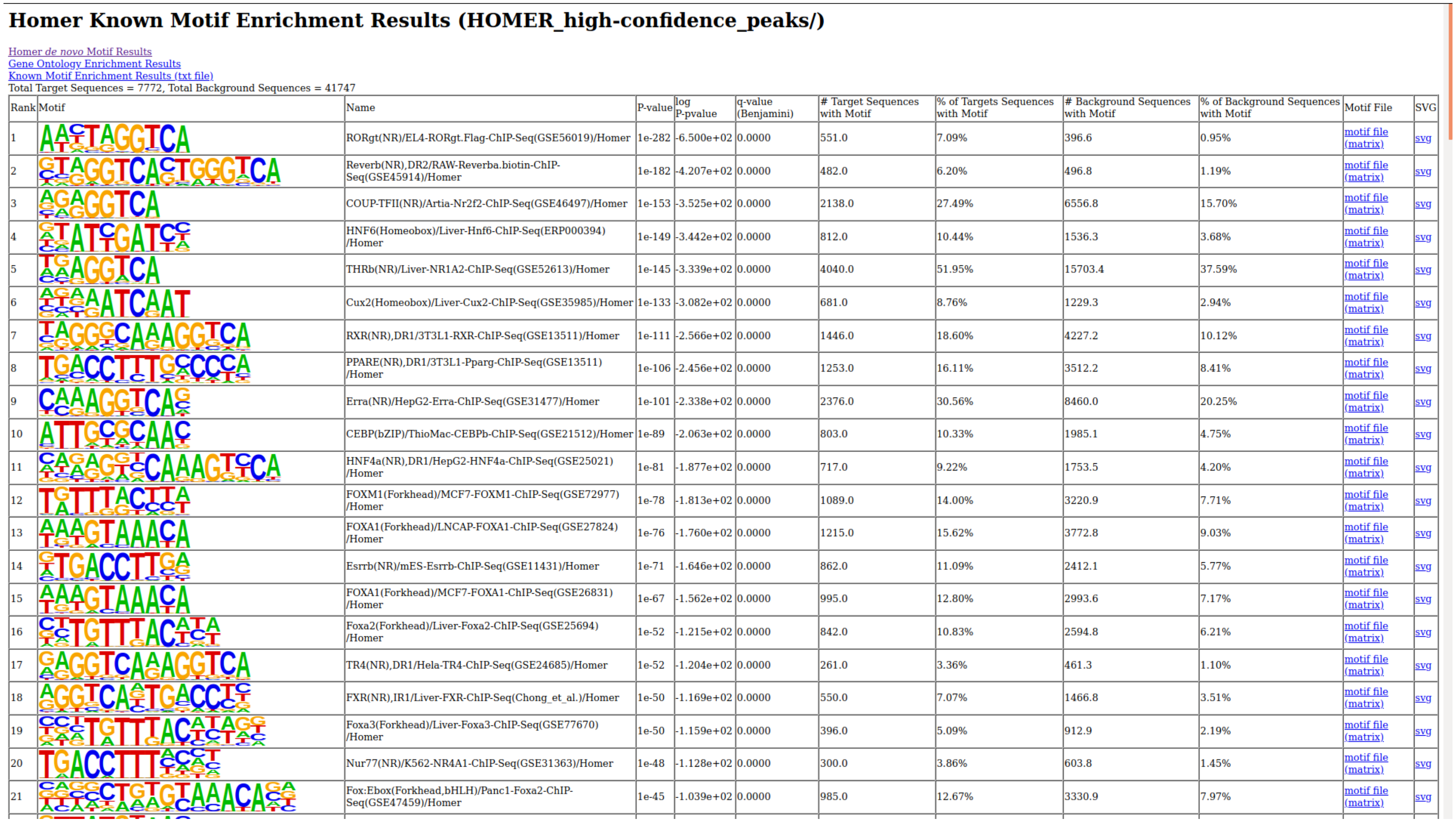


Fig. S5. A. Circadian wheel-running activity of *Reverbα*$^{-/-}$ mice and WT littermate controls under 12hr:12hr light:dark (LD) and constant darkness (DD) conditions. Representative actigrams shown on left, length of free-running period quantified on right. n=36-39 per group. **B.** Circadian patterns of food intake in single-housed *Reverbα*$^{-/-}$ (teal) and WT mice (black). Left plot shows food intake per two hour time window, middle plot shows standard deviation of data within each window, right plot shows total food intake over 24 hours. n=12-14 per group.

Data shown as individual data points plus mean +/- SEM, or with mean alone. **P<0.01, unpaired t-test (A, B).

Table S1. Known motif analysis of HaloREVERBα sites, random background

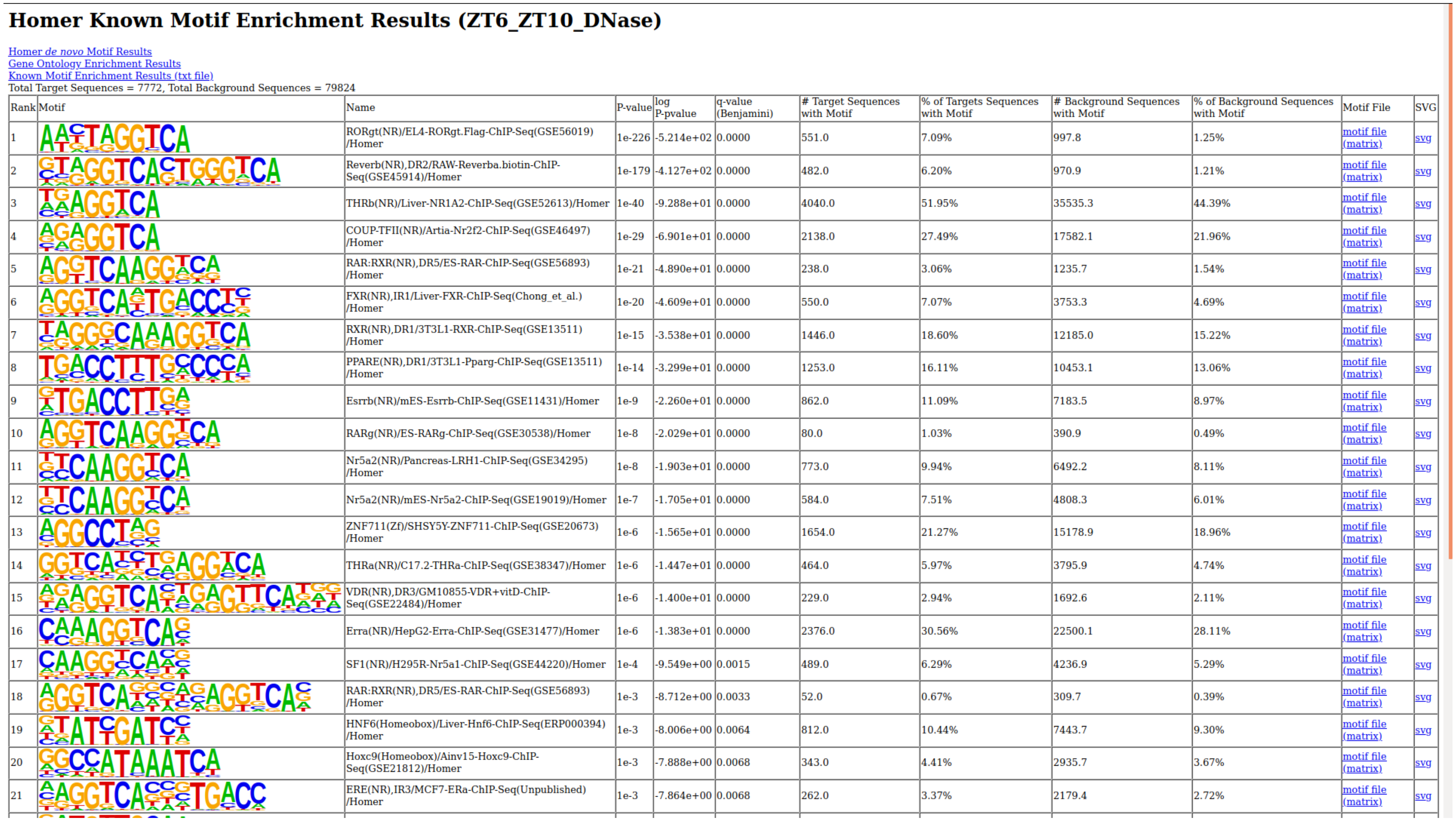


Homer Known Motif Enrichment Results (HOMER_high-confidence_peaks/)

Homer *de novo* Motif Results
Gene Ontology Enrichment Results
Known Motif Enrichment Results (txt file)
Total Target Sequences = 7772, Total Background Sequences = 41747

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif	Motif File	SVG
1		RORgt(NR)/EL4-RORgt.Flag-ChIP-Seq(GSE56019)/Homer	1e-282	-6.500e+02	0.0000	551.0	7.09%	396.6	0.95%	motif file (matrix)	svg
2		Reverb(NR),DR2/RAW-Reverba.biotin-ChIP-Seq(GSE45914)/Homer	1e-182	-4.207e+02	0.0000	482.0	6.20%	496.8	1.19%	motif file (matrix)	svg
3		COUP-TFII(NR)/Artia-Nr2f2-ChIP-Seq(GSE46497)/Homer	1e-153	-3.525e+02	0.0000	2138.0	27.49%	6556.8	15.70%	motif file (matrix)	svg
4		HNF6(Homeobox)/Liver-Hnf6-ChIP-Seq(ERP000394) /Homer	1e-149	-3.442e+02	0.0000	812.0	10.44%	1536.3	3.68%	motif file (matrix)	svg
5		THRb(NR)/Liver-NR1A2-ChIP-Seq(GSE52613)/Homer	1e-145	-3.339e+02	0.0000	4040.0	51.95%	15703.4	37.59%	motif file (matrix)	svg
6		Cux2(Homeobox)/Liver-Cux2-ChIP-Seq(GSE35985)/Homer	1e-133	-3.082e+02	0.0000	681.0	8.76%	1229.3	2.94%	motif file (matrix)	svg
7		RXR(NR),DR1/3T3L1-RXR-ChIP-Seq(GSE13511)/Homer	1e-111	-2.566e+02	0.0000	1446.0	18.60%	4227.2	10.12%	motif file (matrix)	svg
8		PPARE(NR),DR1/3T3L1-Pparg-ChIP-Seq(GSE13511) /Homer	1e-106	-2.456e+02	0.0000	1253.0	16.11%	3512.2	8.41%	motif file (matrix)	svg
9		Erra(NR)/HepG2-Erra-ChIP-Seq(GSE31477)/Homer	1e-101	-2.338e+02	0.0000	2376.0	30.56%	8460.0	20.25%	motif file (matrix)	svg
10		CEBP(bZIP)/ThioMac-CEBPb-ChIP-Seq(GSE21512)/Homer	1e-89	-2.063e+02	0.0000	803.0	10.33%	1985.1	4.75%	motif file (matrix)	svg
11		HNF4a(NR),DR1/HepG2-HNF4a-ChIP-Seq(GSE25021) /Homer	1e-81	-1.877e+02	0.0000	717.0	9.22%	1753.5	4.20%	motif file (matrix)	svg
12		FOXM1(Forkhead)/MCF7-FOXM1-ChIP-Seq(GSE72977) /Homer	1e-78	-1.813e+02	0.0000	1089.0	14.00%	3220.9	7.71%	motif file (matrix)	svg
13		FOXA1(Forkhead)/LNCAP-FOXA1-ChIP-Seq(GSE27824) /Homer	1e-76	-1.760e+02	0.0000	1215.0	15.62%	3772.8	9.03%	motif file (matrix)	svg
14		Esrrb(NR)/mES-Esrrb-ChIP-Seq(GSE11431)/Homer	1e-71	-1.646e+02	0.0000	862.0	11.09%	2412.1	5.77%	motif file (matrix)	svg
15		FOXA1(Forkhead)/MCF7-FOXA1-ChIP-Seq(GSE26831) /Homer	1e-67	-1.562e+02	0.0000	995.0	12.80%	2993.6	7.17%	motif file (matrix)	svg
16		Foxa2(Forkhead)/Liver-Foxa2-ChIP-Seq(GSE25694) /Homer	1e-52	-1.215e+02	0.0000	842.0	10.83%	2594.8	6.21%	motif file (matrix)	svg
17		TR4(NR),DR1/Hela-TR4-ChIP-Seq(GSE24685)/Homer	1e-52	-1.204e+02	0.0000	261.0	3.36%	461.3	1.10%	motif file (matrix)	svg
18		FXR(NR),IR1/Liver-FXR-ChIP-Seq(Chong_et_al.)/Homer	1e-50	-1.169e+02	0.0000	550.0	7.07%	1466.8	3.51%	motif file (matrix)	svg
19		Foxa3(Forkhead)/Liver-Foxa3-ChIP-Seq(GSE77670) /Homer	1e-50	-1.159e+02	0.0000	396.0	5.09%	912.9	2.19%	motif file (matrix)	svg
20		Nur77(NR)/K562-NR4A1-ChIP-Seq(GSE31363)/Homer	1e-48	-1.128e+02	0.0000	300.0	3.86%	603.8	1.45%	motif file (matrix)	svg
21		Fox:Ebox(Forkhead,bHLH)/Panc1-Foxa2-ChIP-Seq(GSE47459)/Homer	1e-45	-1.039e+02	0.0000	985.0	12.67%	3330.9	7.97%	motif file (matrix)	svg

Table S2. Known motif analysis of HaloREVERBα sites, DNase background

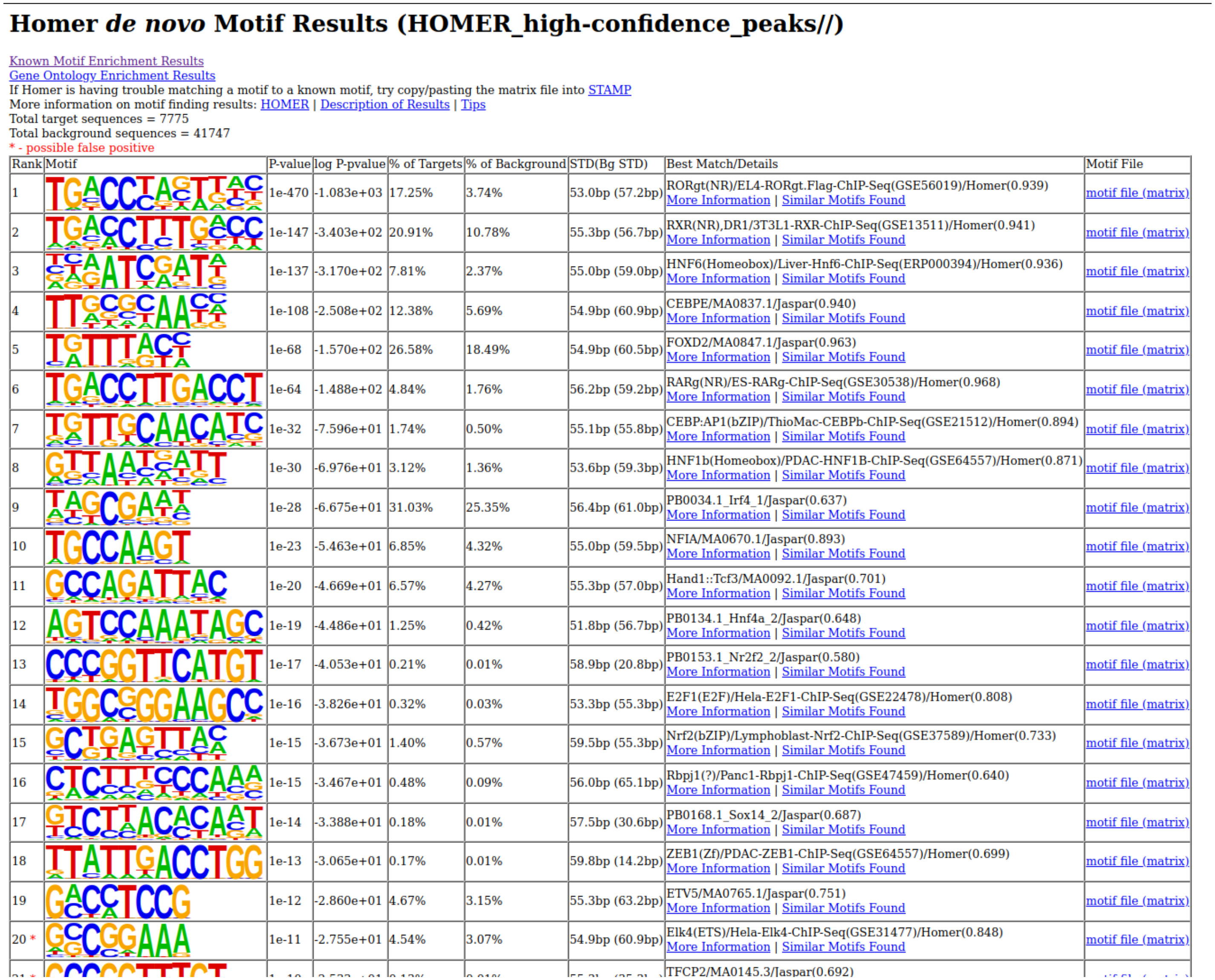


Homer Known Motif Enrichment Results (ZT6_ZT10_DNase)

Homer *de novo* Motif Results
Gene Ontology Enrichment Results
Known Motif Enrichment Results (txt file)
Total Target Sequences = 7772, Total Background Sequences = 79824

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif	Motif File	SVG
1		RORgt(NR)/EL4-RORgt.Flag-ChIP-Seq(GSE56019)/Homer	1e-226	-5.214e+02	0.0000	551.0	7.09%	997.8	1.25%	motif file (matrix)	svg
2		Reverb(NR),DR2/RAW-Reverba.biotin-ChIP-Seq(GSE45914)/Homer	1e-179	-4.127e+02	0.0000	482.0	6.20%	970.9	1.21%	motif file (matrix)	svg
3		THRb(NR)/Liver-NR1A2-ChIP-Seq(GSE52613)/Homer	1e-40	-9.288e+01	0.0000	4040.0	51.95%	35535.3	44.39%	motif file (matrix)	svg
4		COUP-TFII(NR)/Artia-Nr2f2-ChIP-Seq(GSE46497)/Homer	1e-29	-6.901e+01	0.0000	2138.0	27.49%	17582.1	21.96%	motif file (matrix)	svg
5		RAR:RXR(NR),DR5/ES-RAR-ChIP-Seq(GSE56893)/Homer	1e-21	-4.890e+01	0.0000	238.0	3.06%	1235.7	1.54%	motif file (matrix)	svg
6		FXR(NR),IR1/Liver-FXR-ChIP-Seq(Chong_et_al.)/Homer	1e-20	-4.609e+01	0.0000	550.0	7.07%	3753.3	4.69%	motif file (matrix)	svg
7		RXR(NR),DR1/3T3L1-RXR-ChIP-Seq(GSE13511)/Homer	1e-15	-3.538e+01	0.0000	1446.0	18.60%	12185.0	15.22%	motif file (matrix)	svg
8		PPARE(NR),DR1/3T3L1-Pparg-ChIP-Seq(GSE13511)/Homer	1e-14	-3.299e+01	0.0000	1253.0	16.11%	10453.1	13.06%	motif file (matrix)	svg
9		Esrrb(NR)/mES-Esrrb-ChIP-Seq(GSE11431)/Homer	1e-9	-2.260e+01	0.0000	862.0	11.09%	7183.5	8.97%	motif file (matrix)	svg
10		RARg(NR)/ES-RARg-ChIP-Seq(GSE30538)/Homer	1e-8	-2.029e+01	0.0000	80.0	1.03%	390.9	0.49%	motif file (matrix)	svg
11		Nr5a2(NR)/Pancreas-LRH1-ChIP-Seq(GSE34295)/Homer	1e-8	-1.903e+01	0.0000	773.0	9.94%	6492.2	8.11%	motif file (matrix)	svg
12		Nr5a2(NR)/mES-Nr5a2-ChIP-Seq(GSE19019)/Homer	1e-7	-1.705e+01	0.0000	584.0	7.51%	4808.3	6.01%	motif file (matrix)	svg
13		ZNF711(Zf)/SHSY5Y-ZNF711-ChIP-Seq(GSE20673)/Homer	1e-6	-1.565e+01	0.0000	1654.0	21.27%	15178.9	18.96%	motif file (matrix)	svg
14		THRa(NR)/C17.2-THRa-ChIP-Seq(GSE38347)/Homer	1e-6	-1.447e+01	0.0000	464.0	5.97%	3795.9	4.74%	motif file (matrix)	svg
15		VDR(NR),DR3/GM10855-VDR+vitD-ChIP-Seq(GSE22484)/Homer	1e-6	-1.400e+01	0.0000	229.0	2.94%	1692.6	2.11%	motif file (matrix)	svg
16		Erra(NR)/HepG2-Erra-ChIP-Seq(GSE31477)/Homer	1e-6	-1.383e+01	0.0000	2376.0	30.56%	22500.1	28.11%	motif file (matrix)	svg
17		SF1(NR)/H295R-Nr5a1-ChIP-Seq(GSE44220)/Homer	1e-4	-9.549e+00	0.0015	489.0	6.29%	4236.9	5.29%	motif file (matrix)	svg
18		RAR:RXR(NR),DR5/ES-RAR-ChIP-Seq(GSE56893)/Homer	1e-3	-8.712e+00	0.0033	52.0	0.67%	309.7	0.39%	motif file (matrix)	svg
19		HNF6(Homeobox)/Liver-Hnf6-ChIP-Seq(ERP000394)/Homer	1e-3	-8.006e+00	0.0064	812.0	10.44%	7443.7	9.30%	motif file (matrix)	svg
20		Hoxc9(Homeobox)/Ainv15-Hoxc9-ChIP-Seq(GSE21812)/Homer	1e-3	-7.888e+00	0.0068	343.0	4.41%	2935.7	3.67%	motif file (matrix)	svg
21		ERE(NR),IR3/MCF7-ERa-ChIP-Seq(Unpublished)/Homer	1e-3	-7.864e+00	0.0068	262.0	3.37%	2179.4	2.72%	motif file (matrix)	svg

Table S3. *De novo* motif analysis of HaloREVERBα sites, random background

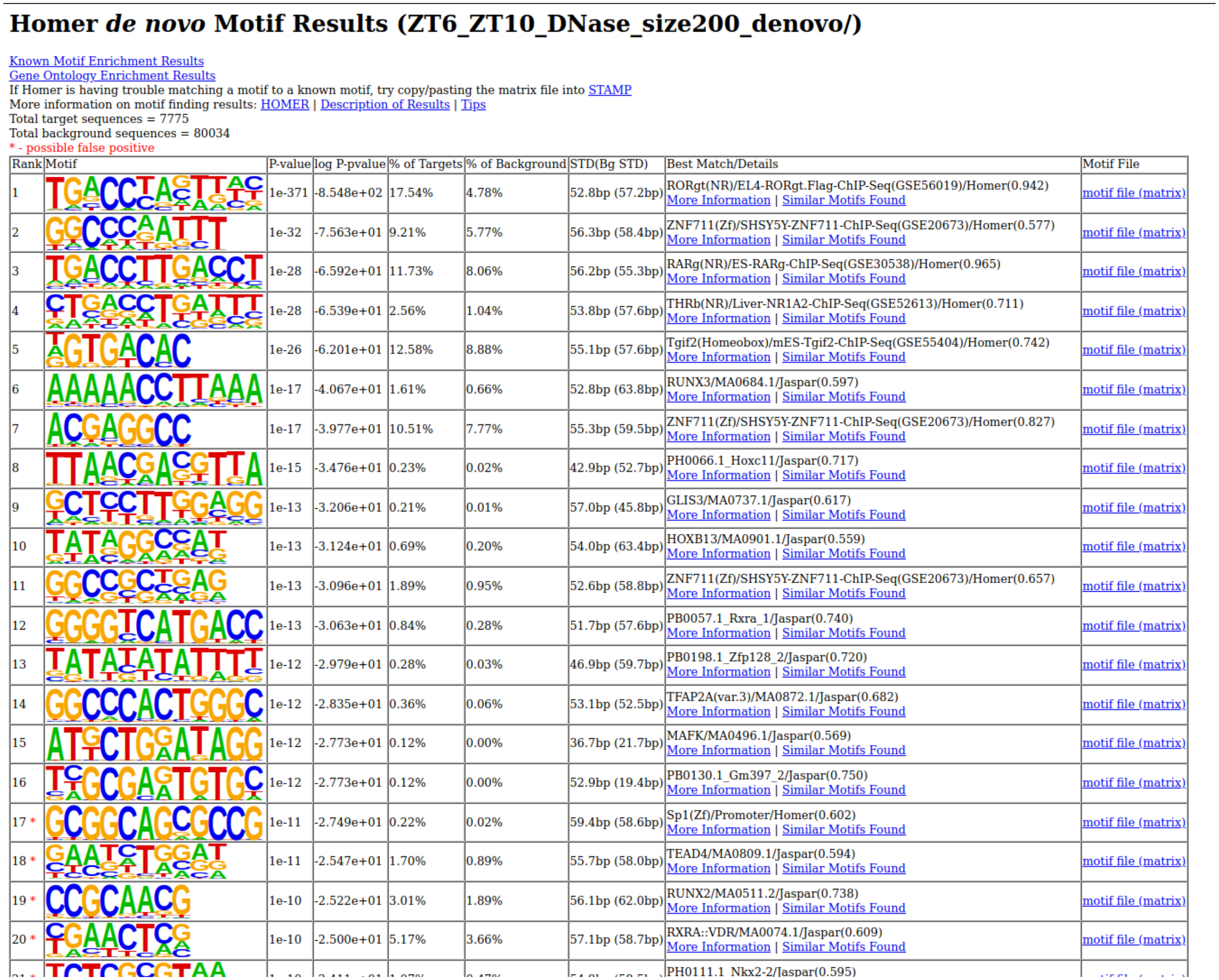


Homer *de novo* Motif Results (HOMER_high-confidence_peaks//)

Known Motif Enrichment Results
Gene Ontology Enrichment Results
If Homer is having trouble matching a motif to a known motif, try copy/pasting the matrix file into STAMP
More information on motif finding results: HOMER | Description of Results | Tips
Total target sequences = 7775
Total background sequences = 41747
* - possible false positive

Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details	Motif File
1		1e-470	-1.083e+03	17.25%	3.74%	53.0bp (57.2bp)	RORgt(NR)/EL4-RORgt.Flag-ChIP-Seq(GSE56019)/Homer(0.939) More Information | Similar Motifs Found	motif file (matrix)
2		1e-147	-3.403e+02	20.91%	10.78%	55.3bp (56.7bp)	RXR(NR),DR1/3T3L1-RXR-ChIP-Seq(GSE13511)/Homer(0.941) More Information | Similar Motifs Found	motif file (matrix)
3		1e-137	-3.170e+02	7.81%	2.37%	55.0bp (59.0bp)	HNF6(Homeobox)/Liver-Hnf6-ChIP-Seq(ERP000394)/Homer(0.936) More Information | Similar Motifs Found	motif file (matrix)
4		1e-108	-2.508e+02	12.38%	5.69%	54.9bp (60.9bp)	CEBPE/MA0837.1/Jaspar(0.940) More Information | Similar Motifs Found	motif file (matrix)
5		1e-68	-1.570e+02	26.58%	18.49%	54.9bp (60.5bp)	FOXD2/MA0847.1/Jaspar(0.963) More Information | Similar Motifs Found	motif file (matrix)
6		1e-64	-1.488e+02	4.84%	1.76%	56.2bp (59.2bp)	RARg(NR)/ES-RARg-ChIP-Seq(GSE30538)/Homer(0.968) More Information | Similar Motifs Found	motif file (matrix)
7		1e-32	-7.596e+01	1.74%	0.50%	55.1bp (55.8bp)	CEBP:AP1(bZIP)/ThioMac-CEBPb-ChIP-Seq(GSE21512)/Homer(0.894) More Information | Similar Motifs Found	motif file (matrix)
8		1e-30	-6.976e+01	3.12%	1.36%	53.6bp (59.3bp)	HNF1b(Homeobox)/PDAC-HNF1B-ChIP-Seq(GSE64557)/Homer(0.871) More Information | Similar Motifs Found	motif file (matrix)
9		1e-28	-6.675e+01	31.03%	25.35%	56.4bp (61.0bp)	PB0034.1_Irf4_1/Jaspar(0.637) More Information | Similar Motifs Found	motif file (matrix)
10		1e-23	-5.463e+01	6.85%	4.32%	55.0bp (59.5bp)	NFIA/MA0670.1/Jaspar(0.893) More Information | Similar Motifs Found	motif file (matrix)
11		1e-20	-4.669e+01	6.57%	4.27%	55.3bp (57.0bp)	Hand1::Tcf3/MA0092.1/Jaspar(0.701) More Information | Similar Motifs Found	motif file (matrix)
12		1e-19	-4.486e+01	1.25%	0.42%	51.8bp (56.7bp)	PB0134.1_Hnf4a_2/Jaspar(0.648) More Information | Similar Motifs Found	motif file (matrix)
13		1e-17	-4.053e+01	0.21%	0.01%	58.9bp (20.8bp)	PB0153.1_Nr2f2_2/Jaspar(0.580) More Information | Similar Motifs Found	motif file (matrix)
14		1e-16	-3.826e+01	0.32%	0.03%	53.3bp (55.3bp)	E2F1(E2F)/Hela-E2F1-ChIP-Seq(GSE22478)/Homer(0.808) More Information | Similar Motifs Found	motif file (matrix)
15		1e-15	-3.673e+01	1.40%	0.57%	59.5bp (55.3bp)	Nrf2(bZIP)/Lymphoblast-Nrf2-ChIP-Seq(GSE37589)/Homer(0.733) More Information | Similar Motifs Found	motif file (matrix)
16		1e-15	-3.467e+01	0.48%	0.09%	56.0bp (65.1bp)	Rbpj1(?)/Panc1-Rbpj1-ChIP-Seq(GSE47459)/Homer(0.640) More Information | Similar Motifs Found	motif file (matrix)
17		1e-14	-3.388e+01	0.18%	0.01%	57.5bp (30.6bp)	PB0168.1_Sox14_2/Jaspar(0.687) More Information | Similar Motifs Found	motif file (matrix)
18		1e-13	-3.065e+01	0.17%	0.01%	59.8bp (14.2bp)	ZEB1(Zf)/PDAC-ZEB1-ChIP-Seq(GSE64557)/Homer(0.699) More Information | Similar Motifs Found	motif file (matrix)
19		1e-12	-2.860e+01	4.67%	3.15%	55.3bp (63.2bp)	ETV5/MA0765.1/Jaspar(0.751) More Information | Similar Motifs Found	motif file (matrix)
20 *		1e-11	-2.755e+01	4.54%	3.07%	54.9bp (60.9bp)	Elk4(ETS)/Hela-Elk4-ChIP-Seq(GSE31477)/Homer(0.848) More Information | Similar Motifs Found	motif file (matrix)
							TFCP2/MA0145.3/Jaspar(0.692)	

Table S4. *De novo* motif analysis of HaloREVERBα sites, DNase background



Homer *de novo* Motif Results (ZT6_ZT10_DNase_size200_denovo/)

Known Motif Enrichment Results
Gene Ontology Enrichment Results
If Homer is having trouble matching a motif to a known motif, try copy/pasting the matrix file into STAMP
More information on motif finding results: HOMER | Description of Results | Tips
Total target sequences = 7775
Total background sequences = 80034
* - possible false positive

Rank	Motif	P-value	log P-pvalue	% of Targets	% of Background	STD(Bg STD)	Best Match/Details	Motif File
1		1e-371	-8.548e+02	17.54%	4.78%	52.8bp (57.2bp)	RORgt(NR)/EL4-RORgt.Flag-ChIP-Seq(GSE56019)/Homer(0.942) More Information | Similar Motifs Found	motif file (matrix)
2		1e-32	-7.563e+01	9.21%	5.77%	56.3bp (58.4bp)	ZNF711(Zf)/SHSY5Y-ZNF711-ChIP-Seq(GSE20673)/Homer(0.577) More Information | Similar Motifs Found	motif file (matrix)
3		1e-28	-6.592e+01	11.73%	8.06%	56.2bp (55.3bp)	RARg(NR)/ES-RARg-ChIP-Seq(GSE30538)/Homer(0.965) More Information | Similar Motifs Found	motif file (matrix)
4		1e-28	-6.539e+01	2.56%	1.04%	53.8bp (57.6bp)	THRb(NR)/Liver-NR1A2-ChIP-Seq(GSE52613)/Homer(0.711) More Information | Similar Motifs Found	motif file (matrix)
5		1e-26	-6.201e+01	12.58%	8.88%	55.1bp (57.6bp)	Tgif2(Homeobox)/mES-Tgif2-ChIP-Seq(GSE55404)/Homer(0.742) More Information | Similar Motifs Found	motif file (matrix)
6		1e-17	-4.067e+01	1.61%	0.66%	52.8bp (63.8bp)	RUNX3/MA0684.1/Jaspar(0.597) More Information | Similar Motifs Found	motif file (matrix)
7		1e-17	-3.977e+01	10.51%	7.77%	55.3bp (59.5bp)	ZNF711(Zf)/SHSY5Y-ZNF711-ChIP-Seq(GSE20673)/Homer(0.827) More Information | Similar Motifs Found	motif file (matrix)
8		1e-15	-3.476e+01	0.23%	0.02%	42.9bp (52.7bp)	PH0066.1_Hoxc11/Jaspar(0.717) More Information | Similar Motifs Found	motif file (matrix)
9		1e-13	-3.206e+01	0.21%	0.01%	57.0bp (45.8bp)	GLIS3/MA0737.1/Jaspar(0.617) More Information | Similar Motifs Found	motif file (matrix)
10		1e-13	-3.124e+01	0.69%	0.20%	54.0bp (63.4bp)	HOXB13/MA0901.1/Jaspar(0.559) More Information | Similar Motifs Found	motif file (matrix)
11		1e-13	-3.096e+01	1.89%	0.95%	52.6bp (58.8bp)	ZNF711(Zf)/SHSY5Y-ZNF711-ChIP-Seq(GSE20673)/Homer(0.657) More Information | Similar Motifs Found	motif file (matrix)
12		1e-13	-3.063e+01	0.84%	0.28%	51.7bp (57.6bp)	PB0057.1_Rxra_1/Jaspar(0.740) More Information | Similar Motifs Found	motif file (matrix)
13		1e-12	-2.979e+01	0.28%	0.03%	46.9bp (59.7bp)	PB0198.1_Zfp128_2/Jaspar(0.720) More Information | Similar Motifs Found	motif file (matrix)
14		1e-12	-2.835e+01	0.36%	0.06%	53.1bp (52.5bp)	TFAP2A(var.3)/MA0872.1/Jaspar(0.682) More Information | Similar Motifs Found	motif file (matrix)
15		1e-12	-2.773e+01	0.12%	0.00%	36.7bp (21.7bp)	MAFK/MA0496.1/Jaspar(0.569) More Information | Similar Motifs Found	motif file (matrix)
16		1e-12	-2.773e+01	0.12%	0.00%	52.9bp (19.4bp)	PB0130.1_Gm397_2/Jaspar(0.750) More Information | Similar Motifs Found	motif file (matrix)
17 *		1e-11	-2.749e+01	0.22%	0.02%	59.4bp (58.6bp)	Sp1(Zf)/Promoter/Homer(0.602) More Information | Similar Motifs Found	motif file (matrix)
18 *		1e-11	-2.547e+01	1.70%	0.89%	55.7bp (58.0bp)	TEAD4/MA0809.1/Jaspar(0.594) More Information | Similar Motifs Found	motif file (matrix)
19 *		1e-10	-2.522e+01	3.01%	1.89%	56.1bp (62.0bp)	RUNX2/MA0511.2/Jaspar(0.738) More Information | Similar Motifs Found	motif file (matrix)
20 *		1e-10	-2.500e+01	5.17%	3.66%	57.1bp (58.7bp)	RXRA::VDR/MA0074.1/Jaspar(0.609) More Information | Similar Motifs Found	motif file (matrix)
							PH0111.1_Nkx2-2/Jaspar(0.595)	

Table S5. GIGGLE output for HaloREVERBα sites

GSM_ID	Factor	Biosource	GIGGLE_score
GSM890125	NR1D2	Epithelium;Liver	2183.43348
GSM647027	NCOR1	Hepatocyte;Liver	2030.090601
GSM2406335	HNF4A	Liver	2011.159414
GSM647029	NR1D1	Hepatocyte;Liver	2000.541779
GSM1659699	HDAC3	Liver	1971.84942
GSM647024	HDAC3	Hepatocyte;Liver	1961.619638
GSM2287957	HDAC3	Liver	1943.174958
GSM1659695	HDAC3	Liver	1931.463445
GSM2406342	HNF4A	Liver	1930.922742
GSM2406341	HNF4A	Liver	1918.547106
GSM1044697	HDAC3	Epithelium;Liver	1916.908297
GSM2287955	HDAC3	Liver	1913.488117
GSM2287956	HDAC3	Liver	1905.265888
GSM2406329	HDAC3	Liver	1903.926047
GSM2406330	HDAC3	Liver	1896.90569
GSM2406336	HNF4A	Liver	1892.608977
GSM2287952	HDAC3	Liver	1886.231319
GSM2287954	HDAC3	Liver	1870.257728
GSM1659696	HDAC3	Liver	1862.933693
GSM2287953	HDAC3	Liver	1857.278636
GSM647028	NCOR1	Hepatocyte;Liver	1849.188389
GSM647023	HDAC3	Hepatocyte;Liver	1838.643677
GSM1163179	PPARA	Liver	1819.370416
GSM647022	HDAC3	Hepatocyte;Liver	1819.27416
GSM864672	PPARA	Hepatocyte;Liver	1803.517627
GSM2406331	HDAC3	Liver	1790.967104
GSM1163177	PPARA	Liver	1789.423476
GSM1163173	PPARA	Liver	1771.382774
GSM1163175	PPARA	Liver	1756.079456
GSM864674	RXRA	Hepatocyte;Liver	1749.982626
GSM864671	PPARA	Hepatocyte;Liver	1740.280577
GSM1659697	HDAC3	Liver	1726.916984
GSM864678	RXRA	Hepatocyte;Liver	1722.713073
GSM784034	STAT5B	Hepatocyte;Liver	1720.547427
GSM864677	RXRA	Hepatocyte;Liver	1712.28847
GSM864669	NR1H2	Hepatocyte;Liver	1701.08137
GSM864673	RXRA	Hepatocyte;Liver	1700.948838
GSM864676	RXRA	Hepatocyte;Liver	1700.912184
GSM2218849	NR1D1	Liver	1700.226489
GSM864668	NR1H2	Hepatocyte;Liver	1700.119511
GSM784035	STAT5B	Hepatocyte;Liver	1695.709283
GSM784036	STAT5B	Hepatocyte;Liver	1688.784262
GSM784037	STAT5B	Hepatocyte;Liver	1684.741875
GSM2218850	NR1D1	Liver	1682.64997
GSM2218847	NR1D1	Liver	1678.782331
GSM2218851	NR1D1	Liver	1675.890775
GSM1163176	RXRA	Liver	1672.116631

GSM1163174	RXRA	Liver	1670.005189
GSM864675	RXRA	Hepatocyte;Liver	1669.224104
GSM784033	STAT5B	Hepatocyte;Liver	1667.554515
GSM1263820	ESR1	Epithelium;Liver	1663.793934
GSM2218846	NR1D1	Liver	1657.242274
GSM840528	NR1D1	Epithelium;Liver	1650.28428
GSM1514929	PPARA	Epithelium;Liver	1640.684169
GSM1659689	NR1D1	Liver	1638.885877
GSM784041	BCL6	Hepatocyte;Liver	1637.814977
GSM784040	BCL6	Hepatocyte;Liver	1636.935823
GSM1163172	RXRA	Liver	1636.878473
GSM1659693	RORC	Liver	1627.561398
GSM784038	BCL6	Hepatocyte;Liver	1615.0622
GSM1463852	ONECUT1	Liver	1612.163861
GSM2699481	RORA	Liver	1605.344092
GSM1437734	RORA	Liver	1603.032306
GSM717562	FOXA2	Hepatocyte;Liver	1602.869545
GSM634623	FOXA2	Hepatocyte;Liver	1602.869545
GSM1299603	RXRA	Liver	1601.210051
GSM1936964	NR3C1	L 101;Liver	1588.070223
GSM1163178	RXRA	Liver	1587.187126
GSM2068830	FOXA2	Liver	1585.081425
GSM1936963	NR3C1	L 101;Liver	1582.650403
GSM784039	BCL6	Hepatocyte;Liver	1579.161178
GSM784043	BCL6	Hepatocyte;Liver	1573.085937
GSM1724239	FOXA2	3C10;Liver	1571.069361
GSM1477607	FOXA2	Epithelium;Liver	1570.141139
GSM982750	CRY2	Epithelium;Liver	1567.460856
GSM784031	STAT5B	Hepatocyte;Liver	1561.993883
GSM1138337	RXRA	Liver	1559.314539
GSM1299600	RXRA	Liver	1559.314539
GSM2218848	NR1D1	Liver	1559.124541
GSM1446062	NR3C1	Liver	1557.779831
GSM1463853	ONECUT1	Liver	1556.601189
GSM1030547	TBP	10T1/2;Fibroblast;Embryo	1555.033111
GSM840529	NR1D2	Epithelium;Liver	1553.425577
GSM864670	NR1H2	Hepatocyte;Liver	1551.128388
GSM1588480	ARID1A	Hepatocyte;Liver	1545.633094
GSM1390706	GTF2E2	Epithelium;Liver	1545.0311
GSM784042	BCL6	Hepatocyte;Liver	1541.775505
GSM982748	CRY2	Epithelium;Liver	1537.463406
GSM1236494	NCOR2	Epithelium;Liver	1536.7177
GSM1724234	FOXA2	3C10;Liver	1534.81178
GSM1854433	CEBPB	Liver	1533.734973
GSM1446074	NR3C1	Liver	1533.537235
GSM541305	RXRA	Epithelium;Liver	1527.602597
GSM1936965	NR3C1	L 101;Liver	1524.949364
GSM982774	POLR2A	Epithelium;Liver	1523.254675
GSM784027	STAT5B	Hepatocyte;Liver	1522.240421
GSM982753	CRY2	Epithelium;Liver	1522.13382
GSM1211424	ESR1	Liver	1521.456415

GSM982773	POLR2A	Epithelium;Liver	1520.085638
GSM1390699	TBP	Epithelium;Liver	1519.671267
GSM1659687	NR1D1	Liver	1518.292957
GSM982781	POLR2A	Epithelium;Liver	1518.29246
GSM1659686	NR1D1	Liver	1512.922211
GSM1384739	FOXA2	Liver	1512.532722
GSM1854437	CEBPB	Liver	1508.235425
GSM1390703	GTF2B	Epithelium;Liver	1508.046852
GSM1446072	NR3C1	Liver	1507.353969
GSM1446064	NR3C1	Liver	1503.865292
GSM982779	POLR2A	Epithelium;Liver	1501.814302
GSM541292	RXRA	Epithelium;Liver	1500.507728
GSM2055885	CEBPB	Liver	1500.449589
GSM982731	PER1	Epithelium;Liver	1500.037154
GSM2406344	HNF4A	Liver	1498.9951
GSM878679	CUX2	Epithelium;Liver	1498.164972
GSM967657	TBP	TSC;Trophoblast Stem Cell;Embryo	1497.126492
GSM1390704	GTF2B	Epithelium;Liver	1496.263974
GSM1446071	NR3C1	Liver	1495.827147
GSM1854435	CEBPB	Liver	1495.568214
GSM982777	POLR2A	Epithelium;Liver	1494.83651
GSM1390705	GTF2E2	Epithelium;Liver	1494.415547
GSM2102917	POLR2A	Mammary Gland	1494.279826
GSM1390700	TBP	Epithelium;Liver	1493.85364
GSM864689	POLR2A	Hepatocyte;Liver	1493.831068
GSM1106101	CDK9	Embryonic Fibroblast;Embryo	1492.865879
GSM982780	POLR2A	Epithelium;Liver	1492.32652
GSM1037673	POLR2A	Epithelium;Liver	1492.044067
GSM2406343	HNF4A	Liver	1490.244493
GSM423364	POLR2A	Neural Progenitor Cell;Embryo	1489.940084
GSM1446063	NR3C1	Liver	1489.734067
GSM541304	RXRA	Epithelium;Liver	1488.487382
GSM982782	POLR2A	Epithelium;Liver	1486.362001
GSM1854432	CEBPB	Liver	1483.989521
GSM2406338	HNF4A	Liver	1482.937646
GSM982778	POLR2A	Epithelium;Liver	1482.877728
GSM1463855	ONECUT1	Liver	1482.850586
GSM864683	POLR2A	Hepatocyte;Liver	1482.140241
GSM2055884	FOXA3	Liver	1480.690358
GSM1301670	CLOCK	Liver	1480.625377
GSM541301	RXRA	Epithelium;Liver	1480.562139
GSM2055886	CEBPB	Liver	1479.700154
GSM982746	CRY1	Epithelium;Liver	1477.846077
GSM1463857	ONECUT1	Liver	1477.613594
GSM1236495	NCOR2	Epithelium;Liver	1477.134236
GSM541295	RXRA	Epithelium;Liver	1475.121913
GSM982751	CRY2	Epithelium;Liver	1474.830513
GSM863769	TCF4	Hepatocyte	1474.039259
GSM982737	PER2	Epithelium;Liver	1473.402112
GSM1437733	NFIL3	Liver	1473.137772
GSM982736	PER2	Epithelium;Liver	1470.586395

GSM1446065	NR3C1	Liver	1469.596156
GSM864687	POLR2A	Hepatocyte;Liver	1467.725323
GSM2790896	BRDT	Skeletal Muscle	1467.185397
GSM982752	CRY2	Epithelium;Liver	1467.166719
GSM1463859	ONECUT1	Liver	1465.149893
GSM918738	POLR2A	Epithelium;Liver	1465.105278
GSM2055887	HNF4A	Liver	1463.847654
GSM2633466	BRD4	Preadipocyte	1463.550631
GSM874951	POLR2B	Epithelium;Liver	1458.862009
GSM1382346	POLR2A	Fibroblast;Embryo	1457.108117
GSM2406332	PROX1	Liver	1456.758334
GSM2100638	TBP	Testis	1456.009931
GSM982738	PER2	Epithelium;Liver	1455.213386
GSM541300	RXRA	Epithelium;Liver	1455.208271
GSM1463856	ONECUT1	Liver	1455.196457
GSM982743	CRY1	Epithelium;Liver	1454.047397
GSM2100637	TBP	Testis	1453.380479
GSM982745	CRY1	Epithelium;Liver	1452.967436
GSM982757	CREBBP	Epithelium;Liver	1452.016604
GSM542588	POLR2A	Hepatocyte;Liver	1450.611062
GSM2470637	BRD4	AT-3	1449.816267
GSM784030	STAT5B	Hepatocyte;Liver	1449.721241
GSM1514931	PPARA	Epithelium;Liver	1449.423749
GSM1947436	POLR2A	B Lymphocyte	1449.317336
GSM1199137	POLR2A	3T3-L1;Preadipocyte;Adipose	1449.289952
GSM1865397	POLR2A	C2C12;Myoblast;Muscle	1448.72629
GSM1272601	THRB	Liver	1448.541893
GSM1635081	POLR2A	lens	1448.179111
GSM2406337	HNF4A	Liver	1447.978376
GSM917525	POLR2A	Embryonic Fibroblast;Embryo	1447.97538
GSM1947442	POLR2A	B Lymphocyte	1446.780764
GSM1106084	POLR2A	Embryonic Fibroblast;Embryo	1446.568615
GSM1111748	NR3C1	Liver	1446.196358
GSM982688	ARNTL	Epithelium;Liver	1446.120337
GSM982758	CREBBP	Epithelium;Liver	1445.992735
GSM2087162	ESR2	Epididymal White Adipose Tissue	1445.821914
GSM851319	POLR2A	Epithelium;Placenta	1445.594093
GSM1106087	POLR2A	Embryonic Fibroblast;Embryo	1443.871784
GSM864681	POLR2A	Hepatocyte;Liver	1443.77893
GSM2220070	POLR2A	Liver	1443.450411
GSM2065678	POLR2A	Epithelium;Intestine	1442.964878
GSM864679	POLR2A	Hepatocyte;Liver	1442.593231
GSM1267724	POLR2A	Epithelium;Forelimb	1442.457422
GSM864685	POLR2A	Hepatocyte;Liver	1441.109221
GSM864688	POLR2A	Hepatocyte;Liver	1441.06736
GSM917531	POLR2A	Embryonic Fibroblast;Embryo	1440.515769
GSM1087778	ARNTL	Liver	1440.391539
GSM2790892	BRD4	Skeletal Muscle	1439.679395
GSM541306	POLR2A	Epithelium;Liver	1439.577082
GSM1122543	POLR2A	Epithelium;Liver	1439.397792
GSM1199136	POLR2A	3T3-L1;Preadipocyte;Adipose	1439.118223

Table S6. Reactome pathway enrichment of differentially expressed genes in liver of *Reverbα*$^{Flox2\text{-}6}$*Alb*^{CreERT2} mice (20 terms with smallest Padj values shown).

ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count
R-MMU-425366	Transport of bile salts and organic acids, metal ions and amine compounds	8/116	76/8828	6.25E-06	0.00238	0.0023	8
R-MMU-425407	SLC-mediated transmembrane transport	11/116	226/8828	0.00018	0.034251	0.0334	11
R-MMU-383280	Nuclear Receptor transcription pathway	5/116	50/8828	0.000475	0.060317	0.0588	5
R-MMU-204998	Cell death signalling via NRAGE, NRIF and NADE	5/116	68/8828	0.001937	0.184534	0.18	5
R-MMU-425410	Metal ion SLC transporters	3/116	21/8828	0.002474	0.18852	0.1839	3
R-MMU-193648	NRAGE signals death through JNK	4/116	49/8828	0.003803	0.231702	0.226	4
R-MMU-193704	p75 NTR receptor-mediated signalling	5/116	83/8828	0.004619	0.231702	0.226	5
R-MMU-170834	Signaling by TGF-beta Receptor Complex	4/116	54/8828	0.005399	0.231702	0.226	4
R-MMU-73887	Death Receptor Signalling	6/116	124/8828	0.005745	0.231702	0.226	6
R-MMU-2022090	Assembly of collagen fibrils and other multimeric structures	4/116	57/8828	0.006544	0.231702	0.226	4
R-MMU-194840	Rho GTPase cycle	6/116	128/8828	0.00669	0.231702	0.226	6
R-MMU-1251985	Nuclear signaling by ERBB4	2/116	12/8828	0.010367	0.290013	0.2828	2
R-MMU-1475029	Reversible hydration of carbon dioxide	2/116	12/8828	0.010367	0.290013	0.2828	2
R-MMU-1236394	Signaling by ERBB4	3/116	35/8828	0.010657	0.290013	0.2828	3
R-MMU-200425	Import of palmitoyl-CoA into the mitochondrial matrix	2/116	14/8828	0.014051	0.310599	0.3029	2
R-MMU-2173791	TGF-beta receptor signaling in EMT (epithelial to mesenchymal transition)	2/116	14/8828	0.014051	0.310599	0.3029	2
R-MMU-5633008	TP53 Regulates Transcription of Cell Death Genes	2/116	14/8828	0.014051	0.310599	0.3029	2
R-MMU-416482	G alpha (12/13) signalling events	4/116	72/8828	0.014674	0.310599	0.3029	4
R-MMU-194068	Bile acid and bile salt metabolism	3/116	44/8828	0.019807	0.395401	0.3856	3
R-MMU-1474290	Collagen formation	4/116	81/8828	0.021702	0.395401	0.3856	4

Table S7. Reactome pathway enrichment of differentially expressed genes in liver of *Reverbα*$^{-/-}$ mice (20 terms with smallest Padj values shown).

ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count
R-MMU-1428517	The citric acid (TCA) cycle and respiratory electron transport	73/1649	133/8828	5.40E-21	5.73E-18	4.87E-18	73
R-MMU-1430728	Metabolism	459/1649	1730/8828	1.07E-19	5.70E-17	4.85E-17	459
R-MMU-163200	Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	51/1649	82/8828	3.05E-18	1.08E-15	9.18E-16	51
R-MMU-611105	Respiratory electron transport	38/1649	59/8828	1.21E-14	3.20E-12	2.72E-12	38
R-MMU-6799198	Complex I biogenesis	35/1649	54/8828	1.03E-13	2.18E-11	1.86E-11	35
R-MMU-77289	Mitochondrial Fatty Acid Beta-Oxidation	24/1649	36/8828	3.43E-10	6.07E-08	5.16E-08	24
R-MMU-72766	Translation	78/1649	223/8828	3.95E-09	5.99E-07	5.09E-07	78
R-MMU-8953854	Metabolism of RNA	150/1649	551/8828	2.43E-07	3.22E-05	2.74E-05	150
R-MMU-5419276	Mitochondrial translation termination	36/1649	85/8828	3.57E-07	4.21E-05	3.58E-05	36
R-MMU-5368287	Mitochondrial translation	36/1649	86/8828	5.05E-07	5.36E-05	4.56E-05	36
R-MMU-5389840	Mitochondrial translation elongation	35/1649	83/8828	5.88E-07	5.67E-05	4.82E-05	35
R-MMU-392499	Metabolism of proteins	369/1649	1607/8828	1.06E-06	9.38E-05	7.98E-05	369
R-MMU-1592230	Mitochondrial biogenesis	16/1649	26/8828	1.63E-06	0.0001328	0.0001129	16
R-MMU-163210	Formation of ATP by chemiosmotic coupling	12/1649	18/8828	1.05E-05	0.0007448	0.0006333	12
R-MMU-8949613	Cristae formation	12/1649	18/8828	1.05E-05	0.0007448	0.0006333	12
R-MMU-72203	Processing of Capped Intron-Containing Pre-mRNA	69/1649	228/8828	1.27E-05	0.000845	0.0007185	69
R-MMU-9609507	Protein localization	38/1649	106/8828	2.06E-05	0.0012839	0.0010916	38
R-MMU-74160	Gene expression (Transcription)	237/1649	1015/8828	4.38E-05	0.0024087	0.002048	237
R-MMU-8978868	Fatty acid metabolism	53/1649	169/8828	4.40E-05	0.0024087	0.002048	53
R-MMU-196780	Biotin transport and metabolism	8/1649	Oct-28	4.58E-05	0.0024087	0.002048	8

Table S8. Primer sequences for qPCR

Gene	Forward Primer (5’-3’)	Reverse Primer (5’-3’)
Aacs	CGACAGAGTCGCCCTTTACG	TGTTGGGTAGATAGCCGACCA
Actb	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT
Aldh1a1	ATACTTGTCGGATTTAGGAGGCT	GGGCCTATCTTCCAAATGAACA
Aldh1a7	ACTTGGAAGTTAGGCCCTGC	TGTGAAGGACACTTTGTCGATG
Bmal1	GTCGAATGATTGCCGAGGAA	GGGAGGCGTACTTGTGATGTTC
Cox6a1	TCAACGTGTTCCTCAAGTCGC	AGGGTATGGTTACCGTCTCCC
Cry1	TCGCCGGCTCTTCCAA	TCAAGACACTGAAGCAAAAATCG
Hprt	GTTGGATACAGGCCAGACTTTGTTG	GATTCAACTTGCGCTCATCTTAGGC
Irs2	ACCGACTTGGTCAGCGAAG	CACGAGCCCGTAGTTGTCAT
Lhpp	GACATCTCCGGGGTGCTATG	CTTTCAGCGGGGACTGTTTCA
Ndufa8	GGAGCTGCCAACTCTGGAAG	CCAGCGGCACAGCATAAAC
Ndufs7	GTTCATCAGAGTGTAGCCACTG	CAGGCCGAAGGTCATAGGC
Nfil3	GCTCTTTTGTGGACGAGCAT	ACCGAGGACACCTCTGACAC
Npas2	CAGCTTGAACCCAAAGGAAT	CCATTACAGGAGGGGCTAGG
Pcsk4	CTCAACATCCTAAAGGCTTGGAA	GGGTGGTCTTTCTCAATGCC
Per1	TGAAGCAAGACCGGGAGAG	CACACACGCCATCACATCAA
Per2	GCCTTCAGACTCATGATGACAGA	TTTGTGTGCCTCAGCTTTGG
Plin2	AAGAGGCCAAACAAAAGAGCCAGGAGACCA	ACCCTGAATTTTCTGGTTGGCACTGTGCAT
Plin5	TGTCCAGTGCTTACAACTCGG	CAGGGCACAGGTAGTCACAC
Ppib	GGAGATGGCACAGGAGGAAA	CCGTAGTGCTTCAGTTTGAAGTTCT
Rev-erbα	GTCTCTCCGTTGGCATGTCT	CCAAGTTCATGGCGCTCT
Rev-erbβ	CAGGAGGTGTGATTGCCTACA	GGACGAGGACTGGAAGCTAAT
Scd1	CGCTGGTGCCCTGGTACTGC	CAGCCAGGTGGCGTTGAGCA
Uck1	ACCGCTAGTGGCAAGTCAAC	AGAACCTTGTAGAAGCAGTCCT
Uqcr11	CACATGCGTAGTGCTCCAGG	CGGCTGTGGGAATCCAGTTT

Table S9. Published datasets used

Dataset	**Source**	**Identifier**
Genome Reference Consortium Mouse Build 38 (mm10)	http://genome.ucsc.edu/cgi-bin/hgGateway?db=mm10	GCA_000001635.2
GENCODE Release M16 mouse genome annotation	https://www.gencodegenes.org/mouse/release_M16.html	GENCODE M16
Liver REVERBα ZT8 ChIP-seq raw data	Cho et al., 2012	GEO: GSE34020; SRR385650
Liver ZT8 input raw data	Cho et al., 2012	GEO: GSE34020; SRR385652
Liver REVERBα ZT10 WT ChIP-seq raw data (two replicates)	Kim et al., 2018	GEO: GSE104129; SRR6059484, SRR6059485
Liver REVERBα ZT10 REVERBα KO ChIP-seq raw data (two replicates)	Kim et al., 2018	GEO: GSE104129; SRR6059486, SRR6059487
Liver HDAC3 ZT10 ChIP-seq raw data (three replicates)	Feng et al., 2011	GEO: GSE26345; SRR351386, SRR351387, SRR351388
Liver NCOR ZT10 ChIP-seq raw data	Feng et al., 2011	GEO: GSE26345; SRR351391
Liver ZT10 input raw data	Feng et al., 2011	GEO: GSE26345; SRR351397
Liver ZT6 DNase-seq raw data	Sobel et al., 2017	GEO: GSE60430; SRR1551954
Liver ZT10 DNase-seq raw data	Sobel et al., 2017	GEO: GSE60430; SRR1551955
Circadian gene rhythmicity analysis results (mouse liver)	Koike et al., 2012	Tables S6, S7 from that paper
Mouse liver TAD boundaries (BED file)	Kim et al., 2018	GEO: GSE104129; GSE104129_MainTads_List_mm9.bed.gz
Mouse liver subTAD boundaries (BED file)	Kim et al., 2018	GEO: GSE104129; GSE104129_SubTads-List_mm9.bed.gz
Liver ZT10 RNA-seq raw counts data	Guan et al., 2020	GEO: GSE143524; GSE143524_Ad_lib_feeding_counts.txt.gz