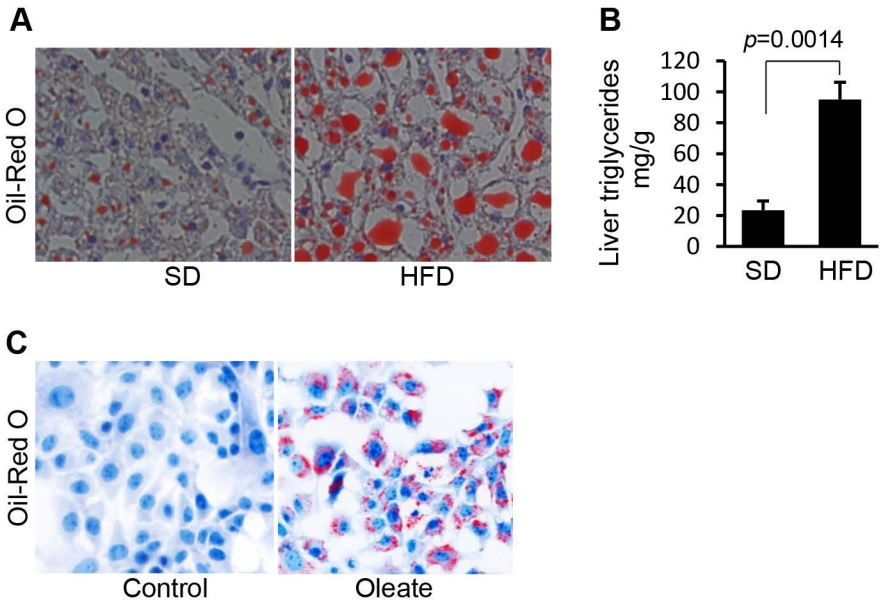
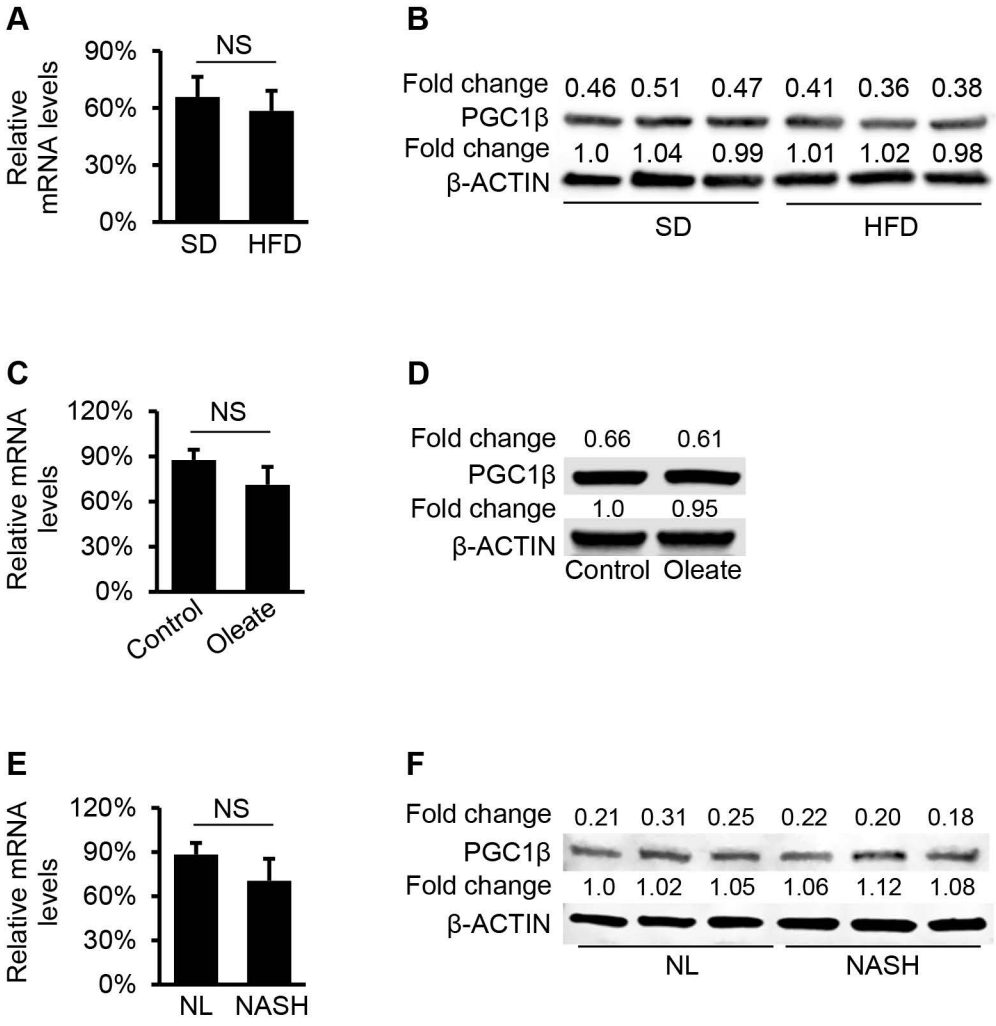
Supporting Fig. 1

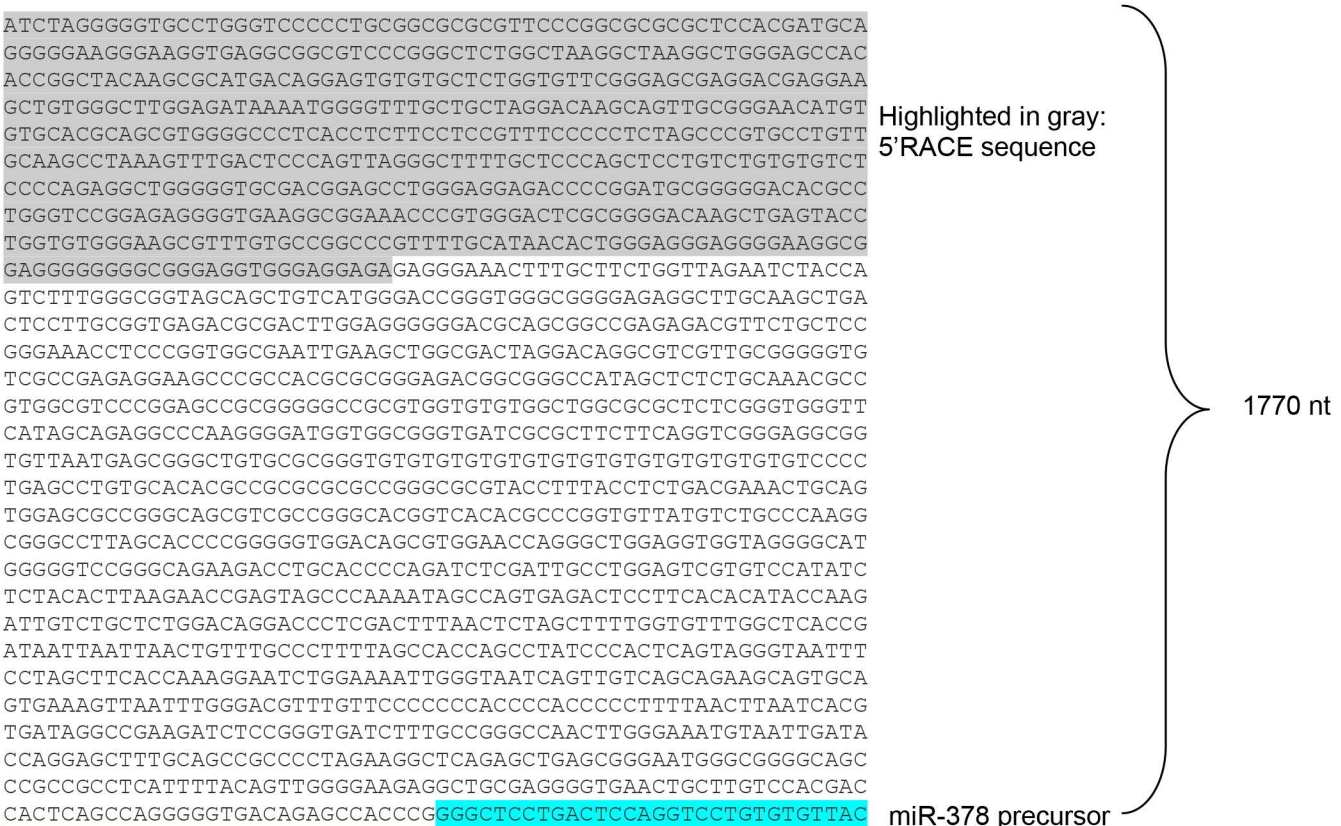


Supporting Fig. 2



Supporting Fig. 3

(A) Full length of Pri-miR-378 (3,279 bp)

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```

Forward primer of 5'RACE: CTAATACGACTCACTATAGGGCAAGCAGTGGTATCAACGCAGAGT
Reverse primer of 5'RACE: ATTAACACCGCCTCCCGACCTG

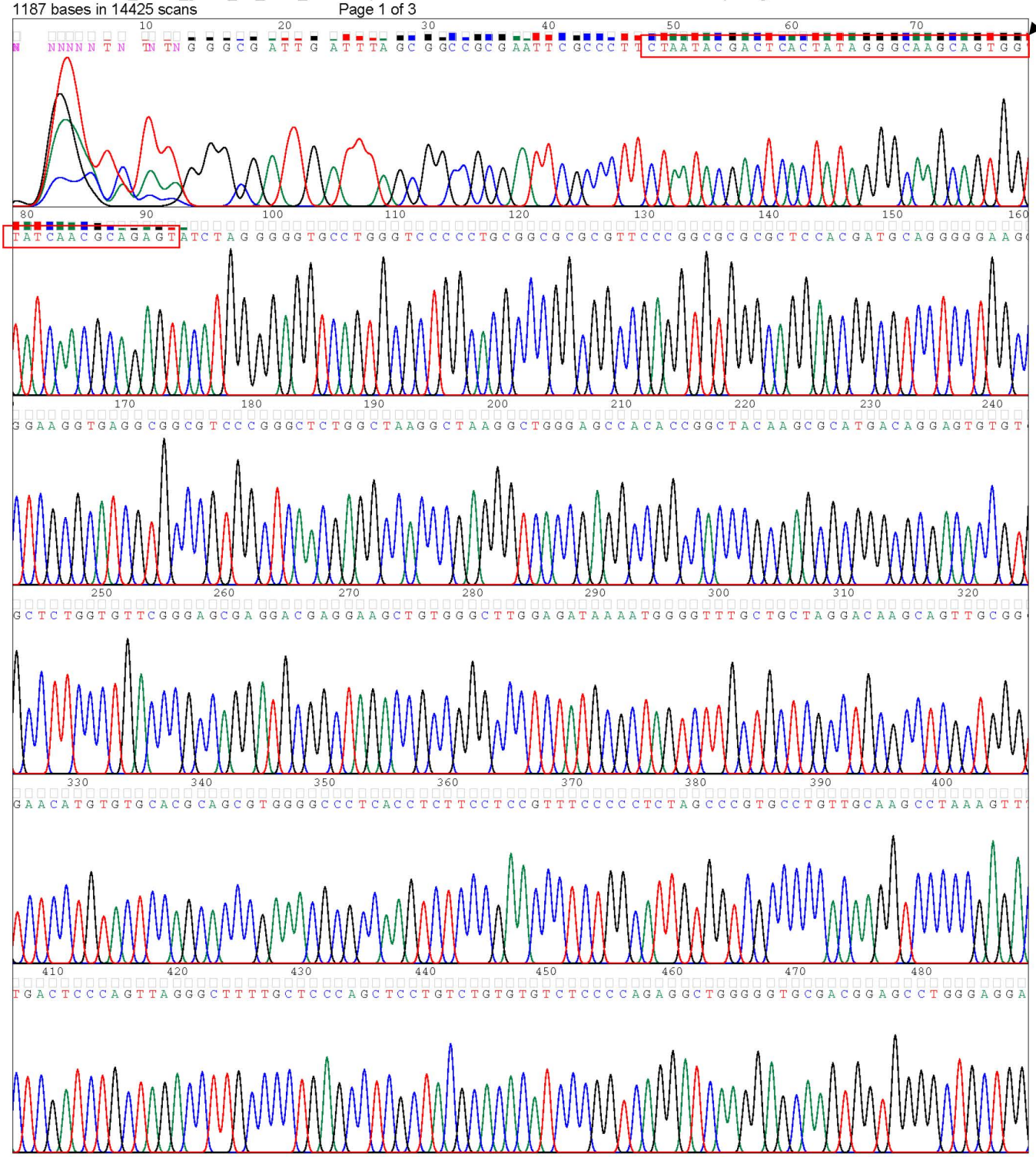
(B) Sequencing of 5'RACE product

File: 3C6_G11_083.ab1
Comment: 16261_MSH1_gDNA_4D_3730_1
1187 bases in 14425 scans

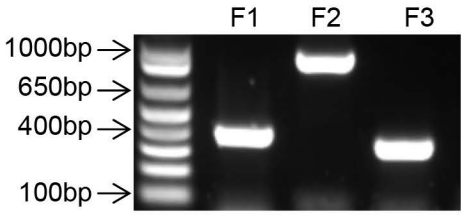
Run Ended: Jul 12, 2016, 19:22:55
Sample: 3C1
Page 1 of 3

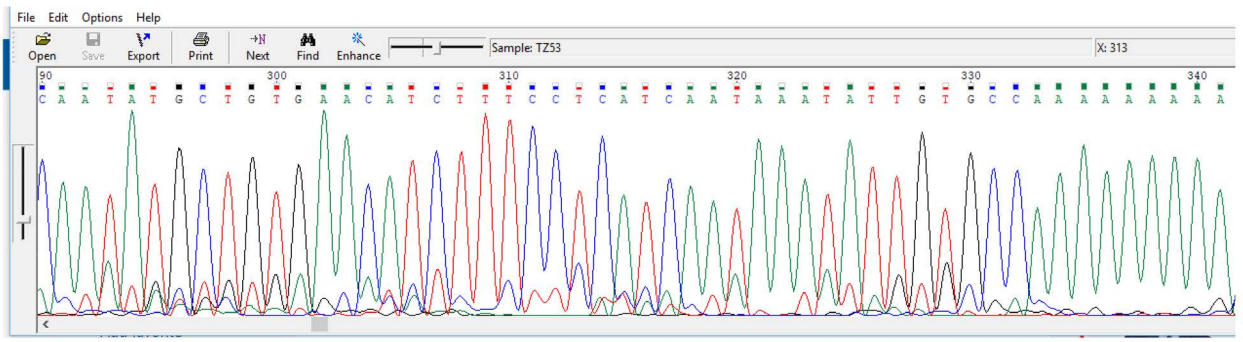
Signal A:4902 C:4735 G:5185 T:3480
Lane: 93 Base spacing: 14.78

Location of the 5'RACE forward primer



(C) PCR production of 3'RACE and Sequencing of 3'RACE product





Forward primer 1 (F1): CAGTGTTAGAAAACACTGCTAAGTG
Forward primer 2 (F2): ACTTTATGTGTTTGAGTCTATCCA
Forward primer 3 (F3): AACTTTGTTCTCTTCCACAAAATGGG

(D) miR-378 promoter sequence

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Transcription start site (TTS) was highlighted in pink and binding site of LXRα was highlighted in yellow.

Primers for cloning miR-378 promoter:

Forward primer: CTACCTCTGGTAAACTGGAGAAATAG. Highlighted in green
Reverse primer: GAACACCAGAGCACACACTCCTGTC. Highlighted in green

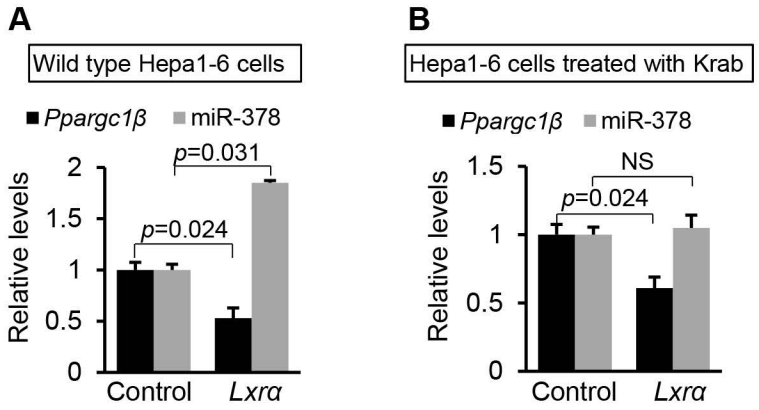
Primers to mutate the binding site for LXRα

Forward primer: CTGATTTCTCCGCCTTTGTGCGTGTCTCCC
Reverse primer: GGGAGACACGCACAAAGGCGGAGAAATCAG

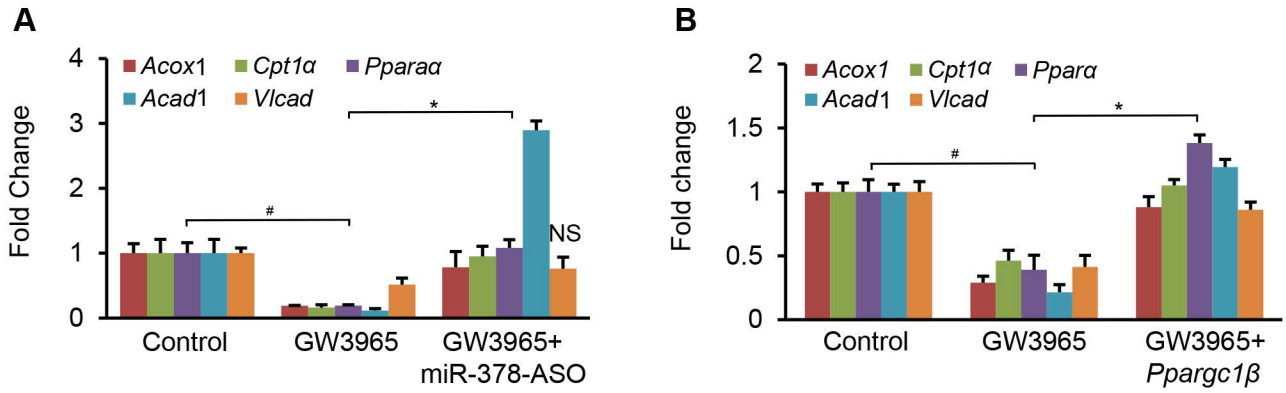
Primers for ChIP assay (highlighted in red)

GAGGCCAATGGGCCCGAGAGGCTG
GCTTTTAAAGCCGCAGTGCTCTGCAAC

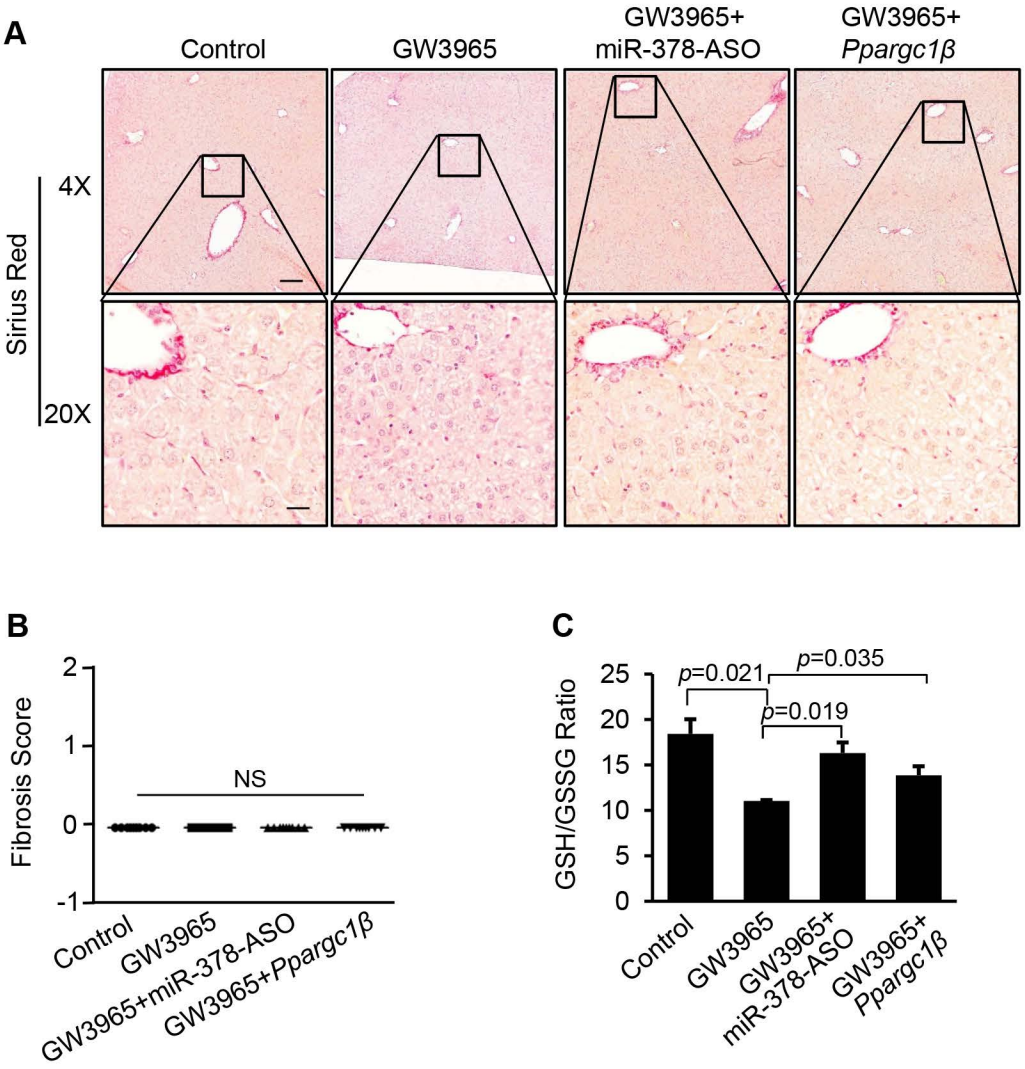
Supporting Fig. 4



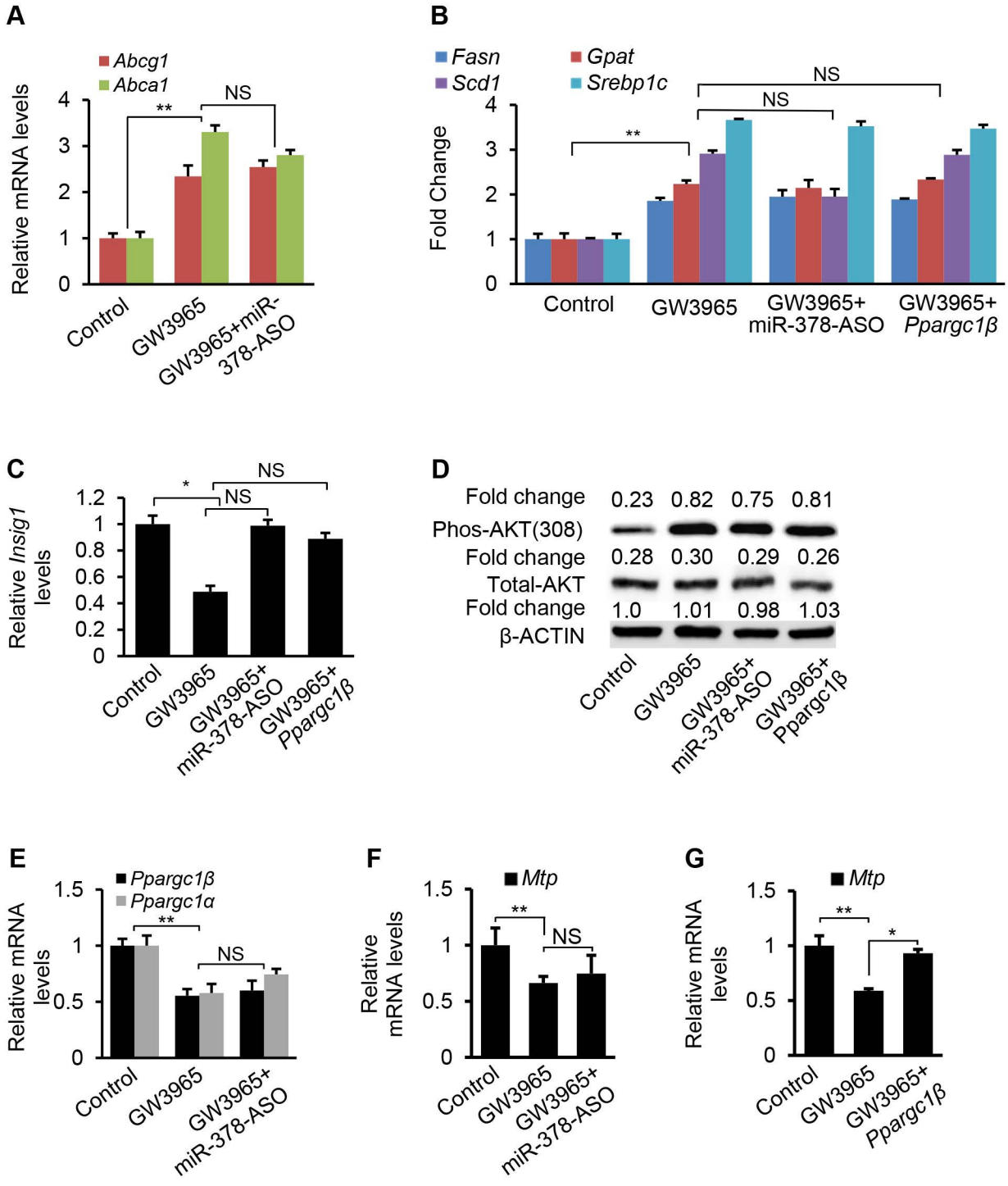
Supporting Fig. 5



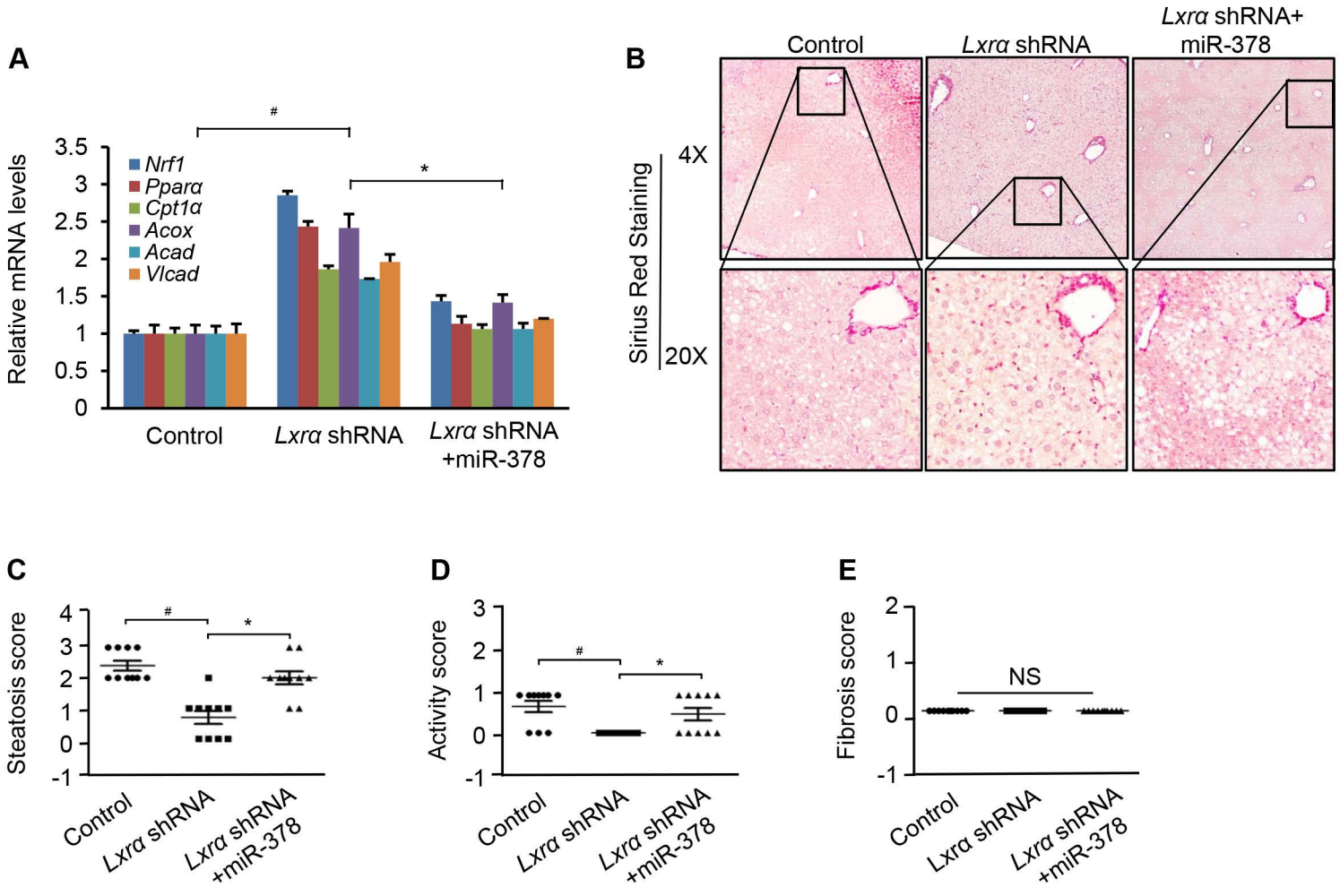
Supporting Fig. 6



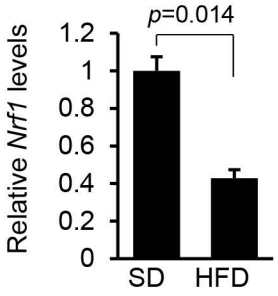
Supporting Fig. 7



Supporting Fig. 8



Supporting Fig. 9



Supplementary Data

Supplementary Data including materials and methods, nine figures, three tables, and figure legends can be found with this article online.

Establishment of Dietary Obese Mice

To determine the effect of hepatosteatosis on miRNA expression, eight-week-old wild-type male C57Bl/6 mice (Jackson Laboratory, *n*=6) were maintained on either normal chow diet (Open Source D12450B: 10% Kcal fat) or a high fat diet (Open Source D12492: 60% Kcal fat) for 8 weeks as described by Vickers et al (1). After such time, livers were collected and flash-frozen for miRNA and gene expression analysis.

Identification of miR-378 Primary Transcript

MiR-378 precursor sequence was downloaded from the Sanger Institute (http://microrna.sanger.ac.uk/sequences/), and was used as a query to search the EST (Expressed sequence tag) and lncRNA database using BLASTN. ESTs with reverse transcription direction as compared to query were removed from the BLAST hits. After filtering, we identified an EST that contains miR-378 precursor (AK045690.1).

Northern Blot Analysis

Total RNA was extracted from livers of mice treated with SD and HFD using Trizol Reagent (Invitrogen). RNA probes of the mouse β-actin and primary transcript of miR-378 were labeled with biotin-11-UTP using the MAXIscript® *In Vitro* Transcription Kit (Ambion). A 2 μg aliquot of biotin-labeled RNA probe was used to hybridize using NorthernMax (Ambion). In brief, 30 μg of total RNA was fractionated on a denaturing agarose gel, transferred to Nylon^{N+} membranes

by a capillary method and fixed by ultraviolet cross-linking. Membranes were probed with biotin-labeled RNA. Pre-hybridization and hybridizations were performed in ULTRAhyb® Ultrasensitive Hybridization Solution at 65°C. The labeled probes were heated for 3 min at 70°C before adding the pre-hybridization solution. After hybridization, membranes were washed at low stringency in 2×SSC, 0.1% SDS at room temperature for 5 min x 2 or at high stringency in 0.1 SSC, 0.1% SDS at 65°C for 15 min x 2. A chemiluminescent procedure BrightStar® BioDetect™ Kit (Ambion) was used to visualize the probes.

Fatty Acid Treatment of HepG2 Cells

Sodium oleate was obtained from Sigma-Aldrich and dissolved in DMEM medium with 1% fatty acid free bovine serum albumin (BSA) (Sigma). Oleate treatment of HepG2 cells was carried out as previously described with minor revision (2). Specifically, HepG2 cells were plated in 4-well chamber slides with DMEM medium supplemented with 10% FBS (Invitrogen). After 24 hours, HepG2 cells were treated with either control medium (DMEM supplemented with 1% fatty acid free BSA), or medium containing oleate (0.5 mM). The cells were cultured for another 24 hours, after which lipid accumulation and miR-378 expression were determined by Oil-Red O Staining (Sigma-Aldrich) and qRT-PCR, respectively.

miRNA Transfection and Gene Expression

An aliquot of 5×10^4 Hepa1-6 cells was seeded in a 24-well plate and allowed to adhere overnight. To determine the effects of *Lxrα* overexpression and knockdown on gene expression, Hepa1-6 cells cultured in the DMEM with 10% FBS were transfected with MC-*TTR*-*Lxrα* or MC-*TTR*-*Lxrα*-shRNA (500 ng/well) using Lipofectamine 3000. After 24 hours of transfection, cells were washed using cold PBS and total RNA was isolated for gene expression analysis.

Reporter Vector Construction and Luciferase Assay

To generate luciferase reporter vectors, the promoters of *Ppargc1β* and miR-378 were amplified from mouse genomic DNA using PCR, and inserted into pGL3-basic vector (Promega), referred as pGL3-miR-378 and pGL3-*Ppargc1β*. Two bases of the binding site for LXRα within the promoter of miR-378 were mutated using QuikChange II Site-Directed Mutagenesis Kit (Agilent Technologies) per the manufacture's instruction, and referred as pGL3-Mu-miR-378. 5×10^4 Hepa1-6 cells were plated per well in a 24-well plate prior to transfection. After 24 hours, 200 ng of the luciferase reporter vector and *Lxrα* expression vector (200 ng) as well as 30 ng of β-*gal* plasmid pSV-β-Galactosidase were transfected into Hepa1-6 cells using Lipofectamine 2000 (Invitrogen). Hepa1-6 cells treated with pGL3-miR-378 and empty vector were used as control. After 24 hours of transfection, luciferase and β-galactosidase assays were done using the Luciferase Assay System and Beta-Glo® Assay System (Promega). Luciferase activities were normalized to those of galactosidase; wells were transfected in triplicate; and each well was also assayed in triplicate.

Absolute Quantitative PCR

The absolute quantification method was used to determine copy numbers of miR-378 and *Ppargc1β* mRNA by comparing PCR signal to a standard curve. Plasmid calibrators were constructed by sub-cloning DNA fragments containing miR-378 or *Ppargc1β* exon 1 into PCR-II vector (Invitrogen); and the recombinant plasmids were referred as to PCR-II-miR-378 and PCR-II-Pparg1β. To create a standard curve, the copy number of 1 μg PCR-II-miR-378 or PCR-II-Pparg1β was calculated according to the molecular weight of the vectors and insert. A total of 10 ng purified plasmid was linearized with 10 U of *EcoR* I restriction enzyme. The linearized

plasmids were serially diluted 10-fold to cover 5 points of a logarithmic range from $3x10^5$ to 30 copies. Standard curves were constructed by plotting the mean Ct of repeatable measure (y-axis) for each plasmid range point against the corresponding log of the known copy number (x-axis).

RNA Isolation and Quantitative Reverse Transcription-PCR (qRT-PCR)

Total RNA was isolated with miRNeasy Mini Kit (Qiagen). To assess gene expression, 1 μg RNA was used for cDNA synthesis with Superscript III reverse transcription reagent (Invitrogen). PCR amplification was performed at 50°C for 2 minutes and 95°C for 10 minutes, followed by 40 cycles at 95°C for 15 seconds and 60°C for 1 minute in a 7900 real time-PCR system with SYBR green (Applied Biosystems). For each sample, we analyzed β-actin, GAPDH or 18S rRNA expression to normalize target gene expression. Primers for qRT-PCR were designed with Primer Express software (Applied Biosystems).

To determine levels of miRNA expression, 10 ng RNA were used for miRNA-specific cDNA synthesis with the TaqMan MicroRNA Reverse Transcription Kit and Taqman MicroRNA Assays (all Applied Biosystems). PCR amplification was performed at 95°C for 10 minutes, followed by 40 cycles at 95°C for 15 seconds and 60°C for 1 minute in a 7900 real time-PCR system (Applied Biosystems). The small RNA SNORNA202 and RNU6B were used to normalize target miRNA expression. Relative changes in gene and miRNA expression were determined using the $2^{-\Delta\Delta Ct}$ method (3).

Chromatin Immunoprecipitation (ChIP) Assay

Approximately 130 mg of livers from mice treated with HFD was used for ChIP assay. ChIP assay was performed using the ChIP Assay Kit (Abcam, ab500) based on the manufacture's

protocol. Anti-LXRα antibody (Abcam) was added to the chromatin solution and gently rotated overnight at 4°C. The protein A agarose slurry was added to the antibody-bound chromatin solution and incubated at 4°C for 1 hour with constant rotation. The binding region for LXRα was detected in PCR reactions. A 10 kb region downstream from the binding site was used as a negative control and chromatin solution was reserved for input control. Primers flanking the binding site of LXRα within the murine miR-378 promoter were: forward, 5′-GAGGCCAATGGGCCCGAGAGGCTG -3′ and reverse, 5′-GCTTTTAAAGCCGCAGTGCTCTGCAAC -3′. The negative control primers were: forward, 5′- CTTCTATATGAAGAGACAGAGTAC -3′ and reverse, 5′-TGGAGTCCCTGCTATGTAGAGCCAG -3′.

Hepatic Lipid Analysis

Mouse liver (100 mg) was placed in 1 ml chloroform/methanol (2:1) mixture and incubated on mice for 10 minutes before homogenization. Lipids were extracted from liver homogenates through room temperature orbital shaking (2 hours) followed by centrifugation (5000 RPM for 5 minutes). Supernatants were collected and washed with 0.4 ml chloroform/methanol (2:1) mixture by centrifugation at 5000 RPM for 20 minutes (room temperature). New supernatants were washed with 0.2 volume of 0.9% NaCl. After centrifuging for 5 minutes at 5000 RPM, supernatants were removed and lower-phase was dried at 42°C. Dried lipids were re-suspended in 2% Triton X-100. Liver triglycerides were quantified via a colorimetric assay using a triglyceride assay kit from Roche Diagnostics according to the manufacturer's protocols.

Western Blots and Antibodies

Proteins were extracted in RIPA buffer (Cell Signaling Technology) containing proteases inhibitors and PhosSTOP phosphatase inhibitor cocktail (Roche, Indianapolis, IN, USA). Protein concentration was measured using a Pierce BCA Protein Assay Kit and 25~50 μg of total lysate was loaded and immunoblotted for regular Western blot. Monoclonal anti-AKT (Cat. No. 4691), anti-phospho-AKT (Cat. No. 4056), anti-DGCR8 (Cat. No. 6914) and anti-DICER1 (Cat. No. 3363) were purchased from Cell Signaling. Anti-β-ACTIN (Cat. No. 6914) was purchased from Novus Biologicals. Anti-PGC1β (Cat. No. ab176328) was purchased from Abcam.

Histological Analysis

Liver specimens were fixed in 10% formalin; the sections were stained with hematoxylin and eosin (H&E). Liver sections (5-μm) were de-paraffinized and stained with Sirius Red staining following manufacturer's protocol. For Oil-Red staining, liver samples were embedded in Tissue-Tek OCT embedding compound and frozen on dry ice. 10 to 12 μm sections were cut with a Leica CM3050 S cryostat, air-dried, and fixed in 10% formalin. Briefly, sections were rinsed with 60% isopropanol and stained for 20 min with prepared Oil Red O solution (0.5% in isopropanol followed by dilution to 60% with distilled water and filtered).

dCas9-KRAB Plasmid Design and Construction for CRISPR interference (CRISPRi)

Vector of dCas9-KRAB was a gift from Charles Gersbach (Addgene plasmid$^{\#}$ 71236). A sgRNA was designed based on the promoter region of miR-378 (miR-378-sgRNA: AGACACGCACAGGTCAAAGG). miR-378-sgRNA was used to prevent LXRα from binding to the binding site of LXRα within the promoter region of miR-378. miR-378-sgRNA was inserted into dCas9-KRAB vector and referred as to dCas9-KRAB-miR-378-sgRNA. Puromycin

was used to establish two Hepa1-6 stable cells stably expressing dCas9-KRAB-miR-378-sgRNA or dCas9-KRAB (control).

Scores of SAF

The morphological features of steatosis, ballooning, and lobular inflammation were semi-quantitatively graded on H&E-stained sections; and fibrosis was staged on Sirius Red-stained sections. The steatosis score (S) was assessed based on the quantities of large or medium-sized lipid droplets from 0 to 3 (S0: <5%; S1: 5%-33%, mild; S2: 34%-66%, and moderate; S3: >67%). Activity grade (A, from 0-4) was the unweighted addition of hepatocyte ballooning (0-2) and lobular inflammation (0-2). A0 (A=0), A1 (A=1), A2 (A=2), and A3 (A=3) represent no activity, mild activity, moderate activity and severe activity, respectively. Stage of fibrosis (F) was staged on a 0-4 scale as follows: stage 0, absence of fibrosis; stage 1, perisinusoidal or portal fibrosis; stage 2: perisinusoidal and periportal fibrosis without bridging; stage 3: bridging fibrosis; and stage 4: cirrhosis.

GSH/GSSG Ratio Assay

Fresh liver tissues were rinsed three times using ice-cold PBS (pH 7.4). After that, livers were homogenized in 200 μL ice cold Mammalian Lysis Buffer (PBS containing 0.5% NP-40) using a homogenizer. The ratio of GSH/GSSG was determined using GSH/GSSG Ratio Detection Assay Kit II (Abcam, Cat. No. ab138881) following the manufacturer's instruction.

Semi-quantitative RT-PCR Analyses

Total RNA was isolated using RNeasy Mini kit (Qiagen). RNAs were reverse transcribed into cDNA using SuperScript III reverse transcriptase (Invitrogen). Primer sequences used to amply pri-miR-378 are: Pri-miR-378-F: TTGGCTGAAAAGCGGATGAGAGAGGC and Pri-miR-378-

R: CAGGGAAAGTTTGG GGGAGGAGAGGG. To control equal cDNA amount in each reaction, PCR was performed with primers corresponding to GAPDH as follow: GAPDH-F: TGAAGGTCGGAGTCAACG GATTTGGT, GAPDH-R: CATGTGGGCCATGAGGTCCACCAC. PCR amplification was performed at 95°C for 2 minutes, followed by 35 cycles at 94°C for 30 seconds, 60°C for 30 seconds and 72°C for 1 min and final extension at 72°C for 10 min in an Eppendorf Mastercycler Pro PCR system. PCR products were separated on a 1.2% agarose gel and visualized after ethidium bromide staining.

RACE Mapping of miR-378 Primary Transcript

Total RNA was isolated from livers of SD-treated mice or HFD-treated using RNeasy Mini Kit (Qiagen, Cat. No.: 74104). Poly A^+ mRNA was isolated from livers of SD-treated mice or HFD-treated using polyA Spin mRNA isolation kit (New England Biolabs, Cat. No.: S1560S). SMARTer® RACE 5'/3' Kit (Clontech, Cat. No.: 634860) was used to perform 3'RACE and 5'RACE. The first strand cDNA was synthesized at 42°C for 90 minutes with 100 U SMARTScribe Reverse Transcriptase using 1 μg of mRNA, followed by 70°C for 10 minutes. 3' end of pri-miR-378 and 5' end of pri-miR-378 was amplified by a polymerase chain reaction with 94°C denaturation step and then 30 cycles of touchdown annealing temperature. Primer sequences to amplify 5' and 3' cDNA fragments of pri-miR-378 were listed in Supporting Fig. 3.

Measurement of Oxygen Consumption Rate

OCR of hepatocytes was measured using the XF24 extracellular flux analyzer from Seahorse Bioscience. Primary mouse hepatocytes were seeded into collagen-coated XF24 plates (Seahorse Bioscience) at 4×10^4 cells/well in DMEM with 10% FBS and allowed to adhere for 2 hours. After removing DMEM, cells then were washed with Krebs–Henseleit buffer (KHB;

111 mM NaCl, 4.7 mM KCl, 2 mM $MgSO_4$, 1.2 mM Na_2HPO_4, 2.5 mM glucose, and 0.5 mM carnitine). After washing, 600 µl KHB was added to each well containing cells, and the plate was pre-incubated in the CO_2-free incubator at 37 °C for 1 hour. After incubation, 75 µl BSA or BSA complexed palmitic acid was injected into XF-24 cartridge. XF-24 cartridge with XF Cell Mito Stress Test compounds (1 µm oligomycin, 0.1 µm FCP and 10 nM rotenone) onto the XF24 Analyzer to measure fatty acid-stimulated oxygen consumption. Duration of mixing, waiting and measuring were 3, 2, and 3 min, respectively. Mitochondrial oxygen consumption rates were calculated from the difference between the maximal respiratory rate (in the presence of FCCP) and the respiratory rate after addition of rotenone. These experiments were repeated 3 times using 5 different mice per group under the same conditions.

GW3965 Treatment of Hepa1-6 Cells

Mouse hepatoma Hepa1-6 cells were cultured in DMEM medium supplemented with 10% fetal bovine serum (FBS) and penicillin/streptomycin. All cells were split prior to the establishment of confluence and incubated at 37℃ in a humidified incubator with 5% CO_2. Cells were seeded at a density of 1×10^4 cells in 24-well plates. After 18 hours, cells were treated with 0.5 µM or 1 µM GW3965 or vehicle (control) for 24 hours.

References:

1. Farrell GC, McCullough AJ, Day CP. Non-Alcoholic Fatty Liver Disease: A Practical Guide 2013.
2. Caldwell SH, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. Gastroenterology 2004;127:S97-S103.
3. Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology 2002;36:1349-1354.

Supporting Figure Legends

Supporting Fig. 1 HFD treatment induces hepatosteatosis. (A) Oil-Red staining of livers from mice treated with either standard diet (SD) (*n*=6) or high fat diet (HFD) (*n*=6) for 8 weeks. **(B)** Hepatic lipid content in mice after 8 weeks of SD or HFD treatment. (**C**) Oleate treatment led to intracellular lipid accumulation in HepG2 cells. HepG2 cells treated with DMEM medium without oleate served as the control. Data represent mean ± SEM. Student *t* test was used to evaluate the statistical significance. *P* values are indicated.

Supporting Fig. 2 Hepatic lipid accumulation had no effect on protein levels of PGC1β. (A-B) mRNA and protein levels of PGC1β in mice treated with SD (*n*=3) and HFD (*n*=3) for eight weeks. (**C-D**) mRNA and protein levels of PGC1β in HepG2 cells treated with oleate (0.5 mM). HepG2 cells treated with DMEM medium without oleate served as the control. (**E-F**) mRNA and protein levels of PGC1β in liver tissues from normal individuals (*n*=3) and NAFLD patients (*n*=3). Student's *t* test was used for statistical analysis. Data represents mean ± SEM. NS: no significance

Supporting Fig. 3 Identification of miR-378 primary transcript and its promoter. (A) Full length of miR-378 primary transcript (Pri-miR-378). 5'RACE sequence was highlighted in gray; miR-378 precursor sequence was highlighted in blue. Full length of Pri-miR-378 is 3279 bp. (**B**) Sequencing result of 5'RACE PCR product. (**C**) PCR product of 3'RACE and its sequencing result. Three primers listed were used to perform 3'RACE PCR. (**D**) Promoter sequence of miR-378 and primer sequences used to clone miR-378 promoter. Primers used to amplify miR-378 promoter and mutate two binding site for LXRα within the promoter were listed.

Supporting Fig. 4 Insert of a transcription "block" within the promoter region of miR-378 impaired the ability of LXRα to induce expression of miR-378. (A) Overexpression of *Lxrα* led to increased miR-378 and reduced mRNA levels of *Ppargc1β* in Hepa1-6 cells stably expressing dCas9-KRAB. Hepa1-6 cells stably expressing dCas9-KRAB-control-sgRNA were transfected with either empty vector (control) or MC-*TTR*-Lxrα. (**B**) Overexpression of *Lxrα* failed to induce expression of miR-378 but still repressed expression of *Ppargc1β* in Hepa1-6 cells stably expressing dCas9-KRAB-miR-378-sgRNA. Hepa1-6 cells stably expressing dCas9-KRAB-miR-378-sgRNA were transfected with either empty vector (control) or MC-*TTR*-Lxrα. Student's *t* test was used for statistical analysis. Data represents mean ± SEM. NS: no significance.

Supporting Fig. 5 Both PGC1β and miR-378 mediates the inhibitory effect of LXRα on expression of genes involved in FAO. (**A**) mRNA levels of *Acox1*, *Cpt1a*, *Pparα*, *Acad1*, and *Vlcad* in three groups of Hepa1-6 cells treated with scramble and 2% DMSO (control), GW3965, or a combination of GW3965 and miR-378-ASO. $^{\#}p < 0.05$ (GW3965 versus control); $^{*}p < 0.05$ (GW3965 + miR-378-ASO versus GW3965) (**B**) mRNA levels of *Acox1*, *Cpt1a*, *Pparα*, *Acad1*, and *Vlcad* in three groups of Hepa1-6 cells treated with empty vector and 2% DMSO, GW3965 or a combination of GW3965 and MC-*TTR*-*Ppargc1β*. Data represent mean ± SEM. The data shown are representative of an experiment repeated three times and conducted in triplicate. $^{\#}p < 0.05$ (GW3965 versus control); $^{*}p < 0.05$ (GW3965 + *Ppargc1β* versus GW3965) (ANOVA Test)

Supporting Fig. 6 Sirius staining of livers in four groups of mice treated with DMSO, GW3965 or a combination of GW3965 and miR-378-ASO or MC-*TTR*-Ppargc1β. (**A**) Sirius staining of livers in four groups of mice DMSO (control), GW3965 or a combination of GW3965 and miR-378-ASO or MC-*TTR*-Ppargc1β. (**B**) Fibrosis score in livers of the above four groups

of mice. (**C**) GSH/GSSG ratio in livers of four groups of mice. ANOVA test was used to evaluate the statistical significance. Data represents mean ± SEM. NS: no significance

Supporting Fig. 7 mRNA levels of *Lxrα* target genes in four groups of mice treated with DMSO, GW3965 or a combination of GW3965 and miR-378-ASO or MC-*TTR*-Ppargc1β. (**A**) mRNA levels of *Abca1* and *Abcg1* in livers of four groups of mice treated with DMSO, GW3965 or a combination of GW3965 and miR-378-ASO. (**B**) mRNA levels of *Srebp1c* and lipogenic genes including *Scd1*, *Fasn* and *Gpat* in livers of four groups of mice treated with DMSO, GW3965 or a combination of GW3965 and miR-378-ASO or MC-*TTR*-Ppargc1β. (**C**) mRNA levels of *Insig1* in livers of four groups of mice. (**D**) Levels of total and phosphorylated AKT1 in livers of mice treated with DMSO, GW3965 or a combination of GW3965 and miR-378-ASO or MC-*TTR*-Ppargc1β. (**E**) mRNA levels of *Ppargc1β* and *Ppargc1α* in livers of mice treated with DMSO, GW3965 or a combination of GW3965 with miR-378-ASO. (**F**) mRNA levels of *Mtp* in mice treated with DMSO, GW395 or a combination of GW3965 and miR-378-ASO. (**G**) mRNA levels of *Mtp* in mice treated with DMSO, GW3965 or a combination of GW3965 and MC-*TTR*-Ppargc1β. ANOVA Test was used to compare statistical difference among multiple groups. Data represents mean ± SEM. NS: no significance. *$p < 0.05$ and **$p < 0.01$

Supporting Fig. 8 miR-378 mediated the inhibitory effect of *Lxrα* on FAO. (A) mRNA levels of *Nrf1*, *Pparα*, *Cpt1α*, *Acox*, *Acad*, and *Vlcad* that are involved in FAO in three groups of mice treated with empty vector (control, *n*=10), MC-*TTR*-LxrαshRNA (*n*=10), and a combination of MC-*TTR*-*Lxrα*shRNA and MC-*TTR*-miR-378 (*n*=10). (**B**) Sirius staining of livers from three groups of mice treated with empty vector (control, *n*=10), MC-*TTR*-LxrαshRNA (*n*=10), and a combination of MC-*TTR*-LxrαshRNA and MC-*TTR*-miR-378 (*n*=10). (**C-E**) Steatosis score,

activity score and fibrosis score in livers of the above four groups of mice. ANOVA Test was used to compare statistical difference among multiple groups. Data represents mean ± SEM. NS: no significance. $^{\#}p < 0.05$ (*Lxrα* shRNA versus control); $^{*}p < 0.05$ (*Lxrα* shRNA + miR-378 versus *Lxrα* shRNA).

Supporting Fig. 9 Reduced mRNA levels of *Nrf1* in livers of HFD-treated mice. Eight-week-old male **C**57Bl/6 mice were kept on the HFD or SD for 8 weeks. After that, livers of mice were collected for gene expression analysis. Student *t* test was used to evaluate the statistical significance. Data represents mean ± SEM.

Supporting Table 1 The etiology of human NAFLD and normal liver samples

Supporting Table 2 Body and liver weight as well as serum chemistry analysis of four groups of mice treated with DMSO, GW3965, or a combination of GW3965 with miR-378-ASO or MC-*TTR*-Ppargc1β. Eight-week-old wild-type C57Bl/6 mice were maintained on the SD were treated with either DMSO (control, *n*=9), GW3965 (*n*=9), and a combination of GW3965 and miR-378-ASO or MC-*TTR*-Ppargc1β (*n*=9). Mini-circle vectors were injected into mice at a dose of 1.5 mg/kg body weight by tail vein weekly. After 8 weeks of treatment, mice were sacrificed for serum analysis. Data represent mean ± SEM. ANOVA Test was used for statistical analysis.

Supporting Table 3 Body and liver weight as well as serum chemistry analysis of three groups of mice treated with empty vector, MC-*TTR*-Lxrα shRNA or a combination of MC-*TTR*-LxrαshRNA and MC-*TTR*-miR-378. Eight-week-old wild-type C57Bl/6 mice were maintained on the HFD for 8 weeks. After that, mice kept on HFD were divided into three groups: the first group received MC-*TTR*-miR-378-MM (*n*=10); the second group was treated

with MC-*TTR*-LxrαshRNA (*n*=10); and the third group was treated with MC-*TTR*-LxrαshRNA and MC-*TTR*-miR-378 (*n*=10). Mini-circles that were complexed with *in vivo*-jetPEI (Polyplus Transfection, Strasbourg, France) were injected into mice weekly for 8 weeks via tail vein (1.5 mg/kg body weight). Data represent mean ± SEM. ANOVA Test was used for statistical analysis.

Supporting Table 1 The etiology of human NAFLD and normal liver samples

Normal livers

KULCTBID	KULCTB DESIGNATION	PATHOLOGICAL DX	PATHOLOGICAL COMMENTS	STAGE	GRADE	% STEATOSIS	REJECTION INDEX	AGE	SEX	RACE	BMI	ALCOHOL (EVER)	ALCOHOL (ENDED)	ALCOHOL CONSUMPTION LEVEL
L542D	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	*	*	52	F	African-American	30.7	Yes	Unreported	Occasional
L544D	Normal (Donor)	No diagnostic abnormalities	Anoxia (Narcotic overdose)	*	*	<5	*	24	M	Caucasian	31.9	Yes	Unreported	Moderate
L552D	Normal (Donor)	Minimal steatosis	Stroke (Intracranial hemorrhage)	*	*	5-10	*	41	F	Caucasian	33.7	Yes	Unreported	Occasional
L555D	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	*	*	46	M	Caucasian	22.2	Yes	Unreported	Occasional
L572D	Normal (Donor)	No diagnostic abnormalities	Anoxia (Cardiovascular)	*	*	<10	*	61	F	Caucasian	31.7	Yes	Unreported	Occasional
L574D	Normal (Donor)	No diagnostic abnormalities	Gunshot wound (Head)	*	*	*	*	17	M	Caucasian	28.2	No	NA	NA
L611D	Normal (Donor)	No diagnostic abnormalities	Benign ganglioneuroma (Kidney)	*	*	<5	*	11	M	African-American	29.5	No	NA	NA
L617D	Normal (Donor)	No diagnostic abnormalities	Bacterial meningitis (all culture negative)	*	*	*	*	19	M	Caucasian	26.8	No	Unreported	NA
L623D	Normal (Donor)	No diagnostic abnormalities	Anoxia (Cardiovascular)	*	*	*	*	54	F	Caucasian	29.5	No	NA	NA
L652D	Normal (Donor)	Mild steatosis	Stroke (Intracranial hemorrhage)	*	*	*	*	75	F	Caucasian	18.1	No	NA	NA
L655D	Normal (Donor)	No diagnostic abnormalities	Head trauma (Blunt injury)	*	*	*	*	44	F	Caucasian	24.8	Yes	Unreported	Moderate
1118688	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	*	*	61	F	Asian	23.4	No	Unreported	NA
1118689	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	*	*	49	F	Asian	21.3	No	Unreported	NA
1118690	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	*	*	38	F	Asian	29.6	No	Unreported	NA
1118691	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	<5	*	26	M	Asian	22.4	No	Unreported	NA
1118692	Normal (Donor)	No diagnostic abnormalities	Anoxia (Cardiovascular)	*	*	*	*	51	M	Asian	19.9	No	Unreported	NA
1118693	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	*	*	55	M	Asian	23.3	No	Unreported	NA
1118694	Normal (Donor)	No diagnostic abnormalities	Stroke (Intracranial hemorrhage)	*	*	*	*	46	M	Asian	27.5	Yes	Unreported	Occasional
1118695	Normal (Donor)	Mild steatosis	Stroke (Intracranial hemorrhage)	*	*	<5	*	56	M	Asian	33.6	No	Unreported	NA

Simple Steatosis

L407D	NAFLD	Steatosis	Anoxia (Cardiovascular)	*	*	15	*	29	M	Hispanic	25.2	Unreported	Unreported	Unreported
L446D	NAFLD	Steatosis	Gunshot wound (Head)	*	*	15	*	31	M	Caucasian	28.8	Yes	Unreported	Occasional
L548D	NAFLD	Steatosis	Abdominal abscess	*	*	15	*	46	M	Caucasian	23.3	Yes	Unreported	Occasional
L676D	NAFLD	Steatosis	Head trauma (Blunt injury); HCV Positive	*	*	30	*	17	M	Caucasian	32.5	Yes	Unreported	Moderate
L978D	NAFLD	Steatosis	No evidence of preservation injury, Anoxia (Cardiovascular)	*	*	20	*	41	M	African-American	31.7	Yes	Ongoing	Occasional
L1059D	NAFLD	Steatosis	Preservation injury, Anoxia (Cardiovascular)	*	*	30	*	48	M	Caucasian	36.4	Yes	Unreported	Occasional
L1068D	NAFLD	Steatosis	Microvesicular in transition to macrovesicular,portal mild chronic inflammation with and increased number of bile duct, Head Trauma (Blunt Injury)	*	*	40	*	58	F	Caucasian	69.6	Yes	NA	Occasional
1118665	NAFLD	Steatosis	Anoxia (Cardiovascular)	*	*	16	*	37	M	Asian	37.1	No	Unreported	NA
1118666	NAFLD	Steatosis	Anoxia (Cardiovascular)	*	*	24	*	41	M	Asian	33.6	No	Unreported	NA
1118667	NAFLD	Steatosis	Preservation injury, Anoxia	*	*	22	*	36	M	Asian	36.1	No	Unreported	NA

			(Cardiovascular)											
1118668	NAFLD	Steatosis	Preservation injury, Anoxia (Cardiovascular)	*	*	30	*	35	M	Asian	35.5	No	Unreported	NA

NASH without cirrhosis

Sample ID	Pathological Comments	Necrosis %	Fibrosis on H&E	Fibrosis on trichrome	Steatosis %	Age	Gender	Ethnicity	BMI	COD	Diabetes	Alcohol	Alcohol Consumption
H957	Focal mild chronic portal inflammation	0	None	NA	25	42	M	African American	42.734	ICH-stroke	Yes	Yes	Occasional
H958	Steatohepatitis; occasional ballooned hepatocytes	0	At least Brunt Stage 2; maybe focal bridging fibrosis (Brunt Stage 3/4)	yes	90	47	M	Caucasian	40.7	CVA	Yes	Yes	Occasional
H981	Lots of small bubble artifact/warm ischemic changes	0	Brunt Stage 2/4	yes	50	51	M	Caucasian	35.94	Head Trauma-MVA	Yes	Yes	Occasional
H1027	Steatohepatitis, scattered ballooned hepatocytes, centriolobular steatosis	No	None	NA	50	63	F	Caucasian	43	ICH-stroke	Yes	No	NA
H1028	Steatohepatitis, scattered ballooned hepatocytes	No	None	NA	70	51	F	African American	40	CVA-stroke	Yes	No	NA
H1060	Steatohepatitis, scattered ballooned hepatocytes	No	None	NA	50	49	M	Hispanic	44.9	ICH-stroke	Yes	No	NA
H1069	Steatohepatitis, scattered ballooned hepatocytes	No	None	NA	25	39	M	Caucasian	62.7	CVA	No	No	NA
H1075	Steatosis	No	None	NA	20	56	M	Caucasian	43.7	CVA	No	No	NA
H1081	Steatohepatitis, scattered ballooned hepatocytes, Focal mild chronic portal inflammation	No	None	NA	80	55	M	Caucasian	32.5	CVA	Yes	Yes	Occasional
H1097	Steatohepatitis, scattered ballooned hepatocytes	No	None	NA	65	36	M	Caucasian	37	Stroke	Yes	Yes	Occasional
H1235	Steatosis 30-40%	No	None	no	30-40	38	M	Caucasian	31.9	CVA	No	Yes	Occasional
1118682	Steatohepatitis, scattered ballooned hepatocytes, centriolobular steatosis	Yes	Fibrosis on H&E	yes	33	44	M	Ascian	31.3	ICH-stroke	No	No	NA
1118683	Steatohepatitis, scattered ballooned hepatocytes	Yes	Fibrosis on H&E	yes	34	48	M	Asian	29.8	ICH-stroke	No	No	NA
1118684	Steatohepatitis, scattered ballooned hepatocytes	Yes	Fibrosis on H&E	yes	28	52	M	Asian	35.4	ICH-stroke	Yes	No	Occasional

Supporting Table 2

	Food intake	Body weight	Liver weight	LW/BW	ALP (U/L)	ALT (U/L)	AST (U/L)	Gluc (mg/dL)	Chol (mg/dL)	Trig (mg/dL)
DMSO	3.8 ± 0.8 g	29.73±2.81	1.24±0.11	0.041±0.008	74.3±7.0	44.5±3.1	90.5±9.1	125.3±9.1	124.5±11.1	83.5±6.1
GW3965	3.7 ± 0.9 g	30.49±2.21	1.62±0.12[a]	0.053±0.007[a]	64.5±6.1	68.5±5.5	110.3±10.8	89.0±5.2[a]	103.3±14.1	124.3±7.8[a]
GW3965+miR-378-ASO	4.2 ± 1.1 g	29.56±3.82	1.40±0.09[b]	0.047±0.008	54.3±3.1	34.5±4.6[b]	70.5±6.6	85.0±9.1	97.0±6.9	83.5±6.2[b]
GW3965+Ppargc1β	3.9 ± 1.0 g	29.80±1.66	1.43±0.1[c]	0.048±0.008	54.5±2.1	48.5±5.1[c]	100.3±11.8	99.0±9.8	93.3±8.6	95.0±4.1[c]

Data represent mean ± SEM. [a]$p < 0.05$ (GW3965 treatment group versus DMSO group), [b]$p < 0.05$ (GW3965 + miR-378-ASO group versus DMSO group), and [c]$p < 0.05$ (GW3965 + *Ppargc1β* group versus DMSO group), LW: liver weight; BW: body weight.

Supporting Table 3

	Food intake	Body weight	Liver weight	LW/BW	ALP (U/L)	ALT (U/L)	AST (U/L)	Gluc (mg/dL)	Chol (mg/dL)	Trig (mg/dL)
Scramble control	4.2±1.14	38.2±4.2	1.78±0.14	0.046±0.0048	61.75±8.8	150.75±22.8	219.75±29.8	182.23±16.8	151.75±18.8	108.25±21.8
Lxrα shRNA	3.98±0.88	39.1±5.2	1.45±0.12$^{\#}$	0.037±0.0046$^{\#}$	58.75±12.8	120.25±34.8	189.25±32.8	222.25±22.8$^{\#}$	134.45±24.2	67.25±7.8$^{\#}$
Lxrα shRNA + miR-378	4.38±1.22	40.8±5.1	1.69±0.18*	0.041±0.0052	55.75±14.8	268.25+42.5*	381.25±77.8*	208.75±32.8	140.75±19.8	105.75±9.8*

Data represent mean ± SEM. $^{\#}p < 0.05$ (*Lxrα* shRNA versus control); and $^{*}p < 0.05$ (*Lxrα* shRNA + miR-378 versus *Lxrα* shRNA). LW: liver weight; BW: body weight