

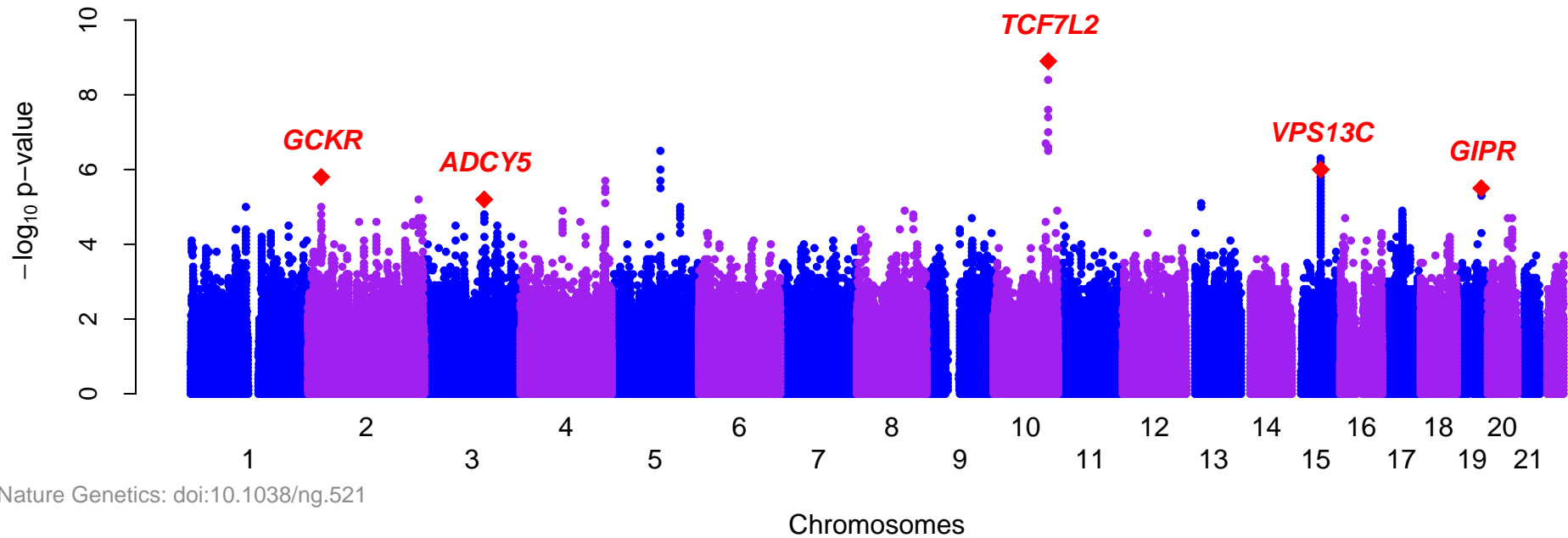
Supplementary Information for Genetic Variation in Gastric Inhibitory Polypeptide Receptor

(GIPR) Impacts the Glucose and Insulin Responses to an Oral Glucose Challenge

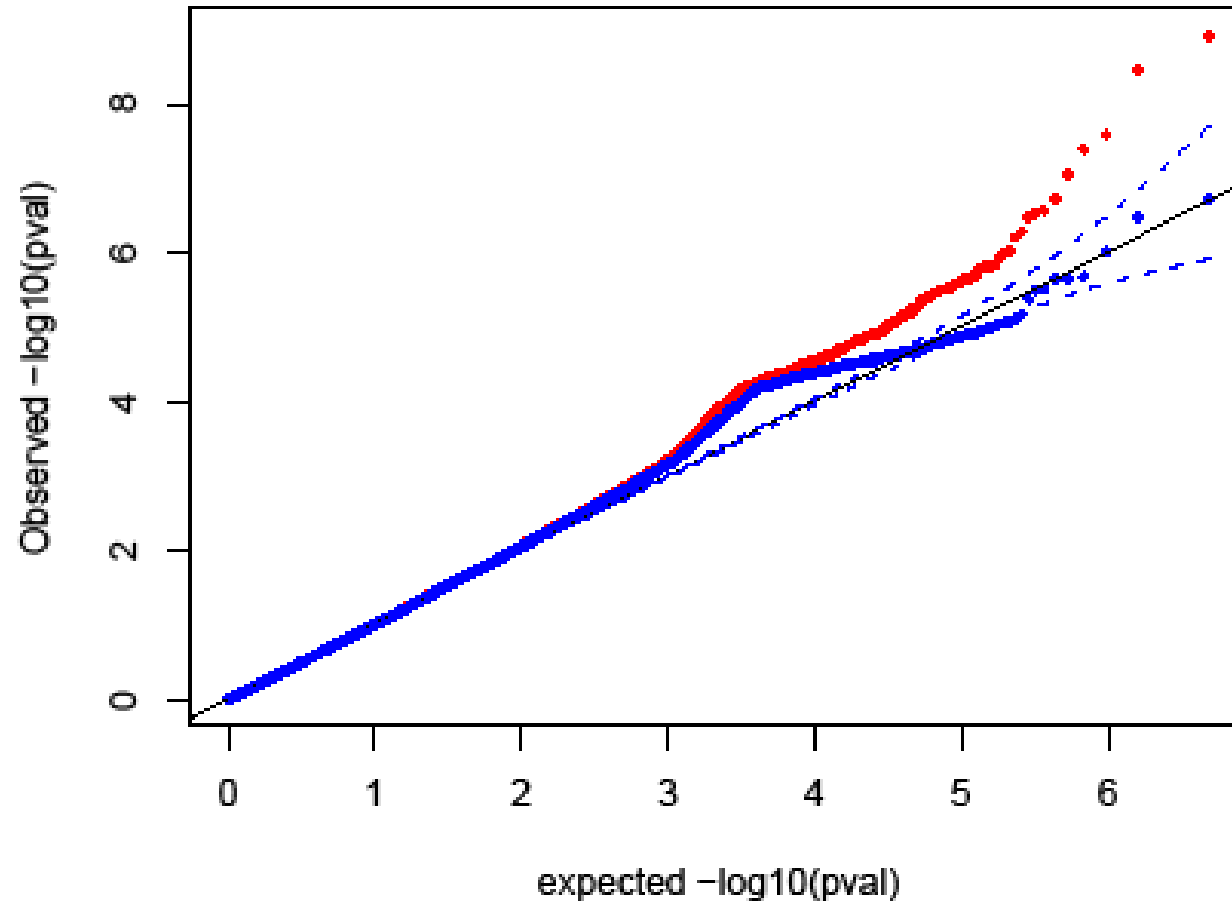
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Supplementary Figure 1. Manhattan and QQ plots of the association P values for 2-hr glucose (BMI-adjusted) in the discovery meta-analysis of 9 GWAS, (a) Manhattan plot. Directly genotyped and imputed SNPs are plotted with their meta-analysis P values (as $-\log_{10}$ values) as a function of genomic position (NCBI Build 36; hg18). SNPs that achieved genome-wide significance in combined discovery and replication meta-analyses are highlighted. The strong signal on chr 5 represents the *SLCO4C1* locus, which was highly significant in the discovery sample, but did not replicate and did not remain genome-wide significant. Note that SNPs were selected for replication based on four interim z-score based analyses. (b) Quantile-quantile (Q-Q) plot. The expected null distribution is plotted along the black diagonal, the entire distribution of observed P values is plotted in red ($\lambda=1.008$), and a distribution that excludes the five novel 2-hr glucose loci is plotted in blue ($\lambda=1.007$). Blue dashed lines represent 95% confidence intervals for the null distribution. The observed deviation from expectation in both distributions could represent additional loci that await discovery in studies with greater statistical power.



b



Supplementary Table 2. Meta-analysis of association results for 2-hr glucose across discovery and replication cohorts.

SNP	Chr	Position (NCBI B36) (bp)	Nearest Gene	Effect Allele/non-effect allele	Effect allele frequency	Discovery (BMI-adj)				Replication (BMI-adj)				Discovery + Replication (BMI-adj)				Discovery + Replication					
						N	Effect (SE)	p-value		N	Effect (SE)	p-value		N	Effect (SE)	p-value	p-value _{het}	N	Effect (SE)	p-value	p-value _{het}		
rs17187140	1	206,376,398	PLXNA2	a/g	0.1	13,563	0.15	0.037	6.29x10 ⁻⁵	13,377	-0.04	0.029	0.12	26,940	0.03	0.023	0.21	0.015	26,453	0.03	0.023	0.18	0.011
rs1260326	2	27,584,444	GCKR	t/c	0.40	15,234	0.09	0.019	1.53x10⁻⁶	23,166	0.06	0.014	5.33x10⁻⁶	38,400	0.07	0.011	7.05x10⁻¹¹	0.092	37,928	0.07	0.011	3.0x10⁻¹⁰	0.1092
rs4971652	2	50,245,662	NRXN1	a/g	0.84	15,184	0.10	0.026	2.20x10 ⁻⁴	12,173	0.01	0.027	0.82	27,357	0.05	0.019	5.53x10 ⁻³	0.19	26,873	0.05	0.019	4.21x10 ⁻³	0.093
rs12618178	2	54,908,792	?	a/c	0.20	15,234	-0.09	0.024	1.04x10 ⁻⁴	14,354	0.01	0.022	0.63	29,588	-0.04	0.016	0.023	0.011	29,129	-0.04	0.016	0.014	8.94x10 ⁻³
rs7604361	2	106,068,242	(C2orf40)	t/g	0.01	12,131	0.49	0.116	2.71x10 ⁻⁵	9,707	0.03	0.107	0.77	21,838	0.24	0.079	2.23x10 ⁻³	0.012	21,880	0.23	0.079	4.14x10 ⁻³	0.011
rs16847412	2	142,335,384	LRP1B	t/c	0.93	15,234	-0.14	0.032	2.33x10 ⁻⁵	17,104	-0.03	0.024	0.22	32,338	-0.07	0.019	4.56x10 ⁻⁴	0.05	32,382	-0.07	0.020	6.12x10 ⁻⁴	0.027
rs1955086	2	222,400,290	(EPHA4)	t/c	0.75	15,234	-0.08	0.023	2.22x10 ⁻⁴	21,758	0.00	0.014	0.73	36,992	-0.03	0.012	0.025	0.11	36,542	-0.03	0.012	0.028	0.18
rs6726280	2	230,201,928	DNER	a/c	0.17	15,234	0.12	0.027	6.71x10 ⁻⁶	23,448	0.01	0.016	0.71	38,682	0.04	0.014	8.35x10 ⁻³	1.39x10 ⁻³	38,202	0.04	0.014	9.40x10 ⁻³	3.24x10 ⁻⁴
rs12374129	3	78,626,542	(ROBO1)	t/c	0.15	15,234	0.09	0.023	2.55x10 ⁻⁴	12,239	-0.02	0.023	0.42	27,473	0.03	0.016	0.049	0.17	27,297	0.04	0.016	0.018	0.26
rs2877716	3	124,577,141	ADCY5	t/c	0.23	15,214	-0.10	0.022	6.26x10⁻⁶	29,483	-0.09	0.013	1.21x10⁻¹¹	44,697	-0.09	0.011	4.19x10⁻¹⁶	5.85x10⁻⁸	44,225	-0.09	0.011	7.41x10⁻¹⁶	3.17x10⁻⁷
rs9845279	3	158,795,136	(C3orf55)	c/g	0.56	12,909	-0.10	0.026	9.46x10 ⁻⁵	12,017	0.00	0.018	0.99	24,926	-0.03	0.015	0.023	1.57x10 ⁻⁴	24,438	-0.03	0.015	0.022	2.97x10 ⁻⁴
rs309795	4	177,703,271	(VEGFC)	a/c	0.43	15,234	-0.09	0.019	2.22x10 ⁻⁶	14,529	0.01	0.017	0.44	29,763	-0.03	0.013	9.44x10 ⁻³	1.30x10 ⁻⁴	29,284	-0.03	0.013	0.02	1.25x10 ⁻⁴
rs10037968	5	101,582,380	(SLCO4C1)	t/c	0.99	15,234	0.19	0.037	3.31x10 ⁻⁷	21,689	0.03	0.021	0.10	36,923	0.07	0.019	7.49x10 ⁻⁵	1.79x10 ⁻³	36,423	0.07	0.019	2.86x10 ⁻⁴	4.05x10 ⁻³
rs13265179	8	9,232,104	PPP1R3B	a/c	0.10	15,234	-0.11	0.028	1.18x10 ⁻⁴	6,958	-0.09	0.049	0.064	22,192	-0.10	0.024	2.06x10 ⁻⁵	0.21	22,023	-0.11	0.025	1.69x10 ⁻⁵	0.12
rs12545656	8	99,548,888	STK3	a/g	0.93	15,234	-0.19	0.043	1.28x10 ⁻⁵	14,533	-0.01	0.037	0.85	29,767	-0.08	0.028	2.71x10 ⁻³	9.77x10 ⁻³	29,288	-0.08	0.029	4.63x10 ⁻³	4.06x10 ⁻³
rs2439649	9	110,915,284	C9orf5	a/g	0.58	15,234	-0.07	0.019	2.22x10 ⁻⁴	14,053	0.00	0.018	0.86	29,287	-0.03	0.013	7.87x10 ⁻³	0.023	28,796	-0.04	0.013	6.26x10 ⁻³	0.013
rs12243326	10	114,778,805	TCF7L2	t/c	0.79	15,215	-0.13	0.022	1.20x10⁻⁹	23,351	-0.05	0.017	1.27x10⁻³	38,566	-0.08	0.013	4.23x10⁻¹⁰	1.08x10⁻³	38,078	-0.07	0.013	1.12x10⁻⁷	1.76x10⁻³
rs12873155	13	31,609,703	FRY	t/c	0.40	15,234	0.09	0.019	8.81x10 ⁻⁶	11,584	0.00	0.023	0.88	26,818	0.05	0.015	1.05x10 ⁻³	0.075	26,358	0.04	0.015	3.31x10 ⁻³	0.041
rs2585509	13	77,590,882	(EDNRB)	t/c	0.31	15,234	-0.08	0.020	1.65x10 ⁻⁴	9,791	-0.02	0.029	0.53	25,025	-0.06	0.017	5.86x10 ⁻⁴	0.23	24,526	-0.06	0.017	2.05x10 ⁻⁴	0.3
rs17271305	15	60,120,272	VPS13C	a/g	0.58	15,234	-0.09	0.019	1.04x10⁻⁶	15,633	-0.05	0.015	1.58x10⁻³	30,867	-0.06	0.012	4.11x10⁻⁸	0.22	30,906	-0.06	0.012	1.30x10⁻⁷	0.075
rs12448015	16	22,665,124	(HS3ST2)	a/g	0.97	15,234	-0.21	0.052	7.42x10 ⁻⁵	8,575	-0.18	0.090	0.043	23,809	-0.20	0.045	8.93x10 ⁻⁶	0.042	23,299	-0.20	0.046	1.46x10 ⁻⁵	0.027
rs7184872	16	27,374,838	(GTF3C1)	t/g	0.84	15,234	-0.11	0.030	3.01x10 ⁻⁴	23,660	0.01	0.016	0.59	38,894	-0.02	0.014	0.21	0.15	38,421	-0.02	0.014	0.11	0.098
rs1060253	16	86,423,639	SLC7A5	c/g	0.32	15,234	0.09	0.022	5.08x10 ⁻⁵	14,598	-0.02	0.019	0.23	29,832	0.03	0.014	0.073	8.41x10 ⁻⁴	29,345	0.01	0.015	0.33	3.69x10 ⁻⁴
rs17426106	17	41,184,706	CRHR1	c/g	0.22	10,031	-0.11	0.026	3.21x10 ⁻⁵	11,733	-0.01	0.029	0.69	21,764	-0.07	0.020	8.34x10 ⁻⁴	0.012	21,278	-0.06	0.020	1.10x10 ⁻³	0.026
rs9952194	18	55,862,008	(PMAIP1)	t/c	0.79	15,234	0.08	0.021	9.33x10 ⁻⁵	11,443	0.01	0.023	0.78	26,677	0.05	0.016	2.28x10 ⁻³	0.22	26,167	0.05	0.016	8.54x10 ⁻⁴	0.16
rs12985777	19	2,219,055	?	t/c	0.26	15,200	0.07	0.022	2.31x10 ⁻³	9,663	0.05	0.032	0.090	24,863	0.06	0.018	5.19x10 ⁻⁴	0.59	24,368	0.06	0.019	1.10x10 ⁻³	0.57
rs4804519	19	10,669,770	QTRT1	t/c	0.63	15,234	0.07	0.020	3.31x10 ⁻⁴	12,987	0.01	0.022	0.65	28,221	0.04	0.015	3.07x10 ⁻³	0.49	28,266	0.04	0.015	3.34x10 ⁻³	0.59
rs10423928	19	50,874,144	GIPR	a/t	0.18	11,268	0.15	0.032	3.33x10⁻⁶	30,620	0.09	0.013	2.30x10⁻¹¹	41,888	0.09	0.012	1.98x10⁻¹⁵	1.85x10⁻⁵	41,099	0.08	0.012	3.20x10⁻¹²	8.21x10⁻⁵
rs2822664	21	14,743,816	SAMSN1	a/g	0.97	12,130	-0.25	0.073	6.53x10 ⁻⁴	10,242	-0.07	0.075	0.37	22,372	-0.16	0.052	2.12x10 ⁻³	0.29	21,872	-0.14	0.053	7.18x10 ⁻³	0.24

						models with further adjustment for fasting glucose																	
SNP	Chr	Position (NCBI B36) (bp)	Nearest Gene	Effect Allele/non-	Effect allele frequency	Discovery (FG-adj, BMI-adj)			Replication (FG-adj, BMI-adj)			Discovery + Replication (FG-adj, BMI-adj)				Discovery + Replication (FG-adj)							
						N	Effect (SE)	p-value	N	Effect (SE)	p-value	N	Effect (SE)	p-value	p-value _{net}	N	Effect (SE)	p-value	p-value _{net}				
rs17187140	1	206,376,398	PLXNA2	a/g	0.1	13,358	0.15	0.036	3.37 × 10 ⁻⁵	13,939	-0.04	0.028	0.14	27,297	0.03	0.022	0.16	0.016	26,819	0.03	0.023	0.14	8.21 × 10 ⁻³
rs1260326	2	27,584,444	GCKR	t/c	0.40	15,029	0.12	0.018	3.77 × 10⁻¹¹	22,624	0.09	0.014	1.04 × 10⁻¹¹	37,653	0.10	0.011	9.23 × 10⁻²¹	0.099	37,181	0.11	0.011	2.26 × 10⁻²¹	0.10
rs4971652	2	50,245,662	NRXN1	a/g	0.84	14,979	0.08	0.026	1.14 × 10 ⁻³	11,658	0.01	0.026	0.76	26,637	0.05	0.018	0.011	0.26	26,673	0.05	0.018	0.011	0.16
rs12618178	2	54,908,792	?	a/c	0.20	15,029	-0.09	0.023	5.03 × 10 ⁻⁵	13,840	0.01	0.021	0.56	28,869	-0.04	0.016	0.02	0.014	28,390	-0.04	0.016	0.015	8.37 × 10 ⁻³
rs7604361	2	106,068,242	(C2orf40)	t/g	0.01	10,696	0.53	0.120	9.43 × 10 ⁻⁶	10,803	0.06	0.105	0.56	21,499	0.27	0.079	7.74 × 10 ⁻⁴	3.79 × 10 ⁻³	21,016	0.24	0.080	3.32 × 10 ⁻³	4.29 × 10 ⁻³
rs16847412	2	142,335,384	LRP1B	t/c	0.93	15,029	-0.12	0.032	1.64 × 10 ⁻⁴	17,087	-0.02	0.024	0.33	32,116	-0.06	0.019	2.41 × 10 ⁻³	0.036	31,634	-0.06	0.019	3.78 × 10 ⁻³	0.018
rs1955086	2	222,400,290	(EPHA4)	t/c	0.75	15,029	-0.08	0.022	2.38 × 10 ⁻⁴	21,241	-0.01	0.014	0.62	36,270	-0.03	0.012	0.018	0.070	35,793	-0.02	0.012	0.037	0.11
rs6726280	2	230,201,928	DNER	a/c	0.17	15,029	0.11	0.026	3.45 × 10 ⁻⁵	22,903	0.01	0.016	0.71	37,932	0.03	0.014	0.013	0.014	37,455	0.03	0.014	0.02	6.46 × 10 ⁻³
rs12374129	3	78,626,542	(ROBO1)	t/c	0.15	15,029	0.07	0.023	1.98 × 10 ⁻³	11,912	-0.02	0.022	0.38	26,941	0.02	0.016	0.12	0.27	26,889	0.03	0.016	0.072	0.42
rs2877716	3	124,577,141	ADCY5	t/c	0.23	15,009	-0.08	0.022	2.24 × 10⁻⁴	28,938	-0.07	0.013	1.65 × 10⁻⁸	43,947	-0.07	0.011	1.68 × 10⁻¹¹	4.74 × 10⁻⁸	43,480	-0.08	0.011	7.98 × 10⁻¹²	2.14 × 10⁻⁷
rs9845279	3	158,795,136	(C3orf55)	c/g	0.56	12,704	-0.10	0.025	4.03 × 10 ⁻⁵	12,596	-0.01	0.018	0.71	25,300	-0.04	0.015	7.14 × 10 ⁻³	4.61 × 10 ⁻⁴	25,342	-0.04	0.015	6.76 × 10 ⁻³	9.44 × 10 ⁻⁴
rs309795	4	177,703,271	(VEGFC)	a/c	0.43	15,029	-0.09	0.019	5.59 × 10 ⁻⁶	12,891	0.01	0.017	0.49	27,920	-0.03	0.013	9.81 × 10 ⁻³	1.06 × 10 ⁻⁴	28,545	-0.03	0.013	0.017	2.09 × 10 ⁻⁴
rs10037968	5	101,582,380	(SLCO4C1)	t/c	0.99	15,029	0.20	0.036	2.14 × 10 ⁻⁸	21,129	0.03	0.021	0.094	36,158	0.08	0.018	2.17 × 10 ⁻⁵	6.18 × 10 ⁻⁴	35,674	0.07	0.018	4.91 × 10 ⁻⁵	8.25 × 10 ⁻⁴
rs13265179	8	9,232,104	PPP1R3B	a/c	0.10	15,029	-0.12	0.027	2.50 × 10 ⁻⁵	6,745	-0.13	0.047	6.60 × 10 ⁻³	21,774	-0.12	0.024	5.24 × 10 ⁻⁷	0.18	21,815	-0.12	0.024	3.10 × 10 ⁻⁷	0.13
rs12545656	8	99,548,888	STK3	a/g	0.93	15,029	-0.17	0.042	3.25 × 10 ⁻⁵	13,999	-0.01	0.037	0.86	29,028	-0.08	0.028	4.29 × 10 ⁻³	0.014	28,549	-0.08	0.028	5.07 × 10 ⁻³	3.92 × 10 ⁻⁴
rs2439649	9	110,915,284	C9orf5	a/g	0.58	15,029	-0.07	0.018	4.81 × 10 ⁻⁵	13,507	0.00	0.017	0.97	28,536	-0.04	0.013	4.51 × 10 ⁻³	5.62 × 10 ⁻³	28,588	-0.04	0.013	4.58 × 10 ⁻³	3.11 × 10 ⁻³
rs12243326	10	114,778,805	TCF7L2	t/c	0.79	15,010	-0.12	0.021	3.69 × 10⁻⁹	22,790	-0.05	0.016	5.32 × 10⁻³	37,800	-0.07	0.013	9.99 × 10⁻⁹	3.16 × 10⁻³	37,326	-0.08	0.013	1.17 × 10⁻¹⁰	0.24
rs12873155	13	31,609,703	FRY	t/c	0.40	15,029	0.08	0.019	7.09 × 10 ⁻⁶	11,070	0.00	0.022	0.83	26,099	0.05	0.014	3.70 × 10 ⁻⁴	0.12	25,628	0.05	0.015	8.20 × 10 ⁻⁴	0.067
rs2585509	13	77,590,882	(EDNRB)	t/c	0.31	15,029	-0.06	0.020	9.72 × 10 ⁻⁴	9,245	-0.01	0.028	0.75	24,274	-0.05	0.016	4.03 × 10 ⁻³	0.27	23,788	-0.05	0.016	3.09 × 10 ⁻³	0.24
rs17271305	15	60,120,272	VPS13C	a/g	0.58	15,029	-0.11	0.018	8.52 × 10⁻⁹	15,615	-0.05	0.014	9.97 × 10⁻⁵	30,644	-0.07	0.011	4.33 × 10⁻¹¹	0.29	29,680	-0.07	0.011	8.41 × 10⁻¹¹	0.11
rs12448015	16	22,665,124	(HS3ST2)	a/g	0.97	15,029	-0.19	0.051	2.35 × 10 ⁻⁴	8,034	-0.15	0.086	0.082	23,063	-0.18	0.044	5.12 × 10 ⁻⁵	0.15	22,621	-0.17	0.044	8.44 × 10 ⁻⁵	0.12
rs7184872	16	27,374,838	(GTF3C1)	t/g	0.84	15,029	-0.11	0.029	7.72 × 10 ⁻⁵	23,119	0.01	0.016	0.59	38,148	-0.02	0.014	0.15	0.084	37,193	-0.03	0.014	0.06	0.11
rs1060253	16	86,423,639	SLC7A5	c/g	0.32	15,029	0.09	0.021	1.25 × 10 ⁻⁵	14,057	-0.05	0.019	8.10 × 10 ⁻³	29,086	0.01	0.014	0.35	1.00 × 10 ⁻⁴	28,131	0.02	0.014	0.23	8.07 × 10 ⁻⁵
rs17426106	17	41,184,706	CRHR1	c/g	0.22	10,007	-0.11	0.025	2.01 × 10 ⁻⁵	11,192	0.00	0.028	0.88	21,199	-0.06	0.019	1.16 × 10 ⁻³	3.19 × 10 ⁻³	20,235	-0.05	0.019	6.29 × 10 ⁻³	0.021
rs9952194	18	55,862,008	(PMAIP1)	t/c	0.79	15,029	0.07	0.021	3.18 × 10 ⁻⁴	10,902	0.01	0.022	0.55	25,931	0.05	0.015	2.26 × 10 ⁻³	0.55	25,489	0.05	0.015	9.00 × 10 ⁻⁴	0.50
rs12985777	19	2,219,055	?	t/c	0.26	14,995	0.08	0.022	1.18 × 10 ⁻⁴	9,121	0.05	0.030	0.11	24,116	0.07	0.018	4.48 × 10 ⁻⁵	0.37	23,153	0.07	0.018	5.28 × 10 ⁻⁵	0.41
rs4804519	19	10,669,770	QTRT1	t/c	0.63	15,029	0.08	0.019	3.94 × 10 ⁻⁵	12,979	0.01	0.021	0.58	28,008	0.05	0.014	6.32 × 10 ⁻⁴	0.22	27,049	0.05	0.015	5.28 × 10 ⁻⁴	0.21
rs10423928	19	50,874,144	GIPR	a/t	0.18	11,066	0.16	0.030	1.04 × 10⁻⁷	29,762	0.10	0.013	6.33 × 10⁻¹⁵	40,828	0.11	0.012	2.56 × 10⁻²⁰	3.08 × 10⁻⁵	40,354	0.10	0.012	5.943 × 10⁻¹⁸	4.96 × 10⁻⁵
rs2822664	21	14,743,816	SAMSN1	a/g	0.97	11,928	-0.28	0.070	1.43 × 10 ⁻⁵	10,815	-0.07	0.073	0.35	22,743	-0.18	0.050	3.20 × 10 ⁻⁴	0.21	22,301	-0.17	0.051	6.00 × 10 ⁻⁴	0.14

Chromosomal position is listed according to NCBI build 36 (hg18). The gene closest to the SNP is indicated, a gene name without parenthesis indicates that the lead SNP resides within the listed gene, whereas a gene in parenthesis indicates the closest gene to an intergenic SNP. Effect allele/non-effect allele are defined based on the positive strand of NCBI build 36 (hg18). Effect allele frequencies are from the HapMap phase II CEU sample. Results from the inverse-variance meta-analysis are presented for the discovery samples. A standard set of SNP proxies (with $r^2 > 0.8$ in HapMap phase II CEU samples) were genotyped when the primary SNP failed in replication studies). P -value_{net} is the P value for heterogeneity across joint discovery and replication samples based on the Q statistic. *ADCY5* and *GIPR* SNPs displayed evidence of heterogeneity, and may reflect a differential effect of these SNPs on study samples with primarily normal glucose tolerant (NGT) vs. impaired glucose tolerant (IGT) individuals. All analyses are adjusted for sex, age, study-specific covariates. BMI-adj: these analyses are adjusted for sex, age, study-specific covariates and body mass index. FG-adj: these analyses are adjusted for fasting glucose, sex, age, study-specific covariates.

Supplementary Table 3. Association of 2hr-glucose SNPs with glycemic traits in MAGIC and body mass index (BMI) in GIANT discovery meta-analyses

Chr	SNP	Nearest gene	Effect Allele/ Non-effect Allele		fasting glucose (mmol/L)	HOMA-B	fasting insulin (pmol/L)	HOMA-IR	HbA1c (%)	BMI (kg/m ²)
2	rs1260326	<i>GCKR</i>	T/C	Effect (SE) P-value	-0.027 (0.004) 4.3 x 10 ⁻¹³	-0.003 (0.003) 0.33	-0.015 (0.004) 1.2 x 10 ⁻⁴	-0.020 (0.004) 9.2 x 10 ⁻⁷	-0.004 (0.006) 0.53	0.012 (0.009) 0.17
3	rs2877716	<i>ADCY5</i>	C/T	Effect (SE) P-value	0.023 (0.004) 1.4 x 10 ⁻⁷	-0.013 (0.004) 1.5 x 10 ⁻³	-0.001 (0.005) 0.86	0.002 (0.005) 0.66	0.012 (0.007) 0.068	-0.0057(0.010) 0.59
10	rs12243326	<i>TCF7L2</i>	C/T	Effect (SE) P-value	0.021 (0.004) 6.2 x 10 ⁻⁷	-0.019 (0.004) 1.9 x 10 ⁻⁶	-0.011 (0.005) 0.016	-0.009 (0.005) 0.058	0.017 (0.006) 5.0 x 10 ⁻³	-0.033 (0.009) 4.4 x 10 ⁻⁴
15	rs17271305	<i>VPS13C</i>	G/A	Effect (SE) P-value	-0.009 (0.004) 0.022	0.004 (0.003) 0.23	0.001 (0.004) 0.79	-0.001 (0.004) 0.73	0.007 (0.006) 0.20	0.006 (0.009) 0.49
19	rs10423928	<i>GIPR</i>	A/T	Effect (SE) P-value	-0.013 (0.005) 0.014	0.001 (0.004) 0.86	-0.004 (0.005) 0.46	-0.005 (0.006) 0.32	0.021 (0.015) 0.16	-0.140 (0.035)** 7.5x10 ⁻⁵
				N	34,380-46,240	25,902-36,661	27,315-38,390	26,022-37,127	4,168-17,218	28,225-32,530

Effect allele raises 2h glucose; GIANT consortium BMI association data from Willer et al., 2009 (ref.14 in main text); **data for *GIPR* were not available from the GIANT consortium, and are from Lyssenko et al. (submitted) from a Swedish meta-analysis for N=27,628 .

Supplementary Table 4. Association of rs10423928 [GIPR], rs17271305 [VPS13C] and rs2877716 [ADCY5] with insulinogenic index, AUC (area under the curve) insulin/ glucose, and 2h insulin (adjusted for 2h glucose) within MAGIC and meta-analysis across all studies.

Study sample	GIPR SNP rs10423928 A				ADCY5 SNP rs2877716 C				VPS13C SNP rs17271305 G			
	N	Per allele effect (SE) (BMI adj.)	P-value (BMI adj.)	P-value	N	Per allele effect (SE) (BMI adj.)	P-value (BMI adj.)	P-value	N	Per allele effect (SE) (BMI adj.)	P-value (BMI adj.)	P-value
Insulinogenic index ($\mu\text{U}/\text{mmol}$)¹												
AMISH	674	-0.075 (0.073)	0.61	0.42	527**	-0.004 (0.067)	0.98	0.76	675	-0.142 (0.050)	0.16	0.11
BotniaPPP	4,241	-0.074 (0.018)	4.5x10 ⁻⁵	8.7x10 ⁻⁶	2,811**	-0.029 (0.028)	0.3	0.31	4,121***	0.014 (0.016)	0.4	0.37
DIAGEN	943	-0.077 (0.040)	0.057	0.066	922**	-0.005 (0.042)	0.99	0.98	-	-	-	-
Ely	1,306*	-0.127 (0.035)	2.43x10 ⁻⁴	7.82x10 ⁻⁵	1,360	-0.042 (0.030)	0.16	0.076	-	-	-	-
French Family Members	233	0.090 (0.112)	0.43	0.45	228	0.100 (0.126)	0.43	0.35	216	-0.080 (0.110)	0.44	0.45
French Haguenau	1,244	-0.003 (0.039)	0.94	0.9	1,243	-0.037 (0.037)	0.32	0.19	1,259	0.015 (0.032)	0.63	0.64
French Obese Adults	206	-0.196 (0.121)	0.107	0.07	-	-	-	-	-	-	-	-
Hertfordshire Study	996*	-0.067 (0.042)	0.11	0.12	977	-0.052 (0.037)	0.16	0.25	-	-	-	-
Inter99	5,016	-0.117 (0.023)	2.68x10 ⁻⁷	3.91x10 ⁻⁷	5,059	0.020 (0.021)	0.34	0.26	5,013	0.042 (0.019)	0.029	0.06
METSIM	4,998	-0.057 (0.018)	0.0013	2.98x10 ⁻⁴	5,034**	-0.009 (0.020)	0.64	0.77	-	-	-	-
RISC	1,168	-0.063 (0.035)	0.072	0.027	1,164	-0.022 (0.033)	0.508	0.42	1,153	-0.002 (0.029)	0.94	0.85
ROCHE	545	-0.033 (0.063)	0.61	0.37	551	-0.011 (0.059)	0.85	0.74	551	-0.005 (0.052)	0.92	0.85
ULSAM	922	-0.104 (0.039)	0.007	0.02	910**	-0.029 (0.041)	0.48	0.6	912	0.031 (0.034)	0.36	0.59
Meta-analysis	22,492	-0.076 (0.009)	1.00x10 ⁻¹⁷	2.09x10 ⁻²⁰	20,786	-0.011 (0.009)	0.23	0.22	13,900	0.024 (0.010)	0.013	0.020
AUC (area under the curve) insulin/ glucose (pmol/mmol)²												
AMISH	643	-0.0078 (0.037)	0.92	0.46	505	0.050 (0.036)	0.49	0.3	645	-0.0076 (0.026)	0.89	0.77
Botnia PPP	4,277	-0.050 (0.012)	3.1x10 ⁻⁵	1.6x10 ⁻⁶	2,811	-0.039 (0.018)	0.031	0.065	4,153***	0.0080 (0.011)	0.46	0.47
DIAGEN	950	0.039 (0.026)	0.14	0.11	930	0.026 (0.028)	0.35	0.45	-	-	-	-
Ely	1,196*	-0.069 (0.023)	3.0x10 ⁻³	2.6x10 ⁻⁴	1,245	0.007 (0.020)	0.74	0.38	-	-	-	-
French Family members	272	-0.12 (0.084)	0.14	0.15	266	0 (0.095)	0.97	0.82	250	-0.020 (0.085)	0.84	0.86
French Haguenau	1,159	0.0090 (0.024)	0.71	0.7	1,159	0.032 (0.024)	0.17	0.49	1,173	0.022 (0.020)	0.27	0.31
French Obese Adults	237	-0.057 (0.093)	0.54	0.45	-	-	-	-	-	-	-	-
Hertfordshire	992**	-0.045 (0.030)	0.14	0.13	973	-0.046 (0.027)	0.084	0.2	-	-	-	-
Inter99	4,946	-0.10 (0.022)	4.7x10 ⁻⁶	2.6x10 ⁻⁵	4,984	-0.027 (0.020)	0.18	0.36	4,941	0.0080 (0.018)	0.66	1
METSIM	5,031	-0.038 (0.012)	2.1x10 ⁻³	2.2x10 ⁻⁴	5,066	-0.016 (0.014)	0.25	0.45	-	-	-	-
RISC	1,007	-0.073 (0.025)	4.1x10 ⁻³	7.0x10 ⁻⁴	1,004	0.0004 (0.024)	0.99	0.75	997	-0.017 (0.020)	0.42	0.32
ROCHE	571	-0.040 (0.038)	0.29	0.1	576	0.010 (0.036)	0.78	0.72	576	-0.048 (0.031)	0.12	0.31
ULSAM	928	-0.094 (0.025)	1.6x10 ⁻⁴	1.4x10 ⁻³	916**	-0.0002 (0.026)	0.99	0.81	918	-0.032 (0.022)	0.14	0.047
Meta-analysis	22,209	-0.051 (0.006)	1.3x10 ⁻¹⁶	3.7x10 ⁻²⁰	20,435	0.010 (0.007)	0.16	0.19	13,653	-0.001 (0.007)	0.86	0.76
2h insulin (adjusted for 2h glucose)³												
AMISH	685	0.139 (0.045)	0.13	0.24	534**	0.17 (0.055)	0.13	0.091	688	-0.12 (0.033)	0.16	0.12
BLSA	460	-0.085 (0.056)	0.14	0.10	460	-0.006 (0.053)	0.91	0.93	460	-0.043 (0.042)	0.32	0.38
BotniaPPP	2,725	-0.067 (0.030)	0.028	0.013	2,699**	-0.11 (0.036)	3.0x10 ⁻³	3.06x10 ⁻³	4,214***	-0.012 (0.013)	0.38	0.35
CHS-1	1,658	-0.081 (0.029)	4.43x10 ⁻³	3.08x10 ⁻³	1,658	-0.028 (0.025)	0.27	0.51	1,658	-0.065 (0.024)	5.55x10 ⁻³	0.022
CHS-2	2,786	-0.060 (0.020)	2.90x10 ⁻³	1.60x10 ⁻³	-	-	-	-	-	-	-	-
DGI	-	-	-	-	1,045	-0.015 (0.057)	0.80	0.78	1,045	-0.033 (0.043)	0.45	0.58
DIAGEN	954	-0.062 (0.031)	0.047	0.041	934**	0.020 (0.033)	0.55	0.60	-	-	-	-
Ely	1,357*	-0.027 (0.024)	0.26	0.035	1,411	-0.0038 (0.021)	0.86	0.19	-	-	-	-
FHS	2,637	-0.055 (0.015)	3.08x10 ⁻⁴	3.79x10 ⁻⁵	2,618	-0.016 (0.014)	0.28	0.21	2,637	-0.012 (0.012)	0.32	0.21
FUSION	581	-0.026 (0.039)	0.51	0.57	581	-0.043 (0.041)	0.30	0.24	581	-0.059 (0.032)	0.066	0.043
Fusion Stage 2	286	-0.024 (0.046)	0.60	0.89	271	0.025 (0.055)	0.66	0.83	-	-	-	-
Hertfordshire	1071*	-0.073 (0.038)	0.05	0.046	1,048	-0.037 (0.033)	0.26	0.31	-	-	-	-
Inter99	5,349	-0.034 (0.016)	0.036	0.024	5,388	-0.059 (0.015)	9.86x10 ⁻⁵	5.96x10 ⁻⁴	5,342	-0.048 (0.014)	4.19x10 ⁻⁴	9.38x10 ⁻⁵
METSIM	5,055	-0.020 (0.015)	0.18	0.037	5,094**	-0.053 (0.017)	1.80x10 ⁻³	2.89x10 ⁻³	-	-	-	-
NHANES	528	-0.091 (0.040)	0.021	0.011	525	-0.080 (0.039)	0.039	0.043	528	-0.029 (0.033)	0.82	0.31
RISC	1,141	-0.036 (0.034)	0.24	0.11	1,136	-0.010 (0.032)	0.56	0.49	1,123	-0.057 (0.028)	0.041	0.023
ROCHE	583	-0.084 (0.049)	0.086	0.047	588	0.036 (0.046)	0.44	0.47	588	-0.091 (0.039)	0.021	0.029
Sorbs	-	-	-	-	651	-0.068 (0.048)	0.17	0.19	651	-0.029 (0.037)	0.46	0.59
ULSAM	937	-0.064 (0.029)	0.028	0.046	925**	-0.032 (0.030)	0.29	0.55	927	-0.086 (0.025)	7.32x10 ⁻⁴	1.75x10 ⁻⁴
Whitehall	3,411	-0.042 (0.019)	0.025	2.27x10 ⁻³	3,421	-0.023 (0.017)	0.16	0.19	3,400	-0.033 (0.015)	0.028	0.041
Meta-analysis	32,204	-0.044 (0.006)	1.99x10 ⁻¹³	3.67x10 ⁻¹⁶	30,987	-0.029 (0.006)	1.43x10 ⁻⁶	3.09x10 ⁻⁶	23,842	-0.037 (0.006)	7.45x10 ⁻¹¹	2.58x10 ⁻¹⁰

*rs11672660 proxy for GIPR SNP; **rs11708067 proxy for ADCY5 SNP; ***rs10519116 proxy for VPS13C SNP

1- Additive effect of the risk allele on insulinogenic index using study specific adjustments (including gender and age) with and without BMI adjustment.

2- Additive effect on AUC (area under the curve) insulin/ glucose using study specific adjustments (including gender and age) with and without BMI adjustment.

3- Additive effect of risk alleles on 2h insulin (adjusted for 2h glucose) using study specific adjustments (including gender and age) with and without BMI adjustment.

All outcomes were transformed using the natural logarithm.

Supplementary Table 5. Meta-analysis of GIPR SNP rs10423928 association with acute insulin response (AIR) during an intravenous glucose tolerance test (IVGTT) and with the incretin effect in non-diabetic individuals from up to 4 studies

GIPR SNP rs10423928 A						
Study sample	Acute insulin response during an IVGTT ¹					
	N	Per allele effect (SE) pmol/L*min (BMI adj.)			P-value (BMI adj.)	P-value
FUSION	562	0.070 (0.056)			0.21	0.28
Botnia	487	0.020 (0.023)			0.40	0.24
Denmark	198	0.064 (0.090)			0.48	0.78
EUGENE2-Kuopio	262	0.096 (0.105)			0.36	0.35
Meta-analysis	1509	0.032 (0.020)			0.12	0.10
% Incretin Effect ²						
Study sample	N	TT	TA	AA	P-value (BMI adj.)	P-value
Botnia	351	80.8 +/- 8.7	78.7 +/- 8.9	75.8 +/- 9.7	0.007	0.003
Denmark	198	85.3 +/- 10.6	82.2 +/- 15.3	86.9 +/- 6.2	0.18	0.16
EUGENE2-Kuopio	255	64.8 +/- 15.5	63.4 +/- 13.9	59.9 +/- 13.6	0.054	0.082
Meta-analysis	804				4.3x10 ⁻⁴	3.6x10 ⁻⁴

1-Acute insulin response calculated during an IVGTT. Association analyses for each study were performed as described in methods, and *P*-values were combined using a fixed effects, inverse variance meta-analysis. No evidence of heterogeneity was observed ($P_{\text{heterogeneity}}=0.87$)

2-The percent incretin effect was calculated using the formula $100\% \times (\text{AUCins OGTT} - \text{AUCins IVGTT}) / \text{AUCins OGTT}$. % incretin effect data are uncorrected and untransformed mean values. Association analyses for each study were performed as described in methods, and *P*-values were combined using a fixed effects z-score based meta-analysis. No evidence of heterogeneity was observed ($P_{\text{heterogeneity}}=0.86$)

Supplementary Table 6. Association of *GIPR* rs10423928, *ADCY5* rs2877716 and *VPS13C* rs17271305 with type 2 diabetes (T2D) in up to 27 case-control studies

Study Sample	Ncases/ Ncontrols	<i>GIPR</i> rs10423928 A		<i>ADCY5</i> rs2877716 C		<i>VPS13C</i> rs17271305 G	
		OR(95% CI)	<i>P</i> -value	OR(95% CI)	<i>P</i> -value	OR(95% CI)	<i>P</i> -value
58 BC_OxGN	654/1653	-	-	1.20 (1.02-1.41) [#]	0.030	-	-
ADDITION/ELY	837/1590	1.15 (0.97-1.36)*	0.11	1.31 (1.10-1.55)**	1.89x10 ⁻³	-	-
ARIC	696/6420	1.19 (0.99-1.44)	0.064	1.09 (0.95-1.26)	0.19	0.97 (0.86-1.10)	0.66
CCC	514/500	0.97 (0.77-1.23)*	0.83	1.32 (1.07-1.64)**	9.69x10 ⁻³	-	-
Danish	3514/4906	1.19 (1.07-1.32)	0.0014	1.19 (1.08-1.32)	0.00059	0.91 (0.84-1.00)	0.052
DGDG	679/697	-	-	1.11 (0.92-1.35)	0.28	-	-
deCODE	1465/23194	-	-	1.07 (0.97-1.19)	0.17	-	-
DGI	1022/1075	-	-	1.01 (0.86-1.20)	0.89	1.04 (0.92-1.17)	0.59
DIAGEN	533/743	0.93 (0.77-1.14)	0.48	1.51 (1.22-1.87)**	1.4x10 ⁻⁴	-	-
ERGO	1178/4761	-	-	1.08 (0.98-1.20)	0.13	-	-
EUROSPAN	268/3710	-	-	0.99 (0.79-1.25)	0.95	-	-
FHS	674/8338	0.91 (0.76-1.07)	0.26	1.09 (0.94-1.30)	0.26	1.02 (0.89-1.14)	0.81
French case-control	1107/1190	1.17 (0.91-1.49)	0.22	-	-	0.95 (0.77-1.17)	0.61
FUSION	1161/1174	1.02 (0.88-1.12)	0.84	1.06 (0.91-1.24)	0.44	0.91 (0.81-1.02)	0.12
FUSION stage 2	1180/1251	1.24 (1.09-1.41)	1.4x10 ⁻³	1.10 (0.94-1.28)**	0.22	-	-
GCI Poland	790/803	0.97 (0.81-1.15)	0.70	-	-	1.06 (0.90-1.24)	0.51
GCI US	1010/987	0.99 (0.84-1.18)	0.95	0.94 (0.80-1.11)**	0.48	1.07 (0.93-1.23)	0.36
HPFS	1095/1241	-	-	0.97 (0.84-1.13)	0.71	0.85 (0.75-0.96)***	0.010
KORA	433/1438	-	-	1.14 (0.94-1.38)	0.18	-	-
MDC_MDR	2764/3185	1.10 (0.99-1.22)	0.065	1.20 (1.08-1.33)**	4.6x10 ⁻⁴	-	-
METSIM	879/3582	0.99 (0.87-1.13)	0.85	1.24 (1.06-1.44)	5.5x10 ⁻³	-	-
NHANES	286/1194	1.30 (1.03-1.63)	0.026	1.14 (0.90-1.45)	0.2903	1.26 (1.03-1.53)	0.027
NHS	1467/1754	-	-	1.18 (1.04-1.34)**	0.011	0.98 (0.88-1.10)***	0.77
Norfolk	2779/2271	1.04 (0.92-1.17)*	0.52	1.13 (1.05-1.22)**	7.13x10 ⁻⁴	-	-
Roche	461/600	0.98 (0.77-1.25)	0.86	0.86 (0.69-1.08)	0.21	1.15 (0.95-1.41)	0.16
UKT2DGC	5113/6615	-	-	1.10 (1.04-1.18) [#]	1.7x10 ⁻³	-	-
WTCCC	1924/2938	-	-	1.08 (0.97-1.19)	0.15	0.94 (0.86-1.02)	0.14
N cases/controls		19,091/38,508		35,869/89,798		15,180/32,556	
Meta-analysis (fixed effects)		1.07 (1.03-1.12)	1.8x10⁻⁴	1.12 (1.09-1.15)	4.8x10⁻¹⁸	0.97 (0.94-1.00)	0.083
<i>I</i> ²		39.3% (0-65.3%)		35.2% (0-59.3%)		48.7% (0-72.8%)	
Meta-analysis (random effects)		1.07 (1.02-1.12)	9.6x10⁻³	1.12 (1.08-1.16)	9.4x10⁻¹¹	0.99 (0.94-1.04)	0.62

[#]rs11672660 proxy for *GIPR* SNP; ^{**}rs11708067 proxy for *ADCY5* SNP, [#]rs11717195 proxy for *ADCY5* SNP; ^{***}rs12913951 proxy for *VPS13C* SNP

Note: Meta-analysis of GWAS from DGI, FUSION and WTCCC studies have been published by DIAGRAM (Zeggini et al, 2008).

SUPPLEMENTARY NOTE

Expression analyses

We used commercial cDNAs from the Human MTC panel I for lung, kidney, heart, muscle and liver (BD Biosciences Clontech) and RNAs that were reverse transcribed from the brain, small intestine and adipose tissue (Human Adult Normal 5 Donor Pool, BioChain Institute). Pancreatic islets and sorted beta cells were obtained from human adult brain-dead donors in accordance with the French regulations and the local institutional ethical committee, as previously described.¹ Briefly, pancreatic islets were isolated after ductal distension of the pancreata and digestion of the tissue with Liberase (Roche Diagnostics). Human beta cells were sorted by FACS analysis of semi-purified preparations of islet cells using Newport Green, a specific zinc-fluorescent probe.¹ Total RNA was extracted using Nucleospin RNA II kit (Macherey Nagel) according to the manufacturer's instructions. Samples were treated with DNase 1 (Ambion) to ensure residual genomic contamination was removed. cDNA samples were amplified by standard PCR using the Fast Start Taq (Roche Applied Science). For each sample, 1µg of total RNA was used to generate cDNA by random primed first strand synthesis (Applied Biosystems) according to manufacturer's protocol. Reverse transcription was also performed on beta cells samples in the absence of the enzyme, reverse transcriptase, and these samples used as negative controls. Resulting cDNA for each tissue was diluted 1:10 and 4µl used in a 20µl qRT-PCR reaction with 10µl gene expression mastermix (Applied Biosystems) and 1µl gene specific assay (Applied Biosystems).

Islet Microarrays for expression by genotype

Human islets at Lund University Diabetes Center (LUDC) were provided by the Nordic network for clinical islets transplantation by the courtesy of Dr. Olle Korsgren, Uppsala, Sweden. Total RNA was isolated with the AllPrep DNA/RNA Mini Kit (Qiagen GmbH, Hilden, Germany). RNA quality and concentration were measured using an Agilent 2100 bioanalyzer and Nanodrop ND-1000 equipment, respectively. The microarrays were performed following the Affymetrix standard protocol. Briefly, 100-300 ng total RNA was processed following the GeneChip® Expression 3'-Amplification Reagents One-cycle cDNA synthesis kit instructions (Affymetrix Inc, Santa Clara, CA, USA) to produce double-stranded cDNA. This was used as a template to generate biotin-targeted cRNA following manufacturer's specifications. 15 µg of the biotin labeled cRNA was fragmented to strands between 35 and 200 bases in length, 10 µg of which was hybridized onto the GeneChip® Human Gene 1.0 ST whole transcript based assay overnight in the GeneChip® Hybridization oven 6400 using standard procedures. The arrays were washed and stained in a GeneChip® Fluidics Station 450. Scanning was carried out with the GeneChip® Scanner 3000 and image analysis was performed using GeneChip® Operating Software. The array data were summarized and normalized with Robust Multi-array Analysis (RMA) method using the software "Expression Console" (Affymetrix).

In up to 20 samples, no association was observed between genotypes at rs10423928 and *GIPR*, *EML2* or *SNRPD2* transcripts ($P= 0.76$, 0.56 and 0.36 respectively), or between genotypes at rs2877716 and the *ADCY5* or *SEC22A* transcripts ($P= 0.86$ and 0.79 respectively), or between genotypes at rs17271305 and *FAM148A* transcript ($P= 0.90$). A probe to assay *VPS13C* gene expression was not present on the microarray.

T2D Association Studies

SNPs from three loci (*GIPR*, *ADCY5* and/or *VPS13C*) were genotyped in previously described T2D case-control studies (58BC_OxGN, Addition/ELY, CCC, DIAGEN, French case-

control, FUSION stage 2, GCI Poland, GCI US, MDC_MDR, METSIM, Norfolk Diabetes case-control study, Roche and UKT2DGC). Summary association results for tested SNPs were also obtained from a) published GWAS meta-analysis of the DIAGRAM consortium³⁹ or unpublished GWAS meta-analyses of the DIAGRAM+ consortium (comprising DGDG, DGI, ERGO, EUROSPAN, FUSION, KORA, WTCCC and deCODE), b) unpublished GWAS from the NHS and HPFS studies, and c) GWAS of cohort studies with prevalent cases at baseline (ARIC, FHS). Association of SNPs at the *GIPR*, *VPS13C* and *ADCY5* loci was tested using an additive genetic model, adjusted for study-specific covariates. Genotyped SNPs with a call rate >90%, MAF > 1% and HWE P-value > 10^{-4} were included for analysis, and imputed SNPs were only accepted if $r^2_{\text{hat}} > 0.3$ (MACH) or SNP Info > 0.4 (IMPUTE). Results were combined using an inverse variance meta-analysis assuming fixed effects. Heterogeneity was assessed using the I^2 statistic, and as estimates were over 25%, we performed a second meta-analysis assuming random effects. Future prediction of type 2 diabetes was performed in the Malmo Preventive Project. Analysis details and references for each T2D study are provided below.

ARIC: Details of the Atherosclerosis Risk in Communities (ARIC) Study scan and samples have been described previously.² In brief, the analysis included 696 T2D cases and 6420 non-cases ascertained at the baseline examination (1987-89). Diabetes was defined as self-reported physician diagnosis of diabetes, self-reported use of diabetes medications in the last two weeks, fasting glucose ≥ 126 mg/dL, or casual glucose ≥ 200 mg/dL. Non-cases had fasting glucose < 110 mg/dL. Samples were genotyping using the Affymetrix Genome-Wide Human 6.0 array. The MACH software (v1.0.16) was used to impute untyped or partially typed SNPs. A total of 708,116 directly genotyped SNPs and 1,849,116 imputed SNPs passed QC. ProbABEL software was used to analyze the SNPs by logistic regression assuming an additive model and adjusting for age, gender, field center, and BMI.

DGDG: The Diabetes Gene Discovery Group scan and samples have been described previously.³ In brief, 690 non-obese (Body-mass Index (BMI) <30), family history positive Type 2 Diabetics (T2D) and 730 controls (selected among participants in a longitudinal study (DESIR) 2: healthy subjects with age at exam >45 years and BMI <27) were genotyped for 309,385 autosomal SNPs that passed QC on the Illumina Human Hap300 BeadArray. Genotypes for untyped SNPs were imputed using the IMPUTE software package, of which 2,139,197 SNPs passed imputation QC. 2,557,287 genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model, using the SNPTTEST software package. The analysis was adjusted using genomic control: 1.10 for directly genotyped SNPs and 1.098 for imputed SNPs. The results for the *ADCY5* SNP rs2877716 were extracted for this manuscript.

deCODE: Details of the previous scan and samples have been described previously.^{4,5} In brief, a collection of Icelandic samples consisting of 1,465 T2D cases and 23,194 population controls were genotyped for 281,410 autosomal SNPs that passed QC on either the Illumina HumanHap300/300-duo+ or CNV370-duo Bead Arrays. Genotypes for untyped SNPs were imputed using the IMPUTE software package, of which 2,056,955 SNPs passed imputation QC. 2,338,365 genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model, using the SNPTTEST software package. The analysis was adjusted using genomic control: 1.308 for directly genotyped SNPs and 1.305 for imputed SNPs. The magnitude of the adjustment factor is primarily due to the relatedness of the Icelandic cases and controls.

DGI: Details of the previous scan and samples have been described previously^{6,7}, with one modification. Unlike the previous meta-analysis, we excluded the discordant sibship component because calculation of effect size and uncertainty around that estimate has not been previously determined.

DGI Stage 2 (MDC_MDR, GCI Poland, GCI US,): Clinical characteristics of the samples have been described previously^{6,7}. All three SNPs were genotyped using the iPLEX Sequenom MassArray platform (<http://www.sequenom.com/Assets/pdfs/appnotes/8876-006.pdf>) and analyzed for association with T2D using chi-square analysis.

Malmo Diabetes Registry/Malmo Diet and Cancer Study: The Sweden case control sample consisted of 2,764 cases from the Malmo Diabetes Registry and 3,185 normoglycemic controls from the Malmo Diet and Cancer study. Cases had age of onset >35 years, C-peptide >0.3 nmol/L and were GAD Ab negative, and were frequency matched to controls by age, sex and BMI.

GCI-US sample: The US case-control sample comprised 1,010 cases of European ancestry from the United States matched to 987 control subjects by age, sex, and grandparental country of origin.

GCI-Poland sample. The Poland case-control sample consisted of 790 diabetic cases and 803 control subjects, matched individually by age and sex.

DANISH Case-Control Study: The prioritized polymorphisms were genotyped in 8632 Danes comprising the population-based Inter99 sample of middle-aged people sampled at Research Centre for Prevention and Health⁸, type 2 diabetic patients sampled through the out-patient clinic at Steno Diabetes Center, a population-based group of middle-aged glucose-tolerant subjects recruited from Steno Diabetes Center, and screen detected type 2 patients sampled in Danish part of the ADDITION study sampled by Department of General Practice at University of Aarhus.⁹ Detailed characteristics of study populations have been described.¹⁰ In total, 3589 type 2 diabetic patients and 5043 glucose-tolerant control subjects were genotyped using Taqman allelic discrimination (KBioscience, Herts, UK).

DIAGEN: Subjects from German families with a family history of type 2 diabetes, obesity, or dyslipoproteinaemia were investigated as described elsewhere.¹¹ All subjects were from the city of Dresden and adjoining areas. Exclusion criteria were: known diabetes mellitus, severe renal disease, disease with a strong impact on life expectancy, and therapy with drugs known to influence glucose tolerance (thiazide diuretics, beta blockers, steroids). All individuals underwent a 75g oral glucose tolerance test following an overnight period of fasting (10 hours minimum) with measurements of plasma glucose, insulin, and free fatty acids (NEFA) at fasting and at 30, 60, 90 and 120 minutes after glucose challenge. After a three-year period, some subjects again underwent an oral glucose tolerance test using the same protocol. The cohort was divided into three glucose tolerance groups according to the results of the baseline and follow-up oGTT: normoglycaemic (NGT), impaired glucose tolerance (IGT) including those with impaired fasting glucose (IFG), and type 2 diabetes mellitus based on the WHO/ADA criteria of 1997/1999. As patients underwent oGTT analyses both at inclusion and following the three-year interim, five groups were defined according to the evolution of their diabetic status: those whose disease status remained unchanged as NGT, IGT/IFG and type 2 diabetes, those presenting a regression and those presenting a progression of the disease. Genotyping was performed on 533 T2D cases and 743 controls using Sequenom iPLEX Gold SBE assays at the

National Human Genome Research Institute. SNPs were analyzed using logistic regression with adjustment for sex and an additive model for the genetic effect.

EUROSPAN: In brief, 268 T2D cases and 3,710 controls sampled across 4 genetically isolated populations throughout Europe were genotyped for approximately 288,389 (plus an additional 21,261) SNPs on either the Illumina HumanHap300 or HapMap 370CNV. Genotypes for untyped or partially genotyped SNPs were imputed using the MACH1 software package, of which 2,058,605 passed imputation QC. 2,368,255 SNPs genotyped and imputed SNPs were analyzed using logistic regression assuming an additive model, including covariates for sex and ascertainment province, using the ProbABEL and GenABEL software packages.

Framingham Heart Study (FHS) SNP-Health Association Resource (SHARe): The analysis included 674 cases and 7664 controls from all three generations of Framingham participants. Diabetes was defined as: 1) Cohort (Gen 1): casual glucose ≥ 200 mg/dl at any exam 1-22 or taking diabetes medication (oral or insulin) at any exam 2) Offspring (Gen 2): Fasting plasma glucose ≥ 126 mg/dl at any exam 1-7 or diabetes treatment at any exam. In the Offspring, >99% of diabetes is type 2 diabetes. 3) Gen 3: Fasting ≥ 8 hours and fasting plasma glucose ≥ 126 mg/dl at exam 1 or diabetes treatment at exam 1

Samples were genotyped using the Affymetrix 500K and MIPS 50K SNPs. The MACH (version 1.0.15) software was used to impute 2,543,887 ungenotyped SNPs, 2,411,590 of SNPs passed QC criteria. A total of 2,438,639 directly genotyped and imputed SNPs were analyzed using the logistic regression model using a robust variance estimated via generalized estimating equations with each pedigree as a cluster. Covariates included in the model included, sex, cohort indicator and sex x cohort interaction term. For imputed SNPs, the expected number of alleles (dosage) was used in the analysis. The genomic control lambda was estimated as 1.04 for directly genotyped SNPs and 1.02 for imputed results.

French case-control: T2D cases were recruited at the Endocrinology-Diabetology Department of the Corbeil-Essonnes Hospital. Details about these cases are provided elsewhere.³ Controls were DESIR participants with FPG < 6.1 mmol/l and no current T2D treatment. Individuals with birth place outside metropolitan France and/or with non-European ancestry were excluded after population structure analyses as previously described.¹²

FUSION: Details of the previous scan and samples have been described elsewhere.^{7,13} In brief, the FUSION stage 1 samples consisting of 1,161 Finnish T2D cases and 1,174 Finnish normal glucose tolerant controls approximately frequency matched to cases based on 5-year age category, sex, and birth province were genotyped for 306,244 autosomal SNPs that passed QC using the Illumina HumanHap300 BeadChip (version 1.1). Genotypes for untyped SNPs were imputed using the MACH1 software package, of which 2,106,846 passed imputation QC. 2,413,090 genotyped and imputed SNPs were analyzed using logistic regression assuming an additive model, including covariates for sex, 5-year age category, and birth province. To account for uncertainty in the imputation of untyped SNPs, imputed SNPs were represented by the expected allele count. The analysis was adjusted using genomic control: 1.03 for directly genotyped SNPs and 1.04 for imputed SNPs.

FUSION stage 2: The FUSION study stage 2 sample includes 1211 T2D cases and 1266 NGT controls selected from the Dehko 2D, Health 2000, Finrisk 1987, Finrisk 2002, Savitaipale Diabetes, and Action LADA studies.¹³ FUSION stage 2 samples do not overlap with the

individuals used in the FUSION GWAS. Genotyping was performed using Sequenom iPLEX Gold SBE assays at the National Human Genome Research Institute. SNPs were analyzed using logistic regression with adjustment for sex, 5-year age category and birth province and an additive model for the genetic effect.

GEM (CCC, ADDITION-Ely, Norfolk Diabetes Case-Control Study):

Cambridgeshire case-control study: The Cambridgeshire case-control study is a population based study of type 2 diabetes (T2D) cases, aged 45-76 years, and age and sex matched controls. Cases were randomly selected from general practitioner diabetes registers in Cambridgeshire, UK, and T2D was defined as onset of diabetes after the age of 30 years and without insulin use in the first year after diagnosis.¹⁴ Controls were recruited at random from the same population sampling frames, and individually matched to cases for age, sex and GP practice. Diabetes was excluded in controls by medical record search and by a glycated haemoglobin measurement of less than 6%. The study received ethical approval from the Cambridge Local Research Ethics Committee, and participants provided informed consent. In the current analyses, we include 544 cases and 527 controls, representing all white Europeans who had DNA available and information on body mass index.

ADDITION-Ely case-control study: Previously undiagnosed prevalent cases of T2D, defined using WHO OGTT criteria, were identified via a population-based stepwise screening strategy among 40 to 69 year olds participating in the UK Cambridge arm of the ADDITION study. Current analyses include 799 white European men and women who had DNA available and information on body mass index.⁹ Controls were identified from the MRC Ely study, a population-based cohort of white European men and women aged 35 to 79 years without diagnosed diabetes and from a similar sampling frame as the cases.¹⁵ Based on WHO OGTT criteria, participants were confirmed as controls (n=1,606) or classified as cases (n=92). The Cambridge Research Ethics Committee approved both studies.

Norfolk Diabetes case-control study: The Norfolk Diabetes Case-Control Study is an ongoing study of white European men and women with T2D patients in Norfolk. All T2D patients identified through general practice diabetes registers in Norfolk and local hospital diabetes clinic and retinal screening programme patient registers are invited to participate; a total of 2,908 white European cases were included in the current analyses. Participants with insulin use during the first year of diagnosis, and those with cystic fibrosis, chronic pancreatitis or long term steroid use were excluded from the study. 2,394 controls free of known diabetes at baseline or during follow-up were randomly selected from EPIC-Norfolk participants. The Norfolk study was approved by the Norwich Local Research Ethics Committee.

Genotyping was performed at the MRC Epidemiology Unit using custom TaqMan[®] SNP assays (Applied Biosystems, Warrington, UK), with 10ng of genomic DNA. The call frequency of genotyped samples was >95% and HWE p-values >0.1. Between 2-4% duplicate samples were used per study and these were 97-100% concordant. Associations between each SNP and diabetes were tested using logistic regression analyses, assuming an additive genetic model and adjusting for age, sex and BMI.

HPFS: Details of the Health Professionals Follow-up Study (HPFS) cohorts have been described previously.¹⁶ The cases and controls for the HPFS Type 2 Diabetes (T2D) project were selected among those with a blood sample (N=18,159) using a "nested" case-control study design. Cases of T2D were identified by self-report on biennial follow-up questionnaires and confirmed by a medical record-validated supplementary questionnaire.¹⁷ Controls were defined as those free of

diabetes at the time of diagnosis of the case. Genotyping was performed using the Affymetrix Genome-Wide Human 6.0 array. 742,032 SNPs passed QC in 1,146 T2D cases and 1,241 controls who were of European ancestry. We used PLINK software to analyze the association by logistic regression assuming an additive model.

KORA T2D study: Details of the previous scan and samples have been described previously.^{18,19} In brief, 433 T2D cases and 1,438 nondiabetic control participants of the KORA (Cooperative Health Research in the Region of Augsburg / Kooperative Gesundheitsforschung in der Region Augsburg) surveys S3 (1994/1995), F3 (follow-up of S3, 2004/2005), and S4 (1999-2001) were genotyped for 356,183 autosomal SNPs that passed QC using the Affymetrix GeneChip Human Mapping 500k Array Set. Genotypes for untyped SNPs were imputed using the IMPUTE software package (version 0.3.2) of which 1,969,049 SNPs passed imputation QC. 2,325,232 directly genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model including covariates for age and sex using the SNPTTEST software package. The analysis was adjusted using genomic control: 1.04 for both directly genotyped and imputed SNPs.

Malmö Preventive Project (MPP): In this large population based prospective study from the city of Malmö, Sweden, we included 16,061 non-diabetic subjects, 2,063 of whom developed T2D during a 24.8 year median follow-up period.^{20,21} Diagnosis of diabetes was confirmed from patient records or based upon a fasting plasma glucose ≥ 7.0 mmol/l. We investigated the predictive ability of *ADCY5* (rs2877716) polymorphisms for future type 2 diabetes using logistic-regression analysis adjusted for age and secondary age and BMI. Since men and women were included at different times, we adjusted for this factor using the participation period (coded 0 or 1), sex, and an interaction term (participation period \times sex, which was coded 0 or 1) as covariates in the analyses.

Metabolic Syndrome in Men (METSIM): The METSIM study of men randomly sampled from the town of Kuopio in Eastern Finland (population 95,000) has been described previously.²² Our sample included 879 T2D cases and 3582 NGT controls, aged 45-72 years. Genotyping was performed using iPLEX Gold SBE assays at the National Human Genome Research Institute. We performed logistic regression adjusted for 5-year age category using an additive genetic model.

NHS: Details of the Nurses' Health Study (NHS) cohorts have been described previously.²³ The cases and controls for the NHS Type 2 Diabetes (T2D) project were selected among those with a blood sample (N=32,826) using a "nested" case-control study design. Cases of T2D were identified by self-report on biennial follow-up questionnaires and confirmed by a medical record-validated supplementary questionnaire.¹⁷ Controls were defined as those free of diabetes at the time of diagnosis of the case. Genotyping was performed using the Affymetrix Genome-Wide Human 6.0 array. 706,896 SNPs passed QC in 1,532 T2D cases and 1,754 controls who were of European ancestry. We used PLINK software to analyze the association by logistic regression assuming an additive model.

Roche Study: Details of the sample have been previously described.²⁴ Patients with diabetes mellitus and non-diabetic control subjects, with no personal history or family history of diabetes in first degree relatives and with normal (< 6.1 mmol/l or 110 mg/dl) fasting glucose levels, were recruited and evaluated by the Diabetes Center, Massachusetts General Hospital and the Division of Endocrinology and Metabolism, Brigham and Women's Hospital as part of an observational study of diabetic and pre-diabetic subjects. All SNPs were genotyped using allele-

specific primer extension of multiplex amplified products with detection by matrix-assisted laser desorption ionization–time of flight mass spectroscopy on an iPLEX Sequenom platform. Genotyping call rates were 99% on average, and the average consensus rate based on 254 duplicate samples was 99%. Association analysis was performed using an additive genetic model.

The Rotterdam Study (ERGO): In brief, 1,178 T2D cases and 4,761 controls were genotyped for 500,264 SNPs that passed QC using the Infinium II assay on the HumanHap550 Genotyping BeadChips (Illumina Inc., San Diego, CA, USA). Genotypes for untyped SNPs were imputed using the MACH1 software package, of which 2,067,878 were imputed. 2,568,142 directly genotyped and imputed SNPs were analyzed using logistic regression assuming an additive model, using the ProbABEL and GenABEL software packages. The analysis was adjusted using genomic control: 1.0064 for directly genotyped SNPs and 1.01 for imputed SNPs.

WTCCC: Details of the previous scan and samples have been described previously.⁷ In brief, the WTCCC/UKT2D stage 1 UK samples consisting of 1,924 T2D cases and 2,938 population controls were genotyped for 393,143 autosomal SNPs that passed QC using the Affymetrix GeneChip Human Mapping 500k Array Set. Genotypes for untyped SNPs were imputed using the IMPUTE software package, of which 1,915,393 SNPs passed imputation QC. 2,308,535 directly genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model including two ancestry informative principal components covariates to correct for population structure, using the SNPTTEST software package. The analysis was adjusted using genomic control: 1.06 for directly genotyped SNPs and 1.08 for imputed SNPs.

UK Type 2 Diabetes Genetics Consortium (UKT2DGC) collection and OxGN/58BC (UKRS2): These samples represent an expansion of the “UK Stage 2” samples described previously.^{7,25} The UKT2DGC (“Dundee”) collection study sample of 5113 T2D cases and 6615 controls includes subjects previously described⁷ as RS1 and RS3, together with added tranches of cases and controls ascertained more recently. Since all tranches were ascertained using precisely the same scheme, these are here combined into a single sample. All cases and controls were of European White descent, living in the Tayside region of Dundee when recruited. Cases had T2D diagnosed between the ages of 35- 70 years (inclusive). The diagnosis of diabetes was based on either current prescribed treatment with diabetes-specific medication or, in the case of individuals treated with diet alone, laboratory evidence of hyperglycemia as defined by the World Health Organization. Patients were excluded if they had an established (clinical and/or molecular) diagnosis of monogenic diabetes (e.g. maturity-onset diabetes of the young, mitochondrial diabetes) or if they had been treated with regular insulin therapy within 1 year of diagnosis. Controls were from the same population base, aged below 80 years and had not been diagnosed with diabetes at the time of recruitment (or subsequently). Control subjects were excluded from analysis if laboratory investigations at the time of recruitment provided evidence of hyperglycemia (fasting glucose >7.0 mmol/l, HbA1c >6.4%). The OxGN sample (equivalent to RS2 from previous papers^{7,26} includes 335 T2D cases, and was matched to additional controls from the 1958 Birth Cohort (non-overlapping with those included in the 1500 cohort members studied in the WTCCC).

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