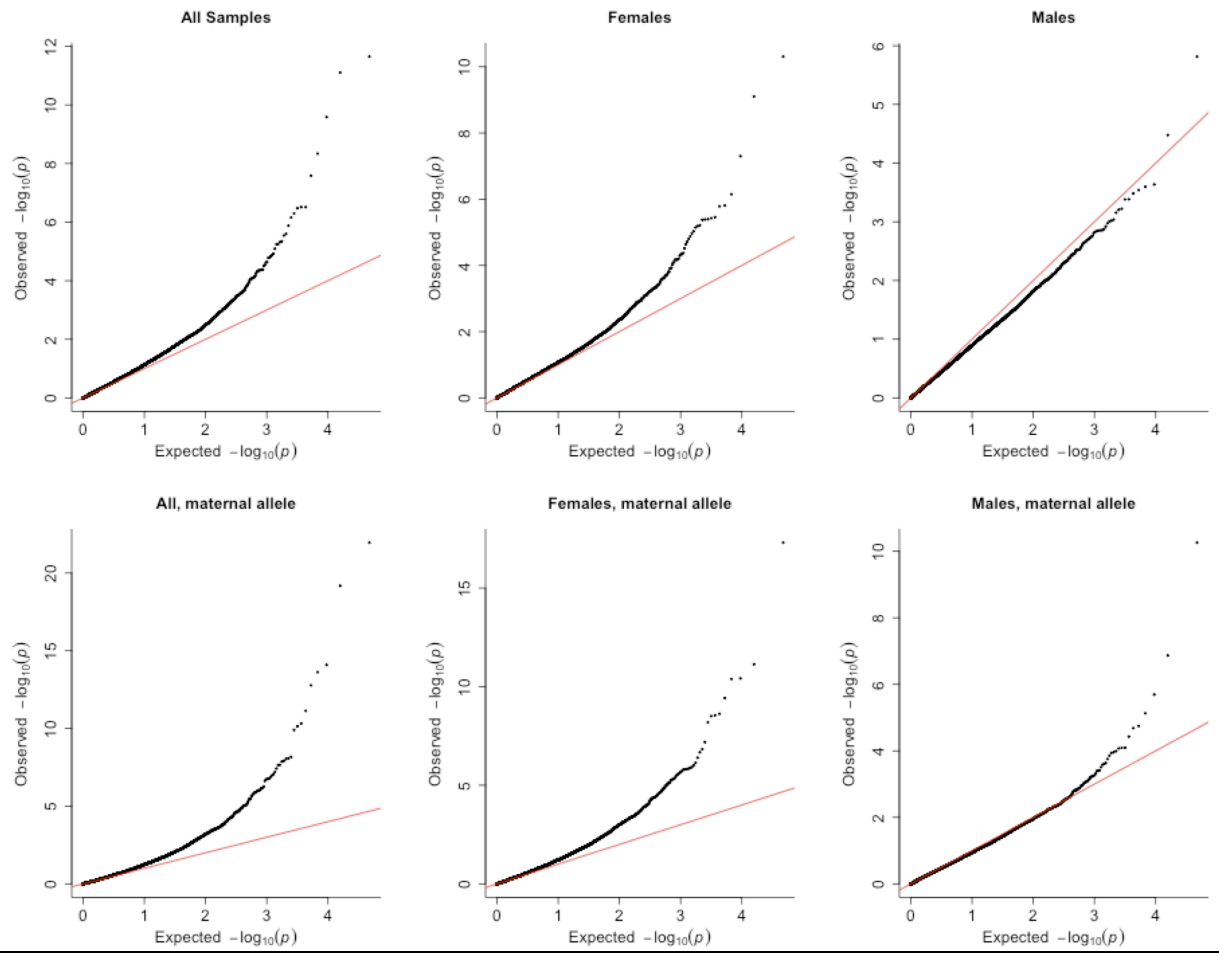
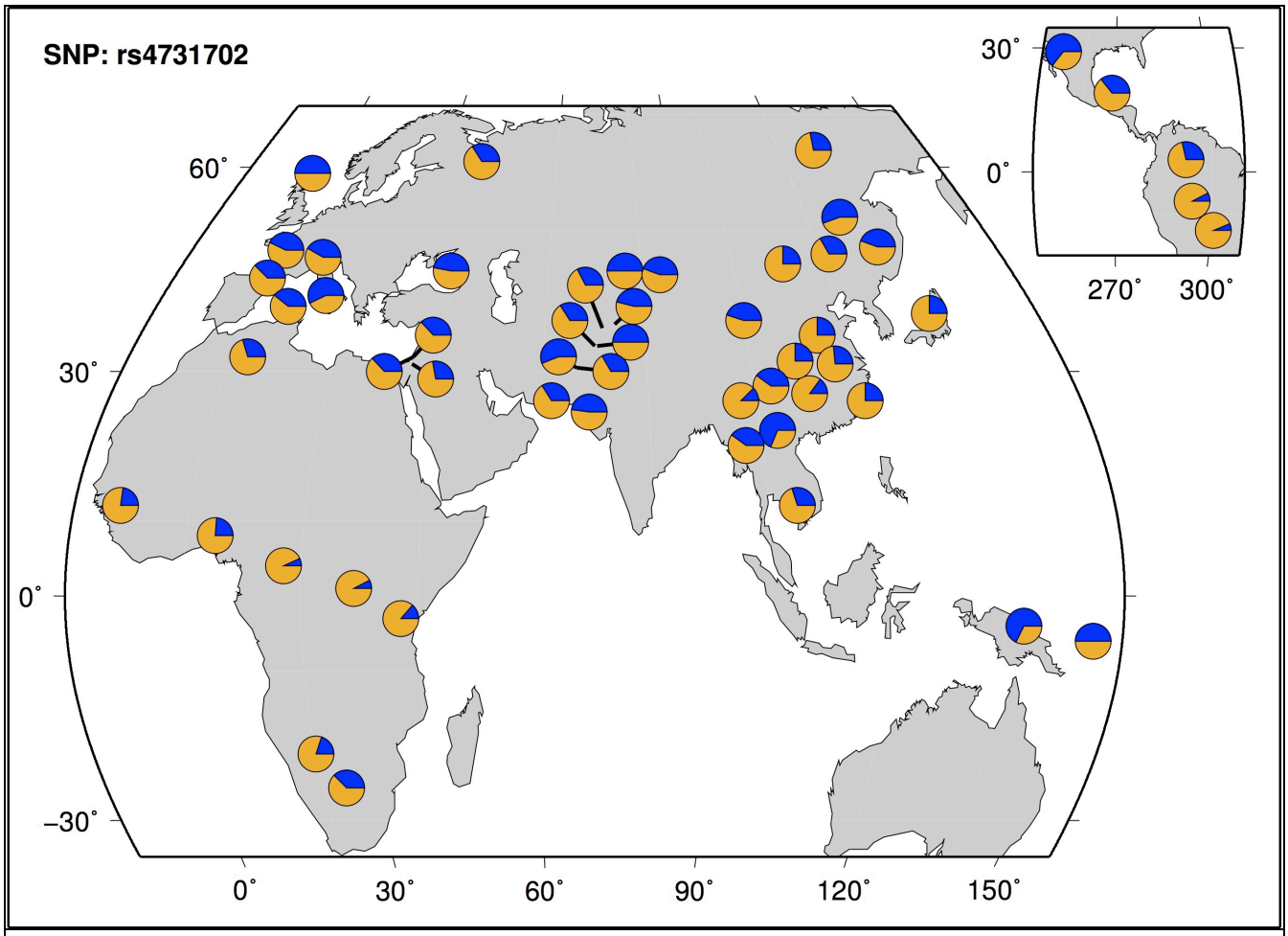


Supplementary Figure 1

Sex-stratified and parent of origin effects on the *KLF14 trans*- eQTL.

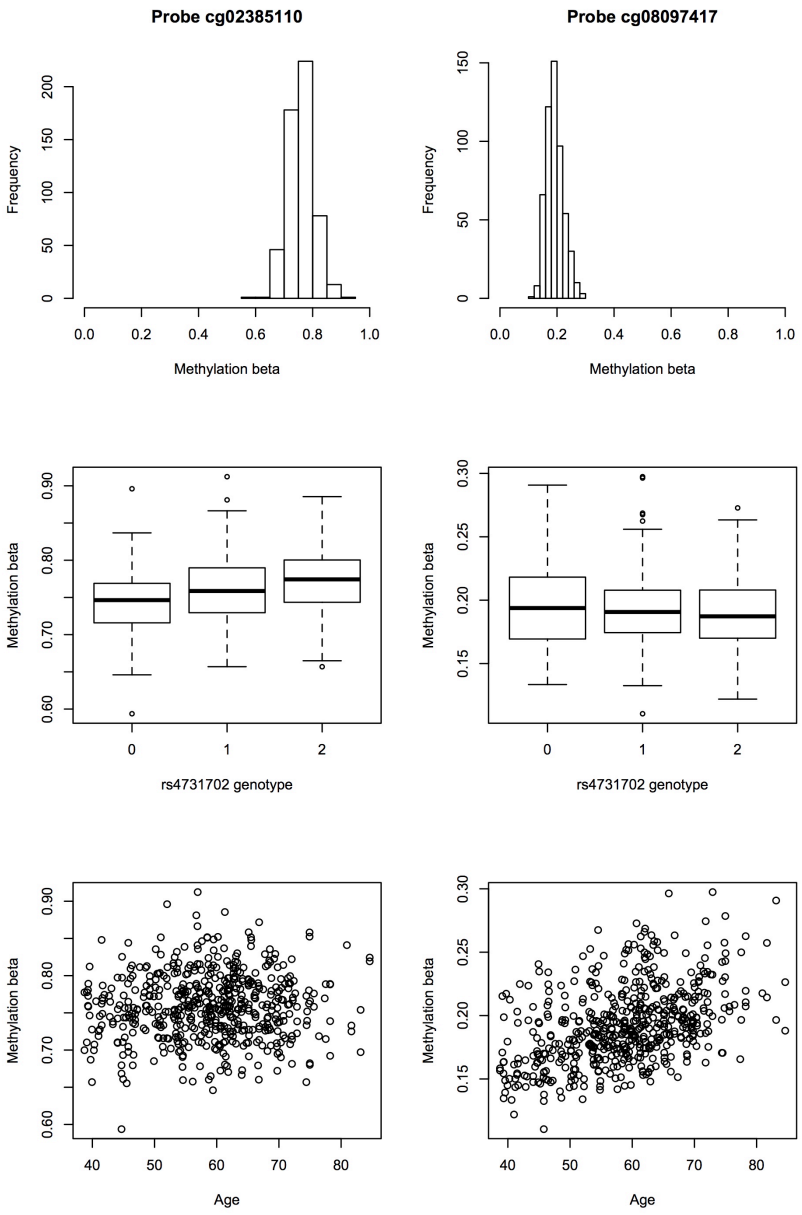
QQ-plots of association between rs473102 and all adipose probes in the deCODE dataset (female N=376 and male N=265). Top row displays results from standard genotypic tests, bottom row displays results for test of association to maternally inherited allele.



Supplementary Figure 2

Geographic distribution of rs4731702 in the Human Genome Diversity Panel.

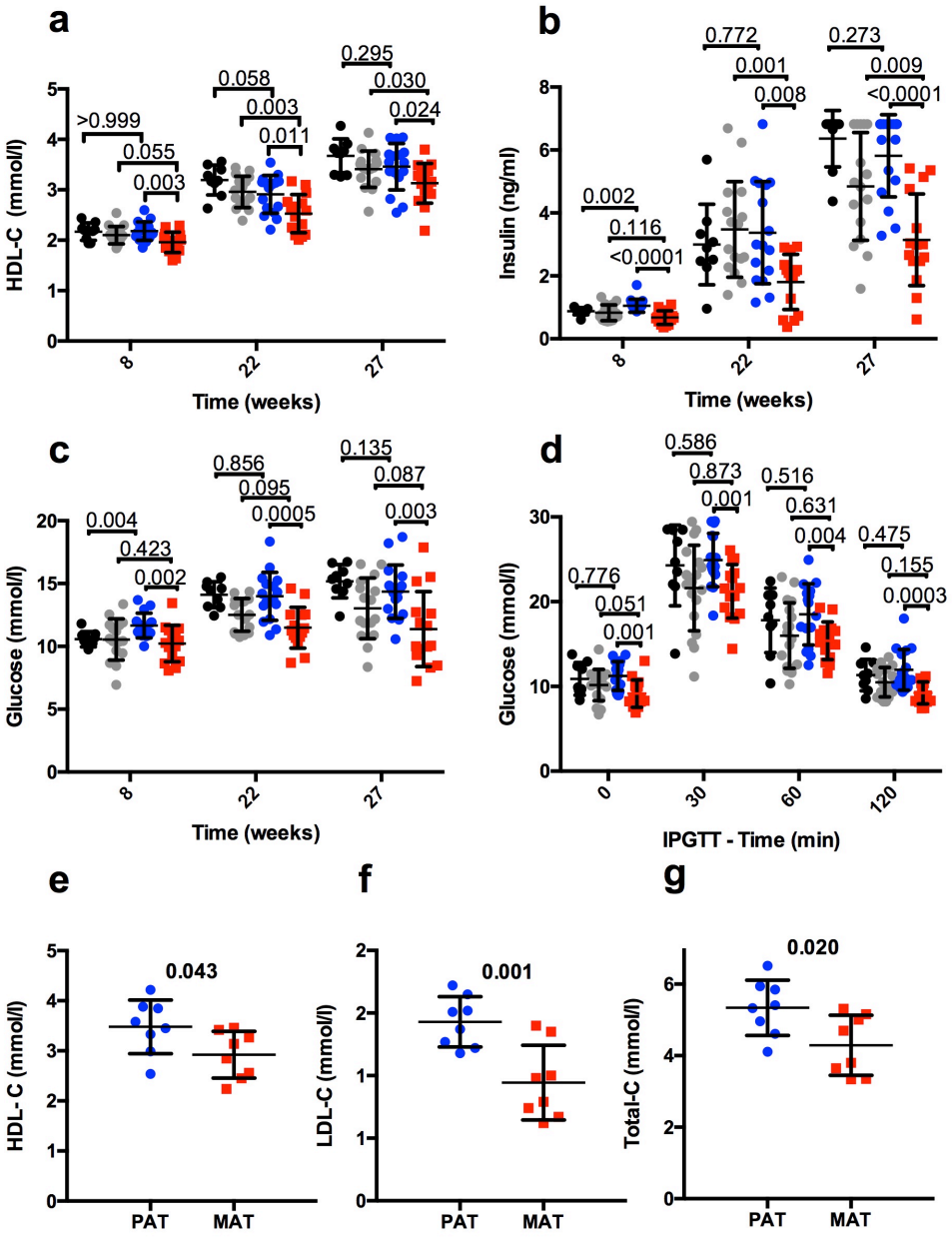
The ancestral T2D risk allele C is colored in orange, the derived allele T in blue. Figure generated from the HGDP Selection Browser at the Pritchard Lab (http://hgdp.uchicago.edu/cgi-bin/gbrowse/HGDP/). rs4731702 does not display evidence of positive selection in the HGDP – with global FST in the 80th percentile genome-wide and non-significant iHS and XP-EHH scores in all populations[71]. Tests for recent positive selection at rs4731702 in samples from the United Kingdom using the Singleton Density Score (SDS) were not significant (*P*=0.20), but the trend was towards a recent increase of the non-risk allele T[72]. By contrast, the *KLF14* transcript does exhibit evidence of intolerance to variation in the ExAC exome aggregation dataset[73] (ExAC constraint scores: Missense z= 2.32; Synonymous z = 2.41) suggesting coding changes in *KLF14* are under purifying selection.



Supplementary Figure 3

Distinct 450K methylation probes at the *KLF14 locus* are associated to rs4731702 vs age

Figure shows results for two 450K probes assayed in the TwinsUK adipose samples (N=603). cg02385110, which is ~3KB upstream of *KLF14* is shown on the left, cg08097417 which is at the *KLF14* transcription start site is shown on the right. The beta distributions (top row), association to rs4731702 (T2D risk allele homozygotes = 2) (middle row) and association to age (bottom row) differ between the two probes. cg02385110 has a higher mean beta value, is associated to rs4731702 (P=2.1x10^{-7}), and is not associated to age (P=0.64). In contrast, cg08097417 is not associated to rs4731702 (P=0.99) but is highly associated to age (P=3.6x10^{-61}). Associations were tested with linear mixed effect models adjusting for batch effects, BMI and famlly structure.



Red heterozygous maternally (MAT) inherited KO allele - equivalent to risk alleles

Blue heterozygous Paternally (PAT) inherited KO allele - equivalent to non-risk

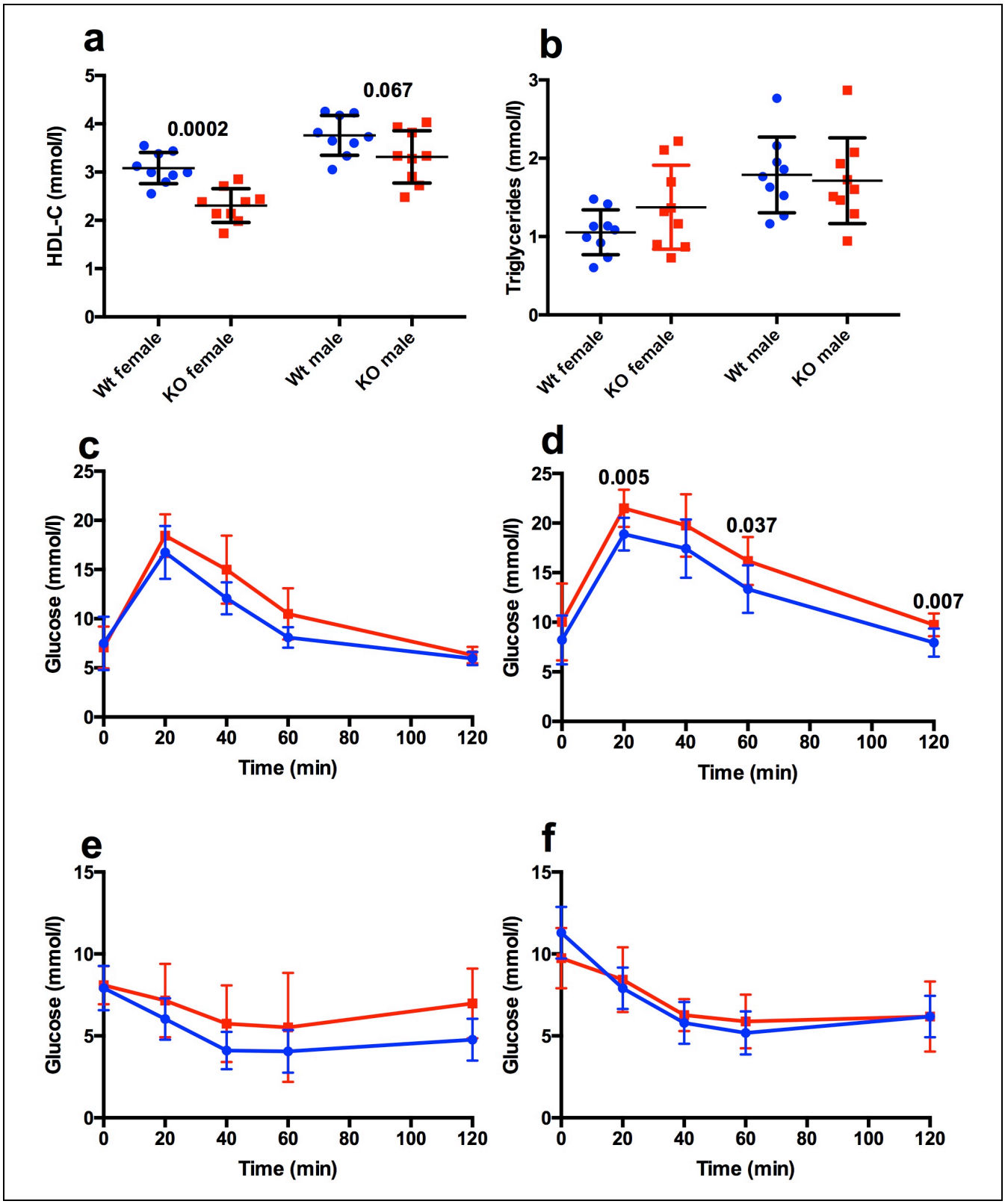
Grey and Black homozygous WILDTYPE (equivalent to non-risk) colonymate mice from the two stocks above:

Grey one wildtype allele from mothers carrying the KO and the other from a wildtype C57BL/6N male
Black one wildtype allele from fathers carrying the KO and the other from a wildtype C57BL/6N female

Supplementary Figure 4

Clinical chemistry analysis of heterozygous *Klf14*$^{tm1(KOMP)Vlcg}$ knockout mice

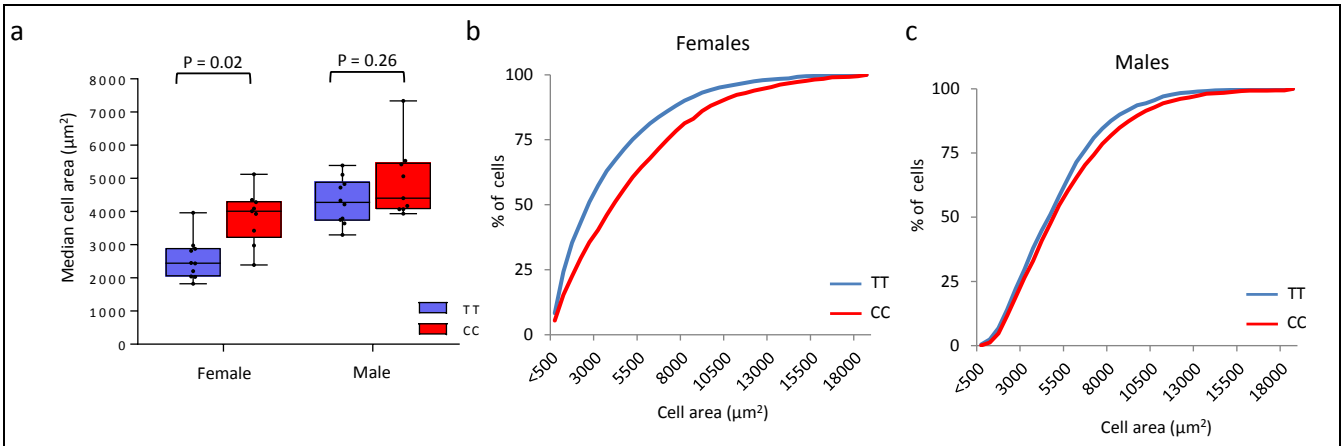
Clinical chemistry parameters were measured in male knockout C57BL/6N *Klf14* mice and their wildtype controls. Since *Klf14* is mono-allelically maternally expressed in mouse and human, we compared heterozygous mice that had inherited the deletion allele from their mother (**heterozygous-MAT**, expressing the deletion) with heterozygous mice that had inherited the deletion allele from their father (**heterozygous-PAT**, not expressing the deletion). We also compared the two groups to their own homozygous wildtype colonymate controls (**wildtype-MAT** and **wildtype-PAT**). This was because we used two separate crosses to produce the MAT and PAT carrier cohorts; one stock from heterozygous mothers and one from heterozygous fathers, each crossed to wildytpe C57BL/6N mice. Mice were fed a standard diet and then switched at 18-weeks of age to a 45kcal% high fat diet. Comparing across the timecourses for **(a)**, HDL-C; **(b)**, insulin; **(c)**, glucose; **(d),** IPGTT by calculating area under the curve, base-lined to t=0 values (data not shown), and analysing with a 1-way ANOVA non-parametric Kruskal-Wallis test and Dunns multiple comparison test we found: that HDL-C **(a)** was lower in MAT compared to either PAT or wildtype-MAT (p= 0.0055 and 0.0086 respectively) and that wildtype-PAT compared to PAT was not significantly (p=0.56) different; that insulin **(b)** was lower in MAT compared to either PAT or wildtype-MAT (p= <0.0003 and 0.0020 respectively) and that wildtype-PAT compared to PAT was not significantly (p>0.99) different; that Glucose **(c)** was lower in MAT compared to PAT (p= <0.0001) and that wildtype–MAT and wildtype-PAT compared to MAT and PAT respectively were not significantly (p=0.79 and >0.99 respectively) different; and that for an IPGTT **(d)** *none* of the group comparisons were significantly different (p>0.99) to each other. Then to examine effects at specific times for **(a)** HDL-C, **(b)** insulin, **(c)** glucose and **(d)** IPGTT individual pairwise comparisons were made at each timepoint using a Mann-Whitney 2-tailed t-test and were significantly reduced in the MAT group compared to PAT group at 8, 22 and 27 weeks in **(a,b,c)** and at all timepoints in **(d)**. The MAT groups were also significantly lower compared to wildtype-MAT for HDL-C and insulin at 22 and 27 weeks. Values are expressed as mean ± SD and in **(a,b,c)** wildtype-MAT n=16, wildtype-PAT n=9, heterozygous-MAT n=15, heterozygous-PAT n=16 and in **(d)** wildtype-MAT n =19, wildtype-PAT n=10, MAT n=16, PAT n=16. For **(e)**, HDL-C; **(f)**, LDL-C and **(g)**, total cholesterol was measured in a 33-week blood sample collected under terminal anaesthetic and was significantly, using an unpaired 2-tailed t-test, reduced in heterozygous-MAT mice compared to PAT mice. Values are expressed as mean ± SD (PAT N =8, MAT N =8). Wildtype MAT grey, wildtype PAT black, MAT KO red, PAT KO blue lines and fill.


a
HDL-C (mmol/l)
0.0002
0.067
Wt female
KO female
Wt male
KO male
b
Triglycerides (mmol/l)
Wt female
KO female
Wt male
KO male
c
Glucose (mmol/l)
Time (min)
d
Glucose (mmol/l)
0.005
0.037
0.007
Time (min)
e
Glucose (mmol/l)
Time (min)
f
Glucose (mmol/l)
Time (min)

Supplementary Figure 5

Clinical chemistry and histological analyses of global CRISPR-Cas9 KO mice

Clinical chemistry parameters were measured in female and male CRISPR-Cas9 knockout (KO) C57BL/6J *Klf14* mice and their wildtype (Wt) controls. Mice were fed a standard diet throughout their lifetimes. **(a)**, HDL-C at 12 weeks of age was significantly reduced in female and reduced with borderline significance in male (unpaired two-tailed t-test). **(b),** triglycerides at 12 weeks of age were not significantly different in females or males (unpaired two-tailed t-test). Comparing across the IPGTT timecourses **(c and d)** by calculating area under the curve, base-lined to t=0 values, (data not shown) and analysing using a Mann-Whitney two-tailed t-test showed there was no significant difference between male or female KO and wildtype mice (p=0.23 and 0.93 respectively). Then in order to make comparisons at each timepoint for **(c and d),** individual pairwise Mann-Whitney 2-tailed t-tests were carried out, and as for AUC no differences were found in the female data, although in males glucose levels were nominally higher at 20, 60 and 120 minutes of the test. **(e and f)**, ITT at 16 weeks was not significantly changed between wildtype and KO groups of either female (e) or male (f) mice, analysed by 2-way ANOVA with repeated measures and Bonferroni correction. Values are expressed as mean ± SD and in **(a,b)** female wildtype n=9, female KO n=9, male Wt n=9, male KO n=9 and in **(c,d,ef)** female wildtype n=9, female KO n=8, male Wt n=9, male KO N=9. Wildtype mice in blue lines and fill, KO mice in red lines and fill.



Supplementary Figure 6

Gluteal adipose tissue of T2D risk allele homozygotes contains fewer, larger mature adipocytes compared to non-risk allele homozygotes**.**

Adipocyte cell area in histological sections of subcutaneous gluteal adipose biopsies from the Oxford BioBank. **a,** Median cell area in female (N=18, mean ± SEM) and male (N=18, mean ± SEM) gluteal biopsies stratified by genotype at rs4731702. **b,** Cumulative frequency distribution of adipocyte cell area in females (N=18). **c,** Cumulative frequency distribution of adipocyte cell area in males (N=18). Statistical significance was assessed using a Wilcoxon signed-rank two-sided test.

Supplementary Material

Regulatory variants at *KLF14* influence type 2 diabetes risk via a female-specific effect on adipocyte size and body composition

Contents:

Supplementary Note

Natural selection at *KLF14*

Despite the geographic range in allele frequency, rs4731702 does not display evidence of positive selection by several tests. rs4731702 is not under positive selection in the Human Genome Diversity Panel (HGDP) – with global FST in the 80th percentile genome-wide and non-significant iHS and XP-EHH scores in all populations[1]. Tests for recent positive selection at rs4731702 in samples from the United Kingdom using the Singleton Density Score (SDS) were not significant (*P*=0.20), but the trend was towards a recent increase of the non-risk, derived allele T[2]. By contrast, the *KLF14* transcript does exhibit evidence of intolerance to variation in the ExAC exome aggregation dataset[3] (ExAC constraint scores: Missense z= 2.32; Synonymous z = 2.41) suggesting coding changes in *KLF14* are under purifying selection.

TwinsUK Data Extended Methods

Biopsy collection Biopsies and blood samples from 856 healthy female twins from the TwinsUK cohort were collected within the MuTHER project[4]. In short, subcutaneous adipose tissue punch biopsies from a photo-protected area of the stomach adjacent and inferior to the umbilicus were obtained from consented individuals and dissected to yield adipose and skin biopsies. Peripheral blood samples were also collected as part of the study and Lymphoblastoid Cell Lines (LCLs) generated via transformation of the B-lymphocyte fraction with Epstein-Barr Virus (EBV).

Genotypes The TwinsUK samples were genotyped on a combination of platforms (HumanHap300, HumanHap610Q, 1M-Duo and 1.2MDuo Illumina arrays) and samples were imputed using the 1000 Genomes[5] phase 1 reference panel using IMPUTE2[6] as described previously[7].

RNA-sequencing and quantification Adipose, skin, LCL and whole blood TwinsUK RNA samples were sequenced and quantified as previously described[7]. In short, reads were mapped to Gencode version 10 and variation in sequencing depth between samples was corrected by normalizing the number of reads to the median number of well-mapped reads. We used only exons that were quantified in more than 90% of the individuals. Exons were rank-normal transformed for downstream analysis.

Preparation, quality control and genetic analysis of large cohorts used in Sex x SNP interaction analysis.

UK Biobank: The UK Biobank recruited more than 500,000 people aged 37-73 years (99.5% were between 40 and 69 years) from across the country in 2006-10. Participants provided a range of information via questionnaires and interviews (such as demographics, health status, and lifestyle); anthropometric measurements, blood pressure readings, and blood, urine and saliva samples were taken for future analysis. This has been described in more detail elsewhere[8]. Genotype data from the May 2015 release was available for a subset of 152,249 participants from UK Biobank. In addition to the quality control metrics performed centrally by UK Biobank, we defined a subset of "white European" ancestry samples (n=120,286) as those who both self-identified as white British and were confirmed as ancestrally "Caucasian" using principal components analyses of genome-wide genetic information. A maximum of 118,193 individuals (62,165 females and 56,027 males) with genotype and valid BMI, height, waist, hip, and type 2 diabetes measures were available for downstream analyses. Prevalent type 2 diabetes status was defined using self-reported medical history and medication in UK Biobank participants[9]. The genotypes of the genetic variant were extracted from UK Biobank's imputation dataset. We excluded individual genotypes if the genotype probability was less than 0.9. We converted the BMI, height, waist, and hip measures to a normal distribution by inverse normalising the variables. Each analysis was adjusted for covariates: age, age^2, sex, six (within UK) ancestry principal components, and array used to measure genotypes.

GERA: The Resource for Genetic Epidemiology on Adult Health and Aging (GERA) is a large multi-ethnic population-based cohort, created for investigating the genetic and environmental basis of age-related diseases [dbGaP phs000674.p1]. T2D status is based on ICD-9 codes in linked electronic medical health records, and quality control of these data have been previously described[10]. We extracted 6,961 T2D cases and 13,922 controls that were genotyped using a custom array to maximise coverage of common and low-frequency variation in non-Hispanic whites[11]. We used multi-dimensional scaling in PLINK[12] to obtain three principal components to correct for population structure. The autosomal genotype scaffold was then pre-phased using SHAPEITv2.5[13]. The resulting haplotypes were imputed, using an updated implementation of IMPUTE[6], up to the Haplotype Reference Consortium panel[14]. The interaction of sex with rs4731702 was evaluated in a logistic regression model, with adjustment for the three principal components as covariates.

WTCCC/ UKT2D (The Wellcome Trust Case Control Consortium/United Kingdom Type 2 Diabetes Genetics consortium). Details of the samples and quality control of GWAS data have been previously described[15],[15]. The clean genotype data was pre-phased using SHAPEITv2.5[13]. The resulting haplotypes were imputed, using an updated implementation of IMPUTE[6], up to the Haplotype Reference Consortium panel[14]. The genotypes of the genetic variant were extracted from imputed dataset. We excluded individual genotypes if the genotype probability was less than 0.9. The interaction of sex with rs4731702 was evaluated in a logistic regression model, with adjustment for sex as covariate.

Construction of Mouse Models

Klf14$^{tm1(KOMP)Vlcg}$ **Deletion Mice** The mouse strain (*Klf14*$^{tm1(KOMP)Vlcg}$) used in this project was generated from targeted embryonic stem (ES) cells for *Klf14* obtained from the KOMP repository www.komp.org, a NCRR-NIH supported mouse repository. The U42-RR024244 ES cells from which this mouse was generated were created by Velocigene from funds provided by the trans-HIH Knock-out Mouse Project (KOMP) (Grant number 5U0101HG004085). Live mice were imported on a C57BL/6NTac USA background and rederived into the MRC Harwell Mary Lyon Centre specified pathogen free (SPF) facility and maintained on C57BL/6NTac. *Klf14*$^{tm1(KOMP)Vlcg}$ mice were kept and studied in accordance with UK Home Office legislation and local ethical guidelines issued by the Medical Research Council (Responsibility in the Use of Animals for Medical Research, July 1993; home office license 30/3146).

CRISPR-Cas9 whole-body knockout The CRISPR-Cas9 whole-body knockout mouse was generated using a guide RNA (gRNA) designed to target the beginning of the *Klf14* gene (**Supplementary Table 10**). In vitro transcribed Cas9 mRNA (100 ng/µl; TriLink BioTechnologies) and gRNA (50 ng/µl) were injected into cytoplasm of fertilized oocytes from C57BL/6J mice. Genomic DNA samples from founder mice were screened for frameshift mutations by PCR and confirmed by Sanger sequencing (primers in **Supplementary Table 11**). The most commonly detected mutant allele was a 7-bp deletion, 5'-GAGTGCC-3', and founder mice with this allele were selected for breeding to obtain litters with both homozygous knockout mice and wild-type mice for experiments.

CRISPR-Cas9 conditional knockout The CRISPR-Cas9 conditional knockout mouse was generated using two gRNAs designed to target sites upstream and downstream of the *Klf14* gene; two single-strand DNA oligonucleotides bearing loxP sequences along with 80-nt homology arms matching the target sites were synthesized (IDT) (**Supplementary Table 10**). In vitro transcribed Cas9 mRNA (100 ng/µl) and gRNAs (25 ng/µl each) and single-strand DNA oligonucleotides (100 ng/µl each) were injected into cytoplasm of fertilized oocytes from C57BL/6J mice. Genomic DNA samples from founders were screened for correct loxP sequences flanking the *Klf14* gene by PCR and confirmed by Sanger sequencing (primers in **Supplementary Table 11**). Offspring of founder mice with correct loxP sequences were screened to identify those in which the two loxP sequences segregated on the same chromosome. Those mice were bred for multiple generations with *Adipoq*-Cre mice of the C57BL/6J background [B6;FVB-Tg(Adipoq-cre)1Evdr/J, The Jackson Laboratory] to obtain litters with both homozygous *Klf14* loxP knock-in mice and wild-type mice that were also positive for *Adipoq*-Cre for experiments. The presence of the *Adipoq*-Cre allele was confirmed by PCR (primers in **Supplementary Table 11**).

Gene Expression in Mouse Models

Klf14$^{tm1(KOMP)Vlcg}$ **Deletion Mice** RNA was extracted from snap frozen subcutaneous tissue, isolated at the same time of day, using phenol chloroform and a RNeasy Mini Kit (Qiagen, UK) according to the manufacture's instructions. RNA integrity was assessed using a 2100 Bioanalyzer (Agilent Technologies) and samples with a RNA

integrity (RIN) number of 8 and above (N=4/group) were selected for RNASeq analysis. These samples were sent to the Oxford Genomics centre where a quality control report was generated and a library of read data compiled. Differentially expressed genes were identified by comparing the RNAseq profiles of male mice inheriting the *Klf14*$^{tm1(KOMP)Vlcg}$ deletion allele from their mother (resulting in no *Klf14* expression) to male mice inheriting the deletion allele from their father (maintained expression from the maternally inherited non-deletion allele).

CRISPR-Cas9 conditional knockout RNA was extracted from snap-frozen subcutaneous adipose tissue from 4-month-old littermates (n = 2 females, 2 males each of wild-type and adipose-specific knockout mice) using TRIzol RNA Isolation Reagent according to the manufacturer's instructions (Thermo Fisher Scientific). Library generation and RNA sequencing were performed at the Bauer Core Facility of Harvard University. On average, about 25 million 75-bp single-end reads were obtained for each sample on the Illumina NextSeq 500 platform. Differentially expressed genes were identified by comparing the RNAseq profiles of knockout mice to wile-type mice.

Supplementary Tables

Cohort	Samples	Platform	Female:Male	Population	Citation
TwinsUK	776	RNAseq	100:0	Healthy female twins from the United Kingdom	Buil *et al,* Nature Genetics 2015
METSIM	770	Affymetrix U219 array	0:100	Healthy men from Finland	Civelek *et al*, AJHG 2017
deCODE	589	Agilent array	58:42	Healthy men and women from Iceland	Emilsson *et al*, Nature, 2008
MGH	701	Agilent array	75:25	Obese bariatric surgery patients from USA	Greenawalt *et al*, Genome Research 2011

Supplementary Table 2| Characteristics of subcutaneous adipose gene expression cohorts used in *trans*-network replication

Tissue	Source	Platform	N	*Cis-eQTL P*	*Trans-EqtI present*
Subcutaneous Adipose	TwinsUK	RNAseq	776	1.8×10^{-36}	Yes
Subcutaneous Adipose	METSIM	Microarray	770	2.4×10^{-6}	Yes
Subcutaneous Adipose	deCODE	Microarray	589	2.6×10^{-10}	Yes
Subcutaneous Adipose	deCODE maternal	Microarray	589	6.6×10^{-20}	Yes
Subcutaneous Adipose	MGH, Greenawalt et al	Microarray	701	1.6×10^{-11}	Yes
Omental Adipose	MGH, Greenawalt et al	Microarray	848	3.6×10^{-7}	Yes
Subcutaneous Adipose	GTEx	RNAseq	298	0.0001	Yes
Visceral Adipose	GTEx	RNAseq	185	0.97	Yes
Skin	TwinsUK	RNAseq	672	0.79	No
Lymphoblastoid Cell Line	TwinsUK	RNAseq	765	Not expressed	No
Whole Blood	TwinsUK	RNAseq	368	Not expressed	No
Skeletal Muscle	Keildson et al	Microarray	200	Not significant	No
Skeletal Muscle	GTEx	RNAseq	361	Not significant	No
Pancreatic Islets	Van de Bunt et al	RNAseq	118	Not significant	No
Monocytes	Zeller et al	Microarray	1,490	Not significant	NA
Liver	MGH, Greenawalt et al	Microarray	651	Not significant	No
Liver	Innocenti et al	Microarray	266	Not significant	NA
Whole Blood	Westra et al	RNAseq & Microarray	5,311	Not significant	No
Monocytes/Macrophages	Cardiogenics	Microarray	758	Not significant	NA
Dendritic Cells	PhenoGenetic	Microarray	534	Not significant	NA
CD4+ T Cells	Raj et al	Microarray	407	Not significant	NA
CD19+ B cells	Fairfax et al	Microarray	283	Not significant	NA
Lung	Hao et al	Microarray	1,111	Not significant	NA
10 Brain regions	UK Brain Expression Consortium, Ramasamy et al	Microarray	134	Not significant	No
Remaining 41 GTEx tissues	GTEx	RNAseq	70-338	Not significant	No

Supplementary Table 3 | *KLF14 cis*-eQTL is limited to adipose tissue. Association between *KLF14* expression and T2D associated SNP rs4731702. Most published studies only report summary statistics for significant eQTLs – 'Not significant' means the study did not find a *cis*-eQTL between rs4731702 *KLF14,* in some cases this may mean *KLF14* was not expressed in that tissue. The *trans*-eQTL was considered present if at least one *trans*-gene had $P < 0.05$, Bonferonni corrected for the number of *trans*-genes quantified in that dataset. Datasets where *trans*-analysis or raw genotypes were unavailable are marked 'NA'.

Test	Sample	*P*	β	Standard Error
Standard	All	2.6×10^{-10}	-0.023	0.0036
Maternal Allele	All	6.6×10^{-20}	-0.046	0.0049
Paternal Allele	All	0.89	-0.001	0.0051
Standard	Females	1.1×10^{-05}	-0.020	0.0045
Standard	Males	1.5×10^{-06}	-0.027	0.0056
Maternal Allele	Females	4.1×10^{-11}	-0.044	0.0064
Maternal Allele	Males	5.5×10^{-11}	-0.051	0.0074
Paternal Allele	Females	0.96	-0.0003	0.0066
Paternal Allele	Males	0.85	0.002	0.0077

Supplementary Table 4 | Sex-stratified and parent of origin effects on the *KLF14 cis*-eQTL. Association between rs4731702 and adipose expression of *KLF14* in the deCODE dataset (female N=376 and male N=265). The T2D risk allele C is the reference allele.

	KLF14 expression x Trait		Genes associated to trait (%)		Enrichment for association in *KLF14* network	
Trait	***P***	**Direction**	***KLF14* Network genes**	**All expressed genes excluding *KLF14* Network**	**OR**	***P***
Combined Insulin Resistance Phenotype*	1.08×10^{-3}	-	151 (39%)	5,261 (28%)	1.66	1.82×10^{-6}
Fasting Insulin	8.08×10^{-6}	-	200 (52%)	7,254 (39%)	1.70	1.88×10^{-7}
Fasting Glucose	1.63×10^{-6}	-	10 (3%)	301 (2%)	1.63	0.10
HOMA-IR	5.73×10^{-7}	-	200 (52%)	7,234 (39%)	1.73	8.82×10^{-8}
BMI	0.90	-	373 (97%)	16,472 (88%)	4.38	9.08×10^{-10}
HDL	0.04	+	300 (78%)	12,014 (65%)	1.96	8.28×10^{-9}
LDL	0.76	-	3 (0.78%)	68 (0.36%)	2.16	0.17
Triglycerides	0.51	-	267 (70%)	10,585 (57%)	1.76	1.78×10^{-7}
Whole Body Fat	0.12	-	139 (36%)	4,680 (25%)	1.68	1.47×10^{-6}
Waist-hip ratio	0.09	-	140 (36%)	4,511 (24%)	1.81	5.97×10^{-8}
Android/Gynoid Ratio	1.75×10^{-3}	-	314 (82%)	12,706 (68%)	2.12	9.55×10^{-10}
Adiponectin	0.90	-	46 (12%)	1,295 (7%)	1.81	3.313×10^{-4}
Leptin	0.65	-	13 (4%)	249 (2%)	2.60	2.60×10^{-3}

Supplementary Table 7 | Expression of *KLF14* and the 385 *trans*-genes are enriched for association to concurrently measured metabolic traits. Association between adipose expression in TwinsUK (N = 776 females) and concurrently measured metabolic traits. All associations were adjusted for body-mass index (BMI), except to BMI itself. In *KLF14* expression vs Trait columns, *P* reports the p value of the association between *KLF14* expression and the corresponding trait and Direction reports whether the association was direct (+) or inverse (-). Genes associated to trait columns list the number of genes in each category which were associated to the respective trait at FDR 5%. Significance of enrichment for trait-association in the *KLF14* network genes compared to all adipose genes was assessed using a one-tailed Fisher's exact test. OR, odds ratio; BMI, body-mass index, HDL, high density lipoprotein; LDL, low density lipoprotein. *Association with insulin resistance was assessed via a combined insulin resistance phenotype consisting of association with fasting insulin, HDL and triglycerides with a directionality consistent with risk or protection from a phenotype of insulin resistance.

Guide RNA	Protospacer	PAM	Single-strand olionucleotide sequence
Klf14 whole-body knockout	5’-GGACATAGACACCAGGCACT-3’	5’-CGG-3’	N/A
Klf14 conditional knockout upstream	5’-GCGGTGATCTATTGGCGACA-3’	5’-AGG-3’	5’GCGAAACAAAGTTTTCTCATTTAGCAGTTCGGCTGTTAATGCAGGATCGGC AGCCTTGTCGAATTCATAACTTCGTATAATGTATGCTATACGAAGTTATGCCA ATAGATCACCGCGTAGCCATTAATTAATAGCGTTTTGAATCAGAAACGGTTTT AAC-3’
Klf14 conditional knockout downstream	5’-GTCGGACTCTGGAGAGGGAC-3’	5’-TGG-3’	5’CGTTCATTTCAGAAGATGTTTGTGTTGCAGGACTTCCTGCTATCTTCTGGCT CCCAGTCCGAATTCATAACTTCGTATAATGTATGCTATACGAAGTTATCTCTC CAGAGTCCGACAAGTTTGTCTGAACCCATCCCCAGTGCGGAGCAACCAGTCT GTA-3’

Supplementary Table 10 | Guide RNAs used in CRISPR-Cas9 mouse models

PCR primer	Oligonucleotide sequence
Klf14 whole-body knockout forward	5’-AGCTCGTCTGGCTCCAAG-3’
Klf14 whole-body knockout reverse	5’-GGGCACCACAGCTTAAATCA-3’
Klf14 conditional knockout upstream forward	5’-TTCTATTTCAAGCGGGGATG-3’
Klf14 conditional knockout upstream reverse	5’-CTTGTCTGCGCTTTCTCTCC-3’
Klf14 conditional knockout downstream forward	5’-GCAGGCTGTTTGGAAGAAAC-3’
Klf14 conditional knockout downstream reverse	5’-CATGGTGGAAAGCTCTGGTT-3’
Adipoq-Cre forward	5’-GGATGTGCCATGTGAGTCTG-3’
Adipoq-Cre reverse	5’-ACGGACAGAAGCATTTTCCA-3’

Supplementary Table 11 | PCR primers used in CRISPR-Cas9 mouse models

Supplementary References

1 Pickrell, J. K. *et al.* Signals of recent positive selection in a worldwide sample of human populations. *Genome Res* **19**, 826-837, doi:10.1101/gr.087577.108 (2009).

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