

SUPPLEMENTARY DATA

Supplementary Table S1. Characteristics of genotyped HCHS/SOL participants

	T2D cases	Controls
No. of participants, n	2499	5247
Age, years	55 (10)	39 (13)
Sex, n		
Men	995	2076
Women	1504	3171
BMI, kg/m ²	32.2 (6.5)	28.1 (5.6)
Genetic analysis group, n		
Central American	244	591
Cuban	396	918
Dominican	217	523
Mexican	965	1914
Puerto Rican	557	840
South American	113	450

Data are mean (SD) or sample size (n).

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Supplementary Table S2. Results of primary and conditional analyses at the *KCNQ1* locus in the HCHS/SOL

	Risk	Other	RAF	Primary analysis*		Conditioned on rs163184†	Conditioned on rs163184 and rs2237896†	Conditioned on rs163184, rs2237896 and rs1049549†
				OR (95% CI)	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>
Index SNP: rs163184	G	T	0.41	1.24 (1.4-1.34)	1.1×10^{-7}	-	-	-
Primary lead SNP: rs2283228	A	C	0.79	1.50 (1.35-1.66)	8.4×10^{-13}	1.2×10^{-7}	0.16	0.12
First conditional lead SNP: rs2237896	G	A	0.82	1.54 (1.38-1.72)	9.8×10^{-13}	6.8×10^{-8}	-	-
Second conditional lead SNP: rs1049549	C	T	0.06	1.49 (1.27-1.75)	5.5×10^{-6}	2.9×10^{-7}	1.5×10^{-5}	-
Third conditional lead SNP: rs3888647	G	A	0.74	1.15 (1.05-1.26)	0.005	0.009	1.1×10^{-4}	2.9×10^{-5}

*ORs (95% CI) and *P*-values were estimated using GMMAT, incorporating covariance matrices corresponding to genetic relatedness (kinship), household, and census block group as random effects, and adjusting for center, age, sex, the first five PCs and sampling weights.

†SNPs were added as covariate in the above GMMAT models for conditional analyses.

RAF, risk allele frequency

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Supplementary Table S3. Correlation coefficients (r) between risk alleles of SNPs at *KCNQ1* in the HCHS/SOL

SNP	rs1049549	rs2283228	rs163184	rs2237896
rs1049549	1			
rs2283228	0.09	1		
rs163184	-0.12	0.39	1	
rs2237896	0.13	0.91	0.35	1
rs3888647	0.13	-0.22	0.04	-0.28

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Supplementary Table S4. Haplotypes of *KCNQ1* and T2D in the HCHS/SOL

Haplotype* rs1049549-rs163184 -rs2237896 -rs3888647	Frequency	OR for T2D	P
<u>T-G-G-G</u>	0.30	ref	
T-T- <u>G-G</u>	0.23	0.93	0.18
T-T-A- <u>G</u>	0.17	0.61	1.2 × 10 ⁻¹⁴
T-T- <u>G-A</u>	0.13	0.74	1.4 × 10 ⁻⁵
<u>T-G-G-A</u>	0.10	0.86	0.03
<u>C-T-G-G</u>	0.02	1.27	0.07
<u>C-T-G-A</u>	0.02	1.11	0.45
<u>C-G-G-G</u>	0.01	2.00	9.6 × 10 ⁻⁴
<u>C-G-G-A</u>	0.01	0.94	0.80
T-T-A-A	0.01	0.38	6.8 × 10 ⁻¹¹

*Haplotypes of *KCNQ1* were estimated using 4 variants, SNPs, rs1049549, rs163184, rs2237896 and rs3888647. Alleles with underlines are risk alleles of these SNPs for T2D.

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Supplementary Table S5. Characteristics of 80 known index SNPs and their associations with T2D in the HCHS/SOL

SNP	Nearest Gene	Chr	Position	Allele		Previous Studies			Results in the HCHS/SOL					Power ‡
				Risk*	Other	Race/ethnicity	Biological function	Ref	RAF	OR (95% CI)†	P†	Pint	Generalization	
rs17106184	<i>FAF1</i>	1	50909985	G	A	Multiethnic	Unknown	(1)	0.93	1.06 (0.90-1.24)	0.49	0.34	No	0.3%
rs10923931	<i>NOTCH2</i>	1	120517959	T	G	European	Unknown	(2)	0.13	1.12 (0.99-1.26)	0.06	0.48	No	6.2%
rs2075423	<i>PROX1</i>	1	214154719	G	T	European	Beta-cell function	(3)	0.68	1.03 (0.95-1.12)	0.42	0.17	No	0.4%
rs780094	<i>GCKR</i>	2	27741237	C	T	European	Insulin resistance	(4)	0.65	1.04 (0.96-1.13)	0.33	0.95	No	0.7%
rs10203174	<i>THADA</i>	2	43690030	C	T	European	Beta-cell function	(2)	0.88	1.14 (1.01-1.30)	0.03	0.32	No	7.4%
rs243088	<i>BCL11A</i>	2	60568745	T	A	European	Unknown	(3)	0.56	1.03 (0.96-1.12)	0.39	0.93	No	0.5%
rs6723108	<i>TMEM163</i>	2	135479980	T	G	South Asian	Insulin resistance	(5)	0.86	0.89 (0.80-1.00)	0.04	0.47	No	7.5%
rs7560163	<i>RND3/RBM43</i>	2	151637936	C	G	African American	Unknown	(6)	0.98	0.88 (0.67-1.16)	0.37	0.57	No	0.6%
rs7593730	<i>RBMS1</i>	2	161171454	C	T	European	Insulin resistance	(7)	0.82	1.13 (1.02-1.25)	0.02	0.49	No	10.7%
rs3923113	<i>GRB14</i>	2	165501849	A	C	South Asian	Insulin resistance	(8)	0.68	1.17 (1.07-1.28)	3.5×10 ⁻⁴	0.25	Yes	48.7%
rs2943640	<i>IRS1</i>	2	227093585	C	A	European	Insulin resistance	(3)	0.80	1.08 (0.98-1.19)	0.14	0.18	No	2.2%
rs1801282	<i>PPARG</i>	3	12393125	C	G	European	Insulin resistance	(3)	0.91	1.18 (1.02-1.35)	0.02	0.99	No	8.9%
rs7612463	<i>UBE2E2</i>	3	23336450	C	A	East Asian	Beta-cell function	(9)	0.90	1.08 (0.95-1.22)	0.26	0.12	No	0.9%
rs831571	<i>PSMD6</i>	3	64048297	C	T	East Asian	Insulin resistance	(10)	0.87	1.12 (1.00-1.26)	0.05	0.22	No	5.0%
rs6795735	<i>ADAMTS9</i>	3	64705365	C	T	European	Insulin resistance	(2)	0.30	1.08 (0.99-1.17)	0.09	0.40	No	4.1%
rs11717195	<i>ADCY5</i>	3	123082398	T	C	European	Beta-cell function	(3)	0.75	1.24 (1.13-1.36)	5.1×10 ⁻⁶	0.38	Yes	76.5%
rs4402960	<i>IGF2BP2</i>	3	185511687	T	G	European	Beta-cell function	(3)	0.29	1.16 (1.06-1.26)	8.1×10 ⁻⁴	0.25	Yes	44.0%
rs16861329	<i>ST6GAL1</i>	3	186666461	C	T	South Asian	Beta-cell function	(8)	0.78	1.07 (0.97-1.18)	0.18	0.01	No	1.8%
rs6808574	<i>LPP</i>	3	187740523	C	T	Multiethnic	Unknown	(1)	0.75	1.08 (0.99-1.19)	0.08	0.88	No	3.9%
rs6815464	<i>MAEA</i>	4	1309901	C	G	East Asian	Beta-cell function	(10)	0.79	1.12 (1.01-1.24)	0.03	0.39	No	10.5%
rs4458523	<i>WFS1</i>	4	6289986	G	T	European	Beta-cell function	(3)	0.69	1.12 (1.03-1.22)	0.01	0.69	Yes	18.9%
rs6813195	<i>TMEM154</i>	4	153520475	C	T	Multiethnic	Beta-cell function	(1)	0.63	1.11 (1.02-1.20)	0.01	0.30	No	15.0%
rs702634	<i>ARL15</i>	5	53271420	A	G	Multiethnic	Insulin resistance	(1)	0.80	1.09 (0.99-1.20)	0.07	0.32	No	4.1%
rs459193	<i>ANKRD55</i>	5	55806751	G	A	European	Insulin resistance	(3)	0.73	1.08 (0.99-1.17)	0.10	0.83	No	3.0%
rs6878122	<i>ZBED3</i>	5	76427311	G	A	European	Unknown	(3)	0.32	1.17 (1.08-1.28)	1.7×10 ⁻⁴	0.82	Yes	59.5%
rs9502570	<i>SSRI/RREB1</i>	6	7258617	C	T	Multiethnic	Unknown	(1)	0.72	0.96 (0.88-1.05)	0.35	0.14	No	0.6%
rs7756992	<i>CDKAL1</i>	6	20679709	G	A	European	Beta-cell function	(3)	0.33	1.13 (1.04-1.23)	2.6×10 ⁻³	0.02	Yes	30.1%
rs3132524	<i>POU5F1/TCF19</i>	6	31136714	C	T	Multiethnic	Unknown	(1)	0.79	1.12 (1.02-1.23)	0.02	0.27	No	9.8%
rs9470794	<i>ZFAND3</i>	6	38106844	C	T	East Asian	Unknown	(10)	0.10	1.09 (0.96-1.23)	0.19	0.46	No	1.6%
rs1535500	<i>KCNK16</i>	6	39284050	T	G	East Asian	Unknown	(10)	0.52	1.03 (0.95-1.11)	0.53	0.34	No	0.3%
rs17168486	<i>DGKB</i>	7	14898282	T	C	European	Beta-cell function	(3)	0.33	1.11 (1.02-1.22)	0.02	0.20	No	17.0%
rs849135	<i>JAZF1</i>	7	28196413	G	A	European	Beta-cell function	(3)	0.63	1.19 (1.10-1.29)	2.1×10 ⁻⁵	0.33	Yes	70.3%
rs10278336	<i>GCK</i>	7	44245363	A	G	European	Beta-cell function	(3)	0.66	1.09 (1.00-1.18)	0.05	0.43	No	6.0%
rs6467136	<i>GCCI</i>	7	127164958	G	A	East Asian	Unknown	(10)	0.48	1.06 (0.99-1.15)	0.11	0.41	No	3.0%
rs791595	<i>MIR129-LEP</i>	7	127862802	A	G	East Asian	Insulin resistance	(11)	0.19	1.05 (0.95-1.16)	0.38	0.12	No	0.4%
rs13233731	<i>KLF14</i>	7	130437689	G	A	European	Insulin resistance	(3)	0.61	1.08 (1.00-1.16)	0.06	0.81	No	4.7%
rs516946	<i>ANK1</i>	8	41519248	C	T	European	Beta-cell function	(3)	0.77	1.22 (1.11-1.33)	3.7×10 ⁻³	0.12	Yes	60.6%
rs7845219	<i>TP53INP1</i>	8	95937502	T	C	European	Unknown	(3)	0.46	1.07 (0.99-1.16)	0.08	0.43	No	4.1%
rs3802177	<i>SLC30A8</i>	8	118185025	G	A	European	Beta-cell function	(2)	0.76	1.03 (0.94-1.13)	0.50	0.81	No	0.3%
rs7041847	<i>GLIS3</i>	9	4287466	A	G	East Asian	Beta-cell function	(10)	0.61	1.09 (1.01-1.18)	0.03	0.14	No	8.4%
rs17584499	<i>PTPRD</i>	9	8879118	T	C	East Asian	Unknown	(12)	0.19	0.97 (0.88-1.07)	0.61	0.90	No	0.2%
rs10811661	<i>CDKN2A/B</i>	9	22134094	T	C	European	Beta-cell function	(3)	0.87	1.05 (0.93-1.17)	0.44	0.71	No	0.4%
rs17791513	<i>TLE4</i>	9	81905590	A	G	European	Unknown	(3)	0.88	1.09 (0.97-1.23)	0.16	0.70	No	1.7%
rs2796441	<i>TLE1</i>	9	84308948	G	A	European	Unknown	(3)	0.57	1.14 (1.05-1.24)	1.2×10 ⁻³	0.63	Yes	37.1%
rs11257655	<i>CDC123</i>	10	12307894	T	C	European	Beta-cell function	(3)	0.24	1.21 (1.11-1.33)	2.0×10 ⁻⁵	0.24	Yes	76.3%
rs1802295	<i>VPS26A</i>	10	70931474	T	C	South Asian	Beta-cell function	(8)	0.22	0.96 (0.88-1.06)	0.41	0.64	No	0.4%

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rs12571751	ZMIZ1	10	80942631	A	G	European	Unknown	(3)	0.53	1.02 (0.95-1.10)	0.58	0.52	No	0.2%
rs1111875	HHEX/IDE	10	94462882	C	T	European	Beta-cell function	(3)	0.65	1.12 (1.03-1.21)	0.01	0.33	No	17.4%
rs7903146	TCF7L2	10	114758349	T	C	European	Beta-cell function	(2)	0.25	1.36 (1.25-1.49)	1.3×10 ⁻¹¹	0.29	Yes	99.9%
rs10886471	GRK5	10	121149403	C	T	East Asian	Insulin resistance	(13)	0.54	1.01 (0.93-1.09)	0.88	0.82	No	0.1%
rs2334499	DUSP8	11	1696849	T	C	European	Beta-cell function	(3)	0.42	0.91 (0.84-0.99)	0.02	0.63	No	10.4%
rs3842770	INS-IGF2	11	2178670	A	G	African American	Beta-cell function	(14)	0.04	1.23 (1.01-1.52)	0.04	0.53	No	4.9%
rs163184	KCNQ1	11	2847069	G	T	European	Beta-cell function	(3)	0.41	1.24 (1.14-1.34)	1.1×10 ⁻⁷	0.35	Yes	94.6%
rs5215	KCNJ11	11	17408630	C	T	European	Beta-cell function	(2)	0.33	1.07 (0.99-1.17)	0.09	0.10	No	4.0%
rs1552224	ARAPI/CENTD2	11	72433098	A	C	European	Beta-cell function	(2)	0.92	1.16 (1.00-1.34)	0.04	0.28	No	5.7%
rs10830963	MTNR1B	11	92708710	G	C	European	Beta-cell function	(3)	0.20	1.28 (1.17-1.41)	1.5×10 ⁻⁷	0.62	Yes	95.0%
rs11063069	CCND2	12	4374373	G	A	European	Unknown	(3)	0.15	0.92 (0.82-1.02)	0.12	0.11	No	2.5%
rs10842994	KLHDC5	12	27965150	C	T	European	Unknown	(3)	0.85	1.02 (0.91-1.13)	0.76	0.46	No	0.1%
rs2261181	HMG2A	12	66212318	T	C	European	Insulin resistance	(3)	0.11	1.07 (0.94-1.21)	0.29	0.10	No	0.9%
rs7955901	TSPAN8	12	71433293	C	T	European	Beta-cell function	(3)	0.50	1.06 (0.98-1.14)	0.15	0.45	No	2.1%
rs12427353	HNF1A	12	121426901	G	C	South Asian	Unknown	(8)	0.89	1.13 (1.00-1.27)	0.06	0.39	No	4.8%
rs1727313	MPHOSPH9	12	123640853	G	C	Multiethnic	Unknown	(1)	0.19	1.01 (0.91-1.11)	0.90	0.60	No	0.1%
rs1359790	SPRY2	13	80717156	G	A	East Asian	Beta-cell function	(15)	0.70	1.07 (0.99-1.17)	0.11	0.82	No	3.1%
rs7403531	RASGRP1	15	38822905	T	C	East Asian	Beta-cell function	(13)	0.33	1.21 (1.11-1.31)	6.3×10 ⁻⁶	0.99	Yes	82.9%
rs7163757	C2CD4A	15	62391608	C	T	East Asian	Beta-cell function	(9)	0.51	1.04 (0.96-1.12)	0.35	0.32	No	0.6%
rs7178572	HMG20A	15	77747190	G	A	South Asian	Unknown	(8)	0.62	1.06 (0.98-1.15)	0.12	0.24	No	2.6%
rs11634397	ZFAND6	15	80432222	G	A	European	Unknown	(2)	0.58	1.04 (0.96-1.13)	0.29	0.46	No	0.8%
rs2028299	AP3S2	15	90374257	C	A	South Asian	Beta-cell function	(8)	0.22	1.02 (0.93-1.12)	0.72	0.01	No	0.1%
rs12899811	PRC1	15	91544076	G	A	European	Beta-cell function	(3)	0.60	1.03 (0.94-1.11)	0.55	0.35	No	0.3%
rs9936385	FTO	16	53819169	C	T	European	Insulin resistance	(3)	0.32	1.07 (0.98-1.16)	0.14	0.39	No	2.5%
rs7202877	BCAR1	16	75247245	T	G	European	Beta-cell function	(3)	0.90	1.02 (0.89-1.16)	0.81	0.67	No	0.1%
rs391300	SRR	17	2216258	C	T	East Asian	Unknown	(12)	0.61	0.89 (0.82-0.97)	0.01	0.88	No	23.8%
rs13342692	SLC16A11	17	6946287	C	T	Hispanic	Unknown	(16)	0.23	0.98 (0.89-1.08)	0.67	0.08	No	0.1%
rs4430796	HNF1B/TCF2	17	36098040	G	A	European	Beta-cell function	(2)	0.46	1.02 (0.94-1.10)	0.67	0.55	No	0.1%
rs12970134	MC4R	18	57884750	A	G	European	Insulin resistance	(3)	0.17	1.00 (0.90-1.11)	0.99	0.38	No	0.1%
rs12454712	BCL2	18	60845884	T	C	Multiethnic	Insulin resistance	(17)	0.66	1.02 (0.94-1.10)	0.69	0.65	No	0.1%
rs10401969	CILP2	19	19407718	C	T	European	Unknown	(3)	0.08	1.01 (0.87-1.16)	0.94	0.24	No	0.1%
rs3786897	PEPD	19	33893008	A	G	East Asian	Insulin resistance	(10)	0.68	1.04 (0.95-1.12)	0.40	0.18	No	0.4%
rs8108269	GIPR	19	46158513	G	T	European	Unknown	(3)	0.37	0.98 (0.90-1.06)	0.56	0.74	No	0.2%
rs4812829	HNF4A	20	42989267	A	G	South Asian	Beta-cell function	(8)	0.37	1.11 (1.02-1.21)	0.02	0.92	No	15.6%

*Risk allele was defined according to a previously reported trans-ethnic meta-analysis

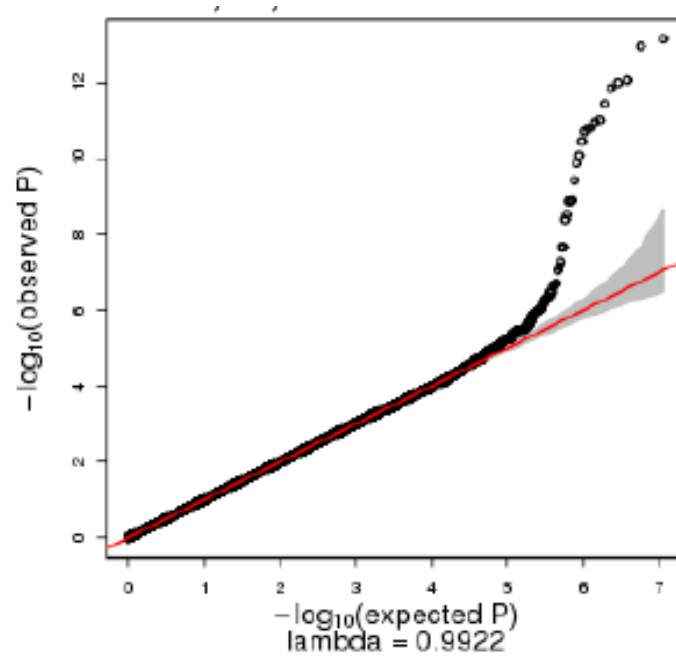
† ORs (95% CI) and *P*-values were estimated using GMMAT, incorporating covariance matrices corresponding to genetic relatedness (kinship), household, and census block group as random effects, and adjusting for center, age, sex, the first five PCs and sampling weights.

‡ Post-hoc power was calculated, under the risk allele frequencies and effect size of SNPs in the SOL for a sample size of 2499 T2D cases and 5247 controls, at a *P* of 6.25×10⁻⁴.

Chr, chromosome; RAF, risk allele frequency as measured on the plus strand.

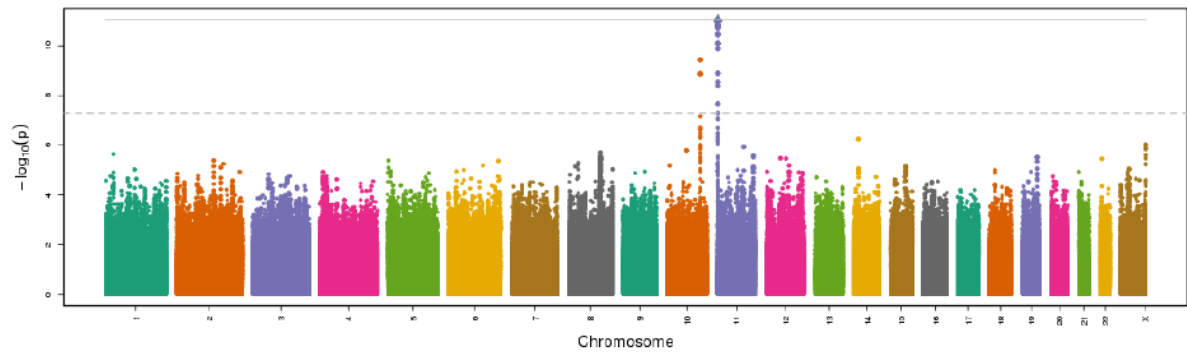
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Supplementary Figure 1. Q-Q plot for the GWAS of T2D the in the HCHS/SOL



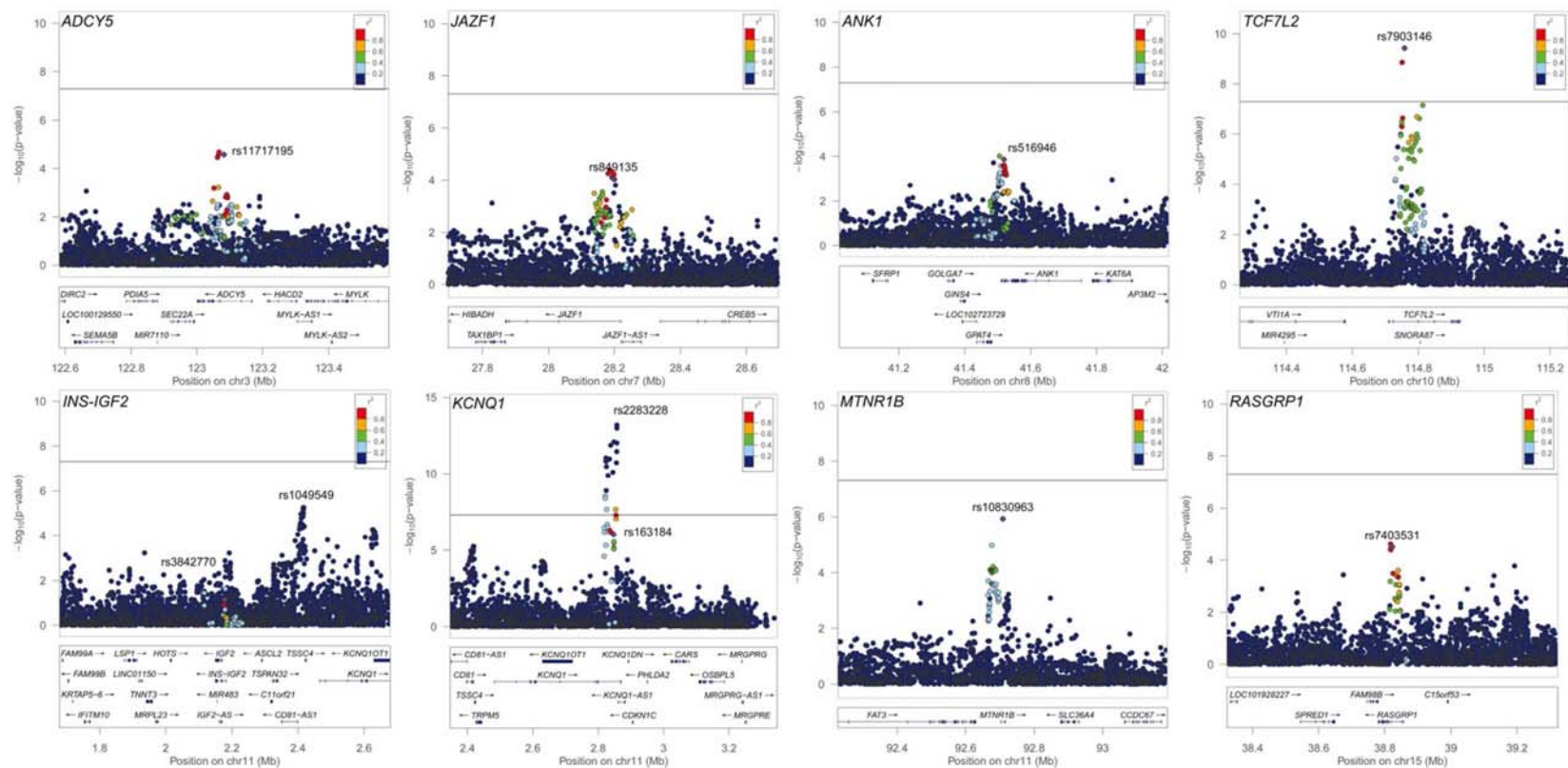
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Supplementary Figure 2. Manhattan plot for the GWAS of T2D in the HCHS/SOL



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Supplementary Figure 3. Regional association plots for 8 known T2D loci with lead SNPs of $P < 6.25 \times 10^{-4}$ (correcting for 80 tested loci) in the HCSH/SOL.



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References

1. Mahajan A, Go MJ, Zhang W, et al. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet* 2014;46:234-244
2. Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 2010;42:579-589
3. Morris AP, Voight BF, Teslovich TM, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet* 2012;44:981-990
4. Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 2010;42:105-116
5. Tabassum R, Chauhan G, Dwivedi OP, et al. Genome-wide association study for type 2 diabetes in Indians identifies a new susceptibility locus at 2q21. *Diabetes* 2013;62:977-986
6. Palmer ND, McDonough CW, Hicks PJ, et al. A genome-wide association search for type 2 diabetes genes in African Americans. *PloS one* 2012;7:e29202
7. Qi L, Cornelis MC, Kraft P, et al. Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes. *Hum Mol Genet* 2010;19:2706-2715
8. Kooner JS, Saleheen D, Sim X, et al. Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci. *Nat Genet* 2011;43:984-989
9. Yamauchi T, Hara K, Maeda S, et al. A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at UBE2E2 and C2CD4A-C2CD4B. *Nat Genet* 2010;42:864-868
10. Cho YS, Chen CH, Hu C, et al. Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians. *Nat Genet* 2012;44:67-72
11. Hara K, Fujita H, Johnson TA, et al. Genome-wide association study identifies three novel loci for type 2 diabetes. *Hum Mol Genet* 2014;23:239-246
12. Tsai FJ, Yang CF, Chen CC, et al. A genome-wide association study identifies susceptibility variants for type 2 diabetes in Han Chinese. *PLoS Genet* 2010;6:e1000847
13. Li H, Gan W, Lu L, et al. A genome-wide association study identifies GRK5 and RASGRP1 as type 2 diabetes loci in Chinese Hans. *Diabetes* 2013;62:291-298
14. Ng MC, Shriner D, Chen BH, et al. Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes. *PLoS Genet* 2014;10:e1004517
15. Shu XO, Long J, Cai Q, et al. Identification of new genetic risk variants for type 2 diabetes. *PLoS Genet* 2010;6:e1001127
16. Williams AL, Jacobs SB, Moreno-Macias H, et al.; SIGMA Type 2 Diabetes Consortium. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. *Nature* 2014;506:97-101
17. Saxena R, Elbers CC, Guo Y, et al. Large-scale gene-centric meta-analysis across 39 studies identifies type 2 diabetes loci. *Am J Hum Genet* 2012;90:410-425