

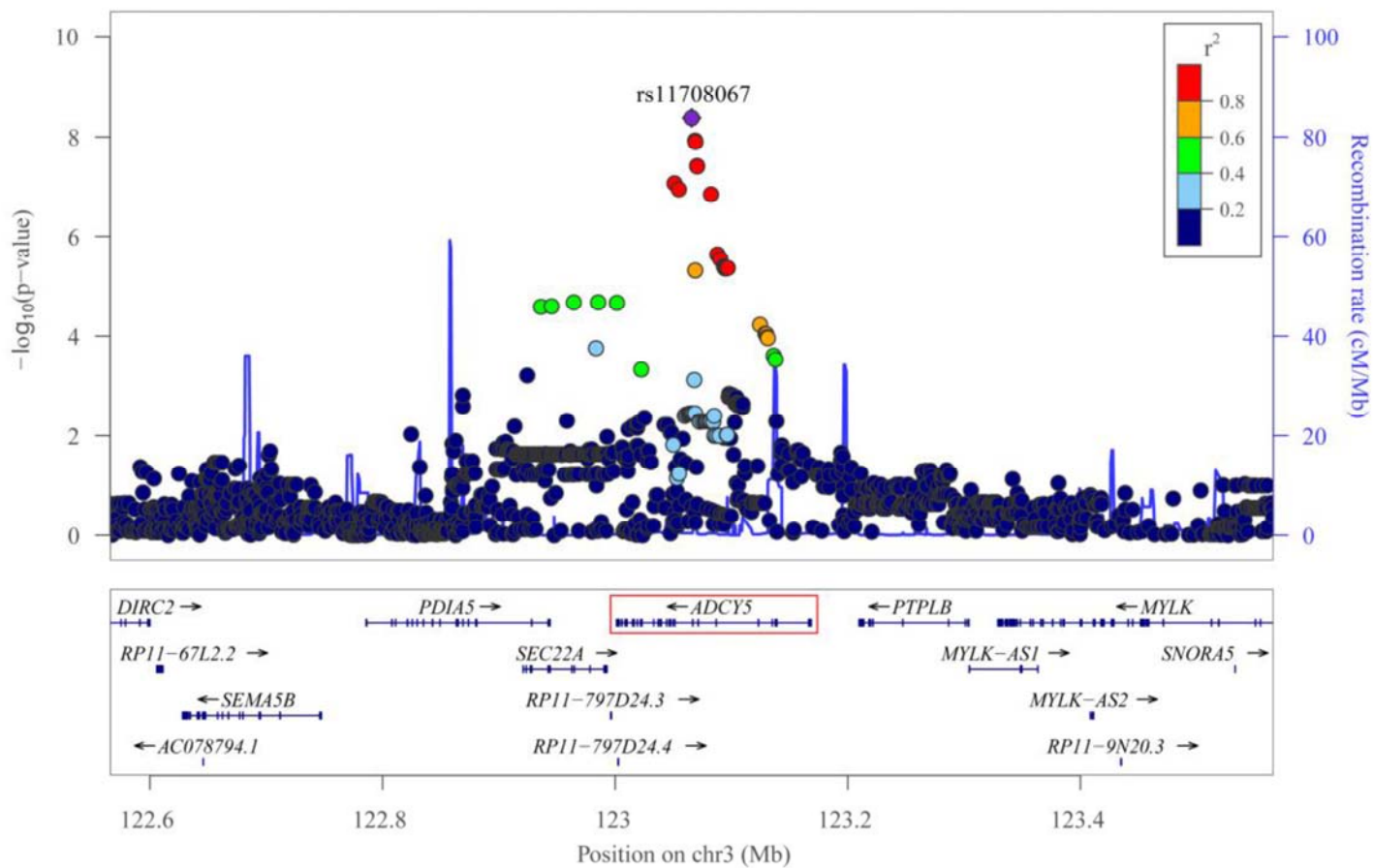
SUPPLEMENTARY DATA

Supplementary Figure 1. The A allele of rs11708067 is associated with decreased *ADCY5* expression in 112 human primary pancreatic islet samples

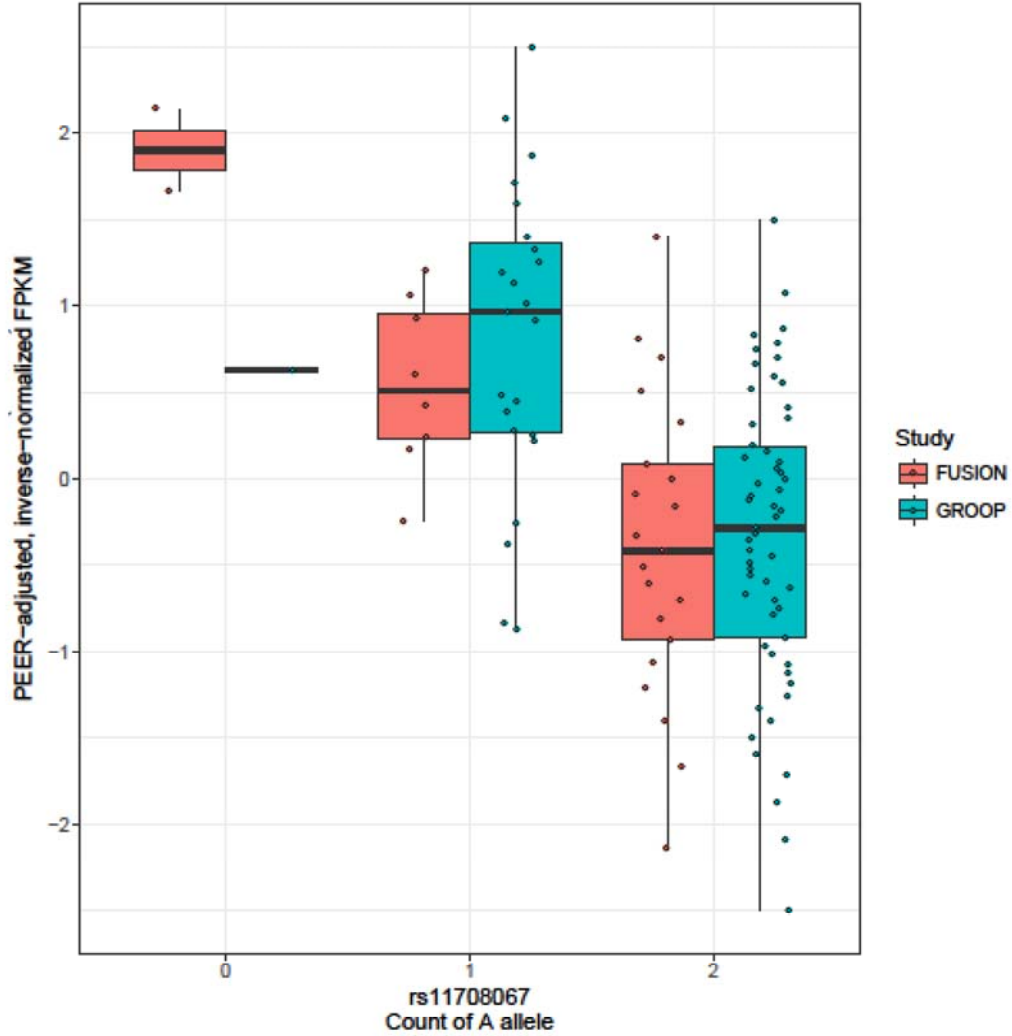
A eQTL data are based on RNA-sequencing of 112 pancreatic islet samples (20). The diamond represents the lead variant, rs11708067, of the eQTL analysis. Circles represent genotyped and imputed DNA variants and LD (r^2) is colored based on 1000 Genomes Phase 3 EUR. Chromosome coordinates correspond to UCSC Genome Browser build hg19. The left Y-axis indicates the $-\log_{10}(\text{p-value})$, the right Y-axis indicates the recombination rate (cM/Mb) and the X-axis indicates the position on chromosome 3 (Mb).

B eQTL data from pancreatic islet samples (shown in A) represented in a box plot. Orange boxes = 31 human pancreatic islet samples from Varshney et al. (20); blue boxes = 81 pancreatic islet samples from a separate study by Fadista et al. (23). Both studies are described in Varshney et al. (20). The y-axis represents *ADCY5* expression, displayed as the PEER-adjusted, inverse normalized values for fragment per kilobase of transcript per million mapped reads (FPKM). The x-axis represents the genotype of rs11708067 for each sample and is shown as the number of A alleles for rs11708067. The solid black horizontal line inside the middle of each of the boxes indicates the median (50th percentile). The top and bottom of each box represent the lower and upper hinges (25th and 75th percentile). The lower whisker represents the smallest y-axis value greater than or equal to the lower hinge – 1.5 times the inter-quartile range of the hinge. The upper whisker represents the largest y-axis value less than or equal to the upper hinge + 1.5 times the inter-quartile range.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

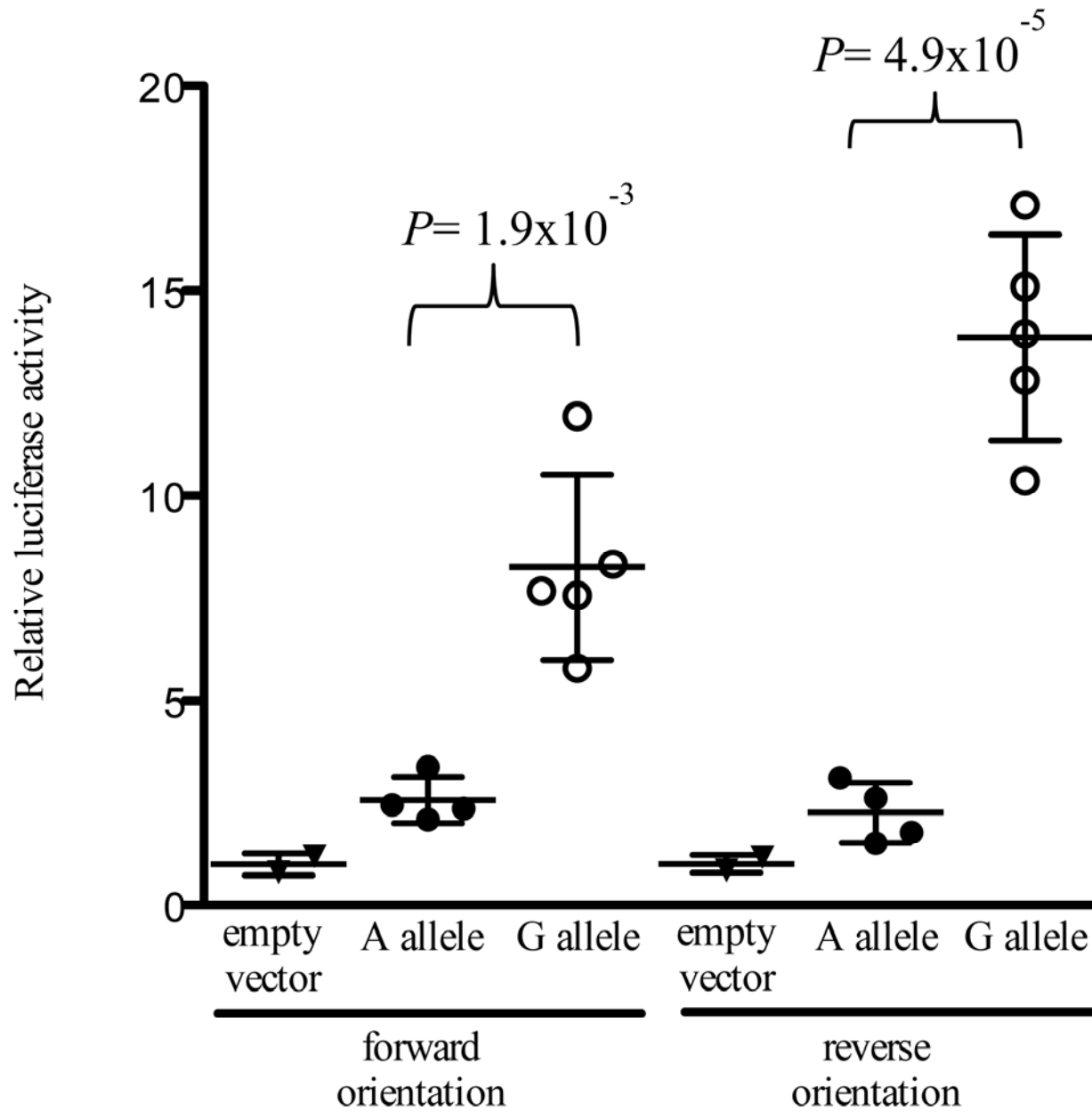


SUPPLEMENTARY DATA

Supplementary Figure 2. rs11708067 exhibits allelic differences in transcriptional activity in MIN6 mouse cells.

231-bp segments containing allele A or G of rs11708067 were cloned into a pGL4.23 luciferase reporter vector upstream of the minimal promoter in both orientations (forward and reverse). The relative luciferase activities of plasmids transfected into MIN6 cells normalized to an empty vector control are shown on the y-axis. Error bars represent standard deviation of 3-5 independent clones per allele (t-tests). Black upside-down triangles = empty vector; black circles = rs11708067 A allele; white circles = rs11708067 G allele.

SUPPLEMENTARY DATA



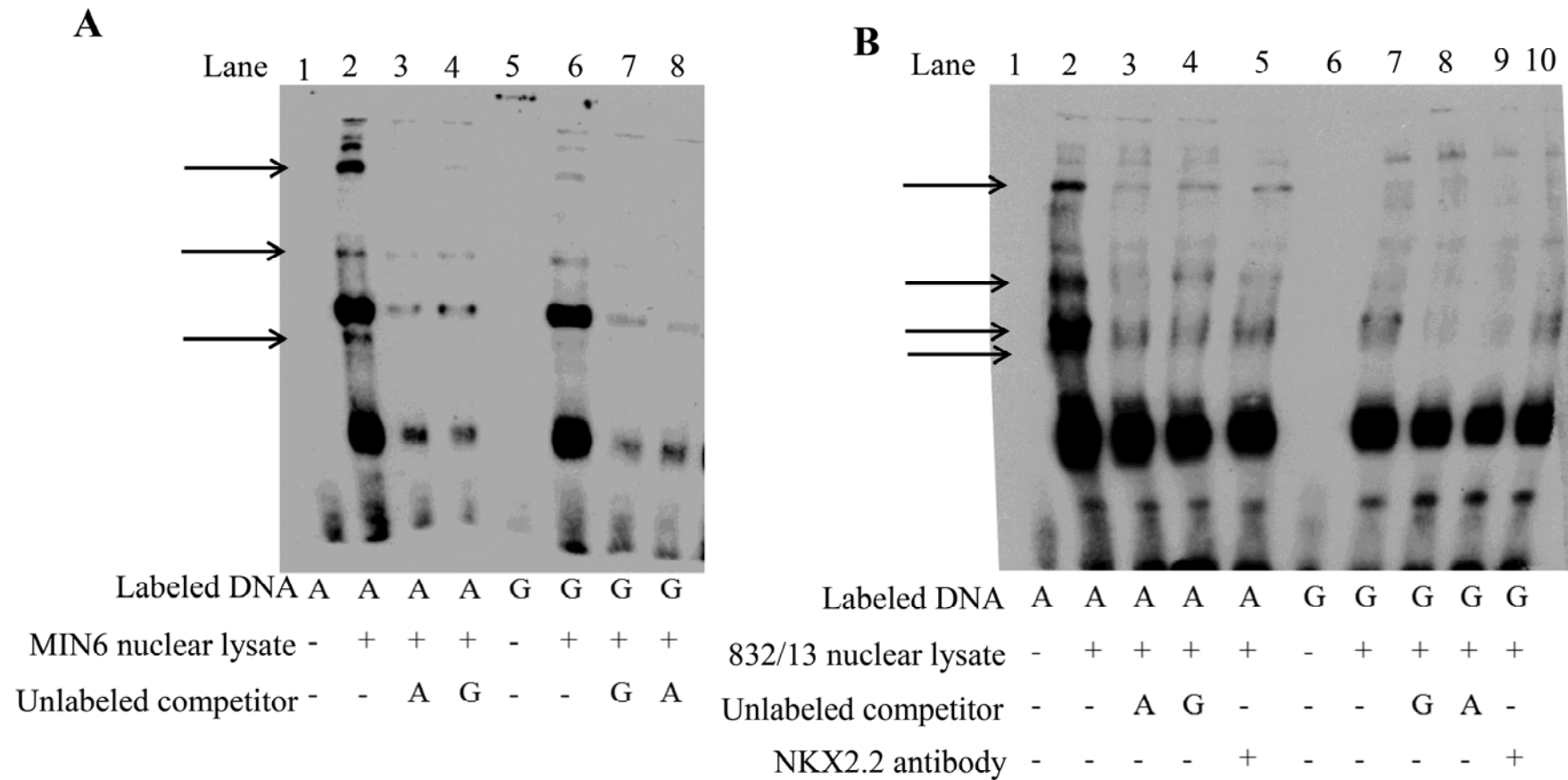
SUPPLEMENTARY DATA

Supplementary Figure 3. The alleles of rs11708067 show allelic differences in nuclear protein binding

Electrophoretic mobility shift assays with biotin-labeled probes containing either the A or G allele of rs11708067.

A Probes were incubated with 3.3 μ g MIN6 mouse nuclear lysate. The arrows indicate differential protein binding to the A allele, which is competed away by 70-fold excess competitor DNA (lane 3). EMSAs were performed on 4 separate days with consistent results.

B Probes were incubated with 4 μ g 832/13 rat insulinoma nuclear lysate. The arrows indicate differential protein binding to the A allele, which is competed away by 125-fold excess competitor DNA containing the A allele (lane 3). EMSAs were performed on 6 separate days with consistent results. In lanes 5 and 10, 8 μ g of NKX2.2 antibody was added to the reactions to test for supershifts.



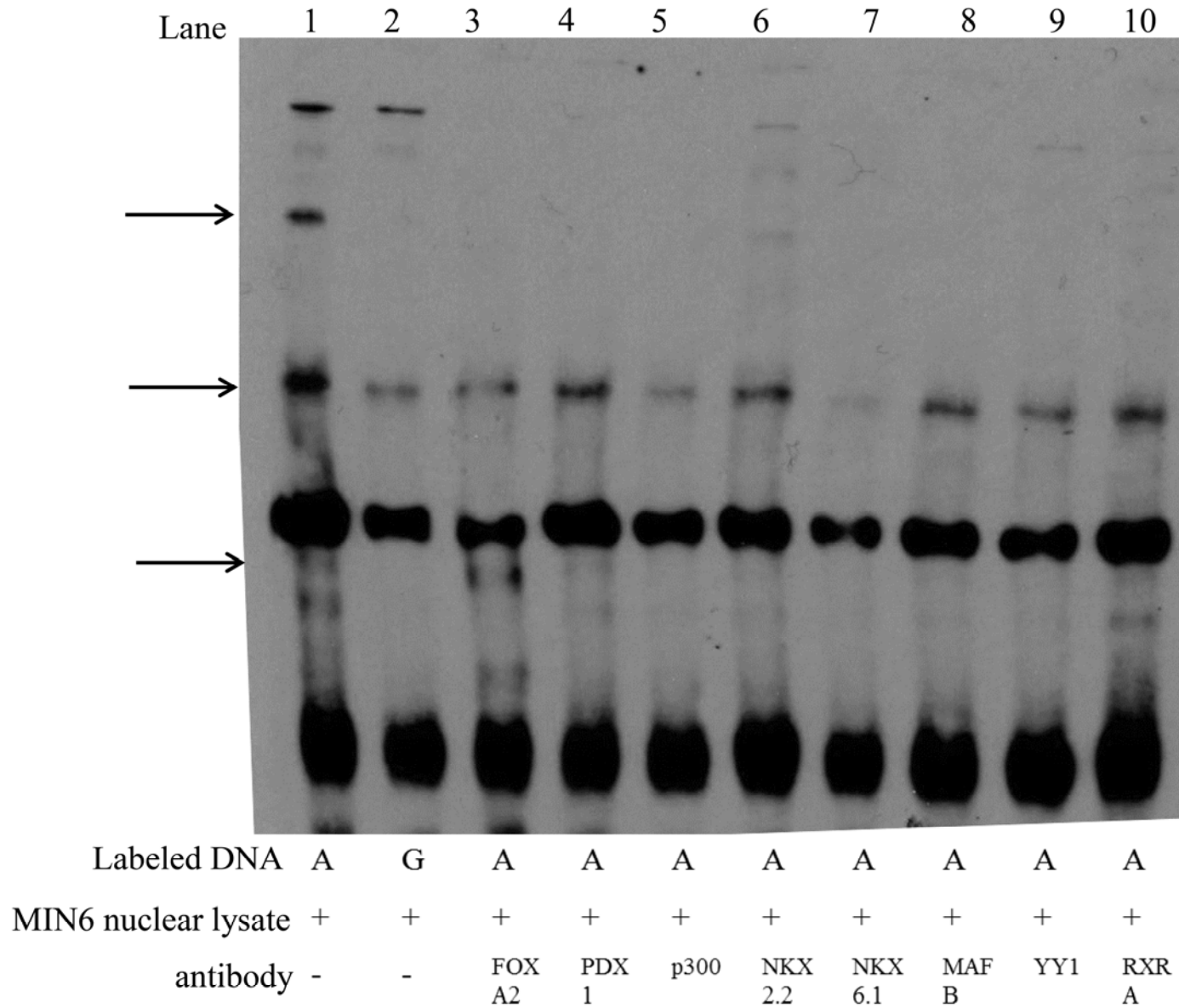
SUPPLEMENTARY DATA

Supplementary Figure 4. Multiple antibodies tested in EMSAs do not show evidence of supershifts

Electrophoretic mobility shift assays with biotin-labeled probes containing either the A or G allele of rs11708067.

Probes were incubated with 3.3 µg MIN6 mouse nuclear lysate and 6 µg of antibodies to FOXA2, PDX1, p300, NKX2.2, NKX6.1, MAFB, YY1 or RXRA. The arrows indicate differential protein binding to the A allele, compared to the G allele (lane 1 vs. lane 2).

SUPPLEMENTARY DATA

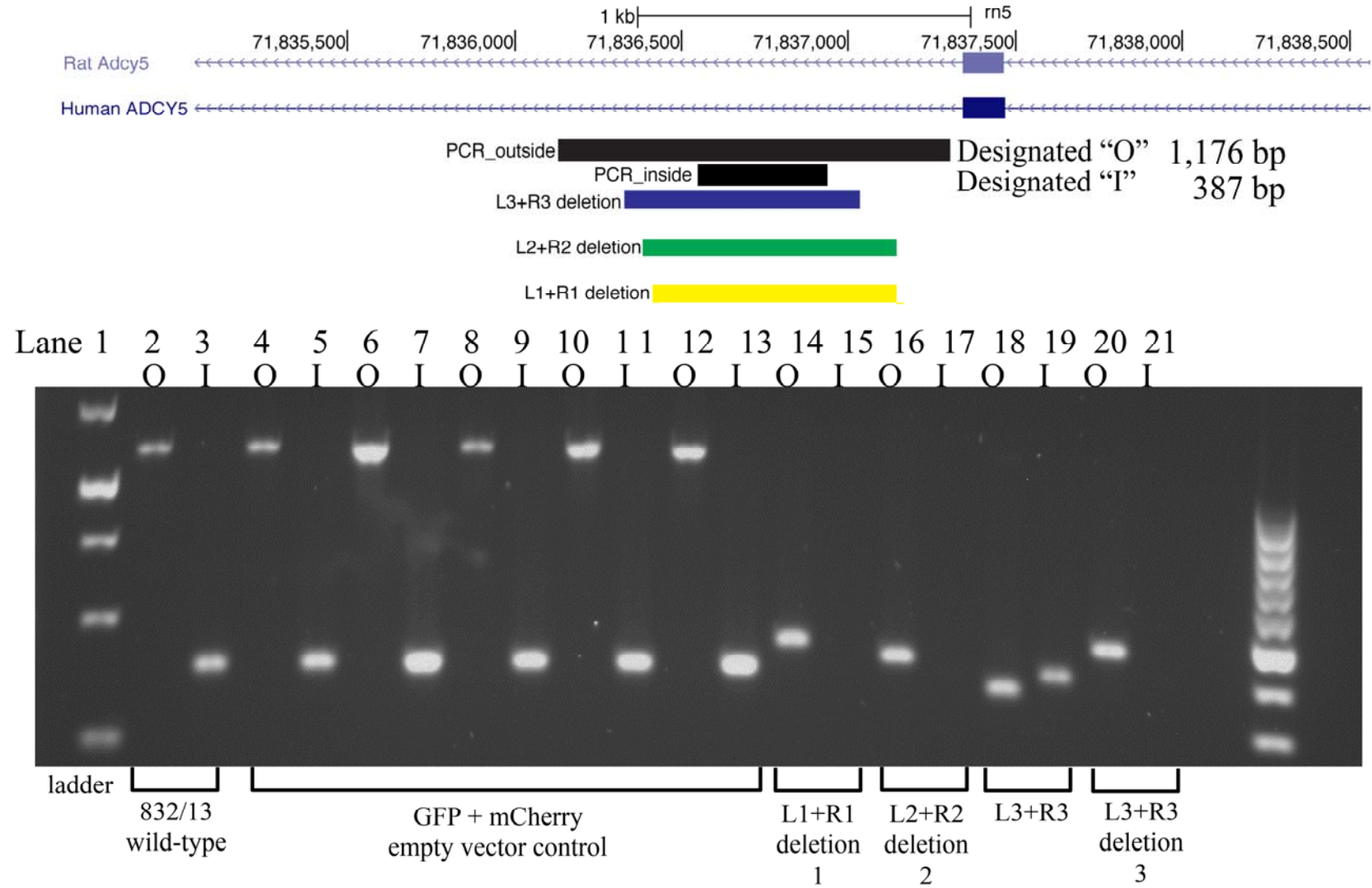


SUPPLEMENTARY DATA

Supplementary Figure 5. PCR amplification and validation of *Adcy5* enhancer homozygous deletions in 832/13 cells

Gel image showing 832/13 wild-type DNA (lanes 2, 3) GFP and mCherry empty vector control DNA (lanes 4-13) and DNA with deletions of the *Adcy5* enhancer element (lanes 14-21). “O” indicates the PCR amplicon using primers outside of the targeted region for deletion via CRISPR-Cas9. “I” indicates amplicon using primers annealing within the targeted region for deletion. In addition to the three clones containing homozygous deletions of the *Adcy5* enhancer region, we identified an additional clone (lanes 18 and 19) that did not appear to have a complete homozygous deletion of the enhancer region. L3+R3 = deletion 3, deletion generated with guide pair 3; L2+R2 = deletion 2, deletion generated with guide pair 2; L1+R1 = deletion 1, deletion generated with guide pair 1.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Figure 6. Sanger sequencing verifies the deleted region of sequence generated via CRISPR-Cas9 and guide pair 1

A Double-stranded sequence (rat genome rn5) targeted for deletion via CRISPR-Cas9. Guide target sequences are indicated in red. B Sanger sequence trace of the homozygous deletion clone generated using CRISPR-Cas9 and guide pair 1. The same “outside” primers (used in the PCR validation) located outside of the target deleted region were used for sequencing. The black box indicates the 15-bp sequence upstream of guide pair 1L sequence, the red box indicates the guide pair 1L sequence, and the blue box indicates the guide pair 1R sequence (shown in A on the 5' top strand). The asterisk highlights the location of the cut site and deleted region (730-bp) of nucleotide sequence.

A 5' TTAGTCTCCTGAACCCCTGTATAGTGGGGATGACGACCTCCACAGGAAAGCACCCAGGAAGACACCATGGACAGGCAGAGGTGTGTGCCTTACTAC
 3' AATCAGAGGACTTGGGGACATATCACCCCTACTGCTGGAGGTGTCTTTTCGTGGGTCCTTCTGTGGTACCTGTCCGTCTCCACACACGGAATGATG

5' CTTACGGGGCTCTTTGGCCATCAGTCACACCGTAGCATCCACTGCACCTCAGCCAGACAGTCGTCGCCCTGGAAGACCGTGCTGATTTCTGGCCAT
 3' GAATGCCCCGAGAAACCGGTAGTCAGTGTGGCATCGTAGGTGACGTGGAGTCGGTCTGTCTCAGCAGCGGACCTTCTGGCAGACTAAAGACCGGTA

5' TTTGGCTCTGCCTGGTACGGAACATGAATAGCTAAAGGGATCCCCAATCGAAGCACCCGTGTATGGTGGCTCTACATTTCTCCTCACAGCCTTGGCCTTT
 3' AAACCGAGACGGACCATGCCTTGTACTTATCGATTTCCTAGGG **GGTTAGCTTCGTGGGCACAT** ACCACGCAGATGTAAAGAGGAGTGTCCGAACCGGAAA

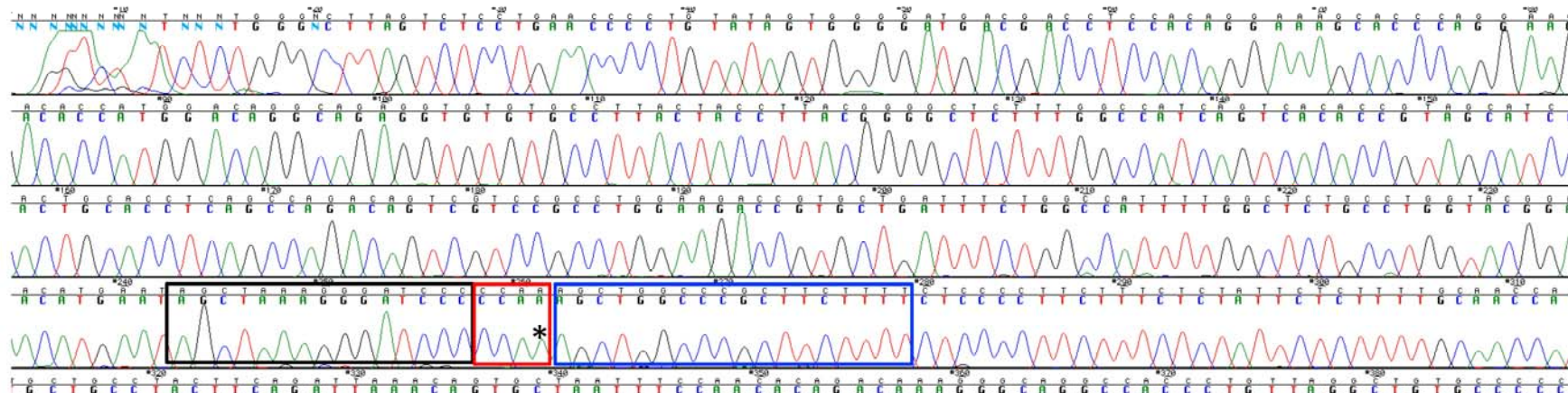
Guide pair 1L

5' GGGTTTT---661-bp--TCCCCAGTAGCTGGCCGCTTCTTTTCTCCCTTCTTTCTCTATTCTCTCTTGCAACCATGCTGCCTACTTCAGATT
 3' CCCAAA---661-bp--AGGGGT **CATCGACCGGGCGAAGA AAA** GAGGGGAAGAAAAGATAAGAGAGAACGTTGGTACGACGGATGAAGTCTAA

Guide pair 1R

5' AACAGTGCTAATTTCCAACACAGACAAAGGGCAGGCCACCCTGTTAGGCTGTGCCCCCTTTAAGGA
 3' TTTGTCACGATTAAGGTTGTGTCTGTTCCCGTCCGGTGGGACAATCCGACACGGGGGAAATTCCT

B Sanger sequence of homozygous deletion clone 1



SUPPLEMENTARY DATA

Supplementary Figure 7. Sanger sequencing verifies the deleted region of sequence generated via CRISPR-Cas9 and guide pair 2 A

Double-stranded sequence (rat genome rn5) targeted for deletion via CRISPR-Cas9. Guide target sequences are indicated in red.

B Sanger sequence trace of the homozygous deletion clone generated using CRISPR-Cas9 and guide pair 2. The same “outside” primers (used in the PCR validation) located outside of the target deleted region were used for sequencing. The black box indicates the 21-bp sequence upstream of guide pair 2L sequence, the red box indicates the guide pair 2L sequence, and the blue box indicates the guide pair 2R sequence (shown in A on the 5' top strand). The asterisk highlights the location of the cut site and deleted region (760-bp) of nucleotide sequence.

A

5' TAGTCTCCTGAACCCCTGTATAGTGGGGATGACGACCTCCACAGGAAAGCACCCAGGAAGACACCATGGACAGGCAGAGGTGTGTGCCTTACT
3' ATCAGAGGACTTGGGGACATATCACCCCTACTGCTGGAGGTGTCC'TTTCGTGGGTCC'TTCTGTGGTACCTGTCCG'TCTCCACACACGGAATGA

5' ACCTTACGGGGCTCTTTGGCCATCAGTCACACCGTAGCATCCACTGCACCTCAGCCAGACAGTCGTCCGCCTGGAAGACCGTGCTGATTT
3' TGGAAATGCCCCGAGAAACCGGTAGTCAGTGTGGCATCGTAGGTGACGTGGAGTCGGTCTGTCAGCAGGCGGACCTTCTGGCAGACTAAA

5' CTGGCCATTTTGGCTCTGCCTGGTACGGAACATGAATAGCTAAAGGGATCCCCAATCGAA---689-bp---TGTGTTCTGTCTTTG
3' GACCGGTAAAACCGAGACGGA **CATGCCTTGTACTTATCGA** TTTCCCTAGGGGTTAGCTT---689-bp---ACACAAGACAGAAAC

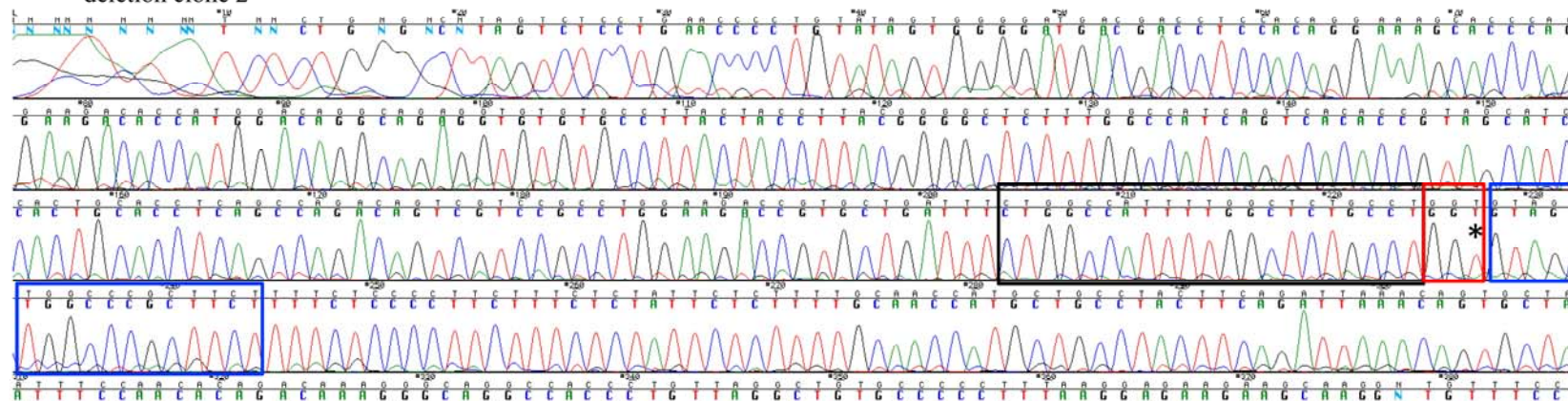
Guide pair 2L

5' TCAGGTGAGCGGTCCCCCAGTAGCTGGCCCGCTTCTTTTCTCCCTTCTTCTCTATTCTCTCTTGAACCATGCTGCCTACTTTCAG
3' AGTCCACACGCCAGGG **GGTCATCGACCGGGCGAAGA** AAAGAGGGGAAGAAAGAGATAAGAGAGAACGTTGGTACGACGGATGAAGTC

Guide pair 2R

5' ATTAAACAGTGCTAATTTCCAACACAGACAAAGGGCAGGCCACCCTGTTAGGCTGTGCCCCCTTTAAGGA
3' TAATTTGTCACGATTAAAGGTTGTGTCTGTTTCCCGTCCGGTGGGACAATCCGACACGGGGGAAATTCCT

B Sanger sequence of homozygous deletion clone 2



SUPPLEMENTARY DATA

Supplementary Figure 8. Sanger sequencing verifies the deleted region of sequence generated via CRISPR-Cas9 and guide pair 2

A Double-stranded sequence (rat genome rn5) targeted for deletion via CRISPR-Cas9. Guide target sequences are indicated in red.

B Sanger sequence trace of the homozygous deletion clone generated using CRISPR-Cas9 and guide pair 3. The same “outside” primers (used in the PCR validation) located outside of the target deleted region were used for sequencing. The black box indicates the 17-bp sequence upstream of guide pair 3L sequence, the red box indicates part of the guide pair 3L sequence, and the blue box indicates part of the guide pair 3R sequence (shown in A on the 5' top strand). The asterisk highlights the location of the cut site and deleted region (721-bp) of nucleotide sequence.

SUPPLEMENTARY DATA

A 5'TTAGTCTCCTGAACCCCTGTATAGTGGGGATGACGACCTCCACAGGAAAGCACCCAGGAAGACACCATGGACAGGCAGAGGTGTGTGCCTTACTACCTTA
 3'AATCAGAGGACTTGGGGACATATCACCCCTACTGCTGGAGGTGTCTTTTCGTGGTCTTCTGTGGTACCTGTCCGTCTCCACACACGGAATGATGGAAT

5'CGGGGCTCTTTGGCCATCAGTCACACCGTAGCATCCACTGCACCTCAGCCAGACAGTCGTCGCGCTGGAAGACCGTGTGATTTCTGGCCATTTTGGCT
 3'GCCCCGAGAAACCGGTAGTCAGTGTGGCATCGTAGGTGACGTGGAGTCGGT **CTGTCAGCAGGCGGACCTTC** TGGCAGCTAAAGACCGGTAACCGCA

5'CTGCCTGGTACGGAACATGA-565-bp--TGATGGCTTGGGGGGGCTTTCTGCCAGATCTCAAACATCCAACCTGAATCTATAAATCAGTTGTTT
 3'GACGGACCATGCCTTGTACT-565-bp--ACTACCGAACCCCCCGAAAGACGGGTCTAGAGTTTGTAGGTTGACTTAGATATTTAGTCAACAAA

Guide pair 3L

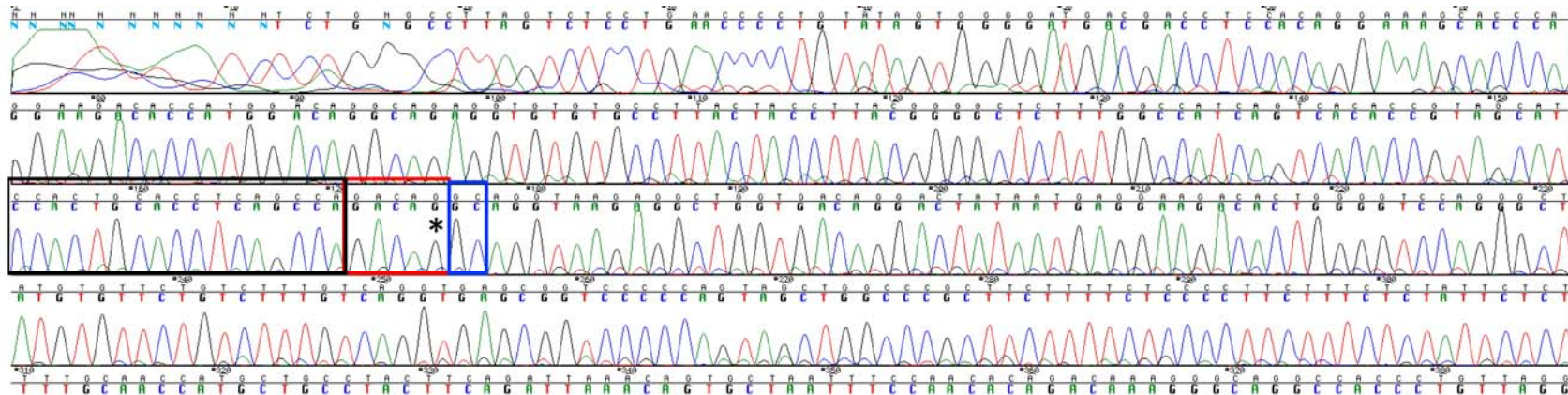
Guide pair 3R

5'GTGCCTCC**TGCACATGGGCTTAGGGGGC**AGGTAAGAGGCTGGTGACAGGACTATAATGAGGAAGACACTGGGGTCCAGGGCTATGTGTTCTGTCTTTGTC
 3'CACGGAGGACGTGTACCCGAATCCCCGTCATTCTCCGACCACTGTCCTGATATTACTCCTTCTGTGACCCAGGTCCCGATACACAAGACAGAAACAG

5'AGGTGAGCGGTCCCCAGTAGCTGGCCCGCTTCTTTTCTCCCTTCTTTCTCTATTCTCTCTTGCAACCATGTCGCCTACTTCAGATTAACAGT
 3'TCCACTCGCCAGGGGGTCATCGACCGGGCGAAGAAAAGAGGGGAAGAAAAGAGATAAGAGAGAACGTTGGTACGACGGATGAAGTCTAATTTGTCA

5'GCTAATTTCCAACACAGACAAAGGGCAGGCCACCCTGTTAGG
 3'CGATTAAGGTTGTGTCTGTTTCCCGTCCGGTGGGACAATCC

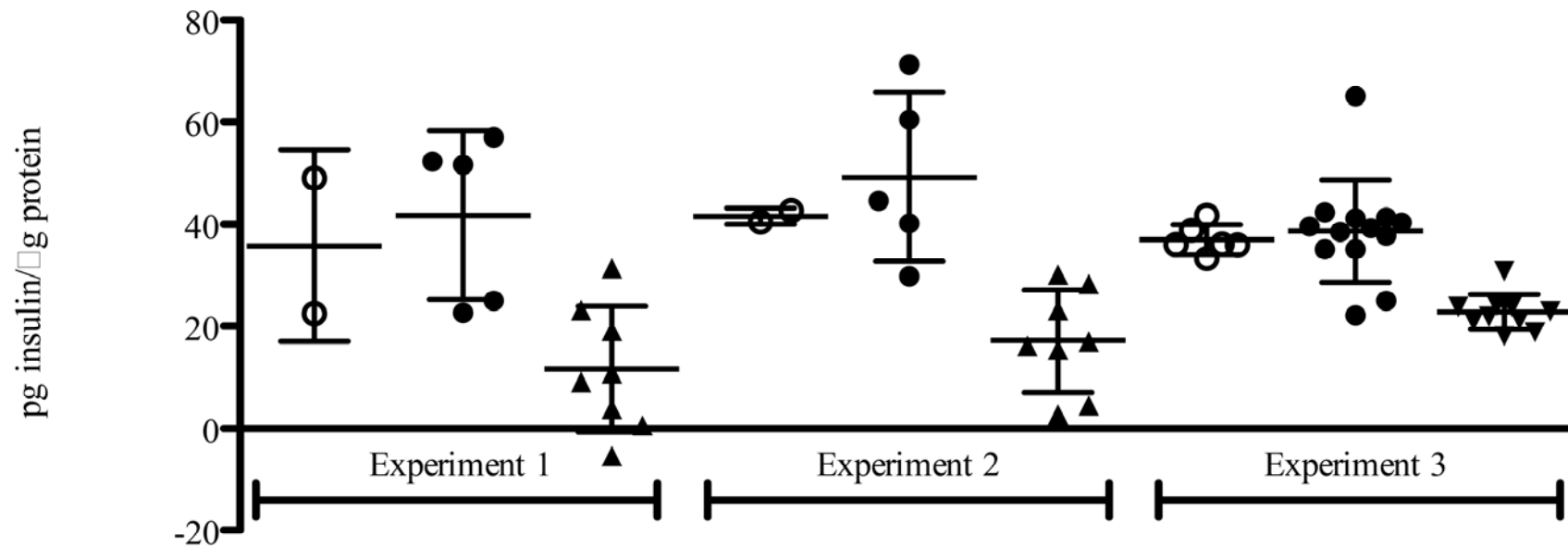
B Sanger sequence of homozygous deletion clone 3



SUPPLEMENTARY DATA

Supplementary Figure 9. Deletion of the orthologous *Adcy5* enhancer element in 832/13 cells leads to reduced insulin secretion at 3 mM glucose concentration

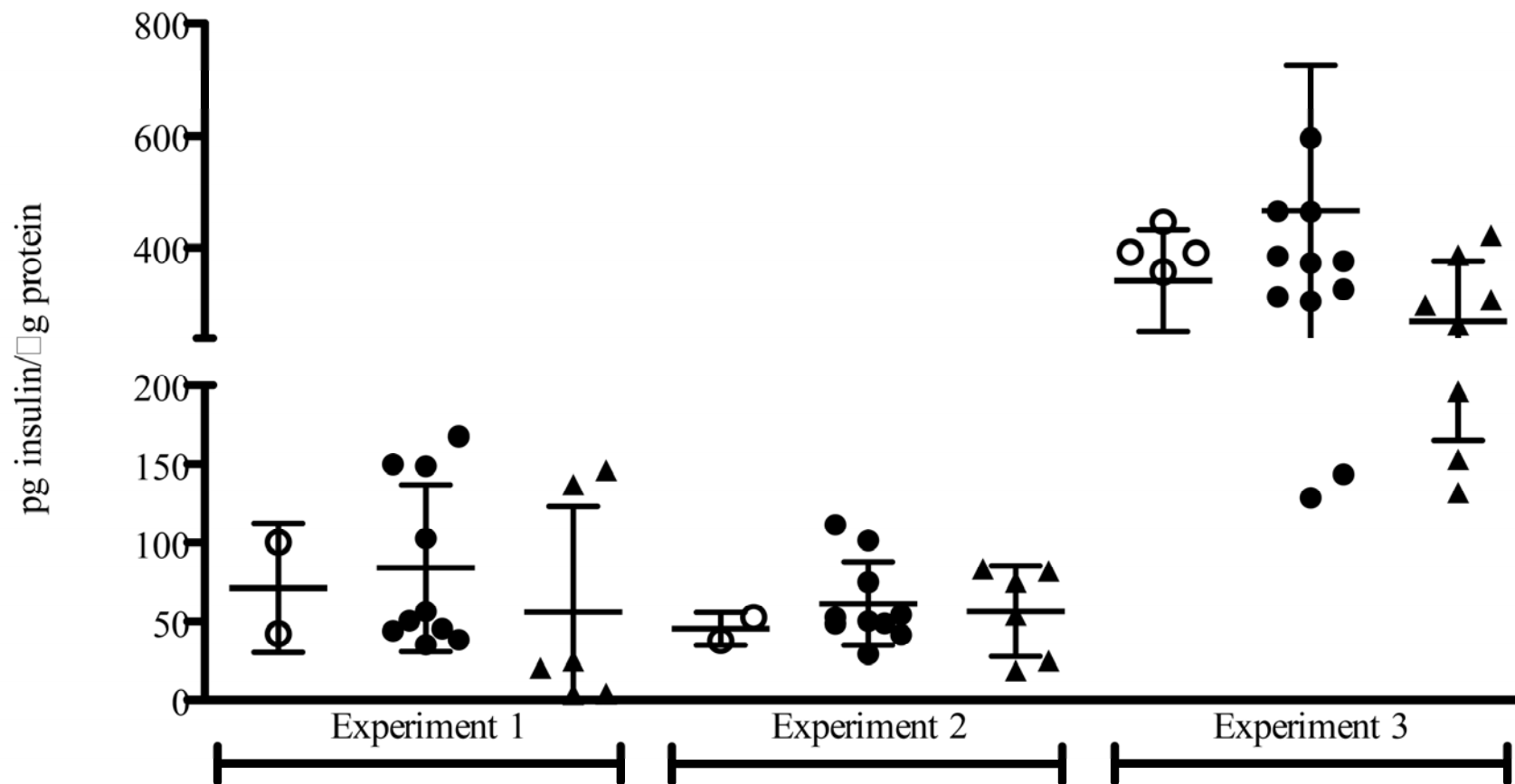
Insulin secretion assays were performed in duplicate or triplicate on three separate occasions. Error bars indicate the standard deviation of 2-5 clones per sample. Unpaired t-tests were performed to compare insulin secretion of enhancer homozygous deletion clones with intact control clones. White circles = WT (wild-type) 832/13 clones; black circles = intact control clones; black triangles = enhancer homozygous deletion clones. Insulin secretion at 3 mM glucose concentration is displayed as pg insulin/ μ g total protein on the y-axis.



SUPPLEMENTARY DATA

Supplementary Figure 10. Deletion of the orthologous *Adcy5* enhancer element in 832/13 cells leads to variable effects at 18 mM glucose concentration

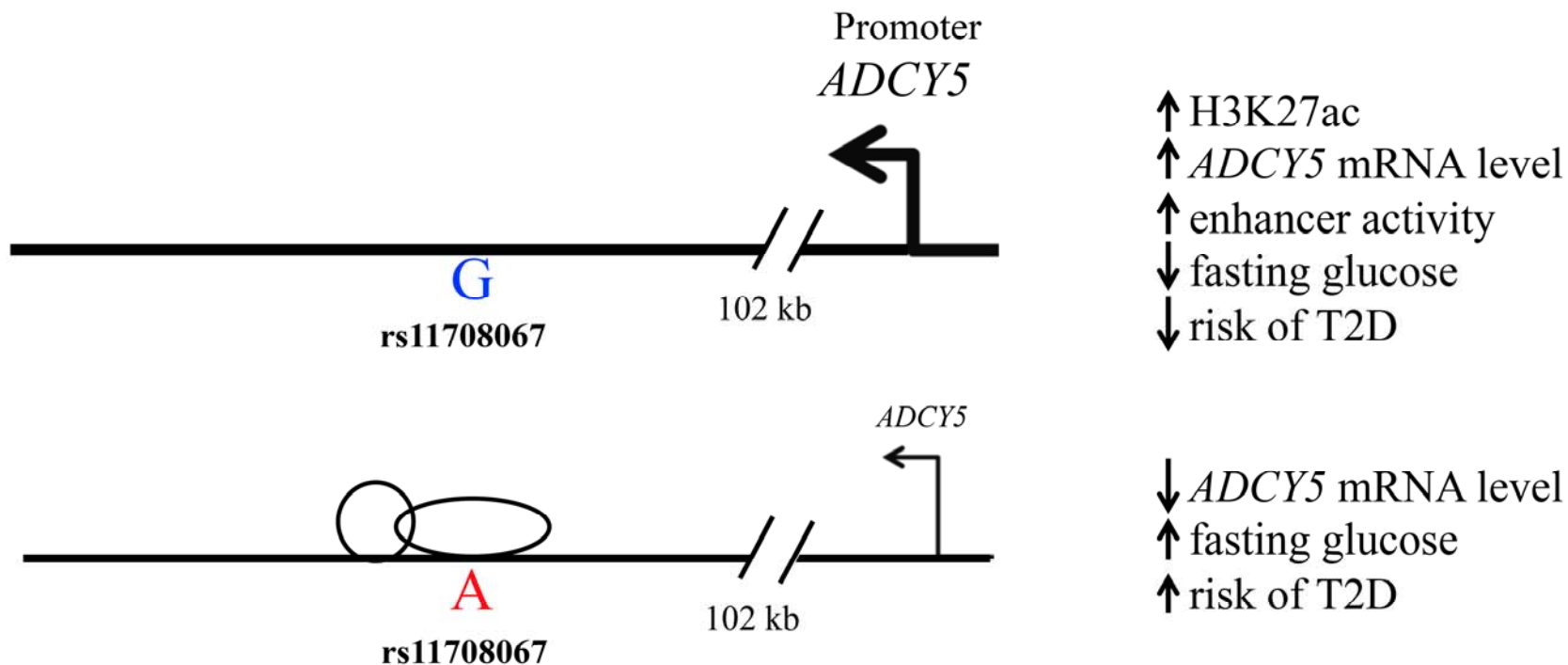
Insulin secretion assays were performed in duplicate or triplicate on three separate occasions. Error bars indicate the standard deviation of 2-5 clones per sample. Unpaired t-tests were performed to compare insulin secretion of enhancer homozygous deletion clones with intact control clones. White circles = WT (wild-type) 832/13 clones; black circles = intact control clones; black triangles = enhancer homozygous deletion clones. Insulin secretion at 18 mM glucose concentration is displayed as pg insulin/ μ g total protein on the y-axis.



SUPPLEMENTARY DATA

Supplementary Figure 11. rs11708067 is a functional regulatory variant at the *ADCY5* locus.

Arrows indicate the transcription start site (TSS) of the *ADCY5* gene. Circles/ovals represent proteins that appear to be bound differentially to the alleles of rs11708067. rs11708067 showed allelic differences in transcriptional enhancer activity, differential protein binding in EMSAs, and evidence of allelic imbalance in H3K27ac ChIP-seq reads. The rs11708067-A allele exhibited lower transcriptional reporter activity and lower H3K27ac enrichment compared to the rs11708067-G allele. The A allele is the allele associated with lower *ADCY5* expression in human pancreatic islets. The A allele is also associated with increased risk of type 2 diabetes.



SUPPLEMENTARY DATA

Supplementary Table 1. Summary of published *ADCY5* SNP associations with type 2 diabetes and glucose-related traits

Alt. allele, alternate allele (type 2 diabetes non-risk allele); LD, linkage disequilibrium (r^2) values; EUR, European individuals; EAS, East Asian individuals; AFR, African individuals. LDlink (8) was used to calculate LD (r^2) values with rs11708067 using 1000 Genomes Phase 3 data. Ref, references; Pop, population; AA, African American individuals; HOMA-B, homeostatic model assessment for pancreatic beta cells; I-I, insulinogenic index. Risk allele refers to the allele associated with increased risk of type 2 diabetes, the allele associated with increased fasting glucose and the allele associated with lower birthweight. Proinsulin-to-insulin conversion refers to proinsulin area under the curve (0-120 minutes)/insulin area under the curve (0-120 minutes). Ref, references, indicated by last name of first author, year of publication, and reference number in parentheses as referenced in main text.

SUPPLEMENTARY DATA

Lead SNP	Risk/ Alt. allele	Effect size or Odds Ratio	LD EUR	LD EAS	LD AFR	Sample size	P value	Trait	Reference	Population
rs2877716	C/T	+0.09 mmol/l	0.84	1	0.11	44,225	4.2E-16	2-hour glucose	Saxena 2010 (12)	EUR
rs2877716	C/T	1.12	0.84	1	0.11	35,869 cases; 89,798 controls	4.8E-18	type 2 diabetes	Saxena 2010 (12)	EUR
rs11708067	A/G	+0.03 mmol/l	1	1	1	118,475	7.1E-22	fasting glucose	Dupuis 2010 (10)	EUR
rs11708067	A/G	-0.02	1	1	1	94,212	2.5E-12	HOMA-B	Dupuis 2010 (10)	EUR
rs9883204	C/T	-30 g	0.83	1	0.051	10,623 discovery; 27,591 replication	7E-15	Birth weight	Freathy 2010 (45)	EUR
rs11708067	A/G	1.23	1	1	1	1678 cases; 1584 controls	9.1E-04	type 2 diabetes	Rees 2011 (5)	South Asian
rs9883204	C/T	0.041 mmol/l	0.83	1	0.051	2,151	0.03	Fasting glucose	Vasan 2011 (13)	Asian Indian
rs9883204	C/T	0.127 mmol/l	0.83	1	0.051	2,151	0.02	2-hour glucose	Vasan 2011 (13)	Asian Indian
rs9883204	C/T	-0.106	0.83	1	0.051	2,151	0.05	reduced I-I	Vasan 2011 (13)	Asian Indian
rs9883204	C/T	-0.058 pmol/l	0.83	1	0.051	2,151	0.01	2-hour insulin	Vasan 2011 (13)	Asian Indian
rs11708067	A/G	0.094	1	1	1	1,778	0.002	Proinsulin- to-insulin conversion	Wagner 2011 (15)	EUR
rs11708067	A/G	0.022 mmol/l	1	1	1	1,778	0.022	2-hour glucose	Wagner 2011 (15)	EUR
rs11717195	T/C	1.11	0.94	1	0.577	34,840 cases; 114,981 controls	6.5E-14	type 2 diabetes	Morris 2012 (3)	EUR
rs9883204	C/T	-29 g	0.83	1	0.051	61,509	5.5E-20	Birth weight	Horikoshi 2013 (14)	EUR
rs11708067	A/G	1.18	1	1	1	2,806 cases; 4,265 controls	4.7E-03	type 2 diabetes	Ng 2013 (6)	AA

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rs11717195	T/C	1.09-1.18	0.94	1	0.58	26,488 cases; 83,964 controls	2.2E-08	type 2 diabetes	DIAGRAM 2014 (4)	Trans-ethnic meta-analysis
rs11708067	A/G	0.022 mmol/l	1	1	1	58,614	1.9E-08	Fasting glucose	Dimas 2014 (42)	EUR
rs11708067	A/G	-0.015	1	1	1	50,908	5.4E-06	HOMA-B	Dimas 2014 (42)	EUR
rs143882978	C/T	-0.462	N/A	N/A	0.005	1035 cases; 740 controls	0.02	type 2 diabetes	Adeyemo 2015 (9)	African
rs11708067	A/G	0.036 mmol/l	1	1	1	20,209	6.3E-06	Fasting glucose	Liu 2016 (11)	AA

SUPPLEMENTARY DATA

Supplementary Table 2. Association analyses of type 2 diabetes-associated variant rs11708067 and glucose-related traits in individuals in the METSIM study.

Trait measurements were adjusted for BMI, age, and age squared and inverse normalized prior to association analyses (26). Positive signs for effect indicate positive direction of effect. The major A-allele, which was previously reported to be associated with increased risk of type 2 diabetes, was used as the effect allele in the association analysis. N, sample size.

Trait	Effect allele	Non-effect Allele	Genotype counts (AA/AG/GG)	N	Effect	P value
Glucose Area Under the Curve (30 min. to 2 hr.)	A	G	6,088/2,266/237	8,591	0.086	4.3E-05
Glucose (2 hr.)	A	G	6,108/2,275/237	8,620	0.084	5.8E-05
Glucose Area Under the Curve	A	G	6,088/2,266/237	8,591	0.083	8.4E-05
Glucose Area Under the Curve (Basal)	A	G	6,088/2,266/237	8,591	0.066	1.6E-03
Fasting glucose	A	G	6,114/2,277/239	8,630	0.059	5.0E-03
Glucose Area Under the Curve (0 to 30 min.)	A	G	6,090/2,266/238	8,594	0.058	5.9E-03
HOMA-B	A	G	6,110/2,276/239	8,625	-0.052	0.015
Glucose (30 min.)	A	G	6,090/2,266/238	8,594	0.049	0.020
Proinsulin (30 min.)	A	G	6,086/2,266/238	8,590	0.044	0.038
Proinsulin (2 hr.)	A	G	6,103/2,276/237	8,616	0.039	0.064
Fasting proinsulin	A	G	6,110/2,276/239	8,625	0.031	0.14
Fasting insulin	A	G	6,111/2,276/239	8,626	-0.017	0.41
Insulin (30 min.)	A	G	6,078/2,265/238	8,581	0.010	0.63
Insulinogenic Index	A	G	6,066/2,257/238	8,561	-0.009	0.66
Insulin Area Under the Curve (0 to 30 min.)	A	G	6,077/2,265/238	8,580	0.008	0.71
Matsuda Index	A	G	6,070/2,263/237	8,570	-0.006	0.77
Insulin secretion (30 min.)	A	G	6,077/2,264/238	8,579	-0.006	0.79
HOMA-IR	A	G	6,111/2,276/239	8,626	-0.005	0.80
Insulin Area Under the Curve (30 min. to 2 hrs.)	A	G	6,071/2,264/237	8,572	-0.005	0.81
Insulin Total Area Under the Curve	A	G	6,070/2,264/237	8,571	-0.004	0.85
Insulin Area Under the Curve (Basal)	A	G	6,070/2,264/237	8,571	-0.001	0.96

SUPPLEMENTARY DATA

Supplementary Table 3. Primer and target sequences for functional assays

Forward indicates forward primer, reverse indicates reverse primer (5'-3' with respect to the genome).

Primer sequences used to amplify DNA for luciferase reporter assays	Sequence	Chromosome 3 position (hg19)
rs11708067 Forward	CCTGGGGAGAAGGAACTCTC	123,065,631-123,065,650
rs11708067 Reverse	GCTCCTTTCACTGCGTGTTT	123,065,842-123,065,861
Oligonucleotide sequences for EMSAs		
rs11708067 A Forward	CAGATTTTGCCTCTATTAAT	123,065,768-123,065,788
rs11708067 A Reverse	ATTAATAGAGTGCAAAATCTG	123,065,768-123,065,788
rs11708067 G Forward	CAGATTTTGCCTCTATTAAT	123,065,768-123,065,788
rs11708067 G Reverse	ATTAATAGAGCGCAAAATCTG	123,065,768-123,065,788
Target DNA sequences for guide RNA design for CRISPR-Cas9-mediated deletion of enhancer element		
Guide pair 1L	TACACGGGTGCTTCGATTGG	71836413-71836432
Guide pair 1R	AAAAGAAGCGGGCCAGCTAC	71837145-71837164
Guide pair 2L	AGCTATTCATGTTCCGTACC	71836382-71836401
Guide pair 2R	AGAAGCGGGCCAGCTACTGG	71837142-71837161
Guide pair 3L	CTTCCAGGCGGACGACTGTC	71836328-71836347
Guide pair 3R	TGCACATGGGCTTAGGGGGC	71837036-71837055
PCR primers for confirming CRISPR-Cas9-mediated deletions of enhancer element		
Inside deletion Forward	TACGTGCAAATCTCGCTGTC	71836550-71836569
Inside deletion Reverse	CACACTTCGCCTCCACTGT	71836918-71836936
Outside deletion Forward	TAGCCAGCTGCATAGCATTG	71836128-71836147
Outside deletion Reverse	GGGAAACAGCCTTGCTTCTT	71837284-71837303

SUPPLEMENTARY DATA

Supplementary Table 4. Summary of type 2 diabetes- and glucose-associated variants and proxies ($r^2 > 0.8$, 1000 Genomes Phase 3, EUR) and overlap with open chromatin and regulatory annotations

ENCODE open chromatin in pancreatic islets were based on ENCODE Open Chromatin by DNase I Hypersensitivity and FAIRE tracks (21,22). Pancreatic islet chromatin states were based on histone modifications H3K4me3, H3K4me1, H3K27me3, H3K36me3, H3K72ac, and H3K27ac (28). ATAC-seq accessible chromatin peaks in two human pancreatic islet samples were based on tracks from Varshney et al. (20). rs11708067 was selected as a candidate regulatory variant for testing in transcriptional reporter assays because it was the only variant to overlap both DNase and FAIRE peaks in islets.

Variant	Chromosome 3 Position (hg19)	ENCODE open chromatin peaks in pancreatic islets	Chromatin state in pancreatic islets	ATAC-seq peaks from two human pancreatic islet samples
rs34642857	123,051,019	DNase	Weak enhancer	
rs72964564	123,054,770		Low signal	
rs11708067	123,065,778	DNase, FAIRE	Weak enhancer	Peaks for both islet samples
rs11719201	123,068,744		Repressed	
rs11720108	123,069,058		Repressed	
rs7614016	123,070,426		Weak enhancer	
rs7613951	123,070,517		Weak enhancer	Peak for one islet sample
rs11717195	123,082,398		Repressed	
rs35841686	123,087,916		Low signal	
rs34970607	123,090,360		Low signal	
rs60223228	123,092,615		Low signal	
rs2124500	123,093,530		Low signal	
rs6794202	123,093,887		Low signal	
rs2877716	123,094,451		Low signal	
rs6798189	123,095,312		Low signal	
rs56371916	123,095,543		Low signal	
rs35543900	123,096,477		Low signal	
rs9883204	123,096,820		Low signal	