**Supplemental references list**

Figure S1. Sequencing of the homologous rs1421085 T>C variant in human and mouse.

Figure S2. The homologous rs1421085 T>C variant protests HFD-induced obesity but shows no change in body weight under chow diet in KIcas9 mice.

Figure S3. The homologous rs1421085 T>C variant protests HFD-induced obesity but shows no change in body weight under chow diet in KIES mice.

Figure S4. Brown adipocyte-specific knock-in homologous rs1421085 T>C variant enhances thermogenesis resists HFD-induced adiposity.

Figure S5. The mRNA expression of potential downstream effectors of rs1421085 T>C variation.

Figure S6. FTO enhances thermogenic capacity of brown adipocytes and partially medicates the increased thermogenesis in rs1421085 T>C knock-in model. (A) The mRNA expression

Figure S7. *Fto* deficiency in BAT impairs thermogenesis and resists HFD-induced adiposity.

Figure S8. FTO protein stabilizes Ucp1 mRNA and increase UCP1 protein expression.

Figure S9. Surgical excision of intrascapular BAT largely reverses HFD-resistance phenotype of KIcas9 mice.

Figure S10. The association of human FTO rs1421085 T>C variation frequency with BMI.

Figure S11. The FTO and UCP1 were colocalized in human embryonic brown adipose tissue.

Figure S12. The association of human FTO rs1421085 T>C variation frequency with ambient environmental temperature, elevation, and latitude.

Figure S13. Sanger sequencing of the 6 kb DNA region centered on the homologous rs1421085 locus in WT and KIcas9 mice.

Table S1. Top 10 off-target sites prediction.

Table S2. Primers for genotyping/qPCR.

Table S3. Primer sequences for lentivirus construction and validation.

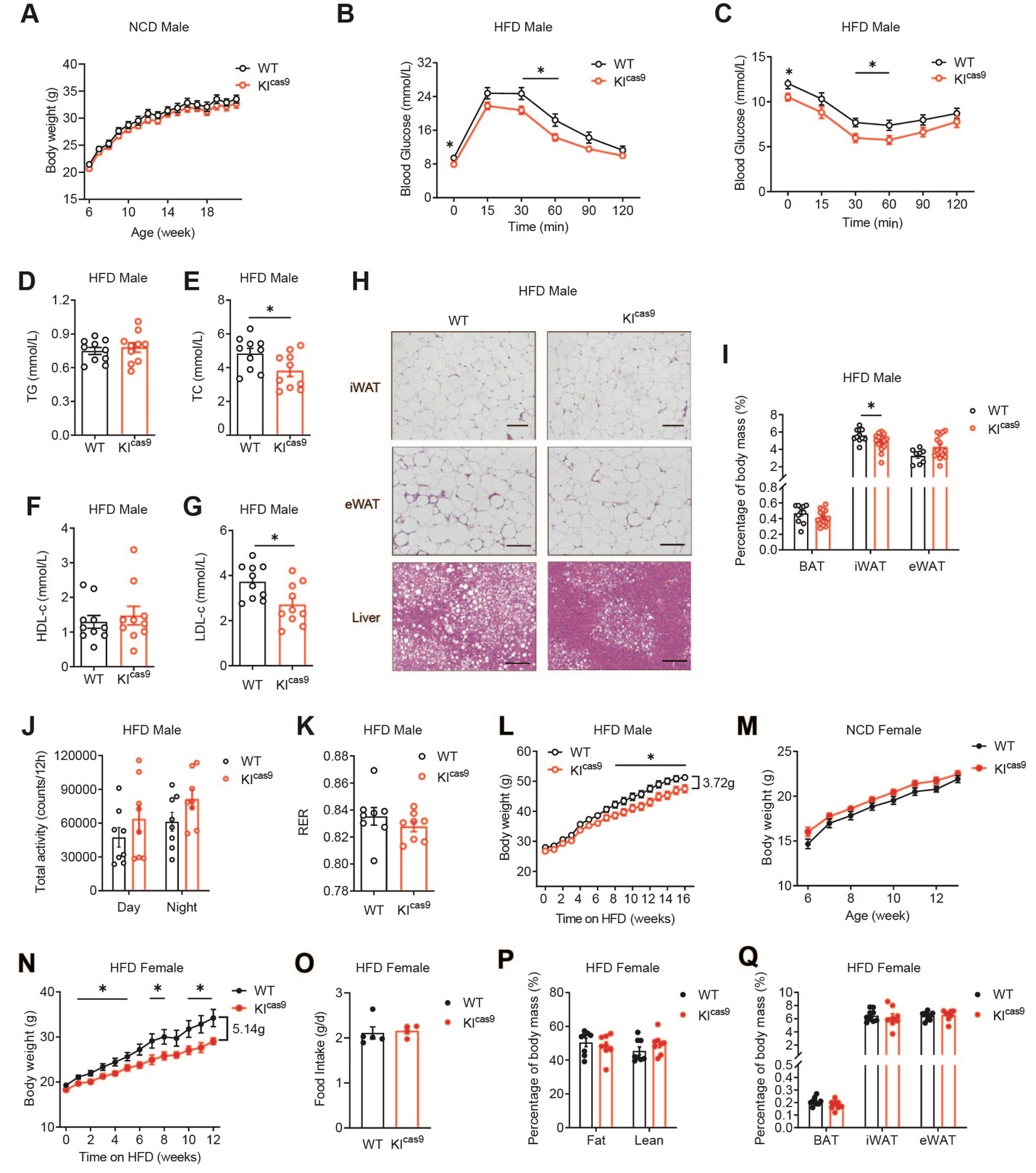
Table S4. Study details included in Meta-anaylsis.

Table S5. Study details included in FTO rs1421085 T>C variant frequency

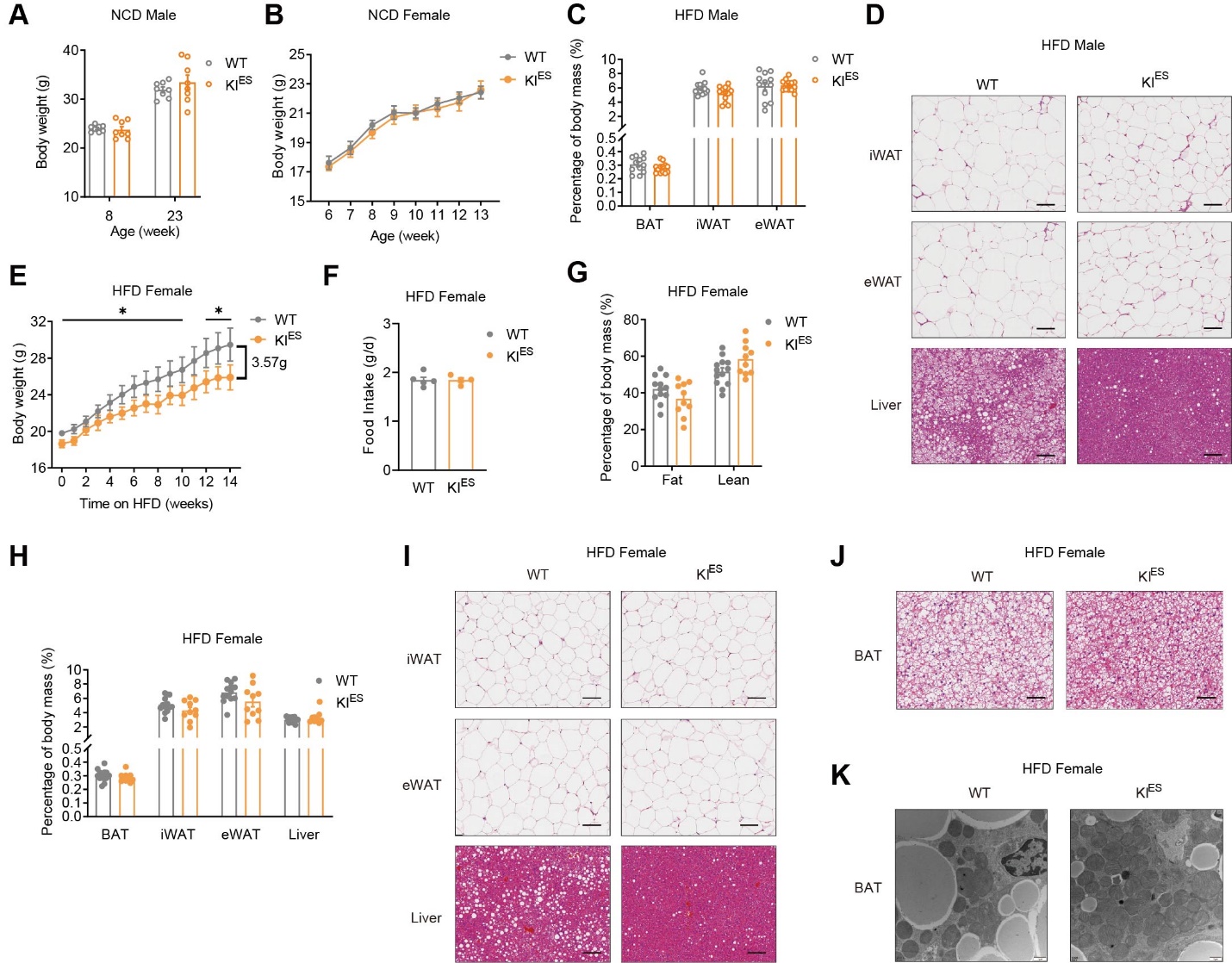
analysis.

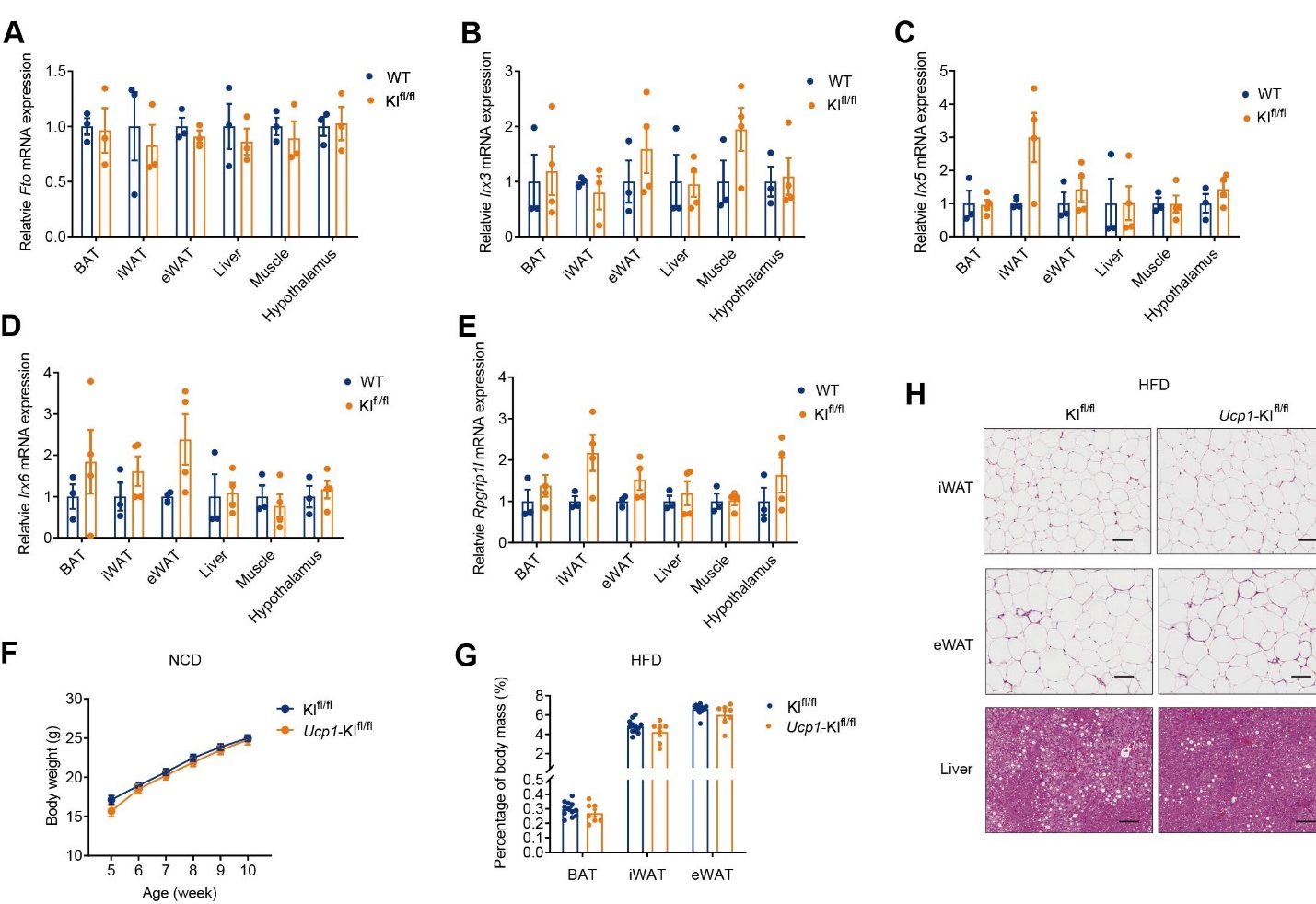
Table S6. Acronym and full name.

**Fig. S1. Sequencing of the homologous rs1421085 T>C variant in human and mouse.** (**A**) Conserved motif module surrounding rs1421085 locus in human and mouse. (**B** and **C**), Sanger sequence analysis of KIcas9 (B) and KIES (C) mice, respectively. (**D**)Floxp (left, top) and Cre expression (left, bottom) and BAT DNA sequence analysis (right) of homologous rs1421085 mutation in KIfl/fl and Ucp1-KIfl/fl mice. Gene sequencing alignment was analyzed with Jalview Version 2 (see **Methods**).

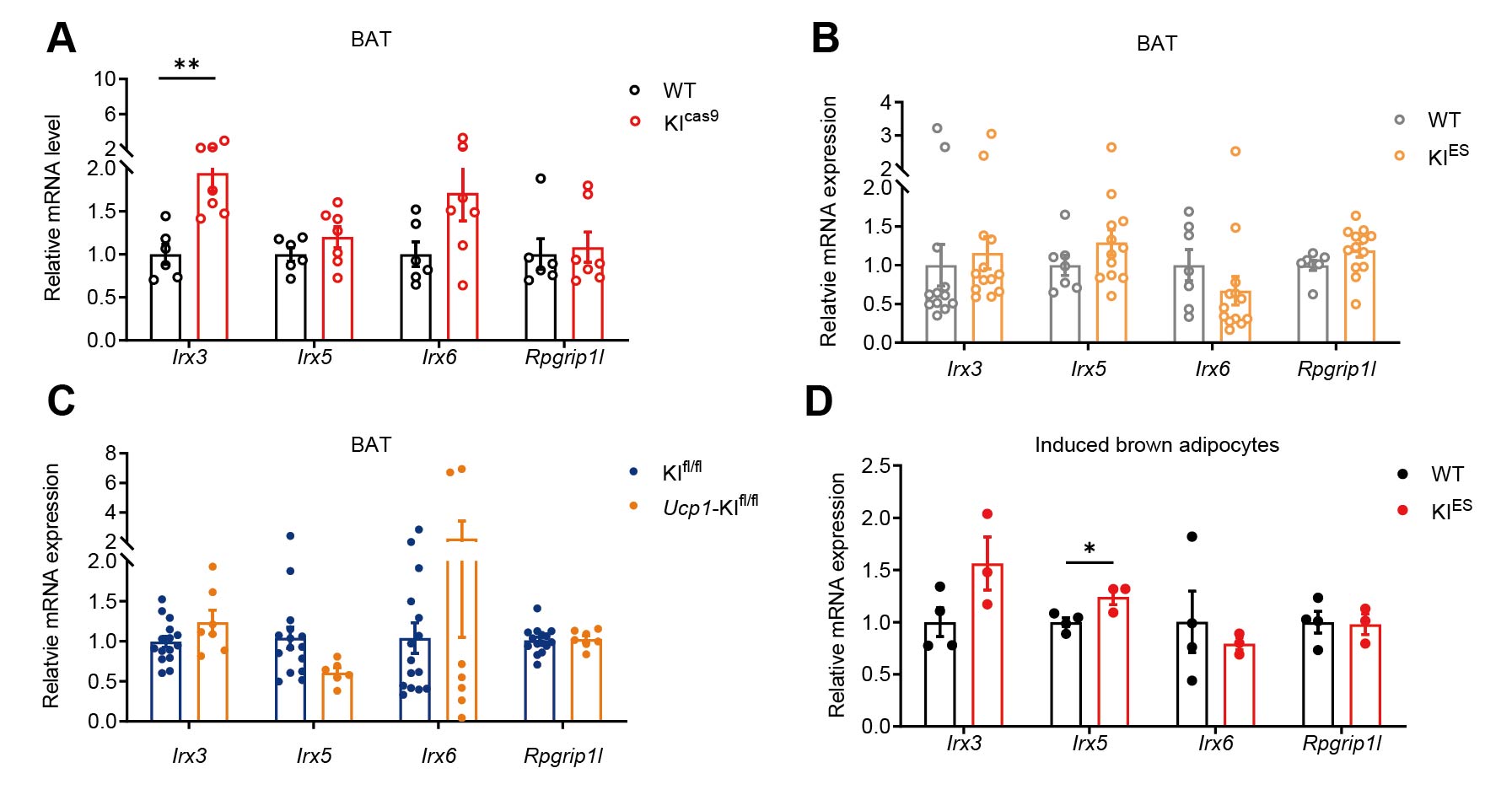


**Fig. S2. The homologous** **rs1421085 T>C variant protests HFD-induced obesity but shows no change in body weight under chow diet in KIcas9 mice.** (**A**) Body weight curve of KIcas9 mice and WT littermates under normal chow diet (NCD) (n= 10:15). (**B** to **J**), IPGTT (B) and ITT(C) tests, plasma triglyceride (D), total cholesterol (TC) (E), HDL-c (F) and LDL-c (G), representative images of H&E staining of iWAT, eWAT and liver (H), BAT, iWAT and eWAT content (I), total physical activities (J) and respiratory exchange ratio (RER) (K) of KIcas9 mice and WT littermates under HFD. n= 17:17 in (B) and (C), n= 10:10 in (D) to (G), n= 8:15 in (H). I, Scale bar, 100 μm. n= 8:8 in (J) and (K). (**L**) The validated diet-induced adiposity phenotype of KIcas9 mice (with F3 generation) under HFD challenge initiating from 11-week-old to 27-week-old (n= 18:19 for KIcas9 and WT, respectively). (**M**) Body weight curve of female KIcas9 and wild-type littermate mice under NCD (n= 21:20). （**N** to **Q**）, Body weight curve (N), average food intake (O), body composition (P), and mass percentage of indicated fat tissue (Q) of female KIcas9 and wild-type littermates under HFD challenge initiating from 8-week-old to 20-week-old. n= 9:8 in (N). average food intake per mouse of individual cage in (O), n= 5:4. n= 8:8 in (P) and (Q). Data are mean ± s.e.m. of biologically independent samples; unpaired two-sided Student’s *t*-test. \* *P* < 0.05.

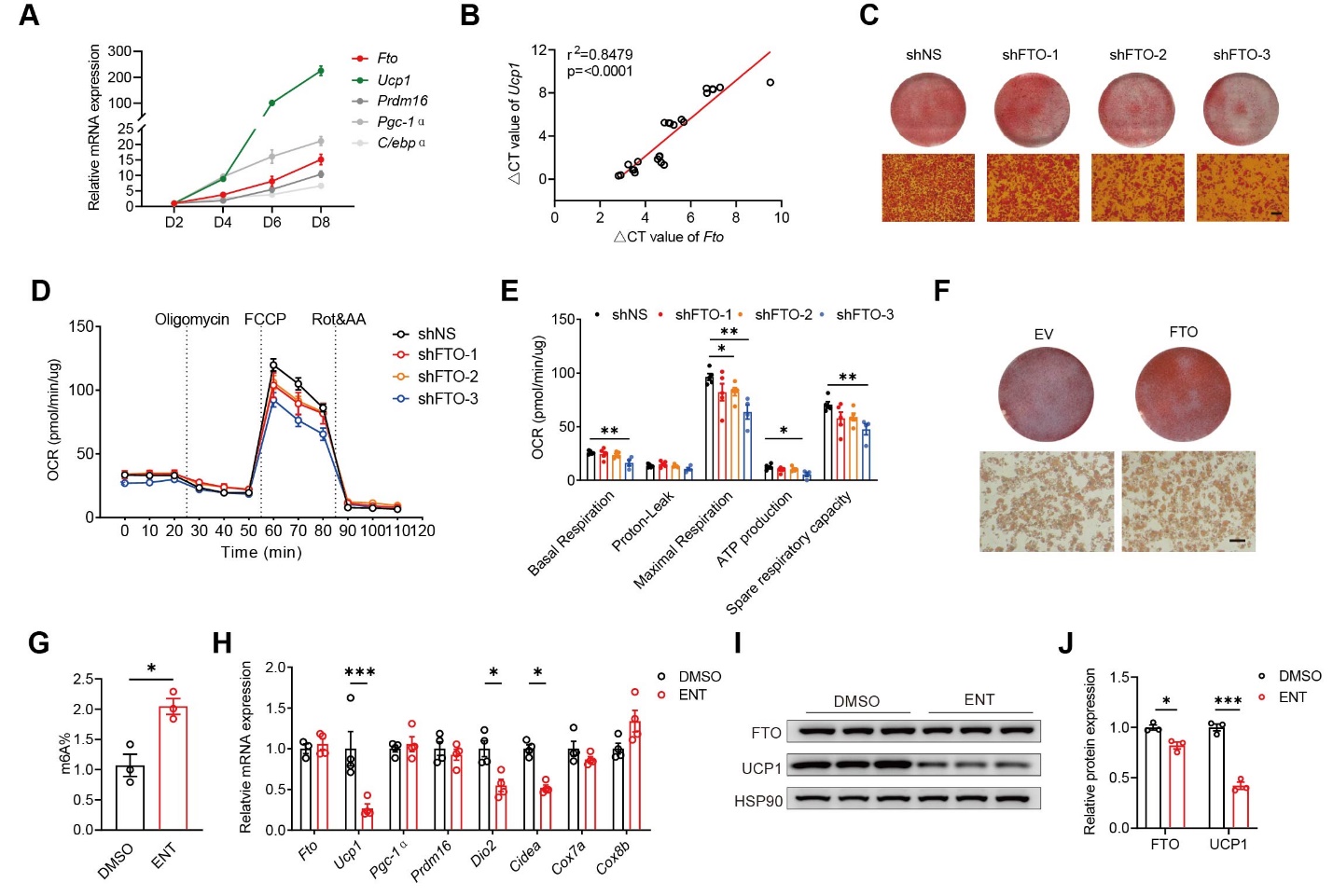
**Fig. S3.** **The homologous** **rs1421085 T>C variant protests HFD-induced obesity but shows no change in body weight under chow diet in KIES mice.** (**A**)Body weight of male KIES and WT mice aged 8- and 23-week-old under NCD (n= 13:10). (**B**)Body weight curve of female KIES and WT mice under NCD (n= 8:8).(**C** to **D**) BAT, iWAT and eWAT content (C), representative images of H&E staining of iWAT, eWAT and liver (D) of male KIES and wild-type littermates under HFD (C, n= 11:16; D, scale bar, 100 μm). (**E** to **K**) Body weight curve (E), average food intake (F), body composition (G) and mass percentage of indicated fat tissues (H), representative images of H&E staining of indicated tissues (I, J) and TEM of BAT (K) of female KIES and wild-type littermate mice under HFD challenge initiating from 10-week-old to 24-week-old (E, n= 16:13; F, n= 5:4 cages; G, H, n= 10–13; I, J, scale bar, 100 μm; K, scale bar, 1 μm).Data are mean ± s.e.m. of biologically independent samples; unpaired two-sided Student’s *t*-test. \* *P* < 0.05



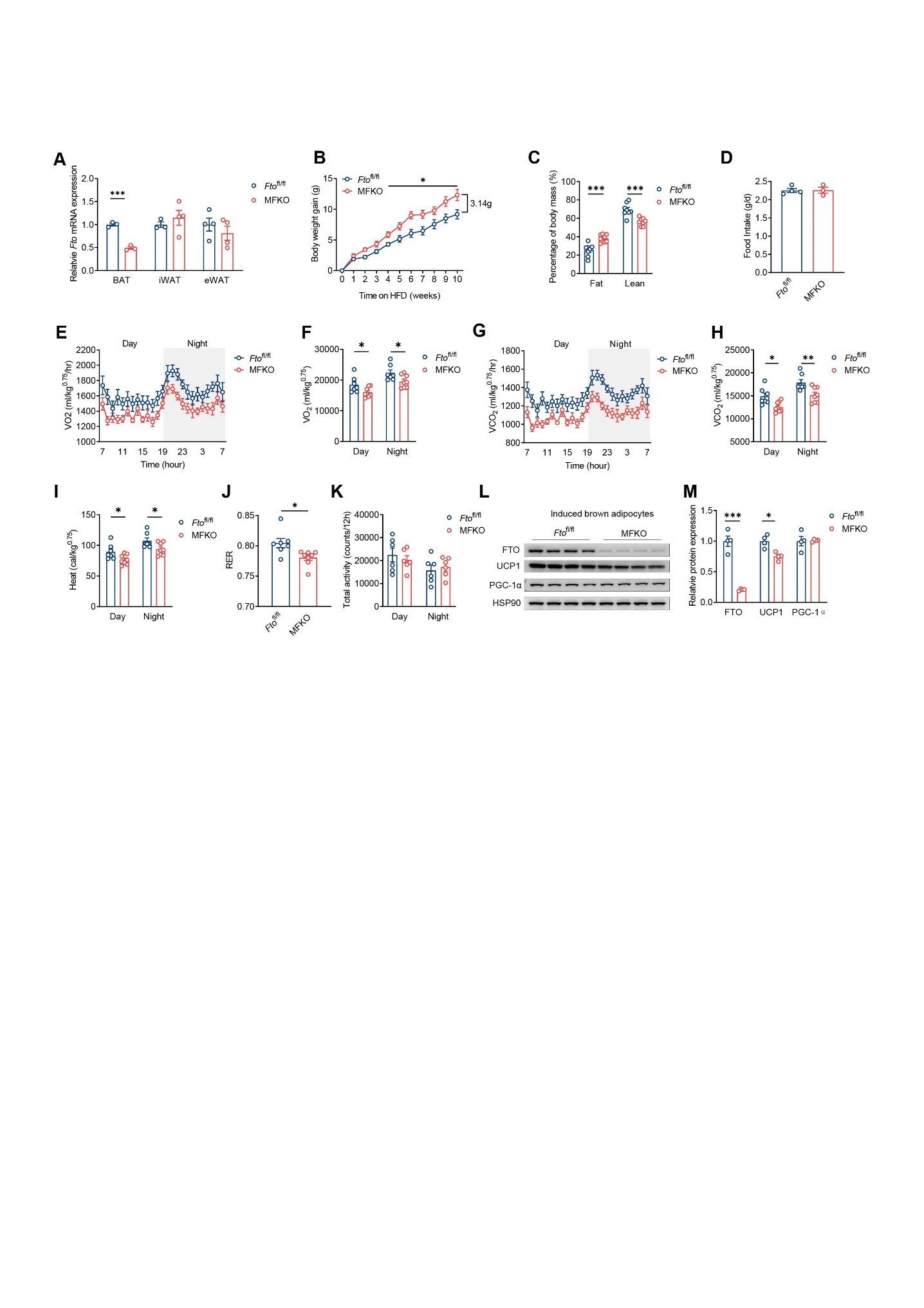
**Fig. S4. Brown adipocyte-specific knock-in homologous rs1421085 T>C variant enhances thermogenesis and resists HFD-induced adiposity.** (**A** to **E**)ThemRNA expression of *Fto* (A), *Irx3* (B), *Irx5* (C), *Irx6* (D), and *Rpgrip1l* (E) in the key tissues related to energy hemostasis of homologous rs1421085fl/fl (KIfl/fl) and wild-type mice (4-5 weeks old male mice; n = 3:4). (**F** and **G**) Body weight curve (F) and mass percentage (G) of *Ucp1*-KIfl/fl mice and KIfl/fl littermates under NCD (n = 12:7). (**H**) The representative H&E images of iWAT, eWAT and liver in *Ucp1*-KIfl/fl mice and KIfl/fl littermates under HFD (Scale bar, 100 μm). Data are mean ± s.e.m. of biologically independent samples.

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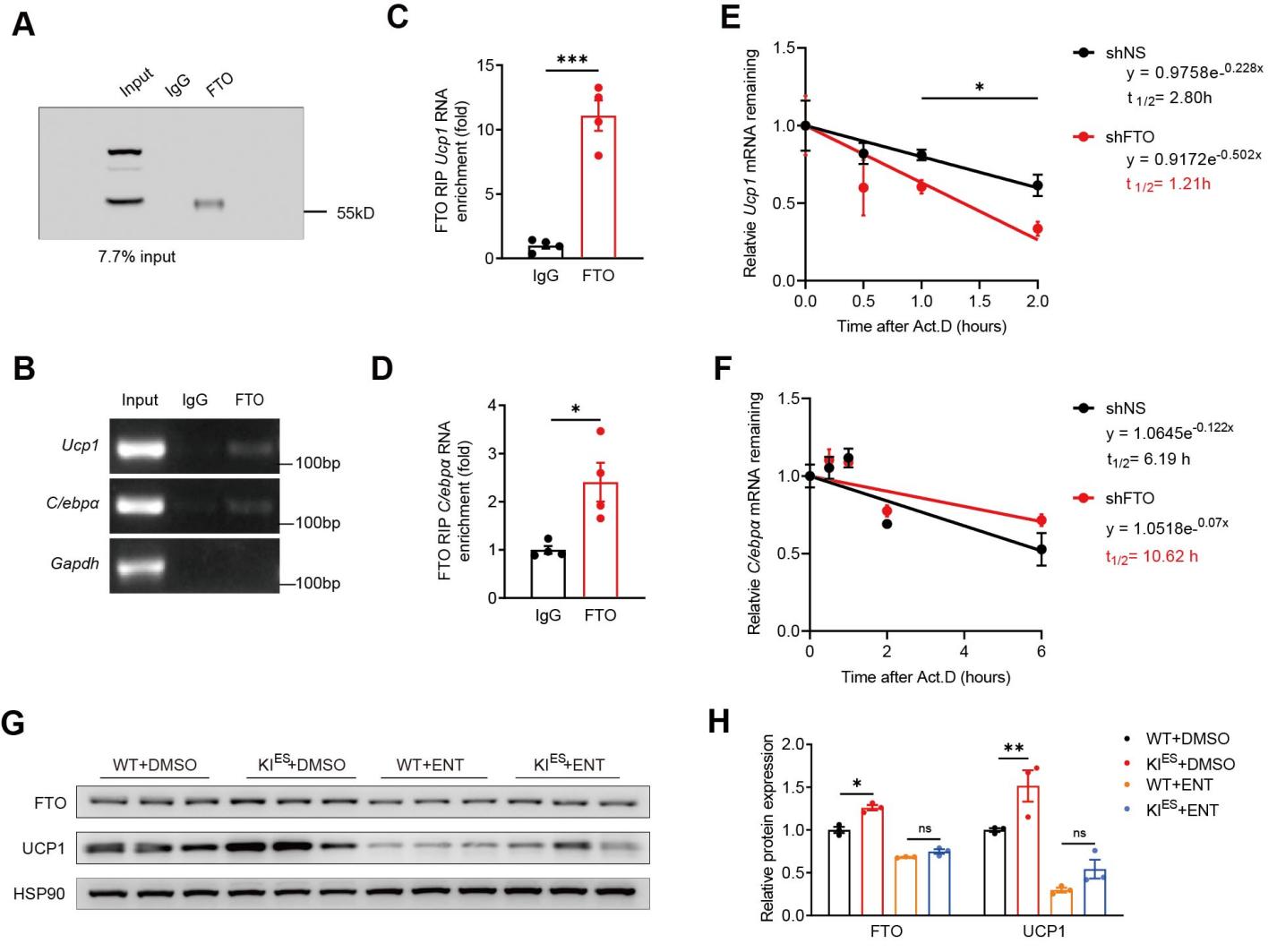
**Fig. S5. The mRNA expression of potential downstream effectors of rs1421085 T>C variation.** (A to D) The mRNA expression of *Irx3*, *Irx5*, *Irx6*, and *Rpgrip1l* in BAT tissues and induced mature brown adipocytes of indicated models (KIcas9, n = 6:7; KIES, n = 7:13; *Ucp1*-KIfl/fl, n = 15:7; induced brown adipocytes derived from KIES BAT SVF, n = 4:3). Data are mean ± s.e.m. of biologically independent samples; unpaired two-sided Student’s *t*-test. \* *P* < 0.05, \*\* *P* < 0.01.

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**Fig. S6. FTO enhances thermogenic capacity of brown adipocytes and partially medicates the increased thermogenesis in rs1421085 T>C knock-in model.** (**A**) The mRNA expressionof *Fto* and thermogenesis-related genes at different time point during brown adipocyte differentiation derived from BAT SVFs (n = 5). (**B**) Correlation analysis of the mRNA levels of *Fto* and *Ucp1* in (A). (**C** to **E**), Oil Red O staining (C), OCR measurement (D, E) of induced brown adipocytes derived from BAT SVFs with *Fto* knockdown. (**F**) Oil Red O staining of induced brown adipocytes derived from BAT SVFs with *Fto* overexpression. (**G**) The m6A abundance in induced mature brown adipocytes in the presence of Entacapone (ENT, 50 μM) or vehicle (n = 3). (**H**) The mRNA expression of thermogenesis-related genes in induced mature brown adipocytes in the presence of ENT or vehicle (n = 4).(**I** and **J**) The protein levels (I) and quantification analysis (J) of FTO and UCP1 in induced mature brown adipocytes in the presence of ENT or vehicle (n = 3). (**C** to **F**) The SVFs were infected with lentivirus 2 days before induction; MOI = 50; (C) and (F), Scale bar, 100 μm. Data are mean ± s.e.m. of biologically independent samples; unpaired two-sided Student’s *t*-test. \* *P* < 0.05, \*\* *P* < 0.01, \*\*\* *P* < 0.001.

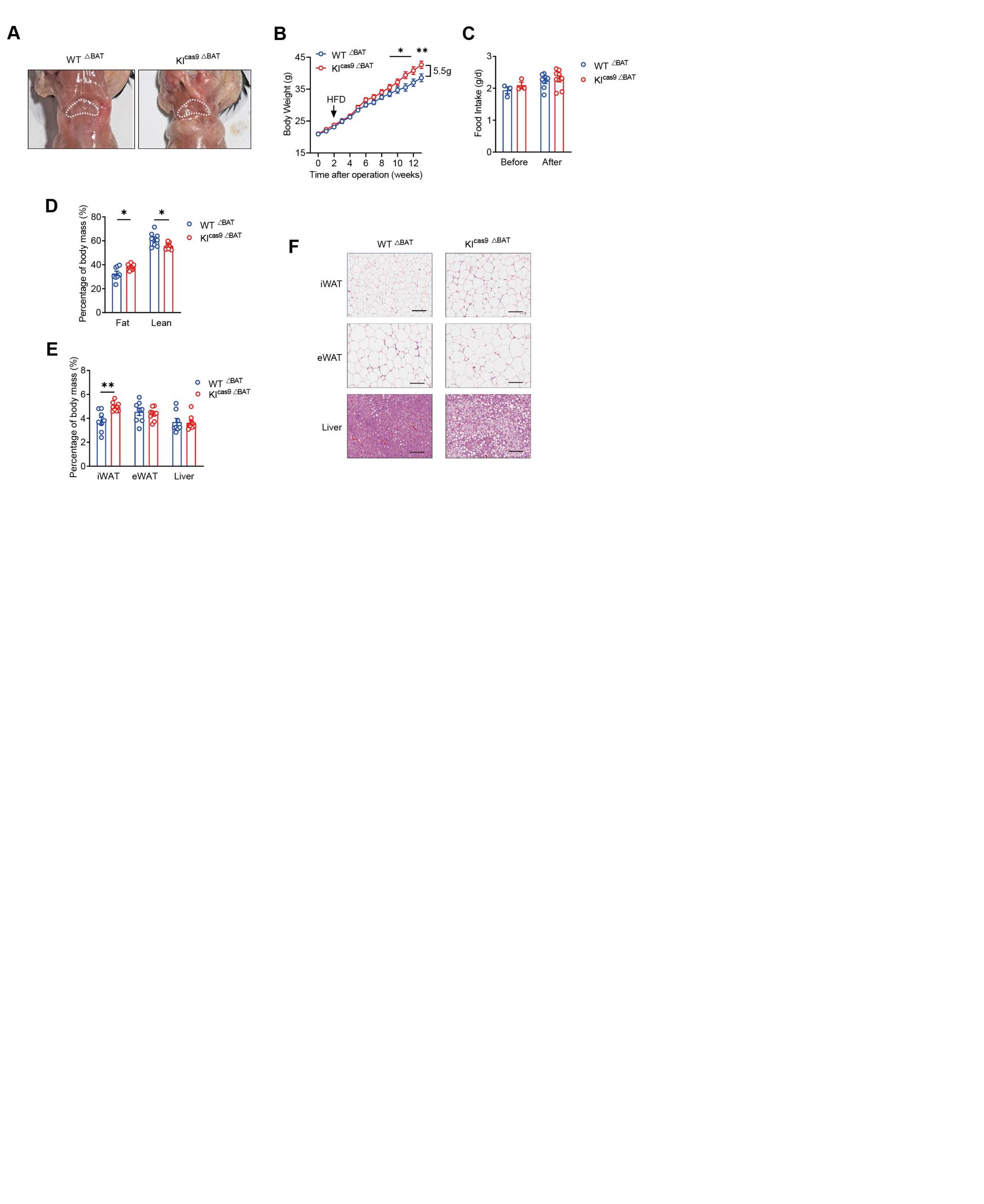
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**Fig. S7. *Fto* deficiency in BAT impairs thermogenesis and resists HFD-induced adiposity.** (**A**) The mRNA expression of *Fto* in indicated adipose tissues in 4-week-old female *Fto*fl/fl; *Myf5*-cre (MFKO) mice and *Fto*fl/fl littermates (n = 4:4). (**B** to **D**) Body weight (B), body composition (C) and average food intake (D) of MFKO mice and littermate controls under HFD challenge initiating from 9-week-old to 19-week-old (n = 9:12). (**E** to **K**) Whole-day and 12h O2 consumption (E, F), CO2 production (G, H), heat generation (I), RER (J) and total physical activities (K) were collected in MFKO mice and littermate controls under HFD challenge (n = 8:8; E-I, normalized to the body weight0.75). (**L** and **M**) The protein expression (L) quantification analysis (M) and of FTO, UCP1 and PGC-1α in induced mature brown adipocytes derived from BAT SVFs of MFKOand littermate control mice (n = 4:4). The data were presented as means ± s.e.m.; unpaired two-sided Student’s *t*-test. \* *P* < 0.05, \*\* *P <* 0.01, \*\*\* *P* < 0.001.

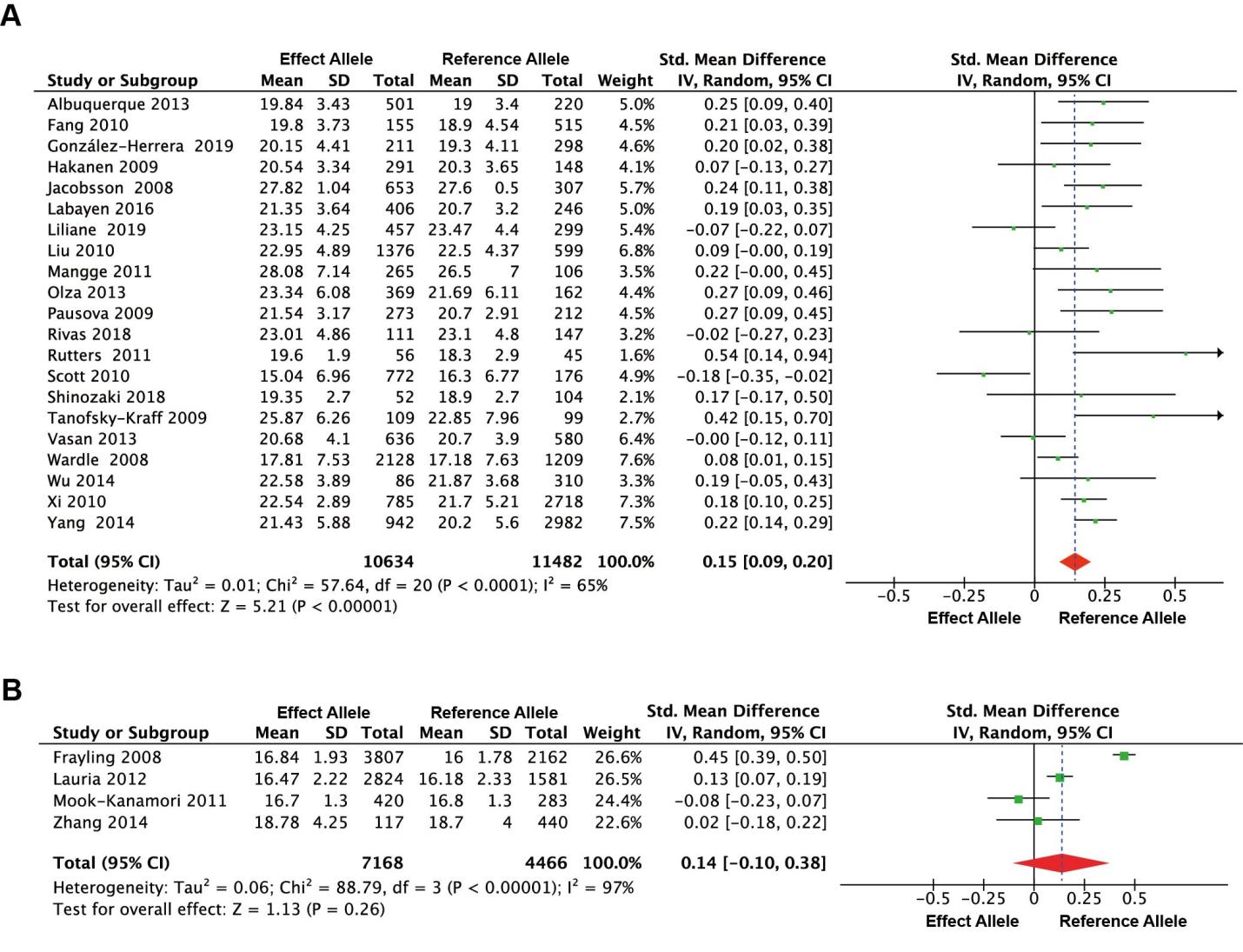
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**Fig. S8. FTO protein stabilizes Ucp1 mRNA and increase UCP1 protein expression.**

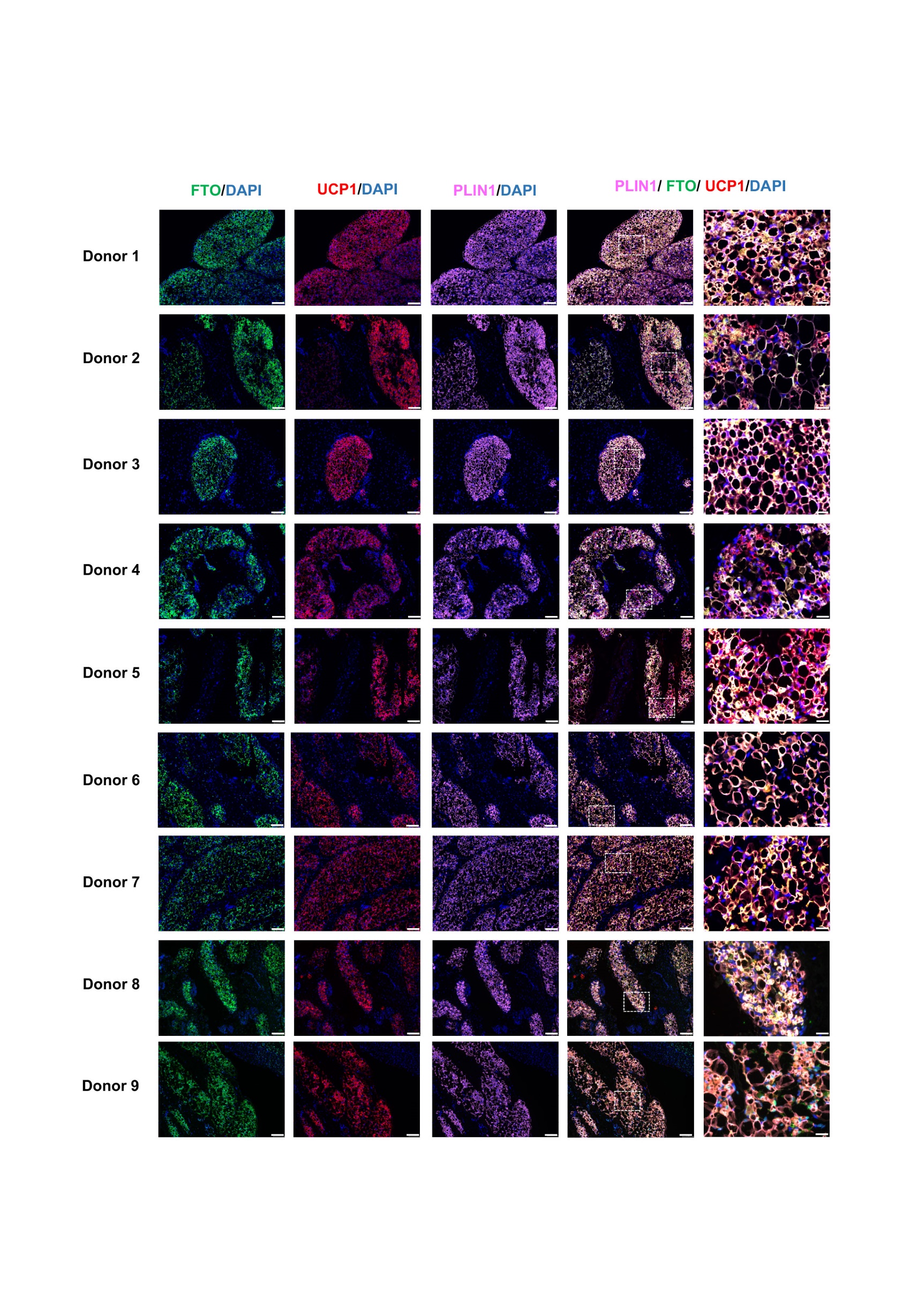
(**A** to **D**) RIP-qPCR analysis of the interaction of FTO protein and target mRNA in induced mature brown adipocytes. Representative immunoblots showing the products of IP by FTO antibody, with IgG as a negative control (A); AGE (B) and qPCR analysis (C, D) of *Ucp1* and *C/ebpα* mRNA abundance of FTO-IP products (n = 4). The enrichment of *Ucp1* and *C/ebpα* mRNA were normalized to input (7.7%). (**E** and **F**) Half-life analysis of *Ucp1* (E) and *C/ebpα* (F) mRNA in induced mature brown adipocytes with *Fto* knockdown. The BAT SVFs were infected with lentivirus 2 days before induction (MOI = 75); Actinomycin D (5 μg/ml) was added on the eighth day of induction; total RNA was isolated at indicated time points (n = 3-4); Calculated half-times t1/2 = In2/Kdecay. (**G** and **H**) The protein expression (G) and quantification analysis (H) of FTO and UCP1 in induced mature brown adipocytes derived from BAT SVFs of KIES and wild-type littermate mice in the presence of ENT or vehicle (n = 3:3). The data were presented as means ± s.e.m.; unpaired two-sided Student’s *t*-test. \* *P* < 0.05, \*\* *P* < 0.01, \*\*\* *P* < 0.001.



**Fig. S9. Surgical excision of intrascapular BAT largely reverses HFD-resistance phenotype of KIcas9 mice.** (**A**) Representative anatomy images showed no obvious regeneration of intrascapular BAT 16 weeks after BAT-surgical deletion in KIcas9 (KIcas9 ΔBAT) and WT littermate (WTΔBAT) mice. White dotted circle indicated interscapular BAT (iBAT) region. (**B** to **F**) Body weight curve (B), average food intake (C), body composition (D), mass percentage of indicated tissues (E), and representative H&E images of iWAT, eWAT and liver (F) inKIcas9 ΔBAT mice and WTΔBAT littermates after HFD (Scale bar, 100 μm). BAT-surgical deletion was performed to mice at 6-week-old, and HFD was provided to mice at 8-week-old; n = 7:9. The data were presented as means ± s.e.m.; unpaired two-sided Student’s *t*-test. \* *P* < 0.05, \*\* *P* < 0.01.

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**Fig. S10. The association of human FTO rs1421085 T>C variation frequency with BMI.** (**A** and **B**) The Forest plot of the association between BMI and human FTO rs1421085 polymorphism in populations with ages older than 8 year-old (A) and younger than 8 year-old (B), respectively. Effect allele, rs1421085\_C; reference allele, rs1421085\_T.

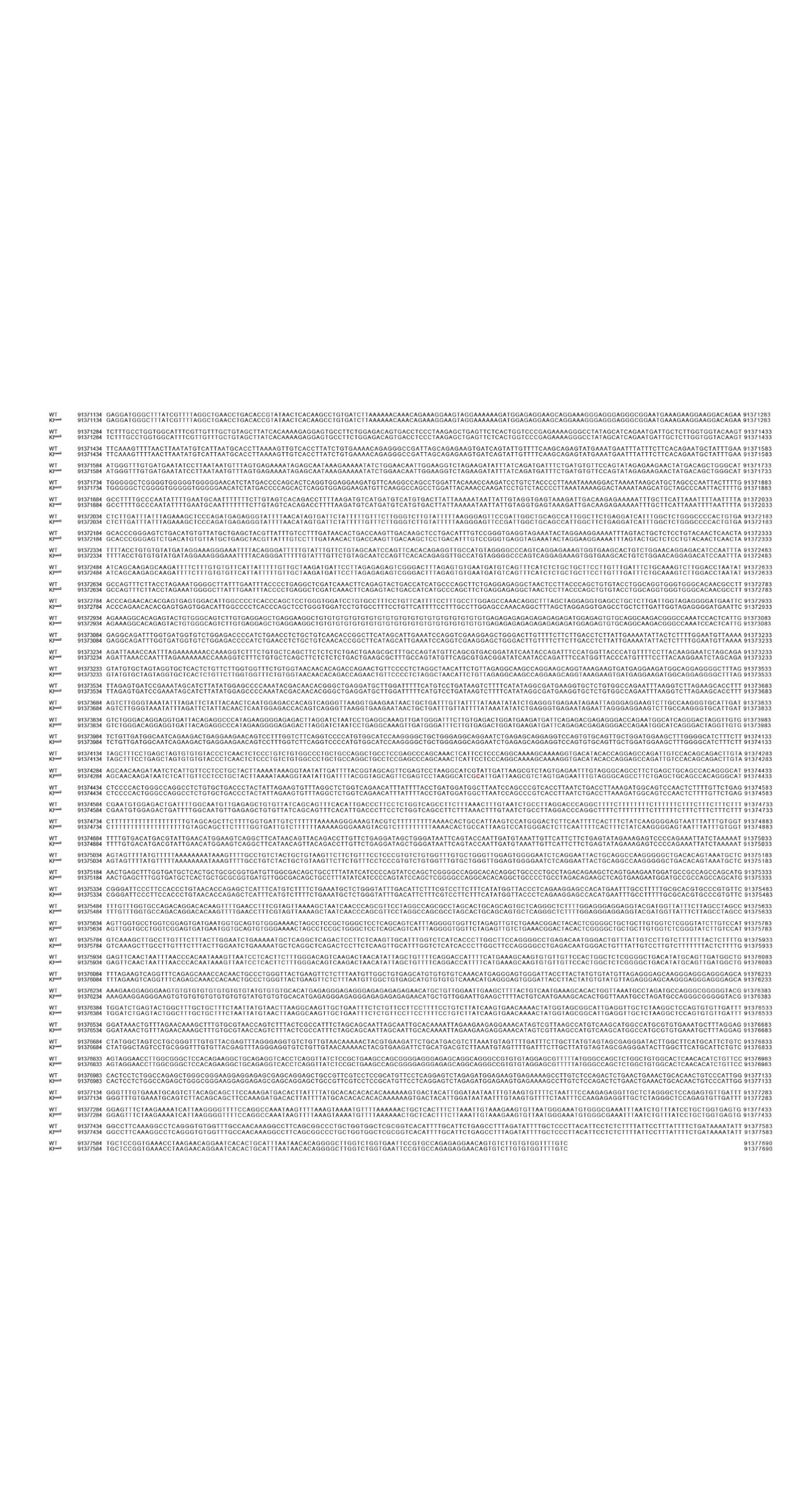
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**Fig. S11. The FTO and UCP1 were colocalized in human embryonic brown adipose tissue.** Representative immunofluorescence (IF) images of FTO (green) and UCP1 (red) in human embryonic brown adipose tissue. The nucleus was stained with DAPI (blue), lipid droplets was

stained with PLIN1 (pink). Left to right: FTO, UCP1, PLIN1, PLIN1/FTO/UCP1/DAPI (scale bar, 100μm), PLIN1/FTO/UCP1/PLIN1(scale bar, 20μm).

图形用户界面, 图表, 散点图

描述已自动生成**Fig. S12. The association of human FTO rs1421085 T>C variation frequency with ambient environmental temperature, elevation, and latitude.** (**A** and **B**) The correlation analysis of effect allele frequencies and CL-corrected (A) or CL-AVG corrected (B) annual mean earth skin temperature. (**C** and **D**) The correlation analysis of effect allele frequency and elevation (C) or longitude (D). Colors and symbols represented populations of different continents. Details of populations are listed in table S5.



**Fig. S13.** **Sanger sequencing of the 6 kb DNA region centered on the homologous rs1421085 locus in WT and KIcas9 mice.** The rs1421085 locus was emphasized in bold.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Coordinates** | **strand** | **MM\*** | **target\_sequence** | **PAM** | **distance** |  | **gene name** |
| chr8:91374360-91374382 | - | 0 | CTTAATCA[ATACGATGCCTT] | AGG | 13354 | I | Fto |
| chr3:5498973-5498995 | - | 4 | GTTTATAA[ATATGATGCCTT] | AGG | 14000 | - | 4930555M17Rik |
| chr14:39161796-39161818 | - | 4 | CTAAAACA[TGACGATGCCTT] | TGG | 58253 | I | Gm20642 |
| chr10:50467540-50467562 | - | 4 | ATGAATCC[ATAAGATGCCTT] | TGG | NA | - | NA |
| chr17:93375023-93375045 | + | 4 | CTGAATAA[TGACGATGCCTT] | CGG | NA | - | NA |
| chr11:90012399-90012421 | - | 4 | CTCCATCT[ATATGATGCCTT] | GGG | 9505 | - | Pctp |
| chr7:91069018-91069040 | + | 4 | ATTAAACC[ATATGATGCCTT] | AGG | 21666 | - | Dlg2 |
| chr2:117820099-117820121 | - | 4 | CTTGAGTA[ATATGATGCCTT] | GGG | 1807 | - | 4930412B13Rik |
| chr15:82106342-82106364 | - | 4 | CTCAAACA[AACCGATGCCTT] | TGG | 666 | I | Mei1 |
| chr10:130452922-130452944 | + | 4 | CTAAACAA[ATACCATGCCTT] | TGG | 0 | E | Vmn2r86 |

**Table S1. Top 10 off-target sites prediction**

*Notes.* MM: Mouse Musculus GRCm38/mm10. Data Analyze: <https://cctop.cos.uni-heidelberg.de:8043/>.

Referrence: https://cctop.cos.uni-heidelberg.de:8043/help.html

|  |  |
| --- | --- |
| **Genotyping Primers** | **sequence (5'→3'）** |
| mouse Fto-F | AGCCCAGCAAACTCATTCCT |
| mouse Fto-R | CAGATTAAGGTGACGGGCTGGAT |
| Fto sequencing | AAGGTGACATACACCAGGAGCC |
| loxP-F | GCCGATTAGCAGAGAAGTGATCAG |
| loxP-R | CTTGAACATCTTCCTCCACCTGAG |
| Cre-F | ATTTGCCTGCATTACCGGTCG |
| Cre-R | CAGCATTGCTGTCACTTGGTC |
|  | |
| **qPCR Primers** | **sequence (5'→3'）** |
| 36B4-F | GAAACTGCTGCCTCACATCCG |
| 36B4-R | GCTGGCACAGTGACCTCACACG |
| Ucp1-F | AGGCTTCCAGTACCATTAGGT |
| Ucp1-R | CTGAGTGAGGCAAAGCTGATTT |
| Fto-F | GACACTTGGCTTCCTTACCTG |
| Fto-R | CTCACCACGTCCCGAAACAA |
| Cox8b-F | GAACCATGAAGCCAACGACT |
| Cox8b-R | GCGAAGTTCACAGTGGTTCC |
| Cox7a-F | CAGCGTCATGGTCAGTCTGT |
| Cox7a-R | AGAAAACCGTGTGGCAGAGA |
| Elovl6 F | CCCGAACTAGGTGACACGAT |
| Elovl6 R | CCAGCGACCATGTCTTTGTA |
| C/EBPα F | GGTTTCGGGTCGCTGGATCTCTAG |
| C/EBPα-R | ACGGCCTGACTCCCTCATCTTAGAC |
| C/ebpβ-F | TTATAAACCTCCCGCTCGGC |
| C/ebpβ-R | TTCCATGGGTCTAAAGGCGG |
| Pgc1α-F | AGCCGTGACCACTGACAACGAG |
| Pgc1α-R | RGCTGCATGGTTCTGAGTGCTAAG |
| Cidea-F | TGCTCTTCTGTATCGCCCAGT |
| Cidea-R | GCCGTGTTAAGGAATCTGCTG |
| Pparγ2-F | GCATGGTGCCTTCGCTGA |
| Pparγ2-R | TGGCATCTCTGTGTCAACCATG |
| Dio2-F | AATTATGCCTCGGAGAAGACCG |
| Dio2-F | GGCAGTTGCCTAGTGAAAGGT |
| Prdm16-F | TGACGGATACAGAGGTGTCAT |
| Prdm16-R | ACGCTACACGGATGTACTTGA |
| Irx3-F | GGCAATGCTTATGGGAGCGA |
| Irx3-R | CGCTGTCTAAGTTTTCCAAATCG |
| Irx5-F | GCACGGATGAGCTCGGCCGCTC |
| Irx5-R | GGGTGATATCCCAAGGAACCTG |
| Irx6-F | CTCAGTATGAGTTCAAGGATGCTG |
| Irx6-R | CTCCCTTGTGGCATTCTTCCTG |
| Fabp4-F | ACACCGAGATTTCCTTCAAACTG |
| Fabp4-R | CCATCTAGGGTTATGATGCTC |
| Rpgrip1l-F | ACTGGAAGACAGATTTTTGCGT |
| Rpgrip1l-R | AACTAGCCGTATTAACTTGGTGG |

**Table S2. Primers for genotyping/qPCR.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Lentiviruse siRNA** | | | | |
| **Marker** | **Gene** | **Gene ID** | **TargetSequence** | **GC%** |
| shFTO-1 | Fto | NM\_011936 | GCTTGAAGACACTTGGCTT |  |
| shFTO-2 | Fto | NM\_011936 | GCATGTCAGACCTTCCTAA |  |
| shFTO-3 | Fto | NM\_011936 | GCTGAGGCAGTTCTGGTTT |  |
| shCtrl | NC |  | TTCTCCGAACGTGTCACGT | 52.6 |
|  | | | | |
| **shRNA and Primers** | | | | |
| **DNA primers** | **Sequence** | | | |
| shFTO-1 F | CCGGGCTTGAAGACACTTGGCTTCTCAAGAGAAAGCCAAGTGTCTTCAAGCTTTTTTG | | | |
| shFTO-1 R | AATTCAAAAAAGCTTGAAGACACTTGGCTTTCTCTTGAGAAGCCAAGTGTCTTCAAGC | | | |
| shFTO-2 F | CCGGGCATGTCAGACCTTCCTAATTCAAGAGATTAGGAAGGTCTGACATGCTTTTTTG | | | |
| shFTO-2 R | AATTCAAAAAAGCATGTCAGACCTTCCTAATCTCTTGAATTAGGAAGGTCTGACATGC | | | |
| shFTO-3 F | CCGGGCTGAGGCAGTTCTGGTTTCTCAAGAGAAAACCAGAACTGCCTCAGCTTTTTTG | | | |
| shFTO-3 R | AATTCAAAAAAGCTGAGGCAGTTCTGGTTTTCTCTTGAGAAACCAGAACTGCCTCAGC | | | |
| shCtrl F | CCGGTTCTCCGAACGTGTCACGTTTCAAGAGAACGTGACACGTTCGGAGAATTTTTTG | | | |
| shCtrl R | AATTCAAAAAATTCTCCGAACGTGTCACGTTCTCTTGAAACGTGACACGTTCGGAGAA | | | |
| CMV-F | CGCAAATGGGCGGTAGGCGTG | | | |

**Table S3. Primer sequences for lentivirus construction and validation.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **FTO & BMI> 8** | | | | | | | |
| **Number** | **Auther** | **Cohort name** | **Publication year** | **Country** | **Ethnicity** | **Genotype** | **DOI** |
| 1 | Josefin A. Jacobsson | National Childhood Obesity Centre at Karolinska University Hospital, | 2008 | Sweden | Swedish | rs9939609 | DOI: 10.1016/j.bbrc.2008.01.087 |
| 2 | I.Labayen | The HELENA cross- sectional study | 2016 | Vitoria, Spain | European | rs9939609 | DOI: 10.1016/j.numecd.2016.07.010 |
| 3 | Liliane dos SantosRodrigues | RPS Cohort of São Luís, Maranhão. | 2019 | Brazil | Brazilian | rs9939609 | DOI: 10.1016/j.jped.2019.05.006 |
| 4 | Gaifen Liu | Georgia Cardiovascular Twin study the LACHY study and the APEX study | 2010 | The Netherlands | European whites and African American | rs9939609 | DOI: 10.1186/1471-2350-11-57 |
| 5 | Bo Xi | Beijing Child and Adolescent Metabolic Syn- drome (BCAMS) study | 2010 | China | Chinese | rs9939609 | DOI: 10.1186/1471-2350-11-107 |
| 6 | Hongyun Fang | NAa | 2010 | China | Chinese | rs9939609 | DOI: 10.1186/1471-2350-11-136 |
| 7 | Josune Olza | NA | 2013 | Spain | European descent | rs9939609 | DOI: 10.1186/1471-2350-14-123 |
| 8 | Marian Tanofsky-Kraff | NA | 2009 | US | Non-Hispanic white and others | rs9939609 | DOI: 10.3945/ajcn.2009.28439 |
| 9 | Lizbeth González-Herrera | NA | 2019 | México | Mayan | rs1421085 | DOI: 10.1002/ajhb.23192 |
| 10 | S K Vasan | NA | 2013 | South India | Hiefly Dravidian in origin, with 1.2% being a mixture of Punjabi and Marwari ethnicity | rs9939609 | DOI: 10.1111/j.2047-6310.2013.00118.x |
| 11 | Maarit Hakanen | STRIP study | 2009 | Finland | Finn | rs9939609 | DOI: 10.1210/jc.2008-1199 |
| 12 | Femke Rutters | Dutch Caucasian cohort | 2011 | Dutch | Dutch Caucasian | rs9939609 | DOI: 10.1210/jc.2010-2413 |
| 13 | David Albuquerque | NA | 2013 | Portuguese | Portuguese | rs9939609 | DOI: 10.1371/journal.pone.0054370 |
| 14 | Junqing Wu | NA | 2014 | China | Chinese | rs9939609 | DOI: 10.1371/journal.pone.0098984 |
| 15 | Min Yang | NA | 2014 | China | Chinese | rs9939609 | DOI: 10.1371/journal.pone.0104574 |
| 16 | Robert A Scott | Growth, Exercise and Nutrition Epidemiological Study in preSchoolers (GENESIS) | 2010 | Greece | Greek | rs17817449 | DOI: 10.1038/ejhg.2010.131 |
| 17 | Zdenka Pausova | Saguenay Youth Study | 2009 | United Kingdom | Saguenay-Lac St Jean(French Canadian Founder Population) | rs9939609 | DOI: 10.1161/CIRCGENETICS.109.857359 |
| 18 | Ana Maria Obregón Rivas | NA | 2018 | Chile | Chilean | rs9939609 | DOI: 10.1016/j.nut.2018.03.001 |
| 19 | Keiko Shinozaki | Shunan Child Health Cohort Study | 2018 | Japan | Japanese | rs1558902 | DOI: 10.1111/ped.13578 |
| 20 | Jane Wardle | Twins’ Early Development Study（TEDS ） | 2008 | UK | United Kingdom children | rs9939609 | DOI: 10.1210/jc.2008-0472 |
| 21 | Harald Mangge | STYrian Juvenile OBesity Study (STYJOBS) | 2011 | Australia | European | rs9939609 | DOI: 10.1155/2011/186368 |
| a. Not available. | | | | | | | |
|  | | | | | | | |
| **FTO & BMI ≤ 8** | | | | | | | |
| **Number** | **Auther** | **Cohort name** | **Publication year** | **Country** | **Ethnicity** | **Genotype** | **DOI** |
| 1 | D O Mook-Kanamori | he Generation R Study | 2011 | Dutch | Dutch ethnicity | rs9939609 | DOI: 10.1007/BF03346689 |
| 2 | Meixian Zhang | Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study | 2014 | China | Chinese | rs9939609 | DOI: 10.1371/journal.pone.0097545 |
| 3 | Fabio Lauria | IDEFICS | 2012 | Italy | White European descent | rs9939609 | DOI: 10.1371/journal.pone.0048876 |
| 4 | Timothy M. Frayling | The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort and the Northern Finland 1966 birth cohort (NFBC1966) | 2008 | England and Finland | English and Finn | rs9939609 | DOI: 10.1126/science.1141634 |
|  | | | | | | | |
| **FTO& Birthweigt** | | | | | | | |
| **Number** | **Auther** | **Cohort name** | **Publication year** | **Country** | **Ethnicity** | **Genotype** | **DOI** |
| 1 | Abel López-Bermejo | Neonatal Unit of the Obstetrics and Gynecology Department of the Hospital Sant Joan de De ́u, | 2008 | Spain | Spanish | rs9939609 | DOI: 10.1210/jc.2007-2343 |
| 2 | Maarit Hakanen | STRIP study | 2009 | Finland | Finn | rs9939609 | DOI: 10.1210/jc.2008-1199 |
| 3 | Bo Xi | Beijing Child and Adolescent Metabolic Syn- drome (BCAMS) study | 2010 | China | Chinese | rs9939609 | DOI: 10.1186/1471-2350-11-107 |
| 4 | Nuananong Seal | NA | 2011 | America | American Indian | rs9939609 | DOI: 10.1089/gtmb.2010.0188 |
| 5 | Tanaka | NA | 2012 | Japan | Japanese | rs1558902 | DOI: 10.5551/jat.11940 |
| 6 | Fleur P Velders | Generation R Study | 2012 | The Netherlands | Northern European descent | rs9939609 | DOI: 10.1371/journal.pone.0049131 |
| 7 | Olivier S Descamps | NA | 2014 | Belgium | European whites | rs9939609 | DOI: 10.1186/s12863-014-0145-0 |
| 8 | Elina Molou | NA | 2015 | Greece | Greek | rs9939609 | DOI: 10.1515/jpem-2014-0320 |
| 9 | Eva Gesteiro | NA | 2016 | Spain | Caucasian | rs9939609 | DOI: 10.1007/s13105-016-0467-7 |
| 10 | Claudiu Mărginean | Obstetrics Gynecology Tertiary Hospital from Romania | 2016 | Romania | Romanian | rs9939609 | DOI: 10.1097/MD.0000000000005551 |
| 11 |  | GOCYb | 2020 | China | Chinese | rs1421085 |  |
| b. data from the Genetics of Obesity in Chinese Youngs (GOCY) study. | | | | | | | |

**Table S4. Study details included in Meta-anaylsis.**

|  |  |  |
| --- | --- | --- |
| **Populations** | **Study Fullname** | **Full name** |
| JPT | 1000Genomes | Japanese in Tokyo, Japan |
| KR | KOREAN population from KRGDB | KOREAN |
| CHB | 1000Genomes | Han Chinese in Beijing, China |
| CHS | 1000Genomes | Southern Han Chinese |
| KHV | 1000Genomes | Kinh in Ho Chi Minh City, Vietnam |
| VI | Vietnamese | Vietnamese |
| CDX | 1000Genomes | Chinese Dai in Xishuangbanna, China |
| BEB | 1000Genomes | Bengali from Bangladesh |
| SI | Siberian | Siberian |
| PJL | 1000Genomes | Punjabi from Lahore, Pakistan |
| QAT | Qatari | Qatari |
| DAG | Genome-wide autozygosity in Daghestan | Daghestan |
| LWK | 1000Genomes | Luhya in Webuye, Kenya |
| FIN | 1000Genomes | Finnish in Finland |
| EST | Genetic variation in the Estonian population | Estonian |
| NS | Northern Sweden | Northern Sweden |
| GWD | 1000Genomes | Gambian in Western Divisions in the Gambia |
| DA | The Danish reference pan genome | Danish |
| TSI | 1000Genomes | Toscani in Italia |
| ESN | 1000Genomes | Esan in Nigeria |
| NL | Genome of the Netherlands Release 5 | Netherlands |
| YRI | 1000Genomes | Yoruba in Ibadan, Nigeria |
| ITU | 1000Genomes | Indian Telugu from the UK |
| STU | 1000Genomes | Sri Lankan Tamil from the UK |
| GBR | 1000Genomes | British in England and Scotland |
| IBS | 1000Genomes | Iberian Population in Spain |
| MSL | 1000Genomes | Mende in Sierra Leone |
| ACB | 1000Genomes | African Caribbeans in Barbados |
| PUR | 1000Genomes | Puerto Ricans from Puerto Rico |
| CLM | 1000Genomes | Colombians from Medellin, Colombia |
| PEL | 1000Genomes | Peruvians from Lima, Peru |
| DOM | The PAGE Study | Dominican |
| CUB | The PAGE Study | Cuban |
| GIH | 1000Genomes | Gujarati Indian from Houston, Texas |
| ASW | 1000Genomes | Americans of African Ancestry in SW USA |
| MX | The PAGE Study | Mexican |
| CEU | 1000Genomes | Utah Residents (CEPH) with Northern and Western European Ancestry |
| MXL | 1000Genomes | Mexican Ancestry from Los Angeles USA |
| NHPI | The PAGE Study | Native Hawaiian |

**Table S5. Study details included in FTO rs1421085 T>C variant frequency analysis.**

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| --- | --- |
| **Abbreviation** | **Full name** |
| AGE | agarose gel electrophoresis |
| ARID5b | AT-rich interactive domain 5B |
| ATCC | American type culture collection |
| BAT | brown adipose tissue |
| BMI | body mass index |
| BMR | basal metabolic rate |
| C/ebpα | CCAAT-enhancer binding protein α |
| Cidea | cell death-inducing DNA fragmentation factor alpha-like effector A |
| Cox7a | cytochrome c oxidase subunit 7A1 |
| Cox8b | cytochrome c oxidase subunit 8B |
| CUX1 | cut like homeobox 1 |
| Dio2 | typeⅡiodothyronine deiodinase |
| DMEM | Dulbecco's modified eagle medium |
| DMSO | dimethyl sulphoxide |
| EGG Consortium | Early Growth Genetics Consortium |
| Elovl6 | elongase of very long chain fatty acids family member 6 |
| ENT | entacapone |
| ES cell | embryonic stem cell |
| eWAT | epididymal white adipose tissues |
| F12 | Ham's F12 nutrient medium |
| FBS | fetal bovine serum |
| FTO/Fto | fat mass and obesity associated |
| GWAS | genome-wide association studies |
| H&E | hematoxylin and eosin stain |
| HDL-c | high-density lipoprotein-cholesterol |
| HFD | high fat diet |
| iBAT | interscapular BAT |
| IBMX | 3-isobutyl-1-methylxanthine |
| IPGTT | intraperitoneal glucose-tolerance tests |
| IRX3/Irx3 | iroquois homeobox 3 |
| ITT | insulin tolerance test |
| iWAT | inguinal white adipose tissue |
| KI | knock-in |
| LDL-c | low-density lipoprotein-cholesterol |
| LGM | Last Glacial Maximum |
| m6A | N6-methyladenosine |
| NCD | normal chow diet |
| OCR | oxygen consumption rate |
| PBS | phosphate buffer solution |
| PCR | polymerase chain reaction |
| Pgc-1α | peroxisome proliferator activated receptor coactivator-1 alpha |
| PLIN1 | perilipin1 |
| Prdm16 | PR domain containing 16 |
| RER | respiratory exchange ratio |
| RIP | RNA immunoprecipitation |
| Rosi | rosiglitazone |
| SNP | single nucleotide polymorphism |
| SVF | stromal vascular fraction |
| T3 | triiodothyronine |
| TC | total cholesterol |
| TEM | transmission electron microscopy |
| TG | triglyceride |
| UCP1 | uncoupling protein 1 |
| WT | wild-type |
| △iBAT | excision of interscapular BAT |

**Table S6. Acronym and full name.**