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Genetic variation in *GIPR* influences the glucose and insulin responses to an oral glucose challenge

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The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturegenetics/.

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Abstract

Glucose levels 2 h after an oral glucose challenge are a clinical measure of glucose tolerance used in the diagnosis of type 2 diabetes. We report a meta-analysis of nine genome-wide association studies (n = 15,234 nondiabetic individuals) and a follow-up of 29 independent loci (n = 6,958–30,620). We identify variants at the *GIPR* locus associated with 2-h glucose level (rs10423928, β (s.e.m.) = 0.09 (0.01) mmol/l per A allele, $P = 2.0 \times 10^{-15}$). The *GIPR* A-allele carriers also showed decreased insulin secretion (n = 22,492; insulinogenic index, $P = 1.0 \times 10^{-17}$; ratio of insulin to glucose area under the curve, $P = 1.3 \times 10^{-16}$) and diminished incretin effect (n = 804; $P = 4.3 \times 10^{-4}$). We also identified variants at *ADCY5* (rs2877716, $P = 4.2 \times 10^{-16}$), *VPS13C* (rs17271305, $P = 4.1 \times 10^{-8}$), *GCKR* (rs1260326, $P = 7.1 \times 10^{-11}$) and *TCF7L2* (rs7903146, $P = 4.2 \times 10^{-10}$) associated with 2-h glucose. Of the three newly implicated loci (*GIPR*, *ADCY5* and *VPS13C*), only *ADCY5* was found to be associated with type 2 diabetes in collaborating studies (n = 35,869 cases, 89,798 controls, OR = 1.12, 95% CI 1.09–1.15, $P = 4.8 \times 10^{-18}$).

Type 2 diabetes (T2D) is defined as a state of chronic hyperglycemia defined as elevated glucose levels measured either when fasting or 2 h after glucose challenge (2-h glucose)

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during an oral glucose tolerance test (OGTT). GWAS have contributed to the identification of many established T2D-associated loci[1]. More recently, collaborative efforts of the Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC) and other investigators have led to the discovery of genetic variation associated with fasting glucose levels in nondiabetic individuals, with *MTNR1B* additionally conferring risk of T2D[2–5]. Not all loci associated with fasting glucose showed association with T2D[3,4], suggesting that GWAS of quantitative traits related to diabetes can also identify physiological loci that provide mechanistic insights into normal trait variation. An accompanying study by MAGIC has identified 16 loci associated with fasting glucose or fasting insulin in a GWAS-based meta-analysis; 9 of these loci are newly identified, and 5 also show evidence for association with T2D[6].

Although there are common mechanisms, such as insulin secretion, that regulate fasting and stimulated glucose levels, there are distinct mechanisms regulating glucose levels after an oral glucose challenge. For example, oral glucose intake engenders the incretin effect, in which intestinal cells release insulin secretagogues, mainly glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP), leading to a higher insulin response compared to that from a matched intravenous glucose stimulation. Additionally, numerous epidemiological studies have shown that OGTT 2-h glucose levels predict cardiovascular disease morbidity and mortality[7], even in the nondiabetic range of hyperglycemia8 and independently of fasting glucose levels9.

Two-hour glucose level is a heritable quantitative trait (heritability (h^2) = 0.40)[10] that has been associated with diabetes, and assessing the genetic contribution to variability in 2-h glucose provides an opportunity to identify genetic variation underlying this trait in nondiabetic individuals and to test the secondary hypothesis that these loci may also contribute to T2D susceptibility. Here we performed a meta-analysis of several 2-h glucose GWAS to expand our understanding of post–oral glucose challenge physiology in nondiabetic individuals.

A meta-analysis combining 9 discovery GWAS (n = 15,234) and replication stages with up to 29 SNPs in 17 studies comprising up to 30,620 individuals of European descent revealed 5 loci associated with 2-h glucose at genome-wide significance ($P = 5 \times 10^{-8}$; see Online Methods, Table 1, Fig. 1, Supplementary Fig. 1 and Supplementary Tables 1 and 2). Three loci were newly associated with 2-h glucose in an analysis adjusted for age, sex, BMI and study-specific covariates: *GIPR* (gastric inhibitory polypeptide receptor, rs10423928, β (s.e.m.) = 0.09 (0.01) mmol/l per A allele, $P = 2.0 \times 10^{-15}$), *VPS13C* (vacuolar protein sorting 13 homolog C, rs17271305, β (s.e.m.) = 0.06 (0.01) mmol/l per G allele, $P = 4.1 \times 10^{-8}$) and *ADCY5* (adenylate cyclase, 5 rs2877716, β (s.e.m.) = 0.09 (0.01) mmol/l per C allele, $P = 4.2 \times 10^{-16}$). The *ADCY5* locus was also identified by an accompanying study reporting meta-analysis in MAGIC for fasting glucose levels (r^2 = 0.82 to the most significant fasting glucose SNP rs11708067)[6]. The remaining loci identified here included the previously published fasting glucose–associated gene *GCKR* (glucokinase (hexokinase 4) regulator, missense SNP rs1260326, $P = 7.1 \times 10^{-11}$)[11] and the established T2D-associated gene *TCF7L2* (transcription factor 7-like 2, rs12243326 with r^2 = 0.79 to most significant T2D SNP rs7903146, $P = 4.2 \times 10^{-10}$)[12].

To determine whether these associations reflected differences in fasting glucose levels or whether they primarily influenced the incremental response to a glucose challenge, we repeated our association analysis including fasting glucose as a covariate (Table 1 and Supplementary Table 2). Adjusting for fasting glucose resulted in increased effect size for the *GCKR*, *GIPR* and *VPS13C* loci and supported their specific role in post-challenge glucose regulation. In contrast, adjusting for fasting glucose slightly decreased the effect for

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the *ADCY5* and *TCF7L2* loci, which suggested that the risk alleles in both genes increase glucose levels both in the fasting and post-challenge state.

In meta-analyses available from MAGIC[6], fasting glycemic traits variants at the *GIPR, VPS13C* and *ADCY5* loci were not associated with fasting insulin or insulin resistance as measured by homeostasis model assessment[13], which may reflect the inadequacy of the crude measures used here or may reflect a lack of power to detect small effects (Supplementary Table 3). Associations of risk alleles in *GCKR* and *TCF7L2* with fasting glycemic traits have been reported previously[6]. In a large Swedish meta-analysis (n = 27,628), the *GIPR* rs10423928 2-h glucose–raising allele was significantly associated with lower BMI ($P_{meta} = 7.5 \times 10^{-5}$, V.L. and L.G., unpublished data).

GIP is one of the two incretin hormones that stimulate insulin response after an oral glucose challenge. It has been shown that the incretin effect is impaired in individuals with T2D[14]; specifically, in individuals with T2D, stimulated GIP secretion appears normal and their insulinotropic response to GIP is reduced[15]. GIPR is therefore a biologically plausible candidate for mediating insulin secretion after oral glucose challenge. We tested associations of *GIPR* variants with indices of oral glucose–stimulated insulin secretion in up to 13 studies with samples measured at multiple times during the OGTT (Table 2 and Supplementary Table 4). The rs10423928 A allele associated with increased 2-h glucose was also associated with lower insulinogenic index (β (s.e.m.) = −0.08 (0.01) μU/mmol, $P = 1.0 \times 10^{-17}$), which represents a reduction in the early phase of insulin secretion[16]. The rs10423928 A allele was also associated with a lower ratio of insulin to glucose area under the curve ($AUC_{ins/gluc}$, β (s.e.m.) = −0.05 (0.01) pmol/mmol, $P = 1.3 \times 10^{-16}$), which is an integrated measure of insulin response over the 2-h OGTT[16]. Furthermore, the rs10423928 A allele was associated with lower 2-h insulin level (adjusted for 2-h glucose, β (s.e.m.) = −0.04 (0.01) pmol/l, $P = 2.0 \times 10^{-13}$).

Because GIP is involved in the insulin response specific to an oral glucose challenge, *GIPR* variation was not expected to influence the insulin response to an intravenous glucose load. We tested the insulin response in 1,509 nondiabetic participants from four studies who underwent an intravenous glucose tolerance test (IVGTT). No association was observed with measures of acute insulin response (AIR) from the IVGTT ($P = 0.12$; Supplementary Table 5), even though the study had >97% power to detect an effect explaining 1% trait variance ($\alpha = 0.05$). We also derived an estimate of the incretin effect by comparing the insulin response to oral versus intravenous glucose administered to the same 804 nondiabetic individuals from the Botnia[17], Denmark and EUGENE2-Kuopio studies18. Individuals carrying the A risk allele of rs10423928 in *GIPR* showed a significantly lower incretin effect (β (s.e.m.) = −0.012 (0.004), $P = 4.3 \times 10^{-4}$; Fig. 2 and Supplementary Table 5). Our results are consistent with animal studies, in which mice with targeted deletion of *Gipr* showed mild glucose intolerance and reduced insulin secretion in response to an oral glucose challenge but showed normal fasting glucose and normal insulin secretion in response to an intraperitoneal glucose challenge[19].

The variant in *GIPR* most significantly associated with 2-h glucose (rs10423928) is an intronic SNP with no known function based on FastSNP (see URL section). Notably, rs10423928 is in strong linkage disequilibrium ($r^2 = 0.93$) with a missense mutation (at rs1800437, resulting in the substitution E354Q). Some groups have explored the E354Q substitution as a candidate for association with T2D. One study showed that people homozygous for the Gln354-encoding allele of this gene had lower fasting and post oral-load C-peptide levels, suggesting a role for *GIPR* in insulin secretion[20]; this is in line with our observations. In small T2D case-control studies, no association has been observed at *GIPR*[20–22]. We performed a meta-analysis of 16 T2D association studies (n = 19,091

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diabetic individuals (cases), 38,508 nondiabetic individuals) and found that the rs10423928 A allele was moderately associated with increased risk of T2D (OR = 1.07, 95% CI 1.03–1.12; $P = 1.8 \times 10^{-4}$; Table 3 and Supplementary Table 6). This result, although suggestive of association, highlights the challenge of genetic approaches to complex diseases, whereby important genes involved in pathophysiology might be difficult to identify even in large case-control collections due to small individual odds ratios[23].

We assessed the mRNA expression patterns of *GIPR* and the nearest upstream (*EML2*) and downstream (*SNRPD2*) genes in a human tissue panel (Fig. 3). All three genes were expressed in the pancreas, but only *GIPR* had strong specific mRNA expression in the sorted pancreatic beta cells, supporting the implication of *GIPR* in insulin secretion. No significant difference in *GIPR*, *EML2* or *SNRPD2* mRNA expression in pancreatic islets was seen based on the rs10423928 genotype (for *GIPR* $P = 0.76$, $n = 19$; Supplementary Note).

As adenylate cyclases have been implicated in the cAMP pathway of GLP-1 and GIP-induced insulin release by beta cells[24,25], we also tested for association of the most significant *ADCY5* variant with measures of insulin response and risk of T2D. The 2-h glucose-raising C allele of rs2877716 was associated with lower 2-h insulin ($P = 1.4 \times 10^{-6}$) but was not associated with $AUC_{ins/gluc}$ ($P = 0.16$) or with the insulinogenic index ($P = 0.23$; Table 2 and Supplementary Table 4). The lack of association with the two latter indices suggests that ACDY5 is unlikely to be directly involved in insulin secretion in response to an oral glucose challenge and may not operate in the same pathway as GIPR. In support of our observations, the mRNA expression pattern of *ADCY5* reported in the recent MAGIC study on fasting glucose traits[6] shows that *ADCY5* is most highly expressed in heart and brain tissues, with weaker expression in the pancreas, islets and sorted beta cells. Finally, we found that the rs2877716 C allele was also associated with increased risk of T2D (OR = 1.12, 95% CI 1.09–1.15, $P = 4.8 \times 10^{-18}$) in a separate meta-analysis of 25 association studies (total $n = 35{,}869$ cases, 89,798 controls; Table 3 and Supplementary Table 6) and was associated with increased risk of developing future T2D in 16,061 individuals from the Malmo Preventive Project (OR = 1.19, 95% CI 1.10–1.29, $P = 3.13 \times 10^{-5}$; see Supplementary Note). Taken together, our results do not support a role for *ADCY5* in early insulin secretion in response to an oral glucose load, but it remains to be determined how it (or another causal gene at the locus) contributes to risk for T2D.

We tested association of the *VPS13C* variant with insulin secretion indices because of its novelty and unknown function (Table 2 and Supplementary Table 4). The risk allele G of rs17271305 associated with higher 2-h glucose was also associated with lower 2-h insulin ($P = 7.5 \times 10^{-11}$). rs17271305 showed no association with $AUC_{ins/gluc}$ ($P = 0.86$) but was nominally associated with insulinogenic index ($P = 0.01$). The *VPS13C* variant was not associated with T2D (OR = 0.97, 95% CI 0.94–1.00, $P = 0.08$) (Table 3 and Supplementary Table 6), suggesting that it may contribute to normal variation in 2-h glucose but not susceptibility to T2D. Investigation of the mRNA expression profiles of *VPS13C* revealed the presence of transcripts in several organs including brain, adipose tissue, liver, pancreas, and, most strongly, in sorted beta cells (Fig. 3). Analysis of the neighboring gene *FAM148A* indicated a pancreatic tissue-specific mRNA expression profile, mainly in beta cells (Fig. 3); however, its expression was not altered by *VPS13C* genotype in pancreatic islets ($P = 0.9$, $n = 19$; Supplementary Note).

VPS13C spans 208 kb on chromosome 15 and encodes a protein homolog of the yeast vacuolar protein sorting 13. This family of proteins is involved in trafficking of membrane proteins between the trans-Golgi network and the prevacuolar compartment[26]. rs17271305, identified by the 2-h glucose meta-analysis, is 101 kb from the *FAM148B* association signal (rs11071657) identified by the MAGIC fasting glucose meta-analysis[6], but could represent

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an independent signal, as rs17271305 is weakly correlated with rs11071657 (r^2 = 0.28 in HapMap CEU, $P_{2\text{-h glucose}}$ = 0.002). Detailed fine-mapping and functional analyses will be needed to definitively establish the causal gene and variant(s) at this locus.

In conclusion, we report a GWAS for glucose levels 2 h after an oral glucose challenge, and we have investigated the role of newly discovered 2-h glucose variants in influencing normal physiology and potentially influencing risk of T2D. We identified five loci associated with 2-h glucose, in *GIPR*, *VPS13C*, *ADCY5*, *GCKR* and *TCF7L2*. As the physiological roles of *GCKR* and *TCF7L2* variants have been examined in detail previously[17,27], we focused on the three newly identified associated loci. *ADCY5* variants are associated with fasting[6] and 2-h glucose levels and with an increased risk of T2D, highlighting the fact that investigation of diabetes-related quantitative traits can lead to identification of additional T2D-associated loci. *VPS13C* variants may contribute to normal variation in 2-h glucose, but their effect on T2D pathogenesis is unclear.

Our association results suggest a role for *GIPR* in the incretin effect and in early pathophysiologic pathways that could lead to impaired glucose tolerance and T2D in humans. Previously, it was hypothesized that patients with T2D might express a smaller amount of GIPR or defective GIPR[28]. Meier *et al.* observed that individuals with T2D and a subgroup of the first-degree relatives of these individuals had a blunted insulin response to GIP, supporting the hypothesis that a defect of the GIPR could be part of the T2D pathophysiology[29]. Future studies should examine how *GIPR* variants may modify response to treatments targeting the enteroinsular axis.

Methods

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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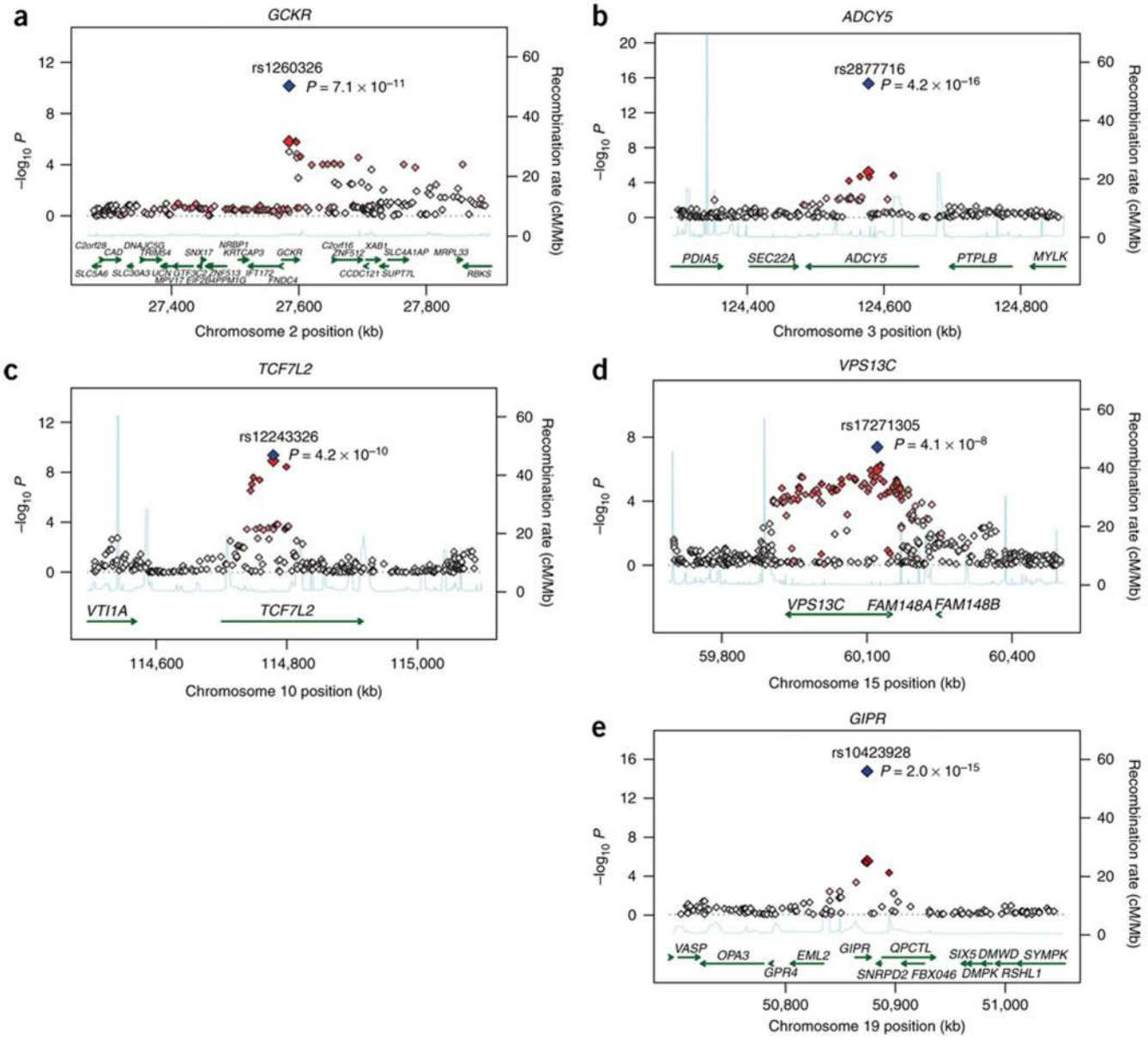

Figure 1.

Regional plots of five genome-wide significant associations for 2 hour glucose based on 2 hour glucose discovery analysis adjusted for age, sex, BMI and study-specific covariates. (**a–e**) For each of the *GCKR* (**a**), *ADCY5* (**b**), *TCF7L2* (**c**), *VPS13C* (**d**) and *GIPR* (**e**) regions, 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; hg 18). In each panel, the SNP taken forward for replication (large red diamond) and joint discovery and replication *P* value (blue diamond) are shown. Estimated recombination rates (HapMap) are plotted to reflect the local linkage disequilibrium structure around the associated SNPs and their correlated proxies ($0 < r^2 < 1$, represented on a white to red scale, based on pairwise r^2 values from HapMap CEU). Gene annotations were taken from the UCSC genome browser.

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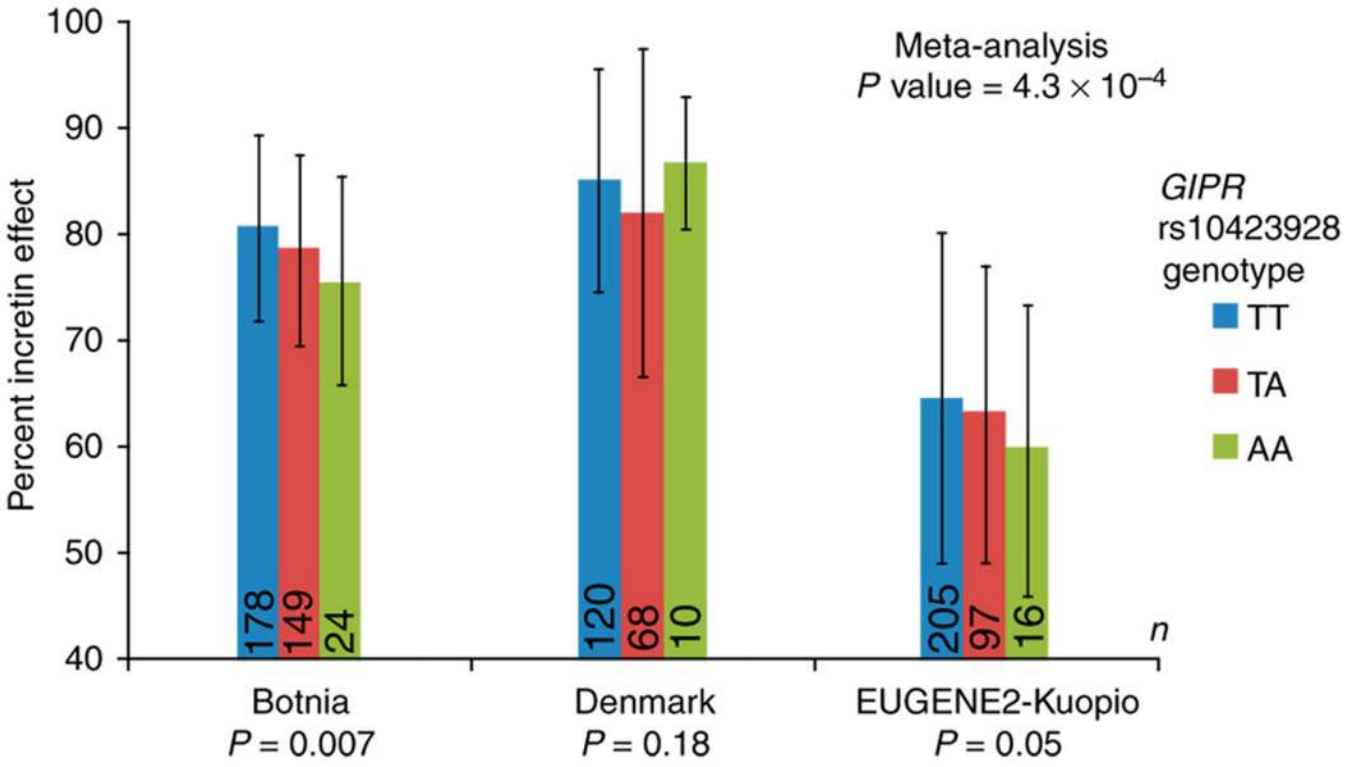

Figure 2.
Percent incretin effect in the Botnia, Denmark and EUGENE2-Kuopio studies of nondiabetic individuals (n = 804) by *GIPR* rs10423928 genotype. Mean and s.d. for each study are displayed by genotype (see Supplementary Table 5 for details). Incretin effect was adjusted for age, sex and BMI and study-specific covariates.

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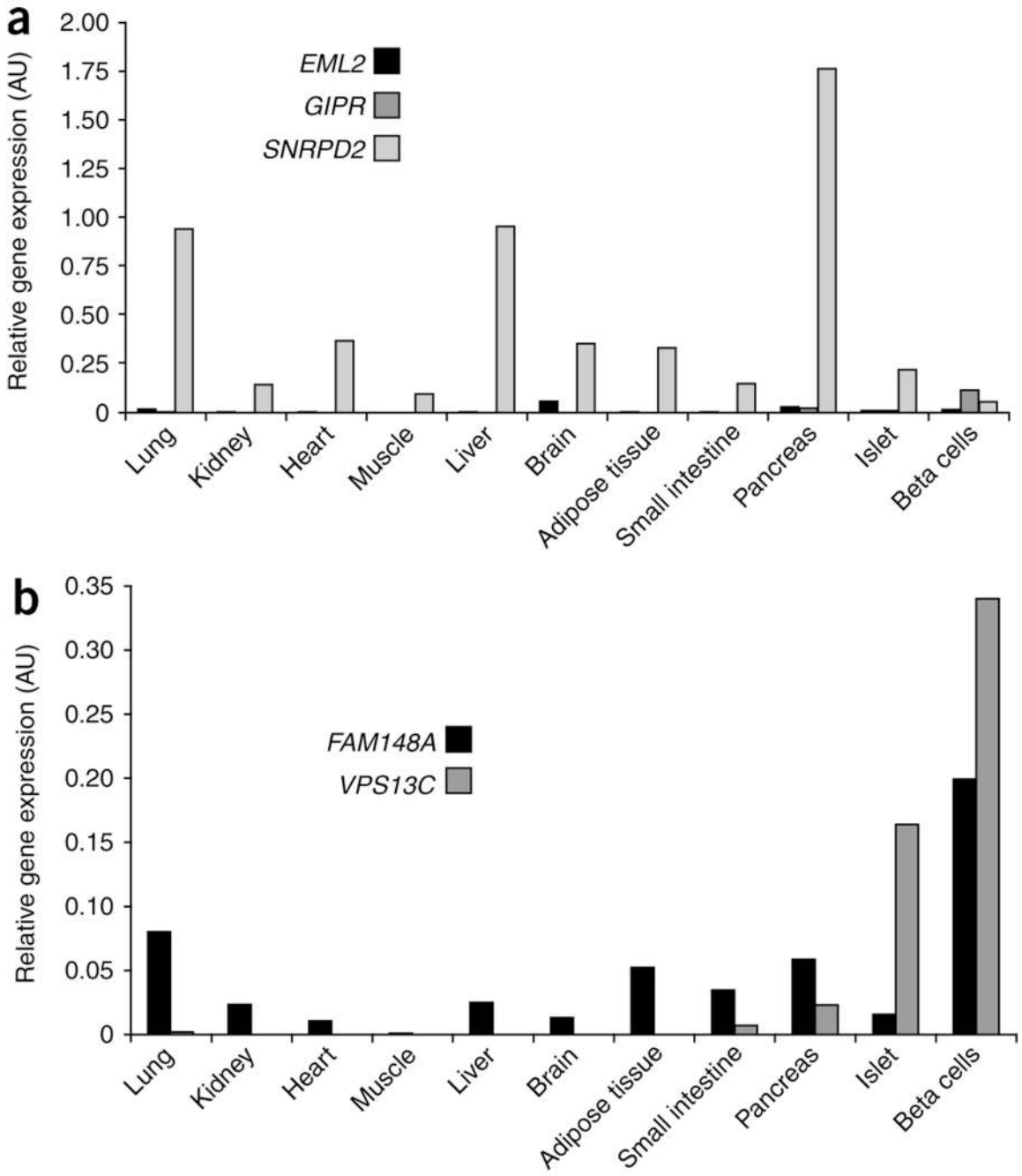

Figure 3.

mRNA expression in human tissues of the genes located in the *GIPR* (**a**) and *VPS13C* (**b**) regions. Expression data is relative expression levels measured by quantitative RT-PCR. All samples were run in triplicate and normalized to the GAPDH relative expression level. AU, arbitrary units.

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Table 1

Genome-wide significant loci for 2-h glucose during an OGTT from 26 studies in nondiabetic individuals

						Discovery		Replication		Discovery and replication			Discovery and replication (FG adj)		
SNP	Chr	Position (bp)	Nearest gene	Alleles (+/−)	Freq (+)[1]	Effect (s.e.m.) mmol/l	*P* value	Effect (s.e.m.) mmol/l	*P* value	Effect (s.e.m.) mmol/l	*P* value	*P* value (no BMI)	Effect (s.e.m.) mmol/l	*P* value	*P* value (no BMI)
rs1260326	2	27584444	*GCKR*	T/C	0.40	0.09 (0.02)	1.53×10^{-6}	0.06 (0.01)	5.33×10^{-6}	0.07 (0.01)	7.05×10^{-11}	3.00×10^{-10}	0.10 (0.01)	9.23×10^{-21}	2.26×10^{-21}
rs2877716	3	124577141	*ADCY5*	C/T	0.77	0.10 (0.02)	6.26×10^{-6}	0.09 (0.01)	1.21×10^{-11}	0.09 (0.01)	4.19×10^{-16}	7.41×10^{-16}	0.07 (0.01)	1.68×10^{-11}	7.98×10^{-12}
rs12243326	10	114778805	*TCF7L2*	C/T	0.21	0.13 (0.02)	1.20×10^{-9}	0.05 (0.02)	1.27×10^{-3}	0.08 (0.01)	4.23×10^{-10}	1.12×10^{-7}	0.07 (0.01)	9.99×10^{-9}	1.17×10^{-10}
rs17271305	15	60120272	*VPS13C*	G/A	0.42	0.09 (0.02)	1.04×10^{-6}	0.05 (0.02)	1.58×10^{-3}	0.06 (0.01)	4.11×10^{-8}	1.30×10^{-7}	0.07 (0.01)	4.33×10^{-11}	8.41×10^{-11}
rs10423928	19	50874144	*GIPR*	A/T	0.18	0.15 (0.03)	3.33×10^{-6}	0.09 (0.01)	2.30×10^{-11}	0.09 (0.01)	1.98×10^{-15}	3.20×10^{-12}	0.11 (0.01)	2.56×10^{-20}	5.94×10^{-18}
						*n*11,268–15,234		15,103–30,121		30,337–43,104			30,114–42,354		

Results from fixed effects, inverse variance meta-analysis of 9 GWA (ARIC, BLSA, CHSstage1&2, CoLaus, DGI, Fenland, FHS, FUSION, Sorbs) and 17 follow-up studies (Amish, BotniaPPP, CHSstage3, DIAGEN, ELY, FrenchFamilyMembers, FrenchHaguenau, FrenchObeseAdults, FUSIONstage2, Hertfordshire, Inter99, METSIM, NHANES, RISC, Roche, ULSAM, Whitehall II) with adjustment for age, sex and BMI. Position based on hg18, NCBI build36. Combined discovery and replication *P* values for 2-h glucose adjusted for age and sex (no BMI), and further adjusted for fasting glucose are also presented. Replication meta-analysis results and joint discovery and replication meta-analysis results include proxy SNPs with $r^2 > 0.8$ in HapMap CEU.

[1] Allele frequencies based on HapMap phase II CEU sample. FG adj, adjusted for fasting glucose in addition to age, sex, BMI and study-specific covariates (center).

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Table 2

Effect of *ADCY5*, *VPS13C* and *GIPR* variants on indices of insulin response during an OGTT

				Insulinogenic index				$AUC_{ins/gluc}$				2-h insulin, adjusted for 2-h glucose			
SNP	**Chr**	**Nearest gene**	**Effect allele**	***n***	**Effect (s.e.m.) μU/mmol (BMI-adj)**	***P* value (BMI-adj)**	***P* value**	***n***	**Effect (s.e.m.) pmol/mmol (BMI-adj)**	***P* value (BMI-adj)**	***P* value**	***n***	**Effect (s.e.m.) pmol/l (BMI-adj)**	***P* value (BMI-adj)**	***P* value**
rs2877716	3	*ADCY5*	C	19,461	−0.011 (0.009)	0.23	0.22	20,435	−0.010 (0.007)	0.16	0.18	30,987	−0.029 (0.006)	1.43×10^{-6}	3.09×10^{-6}
rs17271305	15	*VPS13C*	G	13,911	0.024 (0.010)	0.01	0.02	13,666	−0.001 (0.007)	0.86	0.76	23,842	−0.037 (0.006)	7.45×10^{-11}	2.58×10^{-10}
rs10423928	19	*GIPR*	A	22,529	−0.076 (0.009)	1.00×10^{-17}	2.44×10^{-20}	22,209	−0.051 (0.007)	9.50×10^{-17}	3.39×10^{-20}	32,204	−0.044 (0.006)	1.99×10^{-13}	3.67×10^{-16}

$AUC_{ins/gluc}$, area under the curve for insulin divided by area under the curve for glucose.

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Table 3

Meta-analysis of T2D association studies for SNPs at previously unknown 2-h glucose–associated loci

							T2D fixed effects			T2D random effects	
SNP	**Chr**	**Nearest gene**	**Effect allele**	***n* studies**	***n* cases**	***n* controls**	**OR (95% CI)**	***P* value**	**I^2 (%)**	**OR (95% CI)**	***P* value**
rs2877716	3	*ADCY5*	c	25	35,869	89,798	1.12 (1.09–1.15)	4.8×10^{-18}	35.2 (0–59.3)	1.12 (1.08–1.16)	9.4×10^{-11}
rs17271305	15	*VPS13C*	g	13	15,180	32,556	0.97 (0.94–1.00)	0.083	48.7 (0–72.8)	0.99 (0.94–1.04)	0.62
rs10423928	19	*GIPR*	a	16	19,091	38,508	1.07 (1.03–1.12)	1.8×10^{-4}	39.3 (0–60.3)	1.07 (1.02–1.12)	9.6×10^{-3}

Proxies rs11708067 with $r^2 = 0.82$ in HM CEU to rs2877716 used in eight studies; rs11717195 with $r^2 = 0.95$ in HM CEU used in two studies. Proxy rs12913951 with $r^2 = 0.71$ in HM CEU to rs17271305 used in two studies.

Proxy rs11672660 with $r^2 = 0.95$ in HM CEU to rs10423928 used in three studies.

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