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Supplemental information

3D chromatin maps of the human pancreas reveal lineage-specific regulatory architecture of T2D risk

Chun Su, Long Gao, Catherine L. May, James A. Pippin, Keith Boehm, Michelle Lee, Chengyang Liu, Matthew C. Pahl, Maria L. Golson, Ali Naji, HPAP Consortium, Struan F.A. Grant, Andrew D. Wells, and Klaus H. Kaestner

Supplemental Figure Legends

Supplemental Figure 1. Pancreatic islet cell transcriptomic profile defined using scRNA-seq. A, Clustering of gene expression profile from 5,288 pancreatic cells from organ donors without diabetes identified 9 distinct clusters on UMAP. Endo: endothelial; eps: epsilon (ghrelin producing); mes: mesenchymal; PP: (pancreatic polypeptide producing). B, the expression of marker genes in single cells and donor composition within cell type clusters. C, Pearson correlation of gene expression between donors. D, Pearson correlation of gene expression between cell types. E, Estimate of cell composition in sorted pancreatic cell subsets through integration of scRNA-seq. The cell type composition from bulk RNA-seq data on sorted pancreatic cell subsets were characterized using a list of gene markers obtained from panel B.

Supplemental Figure 2. Pancreatic islet cell chromatin accessibility profile defined using scATAC-seq. A, Clustering of accessible chromatin profile from 12,473 pancreatic cells from organ donors without diabetes identified 9 distinct clusters on UMAP. B, Promoter accessibility of selected marker genes in single cells and donor composition within cell type clusters. Promoters were defined as the window of -1,500 to +500bp around TSS in Gencode V19 annotation. C, scATAC-seq and bulk ATAC-seq accessibility signal around selected marker genes: CPA1 (acinar), GCG (alpha) and IGF2 (beta). Fragments were aggregated for each cell type in scATAC-seq. The coverage for both scATAC-seq and bulk ATAC-seq was normalized using the RPGC method from deeptools. D, Pearson correlation of OCR accessibility between scATAC-seq and bulk ATAC-seq. OCR accessibility were calculated as FPKM by mapping either cell type aggregated fragments from scATAC-seq or fragments of bulk ATAC-seq to the consensus pseudo-bulk peak reference. E, Spearman correlation between t-statistics of cluster-specific genes based on promoter accessibility (scATAC-seq) and gene expression (scRNA-seq).

Supplemental Figure 3. 3D chromatin architecture of pancreatic cell subsets defined by Hi-C assay. A, Stratum-adjusted correlation coefficient (SCC) between Hi-C samples to measure sample reproducibility and interrelationships of cell lineages. B, the number of Topologically Associating Domains (TADs) identified in each cell type. C, the distribution of TAD size in each cell type. D, Aggregate peak analysis (APA) plots of chromatin loops identified by the loop callers Mustache and Fit-Hi-C2. The APA scores were calculated with respect to the enrichment of the center pixel at 4kb resolution and labelled at the top left corner. E, Venn diagram of consensus loop calls across cell types. The consensus loops were collected by merging loop calls from 1kb, 2kb and 4kb resolutions with preference to keep the highest resolution data. F, The number of loops annotated to open chromatin regions (OCR) and genes. OCR (green): both anchors overlapped OCRs; Gene (teal): both anchors overlapped gene promoters (-1,500 to +500bp around the TSS). Gene-OCR (purple): one anchor overlapped an OCR and the other anchor overlapped a gene promoter. G, Z-score distribution of co-accessible promoters and distal OCRs detected by Hi-C chromatin loops. P-values were calculated by two-sided Wilcoxon rank sum test. H, The number of loop anchors overlapped with chromHMM chromatin features. chromHMM chromatin states for acinar and endocrine cells were previously defined in Arda et al. 2018. I, Enrichment of chromatin loops at open chromatin regions and regulatory chromatin

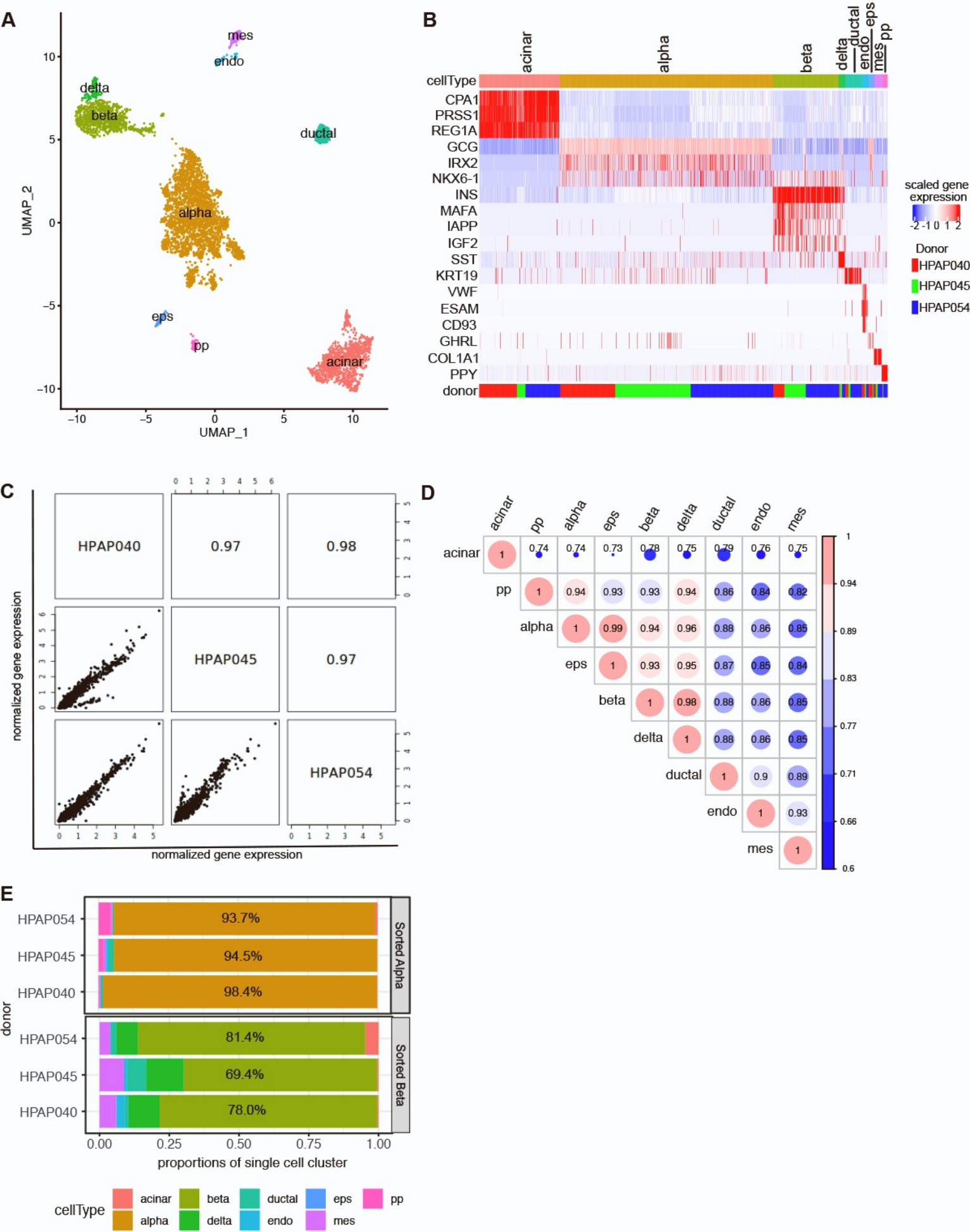
features defined by chromHMM. The enrichment fold change was obtained by comparing called loops to distance-matched random chromatin contacts. The p-value was calculated by a 100-fold permutation test.

Supplemental Figure 4. Illustration of variant-to-gene mapping. The candidate variants were first defined by proxy SNPs within high LD (R2 > 0.8) with sentinel signals from GWAS, and then filtered to proxy SNPs located in open chromatin by peaks called from ATAC-seq. The open proxy SNPs were mapped to candidate genes with two approaches. (1) Distal genes were linked to open SNP-containing peaks with physical interaction evidence from Hi-C loop calls for each cell type (left diagram). (2) Proximal genes whose promoter regions (-1,500bp ~ +500bp of TSS) fall within open SNP-containing peaks.

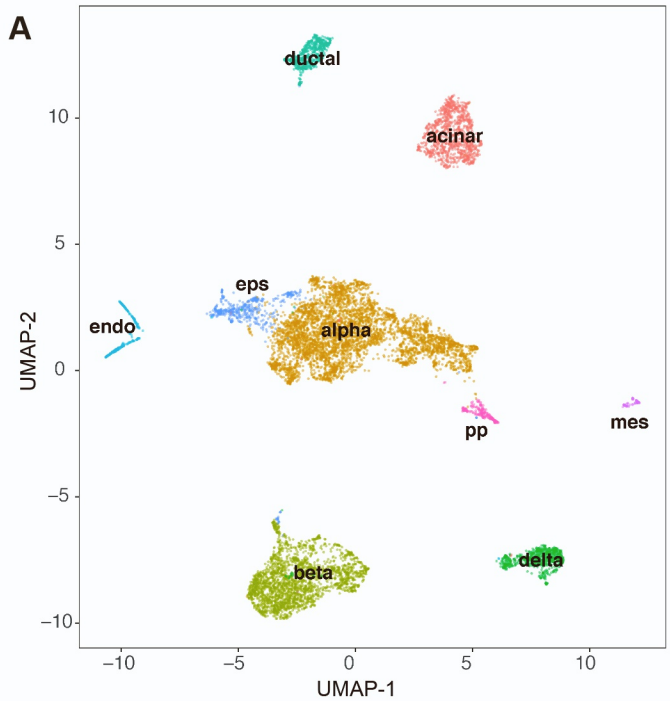
Supplemental Figure 5. Cell type specific implicated genes and examples of likely disruption of transcription factor DNA binding motifs by T2D relevant SNPs. A. Comparison of genes implicated by our approach and that of Rai and colleagues (Rai et al., 2020). Yellow indicates sets of GWAS sentinel:gene pairs specific to this study, cyan indicates genes specific to Rai et al., 2020, and magenta indicates groups implicated in both studies. Sentinel:gene pairs specific to beta cells are highlighted (black: closest gene to sentinel, red not the closest gene). B. Genomic track for KCNQ1 a putative acinar cell specific effector gene. C.Variants at the TH/INS/TRPM5 locus that are in contact loops with the INS or TRPM5 promoter likely disrupt binding of the TFs indicated. D. Disruption of a putative NEUROD2 binding site by rs4234731 in the WSF1 gene. E. Genomic track for DGKB a putative beta cell specific effector gene.

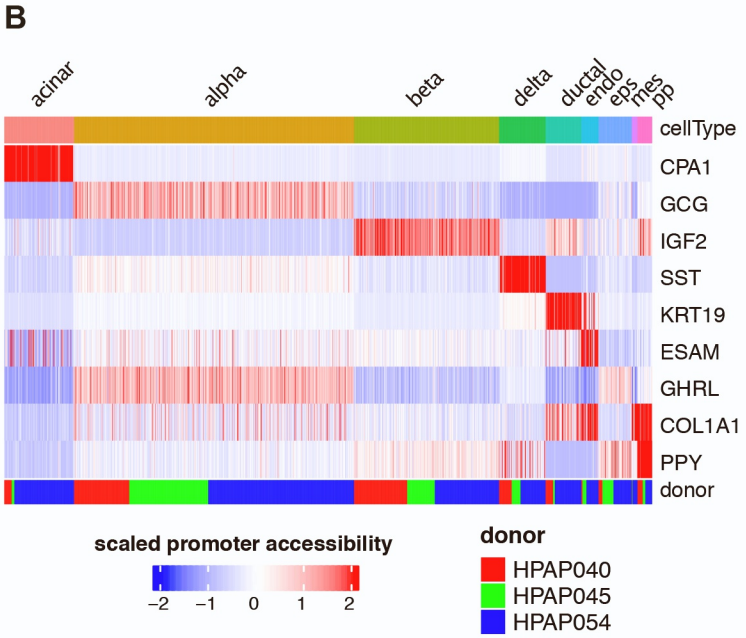
Supplemental Figure 6. Comparison of T2D variant-to-gene mapping with other diabetes relevant traits. A, 'Upset' plot of putative casual-variant-gene pairs across diabetes-related traits. Examined traits include type 2 diabetes (T2D), fasting glucose (FG), Hemoglobin A1C (HbA1c), fasting insulin (FI), 2h glucose (2hGlu) and T1D. Each row corresponds to the set of putative casual-variant to gene pairs in each trait. Each column corresponds to one segment of a Venn diagram obtained by intersecting the traits indicated as black circles. All segments that intersect with T2D are highlighted in red. The number of putative casual-variant to gene pairs in each set and intersecting segment are summarized in the bar graph on top. B, Stacked association plots of T2D with FG and HbA1c at T2D sentinel signal rs10228066. Variant-to-gene mapping implicates rs10228796 as the candidate causal variant and the linked rs10228796 to the candidate effector gene DGKB with beta cell-specific chromatin loops (Supplemental Figure 9C, Supplemental Table 10). C, HyPrColoc identified rs10228796 as a candidate causal variant explaining the shared association signal among T2D, FG and HbA1c. The posterior probability of colocalization between the traits was 0.819 and rs10228796 explained 33.6% of their colocalization.

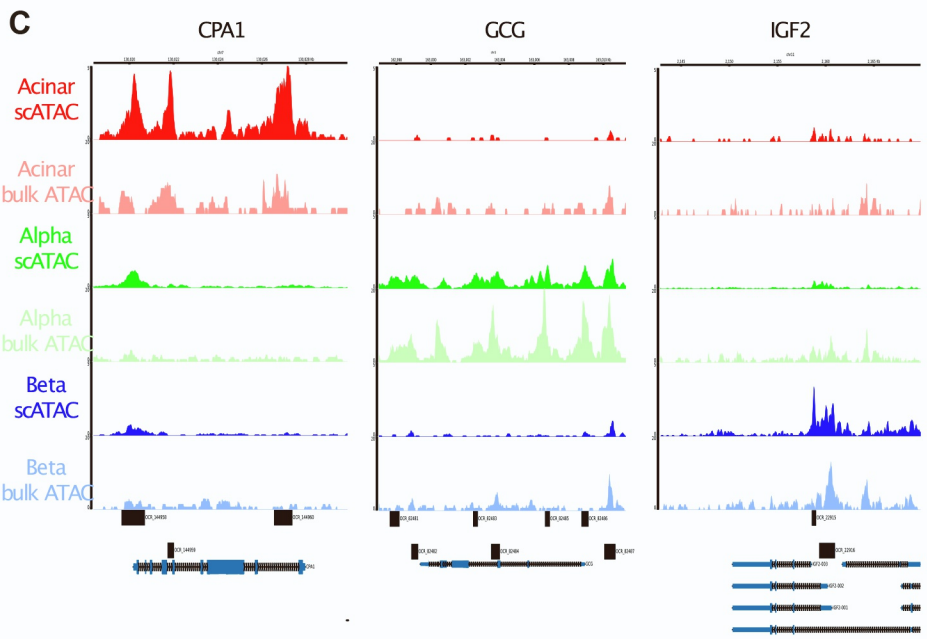
Supplemental Figure 1. Single Cell RNAseq Analysis. Related to Figure 1.

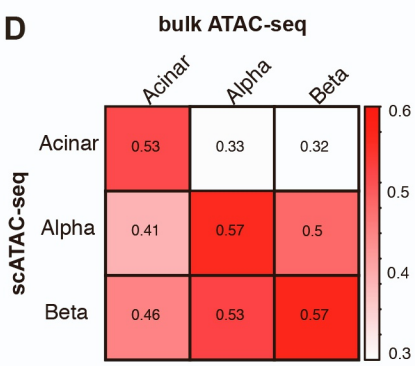


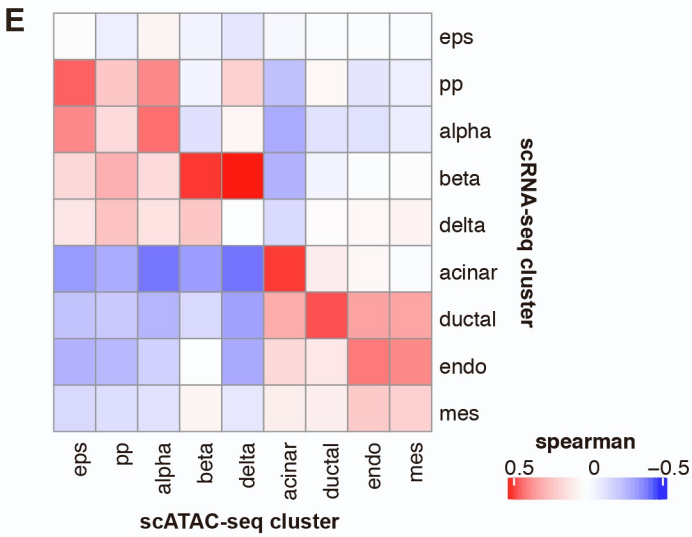
Supplemental Figure 2. Single Cell Chromatin Accessiblity. Related to Figures 2 and 3.



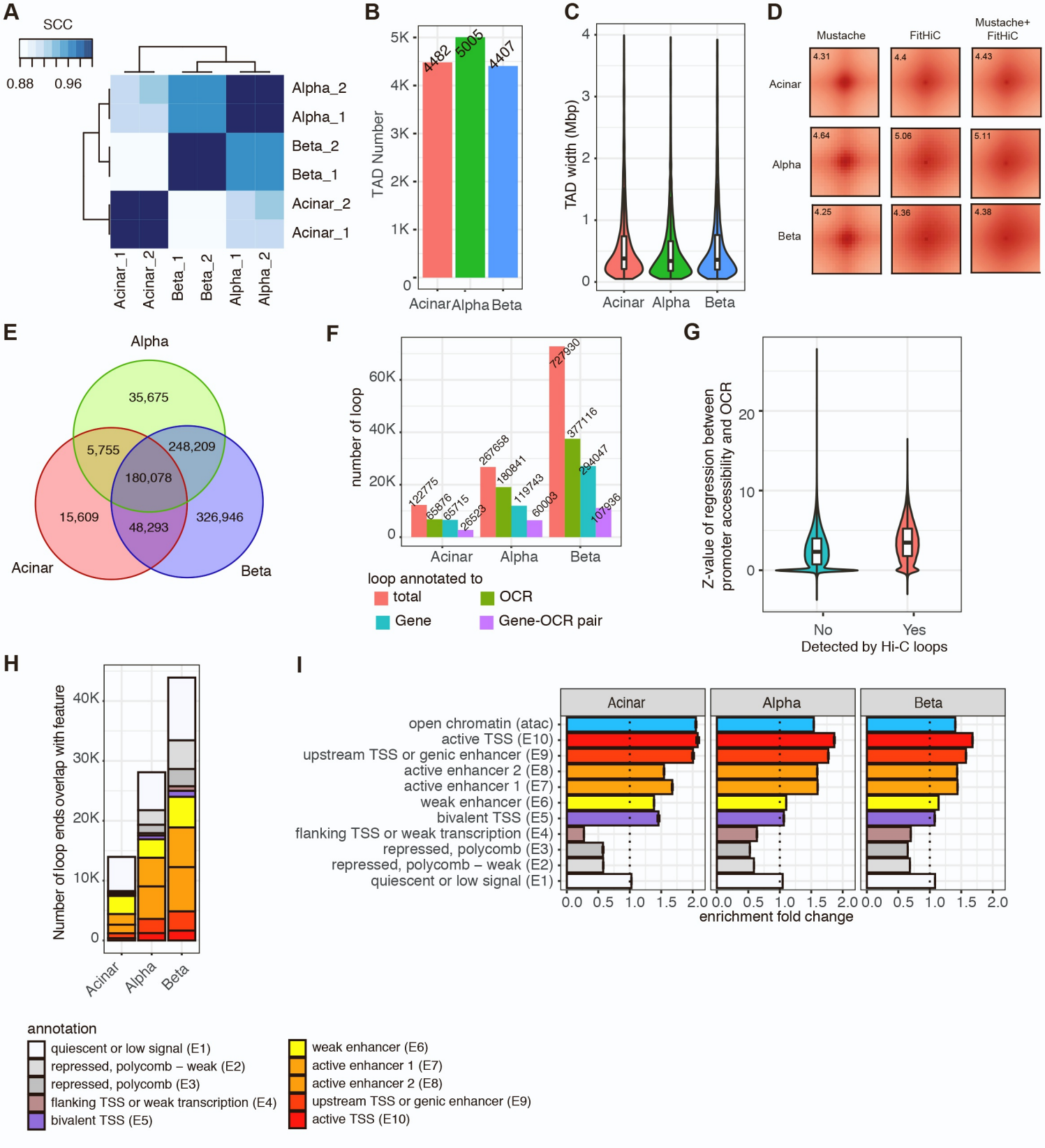




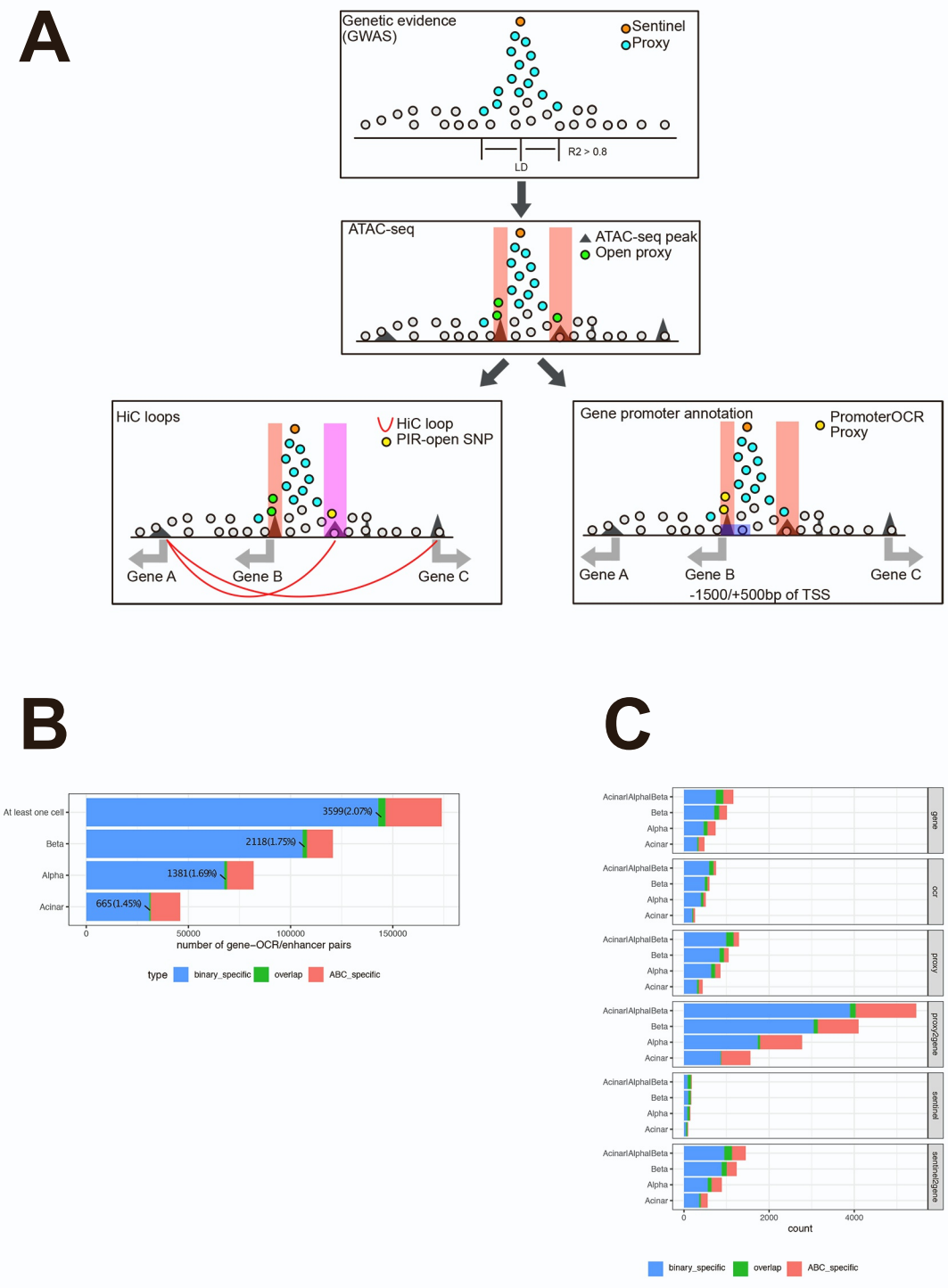




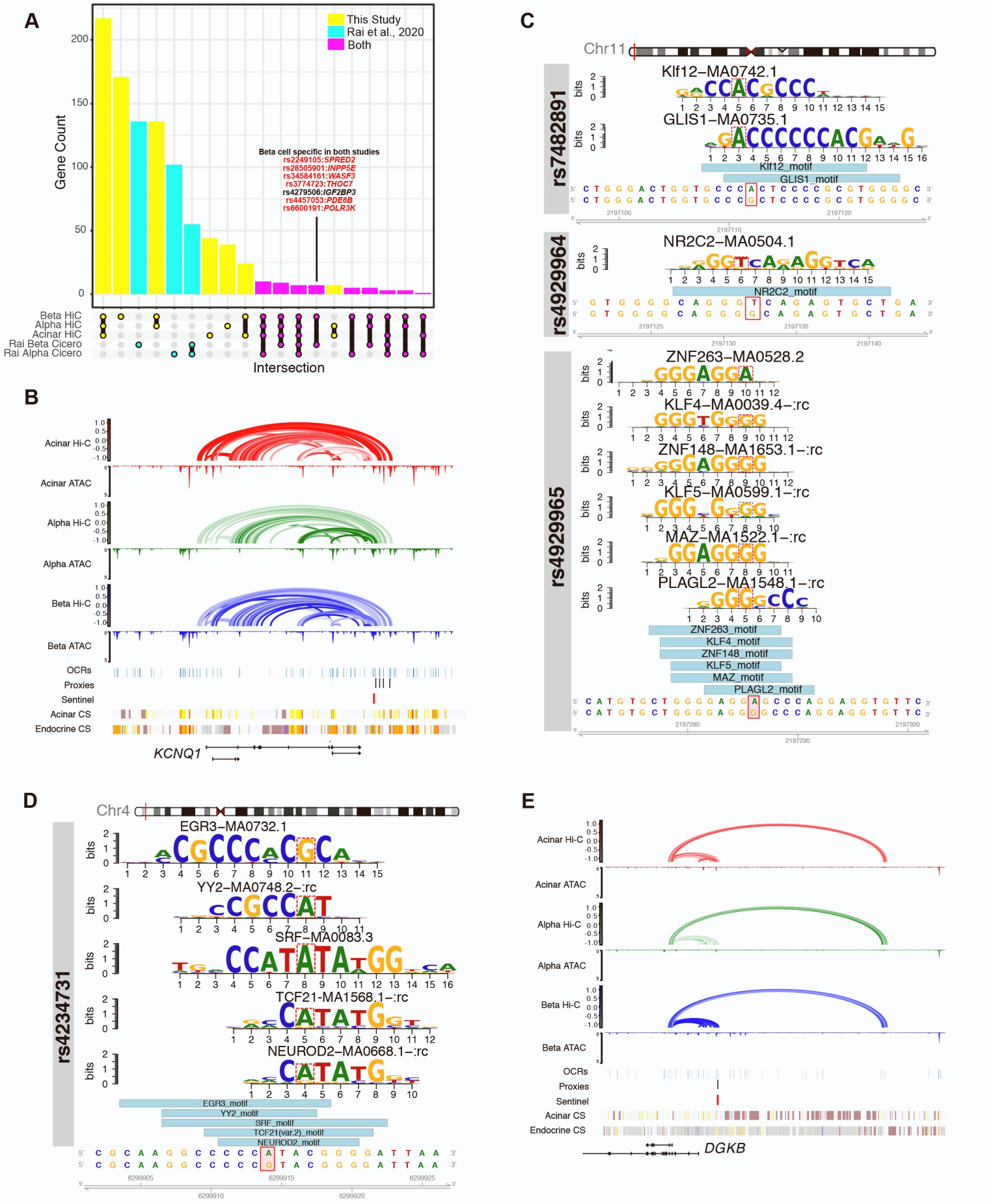
Supplemental Figure 3. Chromatin Loop Analysis. Related to Figure 3.



Supplemental Figure 4. Variant to Gene Mapping. Related to Figures 5 and 6.



Supplemental Figure 5. Cell Type Specific Variant to Gene Mapping. Related to Figures 5 and 6.



Supplemental Figure 6. Co-Occurance of variant-to-gene pairs. Related to Figures 5 and 6.

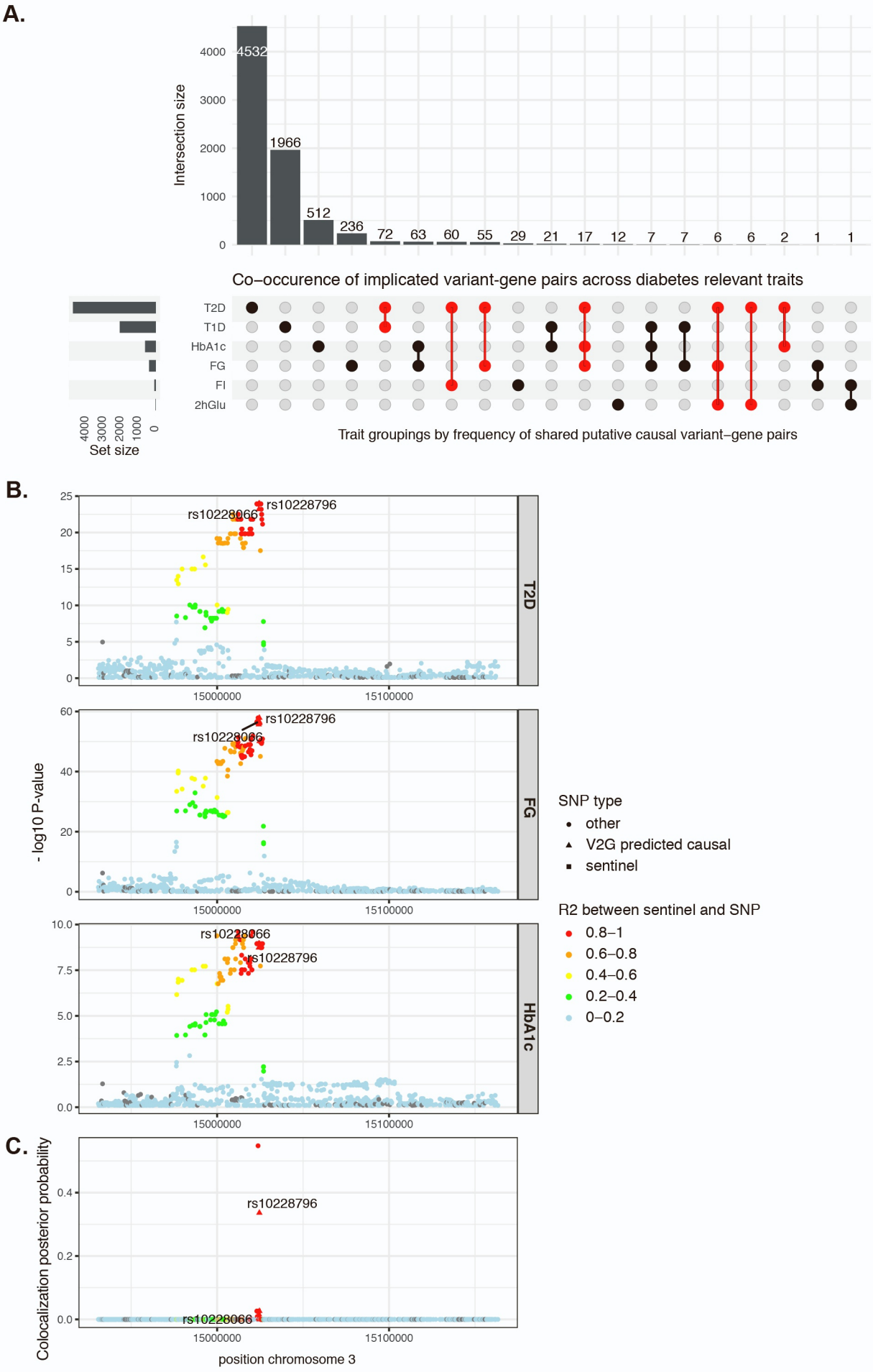


Table S1. Donor Information. Related to Figure 1.

Pancreata from non-diabetic organ donors were collected via the HPAP program and processed for the methodologies indicated.

technique	donor	Age	Sex	BMI	cell number	after filter
scRNA	HPAP040	35	M	23.98	2533	1519
scRNA	HPAP045	27	F	26.2	3744	1480
scRNA	HPAP054	40	F	30.85	2823	2289
bulkRNAseq	HPAP040	35	M	23.98	N/A	N/A
bulkRNAseq	HPAP045	27	F	26.2	N/A	N/A
bulkRNAseq	HPAP054	40	F	30.85	N/A	N/A
scATAC	HPAP040	35	M	23.98	4029	2653
scATAC	HPAP045	27	F	26.2	6093	3308
scATAC	HPAP054	40	F	30.85	7408	6512

technique	donor	Age	Sex	BMI	Cell Types analyzed
hi-C	HPAP040	35	M	23.98	acinar, alpha, beta
hi-C	HPAP045	27	F	26.2	alpha, beta
hi-C	HPAP054	40	F	30.85	acinar
hi-C	HPAP066	58	F	31.07	acinar, alpha, beta
hi-C	HPAP072	19	M	23.1	acinar

Table S2. Summary data for the HiC studies. Related to Figures 1 and 2.

sample	path	input #
Acinar_1_HiC	/mnt/isilon/sfgi/suc1/analyses/grant/hiC/hicup/Acinar_1/hicup/Acinar_1_hicupSummary.txt	2,712,288,871
Acinar_2_HiC	/mnt/isilon/sfgi/suc1/analyses/grant/hiC/hicup/Acinar_2/hicup/Acinar_2_hicupSummary.txt	3,249,462,125
Alpha_1_HiC	/mnt/isilon/sfgi/suc1/analyses/grant/hiC/hicup/Alpha_1/hicup/Alpha_1_hicupSummary.txt	3,471,287,075
Alpha_2_HiC	/mnt/isilon/sfgi/suc1/analyses/grant/hiC/hicup/Alpha_2/hicup/Alpha_2_hicupSummary.txt	2,269,661,813
Beta_1_HiC	/mnt/isilon/sfgi/suc1/analyses/grant/hiC/hicup/Beta_1/hicup/Beta_1_hicupSummary.txt	4,372,601,515
Beta_2_HiC	/mnt/isilon/sfgi/suc1/analyses/grant/hiC/hicup/Beta_2/hicup/Beta_2_hicupSummary.txt	4,693,960,014
Mean		

paired_align #	paired_align	valid_pair #	valid_pair %	same_circularised %	same_dangling_ends %	same_internal %
1,792,267,263	66.08	1,759,335,474	98.16	0.01	0.17	0.3
2,157,447,639	66.39	2,120,779,052	98.3	0.01	0.14	0.27
2,243,257,365	64.62	2,197,350,825	97.95	0.01	0.15	0.32
1,489,241,307	65.62	1,461,577,468	98.14	0.01	0.16	0.31
2,840,479,211	64.96	2,779,936,755	97.87	0.06	0.2	0.41
3,060,110,306	65.19	2,994,589,705	97.86	0.06	0.2	0.42

religation %	contiguous_sequence %	wrong_size %	unique_ditag #	unique_ditag %	usage efficiency
1.35	0	0	1,504,597,088	85.52	55.47%
1.27	0	0	1,776,039,581	83.74	54.66%
1.56	0	0	1,805,610,570	82.17	52.02%
1.37	0	0	1,232,759,953	84.34	54.31%
1.46	0	0	2,196,100,542	79	50.22%
1.46	0	0	2,316,680,304	77.36	49.35%
			1,805,298,006		

Table S3. Summary of Loop Calling from HiC data. Related to Figures 2 and 3.

file
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Acinar_2reps/hic_loops/all/Acinar_2reps.fithic_FDR.fdr1e6.res1000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Acinar_2reps/hic_loops/all/Acinar_2reps.mustache.pt01.res1000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Alpha_2reps/hic_loops/all/Alpha_2reps.fithic_FDR.fdr1e6.res1000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Alpha_2reps/hic_loops/all/Alpha_2reps.mustache.pt01.res1000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Beta_2reps/hic_loops/all/Beta_2reps.fithic_FDR.fdr1e6.res1000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Beta_2reps/hic_loops/all/Beta_2reps.mustache.pt01.res1000.bedpe
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/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Acinar_2reps/hic_loops/all/Acinar_2reps.mustache.pt01.res2000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Alpha_2reps/hic_loops/all/Alpha_2reps.fithic_FDR.fdr1e6.res2000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Alpha_2reps/hic_loops/all/Alpha_2reps.mustache.pt01.res2000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Beta_2reps/hic_loops/all/Beta_2reps.fithic_FDR.fdr1e6.res2000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Beta_2reps/hic_loops/all/Beta_2reps.mustache.pt01.res2000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Acinar_2reps/hic_loops/all/Acinar_2reps.fithic_FDR.fdr1e6.res4000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Acinar_2reps/hic_loops/all/Acinar_2reps.mustache.pt01.res4000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Alpha_2reps/hic_loops/all/Alpha_2reps.fithic_FDR.fdr1e6.res4000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Alpha_2reps/hic_loops/all/Alpha_2reps.mustache.pt01.res4000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Beta_2reps/hic_loops/all/Beta_2reps.fithic_FDR.fdr1e6.res4000.bedpe
/mnt/isilon/sfgi/suc1/analyses/grant/hiC/juicer/Beta_2reps/hic_loops/all/Beta_2reps.mustache.pt01.res4000.bedpe

cell	loop caller	cutoff	resolution	total_LoopN	merge_caller
Acinar_2reps	fithic_FDR	fdr < 1e-6	res1000	90	
Acinar_2reps	mustache	pt < 0.1	res1000	536	626
Alpha_2reps	fithic_FDR	fdr < 1e-6	res1000	369	
Alpha_2reps	mustache	pt < 0.1	res1000	823	1,191
Beta_2reps	fithic_FDR	fdr < 1e-6	res1000	2,657	
Beta_2reps	mustache	pt < 0.1	res1000	3,241	5,862
Acinar_2reps	fithic_FDR	fdr < 1e-6	res2000	7,565	
Acinar_2reps	mustache	pt < 0.1	res2000	5,206	12,542
Alpha_2reps	fithic_FDR	fdr < 1e-6	res2000	21,760	
Alpha_2reps	mustache	pt < 0.1	res2000	9,055	30,263
Beta_2reps	fithic_FDR	fdr < 1e-6	res2000	100,331	
Beta_2reps	mustache	pt < 0.1	res2000	17,300	115,935
Acinar_2reps	fithic_FDR	fdr < 1e-6	res4000	124,634	
Acinar_2reps	mustache	pt < 0.1	res4000	10,524	132,603
Alpha_2reps	fithic_FDR	fdr < 1e-6	res4000	278,357	
Alpha_2reps	mustache	pt < 0.1	res4000	17,656	291,377
Beta_2reps	fithic_FDR	fdr < 1e-6	res4000	781,486	
Beta_2reps	mustache	pt < 0.1	res4000	25,069	797,482

consensus loops within resolution	final consensus loops across cells	consensus loops at each resolution
7,499		7,499
142,709		129,492
938,900	860,565	723,574

Table S4: Gene Ontology Analysis. Related to Figures 2 and 3.

gene set	pathway	fdr	pathway_ge	observed	genes
endocrine-specific genes	enteroendocrine_cell_differentiation	0.01238328	28	8	PAX6,RFX3,GSK3B,CDK6,BMP5,NEUROD1,NKX6-1,INSM1
endocrine-specific genes	glandular_epithelial_cell_development	0.02841586	25	7	PAX6,RFX3,GSK3B,CDK6,BMP5,NKX6-1,INSM1
endocrine-specific genes	columnar_cuboidal_epithelial_cell_development	0.02841586	58	10	PAX6,RFX3,GSK3B,HIF1A,CDK6,C1GALT1,NKX3-2,BMP5,NKX6-1,INS
endocrine-specific genes	type_b_pancreatic_cell_development	0.04452176	20	6	RFX3,GSK3B,CDK6,BMP5,NKX6-1,INSM1
endocrine-specific genes	pancreas_development	0.04452176	78	11	PAX6,ISL1,RFX3,GSK3B,CDK6,NKX3-2,BMP5,MEIS2,NEUROD1,NKX6
endocrine-specific genes	endocrine_pancreas_development	0.09101823	45	8	PAX6,RFX3,GSK3B,CDK6,BMP5,NEUROD1,NKX6-1,INSM1
acinar-specific genes	isoprenoid_metabolic_process	4.38E-04	139	17	DPM1,CYP26B1,AKR1B1,SDC4,APOE,CYP2E1,CYP1B1,CYP2C8,RBP4,
acinar-specific genes	terpenoid_metabolic_process	4.38E-04	120	16	CYP26B1,AKR1B1,SDC4,APOE,CYP2E1,CYP1B1,CYP2C8,RBP4,RLBP1
acinar-specific genes	dna_binding_transcription_factor_activity_rna_polymerase_ii_specific	4.38E-04	1094	59	ZBTB32,BARX2,FOXC1,SP100,PAX2,REST,IKZF5,VSX1,ADNP,TCFL5,I NR1I3,VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,NKX3-1,HOXD4,Z
acinar-specific genes	retinol_metabolic_process	0.00273548	44	9	AKR1B1,CYP1B1,CYP2C8,RBP4,DHRS3,ALDH1A3,CYP27C1,ADH7,AKI
acinar-specific genes	monocarboxylic_acid_binding	0.00273548	68	11	CYP26B1,AFM,AFP,APOC1,S100A8,S100A9,ALB,FFAR4,CYP27C1,SE
acinar-specific genes	sequence_specific_double_stranded_dna_binding	0.00273548	889	48	ZBTB32,BARX2,FOXC1,MCM10,PAX2,REST,IKZF5,TCFL5,ETV2,EBF3 FOXF2,SMAD6,NR1I3,VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,N
acinar-specific genes	fatty_acid_binding	0.0046275	36	8	AFM,AFP,APOC1,S100A8,S100A9,ALB,FFAR4,UGT1A8
acinar-specific genes	cellular_hormone_metabolic_process	0.00856178	130	14	CYP26B1,AFP,REST,AKR1B1,CYP1B1,CYP2C8,RBP4,DHRS3,UGT2B7
acinar-specific genes	endopeptidase_regulator_activity	0.00856178	185	17	BIRC5,SERPINA4,AVP,WFDC2,KNG1,HRG,SLPI,WFDC3,ADRM1,NGF
acinar-specific genes	double_stranded_dna_binding	0.00972106	981	49	ZBTB32,BARX2,FOXC1,MCM10,PAX2,REST,IKZF5,TCFL5,ETV2,EBF3 VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,NKX3-1,HOXD4,NHLH1,
acinar-specific genes	regulatory_region_nucleic_acid_binding	0.00994444	960	48	ZBTB32,BARX2,FOXC1,PAX2,REST,IKZF5,VSX1,TCFL5,ETV2,EBF3,N SMAD6,NR1I3,VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,NKX3-1,
acinar-specific genes	dna_binding_transcription_factor_activity	0.00994444	1334	61	ZBTB32,BARX2,FOXC1,SP100,PAX2,SP140,REST,IKZF5,VSX1,ADNP, MAD6,ZNF287,NR1I3,VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,N
acinar-specific genes	cis_regulatory_region_binding	0.0110201	616	35	PAX2,REST,TCFL5,ETV2,EBF3,NANOG,RFX4,KCNIP3,VAX2,MYB,RBI
acinar-specific genes	primary_alcohol_metabolic_process	0.01419379	89	11	REST,AKR1B1,CYP1B1,CYP2C8,RBP4,ACSS1,DHRS3,ALDH1A3,CYP27
acinar-specific genes	peptidase_regulator_activity	0.0148747	222	18	BIRC5,SERPINA4,AVP,WFDC2,KNG1,HRG,SLPI,WFDC3,ADRM1,NGF
acinar-specific genes	serine_type_endopeptidase_inhibitor_activity	0.01607133	92	11	SERPINA4,WFDC2,HRG,SLPI,WFDC3,COL6A3,SERPINA11,SERPINA5
acinar-specific genes	collagen_containing_extracellular_matrix	0.01607133	408	26	LAMA3,FGFR2,COL4A4,ICAM1,ITGA6,COL9A3,GDF10,SMOC2,KNG1
acinar-specific genes	mechanosensitive_ion_channel_activity	0.01607133	15	5	TMC5,TMC6,PIEZO2,TMC8,TMC7
acinar-specific genes	dna_binding_transcription_repressor_activity	0.01629605	249	19	ZBTB32,REST,IKZF5,TCFL5,KCNIP3,VAX2,GZF1,GSC,MYC,VAX1,NKX
acinar-specific genes	response_to_toxic_substance	0.0168696	539	31	FGFR2,PAX2,EDN1,DNMT3B,ICAM1,AVP,OXT,USP46,APOBEC1,MYI
acinar-specific genes	isoprenoid_binding	0.0168696	36	7	CYP26B1,RBP4,RLBP1,CYP27C1,SERPINA5,ADH7,UGT1A8
acinar-specific genes	sequence_specific_dna_binding	0.02164157	1189	54	ZBTB32,BARX2,FOXC1,MCM10,PAX2,REST,IKZF5,VSX1,TCFL5,ETV2 FOXF2,SMAD6,NR1I3,VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,N
acinar-specific genes	anatomical_structure_arrangement	0.02482279	17	5	PAX2,HOXB2,KCNA2,DLL1,PLXNA4
acinar-specific genes	enzyme_inhibitor_activity	0.02495516	378	24	BIRC5,SERPINA4,AVP,WFDC2,PHACTR1,KNG1,HRG,SLPI,WFDC3,AP
acinar-specific genes	regulation_of_peptidase_activity	0.02682114	455	27	PDCD2,PAX2,REST,BIRC5,SERPINA4,AVP,CSNK2A1,WFDC2,KNG1,H
acinar-specific genes	acute_inflammatory_response	0.04717984	109	11	ICAM1,PIK3CG,IL1B,SAA2,S100A8,AHSG,OSMR,SAA4,IL31RA,CEBPI
acinar-specific genes	negative_regulation_of_molecular_function	0.04717984	1174	52	SP100,PAX2,ARHGAP28,FKBP1A,BIRC5,SERPINA4,ADNP,AVP,CSNK YSF,CYP1B1,AHSG,EPHA1,COMMD7,LYPD1,MGAT5,HHEX,OXA1L,SH
acinar-specific genes	cranial_nerve_structural_organization	0.04717984	11	4	PAX2,HOXB2,KCNA2,PLXNA4
acinar-specific genes	retinoic_acid_metabolic_process	0.04757557	32	6	CYP26B1,CYP2C8,ALDH1A3,CYP27C1,ADH7,UGT1A8
acinar-specific genes	biological_adhesion	0.04757557	1425	60	LAMA3,LIMS2,ADD2,ICAM3,ICAM1,ITGA6,TM9SF4,ICAM4,ICAM5,P ,SMAD6,CYP1B1,CUZD1,ENTPD1,FBLN5,S100A8,ACKR3,ITGA9,EPHA
acinar-specific genes	nuclear_chromosome	0.04757557	1273	55	ZBTB32,BARX2,FOXC1,MCM10,SP100,PAX2,BIRC5,VSX1,ADNP,TCF SMAD6,NR1I3,VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,NKX3-1,
acinar-specific genes	cornified_envelope	0.04757557	45	7	TCHH,SPRR1B,SPRR1A,KAZN,HRNR,SPRR2A,SPRR2F
acinar-specific genes	dna_binding_transcription_activator_activity	0.04757557	427	25	BARX2,FOXC1,ETV2,EBF3,NANOG,RFX4,MYB,RBPJL,HOXD3,MYC,IF

SM1

5-1,INSM1

,RLBP1,DHRS3,PNLIP,ALDH1A3,CYP27C1,ADH7,AKR1B10,UGT1A8
.,DHRS3,PNLIP,ALDH1A3,CYP27C1,ADH7,AKR1B10,UGT1A8
ETV2,EBF3,NANOG,RFX4,IRX4,KCNIP3,VAX2,MYB,RBPJL,FOXA2,GZF1,HOXD1,HOXD3,GSC,SP110,MYC,IRF4, FOXF2,SMAD6,
ZNF524,NHLH1,ZNF217,CEBPB,HOXB2,HOXD8,TGIF1,NHLH2,SOX12,FOXS1,FIGLA,SP140L,FOXD2,FOXE3,LITAF,ZNF580,HMX1,ZGLP1,EBF2,ASCL5
R1B10
RPINA5,UGT1A8
,NANOG,RFX4,KCNIP3,VAX2,MYB,RBPJL,FOXA2,GZF1,HOXD3,GSC,MYC,IRF4,
NKX3-1,HOXD4,NHLH1,ZNF217,CEBPB,HOXB2,HOXD8,TGIF1,NHLH2,SOX12,FOXS1,FIGLA,LITAF,HMX1,EBF2,ASCL5

,ALDH1A3,CYP27C1,ADH7,AKR1B10,UGT1A8
,AHSG,COL6A3,SERPINA11,SERPINA5,SERPINA3,SPINK14,SPINK9
,NANOG,RFX4,KCNIP3,VAX2,MYB,RBPJL,FOXA2,GZF1,HOXD3,GSC,MYC,IRF4,FOXF2,SMAD6,NR1I3,
ZNF217,CEBPB,HOXB2,HOXD8,TGIF1,NHLH2,SOX12,ZCCHC3,FOXS1,FIGLA,LITAF,HMX1,EBF2,ASCL5
ANOG,RFX4,KCNIP3,VAX2,MYB,RBPJL,FOXA2,GZF1,HOXD3,GSC,MYC,IRF4,FOXF2,
HOXD4,NHLH1,ZNF217,CEBPB,HOXB2,HOXD8,TGIF1,NHLH2,SOX12,FOXS1,FIGLA,LITAF,HMX1,EBF2,ASCL5
TCFL5,ETV2,EBF3,NANOG,RFX4,IRX4,KCNIP3,VAX2,MYB,RBPJL,FOXA2,GZF1,HOXD1,HOXD3,GSC,SP110,MYC,IRF4,FOXF2,S5
NKX3-1,HOXD4,ZNF524,NHLH1,ZNF217,CEBPB,HOXB2,HOXD8,TGIF1,NHLH2,SOX12,FOXS1,FIGLA,SP140L,FOXD2,FOXE3,LITAF,ZNF580,HMX1,ZGLP1,EBF2,ASCL
PJL,FOXA2,GZF1,HOXD3,GSC,MYC,IRF4,SMAD6,VAX1,NKX6-2,HHEX,ERG,ETS2,TAL1,FOXQ1,NKX3-1,ZNF217,CEBPB,HOXB2,TGIF1,NHLH2,FOXS1,FIGLA,LITAF,EBF2
7C1,ADH7,AKR1B10
,AHSG,COL6A3,NKX3-1,SERPINA11,SERPINA5,SERPINA3,SPINK14,SPINK9
5,SERPINA3,SPINK14,SPINK9
1,HRG,SLPI,MATN4,APOE,ADAMDEC1,FBLN5,S100A8,AHSG,LAD1,S100A9,COL6A3,HTRA1,THBS2,SERPINA5,SERPINA3,COL13A1,HRNR

6-2,HHEX,ETS2,FOXQ1,ZNF217,CEBPB,TGIF1,FOXS1,HMX1
B,MPST,APOE,CYP2E1,TLR2,CYP1B1,RBP4,FBLN5,S100A8,RGS10,LYPD1,S100A9,ALB,GPX8,BCL2L1,ADH7,ADA,GSTK1,AKR1B10,ZNF580,INMT,SRXN1

,EBF3,NANOG,RFX4,IRX4,KCNIP3,VAX2,MYB,RBPJL,FOXA2,GZF1,HOXD1,HOXD3,GSC,MYC,IRF4,
NKX3-1,HOXD4,NHLH1,ZNF217,CEBPB,HOXB2,HOXD8,TGIF1,NHLH2,SOX12,FOXS1,FIGLA,FOXD2,FOXE3,LITAF,HMX1,ZGLP1,EBF2,ASCL5

POC1,NGF,AHSG,MGAT5,SH3RF2,COL6A3,SOCS3,SERPINA11,SERPINA5,SERPINA3,SPINK14,SPINK9,FGFR1OP,UGT1A8,PINX1
RG,SLPI,WFDC3,ADRM1,NGF,MYC,S100A8,AHSG,S100A9,COL6A3,NKX3-1,MALT1,CASC2,SERPINA11,SERPINA5,SERPINA3,SPINK14,SPINK9
B,SERPINA3
2A1,WFDC2,MAPK8,PHACTR1,DUSP22,KNG1,HRG,TNNT2,SLPI,WFDC3,IL1B,FOXA2,SH3BP4,APOE,APOC1,NGF,D
H3RF2,COL6A3,NKX3-1,TMC8,FOXS1,KCNE1,SOCS3,SERPINA11,SERPINA5,SERPINA3,ADH7,PTPN1,SPINK14,SPINK9,FGFR1OP,UGT1A8,DBNDD2,PINX1,MTRNR2L6

IK3CG,DOCK8,CDH23,MAP3K8,SMOC2,DUSP22,KNG1,HRG,CD58,MYB,LY9,SDC4,IL1B,FOXA2,HOXD3,ADAMDEC1,VTCN1,DYSF,GPNMB,LRRC32L13A1,DLL1,PLXNA4,CLDN23
A1,DOCK5,HABP2,ADAM12,ROBO4,MPZ,ZYX,PDPN,INHBB,S100A9,COL6A3,DACT2,MALT1,CEBPB,SLITRK1,THBS2,PEAR1,AJAP1,ADA,CO
L5,CSNK2A1,EBF3,NANOG,RFX4,IRX4,VAX2,TCP1,LRIF1,RBPJL,FOXA2,HOXD1,HOXD3,GSC,MYC,IRF4,FOXF2,
HOXD4,NHLH1,CEBPB,HOXB2,HOXD8,TGIF1,NHLH2,SOX12,FOXS1,FIGLA,SS18L1,FOXD2,FOXE3,HUS1B,ZNF580,HMX1,EBF2,ASCL5,PINX1

RF4,FOXF2,NR1I3,ERG,HOXD4,NHLH1,CEBPB,HOXB2,HOXD8,NHLH2,SOX12,FIGLA,FOXD2,LITAF,EBF2

Table S8: Enrichment of diabetes-associated genetic risk variants by pancreatic cell type. Related to Figure 5.

Category	Prop._SNPs	Prop._h2	Prop._h2_std	Enrichment	Enrichment_	Enrichment_	fdr
2hGlu.geneAnnotatedOCR_Acinar	0.00855617	0.16764967	0.07526909	19.5940009	8.79705077	0.03046446	0.63975376
2hGlu.geneAnnotatedOCR_Alpha	0.01260285	0.20947575	0.09461634	16.6213057	7.50753791	0.0312846	0.63975376
2hGlu.geneAnnotatedOCR_Beta	0.01366653	0.28189533	0.12457444	20.6267011	9.11529739	0.02708337	0.59583407
atrial_fibrillation.geneAnnotatedOCR_Acinar	0.00855617	-0.0070516	0.0450305	-0.8241541	5.26292515	0.72898969	1
atrial_fibrillation.geneAnnotatedOCR_Alpha	0.01260285	0.09509896	0.05563086	7.54583268	4.41415045	0.14614653	1
atrial_fibrillation.geneAnnotatedOCR_Beta	0.01366653	0.05474646	0.05133715	4.00588021	3.75641586	0.42721354	1
chronotype.geneAnnotatedOCR_Acinar	0.00855617	0.07281258	0.01755409	8.50994717	2.05162882	2.55E-04	0.00763717
chronotype.geneAnnotatedOCR_Alpha	0.01260285	0.10868292	0.02066125	8.62368097	1.63941184	3.91E-06	1.33E-04
chronotype.geneAnnotatedOCR_Beta	0.01366653	0.13621118	0.02342549	9.96677503	1.71407767	2.70E-07	9.71E-06
FG.geneAnnotatedOCR_Acinar	0.00855617	0.1483003	0.04462611	17.3325496	5.21566265	0.00300735	0.08119844
FG.geneAnnotatedOCR_Alpha	0.01260285	0.29933307	0.05645784	23.751229	4.47976917	1.05E-06	3.66E-05
FG.geneAnnotatedOCR_Beta	0.01366653	0.47871629	0.10560444	35.0283845	7.72723414	2.27E-05	7.50E-04
FI.geneAnnotatedOCR_Acinar	0.00855617	0.0693239	0.03755978	8.102209	4.3897868	0.09839489	1
FI.geneAnnotatedOCR_Alpha	0.01260285	0.06595173	0.03798391	5.23308231	3.01391524	0.15335084	1
FI.geneAnnotatedOCR_Beta	0.01366653	0.03286877	0.03664848	2.40505679	2.68162407	0.59594923	1
HbA1c.geneAnnotatedOCR_Acinar	0.00855617	0.08464628	0.03668295	9.8930062	4.28730794	0.03437695	0.63975376
HbA1c.geneAnnotatedOCR_Alpha	0.01260285	0.10465562	0.04659651	8.30412647	3.6973009	0.04231339	0.6770143
HbA1c.geneAnnotatedOCR_Beta	0.01366653	0.18110832	0.05440388	13.251966	3.98081287	0.00154961	0.04493869
HOMA-B.geneAnnotatedOCR_Acinar	0.00855617	0.16305973	0.10297413	19.0575539	12.0350677	0.13426201	1
HOMA-B.geneAnnotatedOCR_Alpha	0.01260285	0.19825909	0.11325182	15.7312958	8.98621047	0.10037413	1
HOMA-B.geneAnnotatedOCR_Beta	0.01366653	0.36140907	0.14635052	26.4448399	10.7086856	0.01316583	0.30281415
HOMA-IR.geneAnnotatedOCR_Acinar	0.00855617	0.0581504	0.10325324	6.79630905	12.0676896	0.63298391	1
HOMA-IR.geneAnnotatedOCR_Alpha	0.01260285	0.0075903	0.11331771	0.60226895	8.99143833	0.96456976	1
HOMA-IR.geneAnnotatedOCR_Beta	0.01366653	0.09594914	0.11296438	7.02074139	8.26577164	0.46151987	1
pancCancer.Rashkin_NatComm2020.geneAnnotatedO	0.00855617	46.0254791	8688.73098	5379.21301	1015492.63	0.00160062	0.04493869
pancCancer.Rashkin_NatComm2020.geneAnnotatedO	0.01260285	10.1579979	408.855324	806.008272	32441.5084	0.03399007	0.63975376
pancCancer.Rashkin_NatComm2020.geneAnnotatedO	0.01366653	15.2616232	4391.98782	1116.71571	321368.293	0.03227247	0.63975376
sleepDuration_selfReported.geneAnnotatedOCR_Acin	0.00855617	0.04147672	0.01805838	4.84757856	2.11056685	0.0680744	1
sleepDuration_selfReported.geneAnnotatedOCR_Alph	0.01260285	0.07214588	0.02144071	5.72457076	1.70125906	0.00571416	0.14285407
sleepDuration_selfReported.geneAnnotatedOCR_Beta	0.01366653	0.10383472	0.02219802	7.59774116	1.62426238	6.89E-05	0.00220545
T1D.Chiou_Nat2021.geneAnnotatedOCR_Acinar	0.00855617	0.09903346	0.11180016	11.5745037	13.0666078	0.39971358	1
T1D.Chiou_Nat2021.geneAnnotatedOCR_Alpha	0.01260285	0.15989746	0.08853903	12.6874095	7.02532087	0.09145148	1
T1D.Chiou_Nat2021.geneAnnotatedOCR_Beta	0.01366653	0.19006722	0.11303459	13.9075018	8.27090954	0.11587556	1
T2D.Mahajan_NatGenet2018b.geneAnnotatedOCR_A	0.00855617	0.12327666	0.04235348	14.4079201	4.95004905	0.00754301	0.18103227
T2D.Mahajan_NatGenet2018b.geneAnnotatedOCR_Al	0.01260285	0.17354021	0.05379666	13.7699228	4.26861178	0.00329411	0.08564687
T2D.Mahajan_NatGenet2018b.geneAnnotatedOCR_B	0.01366653	0.2331373	0.05792345	17.0590036	4.23834547	2.39E-04	0.00740902

Table S14: Genetic variants with likely pleiotropic effects between T2D and glycemic traits. Related to Figures 5 and 6.

input_sentin	coloc traits	multi-trait cc	multi-trait cc	top variant e	posterior pro	v2g causal v	v2g causal v	posterior pro	v2g gene_id	v2g gene_name	T2D
rs11257655	T2D, HbA1c	0.9998	1	rs11257655	1	rs11257655	chr10:123078	0.99999999	ENSG000001	CCDC3	
									ENSG000001	OPTN	
rs11202627	T2D, FI	0.4837	0.9288	rs10788577	0.1239	rs10490920	chr10:896856	0.02765334	ENSG000001	PTEN	
rs7115753	T2D, FG	0.9809	0.9999	rs10838524	0.9988	rs7945565	chr11:45878	7.48E-05	ENSG000001	CRY2	
						rs7945689	chr11:45879	3.06E-05	ENSG000001	CRY2	
						rs1401419	chr11:45879	1.29E-05	ENSG000001	CRY2	
rs77464186	T2D, FG	0.9938	1	rs11603349	0.8479	rs11603334	chr11:72432	6.10E-09	ENSG000001	ARAP1	
									ENSG000001	ATG16L2	
									ENSG000002	RP11-800A3.3	
									ENSG000002	RP11-800A3.4	
									ENSG000002	STARD10	
						rs1552224	chr11:72433	6.10E-09	ENSG000001	ARAP1	
									ENSG000001	ATG16L2	
									ENSG000002	RP11-800A3.3	
									ENSG000002	RP11-800A3.4	
									ENSG000002	STARD10	
						rs7109575	chr11:72463	1.03E-07	ENSG000001	ARAP1	
									ENSG000001	ATG16L2	
									ENSG000002	STARD10	
						rs140130268	chr11:72470	NA	ENSG000001	ARAP1	
									ENSG000001	ATG16L2	
									ENSG000002	STARD10	
rs1005752	T2D, FG	0.9571	1	rs62007299	0.3049	rs62007299	chr15:77711	0.30491706	ENSG000001	HMG20A	
						rs34591043	chr15:77713	0.10483043	ENSG000001	HMG20A	
									ENSG000001	PEAK1	
rs72802342	T2D, T1D	0.9739	1	rs55993634	0.5528	rs72802352	chr16:75240	0.00892121	ENSG000000	BCAR1	
									ENSG000001	CFDP1	
									ENSG000001	CTRB1	
									ENSG000001	CTRB2	
									ENSG000002	RP11-252K23.2	
						rs147630228	chr16:75251	NA	ENSG000001	CTRB1	
									ENSG000002	RP11-252K23.2	
rs6518681	T2D, FG	0.7031	0.9894	rs7286205	0.0582	rs55645000	chr22:30390	0.00965975	ENSG000001	ASCC2	
						rs73883354	chr22:30401	2.65E-04	ENSG000001	ASCC2	
									ENSG000001	CABP7	
									ENSG000002	RP1-76B20.11	
									ENSG000002	RP1-76B20.12	
									ENSG000001	UQCR10	
									ENSG000001	ZMAT5	
						rs6519802	chr22:30476	0.0063823	ENSG000002	CTA-85E5.10	
									ENSG000001	HORMAD2	
									ENSG000001	NEFH	
									ENSG000001	NF2	
									ENSG000001	THOC5	
rs11709077	T2D, FI	0.6065	1	rs11709077	0.865	rs17036160	chr3:123297	0.13163971	ENSG000001	PPARG	
						rs7649970	chr3:123922	1.70E-06	ENSG000001	PPARG	
rs9873618	T2D, FG, HbA	0.9421	1	rs1604038	0.4285	rs5396	chr3:170744	1.10E-11	ENSG000001	SLC2A2	
rs1903002	T2D, FI	0.8956	0.9993	rs13133548	0.2781	rs10012528	chr4:897249	3.91E-04	ENSG000001	FAM13A	
						rs10012624	chr4:897250	0.00127825	ENSG000001	FAM13A	
rs4457053	T2D, FG	0.9849	1	rs4457054	0.2561	rs7732130	chr5:764350	0.08210518	ENSG000001	PDE8B	
									ENSG000001	WDR41	
									ENSG000002	ZBED3-AS1	
rs10228066	T2D, HbA1c,	0.8186	1	rs10487796	0.5478	rs7798124	chr7:150556	2.03E-19	ENSG000001	DGKB	
						rs7798360	chr7:150559	3.05E-15	ENSG000001	DGKB	
						rs10244051	chr7:150638	0.00351715	ENSG000001	DGKB	
						rs10950550	chr7:150639	0.00297837	ENSG000001	DGKB	
						rs10228456	chr7:150639	0.01607244	ENSG000001	DGKB	
						rs10228561	chr7:150639	NA	ENSG000001	DGKB	
						rs10228796	chr7:150641	0.33622332	ENSG000001	DGKB	
						rs10258074	chr7:150642	0.02618626	ENSG000001	DGKB	
						rs2191348	chr7:150642	0.00587885	ENSG000001	DGKB	
						rs2191349	chr7:150643	6.10E-09	ENSG000001	DGKB	
rs878521	T2D, 2hGlu	0.9989	1	rs878521	0.9885	rs878521	chr7:442556	0.9885278	ENSG000000	CAMK2B	
									ENSG000001	DBNL	
									ENSG000001	DDX56	
									ENSG000000	NUDCD3	
									ENSG000001	POLD2	
									ENSG000001	POLM	
rs10097617	T2D, FG	0.9458	0.9996	rs896854	0.7294	rs13262110	chr8:959268	5.25E-05	ENSG000001	NDUFAF6	
						rs896853	chr8:959608	0.02872132	ENSG000001	NDUFAF6	
									ENSG000002	RP11-347C18.3	
						rs896852	chr8:959608	0.01476664	ENSG000001	NDUFAF6	
									ENSG000002	RP11-347C18.3	
						rs2879813	chr8:959609	0.07148914	ENSG000001	NDUFAF6	
									ENSG000002	RP11-347C18.3	
						rs10097617	chr8:959616	0.00889038	ENSG000001	NDUFAF6	
									ENSG000002	RP11-347C18.3	
									ENSG000001	TP53INP1	
						rs10108430	chr8:959617	2.09E-05	ENSG000001	NDUFAF6	
									ENSG000002	RP11-347C18.3	

									ENSG00000131 TP53INP1
						rs7003387	chr8:959619?	0.020074	ENSG00000131 NDUFAF6
									ENSG00000260 RP11-347C18.3
									ENSG00000131 TP53INP1
rs13024606	T2D, FI	0.9692	1	rs13389219	0.8018	rs7607980	chr2:165551?	1.71E-07	ENSG00000085 COBLL1
rs1903002	T2D, FI	0.8956	0.9993	rs13133548	0.2781	rs13133548	chr4:8974017	0.27807708	ENSG00000138 FAM13A
									ENSG00000260 RP11-84C13.1
									ENSG00000138 TIGD2
rs9505097	FG, HbA1c	0.997	1	rs3778321	0.9996	rs76823979	chr6:723666?	3.07E-06	ENSG00000260 RP1-80N2.2
									ENSG00000260 RP1-80N2.3
									ENSG00000260 RP3-470L22.1
									ENSG00000124 RREB1
						rs17672741	chr6:723940?	4.21E-06	ENSG00000260 RP1-80N2.2
									ENSG00000260 RP1-80N2.3
									ENSG00000260 RP3-470L22.1
									ENSG00000124 RREB1