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**Adipocyte-specific inhibition of *Mir221/222* ameliorates diet-induced obesity  
through targeting *Ddit4***

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31 **ABSTRACT**

32 MicroRNAs expressed in adipocytes are involved in transcriptional regulation of target  
33 mRNAs in obesity, but miRNAs critically involved in this process is not well characterized.  
34 Here, we identified upregulation of miR-221-3p and miR-222-3p in the white adipose  
35 tissues in C57BL/6 mice fed with high fat-high sucrose (HFHS) chow by RNA sequencing.  
36 *Mir221* and *Mir222* are paralogous genes and share the common seed sequence and  
37 *Mir221/222AdipoKO* mice fed with HFHS chow demonstrated resistance to the  
38 development of obesity compared with *Mir221/222<sup>flox/y</sup>*. *Ddit4* is a direct target of *Mir221*  
39 and *Mir222*, and the upregulation of *Ddit4* in *Mir221/222AdipoKO* was associated with the  
40 suppression of TSC2 (tuberous sclerosis complex 2)/mammalian target of rapamycin  
41 complex 1 (mTORC1)/S6K (ribosomal protein S6 kinase) pathway. The inhibition of miR-  
42 221-3p and miR-222-3p linked to reduced adipogenesis, and it may be a potential  
43 candidate for miRNA-based therapy.

44  
45 **INTRODUCTION**

46 In obesity, the excess and ectopic accumulation of adipose tissue leads to the clusters of  
47 metabolic disorders such as low-grade inflammation, type 2 diabetes (T2D), dyslipidemia,  
48 hypertension, nonalcoholic fatty liver disorder (NAFLD), cardiovascular diseases (CVDs),  
49 chronic kidney disease (CKD) and cancer. As an endocrine organ, the adipose tissue  
50 communicates with other tissues by secreting peptide hormones, inflammatory cytokines,  
51 signaling lipids and miRNAs packed in exosomes (1). The alteration of expression profile of  
52 miRNA both in cytoplasm and extracellular vesicles leads to changes in the transcriptional  
53 and translational activities of the genes, which control inflammation, whole body insulin  
54 sensitivity, lipid metabolism, adipogenesis of white, beige, and brown adipose tissues(2).  
55 For instance, miR-34a secreted by mature adipocytes in exosomes were transported into  
56 macrophages, suppresses M2 polarization, and stimulates inflammatory responses by  
57 repressing Krüppel-like factor 4(3). Lentivirus-mediated suppression of miR-34a increased

58 the beige and brown fat formation in diet-induced obese mice by increasing fibroblast  
59 growth factor 21 and sirtuin 1(4). The genetic ablation of miR-128-1 in mouse metabolic  
60 disease models resulted in increased energy expenditure, amelioration of diet-induced  
61 obesity and enhanced insulin sensitivity(5). In lipid metabolism, miR-425 overexpression in  
62 mice resulted in the promotion of diet-induced obesity and overexpression of miR-425 in  
63 3T3-L1 cells accelerated adipogenesis and lipogenesis, while knock down of miR-425  
64 remarkably enhanced lipolysis and lipid oxidation(6).

65 We also attempted to identify specific miRNAs critically involved in the process of  
66 obesity, we surveyed expression profile of miRNAs in liver, muscle, white adipose tissues  
67 (WATs), and sera of C57BL/6J mice fed with standard (STD) and high fat-high sucrose  
68 (HFHS) chow by RNA sequencing (GSE61959)(7). miR-221-3p and miR-222-3p are highly  
69 up-regulated in epididymal adipose tissues in mice fed with high fat high sucrose (HFHS).  
70 miR-221 and miR-222 both locate in the close proximity on the X chromosome and share  
71 the identical seed sequence(8). In meta-analysis, circulating miR-221-3p was reduced in  
72 T2D, while miR-222-3p was elevated in obesity and T2D (9). Although miR-221-3p and  
73 miR-222-3p are differentially expressed in sera and adipose tissues, the functional *in vivo*  
74 experiments to elucidate the roles of *Mir221* and *Mir222* in obesity has not been reported.  
75 Here, we investigated the adipocyte specific *Mir221* and *Mir222* knockout  
76 (*Mir221/222AdipoKO*) mice fed with HFHS chow, and they were protected from the  
77 development of obesity by targeting DDIT4 (DNA damage inducible transcript 4)/TSC2  
78 (tuberous sclerosis complex 2)/S6K (ribosomal protein S6 kinase) pathway.

79

## 80 **MATERIALS AND METHODS**

### 81 **Animal Models**

82 We obtained Mir 221 KO cond (*Mir221<sup>tm2</sup>*; EMMA ID, EM:05507) from EMMA (the  
83 European Mouse Mutant Archive) and Helmholtz Zentrum München (Neuherberg,  
84 Germany). The targeting vector cassette composed of *Neo* flanked by FRT and distal loxP

85 sites was inserted outside the genomic region encoding *Mir221* and *Mir222* precursors.  
86 *Neo* was removed by Flp in the conditional KO allele of *Mir 221* KO cond. The conditional  
87 KO allele was confirmed by primer pair; 1544\_29 (5'- GCT CTG TTT TCC TAA GTG ATG  
88 G-3') and 1544\_30 (5'-CTG ACA GGA AGT AAA TCA TCT TAG C-3'). The expected  
89 fragments were 265 bp in wild and 384 bp in conditional KO allele. We also used B6.FVB-  
90 Tg (Adipoq-cre)<sup>1</sup>Evdrl/J to produce *Mir221/222AdipoKO* mice by crossing to *Mir 221* KO  
91 cond. Adipoq-cre transgene was screened by primers, 15381 (5'-ACG GAC AGA AGC ATT  
92 TTC CA-3') and 18564 (5'-GGA TGT GCC ATG TGA GTC TG-3'). The primers, oIMR7338  
93 (5'-CTA GGC CAC AGA ATT GAA AGA TCT-3') and oIMR7339 (5'-GTA GGT GGA AAT  
94 TCT AGC ATC ATC C-3'), were used for internal positive control. The expected sizes for  
95 transgene and internal positive control were 200 bp and 324 bp, respectively. By crossing  
96 male Tg (Adipoq-cre) and female *Mir221<sup>tm2/y</sup>* C57BL/6JJcl mice, we generated male  
97 *Mir221/222<sup>fllox/y</sup>* and male *Mir221/222AdipoKO* littermates.

98 Five-week-old mice were randomly assigned to standard diet (STD) group (MF, Oriental  
99 Yeast, Japan) or high fat high sucrose diet (HFHS) group (D12331, Research Diets, New  
100 Brunswick, NJ). The detailed formulation of STD(10) ([https://www.oyc.co.jp/bio/LAD-](https://www.oyc.co.jp/bio/LAD-equipment/LAD/ingredient.html)  
101 [equipment/LAD/ingredient.html](https://www.oyc.co.jp/bio/LAD-equipment/LAD/ingredient.html) and [https://www.oyc.co.jp/bio/LAD-](https://www.oyc.co.jp/bio/LAD-equipment/LAD/rodents.html)  
102 [equipment/LAD/rodents.html](https://www.oyc.co.jp/bio/LAD-equipment/LAD/rodents.html)) and HFHS  
103 (<https://www.eptrading.co.jp/service/researchdiets/pdf/D12328-D12331.pdf>) diets are  
104 shown in **Supplementary Table 1**. At 22 weeks of age, we obtained various organs and  
105 they were subjected to following experiments.

106

### 107 **3T3-L1 Cell Cultures**

108 3T3-L1 pre-adipocytes were cultured in Dulbecco's modified eagle's medium (DMEM,  
109 2124951, Gibco). On day 0, the cells were treated with the differentiation media; DMEM  
110 supplemented with 10% FBS, 10 µg/ml insulin (I1882, Sigma), 1 µM DEX (D2915, Sigma)  
111 and 0.5 mM IBMX (I5879, Sigma). Then, the media were changed to DMEM supplemented

112 with 10 µg/ml insulin and 10% FBS on day 2 and cultured for 10 or 20 days.

113 Undifferentiated 3T3-L1 cells were subjected to Lentiviral miRNA expression, Lentiviral

114 miRNA inhibition studies, and luciferase reporter assays.

115

### 116 **Human Serum Samples**

117 Human serum samples were collected from 69 patients with type 2 diabetes in Okayama

118 University Hospital and 45 subjects with normal fasting glucose (NGT).

119

### 120 **Insulin Tolerance Test and Glucose Tolerance Test (ITT and GTT)**

121 The 13-week-old mice (n=4 in each experimental group) were fasted for 16 hours in GTT

122 and for 3 hours in ITT. They were then intraperitoneally injected with glucose solution

123 (1 mg/g body weight) and human insulin (1 unit/kg in HFHS groups and 0.75 unit/kg in STD

124 groups) for GTT and ITT, respectively.

125

### 126 **Basal Metabolic Rate, Locomotor Activity, and Food Intake**

127 At 18 weeks of age, O<sub>2</sub>/CO<sub>2</sub> metabolism measuring system (MK-5000, Muromachi Kikai,

128 Tokyo, Japan) were used to quantify oxygen consumption rate and carbon dioxide

129 production for the estimation of  $\dot{V}O_2$  and respiratory quotient (RQ). The locomotor activity

130 was recorded for 24 hours by the frequency of interrupting an infrared sensor (ACTIMO-

131 100, Shinfactory, Fukuoka, Japan). Daily food intake was measured and calculated;

132 daily food intake [g/day/body weight (BW)] = [initial food weight (g) – leftover food weight

133 (g)]/measurement period (days)/BW (g). The 6-10 mice in each experimental group were

134 examined.

135

### 136 **Reverse Transcription-Quantitative Polymerase Chain Reaction (RT-qPCR)**

137 RNAs were extracted from frozen tissues and cultured 3T3-L1 cells with RNeasy Mini kit

138 (74106, Qiagen). The QIAamp Circulating Nucleic Acid Kit (Qiagen) were used for the

139 isolation of total RNAs from serum. For gene expression analyses, cDNAs were prepared  
140 with High-Capacity RNA-to-cDNA Kit (Thermo Fisher Scientific). TaqMan gene expression  
141 primers, *Ddit4* (Mm00512504\_g1), *Rplp0* (Mm00725448\_s1), *Rn18s* (Mm03928990\_g1),  
142 *Adipoq* (Mm00456425\_m1), *Lep* (Mm00434759\_m1), *Lpl* (Mm01345523\_m1), *Srebf1*  
143 (Mm00550338\_m1), *Cebpa* (Mm00514283\_s1), *Fabp4* (Mm00445878\_m1), *Pparg*  
144 (Mm01184322\_m1), *Lipe* (Mm00495359\_m1), *Pnpla2* (Mm00503040\_m1), *Ucp1*  
145 (Mm01244861\_m1), *Cox8b* (Mm00432648\_m1), *Prdm16* (Mm00712556\_m1), *Cidea*  
146 (Mm00432554\_m1), *Ppargc1a* (Mm01208835\_m1), *G6pc* (Mm00839363\_m1), *Gck*  
147 (Mm00439129\_m1), *Fasn* (Mm00662319\_m1), *Ppara* (Mm00440939\_m1), *Il6*  
148 (Mm00446190\_m1), *Ifng* (Mm01168134\_m1), *Tnf* (Mm00443258\_m1), *Il1b*  
149 (Mm01336189\_m1) were used (Thermo Fisher Scientific). For miRNA expression studies,  
150 cDNAs were prepared from total RNAs by TaqMan MicroRNA Reverse Transcription Kit  
151 (Life Technologies). MicroRNA primers, *mmu-miR-222-3p* (CTAAJ3), *hsa-miR-221-3p*  
152 (000524), *hsa-miR-222-3p* (002276), snoRNA202 (001232), snoRNA234 (001234), and  
153 cel-miR-39 (000200) were used (Thermo Fisher Scientific). *Rplp0*, *Rn18s*, snoRNA202,  
154 snoRNA234, and cel-miR-39 were served as the invariant controls. The RT-qPCR was  
155 performed using TaqMan Universal PCR Master mix II (no UNG) at a StepOne Plus Real-  
156 Time PCR system. The quantification was performed by the  $2^{-\Delta\Delta CT}$  analysis method.

157

### 158 **Cloning of Mir221 Host Gene (*Mir221hg*)**

159 Long non-coding RNA, *Mir221hg*, was cloned using SMARTer RACE 5'/3' Kit (634858,  
160 Clontech). 5'- and 3'-RACE-Ready cDNAs from epididymal adipose tissues poly A<sup>+</sup> RNA  
161 were prepared by SMARTScribe Reverse Transcriptase. 5'- and 3'-RACE-Ready cDNAs  
162 were amplified by PCR using 5' GSP (5'-GAT TAC GCC AAG CTT CCA GCA GAC AAT  
163 GTA GC TGT TGC-3') and 3' GSP (5'-GAT TAC GCC AAG CTT TCC AGG TCT GGG GCA  
164 TGA ACC TG-3'), respectively. Furthermore, nested PCR was performed using 5' NGSP  
165 (5'-GAT TAC GCC AAG CTT GTA TGC CAG GTT CAT GCC CCA GAC-3') and 3' NGSP

166 (5'-GAT TAC GCC AAG CTT GCAACA GCT ACA TTG TCT GCT GG-3'). PCR products  
167 were analyzed by agarose/EtBr gel and purified by NucleoSpin Gel and PCR Clean-Up Kit.  
168 The purified RACE products were subcloned into pRACE vector by In-Fusion Cloning  
169 (Clontech). Independent 4 clones of both 5'- and 3'-RACE were sequenced.

170

### 171 **Western Blot Analysis**

172 The epididymal fat tissues from 22-week-old mice and cultured 3T3-L1 cells were  
173 homogenized in RIPA lysis buffer (radioimmunoprecipitation buffer) plus protease inhibitors.  
174 The samples were boiled in SDS-PAGE loading buffer, separated on 12% Mini-PROTEAN  
175 TGX Precast Protein Gels (Bio-Rad), and transferred to a PVDF Blotting Membrane  
176 (cytiva). After blocking with 5% nonfat milk for 1 hour at room temperature (RT), the blots  
177 were incubated with REDD-1/DDIT4 Antibody, rabbit polyclonal (ab106356, RRID:  
178 AB\_10864294), C/EBP $\alpha$  Antibody, rabbit polyclonal (2295, RRID: AB\_10692506), PPAR $\gamma$   
179 (D69) Antibody, rabbit polyclonal (2430, RRID: AB\_823599), mTOR (7C10) Rabbit mAb  
180 (2983, RRID: AB\_2105622), Phospho-mTOR (Ser2448) (D9C2) XP Rabbit mAb (5536,  
181 RRID: AB\_10691552), Akt Antibody, rabbit polyclonal (9272, RRID: AB\_329827), Phospho-  
182 Akt (Thr308) Antibody, rabbit polyclonal (9275, RRID: AB\_329828), p70 S6 Kinase (49D7)  
183 Rabbit mAb (2708, RRID: AB\_390722), Phospho-p70 S6 Kinase (Thr389) Antibody, rabbit  
184 polyclonal (9205, RRID: AB\_330944), Tuberin/TSC2 Antibody, rabbit polyclonal (3612,  
185 RRID: AB\_2207804), Phospho-Tuberin/TSC2 (Thr1462) Antibody, rabbit polyclonal (3611,  
186 RRID: AB\_329855, Cell Signaling Technology) overnight at 4°C. GAPDH (D16H11) XP  
187 Rabbit mAb (HRP Conjugate) (8884, RRID: AB\_11129865) was used as a loading control  
188 (Cell Signaling Technology). After washing three times with Tris-buffered saline (TBS), the  
189 blots were incubated with ECL Donkey Anti-Rabbit IgG, HRP-Conjugated Antibodies  
190 (NA934V, GE healthcare Life science, 1:10000) at RT for 1 hour. The blots were developed  
191 with Pierce ECL Western Blotting Substrate (TE261327, Thermo Fisher Scientific). The  
192 chemiluminescence was analyzed using ImageQuant LAS-4000 mini (FUJIFILM).

193

#### 194 **Morphometric Analysis for Adipocyte Size**

195 Epididymal adipose tissues were fixed by 10% formalin, embedded with paraffin. The 5- $\mu$ m  
196 paraffin sections were prepared and stained with PAS. The images were captured using an  
197 Olympus BX51 microscope. The size of the adipocytes was analyzed by Keyence Hybrid  
198 cell count software. Epididymal adipose tissues were taken from 3-5 individual animals  
199 from each experimental group.

200

#### 201 **Isolation of Stromal Vascular Fraction (SVF) from White Adipose Tissues**

202 SVF was isolated from epididymal adipose tissue of 24-week-old mice. Briefly, fresh mouse  
203 epididymal fat pads were minced and digested with collagenase type 1 (CLS1,  
204 Worthington) in HBSS containing 10% FBS for 45 minutes at 37°C. The mixture was  
205 filtered through a nylon mesh (100  $\mu$ m), then centrifuged at 400 *g* for 1 minute. The  
206 adipocyte fraction was obtained from the supernatant, they were again centrifuged at 800 *g*  
207 for 10 minutes, and the SVF was obtained from the pellet.

208

#### 209 **Identification of *Mir221/222* Target mRNAs**

210 The mRNA microarray was performed by GeneChip Mouse Gene 2.0 array using total RNA  
211 of epididymal fat obtained from 16-week-old mice (1 animal from each group) and analyzed  
212 by Filgen (Nagoya, Japan). The raw data are available in Gene Expression Omnibus (GEO;  
213 <https://www.ncbi.nlm.nih.gov/geo/>) (GSE163921). TargetScan  
214 ([http://www.targetscan.org/vert\\_72/](http://www.targetscan.org/vert_72/)), miRDB (<http://www.mirdb.org/>), Pictar  
215 (<https://pictar.mdc-berlin.de/>) and DIANA-microT v5.0 (<https://bio.tools/DIANA-microT>) and  
216 were used to identify potential target genes for *Mir221/222*.

217

#### 218 **Lentiviral miRNA Expression and Lentiviral miRNA Inhibitor**



219 Lentiviral transduction using pLV-miRNA and pLV-miR-Locker system to 3T3-L1 cells were  
220 performed according to the manufacturer's manual (Biosettia). After transformation to *E.*  
221 *coli* JM109 cells, pLV-[mmu-mir-221] plasmid (mir-p177m, Biosettia), pLV-[mmu-mir-222]  
222 plasmid (mir-p178m, Biosettia), pLV-[mmu-mir-221-3p] locker plasmid (mir-mp0337,  
223 Biosettia), pLV-[mmu-mir-222-3p] locker plasmid (mir-mp0339, Biosettia), pLV-[mir-control]  
224 plasmid (mir-p000, Biosettia), pLV-miR-locker control plasmid (mir-locker-ctrl, Biosettia),  
225 pMDLg/pRRE (12251, Addgene), pRSV/Rev (12253, Addgene), and pMD2.G (12259,  
226 Addgene) were isolated with EndoFree Plasmid Maxi Kit (12362, Qiagen). 293T cells (10 ×  
227 10<sup>7</sup>/5 mL) were transfected with each pLV plasmid, pMDLg/pRRE, pRSV/Rev, pMD2.G,  
228 Lipofectamine LTX, and 1.5 mL Opti-MEM. The supernatants were collected after 48 hours  
229 after transfection. 3T3-L1 cells were transduced with lentivirus stock in complete media  
230 containing 10 µg/mL polybrene for 12 hours, replaced with fresh complete medium

231

### 232 **Luciferase Reporter Assay**

233 To quantitatively evaluate miRNA activity on cloned miRNA target sequence from 3'-  
234 untranslated region (3'-UTR) of *Ddit4*, pmirGLO dual luciferase miRNA Target expression  
235 vector (E1330, Promega) was used. Firstly, the pmirGLO plasmid was linearized by double  
236 digestion with *Xho*I and *Sal*I. The cDNA of *Ddit4* wild type (WT) 3'-UTR was amplified by  
237 PCR and ligated with CIP treated pmirGLO Vector. The primers are Forward-*Xho*I-3'UTR-  
238 *Ddit4*: 5'-GGG GGG CTC GAG CAG CTG CTC ATT GAA GAG TG-3', and Reverse-*Sal*I-  
239 3'UTR-*Ddit4*: 5'-GGG GGG GTCGAC CAA ACC AAC AGA GGA GAC AG-3'. pmirGLO-  
240 *Ddit4* MT 3'-UTR was prepared by site directed mutagenesis by PCR using primers;  
241 Forward-MT-Seed-*Ddit4*: 5'-CTG GAT GTG TAT CTG CAT GTA C-3' and Reverse-MT-  
242 Seed-*Ddit4*: 5'-GTA CAT GCA GAT ACA CAT CCA G-3'. The seed sequence "CGATGTA"  
243 was mutated to "CGTCTA". After transformation to *E. coli* JM109 cells, pmirGLO-*Ddit4* WT  
244 3'-UTR, pmirGLO-*Ddit4* MT 3'-UTR, and pmirGLO no-insert control plasmids were isolated  
245 with EndoFree Plasmid Maxi Kit (12362, Qiagen). 3T3-L1 cells were seeded at a density of

246 120,000 cells/mL, then co-transfected with Syn-mmu-miR-221-3p (MIMAT0000669,  
247 Qiagen), Syn-mmu-miR-222-3p (MIMAT0000670, Qiagen), negative control siRNA  
248 (1027280, Qiagen), inhibitor negative control (1027271, Qiagen), pmirGLO-*Ddit4* WT 3'-  
249 UTR, pmirGLO-*Ddit4* MT 3'-UTR, and pmirGLO no-insert control plasmids. Twenty-four  
250 hours after transfection, the cells were analyzed to measure luciferase activities using the  
251 Dual-Glo Luciferase Assay System and a GloMax 20/20 luminometer (Promega).

252

### 253 **Statistical Analysis**

254 All values were represented as the mean  $\pm$  standard deviation (SD). Statistical analyses  
255 were conducted using IBM SPSS Statistics 23 and GraphPad Prism (version 8.0).  
256 Independent *t*-test, Mann-Whitney's U test, and one-way ANOVA with Tukey test was used  
257 to determine the differences. For correlation, non-parametric Spearman *r* coefficient was  
258 used.  $p < 0.05$  was considered statistically significant.

259

## 260 **RESULTS**

### 261 ***Mir221/222AdipoKO* mice are resistant to diet-induced obesity**

262 To identify miRNAs critically involved in the disease process of obesity and type 2 diabetes  
263 (T2D), we performed miRNA profiling of serum, liver and epididymal fat tissues in  
264 C57BL/6JJcl mice fed with standard (STD) and high fat-high sucrose (HFHS) chow. The  
265 Illumina RNA sequencing data (Gene Expression Omnibus number GSE61959)  
266 demonstrated that the read numbers of *Mir221* and *Mir222* were 5.7 and 8.2-fold up-  
267 regulated in epididymal adipose tissues in HFHS group compared with STD group  
268 (**Supplementary Table 2**). *Mir221* and *Mir222* are paralog genes located in proximity on X  
269 chromosome and they share identical seed sequence. To further investigate the role of  
270 *Mir221/222* in obesity and diabetes, we crossed male Tg (*Adipoq-cre*) mice and female  
271 *Mir221<sup>tm2/y</sup>* C57BL/6JJcl mice and generated male *Mir221/222<sup>flox/y</sup>* and male  
272 *Mir221/222AdipoKO* littermates.

273 Body weight of *Mir221/222AdipoKO* mice fed with HFHS chow was significantly reduced  
274 compared with *Mir221/222<sup>flox/y</sup>* mice (**Figure 1A**). The weight of epididymal, mesenteric,  
275 subdermal, and brown fat was also reduced in *Mir221/222AdipoKO* mice (**Figure 1B**). The  
276 *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO* mice fed with STD chow demonstrated no  
277 significant differences in their body and tissue weight (**Figure 1A and 1B**). The average  
278 size of adipocytes in epididymal adipose tissues derived from *Mir221/222AdipoKO* mice fed  
279 with HFHS chow was smaller compared with *Mir221/222<sup>flox/y</sup>* mice (**Figure 1C**). To  
280 investigate glucose homeostasis, we performed insulin tolerance test (ITT) and glucose  
281 tolerance test (GTT). The blood glucose levels of *Mir221/222AdipoKO* mice fed with HFHS  
282 chow were reduced in GTT and ITT compared with *Mir221/222<sup>flox/y</sup>*, but they did not reach  
283 significant differences (**Figure 1D**). The serum insulin concentrations of  
284 *Mir221/222AdipoKO* mice were significantly lower than *Mir221/222<sup>flox/y</sup>*, suggesting the  
285 improvement of insulin sensitivity in *Mir221/222AdipoKO* mice (**Figure 1D**). To investigate  
286 whether reduced adiposity in *Mir221/222AdipoKO* mice was due to changes in energy  
287 expenditure or energy intake, we measured basal metabolic rates, locomotor activity and  
288 food intake. Basal metabolic rate such as respiratory quotient and oxygen consumption  
289 were not altered between *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO* mice fed with HFHS  
290 chow (**Supplementary Figure 1A and 1B**). The locomotor activity was recorded for 24  
291 hours, most of the activities were observed during the dark phase. Increased activity was  
292 observed in *Mir221/222AdipoKO* mice under HFHS chow compared with *Mir221/222<sup>flox/y</sup>*  
293 during light ( $0.944 \pm 0.309$  vs  $1.60 \pm 0.764$  counts/min,  $p=0.036$ ) and dark ( $6.67 \pm 4.38$  vs  
294  $7.94 \pm 4.38$  counts/min,  $p=0.497$ ) periods (**Supplementary Figure 1C**). Food consumption  
295 were not altered in *Mir221/222AdipoKO* and *Mir221/222<sup>flox/y</sup>* fed with HFHS  
296 (**Supplementary Figure 1D**). Under HFHS chow, serum leptin concentrations were  
297 significantly reduced in *Mir221/222AdipoKO* compared with *Mir221/222<sup>flox/y</sup>* ( $24.5 \pm 2.35$  vs  
298  $21.5 \pm 1.85$  ng/ml,  $p=0.043$ ), while serum adiponectin concentrations were not altered  
299 (**Supplementary Figure 1E and 1F**). In quantitative RT-PCR in epididymal adipose

300 tissues, mRNA expression of *Lep* was significantly reduced in *Mir221/222AdipoKO*. The  
301 genes related to adipogenesis, such as *Pparg*, *Cebpa*, *Ppargc1* and *Prdm16*, were not  
302 altered in *Mir221/222AdipoKO* (**Supplementary Figure 2**).

303

304 **Expression *Mir221* and *Mir222* are highly induced by HFHS chow feeding in mature**  
305 **adipocytes from epididymal adipose tissue**

306 We investigated the expression of *Mir221* and *Mir222* in various organs. Both miR-221-3p  
307 and miR-222-3p were abundantly expressed in brain, kidney, and lung in *Mir221/222<sup>flox/y</sup>*  
308 and they were down-regulated or not altered by the HFHS feeding compared with STD  
309 chow. In contrast, both miR-221-3p and miR-222-3p were significantly upregulated in the  
310 epididymal fat tissues, and such upregulation was canceled in the epididymal fat tissues of  
311 *Mir221/222AdipoKO* fed with HFHS chow (**Figure 2A and 2B**). Next, we investigated the  
312 localization of *Mir221* and *Mir222* in the cell fractions of epididymal adipose tissues. Both  
313 miR-221-3p and miR-222-3p were significantly induced by HFHS chow in mature  
314 adipocytes of *Mir221/222<sup>flox/y</sup>*, while the upregulation was significantly reversed in the  
315 mature adipocyte of *Mir221/222AdipoKO* fed with HFHS chow. In contrast, miR-221-3p and  
316 miR-222-3p were not significantly upregulated in the stromal vascular fraction (SVF) from  
317 *Mir221/222<sup>flox/y</sup>* fed with HFHS chow (**Figure 2C**). We also assessed the expression of miR-  
318 221-3p and miR-222-3p during 3T3-L1 adipocyte differentiation. Both miR-221-3p and miR-  
319 222-3p continuously down-regulated after the induction of adipocyte differentiation  
320 (**Supplementary Figure 3A**). Finally, we assessed the serum concentrations of mmu-miR-  
321 221-3p and mmu-miR-222-3p by quantitative PCR and they were not altered in  
322 *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO* fed with STD and HFHS chow, suggesting serum  
323 mature forms of *Mir221* and *Mir222* were derived from various organs but not exclusively  
324 from adipose tissues (**Supplementary Figure 4A**). In human samples from the subjects  
325 with normal glucose tolerance (NGT, n=45) and impaired glucose tolerance (IGT, n=69),  
326 hsa-miR-221-3p and hsa-miR-222-3p demonstrated negative ( $R^2=0.1311$ ,  $p<0.0001$ ) and

327 positive correlations ( $R^2=0.03841$ ,  $p=0.0441$ ) with HbA1c levels, respectively  
328 **(Supplementary Figure 4B and 4C).**

329

### 330 **Identification of *Mir221hg* and its expression**

331 The miRNA genes are classified as intergenic and intragenic miRNAs, and the intragenic  
332 miRNAs and related host genes share the common transcriptional regulation. The long  
333 non-coding RNA (lncRNA), namely mir-221 host gene (MIR221HG), has been reported in  
334 bovine, which inhibits the adipocyte differentiation in cultured cells(11). Thus, we performed  
335 5' and 3' rapid amplification of cDNA ends (5'/3'RACE) using poly A<sup>+</sup> RNA purified from  
336 epididymal fat tissues of C57BL/6JJcl mice and cloned 1537 bp single exon lncRNA  
337 (*Mir221hg*, MW581002) which overlap *Mir221* **(Supplementary Figure 5A)**. Next, we  
338 designed primers for quantitative PCR of *Mir221hg* and evaluated gene expression in  
339 various tissue. *Mir221hg* was abundantly expressed in brain in *Mir221/222<sup>flox/y</sup>* and they  
340 were upregulated in brain, heart, liver, intestine, spleen by the HFHS feeding compared  
341 with STD chow. The expression of *Mir221hg* was rather low in various adipose tissues and  
342 its lncRNA expression was not changed in *Mir221/222AdipoKO* fed with STD and HFHS  
343 chow **(Supplementary Figure 5B and 5C)**. Although *Mir221hg* lncRNA may be functional  
344 as a reservoir for miR-221-3p, the role of *Mir221hg* lncRNA in adipose tissues was limited  
345 in our experiments.

346

### 347 **miR-221-3p and miR-222-3p target *Ddit4***

348 To investigate the mechanism for the resistance to diet-induced obesity in  
349 *Mir221/222AdipoKO*, we attempted to identify the potential target genes for miR-221-3p  
350 and miR-222-3p. We performed mRNA profiling by GeneChip Mouse Gene 2.0 array using  
351 total RNA purified from epididymal fat tissues of *Mir221/222<sup>flox/y</sup>* fed with STD or HFHS,  
352 *Mir221/222AdipoKO* fed with STD or HFHS chow **(Supplementary Table 3, 4 and 5)**.  
353 Then, we made the list of 355 target genes commonly predicted by TargetScan, miRDB,

354 and DIANA-microT, and their seed sequences were conserved in both human and mouse  
355 genome (**Supplementary Table 6**). By searching upregulated genes in  
356 *Mir221/222AdipoKO* compared with *Mir221/222<sup>fllox/y</sup>* in both STD and HFHS fed groups, we  
357 identified that DNA-damage-inducible transcript 4 (*Ddit4*) demonstrated 1.9-fold and 2.58-  
358 fold upregulation in *Mir221/222AdipoKO* fed with HFHS and STD chow, respectively  
359 (**Supplementary Table 7**). To evaluate miRNA activity of miR-221-3p and miR-222-3p by  
360 the binding to 3'-untranslated region (3'-UTR) of *Ddit4*, we performed luciferase reporter  
361 assay in 3T3-L1 cells. We cloned 3'-UTR regions of *Ddit4* gene and prepared the wild-type  
362 reporter vector, pmirGLO-*Ddit4* WT 3'-UTR, and the mutant vector, pmirGLO-*Ddit4* MT 3'-  
363 UTR, in which mutagenesis was induced on the seed sequence binding site (**Figure 3A**).  
364 The luciferase reporter vectors were co-transfected with Syn-mmu-miR-221-3p or Syn-  
365 mmu-miR-222-3p or negative control siRNA in 3T3-L1 cells. As a result, reporter activity of  
366 pmirGLO-*Ddit4* WT 3'-UTR were significantly inhibited in the presence of both Syn-mmu-  
367 miR-221-3p and Syn-mmu-miR-222-3p. In contrast, Syn-mmu-miR-221-3p or Syn-mmu-  
368 miR-222-3p had almost no effect on the reporter activity of pmirGLO-*Ddit4* MT 3'-UTR  
369 (**Figure 3A**). Next, we checked the expression of *Ddit4* in the epididymal adipose tissues of  
370 *Mir221/222<sup>fllox/y</sup>* and *Mir221/222AdipoKO* fed with HFHS by quantitative PCR and Western  
371 blot. Although the mRNA expression of *Ddit4* was increased in *Mir221/222AdipoKO* without  
372 statistical significance, DDIT4 protein expression was significantly upregulated in the  
373 *Mir221/222AdipoKO* compared with *Mir221/222<sup>fllox/y</sup>* (**Figure 3B**), suggesting the possible  
374 involvement of translational repression by miR-221-3p and miR-222-3p.

375

### 376 **miR-221/222 promotes adipogenesis by DDIT4-mediated inhibition of mTORC1**

377 DDIT4 is known to activate tuberous sclerosis complex 1 (TSC1)/TSC2 complex by the  
378 inhibition of AKT (protein kinase B) and the release of 14-3-3 from TSC2(12). It further  
379 negatively regulates mammalian target of rapamycin complex 1 (mTORC1) (13). Increased  
380 activity of the mTORC1 signaling has been associated with obesity(14), and the knockout

381 mice for the mTORC1 downstream ribosomal protein S6 kinase (S6K) are protected  
382 against diet-induced-obesity(15). Thus, we further checked the inactivated form of p-TSC2  
383 (Thr-1462) and activated form of p-S6K(16) in the epididymal adipose tissues of  
384 *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO*. After overnight fasting, the mice were injected  
385 intraperitoneally with insulin and the epididymal fat tissues were harvested at 7 min after  
386 insulin injection. In *Mir221/222AdipoKO* mice, both p-AKT and p-TSC2 (Thr-1462) were  
387 significantly reduced, and accordingly p-S6K was also significantly reduced (**Figure 4A and**  
388 **4B**). p-mTOR was reduced in *Mir221/222AdipoKO* mice, however, it did not reach the  
389 statistically significant differences (**Figure 4A and 4B**).

390 Since mTOR has been shown to positively regulate adipogenesis and lipogenesis while  
391 inhibiting lipolysis, fatty acid oxidation and ketogenesis(17), we performed adipogenesis  
392 and glycerol assays in 3T3-L1 adipocytes. We constructed lentiviral vector expressing  
393 miRNA inhibitors (pLV-locker 221, pLV-locker 222, pLV-locker control) and miRNA mimics  
394 (pLV 221, pLV 222, pLV control). The efficiency for inhibitors and mimics was confirmed in  
395 3T3-L1 cells at 3-7 days after the transduction (**Supplementary Figure 3B and 3C**).

396 Lentiviral vectors were transduced to 3T3-L1 cells at 2 days before the induction of  
397 differentiation and cultured for 7 days. The pLV-locker 221, pLV-locker 222, and pLV-locker  
398 221/222 did not alter the accumulation of lipid droplets demonstrated by oil red O staining  
399 measured by absorbance at 490 nm (**Figure 5A**). Similarly, pLV 221, pLV 222, and  
400 pLV221/222 only show slight increase in the accumulation of lipid droplets in 3T3-L1 cells  
401 without statistical significance (**Figure 5B**). Western blot analysis demonstrated that the  
402 expression of C/EBP $\alpha$  and PPAR $\gamma$  were not changed by pLV-locker 221 and pLV-locker  
403 222 (**Figure 5C**), while they were significantly up-regulated by treatment with pLV 221 and  
404 pLV 222 (**Figure 5D**). To investigate lipolysis, lentiviral vectors were transduced to the fully  
405 differentiated 3T3-L1 adipocyte and we performed glycerol assay 7 days after lentiviral  
406 transduction. pLV-locker 221/222 and pLV 221/222 did not alter the glycerol release  
407 (**Figure 5E**).

408

409 **DISCUSSION**

410 The adipocyte-specific inhibition of *Mir221/Mir222* expression protected the mice fed with  
411 HFHS chow from the obesity. We demonstrated that the direct target of miR-221-3p and  
412 miR-222-3p was *Ddit4* and the inhibition of *Mir221/Mir222* expression resulted in  
413 upregulation of DDIT4, inactivation of AKT, activation of TSC2 and subsequent inactivation  
414 of S6K, the latter is a major target of mTORC1. The lentivirus-mediated transfer of *Mir222*  
415 gene promoted the adipogenesis demonstrated by up-regulation of C/EBP $\alpha$  and PPAR $\gamma$  in  
416 differentiated 3T3-L1 cells. We concluded that the inhibition of miR-221-3p and miR-222-3p  
417 and DDIT4-mediated inhibition of mTORC1 signaling is one of the major mechanisms for  
418 the protection from diet-induced obesity. The role of *Mir221* in adipogenesis has been  
419 focused by series of investigation and Ahonen et al. reported miR-221-3p overexpression in  
420 Simpson-Golabi-Behmel syndrome (SGBS) preadipocytes inhibited *de novo* lipogenesis  
421 and adipogenesis(18). In our investigation, overexpression by pLV 221 did not alter the  
422 lipogenesis and adipogenesis in 3T3-L1 cells; however, pLV 222 enhanced the  
423 adipogenesis. In bovine adipocyte differentiation, long non-coding RNA (lncRNA),  
424 *MIR221HG*, significantly increased adipocyte differentiation associated with dramatic  
425 increment of PPAR $\gamma$ (11). We also cloned mouse *Mir221hg* with 1,537 bp and identified that  
426 1,054 bp of 5'-flanking region was deleted in *Mir221/222AdipoKO* mice. The expression of  
427 *Mir221hg* is barely detected in brown and WATs in wild type mice and we speculated that  
428 the influence of deletion of *Mir221hg* is minimal in *Mir221/222AdipoKO* mice. Although the  
429 functional studies to elucidate the role of *Mir222* in adipogenesis and lipogenesis were not  
430 reported in cultured adipocytes in previously published studies, we demonstrated that  
431 *Mir222* expression was upregulated in WATs and serum in both obese patients. The  
432 importance of *Mir222* in the pathogenesis of obesity is supported by the analysis of adipose  
433 tissue-specific Dicer knockout mice, in which gonadal adipose tissue was the main source  
434 of serum exosomal miR-222(19). The exosome-packed *Mir222* influenced remote organs,



435 and overexpression of *Mir222* inhibits the expression of IRS-1 by directly binding to  
436 untranslated regions in the muscle(20) and liver(21). In current investigation, we firstly  
437 demonstrated that overexpression of *Mir222* enhanced mTORC1 pathway and promoted  
438 the adipogenesis in 3T3-L1 cells.

439 Under the presence of amino acids, mTORC1 is activated by GTP-bound Rheb. In the  
440 upstream of the Rheb, AKT inhibits TSC2 and TBC1D7 (TBC1 Domain Family Member 7)  
441 complex, which further inhibits the activation of mTORC1 by acting as a GTPase-activating  
442 protein. mTORC1 promotes the lipid synthesis and storage and adipogenesis, while it  
443 inhibits the lipolysis,  $\beta$ -oxidation and ketogenesis. SREBP (sterol regulatory element-  
444 binding protein) processing and activation is promoted by mTORC1 by the activation of  
445 S6K and lipin 1 leading to transcriptional activation of SREBP1, SREBP2, and many other  
446 lipogenic genes. mTORC1 also committed mesenchymal stem cells to adipocyte lineage by  
447 the activation of S6K, promotes the initial step of adipocyte differentiation by inhibiting 4E-  
448 BP1/2 (eIF4E-binding protein 1/2), and completes the final differentiation by the activation  
449 of PPAR $\gamma$ (22). Many researchers screened the agents or intrinsic factors to inhibit  
450 mTORC1 signaling and lipogenesis for the treatment of obesity. Lee et al. reported that  
451 ezetimibe reduced lipid accumulation by inhibiting mTORC1 signaling, leading to the  
452 downregulation of lipogenesis-related genes(23). Shi et al. reported that the inhibition of  
453 miR-196b-5p blocked adipogenesis and lipogenesis by directly targeting TSC1 and  
454 TGFBR1 (transforming growth factor- $\beta$  receptor 1)(24). We demonstrated that the inhibition  
455 of miR-221-3p and miR-222-3p and subsequent DDIT4-mediated inhibition of mTORC1  
456 signaling is a therapeutic target for the treatment of obesity.

457 The activation of mTORC1 links to various pathological processes in adipose tissues  
458 such as inflammation, beige adipogenesis and angiogenesis. mTORC1 loss and gain of  
459 function studies in macrophages resulted in amelioration and exacerbation of inflammatory  
460 response, as well as macrophage polarization to both M1 and M2 profiles(25). miR-221  
461 mediates M1 macrophage polarization(26, 27), while suppression of miR-222 alleviate the

462 inflammatory response(28, 29). However, we did not observe the apparent changes in  
463 gene expression of cytokines such as *Il1b*, *Il6*, *Ifng*, and *Tnf* in adipose tissues in  
464 *Mir221/222AdipoKO* mice (**Supplementary Figure 2**). The phenotyping of T cells and  
465 macrophages in WATs should be performed in the future investigation. In beige  
466 adipogenesis, the adipose-specific deletion of Raptor, a key component of mTORC1,  
467 promoted beige adipogenesis by inhibiting prostaglandins (PGs) synthesized by  
468 cyclooxygenase-2 (COX-2)(30). Supporting this notion, ketoprofen alleviated diet-induced  
469 obesity and promotes the fat browning by the COX-2 and mTORC1-p38 signaling  
470 pathway(31). In our investigation, the genes related to beige adipogenesis such as *Ppargc1*  
471 and *Prdm16* tended to be upregulated in WATs without statistical differences. However, in  
472 WATs in *Mir221/222AdipoKO* mice, apparent beige adipogenesis was not observed by  
473 histological examinations. In tumor microenvironment and angiogenesis, mTORC1 under a  
474 hypoxic condition promotes the translation of hypoxia-inducible factor (HIF) 1-2, which lead  
475 to the expression of angiogenic growth factors such as vascular endothelial growth factor  
476 (VEGF), TGF- $\alpha$ , and platelet-derived growth factor  $\beta$  (PDGF- $\beta$ )(32). *Mir221* and *Mir222*  
477 demonstrated the angiogenic activities in vascular cells(33) and cancers(34), however, we  
478 did not observe the angiogenesis activities in WATs in *Mir221/222AdipoKO* mice.

479

#### 480 **Limitation of Study**

481 We hypothesized that circulating miR-221-3p and miR-222-3p play important roles in both  
482 mouse obese models and the patients with obesity and T2D. However, the circulating  
483 levels of miR-221-3p and miR-222-3p were not altered in *Mir221/222<sup>flox/y</sup>* and  
484 *Mir221/222AdipoKO* mice fed with STD and HFHS. In addition, the human serum levels of  
485 miR-221-3p and miR-222-3p showed correlations with HbA1c, however, they did not show  
486 significant correlations with body weight and BMI. Although we show the roles of miR-221-  
487 3p and miR-222-3p in the adipocytes, we did not clearly demonstrate the role of circulating  
488 miR-221-3p and miR-222-3p in the pathogenesis of obesity. Another limitation is that it is

489 still unknown why *Mir221/222AdipoKO* mice did not show significant improvement of insulin  
490 sensitivity although the body weight was significantly reduced compared with  
491 *Mir221/222<sup>flox/y</sup>* fed with HFHS. Finally, the micronutrient composition is not matched  
492 between the STD and HFHS diets and it may possibly impact the observed outcomes.  
493 Ideally, a matched diet should be used for mineral and vitamin mix.

494

#### 495 **DATA AVAILABILITY**

496 RNA sequencing and mRNA microarray data generated in this study is available at GEO:  
497 GSE61959 and GSE163921.

498

#### 499 **ETHICS STATEMENT**

500 All animal experiments were approved by the Animal Care and Use Committee of the  
501 Department of Animal Resources, Advanced Science Research Center, Okayama  
502 University (OKU-2015547, 2016201, 2016202, 2018479, 2018480, and 2018481). The  
503 observational clinical study was approved by Okayama University Graduate School of  
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505 Committee (#1708-045).

506

#### 507 **CONFLICT OF INTEREST**

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512

#### 513 **Author contributions**

514 SY, DZ, AK, and JW designed the project and experiments and wrote the manuscript. SY,  
515 DZ, AK, NK, RS, and HHA performed animal experiments and analyzed and interpreted

516 data. AN and JE performed culture and molecular biology experiments. SY, AK, NK, RS,  
517 AN, JE, and JW designed and performed clinical study.

518

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528

## 529 **SUPPLEMENTARY MATERIAL**

530 The supplementary Material for this article can be found online.

531

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646

647 **FIGURE LEGENDS**

648 **Figure 1.** The metabolic phenotypes of *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO* male mice  
649 fed with high fat high sucrose (HFHS) or standard (STD) chow. **(A)** Body weight of  
650 *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO* mice fed with HFHS (n=7) or STD chow (n=6),  
651 respectively. **(B)** Tissue weight of *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO* mice fed with  
652 HFHS or STD chow at 24 weeks of age. (Epi, epididymal; Mes, mesenteric; Sub, inguinal;  
653 Brown, Brown adipose tissues) **(C)** Adipocyte area in epididymal adipose tissues of  
654 *Mir221/222<sup>flox/y</sup>* (n=3) and *Mir221/222AdipoKO* (n=5) mice fed with HFHS or STD.

655 Quantitative analyses were carried out on PAS-stained paraffin sections. (D) Insulin  
656 tolerance test (ITT) and glucose tolerance test (GTT) in mice fed with HFHS (n=7) or STD  
657 chow (n=6). Data shown as mean  $\pm$  SD and analyzed by one-way ANOVA with Tukey test  
658 in A and B, and Mann-Whitney's U test in C and D (\*p<0.05; \*\*p<0.01; \*\*\*p<0.001;  
659 \*\*\*\*p<0.0001).

660 **Figure 2.** Expression of Mir221 and Mir222 in *Mir221/222<sup>flox/y</sup>* and *Mir221/222AdipoKO*  
661 male mice fed with high fat high sucrose (HFHS) or standard (STD) chow. (A and B) In  
662 various tissues, the expression of miR-221-3p and miR-222-3p is normalized by  
663 snoRNA202 and snoRNA234. The HFHS-induced up-regulation of miR-221-3p and miR-  
664 222-3p in epididymal adipose tissues was reversed in *Mir221/222AdipoKO* (red asterisks).  
665 (Epi, epididymal; Mes, mesenteric; Sub, inguinal; Brown, Brown adipose tissues) (C)  
666 Serum concentration of miR-221-3p and miR-222-3p. HFHS *Mir221/222<sup>flox/y</sup>* (n=3), HFHS  
667 *Mir221/222AdipoKO* (n=5), STD *Mir221/222<sup>flox/y</sup>* (n=5) and STD *Mir221/222AdipoKO* mice  
668 (n=6). Data shown as mean  $\pm$  SD and analyzed by one-way ANOVA with Tukey test  
669 (\*p<0.05; \*\*p<0.01; \*\*\*p<0.001; \*\*\*\*p<0.0001).

670 **Figure 3.** Dual-luciferase reporter assay for *Ddit4* 3'UTR and expression of *Ddit4* in mice.  
671 (A) Dual-luciferase reporter assay using pmirGLO-*Ddit4* WT 3'-UTR, pmirGLO-*Ddit4* MT 3'-  
672 UTR, and pmirGLO no-insert control plasmids. 3T3-L1 cells were co-transfected with Syn-  
673 mmu-miR-221-3p (n=4), Syn-mmu-miR-222-3p (n=4), negative control siRNA (n=8). (B)  
674 Quantitative RT-PCR for *Ddit4* in epididymal adipose tissues of *Mir221/222<sup>flox/y</sup>* (n=4) and  
675 *Mir221/222AdipoKO* (n=8) mice fed with high fat high sucrose (HFHS). Western blot  
676 analyses for DDIT4 and GAPDH (glyceraldehyde-3-phosphate dehydrogenase) in  
677 epididymal adipose tissues of *Mir221/222<sup>flox/y</sup>* (n=3) and *Mir221/222AdipoKO* (n=7) mice fed  
678 with high fat high sucrose (HFHS). Data shown as mean  $\pm$  SD and analyzed by Mann-  
679 Whitney's U test (\*p<0.05; \*\*p<0.01).



680 **Figure 4.** Western blot analyses. **(A)** Western blot analyses for AKT (protein kinase B),  
681 TSC2 (tuberous sclerosis complex 2), mTOR (mammalian target of rapamycin) and S6K  
682 (ribosomal protein S6 kinase) in *Mir221/222<sup>flox/y</sup>* (n=3) and in epididymal adipose tissues of  
683 *Mir221/222AdipoKO* (n=5) male mice fed with high fat high sucrose (HFHS). Activated form  
684 of p-AKT and Inactivated form of p-TSC2 (Thr-1462) and activated form of p-S6K are  
685 shown. **(B)** Densitometric analyses of Western blots. Data shown as mean  $\pm$  SD and  
686 analyzed by Mann-Whitney's U test (\*p<0.05).

687 **Figure 5.** Adipogenesis, lipogenesis and lipolysis in 3T3-L1 cells. Lentiviral vectors were  
688 transduced to 3T3-L1 cells at 2 days before the induction of differentiation and cultured for  
689 7 days. **(A)** Oil-red O staining of differentiated 3T3-L1 cells treated with pLV-locker control,  
690 pLV-locker 221, pLV-locker 222, and pLV-locker 221/222. **(B)** Oil-red O staining of  
691 differentiated 3T3-L1 cells treated with pVL control, pLV 221, pLV 222, and pLV221/222.  
692 **(C)** Western blot analysis of PPAR $\gamma$  in differentiated 3T3-L1 cells treated with pLV-locker  
693 control, pLV-locker 221, pLV-locker 222, and pLV-locker 221/222. **(D)** Western blot analysis  
694 of PPAR $\gamma$  in differentiated 3T3-L1 cells treated with pVL control, pLV 221, pLV 222, and  
695 pLV221/222. **(E)** Lipolysis assay in 3T3-L1 cells stimulated with isoproterenol.  
696 Differentiated 3T3-L1 cells were treated with pLV-locker 221/222 and pLV 221/222. Data  
697 shown as mean  $\pm$  SD and analyzed by one-way ANOVA with Tukey test (\*p<0.05;  
698 \*\*p<0.01).

Figure 1

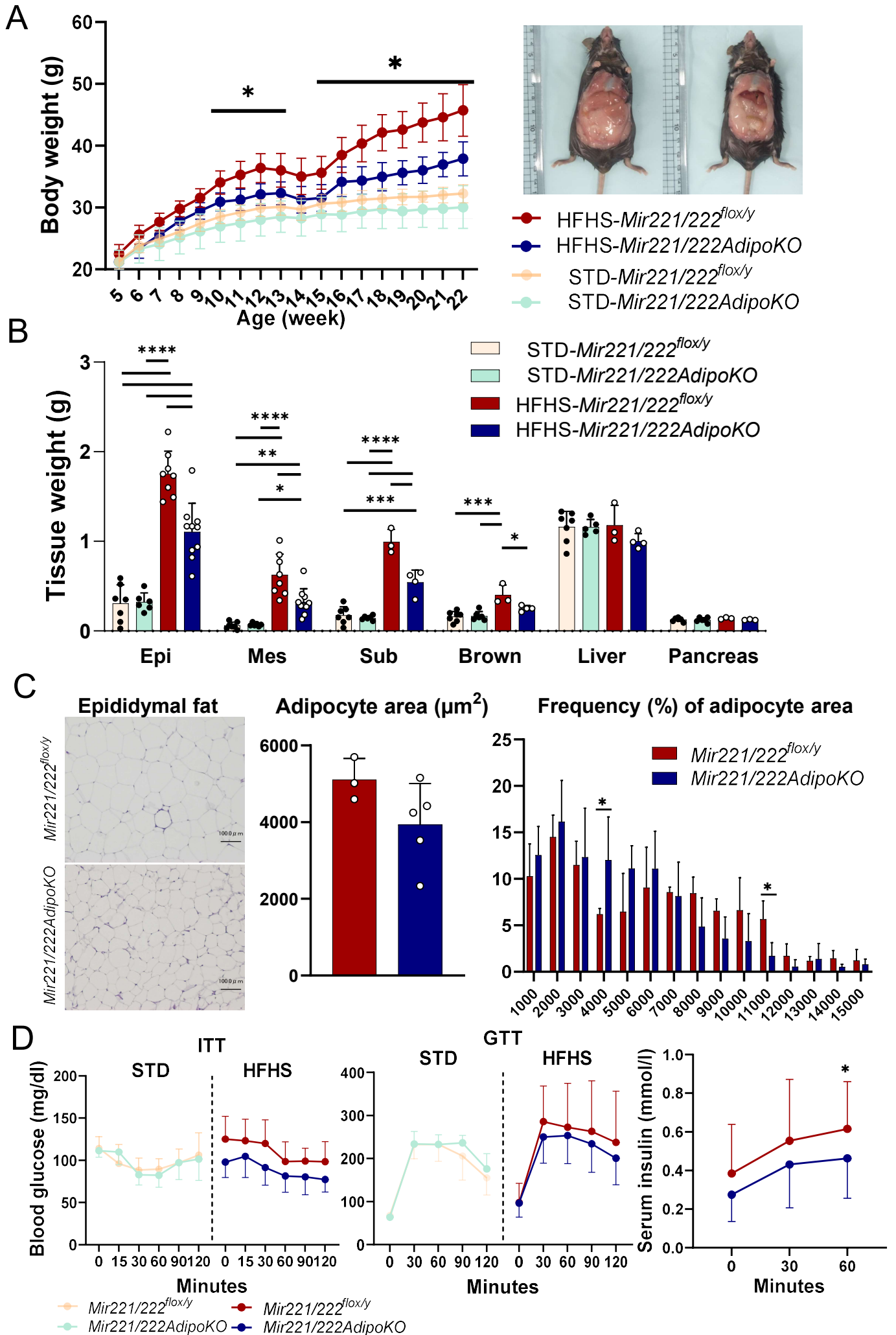


Figure 2

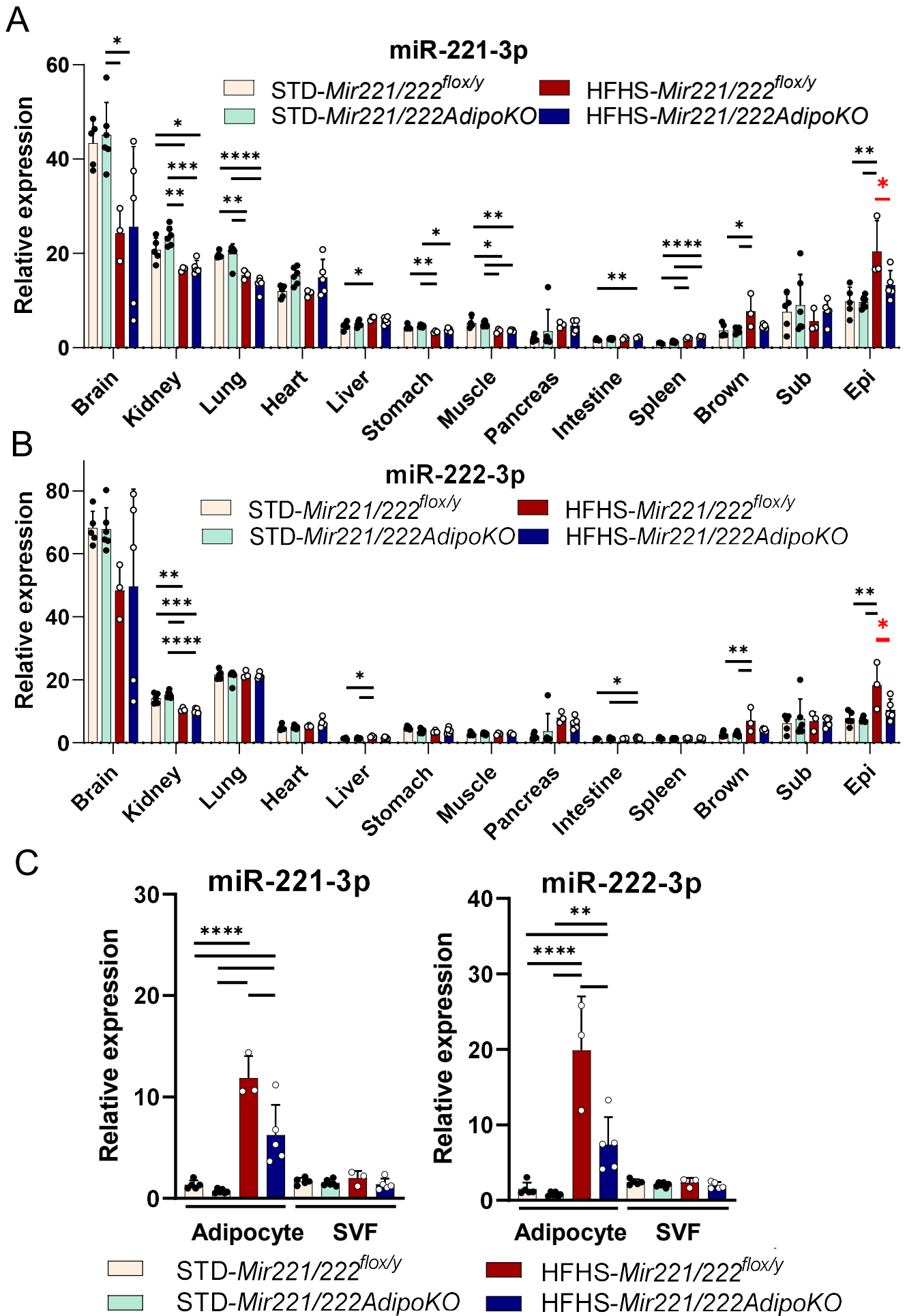
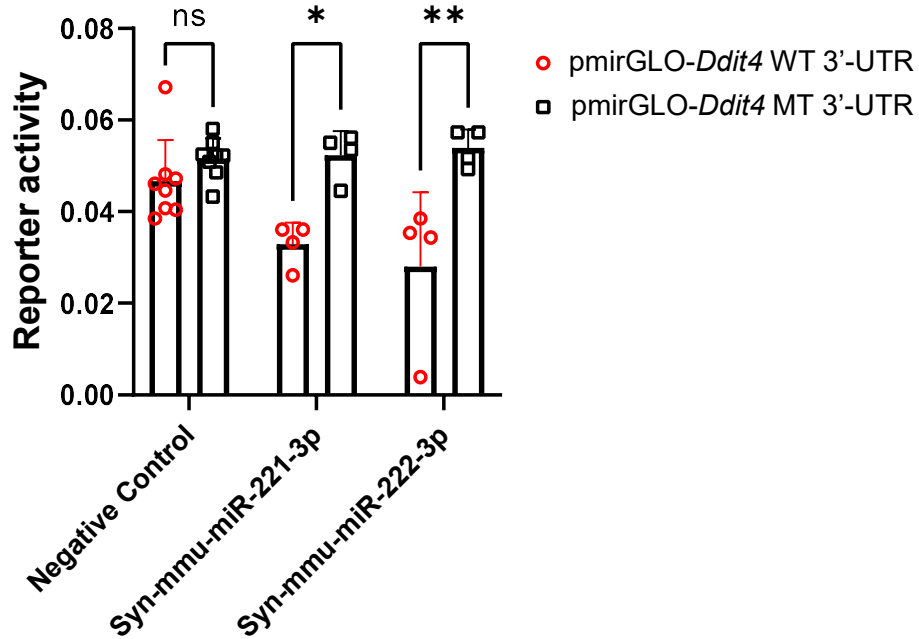


Figure 3

A

Mmu-miR-221 5' A**GCUACAU**UGUCUCGUGGGUUUC  
Mmu-miR-222 5' A**GCUACAU**CUGGCUACUGGGU  
|||||||  
pmirGLO-*Ddit4* WT 3'-UTR 5' TAC**CGATGTA**TGTGTAGGTCGGTCTTCGG  
pmirGLO-*Ddit4* MT 3'-UTR 5' TAC**CGTCTA**TGTGTAGGTCGGTCTTCGG



B

Epididymal fat tissue

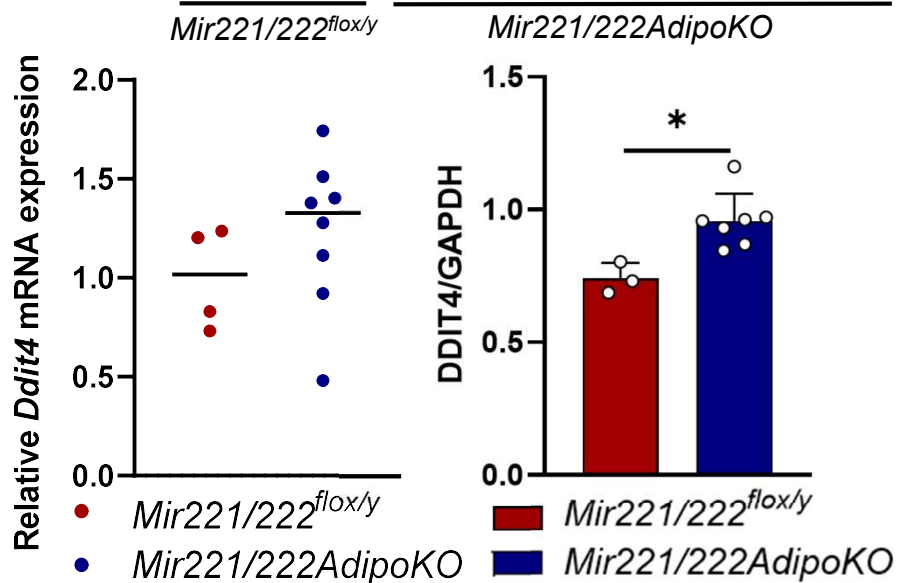
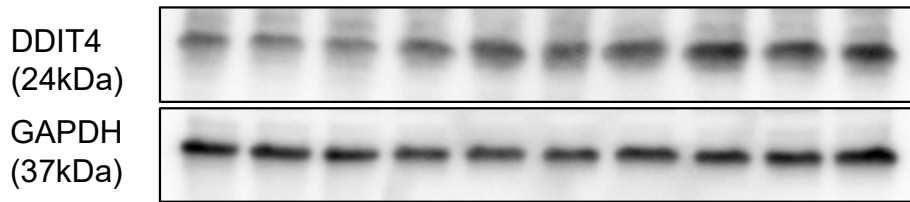
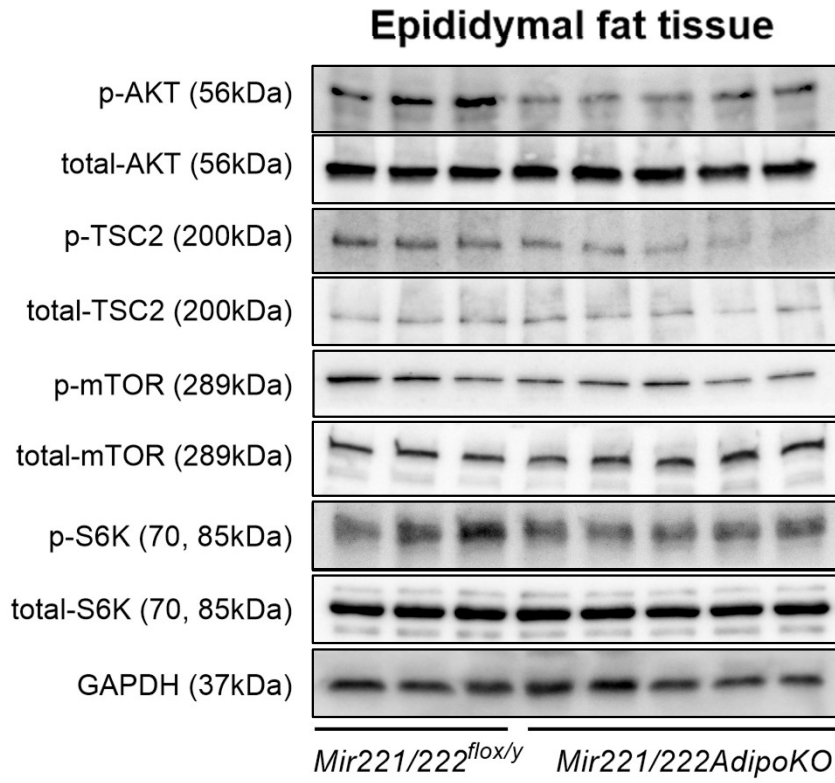


Figure 4

A



B

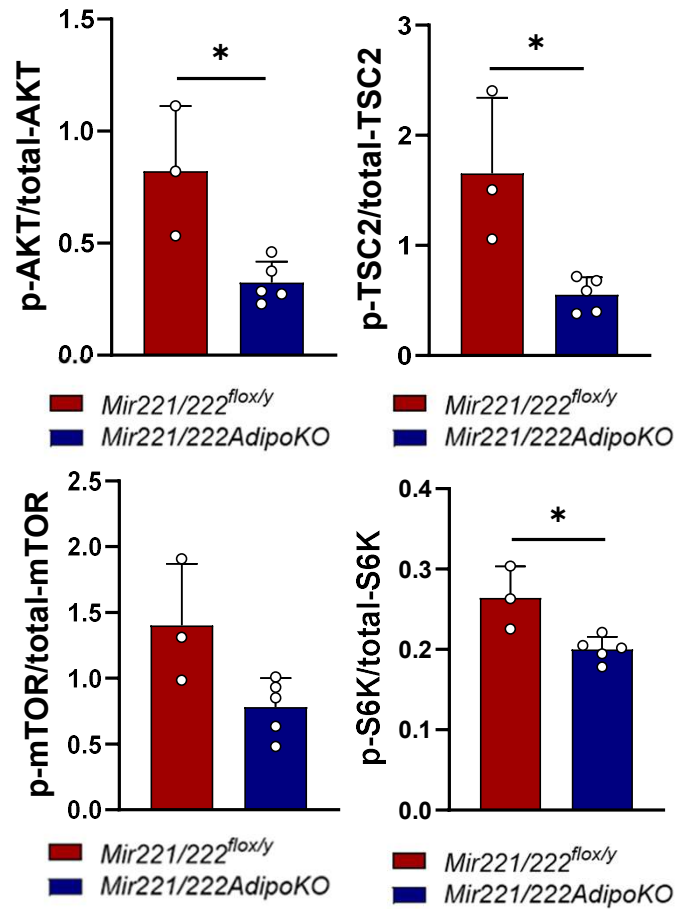
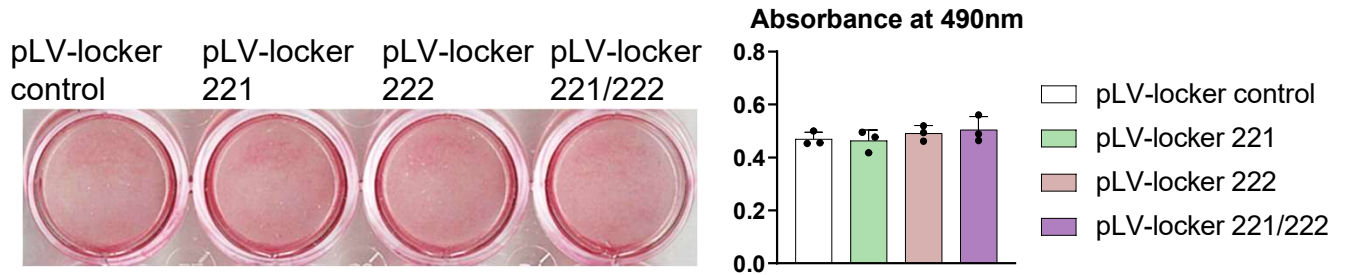
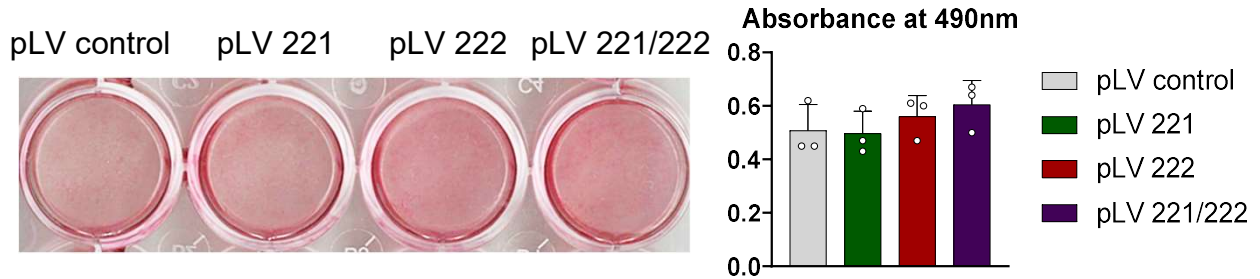


Figure 5

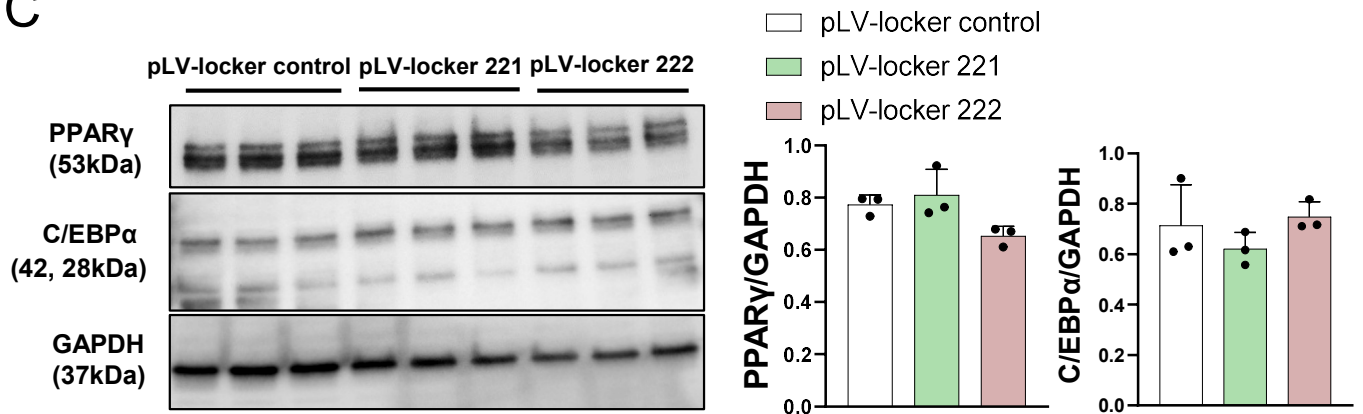
A



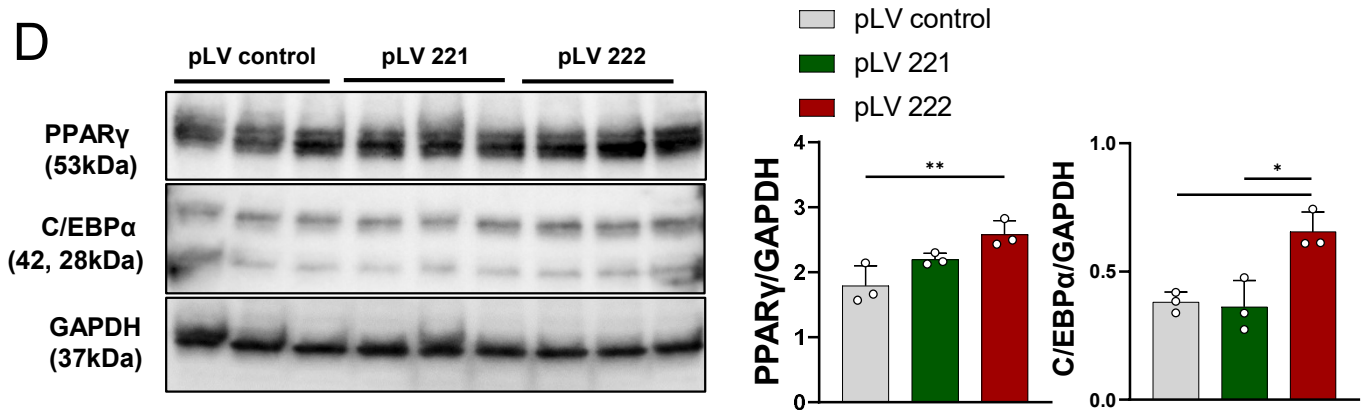
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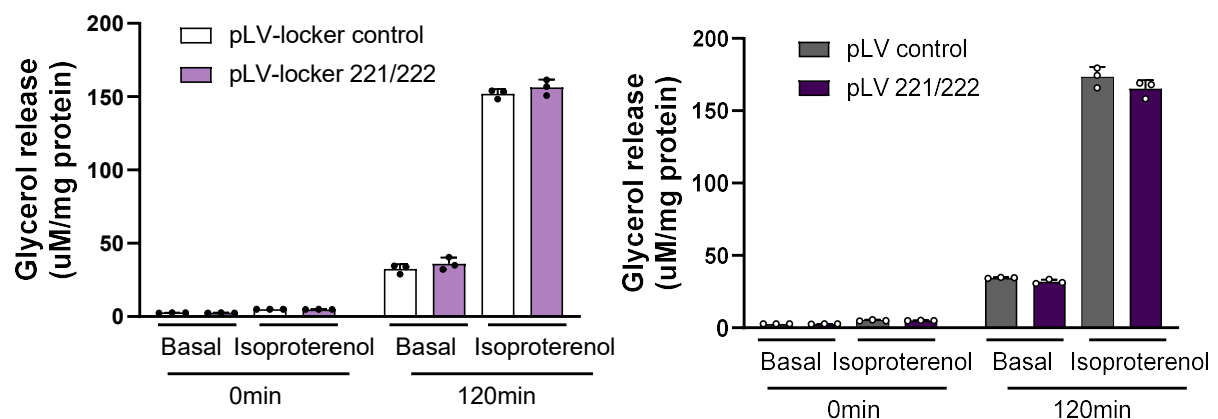
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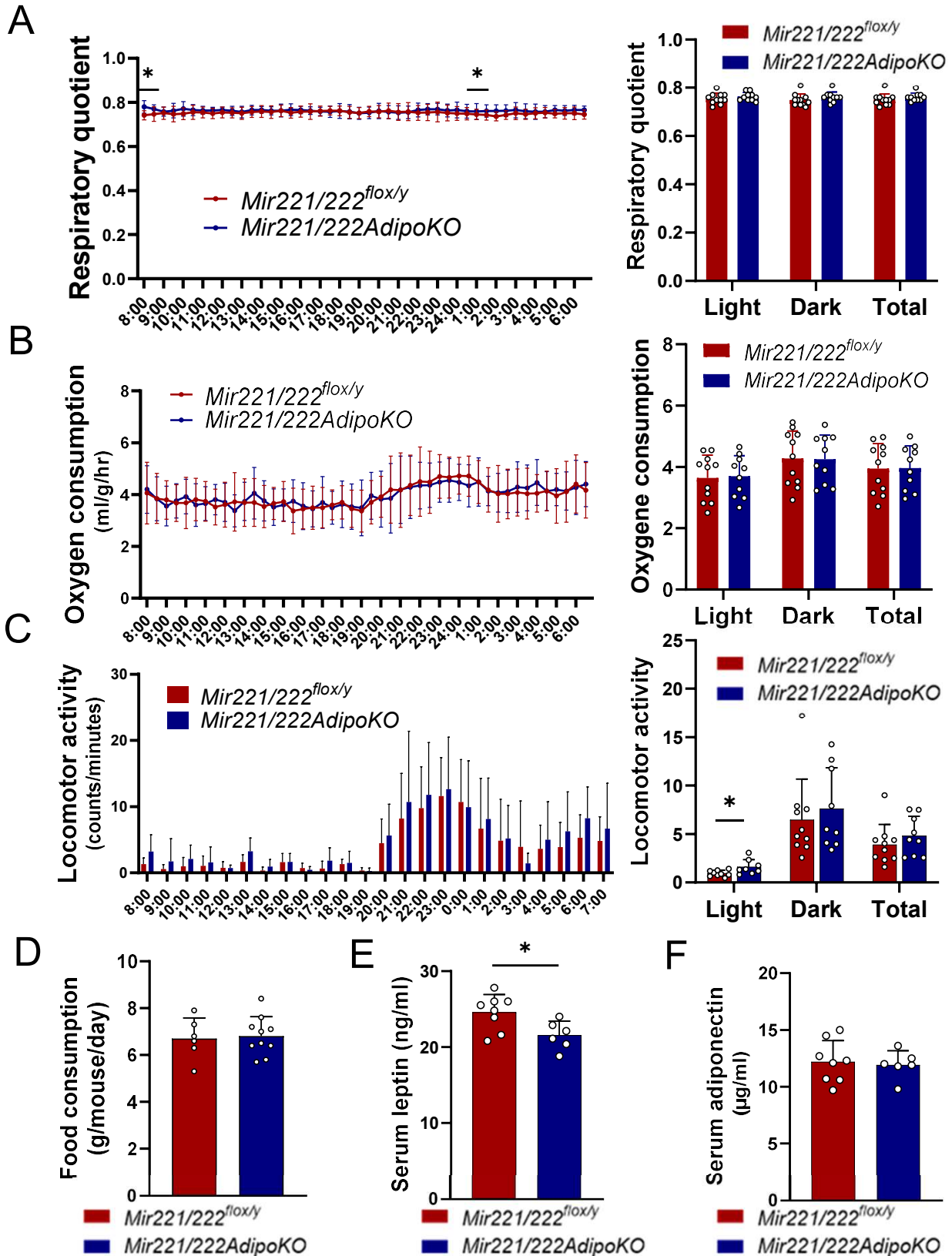
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E

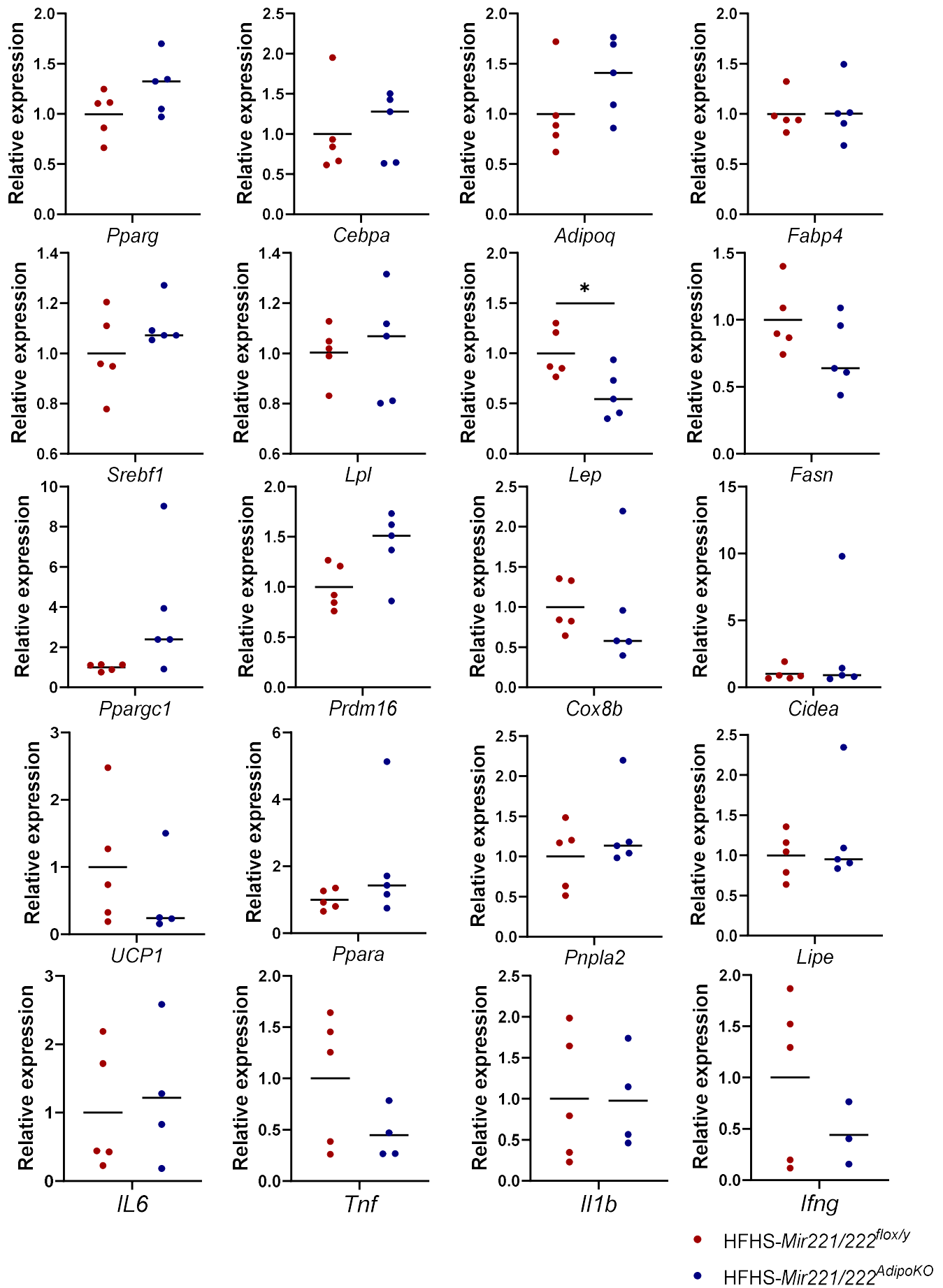


# Supplementary Figure 1



**Supplementary Figure 1.** Basal metabolic rate, locomotor activity and food intake. (**A** and **B**) Respiratory quotient (RQ) and Oxygen consumption rate in *Mir221/222<sup>flox/y</sup>* (n=11) and *Mir221/222AdipoKO* (n=10) mice fed with HFHS (high fat high sucrose) chow. (**C**) Locomotor activity in *Mir221/222<sup>flox/y</sup>* (n=10) and *Mir221/222AdipoKO* (n=9) mice fed with HFHS chow. (**D**) Food consumption in *Mir221/222<sup>flox/y</sup>* (n=5) and *Mir221/222AdipoKO* (n=10) mice fed with HFHS chow. (**E**) Serum leptin levels in *Mir221/222<sup>flox/y</sup>* (n=8) and *Mir221/222AdipoKO* (n=6) mice fed with HFHS chow. (**F**) Serum adiponectin levels in *Mir221/222<sup>flox/y</sup>* (n=8) and *Mir221/222AdipoKO* (n=6) mice fed with HFHS chow. Data shown as mean  $\pm$  SD and analyzed by Mann-Whitney's U test (\*p<0.05).

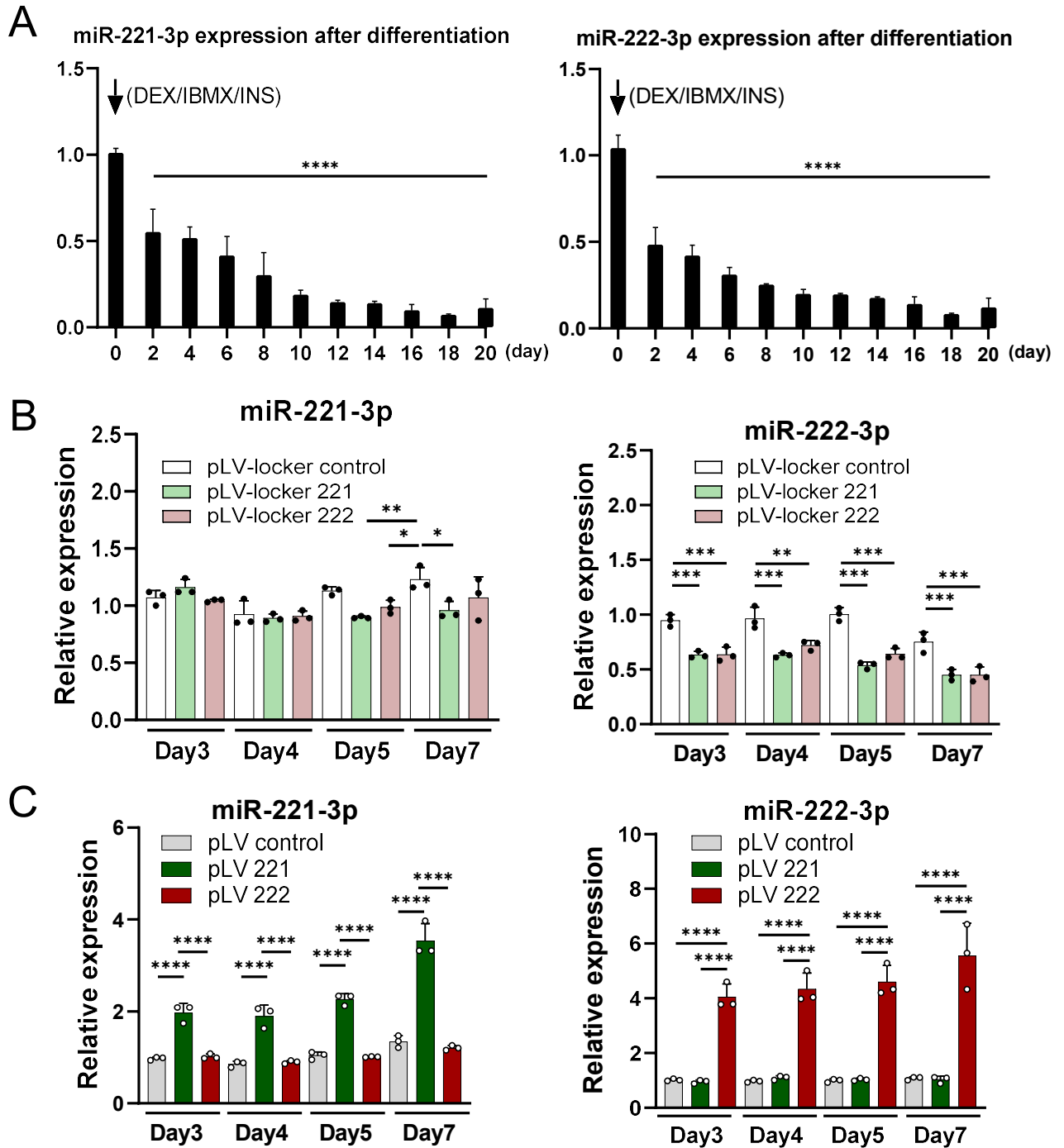
# Supplementary Figure 2



**Supplementary Figure 2.** mRNA expression of various genes. *Mir221/222<sup>flox/y</sup>* (n=5) and *Mir221/222<sup>AdipoKO</sup>* (n=5) mice fed with HFHS (high fat high sucrose) chow. Data shown as mean ± SD and analyzed by Mann-Whitney's U test (\*p<0.05).

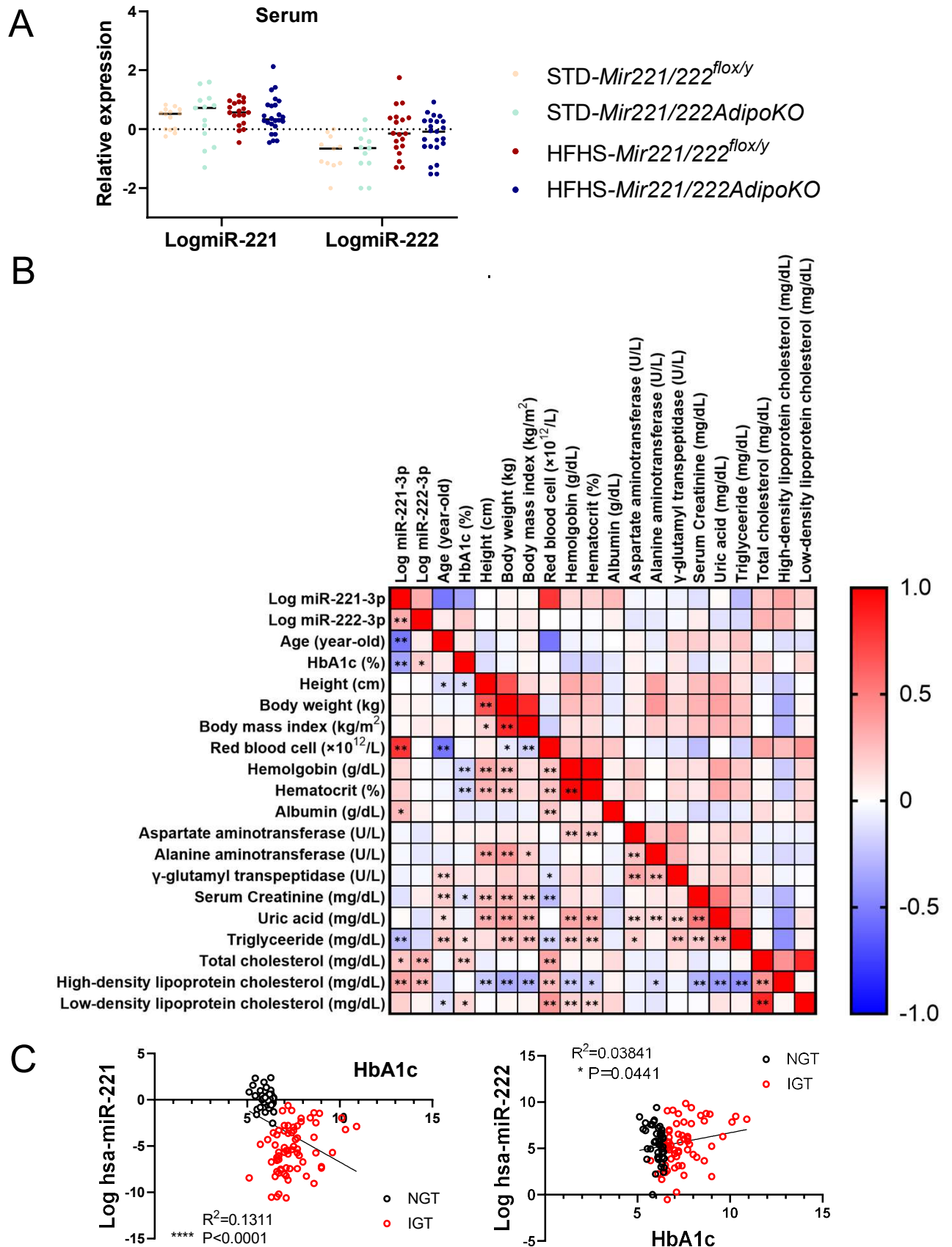


# Supplementary Figure 3



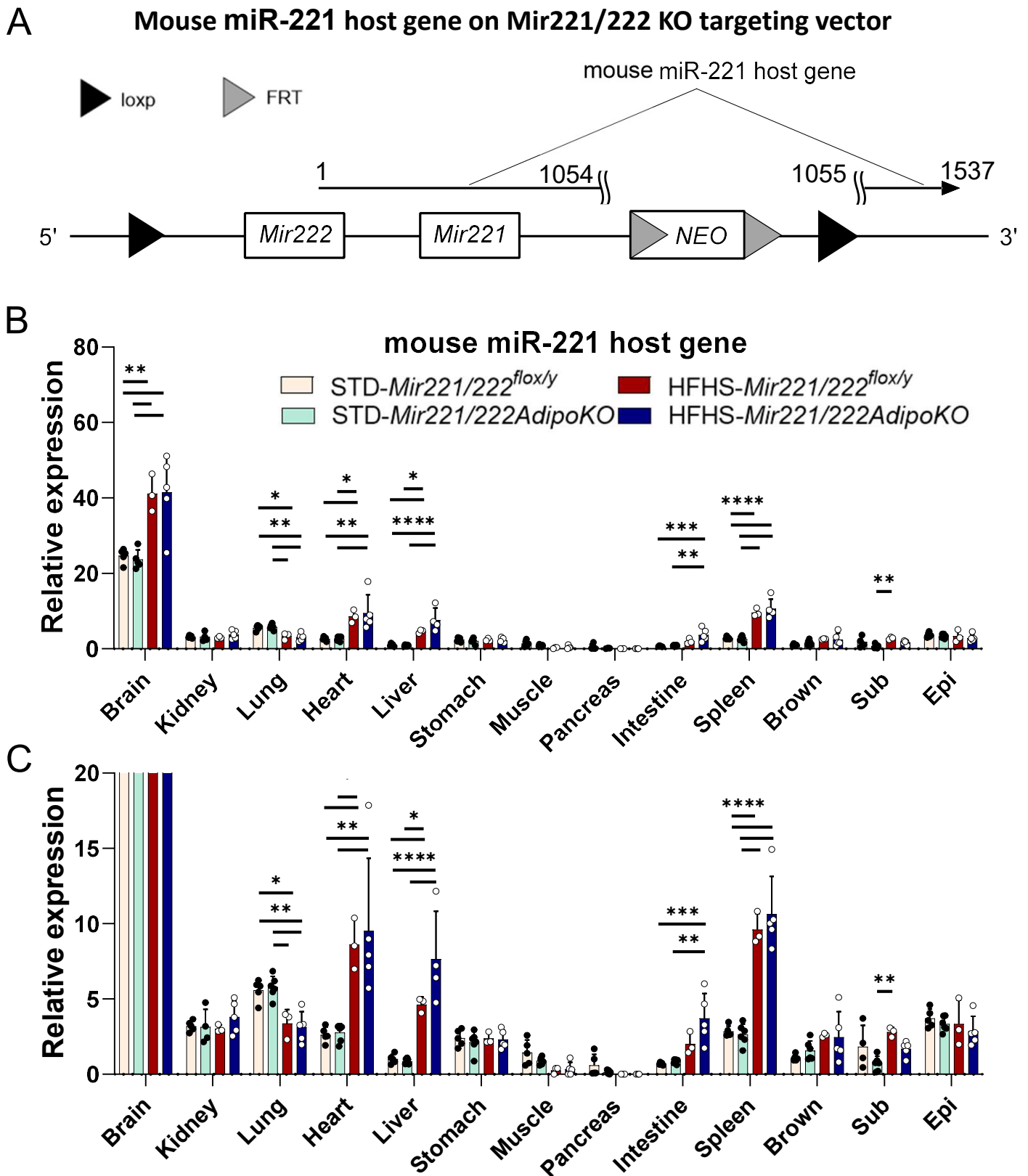
**Supplementary Figure 3.** Expression of miR-221-3p and miR-222-3p in 3T3-L1 cells. **(A)** Expression of miR-221-3p and miR-222-3p after the induction of adipocyte differentiation by dexamethasone, isobutylmethylxanthine, 1-methyl-3-isobutylxanthine and insulin (DEX/IBMX/INS). (n=3) **(B)** Expression of miR-221-3p and miR-222-3p in 3T3L1 cells treated with pLV-locker control, pLV-locker 221, and pLV-locker 222. **(C)** Expression of miR-221-3p and miR-222-3p in 3T3-L1 cells treated with pVL control, pLV 221, and pLV 222. Data shown as mean  $\pm$  SD and analyzed one-way ANOVA with Tukey test (\* $p$ <0.05; \*\* $p$ <0.01; \*\*\* $p$ <0.001; \*\*\*\* $p$ <0.0001).

# Supplementary Figure 4



**Supplementary Figure 4.** Serum concentration of miR-221-3p and miR-222-3p levels in mice and human. **(A)** Serum concentrations of miR-221-3p and miR-222-3p levels in *Mir221/222<sup>flox/y</sup>* (n=14) and *Mir221/222AdipoKO* (n=13) mice fed with STD (standard) chow, *Mir221/222<sup>flox/y</sup>* (n=19) and *Mir221/222AdipoKO* (n=24) mice fed with HFHS (high fat high sucrose) chow. **(B)** Simple correlations of serum miR-221-3p and miR-222-3p levels with various clinical parameters in the subjects with normal glucose tolerance (NGT, n=45) and impaired glucose tolerance (IGT, n=69) (n=114). In correlation matrix, Spearman's rank correlation coefficient is shown. \*p<0.05, \*\*p<0.01. **(C)** Log hsa-miR-221-3p negatively correlates with HbA1c, while Log hsa-miR-222-3p positively correlates with HbA1c.

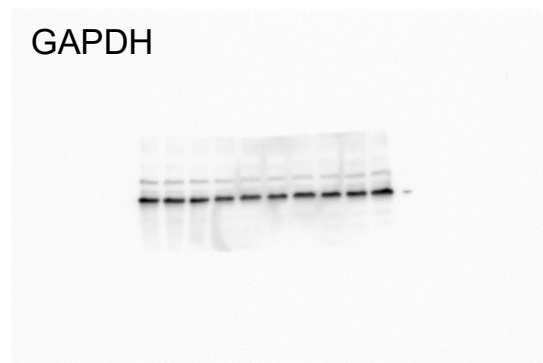
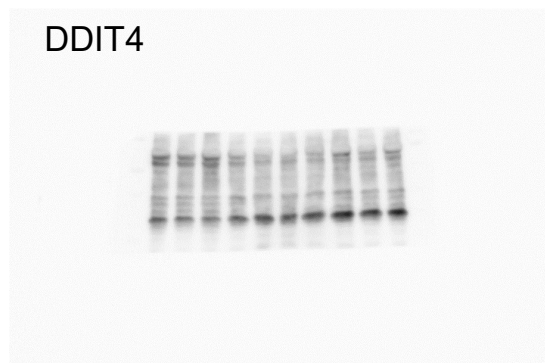
# Supplementary Figure 5



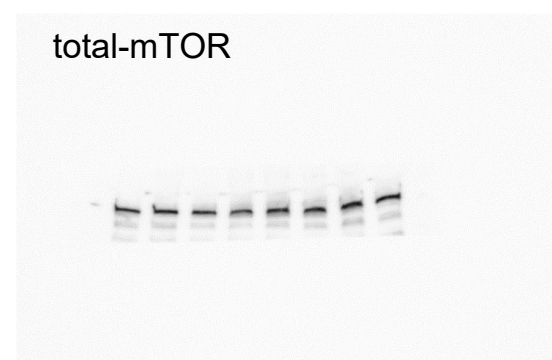
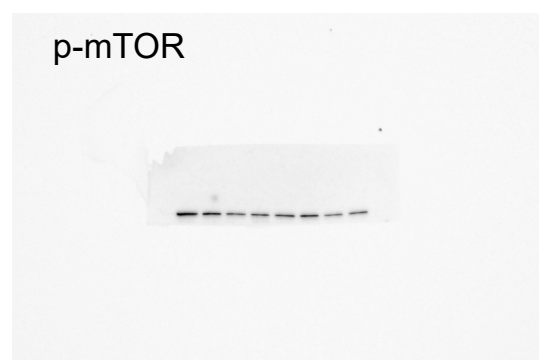
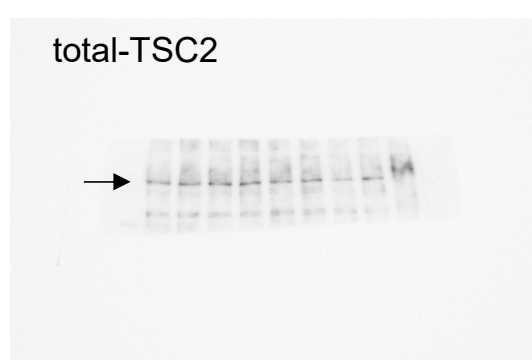
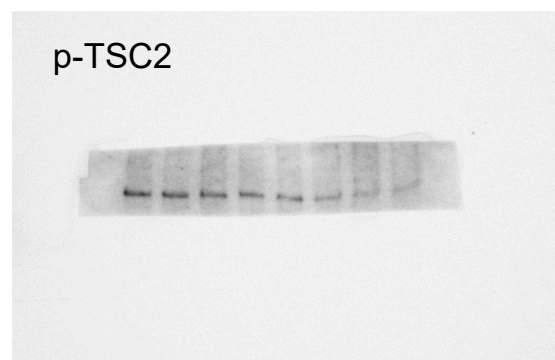
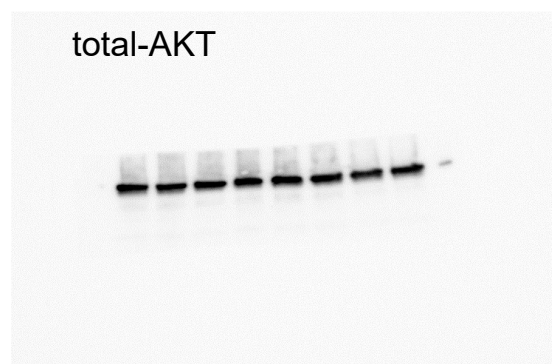
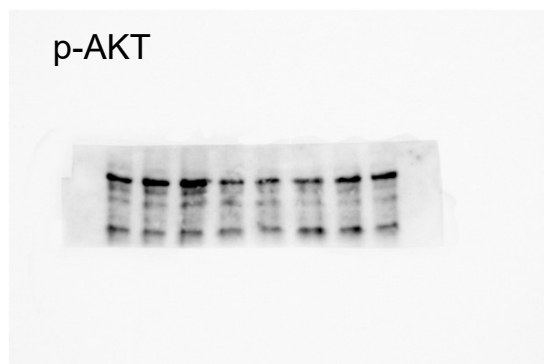
**Supplementary Figure 5.** Expression of miR-221 host gene (*Mir221hg*) in various tissues. **(A)** *Mir221/222* KO targeting vector map and location of miR-221 host gene (*Mir221hg*). The single exon of *Mir221hg* is disrupted by NEO. **(B and C)** Expression of *Mir221hg* in various tissues in *Mir221/222<sup>flox/y</sup>* (n=5) and *Mir221/222AdipoKO* (n=6) mice fed with STD (standard) chow, *Mir221/222<sup>flox/y</sup>* (n=3) and *Mir221/222AdipoKO* (n=5) mice fed with HFHS (high fat high sucrose) chow. Whole range of relative expression (0 to 80) is shown in panel **B** and narrow range (0 to 20) in panel **C**. Data shown as mean  $\pm$  SD and analyzed by one-way ANOVA with Tukey test. (\*p<0.05; \*\*p<0.01; \*\*\*p<0.001; \*\*\*\*p<0.0001).

# Supplementary Figure 6

Uncropped images in Figure 3B



Uncropped images in Figure 4A



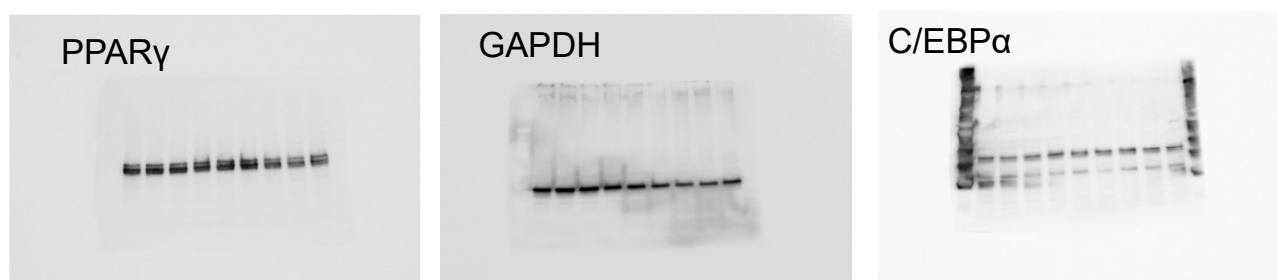
# Supplementary Figure 7

Uncropped images in Figure 4A

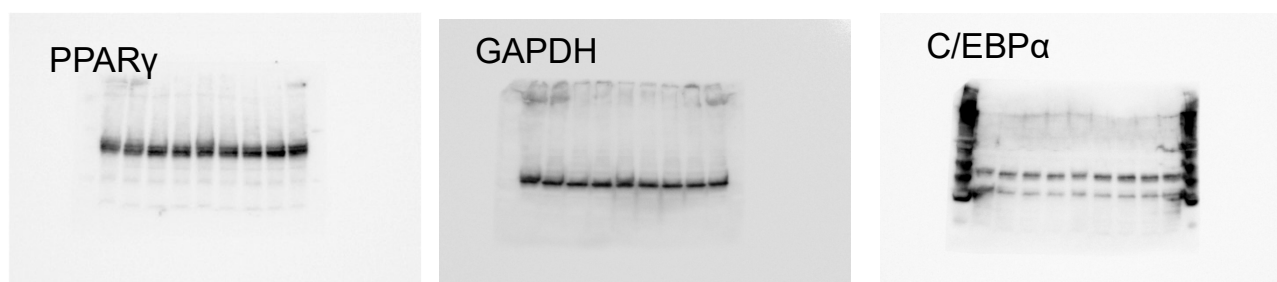


Uncropped images in Figure 5C,D

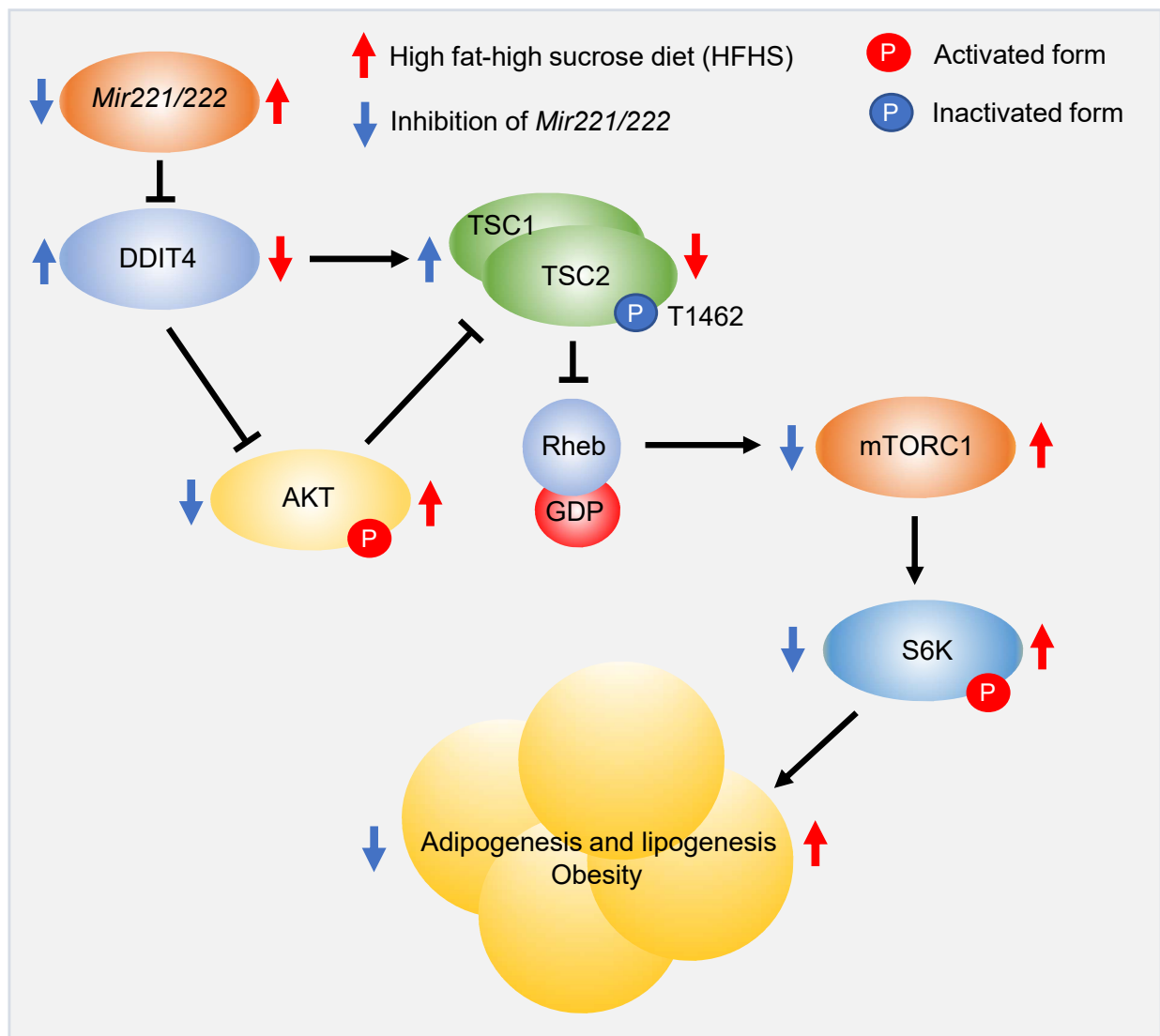
C



D



# Supplementary Figure 8



**Supplementary Figure 8.** Ddit4 is a direct target of miR-221-3p and miR-222-3p and it inhibits mTORC1 pathway.

**Supplementary Table 1.** Formulation of standard (STD) and high fat-high sucrose (HFHS) chow.

	Nutrients / 1000 g chow	STD	HFHS
		(MF, Oriental Yeast, Japan*)	(D12331, Research Diets, New Brunswick, NJ**)
Macronutrients	Protein (g)	226.6	230
	Carbohydrate (g)	553	345
	Fat (g)	51	358.5
Carbohydrate contents	Maltodextrin (g)	0	170
	Corn starch (g)	0	0
	Sucrose (g)	0	175
		553 (as soluble nitrogen-free product from crude mixture of corn, wheat and rice bran)	
Vitamin	Vit A (IU)	12830	4000
	Vit D3 (IU)	1370	1000
	Vit E (mg)	91	50
	Vit K3 (mg)	0.4	0.5
	Vit B1 (mg)	20.5	6
	Vit B2 (mg)	11	6
	Vit B6 (mg)	8.7	7
	Vit B12 ( $\mu$ g)	55	10
	Biotin ( $\mu$ g)	270	200
	Pantothenic acid (mg)	24.5	16
	Niacin (mg)	106.1	30
	Choline (g)	1.8	0.62
Folic acid (mg)	1.7	2	
Mineral	Ca (g)	10.7	5.94
	P (g)	8.3	4.57
	Mg (g)	2.4	0.57
	Na (g)	1.9	1.14
	K (g)	9	4.11
	Fe (mg)	106	42.3
	Cu (mg)	7.8	6.86
	Zn (mg)	48.9	33.1
Mn (mg)	48.4	67.4	
Total calories (kcal)		3590	5560

\*<https://www.oyc.co.jp/bio/LAD-equipment/LAD/ingredient.html> and <https://www.oyc.co.jp/bio/LAD-equipment/LAD/rodents.html>

\*\*<https://www.eptrading.co.jp/service/researchdiets/pdf/D12328-D12331.pdf>

Supplementary Table 2 RNA sequencing data sera, liver and epididymalfat tissues in C57BL/6J mice fed with standard (STD) and high fat-high sucrose chow (HFHS).

miRBase Name	miRBase Accession	LINK	s1 (Serum-High fat high sucrose chow)	s2 (Liver-High fat high sucrose chow)	s3 (Epididymal fat-High fat high sucrose chow)	s5 (Serum-Normal chow)	s6 (Liver-Normal chow)	s7 (Epididymal fat-Normal chow)	Total	s1/s5	s2/s6	s3/s7
mmu-mir-504	MI0005515	<a href="#">miRBase LINK</a>	5	0	1,177	5	0	29	1,216	1.000	#DIV/0!	40.586
mmu-mir-703	MI0004687	<a href="#">miRBase LINK</a>	1	112	13	4	170	1	301	0.250	0.659	13.000
mmu-mir-298	MI0000398	<a href="#">miRBase LINK</a>	188	28	3,175	379	30	249	4,049	0.496	0.933	12.751
mmu-mir-335	MI0000817	<a href="#">miRBase LINK</a>	137	2,673	110,365	54	1,504	8,778	123,511	2.537	1.777	12.573
mmu-mir-342	MI0000627	<a href="#">miRBase LINK</a>	2,027	1,124	19,320	3,427	707	2,040	28,645	0.591	1.590	9.471
mmu-mir-222	MI0000710	<a href="#">miRBase LINK</a>	1,039	1,763	22,488	2,231	1,578	2,759	31,858	0.466	1.117	8.151
mmu-mir-296	MI0000394	<a href="#">miRBase LINK</a>	287	10	454	387	20	63	1,221	0.742	0.500	7.206
mmu-mir-211	MI0000708	<a href="#">miRBase LINK</a>	17	18	7	23	9	1	75	0.739	2.000	7.000
mmu-mir-18b	MI0005483	<a href="#">miRBase LINK</a>	4	3	7	7	0	1	22	0.571	#DIV/0!	7.000
mmu-mir-1193	MI0006298	<a href="#">miRBase LINK</a>	0	0	26	0	1	4	31	#DIV/0!	0.000	6.500
mmu-mir-122	MI0000256	<a href="#">miRBase LINK</a>	723	392,484	409	494	367,471	65	761,646	1.464	1.068	6.292
mmu-mir-669d	MI0006281	<a href="#">miRBase LINK</a>	0	0	12	0	0	2	14	#DIV/0!	#DIV/0!	6.000
mmu-mir-301b	MI0004122	<a href="#">miRBase LINK</a>	80	7	91	107	4	16	305	0.748	1.750	5.688
mmu-mir-221	MI0000709	<a href="#">miRBase LINK</a>	7,180	6,724	38,010	9,165	7,541	6,710	75,330	0.783	0.892	5.665
mmu-mir-802	MI0004249	<a href="#">miRBase LINK</a>	167	33,519	25	64	7,020	5	40,800	2.609	4.775	5.000
mmu-mir-592	MI0004127	<a href="#">miRBase LINK</a>	27	66	25	24	348	6	496	1.125	0.190	4.167
mmu-mir-412	MI0001164	<a href="#">miRBase LINK</a>	0	0	4	0	0	1	5	#DIV/0!	#DIV/0!	4.000
mmu-mir-494	MI0003532	<a href="#">miRBase LINK</a>	4	3	252	29	5	67	360	0.138	0.600	3.761
mmu-mir-499	MI0004676	<a href="#">miRBase LINK</a>	56	9	82	109	5	23	284	0.514	1.800	3.565
mmu-mir-31	MI0000579	<a href="#">miRBase LINK</a>	297	8,935	189	382	11,471	55	21,329	0.777	0.779	3.436
mmu-mir-146a	MI0000170	<a href="#">miRBase LINK</a>	2,113	2,851	9,532	4,266	4,742	2,822	26,326	0.495	0.601	3.378
mmu-mir-147	MI0005482	<a href="#">miRBase LINK</a>	4	4	96	7	6	29	146	0.571	0.667	3.310
mmu-mir-692-1	MI0004660	<a href="#">miRBase LINK</a>	3	76	16	7	63	5	170	0.429	1.206	3.200
mmu-mir-1199	MI0006307	<a href="#">miRBase LINK</a>	8	8	22	9	4	7	58	0.889	2.000	3.143
mmu-mir-679	MI0004638	<a href="#">miRBase LINK</a>	3	1	90	7	1	29	131	0.429	1.000	3.103
mmu-mir-190	MI0000232	<a href="#">miRBase LINK</a>	1	485	713	0	325	231	1,755	#DIV/0!	1.492	3.087
mmu-mir-146b	MI0004665	<a href="#">miRBase LINK</a>	663	676	20,505	1,766	859	6,707	31,176	0.375	0.787	3.057
mmu-mir-380	MI0000797	<a href="#">miRBase LINK</a>	1	6	207	5	6	68	293	0.200	1.000	3.044
mmu-mir-20b	MI0003536	<a href="#">miRBase LINK</a>	5	6	57	10	6	19	103	0.500	1.000	3.000
mmu-mir-684-1	MI0004647	<a href="#">miRBase LINK</a>	1	3	6	0	10	2	22	#DIV/0!	0.300	3.000
mmu-mir-684-2	MI0004648	<a href="#">miRBase LINK</a>	1	3	6	0	10	2	22	#DIV/0!	0.300	3.000
mmu-mir-704	MI0004688	<a href="#">miRBase LINK</a>	1	2	3	2	8	1	17	0.500	0.250	3.000
mmu-mir-669e	MI0006300	<a href="#">miRBase LINK</a>	0	0	3	0	0	1	4	#DIV/0!	#DIV/0!	3.000
mmu-mir-376a	MI0000793	<a href="#">miRBase LINK</a>	7	7	366	0	10	132	522	#DIV/0!	0.700	2.773
mmu-mir-455	MI0004679	<a href="#">miRBase LINK</a>	54	4,687	882	59	5,597	324	11,603	0.915	0.837	2.722
mmu-mir-487b	MI0003534	<a href="#">miRBase LINK</a>	15	1	208	26	0	77	327	0.577	#DIV/0!	2.701
mmu-mir-496	MI0004589	<a href="#">miRBase LINK</a>	2	1	262	11	6	97	379	0.182	0.167	2.701
mmu-mir-551b	MI0004131	<a href="#">miRBase LINK</a>	3	116	8	1	27	3	158	3.000	4.296	2.667
mmu-mir-340	MI0000623	<a href="#">miRBase LINK</a>	1,859	27,006	19,256	2,661	22,296	7,227	80,305	0.699	1.211	2.664
mmu-mir-376b	MI0001162	<a href="#">miRBase LINK</a>	3	9	362	11	14	136	535	0.273	0.643	2.662
mmu-mir-370	MI0001165	<a href="#">miRBase LINK</a>	7	0	53	6	0	20	86	1.167	#DIV/0!	2.650
mmu-mir-377	MI0000794	<a href="#">miRBase LINK</a>	11	2	271	11	3	103	401	1.000	0.667	2.631
mmu-mir-142	MI0000167	<a href="#">miRBase LINK</a>	37,026	17,590	58,187	39,676	9,631	22,754	184,864	0.933	1.826	2.557
mmu-mir-692-2	MI0004661	<a href="#">miRBase LINK</a>	10	328	66	56	254	26	740	0.179	1.291	2.538
mmu-mir-433	MI0001525	<a href="#">miRBase LINK</a>	21	0	191	45	2	76	335	0.467	0.000	2.513
mmu-mir-214	MI0000698	<a href="#">miRBase LINK</a>	170	682	3,121	250	655	1,245	6,123	0.680	1.041	2.507
mmu-mir-543	MI0003519	<a href="#">miRBase LINK</a>	0	3	102	21	3	41	170	0.000	1.000	2.488
mmu-mir-369	MI0003535	<a href="#">miRBase LINK</a>	4	11	718	29	12	291	1,065	0.138	0.917	2.467
mmu-mir-155	MI0000177	<a href="#">miRBase LINK</a>	123	122	1,336	251	105	542	2,479	0.490	1.162	2.465
mmu-mir-669a-2	MI0004667	<a href="#">miRBase LINK</a>	15	49	439	62	41	180	786	0.242	1.195	2.439
mmu-mir-501	MI0004703	<a href="#">miRBase LINK</a>	60	65	342	106	66	141	780	0.566	0.985	2.426
mmu-mir-669a-1	MI0004523	<a href="#">miRBase LINK</a>	165	512	4,545	668	416	1,880	8,186	0.247	1.231	2.418
mmu-mir-411	MI0001163	<a href="#">miRBase LINK</a>	136	350	35,343	272	498	14,732	51,331	0.500	0.703	2.399
mmu-mir-299	MI0000399	<a href="#">miRBase LINK</a>	15	4	735	31	17	310	1,112	0.484	0.235	2.371
mmu-mir-130b	MI0000408	<a href="#">miRBase LINK</a>	4,382	91	614	5,414	88	260	10,849	0.809	1.034	2.362
mmu-mir-297b	MI0004674	<a href="#">miRBase LINK</a>	1	9	30	0	0	13	53	#DIV/0!	#DIV/0!	2.308
mmu-mir-136	MI0000162	<a href="#">miRBase LINK</a>	182	185	8,157	428	288	3,543	12,783	0.425	0.642	2.302
mmu-mir-106a	MI0000406	<a href="#">miRBase LINK</a>	3	2	16	3	1	7	32	1.000	2.000	2.286
mmu-mir-449c	MI0004645	<a href="#">miRBase LINK</a>	1	0	25	0	0	11	37	#DIV/0!	#DIV/0!	2.273
mmu-mir-18a	MI0000567	<a href="#">miRBase LINK</a>	754	261	410	823	214	181	2,643	0.916	1.220	2.265
mmu-mir-652	MI0004965	<a href="#">miRBase LINK</a>	1,121	348	1,394	1,288	265	616	5,032	0.870	1.313	2.263
mmu-mir-9-1	MI0000720	<a href="#">miRBase LINK</a>	3	25	259	9	6	115	417	0.333	4.167	2.252
mmu-mir-9-2	MI0000157	<a href="#">miRBase LINK</a>	3	25	259	9	6	115	417	0.333	4.167	2.252
mmu-mir-297a-6	MI0005491	<a href="#">miRBase LINK</a>	0	0	18	20	2	8	48	0.000	0.000	2.250
mmu-mir-297a-1	MI0000395	<a href="#">miRBase LINK</a>	0	0	9	10	1	4	24	0.000	0.000	2.250
mmu-mir-297a-2	MI0000397	<a href="#">miRBase LINK</a>	0	0	9	10	1	4	24	0.000	0.000	2.250
mmu-mir-511	MI0005554	<a href="#">miRBase LINK</a>	332	663	985	683	687	439	3,789	0.486	0.965	2.244
mmu-mir-540	MI0003518	<a href="#">miRBase LINK</a>	55	6	497	147	8	222	935	0.374	0.750	2.239
mmu-mir-598	MI0005556	<a href="#">miRBase LINK</a>	12	162	264	5	176	118	737	2.400	0.920	2.237
mmu-mir-9-3	MI0000721	<a href="#">miRBase LINK</a>	3	25	259	9	6	116	418	0.333	4.167	2.233
mmu-mir-223	MI0000703	<a href="#">miRBase LINK</a>	1,534	857	7,087	2,369	671	3,189	15,707	0.648	1.277	2.222
mmu-mir-382	MI0000799	<a href="#">miRBase LINK</a>	7	4	333	38	8	150	540	0.184	0.500	2.220
mmu-mir-205	MI0000248	<a href="#">miRBase LINK</a>	2,127	108	71	6,337	43	32	8,718	0.336	2.512	2.219
mmu-mir-409	MI0001160	<a href="#">miRBase LINK</a>	125	25	1,891	374	40	857	3,312	0.334	0.625	2.207
mmu-mir-379	MI0000796	<a href="#">miRBase LINK</a>	1	10	784	11	25	356	1,187	0.091	0.400	2.202
mmu-mir-337	MI0000615	<a href="#">miRBase LINK</a>	53	11	1,263	115	21	574	2,037	0.461	0.524	2.200
mmu-mir-323	MI0000592	<a href="#">miRBase LINK</a>	1	1	39	14	0	18	73	0.071	#DIV/0!	2.167
mmu-mir-297c	MI0005492	<a href="#">miRBase LINK</a>	0	7	26	0	0	12	45	#DIV/0!	#DIV/0!	2.167
mmu-mir-466d	MI0005546	<a href="#">miRBase LINK</a>	2	4	28	11	5	13	63	0.182	0.800	2.154
mmu-mir-410	MI0001161	<a href="#">miRBase LINK</a>	149	51	5,073	477	40	2,383	8,173	0.312	1.275	2.129
mmu-mir-297a-4	MI0005489	<a href="#">miRBase LINK</a>	0	8	36	10	1	17	72	0.000	8.000	2.118
mmu-mir-297a-3	MI0005488	<a href="#">miRBase LINK</a>	0	7	36	10	1	17	71	0.000	7.000	2.118
mmu-mir-363	MI0000765	<a href="#">miRBase LINK</a>	21	5	110	71	3	52	262	0.296	1.667	2.115
mmu-mir-485	MI0003492	<a href="#">miRBase LINK</a>	48	7	338	157	3	160	713	0.306	2.333	2.113
mmu-mir-34c	MI0000403	<a href="#">miRBase LINK</a>	230	153	7,548	295	357	3,585	12,168	0.780	0.429	2.105
mmu-mir-141	MI0000166	<a href="#">miRBase LINK</a>	273	404	88	370	272	42	1,449	0.738	1.485	2.095
mmu-mir-329	MI0000605	<a href="#">miRBase LINK</a>	21	10	888	72	14	424	1,429	0.292	0.714	2.094
mmu-mir-376c	MI0003533	<a href="#">miRBase LINK</a>	2	8	249	6	3	120	388	0.333	2.667	2.075
mmu-mir-541	MI0003521	<a href="#">miRBase LINK</a>	769	207	15,707	1,541	288	7,593	26,105	0.499	0.719	2.069
mmu-mir-542	MI0003522	<a href="#">miRBase LINK</a>	17	224	534	31	185	259	1,250	0.548	1.211	2.062
mmu-mir-467a			8	170	1,476	8	171	716	2,549	1.000	0.994	2.061
mmu-mir-434	MI0001526	<a href="#">miRBase LINK</a>	2,057	403	37,349	5,758	670	18,279	64,516	0.357	0.601	2.043



mmu-mir-199a-1	MI0000241	<a href="#">miRBase LINK</a>	4,296	18,270	111,847	9,449	25,278	55,294	224,434	0.455	0.723	2.023
mmu-mir-199a-2	MI0000713	<a href="#">miRBase LINK</a>	4,297	18,289	111,987	9,449	25,297	55,364	224,683	0.455	0.723	2.023
mmu-mir-27b	MI0000142	<a href="#">miRBase LINK</a>	22,994	253,279	390,605	29,301	245,960	193,911	1,136,050	0.785	1.030	2.014
mmu-mir-34b	MI0000404	<a href="#">miRBase LINK</a>	36	11	547	20	30	273	917	1.800	0.367	2.004
mmu-mir-375	MI0000792	<a href="#">miRBase LINK</a>	8,270	137	12	4,163	133	6	12,721	1.987	1.030	2.000
mmu-mir-200c	MI0000694	<a href="#">miRBase LINK</a>	72	54	22	119	40	11	318	0.605	1.350	2.000
mmu-mir-466b-3	MI0000504	<a href="#">miRBase LINK</a>	7	6	54	8	6	27	108	0.875	1.000	2.000
mmu-mir-539	MI00003520	<a href="#">miRBase LINK</a>	2	0	14	0	0	7	23	#DIV/0!	#DIV/0!	2.000
mmu-mir-547	MI00003523	<a href="#">miRBase LINK</a>	0	1	2	0	10	1	14	#DIV/0!	0.100	2.000
mmu-mir-669h	MI00006289	<a href="#">miRBase LINK</a>	0	0	2	0	0	1	3	#DIV/0!	#DIV/0!	2.000
mmu-mir-199b	MI0000714	<a href="#">miRBase LINK</a>	4,178	17,125	107,930	9,223	24,025	54,220	216,701	0.453	0.713	1.991
mmu-mir-181d	MI0000450	<a href="#">miRBase LINK</a>	1,317	353	2,840	2,036	506	1,429	8,481	0.647	0.698	1.987
mmu-mir-674	MI00004611	<a href="#">miRBase LINK</a>	417	377	1,656	623	267	836	4,176	0.669	1.412	1.981
mmu-mir-230b	MI0000141	<a href="#">miRBase LINK</a>	485	8,475	16,917	745	8,883	8,549	44,054	0.651	0.954	1.979
mmu-mir-495	MI00004639	<a href="#">miRBase LINK</a>	0	8	220	9	8	114	359	0.000	1.000	1.930
mmu-mir-134	MI0000160	<a href="#">miRBase LINK</a>	16	5	239	101	9	124	494	0.158	0.556	1.927
mmu-mir-431	MI00001524	<a href="#">miRBase LINK</a>	41	11	1,110	158	9	579	1,908	0.259	1.222	1.917
mmu-mir-466c			24	33	276	21	45	144	543	1.143	0.733	1.917
mmu-mir-669a-3	MI00004668	<a href="#">miRBase LINK</a>	15	23	157	48	6	82	331	0.313	3.833	1.915
mmu-mir-181c	MI0000724	<a href="#">miRBase LINK</a>	5,818	5,782	34,967	8,210	10,013	18,384	83,174	0.709	0.577	1.902
mmu-mir-32	MI0000691	<a href="#">miRBase LINK</a>	22	1,000	1,235	7	656	650	3,570	3.143	1.524	1.900
mmu-mir-505	MI00004706	<a href="#">miRBase LINK</a>	28	79	112	27	58	59	363	1.037	1.362	1.898
mmu-mir-15b	MI0000140	<a href="#">miRBase LINK</a>	3,219	1,918	5,791	3,407	1,569	3,074	18,978	0.945	1.222	1.884
mmu-mir-466b-1	MI00005502	<a href="#">miRBase LINK</a>	48	54	438	48	53	234	875	1.000	1.019	1.872
mmu-mir-466a	MI00002401	<a href="#">miRBase LINK</a>	8	8	71	7	10	38	142	1.143	0.800	1.868
mmu-mir-500	MI00004702	<a href="#">miRBase LINK</a>	34	141	627	74	162	337	1,375	0.459	0.870	1.861
mmu-mir-322	MI0000590	<a href="#">miRBase LINK</a>	281	1,774	18,296	320	1,581	9,847	32,099	0.878	1.122	1.858
mmu-mir-450b	MI00004705	<a href="#">miRBase LINK</a>	35	278	1,238	37	257	670	2,515	0.946	1.082	1.848
mmu-mir-466b-2	MI00005503	<a href="#">miRBase LINK</a>	8	9	72	8	9	39	145	1.000	1.000	1.846
mmu-mir-450a-1	MI0001653	<a href="#">miRBase LINK</a>	22	514	1,665	16	547	903	3,667	1.375	0.940	1.844
mmu-let-7i	MI0000138	<a href="#">miRBase LINK</a>	36,717	37,261	191,131	43,314	35,448	103,687	447,558	0.848	1.051	1.843
mmu-mir-450a-2	MI00003537	<a href="#">miRBase LINK</a>	22	512	1,654	17	549	901	3,655	1.294	0.933	1.836
mmu-mir-149	MI0000171	<a href="#">miRBase LINK</a>	1,128	2,485	2,990	1,681	598	1,635	10,517	0.671	4.156	1.829
mmu-mir-34a	MI0000584	<a href="#">miRBase LINK</a>	31	784	5,181	63	427	2,838	9,324	0.492	1.836	1.826
mmu-mir-466e	MI0000506	<a href="#">miRBase LINK</a>	16	16	142	16	18	78	286	1.000	0.889	1.821
mmu-mir-300	MI0000400	<a href="#">miRBase LINK</a>	65	41	2,666	179	53	1,469	4,473	0.363	0.774	1.815
mmu-mir-21	MI0000569	<a href="#">miRBase LINK</a>	33,913	675,905	833,457	57,300	872,282	459,536	2,932,393	0.592	0.775	1.814
mmu-mir-362	MI0000763	<a href="#">miRBase LINK</a>	19	379	709	16	348	392	1,863	1.188	1.089	1.809
mmu-mir-381	MI0000798	<a href="#">miRBase LINK</a>	155	59	4,680	340	85	2,600	7,919	0.456	0.694	1.800
mmu-mir-467b	MI0004671	<a href="#">miRBase LINK</a>	1	16	104	1	17	58	197	1.000	0.941	1.793
mmu-mir-15a	MI0000564	<a href="#">miRBase LINK</a>	13,121	19,585	20,015	12,934	17,333	11,210	94,198	1.014	1.130	1.785
mmu-mir-181a-1	MI0000697	<a href="#">miRBase LINK</a>	50,781	54,617	675,748	91,806	53,250	380,583	1,306,785	0.553	1.026	1.776
mmu-mir-181a-2	MI0000223	<a href="#">miRBase LINK</a>	50,960	54,780	672,973	92,313	53,412	380,437	1,304,875	0.552	1.026	1.769
mmu-mir-148b	MI0000617	<a href="#">miRBase LINK</a>	513	3,255	3,523	540	2,943	1,992	12,766	0.950	1.106	1.769
mmu-mir-182	MI0000224	<a href="#">miRBase LINK</a>	1,221	16,422	1,562	1,891	12,825	888	34,809	0.646	1.280	1.759
mmu-mir-677	MI0000634	<a href="#">miRBase LINK</a>	5	364	237	22	363	135	1,126	0.227	1.003	1.756
mmu-mir-127	MI0000154	<a href="#">miRBase LINK</a>	1,751	714	68,083	3,850	1,120	38,800	114,318	0.455	0.638	1.755
mmu-mir-201	MI0000244	<a href="#">miRBase LINK</a>	4	58	7	3	52	4	128	1.333	1.115	1.750
mmu-mir-128-2	MI0000726	<a href="#">miRBase LINK</a>	2,971	452	944	4,817	322	540	10,046	0.617	1.404	1.748
mmu-mir-666	MI00004553	<a href="#">miRBase LINK</a>	2	1	108	6	0	62	179	0.333	#DIV/0!	1.742
mmu-mir-17	MI0000687	<a href="#">miRBase LINK</a>	1,299	1,972	2,333	1,142	1,540	1,340	9,626	1.137	1.281	1.741
mmu-mir-421	MI0000496	<a href="#">miRBase LINK</a>	2,166	285	1,204	2,543	263	694	7,155	0.852	1.084	1.735
mmu-mir-7a-2	MI0000729	<a href="#">miRBase LINK</a>	3	335	171	5	328	99	941	0.600	1.021	1.727
mmu-mir-24-1	MI0000231	<a href="#">miRBase LINK</a>	335	2,267	13,600	604	2,923	7,887	27,616	0.555	0.776	1.724
mmu-mir-184	MI0000226	<a href="#">miRBase LINK</a>	20	15	98	73	50	57	313	0.274	0.300	1.719
mmu-mir-297a-5	MI0005490	<a href="#">miRBase LINK</a>	0	0	12	10	1	7	30	0.000	0.000	1.714
mmu-mir-128-1	MI0000155	<a href="#">miRBase LINK</a>	3,329	596	1,171	5,477	450	688	11,711	0.608	1.324	1.702
mmu-mir-132	MI0000158	<a href="#">miRBase LINK</a>	471	396	1,704	621	356	1,010	4,558	0.758	1.112	1.687
mmu-mir-126	MI0000153	<a href="#">miRBase LINK</a>	13,581	210,617	507,382	15,175	201,422	301,182	1,249,359	0.895	1.046	1.685
mmu-mir-665	MI0004171	<a href="#">miRBase LINK</a>	1	0	42	10	0	25	78	0.100	#DIV/0!	1.680
mmu-mir-16-1	MI0000565	<a href="#">miRBase LINK</a>	270,173	109,350	189,081	274,399	112,265	113,203	1,068,471	0.985	0.974	1.670
mmu-mir-24-2	MI0000572	<a href="#">miRBase LINK</a>	790	3,781	25,120	1,311	4,695	15,056	50,753	0.603	0.805	1.668
mmu-mir-341	MI0000625	<a href="#">miRBase LINK</a>	25	8	662	69	5	397	1,166	0.362	1.600	1.668
mmu-mir-1-2-as			0	2	5	0	2	3	12	#DIV/0!	1.000	1.667
mmu-mir-16-2	MI0000566	<a href="#">miRBase LINK</a>	270,034	108,238	187,705	274,225	111,159	112,639	1,064,000	0.985	0.974	1.666
mmu-mir-212	MI0000696	<a href="#">miRBase LINK</a>	42	76	326	75	64	196	779	0.560	1.188	1.663
mmu-mir-185	MI0000227	<a href="#">miRBase LINK</a>	91	1,001	765	91	901	462	3,311	1.000	1.111	1.656
mmu-mir-301a	MI0000401	<a href="#">miRBase LINK</a>	1,103	1,619	4,351	1,210	1,203	2,629	12,115	0.912	1.346	1.655
mmu-mir-467c	MI0005512	<a href="#">miRBase LINK</a>	1	5	43	0	4	26	79	#DIV/0!	1.250	1.654
mmu-mir-326	MI0000598	<a href="#">miRBase LINK</a>	212	287	2,204	313	417	1,335	4,768	0.677	0.688	1.651
mmu-mir-668	MI0004134	<a href="#">miRBase LINK</a>	27	0	224	96	2	136	485	0.281	0.000	1.647
mmu-mir-152	MI0000174	<a href="#">miRBase LINK</a>	183	2,975	10,113	298	2,440	6,141	22,150	0.614	1.219	1.647
mmu-mir-452	MI0001734	<a href="#">miRBase LINK</a>	0	3	36	6	4	22	71	0.000	0.750	1.636
mmu-mir-673	MI0004601	<a href="#">miRBase LINK</a>	58	7	453	168	4	277	967	0.345	1.750	1.635
mmu-mir-667	MI0004196	<a href="#">miRBase LINK</a>	18	1	123	51	1	76	270	0.353	1.000	1.618
mmu-mir-186	MI0000228	<a href="#">miRBase LINK</a>	20,174	17,459	51,457	22,453	16,000	31,850	159,393	0.898	1.091	1.616
mmu-mir-19a	MI0000688	<a href="#">miRBase LINK</a>	151	444	149	147	382	93	1,366	1.027	1.162	1.602
mmu-mir-669c	MI0004673	<a href="#">miRBase LINK</a>	1	18	91	10	7	57	184	0.100	2.571	1.596
mmu-mir-700	MI0004684	<a href="#">miRBase LINK</a>	27	52	258	23	72	163	595	1.174	0.722	1.583
mmu-mir-23a	MI0000571	<a href="#">miRBase LINK</a>	4,046	3,914	44,281	7,353	5,152	28,227	92,973	0.550	0.760	1.569
mmu-mir-139	MI0000693	<a href="#">miRBase LINK</a>	339	2,056	9,577	382	1,835	6,106	20,295	0.887	1.120	1.568
mmu-mir-27a	MI0000578	<a href="#">miRBase LINK</a>	2,777	8,389	65,837	3,388	8,827	42,164	131,382	0.820	0.950	1.561
mmu-mir-19b-1	MI0000718	<a href="#">miRBase LINK</a>	1,366	5,002	2,546	1,374	5,222	1,633	17,143	0.994	0.958	1.559
mmu-mir-19b-2	MI0000546	<a href="#">miRBase LINK</a>	1,368	5,031	2,540	1,375	5,241	1,632	17,187	0.995	0.960	1.556
mmu-mir-7a-1	MI0000728	<a href="#">miRBase LINK</a>	51	465	333	33	492	217	1,591	1.545	0.945	1.535
mmu-mir-138-2	MI0000164	<a href="#">miRBase LINK</a>	271	98	1,608	488	60	1,059	3,584	0.555	1.633	1.518
mmu-mir-194-2	MI0000733	<a href="#">miRBase LINK</a>	636	160,390	2,112	566	142,987	1,393	308,084	1.124	1.122	1.516
mmu-mir-338	MI0000619	<a href="#">miRBase LINK</a>	58	581	1,375	64	681	910	3,669	0.906	0.853	1.511
mmu-mir-98	MI0000586	<a href="#">miRBase LINK</a>	1,262	8,984	18,009	1,521	8,447	11,921	50,144	0.830	1.064	1.511
mmu-mir-689-1			1,919	2,643	2,029	2,160	2,465	1,349	12,565	0.888	1.072	1.504
mmu-mir-30b	MI0000145	<a href="#">miRBase LINK</a>	13,651	52,808	70,119	16,874</						

mmu-mir-22	MI0000570	<a href="#">miRBase LINK</a>	338,851	3,965,596	4,079,202	420,007	4,183,928	2,763,563	15,751,147	0.807	0.948	1.476
mmu-mir-188	MI0000230	<a href="#">miRBase LINK</a>	10	58	218	32	49	148	515	0.313	1.184	1.473
mmu-mir-181b-2	MI0000823	<a href="#">miRBase LINK</a>	3,670	2,242	28,133	6,614	2,261	19,128	62,048	0.555	0.992	1.471
mmu-mir-194-1	MI0000236	<a href="#">miRBase LINK</a>	646	159,842	2,109	615	142,468	1,435	307,115	1.050	1.122	1.470
mmu-mir-181b-1	MI0000723	<a href="#">miRBase LINK</a>	3,625	2,174	27,208	6,530	2,188	18,561	60,286	0.555	0.994	1.466
mmu-mir-196a-2	MI0000553	<a href="#">miRBase LINK</a>	6	4	208	15	0	142	375	0.400	#DIV/0!	1.465
mmu-mir-129-2	MI0000585	<a href="#">miRBase LINK</a>	26	17	19	32	23	13	130	0.813	0.739	1.462
mmu-mir-30e	MI0000259	<a href="#">miRBase LINK</a>	61,653	170,748	125,889	80,846	193,521	86,176	718,833	0.763	0.882	1.461
mmu-mir-672	MI0004258	<a href="#">miRBase LINK</a>	25	2	29	48	3	20	127	0.521	0.667	1.450
mmu-mir-669b	MI0004666	<a href="#">miRBase LINK</a>	0	6	29	0	0	20	55	#DIV/0!	#DIV/0!	1.450
mmu-mir-532	MI0003206	<a href="#">miRBase LINK</a>	3,030	3,678	13,418	4,082	3,515	9,271	36,994	0.742	1.046	1.447
mmu-mir-196a-1	MI0000552	<a href="#">miRBase LINK</a>	1	4	166	10	0	115	296	0.100	#DIV/0!	1.443
mmu-mir-374	MI0004125	<a href="#">miRBase LINK</a>	124	744	892	138	797	622	3,317	0.899	0.934	1.434
mmu-mir-129-1	MI0000222	<a href="#">miRBase LINK</a>	22	42	10	23	47	7	151	0.957	0.894	1.429
mmu-mir-154	MI0000176	<a href="#">miRBase LINK</a>	7	6	294	14	14	206	541	0.500	0.429	1.427
mmu-mir-497	MI0004636	<a href="#">miRBase LINK</a>	905	5,291	62,720	1,108	5,683	44,269	119,976	0.817	0.931	1.417
mmu-mir-872	MI0000549	<a href="#">miRBase LINK</a>	680	3,287	8,002	1,134	3,115	5,662	21,880	0.600	1.055	1.413
mmu-mir-30d	MI0000549	<a href="#">miRBase LINK</a>	86,140	170,538	352,452	146,223	200,896	251,104	1,207,353	0.589	0.849	1.404
mmu-mir-1197	MI0006305	<a href="#">miRBase LINK</a>	0	0	7	0	0	5	12	#DIV/0!	#DIV/0!	1.400
mmu-mir-195	MI0000237	<a href="#">miRBase LINK</a>	245	2,198	23,070	321	2,860	16,523	45,217	0.763	0.769	1.396
mmu-mir-351	MI0000643	<a href="#">miRBase LINK</a>	272	2,552	5,554	463	2,370	3,998	15,209	0.587	1.077	1.389
mmu-mir-192	MI0000551	<a href="#">miRBase LINK</a>	55,437	2,530,616	20,099	55,249	2,670,751	14,550	5,346,702	1.003	0.948	1.381
mmu-mir-744	MI0004124	<a href="#">miRBase LINK</a>	5,312	3,379	5,628	8,151	2,647	4,085	29,202	0.652	1.277	1.378
mmu-mir-574	MI0000518	<a href="#">miRBase LINK</a>	1,276	1,495	3,443	2,826	1,397	2,512	12,949	0.452	1.070	1.371
mmu-mir-467d	MI0005513	<a href="#">miRBase LINK</a>	14	27	182	19	10	133	385	0.737	2.700	1.368
mmu-mir-183	MI0000225	<a href="#">miRBase LINK</a>	128	655	75	334	426	55	1,673	0.383	1.538	1.364
mmu-mir-805			66	34,480	8,415	105	50,488	6,215	99,769	0.629	0.683	1.354
mmu-mir-101a	MI0000148	<a href="#">miRBase LINK</a>	1,277	88,769	58,100	1,312	74,119	43,132	266,709	0.973	1.198	1.347
mmu-mir-582	MI0006127	<a href="#">miRBase LINK</a>	108	360	465	268	84	346	1,631	0.403	4.286	1.344
mmu-mir-466f-1	MI0000563	<a href="#">miRBase LINK</a>	2	0	4	0	0	3	9	#DIV/0!	#DIV/0!	1.333
mmu-mir-877	MI0000553	<a href="#">miRBase LINK</a>	141	41	169	245	25	128	749	0.576	1.640	1.320
mmu-mir-491	MI0004680	<a href="#">miRBase LINK</a>	0	5	13	0	5	10	33	#DIV/0!	1.000	1.300
mmu-mir-689-2			17,105	10,236	8,756	32,701	9,330	6,780	84,908	0.523	1.097	1.291
mmu-mir-503	MI0003538	<a href="#">miRBase LINK</a>	24	67	302	41	66	234	734	0.585	1.015	1.291
mmu-let-7f-2	MI0000563	<a href="#">miRBase LINK</a>	16,610	684,828	778,838	25,149	593,665	604,641	2,703,731	0.660	1.154	1.288
mmu-mir-467e	MI0006128	<a href="#">miRBase LINK</a>	3	9	72	2	14	56	156	1.500	0.643	1.286
mmu-mir-449a	MI0001649	<a href="#">miRBase LINK</a>	16	2	45	9	2	35	109	1.778	1.000	1.286
mmu-let-7f-1	MI0000562	<a href="#">miRBase LINK</a>	11,642	621,181	731,371	17,964	543,185	572,647	2,497,990	0.648	1.144	1.277
mmu-mir-702	MI0004686	<a href="#">miRBase LINK</a>	10	10	38	19	2	30	109	0.526	5.000	1.267
mmu-mir-685			728	1,949	1,744	1,116	1,585	1,382	8,504	0.652	1.230	1.262
mmu-mir-26b	MI0000575	<a href="#">miRBase LINK</a>	4,225	87,418	89,191	4,349	85,187	70,989	341,359	0.971	1.026	1.256
mmu-mir-144	MI0000168	<a href="#">miRBase LINK</a>	1,799	4,959	6,557	2,217	2,337	5,264	23,133	0.811	2.122	1.246
mmu-let-7g	MI0000137	<a href="#">miRBase LINK</a>	24,376	121,676	109,960	28,263	143,036	88,635	515,946	0.862	0.851	1.241
mmu-mir-484	MI0003491	<a href="#">miRBase LINK</a>	4,496	1,844	4,994	5,858	1,315	4,045	22,552	0.767	1.402	1.235
mmu-mir-699			8	122	195	30	144	158	657	0.267	0.847	1.234
mmu-mir-324	MI0000595	<a href="#">miRBase LINK</a>	372	297	956	432	198	775	3,030	0.861	1.500	1.234
mmu-mir-758	MI0004129	<a href="#">miRBase LINK</a>	0	0	16	0	0	13	29	#DIV/0!	#DIV/0!	1.231
mmu-mir-423	MI0004637	<a href="#">miRBase LINK</a>	55,077	14,248	16,921	89,556	11,061	13,761	200,624	0.615	1.288	1.230
mmu-mir-493	MI0005514	<a href="#">miRBase LINK</a>	0	1	11	8	1	9	30	0.000	1.000	1.222
mmu-mir-350	MI0000640	<a href="#">miRBase LINK</a>	340	422	1,977	429	427	1,619	5,214	0.793	0.988	1.221
mmu-mir-28	MI0000690	<a href="#">miRBase LINK</a>	691	7,653	8,991	1,027	5,588	7,377	31,327	0.673	1.370	1.219
mmu-let-7e	MI0000561	<a href="#">miRBase LINK</a>	534	3,481	28,628	1,146	5,389	23,560	62,738	0.466	0.646	1.215
mmu-mir-425	MI0001447	<a href="#">miRBase LINK</a>	5,323	4,145	8,496	7,343	3,756	6,993	36,056	0.725	1.104	1.215
mmu-mir-148a	MI0000550	<a href="#">miRBase LINK</a>	10,609	903,788	326,358	11,294	998,441	270,135	2,520,625	0.939	0.905	1.208
mmu-mir-151	MI0000173	<a href="#">miRBase LINK</a>	9,486	31,203	95,030	15,283	27,328	78,781	257,111	0.621	1.142	1.206
mmu-mir-1191	MI0006296	<a href="#">miRBase LINK</a>	8	54	77	3	50	64	256	2.667	1.080	1.203
mmu-mir-451	MI0001730	<a href="#">miRBase LINK</a>	175,527	26,684	63,120	155,992	15,663	52,887	489,873	1.125	1.704	1.193
mmu-let-7a-1	MI0000556	<a href="#">miRBase LINK</a>	22,232	229,736	311,658	32,557	244,268	263,340	1,103,791	0.683	0.941	1.183
mmu-let-7a-2	MI0000557	<a href="#">miRBase LINK</a>	22,147	227,308	310,107	32,488	242,059	262,321	1,096,430	0.682	0.939	1.182
mmu-mir-191	MI0000233	<a href="#">miRBase LINK</a>	65,738	70,411	197,169	98,887	77,767	166,952	676,924	0.665	0.905	1.181
mmu-mir-361	MI0000761	<a href="#">miRBase LINK</a>	636	1,706	2,271	802	1,446	1,938	8,799	0.793	1.180	1.172
mmu-mir-29b-1	MI0000143	<a href="#">miRBase LINK</a>	74	3,496	2,779	103	3,291	2,396	12,139	0.718	1.062	1.160
mmu-let-7d	MI0000405	<a href="#">miRBase LINK</a>	19,639	51,637	74,003	28,501	42,117	64,215	280,112	0.689	1.226	1.152
mmu-mir-33	MI0000707	<a href="#">miRBase LINK</a>	40	725	244	44	431	212	1,696	0.909	1.682	1.151
mmu-mir-200b	MI0000243	<a href="#">miRBase LINK</a>	69	965	216	171	1,558	188	3,167	0.404	0.619	1.149
mmu-mir-140	MI0000165	<a href="#">miRBase LINK</a>	47,426	11,017	18,802	58,767	7,978	16,400	160,390	0.807	1.381	1.146
mmu-mir-466h	MI0005511	<a href="#">miRBase LINK</a>	1	3	16	8	3	14	45	0.125	1.000	1.143
mmu-mir-694	MI0004664	<a href="#">miRBase LINK</a>	0	5	8	6	4	7	30	0.000	1.250	1.143
mmu-mir-29b-2	MI0000712	<a href="#">miRBase LINK</a>	82	3,524	2,730	111	3,061	2,393	11,901	0.739	1.151	1.141
mmu-mir-92b	MI0005521	<a href="#">miRBase LINK</a>	382	43	341	684	119	309	1,878	0.558	0.361	1.104
mmu-let-7c-2	MI0000560	<a href="#">miRBase LINK</a>	72,776	164,719	345,608	118,692	170,389	313,353	1,185,537	0.613	0.967	1.103
mmu-let-7c-1	MI0000559	<a href="#">miRBase LINK</a>	72,525	161,513	342,882	118,216	167,212	311,496	1,173,844	0.613	0.966	1.101
mmu-mir-92a-1	MI0000719	<a href="#">miRBase LINK</a>	261,995	104,687	72,981	307,148	106,440	66,478	919,729	0.853	0.984	1.098
mmu-mir-92a-2	MI0000580	<a href="#">miRBase LINK</a>	99,452	9,614	12,718	113,997	8,089	11,624	255,494	0.872	1.189	1.094
mmu-mir-331	MI0000609	<a href="#">miRBase LINK</a>	59	313	543	66	246	497	1,724	0.894	1.272	1.093
mmu-mir-224	MI0000711	<a href="#">miRBase LINK</a>	86	57	723	145	74	664	1,749	0.593	0.770	1.089
mmu-mir-10a	MI0000685	<a href="#">miRBase LINK</a>	43,250	244,759	1,008,625	60,325	314,615	935,762	2,607,336	0.717	0.778	1.078
mmu-mir-320	MI0000704	<a href="#">miRBase LINK</a>	6,202	2,127	6,702	8,368	2,369	6,222	31,990	0.741	0.898	1.077
mmu-mir-365-2	MI0001645	<a href="#">miRBase LINK</a>	192	2,938	9,649	192	2,696	8,997	24,664	1.000	1.090	1.072
mmu-mir-1198	MI0006306	<a href="#">miRBase LINK</a>	1,567	320	489	1,670	268	456	4,770	0.938	1.194	1.072
mmu-mir-93	MI0000581	<a href="#">miRBase LINK</a>	42,293	14,738	27,822	42,227	14,053	26,003	167,136	1.002	1.049	1.070
mmu-mir-365-1	MI0000768	<a href="#">miRBase LINK</a>	184	2,901	9,541	186	2,657	8,918	24,387	0.989	1.092	1.070
mmu-mir-676	MI0005003	<a href="#">miRBase LINK</a>	3,001	1,716	5,549	4,209	1,221	5,249	20,945	0.713	1.405	1.057
mmu-mir-29c	MI0000577	<a href="#">miRBase LINK</a>	808	23,420	10,962	867	17,393	10,512	63,962	0.932	1.347	1.043
mmu-mir-204	MI0000247	<a href="#">miRBase LINK</a>	242	1	2,752	376	0	2,661	6,032	0.644	#DIV/0!	1.034
mmu-mir-100	MI0000692	<a href="#">miRBase LINK</a>	269	1,910	12,916	476	2,406	12,493	30,470	0.565	0.794	1.034
mmu-let-7b	MI0000558	<a href="#">miRBase LINK</a>	8,013	34,832	68,099	13,088	33,239	66,095	223,366	0.612	1.048	1.030
mmu-mir-101b	MI0000649	<a href="#">miRBase LINK</a>	1,894	215,325	19,259	1,459	154,713	18,731	411,381	1.298	1.392	1.028

mmu-mir-292	MI0000390	<a href="#">miRBase LINK</a>	0	6	1	0	0	1	8	#DIV/0!	#DIV/0!	1.000
mmu-mir-466f-4	MI0006291	<a href="#">miRBase LINK</a>	2	1	2	0	0	2	7	#DIV/0!	#DIV/0!	1.000
mmu-mir-686	MI0004650	<a href="#">miRBase LINK</a>	0	2	1	0	1	1	5	#DIV/0!	2.000	1.000
mmu-mir-693	MI0004662	<a href="#">miRBase LINK</a>	1	1	1	0	0	1	4	#DIV/0!	#DIV/0!	1.000
mmu-mir-7b	MI0000730	<a href="#">miRBase LINK</a>	0	0	2	0	0	2	4	#DIV/0!	#DIV/0!	1.000
mmu-mir-124-1	MI0000716	<a href="#">miRBase LINK</a>	0	0	1	2	0	1	4	0.000	#DIV/0!	1.000
mmu-mir-124-2	MI0000717	<a href="#">miRBase LINK</a>	0	0	1	2	0	1	4	0.000	#DIV/0!	1.000
mmu-mir-124-3	MI0000150	<a href="#">miRBase LINK</a>	0	0	1	2	0	1	4	0.000	#DIV/0!	1.000
mmu-mir-873	MI0005550	<a href="#">miRBase LINK</a>	0	1	1	0	0	1	3	#DIV/0!	#DIV/0!	1.000
mmu-mir-30c-1	MI0000547	<a href="#">miRBase LINK</a>	45,487	191,433	207,508	53,007	166,348	209,769	873,552	0.858	1.151	0.989
mmu-mir-29a	MI0000576	<a href="#">miRBase LINK</a>	10,752	77,404	98,142	13,359	82,945	99,229	381,831	0.805	0.933	0.989
mmu-mir-99b	MI0000147	<a href="#">miRBase LINK</a>	1,551	2,466	21,502	2,364	3,736	21,904	53,523	0.656	0.660	0.982
mmu-mir-200a	MI0000554	<a href="#">miRBase LINK</a>	230	718	156	332	1,377	159	2,972	0.693	0.521	0.981
mmu-mir-30c-2	MI0000548	<a href="#">miRBase LINK</a>	45,632	194,924	210,330	53,221	169,668	214,907	888,682	0.857	1.149	0.979
mmu-mir-187	MI0000229	<a href="#">miRBase LINK</a>	83	383	315	125	526	326	1,758	0.664	0.728	0.966
mmu-mir-330	MI0000607	<a href="#">miRBase LINK</a>	57	128	505	118	111	524	1,443	0.483	1.153	0.964
mmu-mir-218-1	MI0000700	<a href="#">miRBase LINK</a>	30	19	1,432	41	23	1,488	3,033	0.732	0.826	0.962
mmu-mir-218-2	MI0000701	<a href="#">miRBase LINK</a>	22	19	1,392	34	23	1,458	2,948	0.647	0.826	0.955
mmu-mir-1-1	MI0000689	<a href="#">miRBase LINK</a>	30	3	77	38	6	81	235	0.789	0.500	0.951
mmu-mir-25	MI0000689	<a href="#">miRBase LINK</a>	195,450	19,655	47,352	192,381	19,725	49,959	524,522	1.016	0.996	0.948
mmu-mir-874	MI0005479	<a href="#">miRBase LINK</a>	46	243	85	46	114	90	624	1.000	2.132	0.944
mmu-mir-701	MI0004685	<a href="#">miRBase LINK</a>	0	0	15	0	2	16	33	#DIV/0!	0.000	0.938
mmu-mir-671	MI0004133	<a href="#">miRBase LINK</a>	149	1,253	987	220	993	1,060	4,662	0.677	1.262	0.931
mmu-mir-1-2	MI0000689	<a href="#">miRBase LINK</a>	25	3	75	32	6	81	222	0.781	0.500	0.926
mmu-mir-615	MI0005004	<a href="#">miRBase LINK</a>	18	1	1,077	55	3	1,222	2,376	0.327	0.333	0.881
mmu-mir-10b	MI0000221	<a href="#">miRBase LINK</a>	54,948	1,404	2,277,812	74,813	2,390	2,626,307	5,037,674	0.734	0.587	0.867
mmu-mir-103-2	MI0000588	<a href="#">miRBase LINK</a>	27,499	42,040	142,351	29,023	28,914	164,768	434,595	0.947	1.454	0.864
mmu-mir-106b	MI0000407	<a href="#">miRBase LINK</a>	15,968	493	1,681	16,387	347	1,948	36,824	0.974	1.421	0.863
mmu-mir-125a	MI0000151	<a href="#">miRBase LINK</a>	4,192	10,692	72,514	6,653	16,382	84,101	194,534	0.630	0.653	0.862
mmu-mir-107	MI0000684	<a href="#">miRBase LINK</a>	21,491	29,102	18,384	21,360	16,679	21,326	128,342	1.006	1.745	0.862
mmu-mir-103-1	MI0000587	<a href="#">miRBase LINK</a>	27,496	41,808	140,803	29,020	28,764	163,598	431,489	0.947	1.453	0.861
mmu-mir-715	MI0000722	<a href="#">miRBase LINK</a>	24	7	6	43	3	7	90	0.558	2.333	0.857
mmu-mir-138-1	MI0000722	<a href="#">miRBase LINK</a>	7	0	6	23	1	7	44	0.304	0.000	0.857
mmu-mir-130a	MI0000156	<a href="#">miRBase LINK</a>	4,735	34,984	61,132	6,012	27,528	71,682	206,073	0.788	1.271	0.853
mmu-mir-125b-2	MI0000152	<a href="#">miRBase LINK</a>	1,701	6,853	31,682	3,133	7,909	37,227	88,505	0.543	0.866	0.851
mmu-mir-145	MI0000169	<a href="#">miRBase LINK</a>	527	4,783	34,032	739	6,085	40,619	86,785	0.713	0.786	0.838
mmu-mir-190b	MI0005478	<a href="#">miRBase LINK</a>	8	37	48	14	49	58	214	0.571	0.755	0.828
mmu-mir-125b-1	MI0000725	<a href="#">miRBase LINK</a>	1,654	5,705	27,240	3,087	6,755	33,021	77,462	0.536	0.845	0.825
mmu-mir-429	MI0001642	<a href="#">miRBase LINK</a>	421	833	177	887	1,335	215	3,868	0.475	0.624	0.823
mmu-mir-193	MI0000235	<a href="#">miRBase LINK</a>	60	20,655	24,669	55	13,998	30,595	90,032	1.091	1.476	0.806
mmu-mir-30a	MI0000144	<a href="#">miRBase LINK</a>	138,290	1,092,020	1,250,491	195,513	1,174,404	1,551,606	5,402,324	0.707	0.930	0.806
mmu-mir-150	MI0000172	<a href="#">miRBase LINK</a>	36,117	2,616	40,846	54,152	1,326	50,744	185,801	0.667	1.973	0.805
mmu-mir-99a	MI0000146	<a href="#">miRBase LINK</a>	275	3,886	10,906	526	4,188	13,606	33,387	0.523	0.928	0.802
mmu-mir-339	MI0000621	<a href="#">miRBase LINK</a>	312	1,102	2,563	491	1,106	3,206	8,780	0.635	0.996	0.799
mmu-mir-216a	MI0000699	<a href="#">miRBase LINK</a>	14	11	6	9	1	8	49	1.556	11.000	0.750
mmu-mir-133b	MI0000821	<a href="#">miRBase LINK</a>	525	2	99	844	5	133	1,608	0.622	0.400	0.744
mmu-mir-344-1	MI0000630	<a href="#">miRBase LINK</a>	3	2	45	19	1	62	132	0.158	2.000	0.726
mmu-mir-344-2	MI0005495	<a href="#">miRBase LINK</a>	3	2	45	19	1	62	132	0.158	2.000	0.726
mmu-mir-328	MI0000603	<a href="#">miRBase LINK</a>	4,943	730	2,213	6,840	696	3,091	18,513	0.723	1.049	0.716
mmu-mir-210	MI0000695	<a href="#">miRBase LINK</a>	296	369	709	278	348	1,038	3,038	1.065	1.060	0.683
mmu-mir-135b	MI0000646	<a href="#">miRBase LINK</a>	0	0	4	0	0	6	10	#DIV/0!	#DIV/0!	0.667
mmu-mir-378	MI0000795	<a href="#">miRBase LINK</a>	37,243	237,812	234,917	55,688	171,521	366,144	1,103,325	0.669	1.386	0.642
mmu-mir-345	MI0000632	<a href="#">miRBase LINK</a>	202	830	660	238	935	1,106	3,971	0.849	0.888	0.597
mmu-mir-486	MI0003493	<a href="#">miRBase LINK</a>	1,715,391	31,647	92,856	2,085,838	21,114	157,644	4,104,490	0.822	1.499	0.589
mmu-mir-133a-1	MI0000159	<a href="#">miRBase LINK</a>	41,161	90	2,675	79,581	146	4,555	128,208	0.517	0.616	0.587
mmu-mir-133a-2	MI0000820	<a href="#">miRBase LINK</a>	41,106	89	2,673	79,491	146	4,553	128,058	0.517	0.610	0.587
mmu-mir-196b	MI0001151	<a href="#">miRBase LINK</a>	12	4	122	19	6	211	374	0.632	0.667	0.578
mmu-mir-208b	MI0005552	<a href="#">miRBase LINK</a>	11	0	1	35	1	2	50	0.314	0.000	0.500
mmu-mir-193b	MI0005484	<a href="#">miRBase LINK</a>	168	120	2,000	265	111	4,108	6,772	0.634	1.081	0.487
mmu-mir-217	MI0000731	<a href="#">miRBase LINK</a>	5	6	7	8	0	15	41	0.625	#DIV/0!	0.467
mmu-mir-219-2	MI0000741	<a href="#">miRBase LINK</a>	5	21	2	1	13	5	47	5.000	1.615	0.400
mmu-mir-384	MI0001146	<a href="#">miRBase LINK</a>	3	1	3	0	0	9	16	#DIV/0!	#DIV/0!	0.333
mmu-mir-670	MI0004295	<a href="#">miRBase LINK</a>	0	0	1	0	0	3	4	#DIV/0!	#DIV/0!	0.333
mmu-mir-135a-2	MI0000715	<a href="#">miRBase LINK</a>	3	0	1	3	0	4	11	1.000	#DIV/0!	0.250
mmu-mir-135a-1	MI0000161	<a href="#">miRBase LINK</a>	1	0	1	2	0	4	8	0.500	#DIV/0!	0.250
mmu-mir-483	MI0003484	<a href="#">miRBase LINK</a>	6	1	5	21	0	24	57	0.286	#DIV/0!	0.208
mmu-mir-215	MI0000974	<a href="#">miRBase LINK</a>	32,484	494	245	50,380	685	1,930	86,218	0.645	0.721	0.127
mmu-mir-871	MI0005471	<a href="#">miRBase LINK</a>	9	70	0	5	99	1	184	1.800	0.707	0.000
mmu-mir-216b	MI0004126	<a href="#">miRBase LINK</a>	37	10	0	8	3	1	59	4.625	3.333	0.000
mmu-mir-1192	MI0006297	<a href="#">miRBase LINK</a>	0	9	0	0	5	3	17	#DIV/0!	1.800	0.000
mmu-mir-206	MI0000249	<a href="#">miRBase LINK</a>	0	1	0	10	0	1	12	0.000	#DIV/0!	0.000
mmu-mir-720	MI0004678	<a href="#">miRBase LINK</a>	5	2	0	0	0	1	8	#DIV/0!	#DIV/0!	0.000
mmu-mir-713	MI0004698	<a href="#">miRBase LINK</a>	0	0	0	0	0	4	4	#DIV/0!	#DIV/0!	0.000
mmu-mir-207	MI0000250	<a href="#">miRBase LINK</a>	0	0	0	0	0	1	1	#DIV/0!	#DIV/0!	0.000

Supplementary Table 3. The comparison of global mRNA expression in Mir221/222AidpKo and Mir221/222floxy mice fed with standard (STD) chow.

Sample name	Negative control	2Up	Ratio $\geq 2$																					
Test	STD AidpKo 387	54.43	Expression value of test sample $\leq$ Negative control (average)																					
Control	STD floxy 378	60.07	Ratio $\leq 0.5$ and Expression value of test sample $\geq$ Negative control (average)																					
Feature ID	Ensembl	Ensembl	Ensembl	Category	Ratio tag	Gene Accession	Gene Symbol	Gene Descr	mRNA	Accession	Source	mRNA	Accession	Source	Chromosome	GO Biologic	GO Biologic	GO Cellular	GO Cellular	GO Molecu	GO Molecu	miR221	Keyword	
12711066	12.07175	12.72533	0.9449207	-0.08176	0	main	NM_177722	ChromH	microchrome NM_177722 RefSeq	Mus muscu	FALSE	240697	NM_259802	ENB056	chr1	GO:00026 DNA replic	GO:00557 cellula	GO:000367 DNA bindi	GO:001046 negative re	GO:00057 extracellular	GO:003041 peptidase in			
17211305	39.99381	41.28632	0.98898	-0.04587	0	main	NM_05319	Pmcd5	peptidase ir NM_05319 RefSeq	Mus muscu	FALSE	94227	NM_442452	QB8053	chr1	GO:00035 transcrip	GO:00563 nucleu	GO:000372 RNA bindi	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17211548	28.72998	30.91425	0.9230404	-0.105721	0	main	NM_133233	KhdR1	KH domain NM_133233 RefSeq	Mus muscu	FALSE	170771	NM_33659	QBK201	chr1	GO:00035 transcrip	GO:00563 nucleu	GO:000372 RNA bindi	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
66.011734	74.71573	0.8694918	-0.154423	0	main	NM_001166	Spns2	spermatozoa NM_001166 RefSeq	Mus muscu	FALSE	87198	NM_159888	OB1W17	chr1	GO:00035 transcrip	GO:00563 nucleu	GO:000372 RNA bindi	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN				
1724841	45.37232	50.94557	0.7569844	-0.041664	0	main	NM_01047	AdfB2	ARGF with NM_01047 RefSeq	Mus muscu	FALSE	15463	NM_43340	QBK206	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:000372 RNA bindi	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17215585	89.13591	94.31344	0.391284	-0.090600	0	main	NM_13381	ShkpaA	SH3 domain NM_13381 RefSeq	Mus muscu	FALSE	89402	NM_170883	QZG118	chr1	GO:00089 endocytosis	GO:00563 nucleu	GO:000509 GDP-dissoc	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17234663	28.93283	28.79827	1.029217	-0.002752	0	main	NM_010166	ShkpaB	pleckstrin h NM_010166 RefSeq	Mus muscu	FALSE	240753	NM_253558	Q72118	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:000367 molecu	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17217201	48.53498	42.96968	1.1295120	-0.175709	0	main	NM_001166	ShkpaB	pleckstrin h NM_001166 RefSeq	Mus muscu	FALSE	240753	NM_253558	Q72118	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:000367 molecu	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17217854	90.1264	97.1008	0.9214346	-0.118046	0	main	ENSMUSTD1	Dnm12	DENM12 ENSMUSTD1 ENSEMBL	havana.kn	FALSE	322620	NM_337604	Q3U119	chr1	GO:00081 transcrip	GO:00563 nucleu	GO:000508 quan/-nucl	GO:00035 transcrip	GO:00563 nucleu	GO:000367 molecu			
17217901	205.3408	238.9808	0.8582816	-0.181897	0	main	NM_172343	ZbnD1	zinc finger r NM_172343 RefSeq	Mus muscu	FALSE	226470	NM_11971	QB1111	chr1	GO:00035 transcrip	GO:00563 nucleu	GO:000367 molecu	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17220177	28.33733	38.15344	0.7427007	-0.429143	0	main	ENSMUSTL	Mir1725	predicted fo ENSMUSTL ENSEMBL	ensembl.ln	FALSE	---	NM_322735	P94244	---	---	---	---	---	---	---	---	---	---
17222073	223.2658	264.8485	0.8441418	-0.244443	0	main	NM_173377	Trp5bp2	transformasi NM_173377 RefSeq	Mus muscu	FALSE	209456	NM_287455	QB8C79	chr1	GO:00081 transcrip	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17222489	337.2852	305.8741	1.1081911	-0.1422423	0	main	NM_001166	Rak3gp2	RAB3 GTP NM_001166 RefSeq	Mus muscu	FALSE	98732	NM_275841	QB8M67	chr1	GO:00438 regulati	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17234295	18.37661	51.82697	0.361601	-0.0552829	0	main	NM_01206	Actb1	actin beta NM_01206 RefSeq	Mus muscu	FALSE	17454	NM_44006	QB5129	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17222440	160.8323	235.9621	0.6816203	-0.552998	0	main	NM_01957	Rev1	REV1 hnm NM_01957 RefSeq	Mus muscu	FALSE	56210	NM_389103	Q920Q2	chr1	GO:00026 DNA replic	GO:00563 nucleu	GO:000208 magnesi	GO:00026 DNA replic	GO:00563 nucleu	GO:000208 magnesi			
17223138	87.2136	102.9134	0.8744432	-0.238811	0	main	NM_01166	Pgsp1	post-GPI at NM_01166 RefSeq	Mus muscu	FALSE	241062	NM_103536	Q3U0U7	chr1	GO:00050 GPI anch	GO:00578 endoplasm	GO:000451 nucleic ac	GO:00050 GPI anch	GO:00578 endoplasm	GO:000451 nucleic ac			
17223946	17.66826	16.9007	1.0890417	0.1349239	0	main	NM_01015	ErbB4	v-erbB4 eryt NM_01015 RefSeq	Mus muscu	FALSE	13889	NM_442420	QB1527	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17223953	38.89085	27.68103	1.4071158	0.4927381	0	main	NM_01026	Gbp2	gamma-2 h NM_01026 RefSeq	Mus muscu	FALSE	21472	NM_29473	P46291	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17228426	344.0268	377.0215	0.9124569	-0.113217	0	main	NM_00103	Cep350	centrosome NM_00103 RefSeq	Mus muscu	FALSE	170691	NM_260047	D3Y1P2	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17222178	183.1643	249.8493	0.733102	-0.447914	0	main	NM_00972	Atp1b1	ATPase, Nc NM_00972 RefSeq	Mus muscu	FALSE	61931	NM_4550	P14004	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17230463	24.0851	31.4887	0.7634871	-0.0552829	0	main	ENSMUSTL	Mir12657	predicted fo ENSMUSTL ENSEMBL	havana.kn	FALSE	672245	NM_44006	QB5129	chr1	---	---	---	---	---	---	---	---	---
17230602	20.1621	20.01642	0.949291	-0.075078	0	main	NM_17512	Fbxw2b	F-box protei NM_17512 RefSeq	Mus muscu	FALSE	61948	NM_30737	QB8C14	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17230668	296.3055	311.7881	0.9503246	-0.07348	0	main	NM_14755	Maik1	melanoma I NM_14755 RefSeq	Mus muscu	FALSE	338366	NM_4115	QB8214	chr1	GO:00026 chondrocy	GO:00578 endoplasm	GO:000367 molecu	GO:00026 chondrocy	GO:00578 endoplasm	GO:000367 molecu			
17230760	172.25445	86.0554	0.8493974	-0.235488	0	main	NM_17383	Maik1	MAM1 microt NM_17383 RefSeq	Mus muscu	FALSE	226778	NM_7446	QB8V45	chr1	GO:00022 microtub	GO:00573 cytoplasm	GO:00016 nucleic f	GO:00022 microtub	GO:00573 cytoplasm	GO:00016 nucleic f			
17231461	203.3701	203.9778	0.978784	-0.196391	0	main	NM_00954	Esr1	ER chaperone NM_00954 RefSeq	Mus muscu	FALSE	11924	NM_5213	P13095	chr1	GO:00015 adhesion_m	GO:00563 nucleu	GO:00015 adhesion_m	GO:00015 adhesion_m	GO:00563 nucleu	GO:00015 adhesion_m			
17232483	13.10851	13.23052	0.9927307	-0.1133267	0	main	XR_880233	LOC102632	unclear chrR_880233 RefSeq	PREDICTE	FALSE	102632830	---	QB8929	chr10	---	---	---	---	---	---	---	---	---
17232484	146.1333	158.2847	0.9227811	-0.015266	0	main	NM_001166	Cdk19	cyclin-depe NM_001166 RefSeq	Mus muscu	FALSE	78334	NM_20924	QB8WV8	chr10	GO:00046 protei ph	GO:00557 cellula	GO:000016 nucleate t	GO:00046 protei ph	GO:00557 cellula	GO:000016 nucleate t			
17232493	198.2323	205.1681	0.9593231	-0.126069	0	main	NM_00115	Lims1	LIM domain NM_00115 RefSeq	Mus muscu	FALSE	92760	NM_57374	QB8R38	chr10	GO:00016 nucleate t	GO:00563 nucleu	GO:00016 nucleate t	GO:00016 nucleate t	GO:00563 nucleu	GO:00016 nucleate t			
17232457	855.5234	114.5790	0.7478508	-0.191718	0	main	NM_01124	Ramp2b	RAN bindin NM_01124 RefSeq	Mus muscu	FALSE	19386	NM_43169	QB8JUR	chr1	GO:00045 enzymi inh	GO:00563 nucleu	GO:000372 RNA bindi	GO:00045 enzymi inh	GO:00563 nucleu	GO:000372 RNA bindi			
17232511	232.281	400.8118	0.5798157	-0.786334	0	main	NM_02156	Mld	midolin NM_02156 RefSeq	Mus muscu	FALSE	59080	NM_143813	Q3T3P7	chr10	GO:00313 negativ re	GO:00563 nucleu	GO:000190 kinase bindi	GO:00313 negativ re	GO:00563 nucleu	GO:000190 kinase bindi			
17232512	1467.903	1672.027	0.8779162	-0.187842	0	main	NM_11598	Trmp3	tissue inhibi NM_11598 RefSeq	Mus muscu	FALSE	21859	NM_4871	P39876	chr10	GO:000146 negativ re	GO:00557 extracellular	GO:000485 enzymi inh	GO:000146 negativ re	GO:00557 extracellular	GO:000485 enzymi inh			
17232523	15.10829	15.24249	1.001351	-0.035011	0	main	NM_172343	ZbnD1	zinc finger r NM_172343 RefSeq	Mus muscu	FALSE	226470	NM_11971	QB1111	chr1	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17232549	200.7531	198.2105	1.0212878	-0.0183889	0	main	NM_11299	Actr5	actin rhyr NM_11299 RefSeq	Mus muscu	FALSE	237615	NM_44017	QB8T17	chr10	GO:00018 biological_p	GO:00563 nucleu	GO:00018 biological_p	GO:00018 biological_p	GO:00563 nucleu	GO:00485 poly(r) RN			
17232571	237.1332	208.5456	0.994738	-0.007612	0	main	NM_02887	Dnajc14	DnaJ (Hsp4 NM_02887 RefSeq	Mus muscu	FALSE	74330	NM_29619	Q82U14	chr10	GO:00081 transcrip	GO:00578 endoplasm	GO:00016 G-protein c	GO:00081 transcrip	GO:00578 endoplasm	GO:00016 G-protein c			
17232573	28.48137	28.8165	0.9914584	-0.007612	0	main	NM_00115	Lims1	LIM domain NM_00115 RefSeq	Mus muscu	FALSE	92760	NM_57374	QB8R38	chr10	GO:00016 nucleate t	GO:00563 nucleu	GO:00016 nucleate t	GO:00016 nucleate t	GO:00563 nucleu	GO:00016 nucleate t			
17240123	113.1205	113.52564	0.993738	0.0750782	0	main	NM_00851	Chv2	chav2 hnm NM_00851 RefSeq	PREDICTE	FALSE	215890	NM_94461	QB89Z9	chr1	GO:00081 transcrip	GO:00563 nucleu	GO:00018 biological_p	GO:00081 transcrip	GO:00563 nucleu	GO:00018 biological_p			
17240226	246.288	234.4038	1.0463156	-0.0653181	0	main	NM_00853	Mdk3	myristoylate NM_00853 RefSeq	Mus muscu	FALSE	17118	NM_30059	P26645	chr10	---	GO:00573 cytoplasm	GO:000037 actin bindi	---	GO:00573 cytoplasm	GO:000037 actin bindi			
17240332	482.2796	187.1108	2.569131	1.3872225	0	main	NM_02908	Darc4	DNA-damag NM_02908 RefSeq	Mus muscu	FALSE	14747	NM_21697	QB8D37	chr10	GO:00016 response	GO:00562 intracellular	GO:000718 14-3-3 prot	GO:00016 response	GO:00562 intracellular	GO:000718 14-3-3 prot			
17240395	141.48927	104.5482	1.316585	-0.235488	0	main	NM_10103	Chv2	chav2 hnm NM_10103 RefSeq	Mus muscu	FALSE	672245	NM_44006	QB5129	chr1	GO:00015 adhesion_m	GO:00563 nucleu	GO:00015 adhesion_m	GO:00015 adhesion_m	GO:00563 nucleu	GO:00015 adhesion_m			
17240595	537.7865	394.1924	1.362817	-0.104981	0	main	NM_01003	Chv2	CCRN-NOT hnm NM_01003 RefSeq	Mus muscu	FALSE	72068	NM_31553	QB8C33	chr10	GO:00018 biological_p	GO:00563 nucleu	GO:00012 RNA polym	GO:00018 biological_p	GO:00563 nucleu	GO:00012 RNA polym			
17240588	316.8773	293.1328	1.083033	-0.1123709	0	main	NM_17779	Frst2	fibrosiin gr NM_17779 RefSeq	Mus muscu	FALSE	327826	NM_133696											



17519967	58.33921	63.36783	0.920644	-0.119285	0	main	NM_011621 Tpbp	trophoblast	NM_011627 RefSeq	Mus muscu	TRUE	21983	Mm.20864	Q9Z0L0	chr9	---	---	GO:000573 cytoplasm	---	---	GO:000827 zinc ion bin	O
17520815	472.654	686.5726	0.6891247	-0.539258	0	main	NM_00110X Mst2	male-specific	NM_00110X RefSeq	Mus muscu	TRUE	77853	Mm.326206	Q692F8	chr9	---	---	GO:004398 histone H4+	GO:001248 MSL comp	GO:000627	zinc ion bin	O
17520848	192.6177	257.2575	0.7487355	-0.417473	0	main	NM_001094 Azc2	5-azacytidin	NM_001094 RefSeq	Mus muscu	TRUE	27215	Mm.92705	Q9QVFB	chr9	---	---	GO:000027 mitotic cell	GO:000573 cytoplasm	GO:000551	protein bind	O
17523081	65.08034	40.75385	1.5969127	0.6752854	0	main	NM_007391 Acvr2b	activin recep	NM_007391 RefSeq	Mus muscu	TRUE	11481	Mm.390236	P27040	chr9	---	---	GO:000150 skeletal sys	GO:000562 cell	// cytop	GO:000016 nucleotide t	O
17526130	354.3606	396.8731	0.8928814	-0.16346	0	main	NM_007611 Cbl	Casitas B-li	NM_007611 RefSeq	Mus muscu	TRUE	12402	Mm.266871	P22682	chr9	---	---	GO:000716 cell surface	GO:000563 nucleus	// l	GO:000178 phosphotyrc	O
17528714	242.9754	249.4519	0.9740371	-0.037951	0	main	NM_00125X Tcf12	transcriptor	NM_00125X RefSeq	Mus muscu	TRUE	21406	Mm.171615	Q61286	chr9	---	---	GO:000635 transcriptor	GO:000563 nucleus	// l	GO:000367 DNA bindin	O
17529713	466.7708	529.5917	0.8813786	-0.182166	0	main	NM_001114 UZsurp	U2 snRNP-	NM_001114 RefSeq	Mus muscu	TRUE	67958	Mm.292742	Q6NV83	chr9	---	---	GO:000639 RNA proces	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17530930	54.65099	59.80752	0.9137812	-0.130079	0	main	NM_00104Z Sema3b	sema doma	NM_00104Z RefSeq	Mus muscu	TRUE	20347	Mm.4083	Q62177	chr9	---	---	GO:000727 multicellular	GO:000557 extracellular	GO:000487	receptor act	O
17530955	978.2015	842.2397	1.1626162	0.2173749	0	main	NM_00813X Gna2	guanine nuc	NM_00813X RefSeq	Mus muscu	TRUE	14678	Mm.196464	P08752	chr9	---	---	GO:000018 activation of	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17531734	32.60698	28.00312	1.1644017	0.2195888	0	main	NM_016893 Slac	siz homolog	NM_016893 RefSeq	Mus muscu	TRUE	20840	Mm.1414	P97306	chr9	---	---	GO:003460 cellular resp	GO:000573 cytoplasm	GO:000487	metal ion bi	O
17533416	664.2457	858.501	0.7737273	-0.370103	0	main	NM_01002Z Ddx3c	DEAD/DH (A	NM_01002Z RefSeq	Mus muscu	TRUE	13205	Mm.289662	Q62167	chrX	---	---	GO:000237 immune sys	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17536208	564.8925	546.4041	1.0338365	0.048008	0	main	NM_00129X Fmr1	fragile X me	NM_00129X RefSeq	Mus muscu	TRUE	14265	Mm.3451	P35922	chrX	---	---	GO:000681 transport	// GO:000563 nucleus	// l	GO:000372 RNA bindin	O
17536241	106.2006	151.5649	0.7006939	-0.513144	0	main	ENSMUST1 Slvx	snrinhneo	ENSMUST1 ENSEMBL	havana:kn	TRUE	56291	Mm.202561	Q60969	chrX	---	---	GO:000647 protein depl	GO:000573 cytoplasm	GO:000472	phosphoan	O
17539018	15.7973	16.62154	0.9504113	-0.073376	0	main	NM_01372Z Nrk	Nrk related 1	NM_01372Z RefSeq	Mus muscu	TRUE	27206	Mm.482318	Q9R9G8	chrX	---	---	GO:000646 protein phos	GO:000573 cytoplasm	GO:000016	nucleotide t	O
17538395	11.10096	10.32762	1.0748808	0.1041766	0	main	NM_00103Z Zcchc16	zinc finger,	NM_00103Z RefSeq	Mus muscu	TRUE	619287	Mm.387961	Q3URYO	chrX	---	---	GO:000815 biological p	GO:000557 cellular con	GO:000367	nucleic acid	O
17538658	27.22501	22.67239	1.2008802	0.2639961	0	main	NM_001271 Wnk3	WNK lysine	NM_001271 RefSeq	Mus muscu	TRUE	279561	Mm.441474	Q80XP9	chrX	---	---	GO:000646 protein phos	GO:000573 cytoplasm	GO:000016	nucleotide t	O
17539828	28.17557	25.36139	1.1109632	0.151811	0	main	NM_019461 Usp27x	ubiquilin sp	NM_019461 RefSeq	Mus muscu	TRUE	54651	Mm.483107	Q8CEG8	chrX	---	---	GO:000650 proteolysis	GO:000557 cellular con	GO:000362	peptidase a	O
17541343	22.6035	20.20307	1.188151	0.1619716	0	main	NM_00129K Smarca1	SWI/SNF r	NM_00129K RefSeq	Mus muscu	TRUE	93761	Mm.229151	Q6PGB8	chrX	---	---	GO:000073 DNA strand	GO:000079 nuclear chrt	GO:000016	nucleotide t	O
17543840	13.13452	12.28752	1.0689317	0.0961697	0	main	NM_001071 C77370	expressed s	NM_001071 RefSeq	Mus muscu	TRUE	245555	Mm.381907	Q6D1T1	chrX	---	---	GO:000008 mtotic S p	GO:000563 nucleus	// l	GO:000388 DNA-direct	O
17544102	52.66202	66.44264	0.7925913	-0.335351	0	main	ENSMUST1 Brw5	bradomone	ENSMUST1 ENSEMBL	ensembl_h	TRUE	382236	Mm.426127	A2H4L4	chrX	---	---	GO:000701 cytoskeleton	GO:000557 cellular con	GO:000551	protein bind	O
17544939	251.5343	267.6529	0.939778	-0.089608	0	main	NM_001077 Tsc22d3	TSC22 dor	NM_001077 RefSeq	Mus muscu	TRUE	14605	Mm.22216	Q9ZS57	chrX	---	---	GO:000012 negative reg	GO:000563 nucleus	// l	GO:000370 sequence-s	O
17545078	69.16832	93.64679	0.7386086	-0.437118	0	main	NM_01949X Ammcrc1	Alport syndr	NM_01949X RefSeq	Mus muscu	TRUE	56068	Mm.143724	Q9JHT5	chrX	---	---	GO:000815 biological_p	GO:000557 cellular con	GO:000367	molecular_f	O
17545618	50.85996	41.40395	1.2283842	0.2396719	0	main	XM_00652Z P1chd1	palchod dor	XM_00652Z RefSeq	PREDICTE	TRUE	211612	Mm.218811	Q14B62	chrX	---	---	GO:000722 smoothene	GO:000598 plasma mer	GO:000815	hedgehog r	O
17546209	13.46392	15.89333	0.8400062	-0.236153	0	main	NM_011077 Phx	phosphate r	NM_011077 RefSeq	Mus muscu	TRUE	18676	Mm.2529	P70699	chrX	---	---	GO:000650 proteolysis	GO:000578 endoplasm	GO:000422	metalloendc	O
17546834	749.3524	1081.035	0.6931805	-0.528697	0	main	NM_01200X Ddx1y	DEAD (ASP	NM_01200X RefSeq	Mus muscu	TRUE	26900	Mm.302938	Q62095	chrY	---	---	GO:000620 ATP catalo	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17547616	663.494	810.2198	0.8189062	-0.28823	0	main	---	X91866	GenBank	M.musculus	TRUE	---	---	P84244	chr11	---	---	GO:000833 nucleosome	GO:000078 nucleosome	GO:000367	DNA bindin	O
17547837	95.57313	86.08841	1.0849663	0.1176528	0	main	ENSMUST1 Gm21464	predicted gi	ENSMUST1 ENSEMBL	havana:kn	TRUE	10082085	Mm.291443	Q920C8	chr14	---	---	GO:000681 transport	// GO:000573 mitochondri	GO:000538	iron ion tran	O
17547846	99.60606	94.7346	1.05142	0.073339	0	main	ENSMUST1 Gm21464	predicted gi	ENSMUST1 ENSEMBL	havana:kn	TRUE	10082085	Mm.291443	Q920C8	chr14	---	---	GO:000681 transport	// GO:000573 mitochondri	GO:000538	iron ion tran	O
17548283	1204.558	1613.575	0.746515	-0.421757	0	main	NM_008211 H33b	H3 histone,	NM_008211 RefSeq	Mus muscu	TRUE	15081	Mm.371563	P84244	chr3	---	---	GO:000164 estobiast	GO:000022 nuclear chrt	GO:000097	RNA polym	O
17548518	1303.143	1200.466	1.085531	0.1184009	0	main	NM_001081 Gm12657	predicted or	NM_001081 RefSeq	Mus muscu	TRUE	667250	Mm.448778	P84244	chr6	---	---	GO:000164 estobiast	GO:000022 nuclear chrt	GO:000097	RNA polym	O
17548946	1054.596	1431.395	1.0736761	-0.440731	0	main	NM_008211 H33b	H3 histone,	NM_008211 RefSeq	Mus muscu	TRUE	15081	Mm.371563	P84244	chr1	---	---	GO:000164 estobiast	GO:000022 nuclear chrt	GO:000097	RNA polym	O

Supplementary Table 4. The comparison of global mRNA expression in Mir221/222Aidp0K and Mir221/222floxly mice fed with high-fat-high sucrose (HFHS) chow.

Sample name	Sample name		Negative control	Expression value of test sample	Ratio $\geq 2$ Expression value of test sample $\geq$ Negative control (average)	Ratio $\leq 0.5$ Expression value of test sample $\leq$ Negative control (average)	Gene		Chr	Chromosome	GO Biologic	GO Biologic	GO Cellular	GO Molecular	GO Molecular	miR221/222 target gene	Keyword				
	Test	Control					Gene	Symbol										Chr	Gene	Symbol	Chr
1721066	51.6146	10.85042	1.2547496	0.3027994	0	main	NM_177722	Mm2c10	microchrome NM_177722 RefSeq	Mus muscu	FALSE	240697	NM_25980	E9Q56E	chr1	GO:00026 DNA replication	GO:00557 cellular	GO:000367 DNA binding	GO:001046 negative reg	GO:00557 extracellular	GO:0003041 peptidase in
17211305	51.30147	47.63595	1.0789486	0.4619395	0	main	NM_05319	Pm15	peptidase ir NM_05319 RefSeq	Mus muscu	FALSE	94227	NM_42452	QB8Q53	chr1	GO:00035 transcription factor	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:00482 poly(A) RN
17211548	27.61715	25.52265	0.9279114	-0.047409	0	main	NM_13323	KhdR2	KH domain NM_13323 RefSeq	Mus muscu	FALSE	170771	NM_33599	Q9WU10	chr1	GO:00035 transcription factor	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:00482 poly(A) RN
17214841	64.57574	47.07194	1.3755019	0.4595811	0	main	NM_01047	Spa2c1	ARGF4 wnt NM_01047 RefSeq	Mus muscu	FALSE	15463	NM_43340	QBK286	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00067 acrosome	GO:00563 nucleus	GO:000367 molecular_f
17215585	94.51138	50.34522	1.0461338	0.0653908	0	main	NM_13381	ShkP4	SH3-domain NM_13381 RefSeq	Mus muscu	FALSE	98402	NM_17088	QB2118	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00089 endocytosis	GO:00563 nucleus	GO:00509 GDP-dissoc
17234623	27.64325	21.0334	0.762522	-0.1758239	0	main	NM_02298	Trax7b	transferrin NM_02298 RefSeq	Mus muscu	FALSE	67198	NM_15988	Q91W17	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17237291	41.8703	51.58801	1.1612625	-0.301109	0	main	NM_00116	ShobA	pleckstrin h nm_00116 RefSeq	Mus muscu	FALSE	240753	NM_25358	Q710G1	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17237854	97.77634	92.4662	1.0527479	-0.0265769	0	main	ENSMUST1	Znfx1	DENMMAC ENSMUST1 ENSEMBL zinc finger cr NM_17264 RefSeq	havana.kn	FALSE	322620	NM_33760	Q3U119	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17237901	197.4886	215.3270	0.9171629	-0.1785663	0	main	NM_12724	Znfx1	zinc finger cr NM_12724 RefSeq	Mus muscu	FALSE	22470	NM_11971	Q811F1	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17237917	38.81103	25.5553	1.5279292	0.6087229	0	main	ENSMUST1	Gm17275	predicted for ENSMUST1 ENSEMBL ensembl_lir	havana.kn	FALSE	1	NM_32275	P94244	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17237933	23.12286	197.5718	1.1802916	-0.3291433	0	main	NM_17337	Trf3p2	transformin NM_17337 RefSeq	Mus muscu	FALSE	209456	NM_28454	QB8C79	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17237989	275.2593	256.9431	0.917285	0.0939424	0	main	NM_00116	Rab3g2	RAB3 GTP NM_00116 RefSeq	Mus muscu	FALSE	98732	NM_27584	QB8M67	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17237995	17.12078	15.44022	1.0148379	-0.1852929	0	main	NM_02298	Trax7b	transferrin NM_02298 RefSeq	Mus muscu	FALSE	22470	NM_11971	Q811F1	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17238049	135.0599	128.7281	1.0491641	0.0620403	0	main	NM_01957	Rev1	REV1 h omc NM_01957 RefSeq	Mus muscu	FALSE	56210	NM_38103	Q92Q02	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:00028 magnesium a
17238138	68.80113	81.77186	1.0426071	-0.247088	0	main	NM_00116	Pgp1	post-GPI at nm_00116 RefSeq	Mus muscu	FALSE	241062	NM_10353	Q3U1U7	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:00045 nucleas ac
1723846	18.81731	15.54498	1.2101561	0.2751931	0	main	NM_01015	ErbA4	vertebra enyl NM_01015 RefSeq	Mus muscu	FALSE	13889	NM_44240	QB5277	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:00016 nucleotide t
1723853	35.15153	30.81006	0.8691588	-0.304869	0	main	NM_01026	Gbp2	glycylalanine NM_01026 RefSeq	Mus muscu	FALSE	14772	NM_35864	QB4821	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17238426	278.9101	309.3545	0.8951228	-0.158942	0	main	NM_00103	Cep350	centrosome NM_00103 RefSeq	Mus muscu	FALSE	13489	NM_26024	D3Y7P2	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17238178	132.5691	234.3915	0.5658883	-0.822176	0	main	NM_00972	Atp1b1	ATPase, Na NM_00972 RefSeq	Mus muscu	FALSE	61931	NM_4550	P14004	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:00059 sodium:poli
17238463	69.49216	61.92368	0.8851115	-0.1692525	0	main	ENSMUST1	Gm17265	predicted for ENSMUST1 ENSEMBL havana.kn	havana.kn	FALSE	67225	NM_44268	QB5C78	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17239052	156.8367	168.3948	0.9314184	-0.102499	0	main	NM_17512	Fbxw2b	F-box protein NM_17512 RefSeq	Mus muscu	FALSE	61938	NM_30737	QB8JCA	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17239668	249.5798	293.7184	0.8796018	-0.185078	0	main	NM_17738	Ma1	melanoma i NM_17738 RefSeq	Mus muscu	FALSE	338366	NM_41152	QB84A	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:000367 molecular_f
17239780	73.05361	51.96034	1.0495444	0.0915447	0	main	NM_14551	Ma3	MAM protein NM_14551 RefSeq	Mus muscu	FALSE	228778	NM_7445	QB8V45	chr1	GO:00018 biological p	GO:00563 nucleus	GO:000372 RNA binding	GO:00018 biological p	GO:00563 nucleus	GO:00016 nucleotide_f
1723980	208.41126	205.9678	0.99078	-0.02775	0	main	ENSMUST1	Ma3													





17519967	66.36326	77.80013	0.8529968	-0.22388	0	main	NM_011621 Tpbp	trophoblast	NM_011621 RefSeq	Mus muscu	TRUE	21983	Mm.20864	Q9Z0L0	chr9	---	---	GO:000573 cytoplasm	---	---	GO:000827 zinc ion bin	O
17520815	372.401	361.8984	0.9753609	-0.032962	0	main	NM_00110X Msz2	male-specific	NM_00110X RefSeq	Mus muscu	TRUE	77553	Mm.326206	Q692F8	chr9	---	---	GO:004398 histone H4-	GO:007248 MSL comp	GO:000827 zinc ion bin	O	
17520848	200.9676	205.7998	0.9765145	-0.034287	0	main	NM_001048 Azc2	S-saccharin	NM_001048 RefSeq	Mus muscu	TRUE	27215	Mm.92705	Q9QYP8	chr9	---	---	GO:000227 mitotic cell	GO:000573 cytoplasm	GO:000551 protein bind	O	
17523081	63.08196	70.94463	0.8891717	-0.169466	0	main	NM_007391 Acvr2b	activin recep	NM_007391 RefSeq	Mus muscu	TRUE	11481	Mm.390236	P27040	chr9	---	---	GO:000150 skeletal sys	GO:000562 cell	// cytop	GO:000016 nucleotide t	O
17526130	363.0498	339.0826	1.0706819	0.0985299	0	main	NM_007611 Cbl	Casitas B-li	NM_007611 RefSeq	Mus muscu	TRUE	12402	Mm.266871	P22682	chr9	---	---	GO:000716 cell surface	GO:000563 nucleus	// l	GO:000178 phosphotyrc	O
17526714	257.718	235.3805	1.0948995	0.1307985	0	main	NM_001252 Tcf12	transcription	NM_001252 RefSeq	Mus muscu	TRUE	21406	Mm.171615	Q61286	chr9	---	---	GO:000835 transcription	GO:000563 nucleus	// l	GO:000367 DNA bindin	O
17529713	385.1018	331.4807	1.1617624	0.216315	0	main	NM_001114 U2surp	U2 snRNP-	NM_001114 RefSeq	Mus muscu	TRUE	67958	Mm.292742	Q6N983	chr9	---	---	GO:000639 RNA proces	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17530930	60.10501	64.3563	0.9339414	-0.098596	0	main	NM_001042 Sema3b	sema doma	NM_001042 RefSeq	Mus muscu	TRUE	20347	Mm.4083	Q62177	chr9	---	---	GO:000727 multicellular	GO:000557 extracellular	GO:000487 receptor act	O	
17530955	1003.845	986.2798	1.0178096	0.0254676	0	main	NM_008138 Gna2c	guanine nuc	NM_008138 RefSeq	Mus muscu	TRUE	14678	Mm.196464	P08752	chr9	---	---	GO:000018 activation of	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17531724	32.55711	28.70505	1.1341945	-0.1816881	0	main	NM_016893 Slac	src homolog	NM_016893 RefSeq	Mus muscu	TRUE	20840	Mm.1414	P97306	chr9	---	---	GO:003460 cellular resp	GO:000573 cytoplasm	GO:000487 metal ion bi	O	
17533416	688.9457	512.7594	1.3436042	0.4261082	0	main	NM_010028 Ddx3c	DEAD/D(H	NM_010028 RefSeq	Mus muscu	TRUE	13205	Mm.289662	Q62167	chrX	---	---	GO:000237 immune sys	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17536208	861.1144	1145.401	0.7518017	-0.411576	0	main	NM_00129X Fmr1	fragile X me	NM_00129X RefSeq	Mus muscu	TRUE	14265	Mm.3451	P35922	chrX	---	---	GO:000681 transport	// GO:000563 nucleus	// l	GO:000372 RNA bindin	O
17536241	113.162	124.9131	0.9692258	-0.142335	0	main	ENSMUST1 Svx	satellite3	ENSMUST1 ENSEMBL	havana:kn	TRUE	56291	Mm.202561	Q60969	chrX	---	---	GO:000647 protein depl	GO:000573 cytoplasm	GO:000472 phosphora	O	
17539018	18.69999	16.33215	1.1448603	0.1953228	0	main	NM_013724 Nfk	Nfk related	NM_013724 RefSeq	Mus muscu	TRUE	27206	Mm.482318	Q9R0G8	chrX	---	---	GO:000646 protein pho	GO:000573 cytoplasm	GO:000016 nucleotide t	O	
17538395	10.53644	9.817351	1.0732467	0.1019818	0	main	NM_001033 Zcchc16	zinc finger,	NM_001033 RefSeq	Mus muscu	TRUE	619287	Mm.387961	Q3URYO	chrX	---	---	GO:000815 biological p	GO:000557 cellular con	GO:000367 nucleic acid	O	
17538658	22.98368	24.19338	0.9499867	-0.074003	0	main	NM_001027 Wnk3	WNK lysine	NM_001027 RefSeq	Mus muscu	TRUE	279561	Mm.441474	Q80XP9	chrX	---	---	GO:000646 protein pho	GO:000573 cytoplasm	GO:000016 nucleotide t	O	
17539828	29.07195	24.83115	1.1707655	0.2274768	0	main	NM_019461 Usp27x	ubiquitin sp	NM_019461 RefSeq	Mus muscu	TRUE	54651	Mm.483107	Q8C6G8	chrX	---	---	GO:000650 proteolysis	GO:000557 cellular con	GO:000829 peptidase a	O	
17541343	28.04365	21.40386	1.3102146	0.3898031	0	main	NM_00129X Smarca1	SWI/SNF r	NM_00129X RefSeq	Mus muscu	TRUE	93761	Mm.229151	Q6PG88	chrX	---	---	GO:000073 DNA strand	GO:000079 nuclear chr	GO:000016 nucleotide t	O	
17543840	12.0706	12.03887	1.0026356	0.0030774	0	main	NM_001077 C7370	expressed s	NM_001077 RefSeq	Mus muscu	TRUE	245555	Mm.381907	Q6D7T1	chrX	---	---	GO:000008 mtotic S p	GO:000563 nucleus	// l	GO:000388 DNA-direct	O
17544102	56.45731	55.45731	1	0	0	main	ENSMUST1 Brw5	chromosome	ENSMUST1 ENSEMBL	ensembl_h	TRUE	382236	Mm.426127	A2AH44	chrX	---	---	GO:000701 cytoskelet	GO:000557 cellular con	GO:000551 protein bind	O	
17544939	299.5348	360.4171	0.8310782	-0.266944	0	main	NM_001077 Tsc22d3	TSC22 dor	NM_001077 RefSeq	Mus muscu	TRUE	14605	Mm.22216	Q9ZS7	chrX	---	---	GO:000012 negative reg	GO:000563 nucleus	// l	GO:000370 sequence-s	O
17545078	88.37831	95.12606	0.9290652	-0.106148	0	main	NM_01949X Ammcrc1	Alport synd	NM_01949X RefSeq	Mus muscu	TRUE	56068	Mm.143724	Q9JHT5	chrX	---	---	GO:000815 biological_p	GO:000557 cellular con	GO:000367 molecuar_f	O	
17545618	47.19572	57.85563	0.8157488	-0.293801	0	main	XM_006522 P1chd1	palchad dor	XM_006522 RefSeq	PREDICTE	TRUE	211612	Mm.218811	Q14B62	chrX	---	---	GO:000722 smoothene	GO:000598 plasma mer	GO:000815 hedgehog r	O	
17545629	11.86074	13.23708	0.8919801	-0.164917	0	main	NM_011077 Phx	phosphate r	NM_011077 RefSeq	Mus muscu	TRUE	18676	Mm.2529	P70699	chrX	---	---	GO:000650 proteolysis	GO:000578 endoplasm	GO:000422 metalloend	O	
17546834	642.2186	541.8898	1.1851461	0.245055	0	main	NM_01200X Ddx3c	DEAD (asp	NM_01200X RefSeq	Mus muscu	TRUE	26900	Mm.302938	Q62095	chrY	---	---	GO:000620 ATP catalo	GO:000563 nucleus	// l	GO:000016 nucleotide t	O
17547616	821.7177	769.094	1.068423	0.0954829	0	main	---	X91866	GenBank	M.musculu	TRUE	---	---	---	chr11	---	---	GO:000833 nucleosome	GO:000078 nucleosome	GO:000367 DNA bindin	O	
17547837	96.34195	85.62026	1.1251055	0.1700603	0	main	ENSMUST1 Gm21464	predicted	gi ENSMUST1 ENSEMBL	havana:kn	TRUE	10082085	Mm.291443	Q920G8	chr14	---	---	GO:000681 transport	// GO:000573 mitochondr	GO:000538 iron ion tra	O	
17547846	101.3898	97.73033	1.0586083	0.1203681	0	main	ENSMUST1 Gm21464	predicted	gi ENSMUST1 ENSEMBL	havana:kn	TRUE	10082085	Mm.291443	Q920G8	chr14	---	---	GO:000681 transport	// GO:000573 mitochondr	GO:000538 iron ion tra	O	
17548283	1129.61	948.6991	1.1909637	0.2518023	0	main	NM_008211 H33b	H3 histone,	NM_008211 RefSeq	Mus muscu	TRUE	15081	Mm.371563	P84244	chr3	---	---	GO:000164 estoblast	GO:000022 nuclear chr	GO:000097 RNA polym	O	
17548518	1145.085	1182.456	0.9683954	-0.048332	0	main	NM_001081 Gm12657	predicted	gi NM_001081 RefSeq	Mus muscu	TRUE	667250	Mm.449778	P84244	chr6	---	---	GO:000164 estoblast	GO:000022 nuclear chr	GO:000097 RNA polym	O	
17548946	993.8382	828.8755	1.20182	0.2653409	0	main	NM_008211 H33b	H3 histone,	NM_008211 RefSeq	Mus muscu	TRUE	15081	Mm.371563	P84244	chr1	---	---	GO:000164 estoblast	GO:000022 nuclear chr	GO:000097 RNA polym	O	





17519967	77.80013	63.36783	1.2277544	0.296022	0	main	NM_011621 Tpbp	trophoblast	NM_011621 RefSeq	Mus muscu	TRUE	21983	Mm.20864	Q9Z0L0	chr9	---	---	GO:000573 cytoplasm	---	---	O	
17520815	381.8094	686.5728	0.5559849	-0.847194	0	main	NM_00110X Mst2	male-specific	NM_00110X RefSeq	Mus muscu	TRUE	77853	Mm.326206	Q692F8	chr9	---	---	GO:004398 histone H4-	GO:007248 MSL comp	GO:000827 zinc ion bin	O	
17522848	205.7395	257.2575	0.7997415	-0.322394	0	main	NM_00104X Azc2	5-azacytidin	NM_00104X RefSeq	Mus muscu	TRUE	27215	Mm.92705	Q9QV98	chr9	---	---	GO:000027 mitotic cell	GO:000573 cytoplasm	GO:000551 protein bind	O	
17523081	70.94463	40.75385	1.740808	0.7997571	0	main	NM_007391 Acvr2b	activin recep	NM_007391 RefSeq	Mus muscu	TRUE	11481	Mm.390238	P27040	chr9	---	---	GO:000150 skeletal sys	GO:000562 cell	// cytop	GO:000016 nucleotide t	O
17526130	339.0828	396.8731	0.8543859	-0.22704	0	main	NM_007611 Cbl	Casitas B-li	NM_007611 RefSeq	Mus muscu	TRUE	12402	Mm.266871	P22882	chr9	---	---	GO:000716 cell surface	GO:000563 nucleus	// t	GO:000178 phosphotyrc	O
17528714	235.3805	249.4519	0.9435907	-0.083767	0	main	NM_00125X Tcf12	transcription	NM_00125X RefSeq	Mus muscu	TRUE	21406	Mm.171615	Q61286	chr9	---	---	GO:000635 transcription	GO:000563 nucleus	// t	GO:000367 DNA bindin	O
17529713	331.4807	529.5917	0.6259175	-0.675956	0	main	NM_00111X U2surp	U2 snRNP-	NM_00111X RefSeq	Mus muscu	TRUE	67958	Mm.292742	Q6NV83	chr9	---	---	GO:000639 RNA proces	GO:000563 nucleus	// t	GO:000016 nucleotide t	O
17530930	64.3563	59.80752	1.076057	0.1057545	0	main	NM_00104Z Sema3b	sema doma	NM_00104Z RefSeq	Mus muscu	TRUE	20347	Mm.4083	Q62177	chr9	---	---	GO:000727 multicellular	GO:000557 extracellular	GO:000487 receptor act	O	
17530955	988.2798	842.2397	1.1710203	0.2277661	0	main	NM_00813X Gna2	guanine nuc	NM_00813X RefSeq	Mus muscu	TRUE	14678	Mm.196464	P08752	chr9	---	---	GO:000018 activation of	GO:000563 nucleus	// t	GO:000016 nucleotide t	O
17531734	28.70505	28.00312	1.0250651	0.035717	0	main	NM_01688X Slac	siz homolog	NM_01688X RefSeq	Mus muscu	TRUE	20840	Mm.1414	P97306	chr9	---	---	GO:003460 cellular resp	GO:000573 cytoplasm	GO:000487 metal ion bi	O	
17533416	512.7594	858.501	0.5972729	-0.743538	0	main	NM_01002X Ddx3c	DEAD/H (A	NM_01002X RefSeq	Mus muscu	TRUE	13205	Mm.289662	Q62167	chrX	---	---	GO:000237 immune sys	GO:000563 nucleus	// t	GO:000016 nucleotide t	O
17536208	1145.401	546.4041	2.0962526	1.0678126	0	main	NM_00129X Fmr1	fragile X me	NM_00129X RefSeq	Mus muscu	TRUE	14265	Mm.3451	P35922	chrX	---	---	GO:000681 transport	// GO:000563 nucleus	// t	GO:000372 RNA bindin	O
17535241	124.9131	151.5649	0.8241559	-0.278011	0	main	ENSMUST1 Svx	sarim/threo	ENSMUST1 ENSEMBL	havana:kn	TRUE	56291	Mm.202561	Q60969	chrX	---	---	GO:000647 protein depl	GO:000573 cytoplasm	GO:000472 phosphora	O	
17539018	16.33215	16.62154	0.9825895	-0.025339	0	main	NM_01372X Nk	Nk related 1	NM_01372X RefSeq	Mus muscu	TRUE	27206	Mm.482318	Q9R0G8	chrX	---	---	GO:000646 protein pho	GO:000573 cytoplasm	GO:000016 nucleotide t	O	
17538395	9.817351	10.32762	0.9505918	-0.073102	0	main	NM_00103X Zcchc16	zinc finger,	NM_00103X RefSeq	Mus muscu	TRUE	619287	Mm.387961	Q3URYO	chrX	---	---	GO:000815 biological p	GO:000557 cellular	con	GO:000367 nucleic acid	O
17538658	24.19338	22.67239	1.0670856	0.0936759	0	main	NM_00127X Wnk3	WNK lysine	NM_00127X RefSeq	Mus muscu	TRUE	279561	Mm.441474	Q80XP9	chrX	---	---	GO:000646 protein pho	GO:000573 cytoplasm	GO:000016 nucleotide t	O	
17539828	24.83115	25.36139	0.9790026	-0.030483	0	main	NM_019461 Usp27x	ubiquitin sp	NM_019461 RefSeq	Mus muscu	TRUE	54651	Mm.483107	Q8CEG8	chrX	---	---	GO:000650 proteolysis	GO:000557 cellular	con	GO:000823 peptidase a	O
17541343	21.40386	20.20307	1.059436	0.0832965	0	main	NM_00129X Smarca1	SWI/SNF r	NM_00129X RefSeq	Mus muscu	TRUE	93761	Mm.229151	Q6PGB8	chrX	---	---	GO:000073 DNA strand	GO:000079 nuclear chr	GO:000016 nucleotide t	O	
17543840	12.03987	12.29752	0.979764	-0.029494	0	main	NM_00107X C77370	expressed s	NM_00107X RefSeq	Mus muscu	TRUE	245555	Mm.381907	Q5D7T1	chrX	---	---	GO:000008 mtotic S p	GO:000563 nucleus	// t	GO:000388 DNA-direct	O
17544102	56.45731	66.44284	0.8497125	-0.234953	0	main	ENSMUST1 Bwa5	bromodome	ENSMUST1 ENSEMBL	ensembl_h	TRUE	382236	Mm.426127	A2H4L4	chrX	---	---	GO:000701 cytoskeleton	GO:000557 cellular	con	GO:000551 protein bind	O
17544939	360.4171	267.8529	1.346584	0.4293042	0	main	NM_00107X Tsc22d3	TSC22 dor	NM_00107X RefSeq	Mus muscu	TRUE	14605	Mm.22216	Q9ZS57	chrX	---	---	GO:000012 negative reg	GO:000563 nucleus	// t	GO:000370 sequence-s	O
17545078	95.12606	93.64679	1.0157963	0.0226111	0	main	NM_01949X Ammeccr1	Alport synd	NM_01949X RefSeq	Mus muscu	TRUE	56068	Mm.143724	Q9JHT5	chrX	---	---	GO:000815 biological_p	GO:000557 cellular	con	GO:000367 molecular_f	O
17545618	57.85563	41.40395	1.3973457	0.4826889	0	main	XM_00652Z P1chd1	palched dor	XM_00652Z RefSeq	PREDICTE	TRUE	211612	Mm.218811	Q14B62	chrX	---	---	GO:000722 smoothene	GO:000598 plasma mer	GO:000815 hedgehog r	O	
17545629	13.29709	15.89333	0.8384925	-0.25413	0	main	NM_01107X Pknox	phosphate r	NM_01107X RefSeq	Mus muscu	TRUE	18676	Mm.2529	P70699	chrX	---	---	GO:000650 proteolysis	GO:000578 endoplasm	GO:000422 metalloendc	O	
17546834	541.8898	1081.035	0.5012694	-0.996342	0	main	NM_01200X Ddx3y	DEAD (ASP	NM_01200X RefSeq	Mus muscu	TRUE	26900	Mm.302938	Q62095	chrY	---	---	GO:000620 ATP catalo	GO:000563 nucleus	// t	GO:000016 nucleotide t	O
17547616	769.094	810.2198	0.9492412	-0.075153	0	main	---	X91866	GenBank	M.musculu	TRUE	---	---	P84244	chr11	---	---	GO:000833 nucleosome	GO:000078 nucleosome	GO:000367 DNA bindin	O	
17547837	85.62626	86.08841	0.9720532	-0.040948	0	main	ENSMUST1 Gm21464	predicted g	ENSMUST1 ENSEMBL	havana:kn	TRUE	10082085	Mm.291443	Q920C8	chr14	---	---	GO:000681 transport	// GO:000573 mitochondri	GO:000538 iron ion tran	O	
17547846	92.70303	94.7348	0.9785531	-0.031278	0	main	ENSMUST1 Gm21464	predicted g	ENSMUST1 ENSEMBL	havana:kn	TRUE	10082085	Mm.291443	Q920C8	chr14	---	---	GO:000681 transport	// GO:000573 mitochondri	GO:000538 iron ion tran	O	
17548283	948.6991	1613.575	0.5879486	-0.766238	0	main	NM_008211 H33b	H3 histone,	NM_008211 RefSeq	Mus muscu	TRUE	15081	Mm.371563	P84244	chr3	---	---	GO:000164 osteoblast	GO:000022 nuclear chr	GO:000097 RNA polym	O	
17548518	1182.456	1200.466	0.9849975	-0.021808	0	main	NM_001081 Gm12657	predicted r	NM_001081 RefSeq	Mus muscu	TRUE	667250	Mm.448778	P84244	chr6	---	---	GO:000164 osteoblast	GO:000022 nuclear chr	GO:000097 RNA polym	O	
17548946	626.8755	1431.395	0.5776711	-0.79168	0	main	NM_008211 H33b	H3 histone,	NM_008211 RefSeq	Mus muscu	TRUE	15081	Mm.371563	P84244	chr1	---	---	GO:000164 osteoblast	GO:000022 nuclear chr	GO:000097 RNA polym	O	

**Supplementary Table 6.** Validated and predicted target genes for Mir221 and Mir222

RGS6	SUN2	ARID1A	KHDRBS2	KLF3	GRM1	GBX2	PHEX
CDKN1B	ARHGEF7	DDIT4	CPNE8	ANKIB1	RREB1	HNRNPA0	MAGI1
CXCL12	ARF4	NIPAL4	MLLT6	FGF14	PTCHD1	DDX3Y	ANKS1B
TCF12	BRWD1	TPBG	RPH3A	S100PBP	VASH1	INSIG1	CAPRN2
RFX7	RALGAPA1	MEGF9	ATP1B1	ERBB4	CMTM4	FERMT2	LRP10
SEC62	ZFPM2	CNR1	POGZ	EMX2	SPPL3	SPRED2	ZFP90
GABRA1	KIAA1370	NFYB	REV1	CD2AP	MEX3A	HDGF	
HECTD2	ANGPTL2	TSC22D3	USP27X	PHF2	ZNF654	PELI1	
KIT	MIDN	CDK19	CDKN1C	PDGFA	MAPK10	VKORC1L1	
VGLL4	DPP8	FOS	KIAA1267	PLEKHA6	ZEB2	TEAD1	
PAIP1	CHSY1	TOX	MESDC1	CNOT2	ACVR2B	FBXO28	
TP53BP2	MIER3	NAA25	RNPS1	AJAP1	MARCKS	MARK1	
NAP1L5	C3orf70	MSL2	VAPB	CDH2	AAK1	SMARCA1	
ZFAND5	CASZ1	ASPH	CBFB	ADAM11	NFAT5	EFCAB14	
NRK	NSMCE4A	GPM6A	KIAA0368	ITGB8	NDFIP1	PPP6C	
IRX5	YWHAG	AGFG1	LPPR1	HOXA7	STX1B	RC3H2	
DCUN1D1	EIF3J	HIPK1	PAK1	BAZ2B	ANKRD52	CAMK1D	
CLVS2	FOXN2	NFATC3	SPATS2L	TAOK1	TCF4	RFX3	
LRRTM2	CD4	ZCCHC16	CBL	FAM167A	EIF4E3	UBE2E3	
ETV3	DCUN1D4	IGDCC4	CTCF	PBX3	TRPS1	PDCD10	
AP3B2	GPBP1	CREBZF	C11orf87	C14orf147	THRB	U2SURP	
PPP3R1	UBN2	TLE3	HIPK2	SLITRK5	DGKE	DDX3X	
RIMS3	ZNF385A	DNAJC14	TP53INP1	LHFPL2	SLC1A2	THSD7B	
DCAF12	PRUNE	ZFP36L2	FRS2	PTBP2	RNF165	MAGI2	
ZNF652	ARNT	PPP2R2A	ESR1	AMMECR1	C16orf52	PGAP1	
DMRT3	UBE2J1	ZMYM2	SMARCA5	CAPRN1	AGPS	BBC3	
CCDC64	PCDHA9	BRWD3	GNAI2	FOXP1	OSBPL7	STMN1	
EML6	PCDHAC2	NLK	VEZF1	ZNF618	PVRL1	CABYR	
CACNB4	PCDHAC1	SEMA3B	TCF7L2	SRSF2	DNAL1	MED12L	
PLEKHA2	PCDHA13	HNRNPA3	H3F3A	IKZF4	E2F2	HELQ	
NRG1	PCDHA12	IPO7	DKK2	GALNTL4	TNRC6C	SLC25A37	
NTF3	PCDHA11	ANKHD1	IGF2BP2	MAP3K2	SOCS7	MYBL1	
FAM38B	PCDHA10	STYX	DENND1B	C16orf45	SNX29	SYBU	
SCD5	PCDHA8	FMR1	RNF44	AP3M1	WASF2	FAM214A	
MIA3	PCDHA7	SNCB	PKDCC	CEP350	KCNA1	KLC1	
RBM24	PCDHA6	RUNX2	ETS2	TIMP3	KIAA2022	PANK3	
FNDC3A	PCDHA5	METTL10	C17orf63	ATAD2B	RIMBP2	ADAM22	
NOVA1	PCDHA4	WDR37	FAT2	RANBP2	RALA	SNAP29	
TMCC1	PCDHA3	LOC388630	SEC23IP	MON2	FKTN	MCMDC2	
BCL2L11	PCDHA2	BEND4	SLC4A4	PHC2	MAP3K10	PHACTR4	
WDR47	PCDHA1	ST8SIA1	TIPARP	CUX1	SNAP25	CAMTA1	
EIF5A2	GNAI3	ROD1	NUFIP2	SOCS1	ITIH5	ASB4	
HMBOX1	SHANK2	KIAA0494	ARL6IP1	FOXP2	PI15	URI1	
WNK3	SBK1	AZI2	ZADH2	NANOS1	PCDH10	ZBTB41	
C18orf25	ATF7	RAB1A	IGSF3	RAB3GAP2	FNIP2	RAB18	
MYLIP	PAIP2	ITGB3	SH3PXD2B	DLG2	CPEB4	LIMS1	
KIF16B	RSBN1L	HOXC10	PDIK1L	YTHDC1	STAC	GUCY1A2	
BMF	ETS1	ZNF629	KSR1	GAB1	PDZRN4	ATF2	
IRF2	AXIN2	QKI	ATXN1	C2CD2	SDC2	CHD8	
PLCL2	NIPBL	LRFN2	SH3BP4	TBC1D22B	HIPK3	ASB7	

**Supplementary Table 7.** Expression of candidate target genes of miR-221-3p and miR-222-3p in Mir221/222flox/y and Mir221/222AdipoKO mice fed with standard (STD) and high fat-high sucrose (HFHS) chow.

Annotation	Expression value				Ratio					Keyword
	Gene Symbol	STD flox/y	HFHS flox/y	STD AdipoKO	HFHS AdipoKO	STD AdipoKO / STD flox_y	HFHS AdipoKO / HFHS flox_y	HFHS flox_y / STD flox_y	HFHS AdipoKO / STD AdipoKO	
<i>Igf2bp2</i>	118.6727	92.12485	111.7554	233.6214	0.94171111	2.535921632	0.776293537	2.090470796	○	
<i>Foxp2</i>	53.29913	25.92172	46.43985	56.3454	0.871305967	2.173675204	0.486344149	1.213298493	○	
<b><i>Ddit4</i></b>	<b>187.1108</b>	<b>201.7627</b>	<b>482.7296</b>	<b>383.8727</b>	<b>2.579913078</b>	<b>1.902594979</b>	<b>1.078306009</b>	<b>0.795212682</b>	<b>○</b>	
<i>Tiparp</i>	370.4981	370.9203	243.0674	629.3118	0.656055726	1.696622698	1.001139547	2.589042381	○	
<i>Gm13034</i>	89.3279	42.14671	66.82102	71.24998	0.748041989	1.690522938	0.471820226	1.06628094	○	
<i>Cdkn1c</i>	139.7296	64.02979	86.02513	99.0863	0.615654307	1.547503123	0.458240702	1.151829704	○	
<i>Gm17275</i>	38.15434	25.35535	28.33733	38.61103	0.742702665	1.522796175	0.664546943	1.362550036	○	
<i>Ppp2r2a</i>	173.6408	103.3587	136.4849	156.1966	0.786018609	1.511209023	0.59524432	1.144424035	○	
<i>Caprin2</i>	105.009	84.21983	107.7583	127.1511	1.026181565	1.509752513	0.802024874	1.17996572	○	
<i>Fos</i>	250.5789	115.658	96.99457	173.6935	0.387081953	1.501785436	0.461563204	1.790754885	○	
<i>Uri1</i>	666.848	366.2552	624.7025	515.4158	0.936798941	1.407258655	0.549233409	0.825058008	○	
<i>Mark1</i>	85.06554	51.96034	72.25445	73.05361	0.849397418	1.405949422	0.610827134	1.011060357	○	
<i>Cas21</i>	67.4341	63.58655	83.56946	87.91584	1.239275975	1.382616921	0.942943555	1.052009191	○	
<i>Itgb8</i>	54.55101	51.56115	53.44313	71.05316	0.979690935	1.378036758	0.945191482	1.329509705	○	
<i>Agfg1</i>	594.9557	470.1974	450.3722	646.7574	0.756984428	1.375501864	0.790306572	1.436050893	○	
<i>Etv3</i>	409.6244	143.7052	342.2083	197.4402	0.835419716	1.37392523	0.350821875	0.576959121	○	
<i>Tle3</i>	812.1421	684.8116	767.2126	920.5015	0.944677785	1.344167505	0.843216477	1.199799769	○	
<i>Ddx3x</i>	858.501	512.7594	664.2457	688.9457	0.773727346	1.343604232	0.597272921	1.037185036	○	
<i>Cpne8</i>	216.8393	187.5397	240.7783	249.4114	1.110399729	1.329912547	0.864878737	1.035854975	○	
<i>Pvrl1</i>	127.8629	150.1472	130.7448	199.2742	1.022538985	1.327192249	1.174282767	1.524146276	○	
<i>Pdzrn4</i>	20.39221	18.83454	22.20171	24.96736	1.088734865	1.325615598	0.923614459	1.124569234	○	
<i>Ets2</i>	528.1785	309.0158	364.8452	406.857	0.690761173	1.316621998	0.585059407	1.115149658	○	
<i>Smarca1</i>	20.20307	21.40386	22.6035	28.04365	1.118815111	1.310214606	1.059436016	1.240677329	○	