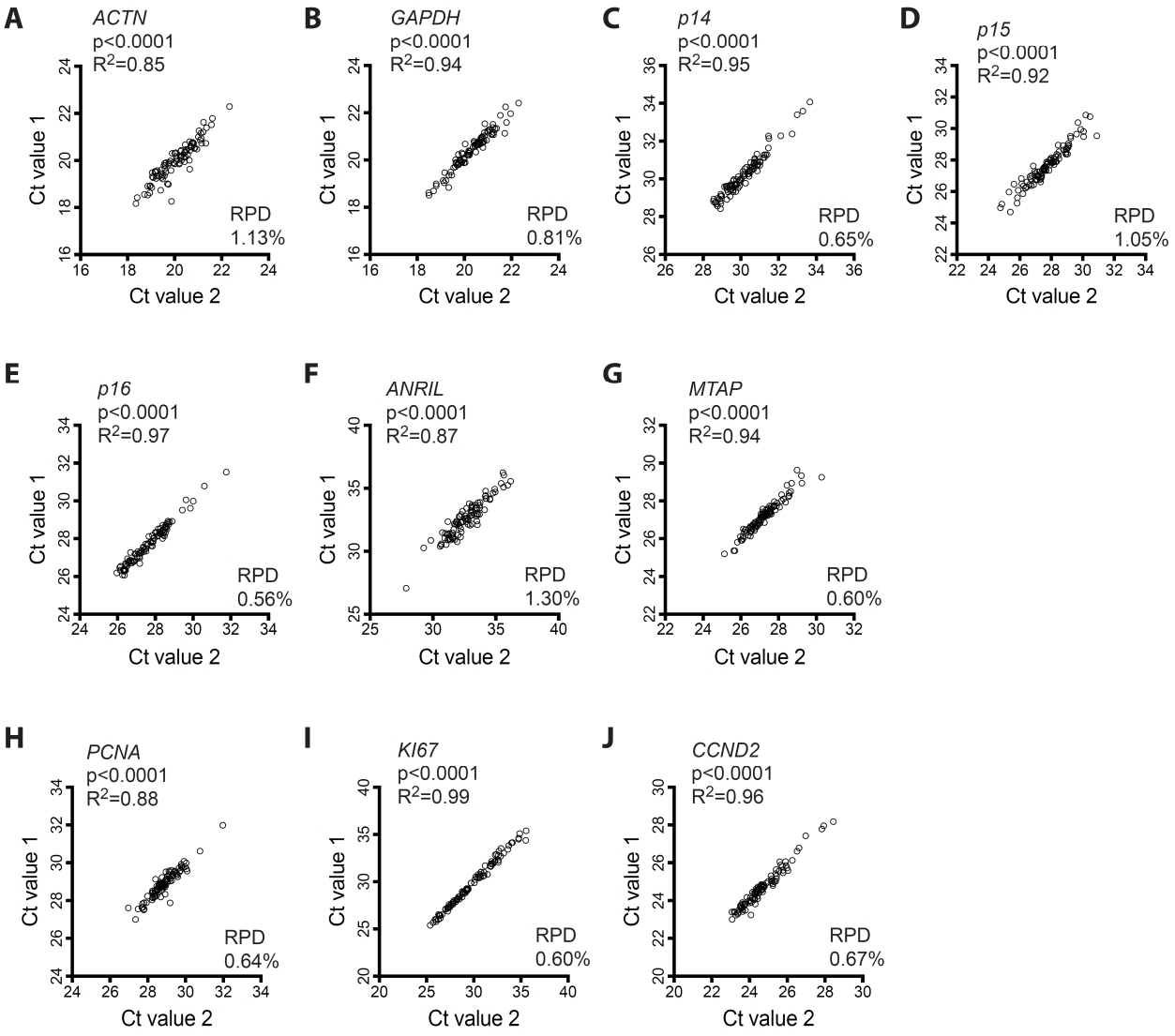
SUPPLEMENTARY DATA

Supplementary Figure 1. Taqman gene expression duplicates show high reproducibility. For each CDKN2A/B locus gene, Taqman Ct values of replicate 1 (Ct value 1) and replicate 2 (Ct value 2) are plotted. The RPD values, the absolute value of the Relative Percentage Differerence, were calculated from the equation RPD=(D1-D2)/(D1+D2)/2X100. RPDs for all genes were well within established goals for biological replicate variability of 10%. Line, p values and R-squared values were calculated by linear regression; n=95 for all panels.



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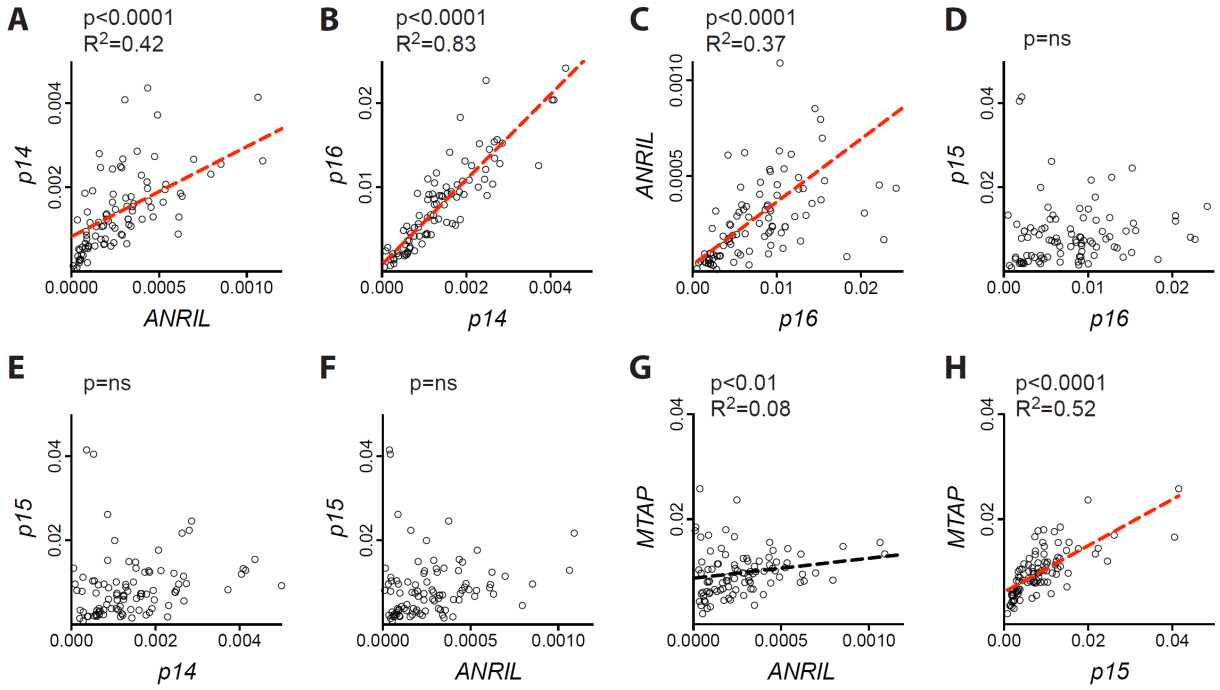
SUPPLEMENTARY DATA

Supplementary Figure 2. *CDKN2A/B* locus gene expression in human islets normalized to *GAPDH*. As observed when normalized to *ACTIN*, *CDKN2A/B* locus genes when normalized to islet *GAPDH* abundance revealed a high degree of correlation between *p14-p16-ANRIL* (A-C). *p15* and *MTAP* showed little or no correlation with *p14*, *p16* or *ANRIL* (D-G). However, *p15* and *MTAP* expression correlated with each other. mRNA abundance is expressed as delta-Ct, normalized to *GAPDH*. Line, p values and R-squared values were calculated by linear regression; n=95 for all panels. Red lines highlight correlations with higher R-squared values.



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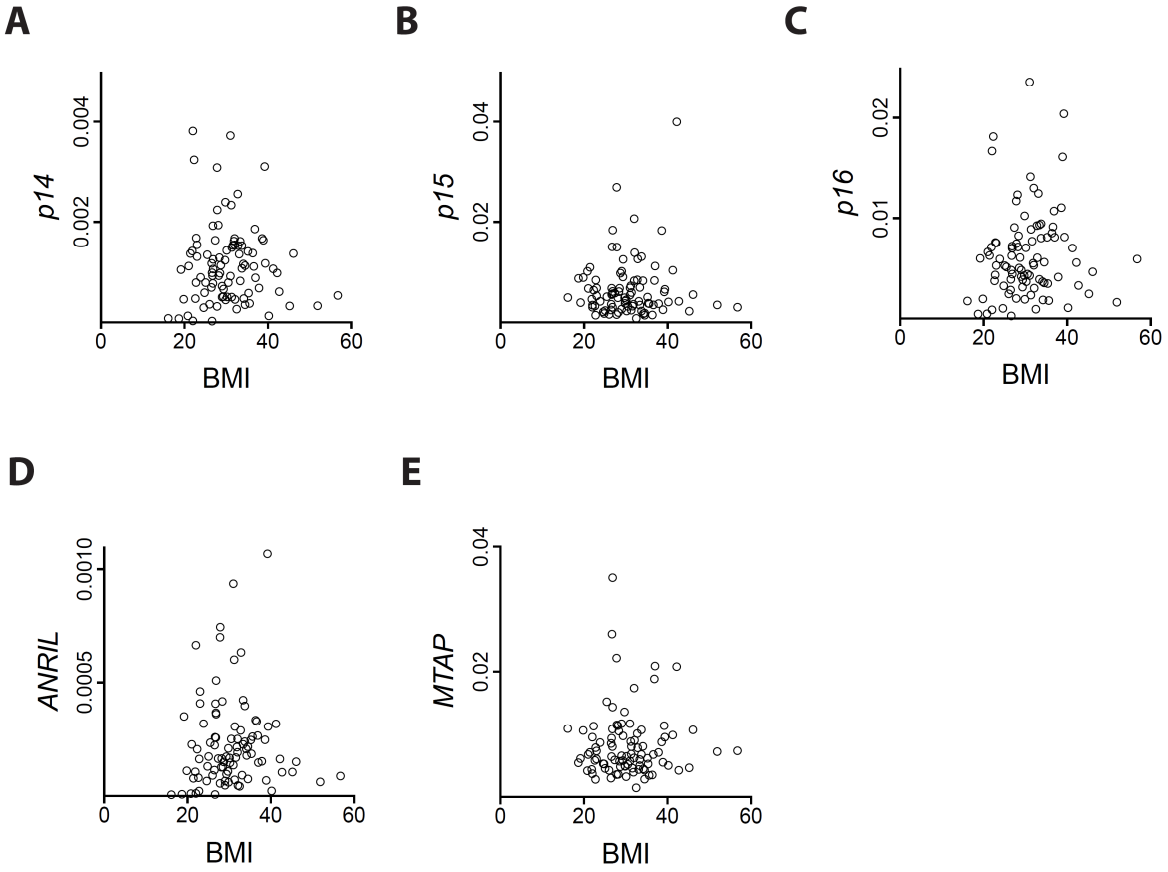
SUPPLEMENTARY DATA

Supplementary Figure 3. Donor BMI did not correlate with locus gene expression. (A-E) Reported donor BMI was compared with islet gene expression by univariate linear regression analysis. No locus gene mRNA abundance was correlated with BMI. mRNA abundance is expressed as delta-Ct, normalized to actin. Statistical analysis was calculated by linear regression; n=92 for all panels. Missing values include the 3 islet samples for which donor BMI was not available.



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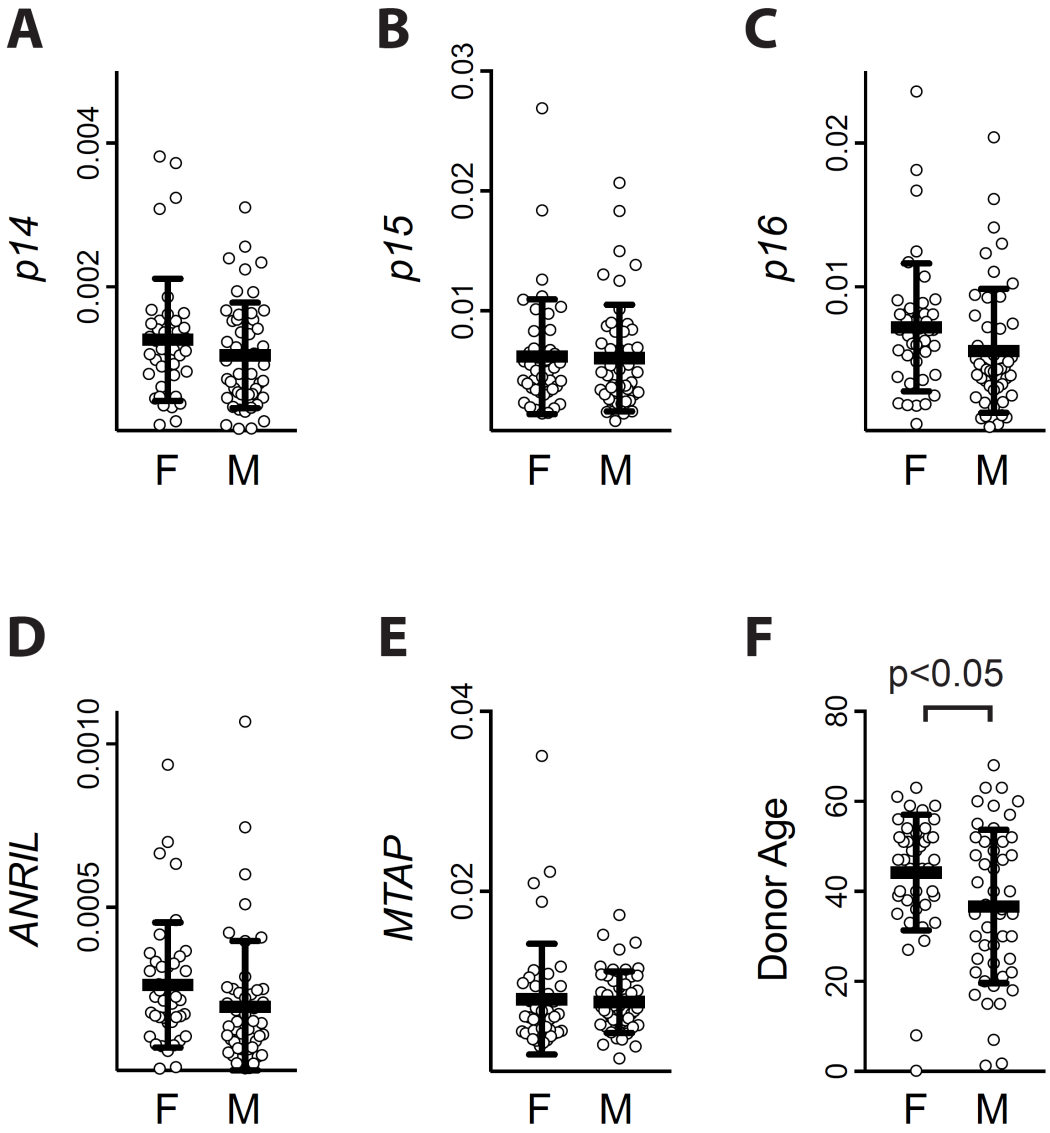
Supplementary Figure 4. Locus gene expression did not vary by donor sex. (A-E) No relationship was observed between locus gene expression and donor sex. F: female; M: male. (F) The mean age of male donors was signi_cantly lower than that of females, owing to an unfortunately high number of teenage and young-adult male donors. After age-matching the male and female cohorts (by removing all samples from both sexes with age < 27 years), reanalysis con_rmed that no locus gene expression correlated with donor sex (data not shown). mRNA abundance is expressed as delta-Ct, normalized to actin. Statistical analysis was calculated by Student's t-test; n=42 females and 48 males for all panels. Missing values include the 5 islet samples for which donor sex was not available.



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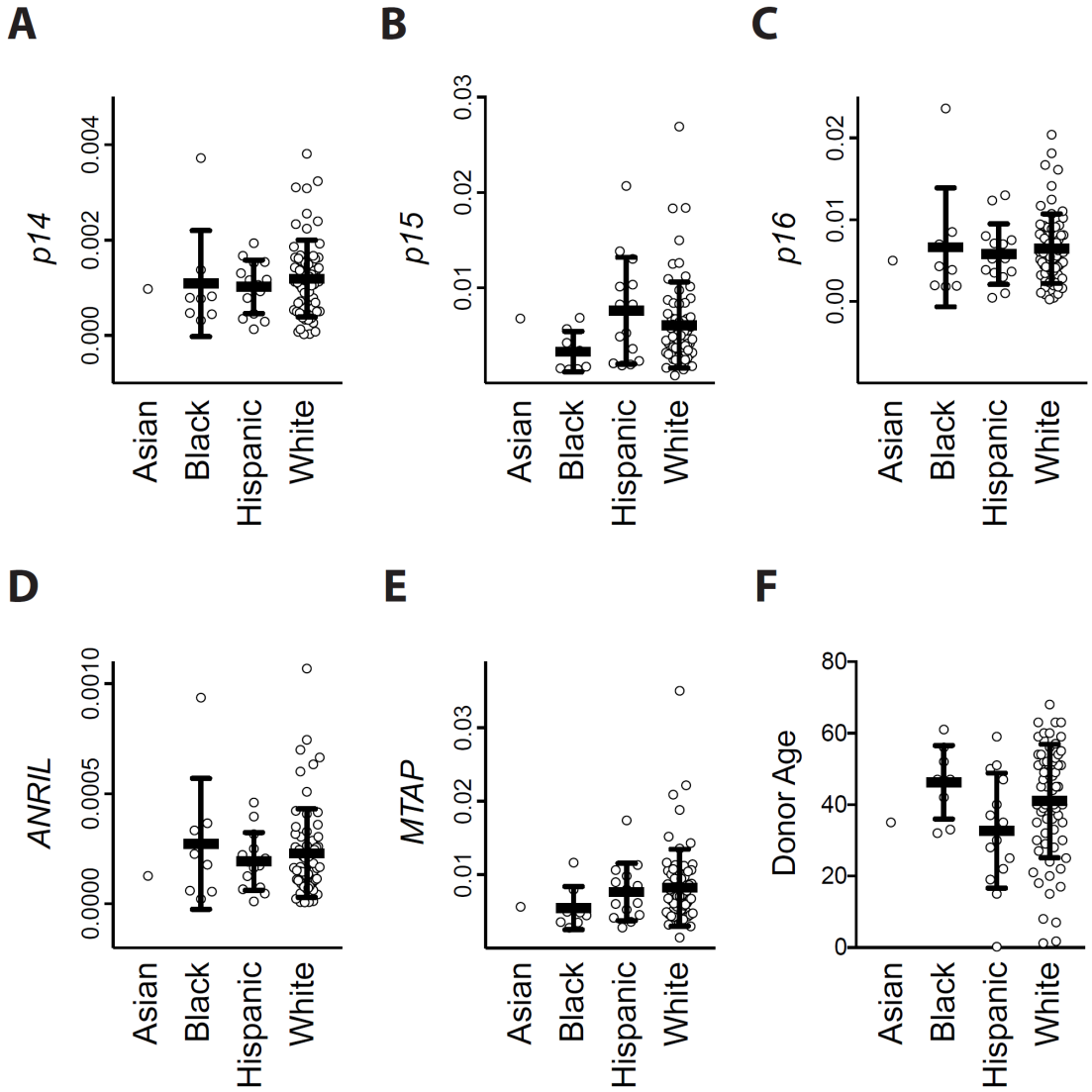
Supplementary Figure 5. Locus gene expression did not di_er by donor ethnicity. (A-E) No relationship was observed between locus genes and donor ethnicity. (F) Mean donor age was not di_erent in the ethnicity categories. mRNA abundance is expressed as delta-Ct, normalized to actin. Statistical analysis was calculated by ANOVA; p=ns for all comparisons. Sample sizes are n=1 (Asian), n=8 (black), n=14 (hispanic) and n=66 (white). Missing values include the 6 islet samples for which donor ethnicity was not available.



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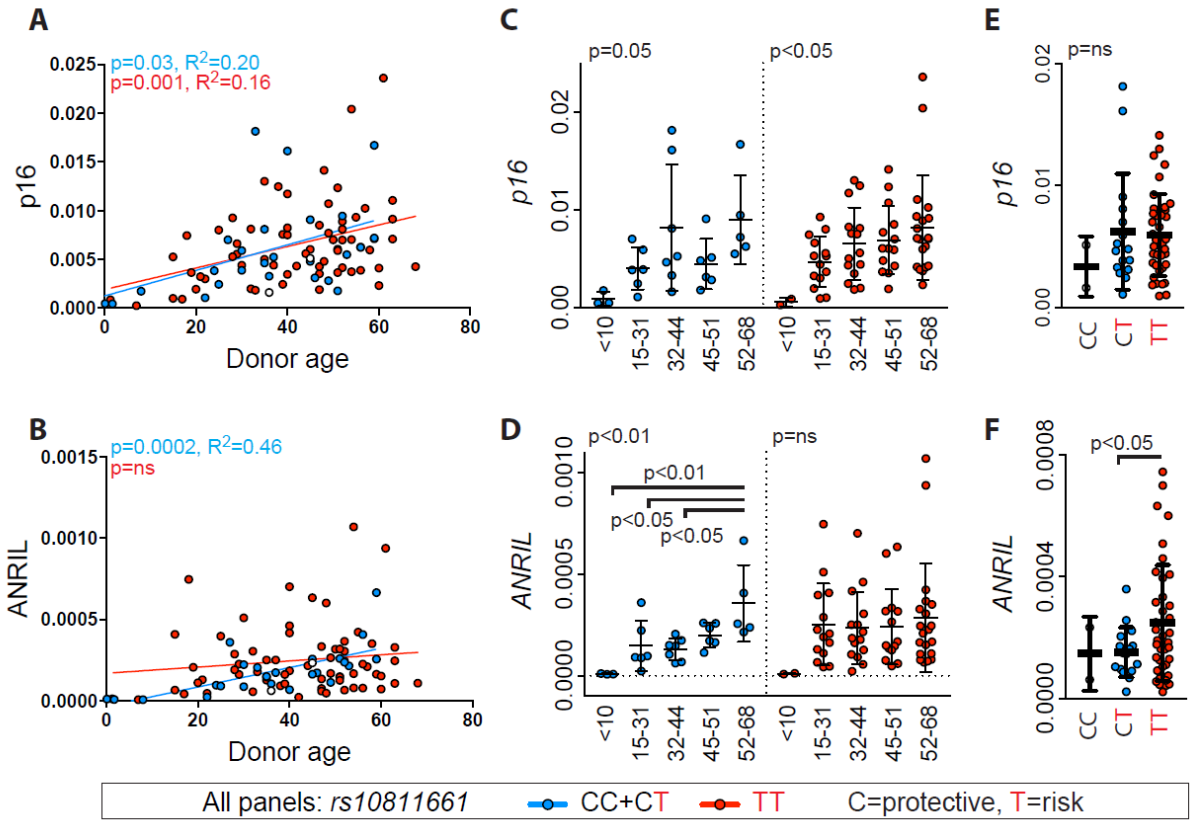
Supplementary Figure 6. Age interacts with genotype at *rs10811661* to determine *ANRIL* abundance; young donors with protective alleles had lower *ANRIL* expression. Similar analysis to Figure 4 for *rs2383208*. (A-B) Expressing *p16* (A) or *ANRIL* (B) abundance as a function of donor age, strati_ed by genotype, showed that unlike *p16*, age-dependence of *ANRIL* was driven by samples of *rs10811661*-CC+CT genotype and was absent in samples with TT genotype. (C-D) Binning analysis of the cohort (non-juvenile samples separated by quartiles) illustrated an age-dependent *ANRIL* increase in CC+CT samples but not in homozygous-risk TT samples. Juveniles <10 years of age showed markedly di_erent biology, independent of genotype. (E-F) In younger donors (ages 10-50; lower threshold de_ned by juvenile cuto_ and upper threshold de_ned by the intersection of the regression curves in (B), which is 50.8) homozygous-risk increased *ANRIL* abundance. mRNA abundance is expressed as delta-Ct, normalized to actin. Statistics by linear regression (A-B), ANOVA (D-F) with overall ANOVA signi_cance in upper left corner and signi_cant pairwise comparisons after correction for multiple comparisons labeled. Sample size: (A-D) n=92 (3 samples missing age) and (E-F) n=57 samples between the ages of 10-50.



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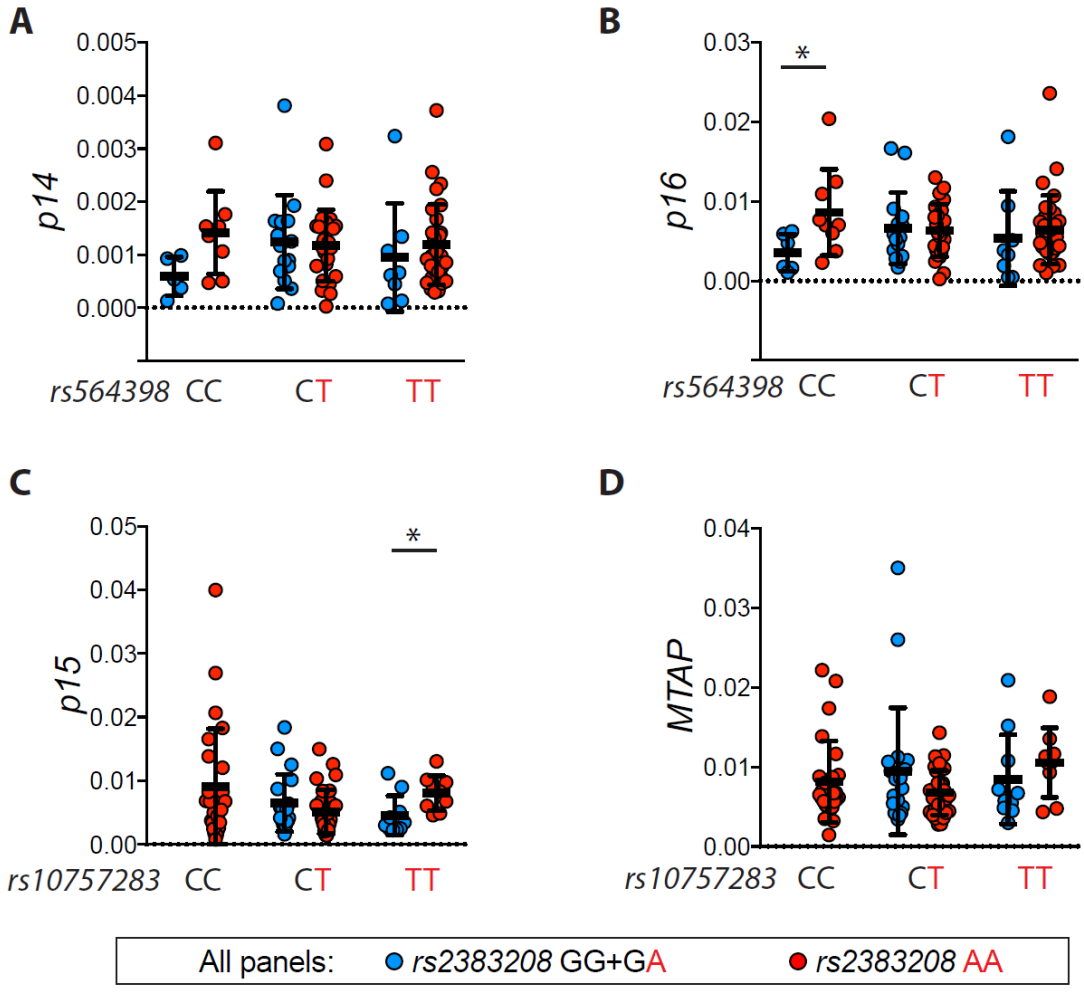
Supplementary Figure 7. Haplotype analysis showing *rs2383208* comparisons. Related to the analysis in Figure 5 for *rs10811661*. (A-B): For *p16*, in homozygous-protective *rs564398-CC* samples, homozygous- risk *rs2383208* increased expression. The same comparison for *p14* did not meet FDR<10% (q-value 17%); for ANRIL, FDR>20% (not shown). (C-D): *rs10757283* and *rs2383208* may collaboratively regulate *p15* expression; for MTAP for the same comparison, FDR>20%. * indicates FDR<10%, our pre-determined risk tolerance for future experiments exploring haplotype hypotheses. mRNA abundance is expressed as delta-Ct, normalized to actin. n=95 for all panels. All other inter-SNP comparisons, both shown and not shown, resulted FDR >10% or had insu_cient data points to evaluate (de_ned as n=2 or fewer). FDR, False Discovery Rate.



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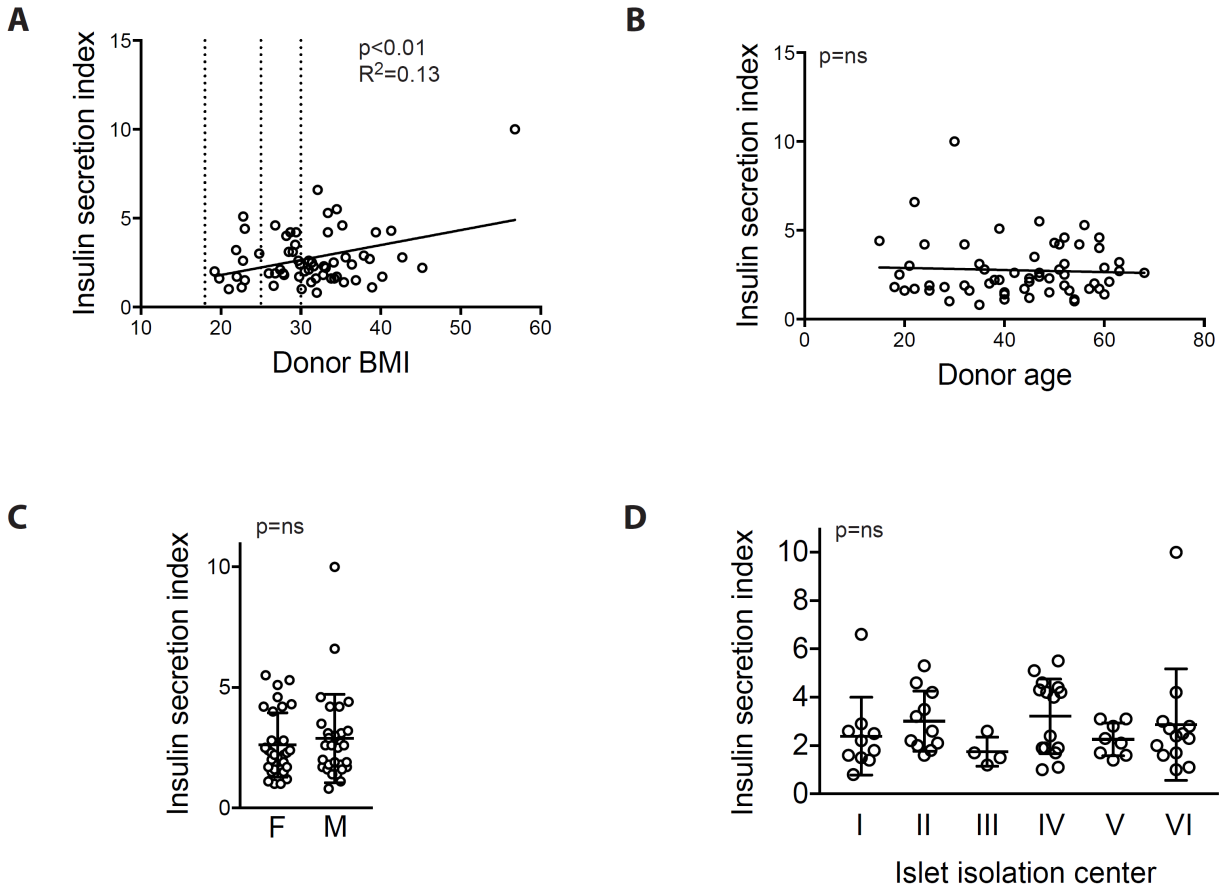
Supplementary Figure 8. Insulin secretion index correlated with donor BMI but was not related to age, sex or isolation center. (A) Insulin secretion index positively correlated with donor BMI. Vertical dotted lines represent demarkations between normal weight (18-25), overweight (25-30) and obese (>30). (B-D) Insulin secretion index was not related to donor age (B), donor sex (C), or isolation center (D). Numerals I-VI refer to the six di_erent islet isolation centers where the IIDP islet samples originated; we do not have insulin secretion data from any non-IIDP samples used in this study. (A-B): n=61; line, p values and R-squared values were calculated by linear regression. (C): n=31 (F), n=30 (M); mean +/- SD, p value by Student's t-test. (D): n=61 samples from all isolation centers combined; mean +/- SD, ANOVA with Bonferroni correction for multiple comparisons.



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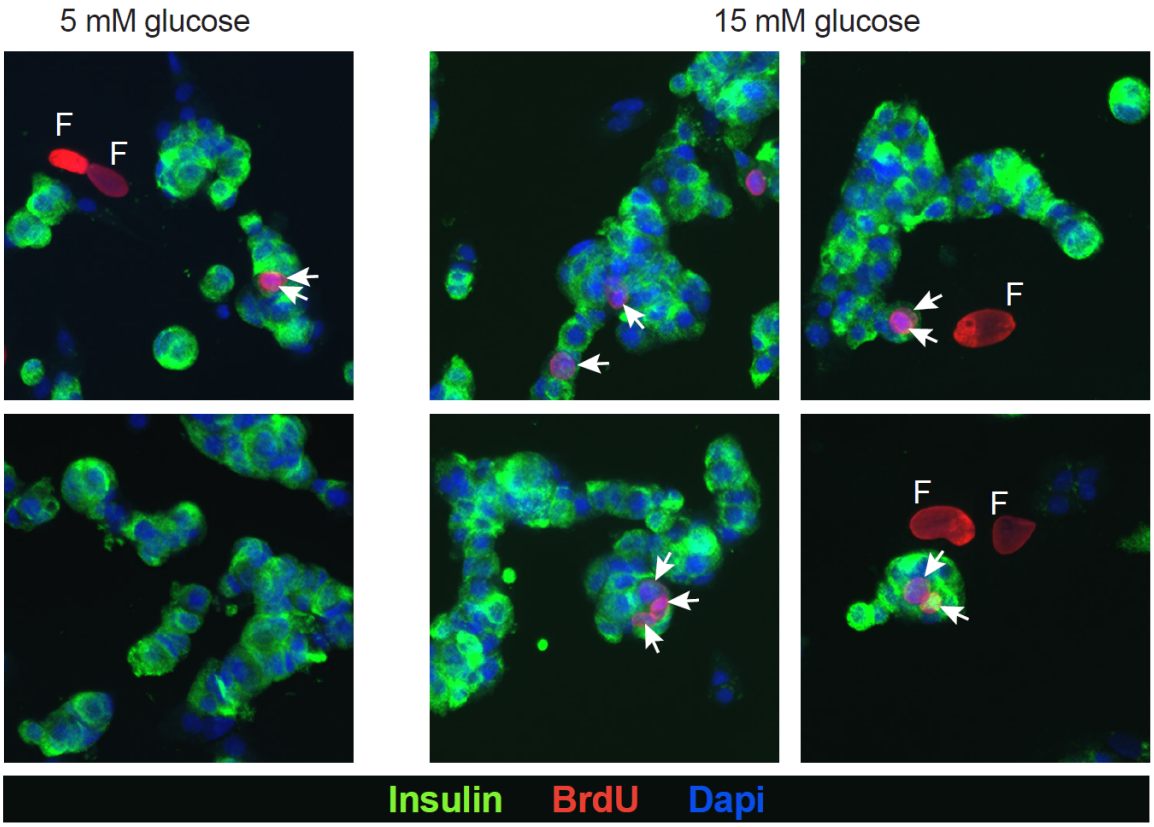
Supplementary Figure 9. Images of dispersed human islet cells cultured for BrdU analysis. Human islets were rested overnight, dispersed using trypsin, and cultured on coverslips for 96 hours in 5mM or 15mM glucose with BrdU included for the entire 96 hours. Coverslips were _xed in paraformaldehyde, immunostained for insulin and BrdU, mounted in Dapi-containing media, and imaged using _uorescent microscopy. Images were blinded and manually counted for total insulin(+) cells and % of insulin(+) BrdU(+) cells to generate the data shown in Figure 7. F, BrdU-staining _broblast. Arrows denote BrdU(+) Insulin(+) cells.



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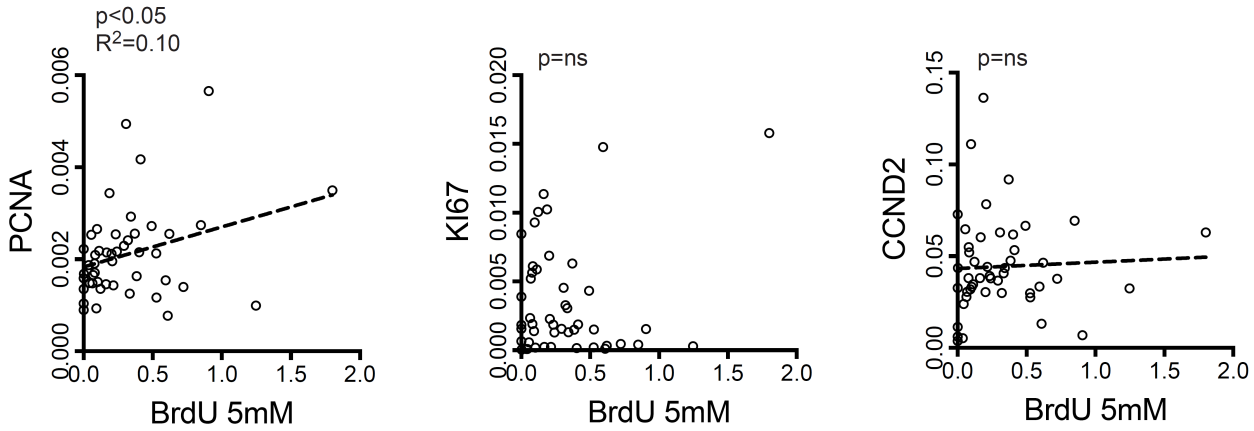
Supplementary Figure 10. Cell cycle gene expression (on whole islets under basal (5mM) glucose culture conditions, same samples as all previous gene expression data), shown in relation to dispersed islet cell BrdU incorporation in basal (5mM) glucose conditions. PCNA was marginally correlated with BrdU%; KI67 and CCND2 were not. mRNA abundance is expressed as delta-Ct, normalized to actin. BrdU 5mM: % of insulin(+) cells that were also BrdU(+) cells, in 5mM glucose cultures. Statistical analysis was calculated by linear regression; n=46 all panels.



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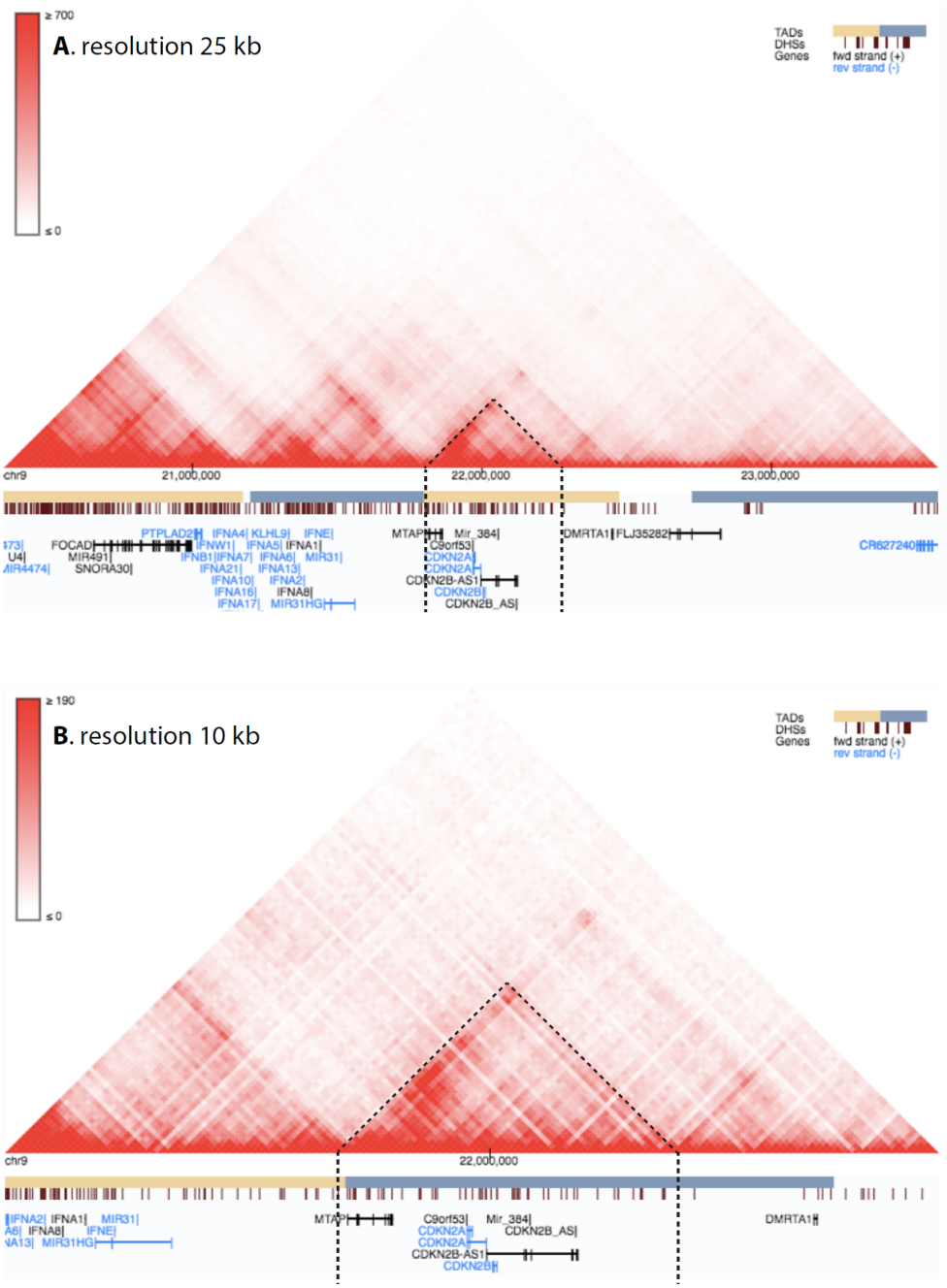
Supplementary Figure 11. Topologically Associated Domain analysis of the human CDKN2A/B locus by Hi-C of lymphoblastoid cell line GM12878. Assmebly: hg19. (A) 25 kb resolution, and (B) 10 kb resolution. Data are from Rao et al, Cell 159(7):1665-1680 (2014), and analysis is by the Yue lab website http://promoter.bx.psu.edu/hi-c/view.php and "The 3D Genome Browser: a web-based browser for visualizing 3D genome organization and long-range chromatin interactions." http://biorxiv.org/content/early/ 2017/02/27/112268, Biorxiv, 2017.



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SUPPLEMENTARY DATA

Supplementary Table 1. Donor characteristics and data obtained for each islet preparation

Sex	Age	BMI	Ethinicity	Cause of Death	SNP genotype and RNA	Insulin secretion	Beta cell proliferation
M	42	22.76	Black	Anoxia	x	x	x
M	40	38.91	White	Unknown	x	x	x
F	54	22.6	White	Cerebrovascular/stroke	x	x	
F	51	35.6	White	Anoxia	x	x	x
F	38	33.1	White	Anoxia	x	x	x
M	22	32.1	Hispanic	Head trauma	x	x	
F	47	34.5	Hispanic	Cerebrovascular/stroke	x	x	
F	39	45.2	White	Anoxia	x	x	x
M	40	35.4	White	Unknown	x	x	
M	46	29.3	Unknown	Cerebrovasular/stroke	x	x	
M	22	40.2	White	Head trauma	x	x	
M	1.8	18.7	White	anoxia	x		
F	0.2	20.8	Hispanic	Anoxia	x		
M	48	31.2	White	Cerebrovascular/stroke	x		x
Unknown	Unknown	Unknown	Unknown	Unknown	x		
M	57	29.8	White	Head Trauma	x	x	
F	45	27.4	White	Cerebrovascular/stroke	x	x	x
F	51	28.7	White	Cerebrovascular/stroke	x	x	x
M	25	33.8	Hispanic	Head Trauma	x	x	x
F	50	41.3	Hispanic	Cerebrovascular/stroke	x	x	
F	49	36.9	White	Cerebrovascular/stroke	x	x	x
F	52	35.2	White	Cerebrovascular/stroke	x	x	
F	47	29.9	Black	Cerebrovascular/stroke	x	x	
F	61	31	Black	Cerebrovascular/stroke	x	x	
F	32	39.4	White	Unknown	x	x	x
F	8	16.1	White	Cerebrovascular/stroke	x		
F	29	21	White	Head trauma	x	x	x
M	7	26.6	White	Anoxia	x		
M	52	29	White	Anoxia	x	x	
F	52	31.4	White	Cerebrovascular/stroke	x	x	x
M	28	32.8	White	Cerebrovascular/stroke	x	x	x
M	15	23	White	Head trauma	x	x	x
M	63	38.6	White	Anoxia	x	x	x
M	35	32	Hispanic	Cerebrovascular/stroke	x	x	x
M	24	29.4	White	Head trauma	x	x	
F	36	42.7	White	Anoxia	x	x	x
M	18	27.9	White	Cerebrovascular/stroke	x	x	x
M	55	33.4	White	Cerebrovascular/stroke	x	x	
F	45	32.9	White	Cerebrovascular/stroke	x	x	x
F	39	22.8	White	Cerebrovascular/stroke	x	x	
F	56	21.43	White	Chronic back pain/stroke	x		
M	19	34.1	Hispanic	Head trauma	x	x	x
M	25	26	White	Cerebrovascular/stroke	x	x	x
M	32	27.8	Black	Head trauma	x	x	x
F	49	31.6	White	Cerebrovascular/stroke	x	x	
F	58	19.2	White	Anoxia	x	x	x
M	21	24.8	White	Head trauma	x	x	x
F	45	26.6	White	Cerebrovascular/stroke	x	x	x
F	56	33.4	Black	Cerebrovascular/stroke	x	x	x
M	35	28.5	Asian	Head trauma	x	x	x
M	30	56.8	White	Anoxia	x	x	
M	63	21.9	White	Cerebrovascular/stroke	x	x	x

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F	54	30.1	White	Cerebrovascular/stroke	x	x	x
M	20	19.8	White	Anoxia	x	x	x
F	52	26.8	Black	Cerebrovascular/stroke	x	x	x
M	37	30.5	White	Head trauma	x	x	x
F	53	31.9	White	Cerebrovascular/stroke	x	x	x
F	59	28.2	Hispanic	Cerebrovascular/stroke	x	x	x
F	33	34.2	Black	Cerebrovascular/stroke	x	x	x
F	40	23	Hispanic	Cerebrovascular/stroke	x	x	x
M	47	31	White	Anoxia	x	x	x
M	1.3	22	White	Head trauma/Blunt Injury	x		
F	44	34.5	White	Cerebrovascular/stroke	x	x	x
F	47	36.4	Black	Anoxia	x	x	x
M	15	24.6	Hispanic	Head trauma	x		x
M	49	26.47	White	Head trauma/Blunt Injury	x		x
F	59	22	White	Cerebrovascular/stroke	x	x	x
M	59	26.8	White	Anoxia	x	x	x
M	68	29.7	White	Cerebrovascular/stroke	x	x	x
M	60	31.3	White	Head trauma	x	x	x
M	60	37.9	White	Anoxia	x	x	x
F	37	25.07	Hispanic	Anoxia	x		
Unknown	Unknown	Unknown	Unknown	Unknown	x		
Unknown	29	42.2	Unknown	Unknown	x		
F	40	27.8	White	Cerebrovascular/stroke	x		
M	28	32	Hispanic	Cerebrovascular/stroke	x		
F	27	26.9	White	Cerebrovascular/stroke	x		
M	51	30.2	White	Cerebrovascular/stroke	x		
M	52	33.7	White	Cerebrovascular/stroke	x		
F	51	23.9	White	Unknown	x		
M	30	26.5	Hispanic	Unknown	x		
M	30	26.9	White	Head trauma	x		
F	63	36.6	White	Cerebrovascular/stroke	x		
Unknown	Unknown	Unknown	Unknown	Unknown	x		
M	45	25.49	White	Head trauma	x		
M	54	39.2	White	Blunt Head Trauma MVA	x		
M	17	32.5	White	Unknown	x		
M	51	28.1	Hispanic	Unknown	x		
Unknown	56	26.7	Unknown	Unknown	x		
F	35	37	White	Cerebrovascular/stroke	x		
M	36	51.9	White	Cerebrovascular/stroke	x		
F	40	28.4	White	Unknown	x		
F	33	22.3	White	Cerebrovascular/stroke	x		
M	35	46.1	White	Unknown	x		
M	48	29	White	Cerebrovascular/stroke	x		

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Supplementary Table 2. Minor Allele Frequencies

CDKN2A/B Locus T2D SNPs tested		rs2383208 G/G G/A A/A	rs10757283 C/C C/T T/T	rs10811661 C/C C/T T/T	rs564398 C/C C/T T/T
Minor allele		G	T	C	C
Risk allele		A	T	T	T
Observed minor allele frequency in this human islet cohort	All (n=95)	16.3%	46.8%	15.3%	36.8%
	Black (n=8)	6.3%	37.5%	0.0%	6.3%
	Hispanic (n=13)	10.7%	42.9%	10.7%	28.6%
	Caucasian (n=62)	18.9%	50.0%	18.2%	42.4%
Observed minor allele frequency in 1000 Genomes	EUR	17.3%	43.9%	16.8%	41.4%

For each SNP the minor allele, risk allele (in red) and observed minor allele frequency (MAF) in this human islet cohort are described. These MAFs are similar to those reported in the large populations tested in the 1000 genomes project (data are shown for EUR, since we have too few samples in non-white categories for accurate comparison).

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Supplementary Table 3.Linkage Disequilibrium

Expected LD (R^2) (from EUR population)

Expected (EUR population) by LDpair		rs564398	rs2383208	rs10811661	rs10757283
	rs564398		0.006	0.007	0.016
	rs2383208	0.006		0.952	0.256
	rs10811661	0.007	0.952		0.258
	rs10757283	0.016	0.256	0.258	

Observed LD (R^2) in our samples

Observed in our samples (n=95)		rs564398	rs2383208	rs10811661	rs10757283
	rs564398		0.040	0.046	0.001
	rs2383208	0.040		0.924	0.221
	rs10811661	0.046	0.924		0.204
	rs10757283	0.001	0.221	0.204	

Expected LD (R^2) (top chart) were calculated using the LDpair function on the NIH-supported LDlink website. The EUR population was selected since the majority of our samples were Caucasian. The observed LD (R^2) in our samples (bottom chart) were calculated using the cubeX web tool at http://www.oege.org/software/cubex/.

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Supplementary Table 4. Multivariable linear models testing relationships between donor characteristics and gene expression

	p14			***p15***			***p16***			***ANRIL***			***MTAP***		
Sex	Point	SE	p	Point	SE	p	Point	SE	p	Point	SE	p	Point	SE	p
Female v. Male	0.0869	0.1578	0.5819	0.9949	1.0280	0.3331	0.8965	0.8675	0.3014	0.0410	0.0426	0.3362	0.6714	1.0426	0.5196
Race/ethnicity															
Black v. White	-0.2308	0.2706	0.3937	-2.7309	11.7634	0.1215	-0.6622	1.4880	0.6563	0.0145	0.0731	0.8428	-2.8995	1.7884	0.1050
Other v. White	-0.0723	0.2016	0.7198	1.2057	1.3136	0.3587	0.0125	1.1084	0.9910	-0.0177	0.0545	0.7454	-0.0933	1.3322	0.4836
Age, per year	0.0186	0.0051	0.0003	-0.0641	0.0332	0.0535	0.1099	0.0280	<0.0001	0.0030	0.0014	0.0304	-0.0178	0.0337	0.5961
BMI, per kg/m^2	-0.0085	0.0107	0.4281	0.0383	0.0697	0.5829	0.0212	0.0588	0.7181	-0.0003	0.0029	0.9063	-0.0108	0.0707	0.8788
Above model, integrating mRNA expression of other locus genes															
p14	-	-	-	2.8584	1.1627	0.0140	4.8178	0.3939	<0.0001	0.1584	0.0424	0.0002	-0.0666	1.2224	0.9566
p15	0.0209	0.0085	0.0140	-	-	-	-0.0892	0.0533	0.0944	0.0000	0.0039	0.9992	0.5201	0.0900	<0.0001
p16	0.1269	0.0104	<0.0001	-0.3209	0.1918	0.0944	-	-	-	0.0033	0.0074	0.6577	0.1248	0.1980	0.5285
ANRIL	0.8076	0.2164	0.0002	0.0028	2.7079	0.9992	0.6317	1.4258	0.6577	-	-	-	3.8463	2.7320	0.1592
MTAP	-0.0005	0.0086	0.9566	0.5005	0.0866	<0.0001	0.0334	0.0529	0.5285	0.0053	0.0038	0.1592	-	-	-

Exploratory multivariable model testing for impact of donor characteristics (sex, race, age, BMI) on gene expression confirmed a positive relationship between donor age and islet abundance of *p14, p15* (marginal association; inverse relationship), *p16* and *ANRIL*. This model did not uncover an impact of sex, race or BMI on expression of these genes. Integrating expression of other locus genes into the model (lower rows) confirmed a significant positive correlation between *p14-ANRIL, p14-p16* and *p15-MTAP*, as well as *p14-p15* (weaker correlation). Point estimate is the difference in gene expression conferred by comparator condition to control condition, or the incremental increase in gene expression conferred by higher amount for linear input variables such as age, BMI and gene expression. SE, standard error of the point estimate. Other: combined all samples of non-white race, since sample size was too small to analyze for those other than black or white. BMI, body mass index.

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Supplementary Table 5. List of SNPs in linkage disequilibrium with SNPs tested in this study

rs2383208										
chr	pos (hg38)	LD(r^2)	LD(D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq
9	22133285	0.93	0.98	rs10965250	G	A	0.05	0.14	0.44	0.16
9	22134069	0.93	0.98	rs10811660	G	A	0.05	0.14	0.44	0.16
9	22134095	0.93	0.98	rs10811661	T	C	0.05	0.14	0.44	0.16
9	22134254	0.93	0.97	rs10811662	G	A	0.1	0.15	0.43	0.17
9	22132730	0.95	0.99	rs10965247	A	G	0.05	0.14	0.44	0.16
9	22132879	0.96	0.98	rs10965248	T	C	0.07	0.14	0.44	0.17
9	22132699	0.97	0.99	rs10965246	T	C	0.07	0.14	0.44	0.17
9	22132077	1	1	rs2383208	A	G	0.17	0.14	0.4	0.17
rs10811661										
chr	pos (hg38)	LD(r^2)	LD(D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq
9	22136490	0.82	0.99	rs1333051	A	T	0.08	0.09	0.15	0.14
9	22132077	0.93	0.98	rs2383208	A	G	0.17	0.14	0.4	0.17
9	22132730	0.94	0.97	rs10965247	A	G	0.05	0.14	0.44	0.16
9	22132699	0.96	0.99	rs10965246	T	C	0.07	0.14	0.44	0.17
9	22132879	0.97	1	rs10965248	T	C	0.07	0.14	0.44	0.17
9	22134254	0.99	1	rs10811662	G	A	0.1	0.15	0.43	0.17
9	22133285	1	1	rs10965250	G	A	0.05	0.14	0.44	0.16
9	22134069	1	1	rs10811660	G	A	0.05	0.14	0.44	0.16
9	22134095	1	1	rs10811661	T	C	0.05	0.14	0.44	0.16
rs10757283										
chr	pos (hg38)	LD(r^2)	LD(D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq
9	22134303	0.91	0.99	rs7019437	C	G	0.23	0.45	0.63	0.41
9	22134652	0.98	0.99	rs7019778	A	C	0.23	0.46	0.64	0.43
9	22133646	0.99	1	rs10217762	T	C	0.2	0.45	0.63	0.43
9	22133985	0.99	1	rs10757282	T	C	0.23	0.45	0.64	0.43
9	22134173	1	1	rs10757283	C	T	0.45	0.47	0.64	0.43
rs564398										
chr	pos (hg38)	LD(r^2)	LD(D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq
9	22015998	0.81	0.91	rs1101329	C	T	0.01	0.21	0.1	0.41
9	22043613	0.81	0.99	rs1412830	C	T	0.01	0.19	0.1	0.37
9	22021173	0.82	0.91	rs597816	T	C	0.01	0.21	0.1	0.41
9	22007358	0.84	-0.99	rs3217977	CA	C	0.96	0.75	0.9	0.55
9	22056360	0.84	-0.93	rs7866783	A	G	0.98	0.79	0.9	0.59
9	22011643	0.85	0.98	rs573687	G	A	0.01	0.19	0.1	0.38
9	21999329	0.86	0.95	rs2811713	G	A	0.01	0.19	0.18	0.39
9	22009699	0.86	-1	rs2069418	G	C	0.98	0.77	0.9	0.55
9	22049480	0.88	-0.94	rs200059580	A	ACT	0.99	0.8	0.9	0.59
9	22015466	0.89	0.98	rs1101330	C	A	0.02	0.19	0.1	0.39
9	22051671	0.89	-0.95	rs944801	G	C	0.99	0.79	0.9	0.59
9	22052735	0.89	-0.95	rs6475604	T	C	0.99	0.8	0.9	0.59
9	22054041	0.89	-0.95	rs7030641	C	T	0.99	0.79	0.9	0.59
9	22003368	0.9	-0.99	rs1063192	G	A	0.99	0.79	0.82	0.57
9	22019130	0.9	1	rs523096	A	G	0.01	0.23	0.1	0.43
9	22019674	0.9	1	rs518394	G	C	0.01	0.23	0.1	0.43
9	22022377	0.9	0.99	rs581876	C	T	0.01	0.19	0.32	0.39
9	22026078	0.9	1	rs615552	T	C	0.01	0.22	0.1	0.43
9	22045318	0.9	-0.96	rs1360589	C	T	0.99	0.79	0.9	0.58
9	22040766	0.94	-0.98	rs1333037	C	T	0.99	0.79	0.9	0.58
9	22036113	0.95	-0.99	rs1008878	G	T	0.97	0.79	0.9	0.58
9	22036368	0.95	-0.99	rs1556515	C	T	0.97	0.79	0.9	0.58
9	22031006	0.96	-1	rs7865618	G	A	0.99	0.8	0.9	0.58
9	22033367	0.96	-1	rs2157719	C	T	0.99	0.8	0.9	0.58
9	22028213	0.98	1	rs142048183	CAT	C	0.01	0.2	0.1	0.41
9	22043927	0.98	0.99	rs1412829	A	G	0.01	0.21	0.1	0.41
9	22026595	0.99	1	rs613312	G	A	0.01	0.2	0.1	0.41
9	22026640	0.99	1	rs543830	A	T	0.01	0.2	0.1	0.41
9	22027403	0.99	1	rs599452	G	A	0.01	0.2	0.1	0.41
9	22029081	0.99	1	rs679038	G	A	0.02	0.2	0.1	0.41
9	22032153	0.99	1	rs634537	T	G	0.02	0.21	0.1	0.41
9	22029548	1	1	rs564398	T	C	0.01	0.2	0.1	0.41

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Multiple SNPs are in linkage disequilibrium with the T2D---associated *CDKN2A/B* SNPs genotyped in this study. Data In this table include all SNPs In HaploReg With LD(r^2) > 0.80, From the EUR Population data (chosen because the majority of our samples were Caucasian). T2D SNPs Genotyped for this study are in red font. Allele Frequencies in AFR, AMR, ASN, EUR are included for reference. Pos, position. Ref, Reference allele. Alt, Alternate allele.

Supplementary Table 6. Multivariable linear models testing for SNP impact on gene expression

	p14			*p15*			*p16*			*ANRIL*			*MTAP*		
	point	SE	p	point	SE	p	point	SE	p	point	SE	p	point	SE	p
rs2383208															
A/A v. G/A	0.1151	0.1679	0.4931	2.0529	1.7650	0.0565	0.4085	0.9206	0.6572	0.0635	0.0450	0.1585	-0.4870	1.1066	0.6599
A/A v. G/G	0.2909	0.5227	0.5779	2.3846	3.3504	0.4766	3.1359	2.8652	0.2738	0.0817	0.1401	0.5598	-3.7195	-3.4444	0.2802
number of risk alleles	0.1234	0.1467	0.4003	1.8169	0.9414	0.0536	0.7264	0.8064	0.3677	0.0573	0.0394	0.1455	-0.8634	0.9693	0.3731
rs10811661															
T/T v. C/T	0.0473	0.1742	0.7862	2.1538	1.1138	0.0531	0.0192	0.9540	0.9839	0.0566	0.0467	0.2259	-0.5684	1.1453	0.6197
T/T v. C/C	0.2730	0.5242	0.6025	2.4398	3.3510	0.4666	3.0297	2.8701	0.2911	0.0806	0.1406	0.5667	-3.7490	3.4458	0.2766
number of risk alleles	0.0729	0.1513	0.6297	1.8850	0.9679	0.0515	0.4498	0.8316	0.5886	0.0519	0.0406	0.2008	-0.9444	0.9963	0.3432
rs10757283															
T/T v. C/T	-0.0318	0.2011	0.8742	1.9756	1.2644	0.1182	0.5558	1.1087	0.6162	-0.0274	0.0548	0.6178	2.5824	1.3227	0.0509
T/T v. C/C	-0.3073	0.2179	0.1586	-1.5806	1.3704	0.2488	-0.9627	1.2017	0.4231	-0.0600	0.0594	0.3127	1.8335	1.4336	0.2009
number of risk alleles	-0.1637	0.1085	0.1316	-1.0181	0.7081	0.1505	-0.5668	0.6011	0.3458	-0.0302	0.0295	0.3058	0.7796	0.7215	0.2799
rs564398															
T/T v. C/T	0.0252	0.1692	0.8814	0.4790	1.0970	0.6624	0.1187	0.9339	0.8988	-0.0102	0.0459	0.8236	-0.1792	1.1199	0.8729
T/T v. C/C	0.2564	0.2379	0.2810	2.2636	1.5427	0.1423	0.8902	1.3133	0.4979	-0.0336	0.0646	0.6032	1.2535	1.5749	0.4261
number of risk alleles	0.1049	0.1133	0.3547	0.9840	0.7350	0.1806	0.3712	0.6248	0.5525	-0.0153	0.0307	0.6183	0.4443	0.7510	0.5541

Exploratory multivariable model testing for impact of *CDKN2A/B* locus T2D SNP genotype, incorporating donor characteristics (sex, race, age, BMI from Supplemental Table 2) on gene expression failed to reveal a significant impact of any genotype on any gene expression. Point estimate is the difference in gene expression relative to protective genotype (individual comparisons) or incremental gene expression for each additional risk allele at that SNP (number of risk alleles). SE, standard error of the point estimate. Risk allele is depicted in red for each SNP.

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Supplementary Table 7. Multivariable models testing determinants of insulin secretion index

		mean difference in insulin secretion index	95% confidence interval	p-value
Isolation center not included in model	Female v. Male	-0.25	(-1.03 - 0.53)	0.5318
	age (per year)	0.00	(-0.03 - 0.03)	0.8951
	African-American v. White	0.02	(-1.09 - 1.13)	0.974
	BMI (per kg/m^2)	0.08	(0.03 - 0.14)	0.0029
Isolation center included in model	Female v. Male	-0.32	(-1.05 - 0.41)	0.3873
	age (per year)	0.00	(-0.03 - 0.03)	0.9665
	African-American v. White	-0.10	(-1.14 - 0.95)	0.8588
	BMI (per kg/m^2)	0.10	(0.02 - 0.17)	0.0171

Multivariable model testing for impact of donor characteristics (sex, age, race, BMI) on insulin secretion index confirmed a positive relationship between donor BMI and insulin secretion, but did not uncover an impact of sex, race or age. Integrating islet isolation center into the model using a generalized estimating equation (GEE) approach to adjust for potential clustering of insulin secretion measurements within islet isolation centers (lower rows) confirmed a significant positive correlation between BMI and insulin secretion index (0.10 units of insulin secretion index per BMI unit, p=0.0171). In a multivariable linear model adjusted for sex, age, ethnicity and BMI, mean insulin secretion values from center IV (see Supplemental figure 8) were higher than the mean values from the other centers, but after Bonferroni adjustment none of the between-center mean comparisons were statistically significant (not shown). BMI, body mass index.

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Supplementary Table 8. Multivariable models testing for impact of SNP genotype on insulin secretion index

	rs10757283			rs10811661			rs2383208			rs564398		
	mean difference in insulin secretion	95% confidence interval	p-value	mean difference in insulin secretion	95% confidence interval	p-value	mean difference in insulin secretion	95% confidence interval	p-value	mean difference in insulin secretion	95% confidence interval	p-value
Female v. Male	-0.32	(-1.16 - 0.52)	0.4583	-0.25	(-1.03 - 0.53)	0.5316	-0.25	(-1.03 - 0.53)	0.5264	-0.24	(-1.04 - 0.55)	0.5503
Age (per year)	0.00	(-0.03 - 0.03)	0.7976	0.00	(-0.03 - 0.03)	0.8704	0.00	(-0.03 - 0.03)	0.8717	0.00	(-0.03 - 0.03)	0.9685
African-American v. White	0.05	(-1.07 - 1.17)	0.9330	0.07	(-1.07 - 1.21)	0.9031	0.04	(-1.07 - 1.16)	0.9387	0.19	(-1.04 - 1.43)	0.7573
BMI (per kg/m^2)	0.08	(0.03 - 0.14)	0.0030	0.08	(0.03 - 0.14)	0.0041	0.08	(0.03 - 0.14)	0.0039	0.09	(0.03 - 0.14)	0.0021
rs10757283												
no risk alleles v. two	-0.03	(-1.16 - 1.11)	0.9655									
one risk allele v. two	0.17	(-0.93 - 1.27)	0.7661									
rs10811661												
one risk allele v. two				0.20	(-0.74 - 1.13)	0.6773						
rs2383208												
one risk allele v. two							0.18	(-0.71 - 1.07)	0.6961			
rs564398												
no risk alleles v. two										0.02	(-1.15 - 1.19)	0.9692
one risk allele v. two										0.45	(-0.42 - 1.32)	0.3123

In multivariable linear models adjusted for sex, age, race and BMI, and for potential clustering of insulin secretion index produced by different islet isolation centers (using a GEE approach), none of the four CDKN2A/B SNP genotypes had any significant association with insulin secretion index. These models confirmed the positive relationship between donor BMI and insulin secretion. BMI, body mass index.

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