**Supplemental table 1. List of oligonucleotide primer pairs used in real time RT-PCR and RT-PCR analysis.**

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| Target Gene | Sense Primer | Antisense Primer |
| HR1 (H) | 5'-GGATGCCAAGAAACCAGGGA-3' | 5'-GGGGTTTGGGATGGTGACTT-3' |
| FAM3A(H) | 5'-GTGTCACATGGATCGTGGTC-3' | 5'- TGCTCATCAGCATCTTGTCC-3' |
| FAM3A(M) | 5'-TCATGAGCAGCGTCAAAGAC-3' | 5'-AGGGTACCTTCATGCAGTGG-3' |
| G6Pase (M) | 5'-AGGAAGGATGGAGGAAGGAA-3' | 5'-TGGAACCAGATGGGAAAGAG-3' |
| PEPCK(M) | 5'-ATCTTTGGTGGCCGTAGACCT-3' | 5'-CCGAAGTTGTAGCCGAAGAA-3' |
| FAS(M) | 5'-CTGCCACAACTCTGAGGACA-3' | 5'-CGGATCACCTTCTTGAGAGCC-3' |
| SREBP1C(M) | 5'-GGAGGCAGAGAGCAGAGATG-3' | 5'-TTGCGATGTCTCCAGAAGTG-3' |
| β-actin (M) | 5'-AGCCATGTACGTAGCCATCC-3' | 5'-GCTGTGGTGGTGAAGCTGTA-3' |
| β-actin (H) | 5'-ACTCTTCCAGCCTTCCTTCC-3' | 5'-TCTCCTTCTGCATCCTGTCG-3' |
| UCP1(M) | 5'-CCTGCCTCTCTCGGAAACAA-3' | 5'-TCTGGGCTTGCATTCTGACC-3' |
| FAM3A Promoter(M) | 5'-CCTCTCCCGTCTCCACTTTC-3' | 5'-CTTTTCCCCTGACCGCCTAC-3' |

M: mouse; H: human. If not indicated, all the primer sequences are referred to mouse origin.

**Supplemental table 2. siRNA sequence mixture against human HR1 mRNA**

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| Dulex Name | SenseSeq | AntisenseSeq |
| HR1-1 (H) | 5'-GGACCAAAGAACACUCGAATT-3' | 5'-UUCGAGUGUUCUUUGGUCCTT-3' |
| HR1-2 (H) | 5'-CGAGUCAAGUGAUUGACAATT-3' | 5'-UUGUCAAUCACUUGACUCGTT-3' |
| HR1-3 (H) | 5'-GGGACUAUGUAGCCGUCAATT-3' | 5'-UUGACGGCUACAUAGUCCCTT-3' |
| HR1-4 (H)  | 5'-GGUUCUAUGCCAAGAUCUATT-3' | 5'-UAGAUCUUGGCAUAGAACCTT-3' |

**Supplemental figure legends:**

**Figure 1. The effects of predicted drugs on FAM3A mRNA and protein levels in HepG2 cells**. A) The expression profile of histamine H1 receptor mRNA among mouse tissues. N=6-8. B) The effects of predicted drugs on FAM3A-promoter luciferase activities. C) The effects of predicted drugs on FAM3A mRNA levels. D) The effects of predicted drugs on FAM3A and pAkt protein levels. E) The effects of predicted drugs on intracellular and extracellular ATP content. HepG2 cells were treated with indicated concentration of drugs for 48 hours. N=3-8, \*P<0.05 versus control cells.

**Figure 2. Doxepin failed to affect physical activity of HFD mice.** HFD mice treated with doxepin (10mg/kg) for 5 weeks were subjected to metabolic cage assays. A-B) Doxepin had little effect on activity of HFD mice. The activity curves were shown in panel A, and AUC data in panel B. C-D) Doxepin had little effect on food intake and water drink in HFD mice. N=6-7, there was no significant difference between two groups.

**Figure 3. Doxepin administration improved fasting hyperglycemia of db/db mice.** Doxepin ameliorated fasting hyperglycemia of db/db mice after 3-week treatment. B) Doxepin treatment increased the thermogenic function of brown adipose tissue in HFD mice. After acute cold exposure for 4 hours, doxepin treatment increased the core body temperature of HFD mice. N=6-8, \*<0.05 versus db/db mice treated with saline.

**Figure 4. Administration of doxepin ameliorated glucose intolerance, insulin resistance and hepatic glucose production of db/db mice.** db/db mice were treated with doxepin for 4-5 weeks, and OGTT, ITT and PTT were performed, respectively. A-B) OGTT after 4-week drug treatment. OGTT data were shown in panel A, and AUC data shown in panel B. C-D) ITT evaluation of insulin resistance after 4.5-week drug treatment. ITT data were shown in panel C, and AUC data shown in panel D. E-F) PTT evaluation of hepatic glucose production after 5-week drug treatment. PTT data were shown in panel E, and AUC data shown in panel F. N=6 for two groups of db/db mice, \*<0.05 versus db/db mice treated with saline.

**Figure 5. Doxepin treatment on FAM3A mRNA level in main metabolic tissues of HFD mice.** A-D) Doxepin treatment on FAM3A mRNA level in epididymal adipose (A), muscle (B), pancreas (C), heart (D) and brain (E). F) Doxepin treatment reduced FAM3A protein level in brain of HFD mice. G) Doxepin treatment increased circulating norepinephrine level in HFD mice. H) Doxepin treatment on liver functions of HFD mice. ALT, alanine aminotransferase; AST, aspartate aminotransferase. The tissues treated by 10mg/kg doxepin were selected for assays. N=7-10, \*<0.05 versus control mice treated with saline.

**Figure 6. Characterization of FAM3A-/- mice by immunohistochemical staining in liver and pancreas tissues**. The results indicated the deficiency of FAM3A protein in tissues.

**Figure 7. Doxepin treatment failed to repress gluconeogenic and lipogenic genes in FAM3A-/- mice fed on HFD.** A) Doxepin failed to increase hepatic ATP content. B) Doxepin failed to reduce the mRNA levels of gluconeogenic and lipogenic genes in FAM3A-/- mouse livers. N=8-10, \*<0.05 versus FAM3A-/- mice treated with saline. C) Doxepin had little effect on FOXO1 nuclear exclusion in cultured FAM3A-/- mouse hepatocytes. The images were the representatives of 3 independent experiments.

**Figure 8. Silencing of H1R failed to affect FAM3A expression and Akt activation in the absence or presence of doxepin.** A) siRNA transfection reduced H1R mRNA level in HepG2 cells. B-D) H1R silencing failed to affect FAM3A expression and Akt phosphorylation. Representative gel images shown in panel B, and quantitative data shown in panels C and D.Cells plated into 6-well plates were transfected with 50 nmol/L siRNA mixture (Beijing Biolino Nucleic Acid Technology Co.,Ltd) against human HR1 mRNA using VigoFect transfection reagent (Vigorous Biotechnology Beijing Co., Ltd.), scrambled siRNA sequences were used as negative control. 6 hours after transfection, cells were treated with drugs for additional 24 hours before being harvested for further analysis. N=3, \*<0.05 versus scramble-treated cells without drug treatment.

**Figure 9. Prediction of potential transcriptor binding sites in the promoters of mouse, rat and human FAM3Agenes**. The binding sites in mouse, rat and human FAM3A gene promoters flanking -2000bp ~ +100bp were analyzed using UCSC Genome Browser and TRANSFAC® 7.0 Public in the following website: http://www.gene-regulation.com/pub/databases.html. Some potential sites with the highest prediction scores were listed. All mouse, rat and human FAM3A gene promoters contain one potential binding site highly specific for HNF4α.

**Figure 10. Inhibition of HNF4α repressed doxepin-induced FAM3A upregulation and Akt phosphorylation in HepG2 cells.** A-B) Plasmid HNF4α overexpression upregulated FAM3A and induced Akt phosphorylation in HepG2 cells. C) Plasmid HNF4α overexpression increased extracellular ATP level in HepG2 cells. D-E) Inhibition of HNF4α blocked drug-induced FAM3A expression and ATP production in HepG2 cells. F) Relative expression of HNF4α in HepG2 cells and mouse hepatocytes. N=3-5, \*<0.05 versus control cells, #<0.05 versus cell groups treated with drugs.

**Figure 11. Doxepin treatment increased nuclear distribution of HNF4α in mouse hepatocytes.** Mouse hepatocytes were treated with 30μM doxepin in the absence or presence of HNF4α inhibitor BI6015 (60μM) for 48 hours before confocal images were obtained.

**Figure 12. Doxepin upregulated UCP1 expression in brown adipose but not white adipose tissues.** A) Relative expression of HNF4α, FAM3A and UCP1 in mouse liver and brown adipose tissues. N=4, \*<0.05 versus livers. B) Doxepin treatment increased HNF4α expression in brown adipose tissue of HFD mice. C) Doxepin treatment had little effect on the expressions of HNF4α, FAM3A and UCP1 in white adipose tissue of HFD mice. D) Doxepin treatment increased nuclear distribution of HNF4α in HFD mouse livers. N=4-7, \*<0.05 versus HFD mice.

**Figure 13. Doxepin treatment had little effect on urine biochemical indicators in old male mice**. db/db mice were treated with doxepin for 1 months as described in experimental procedure. A-D) Doxepin treatment on 24-hour total protein excretion (A), and urine nitrogen (B), creatinine (C), and NAG (N-Acetyl-β-glucosaminase) (D) levels. E-H) Doxepin treatment on 24-hour excretion of Na+ (E), K+ (F), Ca2+ and Cl- in urine and creatinine content (G) in urine of mice. N=6, \*P<0.05 versus control mice.