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**Supplementary Table 1.** Clinical characteristics of the hyperglycemic clamp study groups.

	<b>NTR twin cohort</b>	<b>German cohort</b>	<b>Hoorn cohort</b>	<b>Utrecht cohort</b>
n (NGT/IGT)	120/6	73/33	0/140	64/12
Age (yrs)	31.5 ± 6.3	39.2 ± 12.8	60.4 ± 8.7	46.2 ± 6.6
Gender (M/F)	60/66	48/58	69/71	19/57
BMI (kg/m <sup>2</sup> )	24.1 ± 6.4	25.7 ± 5.5	28.1 ± 4.0	25.9 ± 3.8
Fasting glucose (mmol/l)	4.6 ± 0.4	5.1 ± 0.7	6.3 ± 0.7	4.6 ± 0.5
2-hr glucose (mmol/l)	5.4 ± 1.2	6.6 ± 2.0	8.8 ± 1.7	5.6 ± 1.6
Fasting Insulin (mmol/l)	33 (27-51)	47 (30-67)	62 (46-90)	36 (24-54)
1 <sup>st</sup> phase Glucose SIS (pmol/l)	823 (613-1168)	646 (461-1148)	586 (375-889)	852 (594-1154)
2 <sup>nd</sup> phase Glucose SIS (pmol/l)	218 (166-365)	228 (149-339)	254 (172-350)	260 (191-350)
GLP-1 SIS (pmol/l)	1225 (724-2597)	2633 (1512-3992)	n.d.	n.d.
Arginine SIS (pmol/l)	2115 (1554-3001)	2222 (1552-3289)	n.d.	n.d.
Insulin sensitivity Index (μmol·kg <sup>-1</sup> ·min <sup>-1</sup> ·pmol/l <sup>-1</sup> )	0.22 (0.14-0.31)	0.12 (0.08-0.19)	0.11 (0.07-0.17)	0.18 (0.12-0.28)

Data are means ± SD or median with interquartile range or n. SIS stimulated insulin secretion. n.d. not determined.

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**Supplementary Table 2.** Clinical characteristics of the pharmacogenetic study groups.

	DCS West-Friesland (n=71)		GoDARTS (n=456)	
	GLP-1 RA	DPP4-inhibitors	GLP-1 RA	DPP4-inhibitors
Age (yrs)	58.3 ± 5.8	65.0 ± 10.8 *	58.6 ± 8.2	65.0 ± 9.7 *
Gender (M/F)	9/13	19/30	85/66	160/145
BMI (kg/m <sup>2</sup> )	41.6 ± 6.4	32.4 ± 6.9 *	38.6 ± 5.7	33.3 ± 5.9 *
Diabetes duration (yrs)	9.0 ± 7.6	6.9 ± 3.9	9.6 ± 4.9	10.0 ± 4.9
vildagliptin/sitagliptin/other	-	20/28/1	-	11/280/14
liraglutide/exenatide	18/4	-	83/68	-
<u>Time period (days)</u>	<u>591 ± 244</u>	<u>772 ± 214 *</u>	<u>206 ± 120</u>	<u>204 ± 120</u>
<u>Stopped other medication (% stopped)</u>	<u>14%</u>	<u>24%</u>	<u>46%</u>	<u>15% *</u>
Pre-treatment HbA1c (%; mmol/mol)	7.9 ± 1.1; 63 ± 12	7.3 ± 1.1; 56 ± 12 *	9.5 ± 1.4; 80 ± 15	8.8 ± 1.1; 73 ± 12 *
Treatment HbA1c (%; mmol/mol)	7.4 ± 1.3; 57 ± 14	7.0 ± 1.1; 53 ± 12	8.0 ± 1.4; 64 ± 15.3	8.0 ± 1.4; 64 ± 15.3
Delta HbA1c (%; mmol/mol)	-0.59 ± 1.22; -6.4 ± 13.3	-0.27 ± 1.26; -3.0 ± 13.8	-1.47 ± 1.63; -16.1 ± 17.8	-0.82 ± 1.41; -9.0 ± 15.4*

Data are means with SD or n. Time period is defined as the number of days between baseline and lowest on treatment HbA1c. Stopped other medication reflects the percentage of participants that stopped other glucose lowering medication at or after the introduction of GLP-1 RA or DPP-4 inhibitor.

\* p<0.05 for GLP-1 RA vs DPP4 inhibitor group.

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**Supplementary Table 3.** Clinical characteristics of the chymotrypsin activity study.

	<b>Chymotrypsin activity study</b>		
	<b>All</b>	<b>TT</b>	<b>TG+GG</b>
Age (yrs)	42.6 ± 12.9	42.6 ± 12.9	42.6 ± 13.1
Gender (M/F)	38/42	19/21	19/21
BMI (kg/m <sup>2</sup> )	31.7 ± 4.7	31.5 ± 4.2	31.9 ± 5.2
Fasting plasma glucose (mmol/l)	5.4 ± 0.6	5.4 ± 0.6	5.4 ± 0.6
Fasting plasma insulin (pmol/l)	62 (46-93)	63 (44-105)	62 (46-88)
Fasting GLP-1 (pmol/l)	n.a.	n.a.	n.a.
Fasting GIP (pmol/l)	n.a.	n.a.	n.a.
Fasting glucagon (pmol/l)	n.a.	n.a.	n.a.
Fecal chymotrypsin activity (U/g)	14.5±9.1	12.6±7.2	16.5±10.4 *

Data are means ± SD or median (inter quartile range). n.a. not available. \* P<0.05 for TG+GG versus TT genotypes.

**Supplementary Table 4.** Effects of SNPs associated with GLP-1 stimulated insulin secretion on other measures of beta cell function.

<b>SNP</b>	<b>1<sup>st</sup> phase GSIS</b>	<b>2<sup>nd</sup> phase GSIS</b>	<b>Insulin sensitivity Index</b>	<b>Disposition index</b>	<b>Arginine SIS</b>
rs4148941	-0.025 (0.021) 0.24	-0.035 (0.017) 0.042	+0.013 (0.025) 0.60	-0.004 (0.023) 0.86	-0.052 (0.034) 0.12
rs7202633	+0.016 (0.015) 0.27	+0.012 (0.013) 0.36	+0.004 (0.017) 0.80	+0.021 (0.017) 0.20	+0.0654 (0.019) 5.6*10 <sup>-4</sup>
rs7202877	+0.033 (0.024) 0.17	+0.016 (0.022) 0.47	+0.006 (0.031) 0.85	+0.022 (0.026) 0.40	+0.073 (0.035) 0.038

Data are beta's ± SE and p-values as obtained using SPSS GEE using additive (rs7202633), dominant (rs4148941) or carrier versus non-carriers genetic models (rs7202877). 1<sup>st</sup> and 2<sup>nd</sup> phase GSIS, Insulin Sensitivity Index and Disposition Index were measured in an extended cohort (n=448) as described in detail on page 2 and Supplemental table 1. Data are adjusted for age, gender, BMI, glucose tolerance status, study center and insulin sensitivity index (where appropriate). GSIS = glucose stimulated insulin secretion; Arginine SIS = arginine stimulated insulin secretion.

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**Supplementary Table 5.** Decrease in HbA1c (%) from baseline in response to GLP-1 RA treatment in Dutch type 2 diabetes patients.

SNP	GLP-1 RA			
	11	12	22	p-value
rs4148941	8; -0.82±0.47	12; -0.56±0.38	2; +0.19±0.96	0.64
rs7202633	5; -1.14±0.59	14; -0.44±0.35	3; -0.37±0.75	0.59
rs7202877	19; -0.41±0.27	3; -1.73±0.68	0	0.09

In total 22 patients with type 2 diabetes participated in a study investigating the effects of the above mentioned gene variants on response to GLP-1 RA treatment (liraglutide n=18/ exenatide n=4). Data are n and estimated means ± SE corrected for pre-treatment HbA1c, stopped other baseline medication and time between measures.

**Supplementary Table 6.** Decrease in HbA1c (%) from baseline in response to DPP4-inhibitor treatment in Dutch type 2 diabetes patients.

SNP	DPP4 inhibitors			
	11	12	22	p-value
rs4148941	24; -0.22±0.22	18; -0.29±0.25	7; -0.40±0.41	0.93
rs7202633	14; -0.25±0.30	26; -0.38±0.21	9; -0.02±0.38	0.70
rs7202877	39; -0.43±0.16	10; +0.34±0.33	0	0.041

In total 49 patients with type 2 diabetes participated in a study investigating the effects of the above mentioned gene variants on response to DPP4 inhibitor treatment (vildagliptin n=20/sitagliptin n=28/saxagliptin n=1). Data are n and estimated means ± SE corrected for pre-treatment HbA1c, stopped other baseline medication, time between measures and BMI.

**Supplementary Table 7.** Decrease in HbA1c (%) from baseline in response to GLP-1 RA treatment in UK type 2 diabetes patients.

SNP	GLP-1 RA			
	11	12	22	p-value
rs4148941	61; -1.63±0.16	64; -1.45±0.15	26; -1.16±0.24	0.15
rs7202633	45; -1.54±0.19	77; -1.38±0.14	26; -1.53±0.25	0.85
rs7202877	125; -1.49±0.11	23; -1.46±0.27	0	0.92

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In total 151 patients with type 2 diabetes participated in a study investigating the effects of the above mentioned gene variants on response to GLP-1 RA (liraglutide n=83/ exenatide n=68). Data are n and estimated means  $\pm$  SE corrected for pre-treatment HbA1c, stopped other baseline medication and time between measures.

**Supplementary Table 8.** Decrease in HbA1c (%) from baseline in response to DPP-4 inhibitor treatment in UK type 2 diabetes patients.

SNP	DPP4-inhibitors			p-value
	11	12	22	
rs4148941	117; -0.77 $\pm$ 0.11	138; -0.84 $\pm$ 0.10	50; -0.92 $\pm$ 0.17	0.46
rs7202633	95; -0.88 $\pm$ 0.12	159; -0.78 $\pm$ 0.10	45; -0.92 $\pm$ 0.18	0.99
rs7202877	244; -0.90 $\pm$ 0.07	57; -0.45 $\pm$ 0.16	0	0.014

In total 305 patients with type 2 diabetes participated in a study investigating the effects of the above mentioned gene variants on response to DPP-4 inhibitor treatment (vildagliptin n=11/sitagliptin n=280/other n=14). Data are n and estimated means  $\pm$  SE corrected for pre-treatment HbA1c, stopped other baseline medication, time between measures and BMI.

**Supplementary Table 9.** Phenotypes of patients treated with DPP4-inhibitors carrying different genotypes of rs7202877 near *CTRB1/2*.

genotype	DCS West-Friesland		GoDARTS	
	TT (n=39)	TG + GG (n=10)	TT (n=246)	TG + GG (n=58)
Age (yrs)	64.7 $\pm$ 11.3	66.2 $\pm$ 9.3	65.1 $\pm$ 9.5	63.7 $\pm$ 10.6
Gender (M/F)	16/23	3/7	134/112	24/34
BMI (kg/m <sup>2</sup> )	31.6 $\pm$ 5.1	35.3 $\pm$ 11.5	33.0 $\pm$ 5.8	34.5 $\pm$ 6.1
Diabetes duration (yrs)	6.6 $\pm$ 3.8	8.2 $\pm$ 4.3	9.1 $\pm$ 6.1	8.0 $\pm$ 6.8
eGFR (ml/min/1.73m <sup>2</sup> )	80 $\pm$ 18	89 $\pm$ 27	82 $\pm$ 23	85 $\pm$ 23
Vildagliptin/Sitagliptin /other (n)	21/17/1	7/3/0	8/225/13	3/51/4
<u>Time period (days)</u>	<u>773 <math>\pm</math> 216</u>	<u>771 <math>\pm</math> 219</u>	<u>204 <math>\pm</math> 121</u>	<u>198 <math>\pm</math> 111</u>
<u>Stopped other medication (% stopped)</u>	<u>26%</u>	<u>20%</u>	<u>14%</u>	<u>16%</u>
Pre-treatment HbA1c (%; mmol/mol)	7.2 $\pm$ 1.1; 55 $\pm$ 12	7.4 $\pm$ 0.9; 57 $\pm$ 10	8.8 $\pm$ 1.1; 73 $\pm$ 12	8.9 $\pm$ 1.4; 74 $\pm$ 15
Treatment HbA1c (%; mmol/mol)	6.8 $\pm$ 0.9; 51 $\pm$ 10	7.8 $\pm$ 1.6; 62 $\pm$ 18 *	7.9 $\pm$ 1.2; 63 $\pm$ 13	8.4 $\pm$ 1.8; 68 $\pm$ 20 *
Delta HbA1c (%;	-0.43 $\pm$ 1.22;	+0.36 $\pm$ 1.29;	-0.92 $\pm$ 1.38;	-0.49 $\pm$ 1.54;

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mmol/mol)	-4.7 ± 13.3	+3.9 ± 14.1	-10.1 ± 15.1	-5.4 ± 16.8 *
Delta BMI (kg/m <sup>2</sup> )	-1.0 ± 1.5	-0.6 ± 0.6	-0.4 ± 1.7	-0.3 ± 2.6

Data are means ± SD or n. eGFR estimated glomerular filtration rate. Time period is defined as the number of days between baseline and lowest on treatment HbA1c. Stopped other medication reflects the percentage of participants that stopped other glucose lowering medication at or after the introduction of GLP-1 RA or DPP-4 inhibitor. \* p<0.05 for TG+GG vs TT using ANOVA.

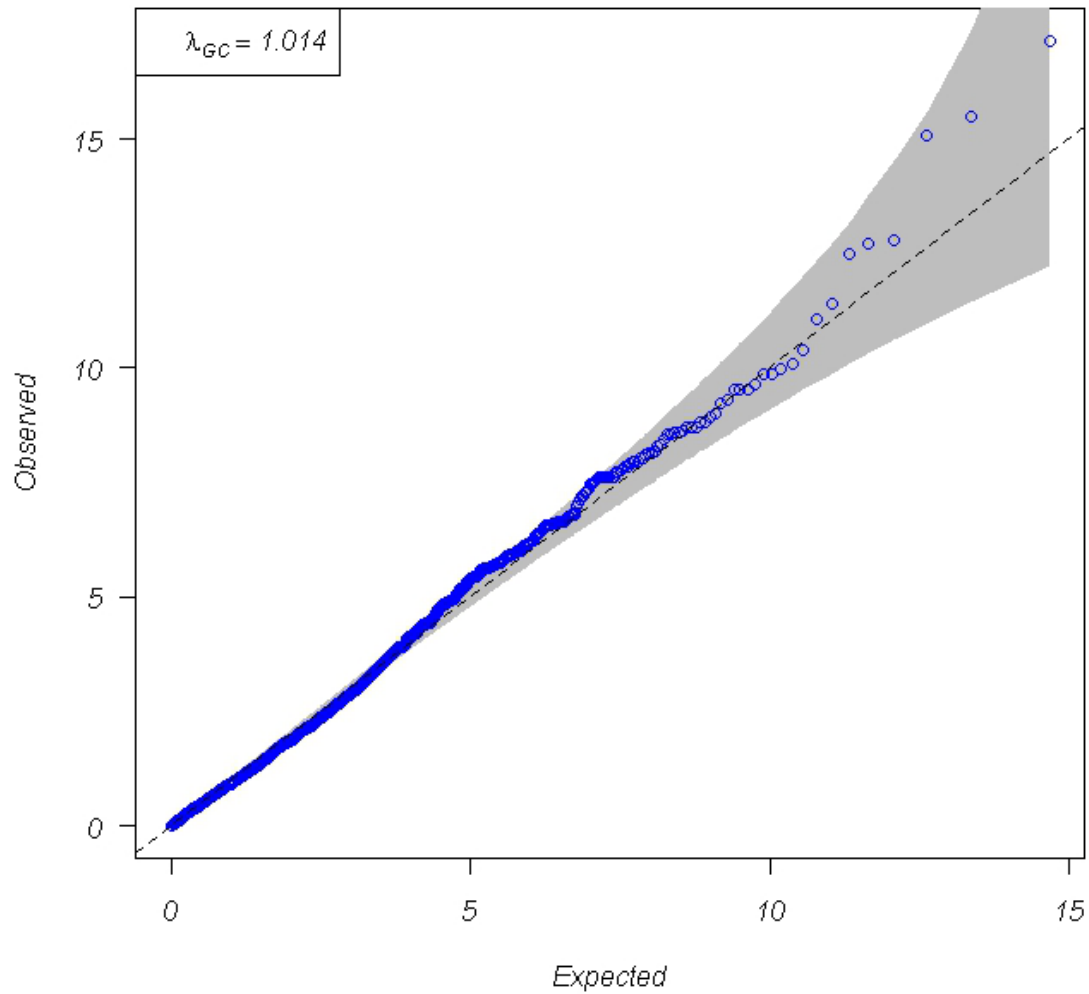
**Supplementary Table 10.** Clinical characteristics and results of incretin secretion during OGTT in healthy non-diabetic participants.

	Dutch Hoorn meal study		Danish study		German study	
	TT (n=126)	TG+GG (n=19)	TT (n=153)	TG+GG (n=28)	TT (n=102)	TG+GG (n=29)
Age (yrs)	53.5 ± 6.5	51.9 ± 7.4	41.0 ± 11.4	41.6 ± 10.7	43.1 ± 12.3	45.6 ± 10.0
Gender (M/F)	60/66	10/9	69/84	12/16	37/65	6/23
BMI (kg/m <sup>2</sup> )	26.6 ± 3.6	26.3 ± 2.2	25.8 ± 4.6	25.9 ± 4.4	31.7 ± 7.5	29.3 ± 5.9
Fasting plasma glucose (mmol/l)	5.3 ± 0.3	5.3 ± 0.4	5.1 ± 0.5	5.1 ± 0.4	5.2 ± 0.4	5.2 ± 0.4
Fasting plasma insulin (pmol/l)	36 (25-55)	40 (32-74)	34 (24-48)	30 (19-50)	52 (36-88)	39 (29-71)
Fasting GLP-1 (pmol/l)	10.0 (8.0-13.0)	9.0 (5.0-14.0)	4.5 (3.0-7.0)	5.3 (3.5-6.4)	17.0 (13.0-23.0)	17.0 (10.5-21.0)
Fasting GIP (pmol/l)	6.5 (1.0-10.0)	7.0 (2.0-15.0)	7.0 (3.0-10.5)	7.5 (4.5-12.0)	14.0 (8.0-19.0)	16.0 (9.0-22.0)
AUC GLP-1 (pmol/l/min)	16.5 (12.9-23.3)	13.5 * (11.1-15.6)	12.2 (8.2-17.8)	11.9 (8.6-15.1)	30.9 (21.8-37.2)	25.4 (21.3-42.0)
AUC GIP (pmol/l/min)	36.9 (29.1-56.8)	36.0 (26.4-51.4)	46.4 (34.7-58.7)	44.9 (33.0-71.0)	68.6 (52.5-86.0)	75.5 (63.9-103.0)

The Dutch Hoorn meal study population represents a random sample of the general population aged 40-65 years (n=208) from the middle-sized town Hoorn in the Netherlands who all underwent an OGTT (1). From this cohort we selected 145 normal glucose tolerant subjects for which incretin measurements and DNA were available. Secondly we used data from a Danish family study representing 61 families (2). From this study we included 181 non-diabetic participants. Finally we used data from a German cohort which includes 131 normal glucose tolerant subjects (3). All subjects participating in this study underwent a standard 2 hour 75g OGTT after overnight fasting and total GLP1 and GIP levels were measured at various time points according standard procedures as described previously (1-3). Areas under the curves (AUC) were calculated using a trapezoidal method. Data are unadjusted means with SD or median (inter quartile range). \* P≤0.05 for TG+GG versus TT genotypes after correction for age, gender, BMI and fasting value.

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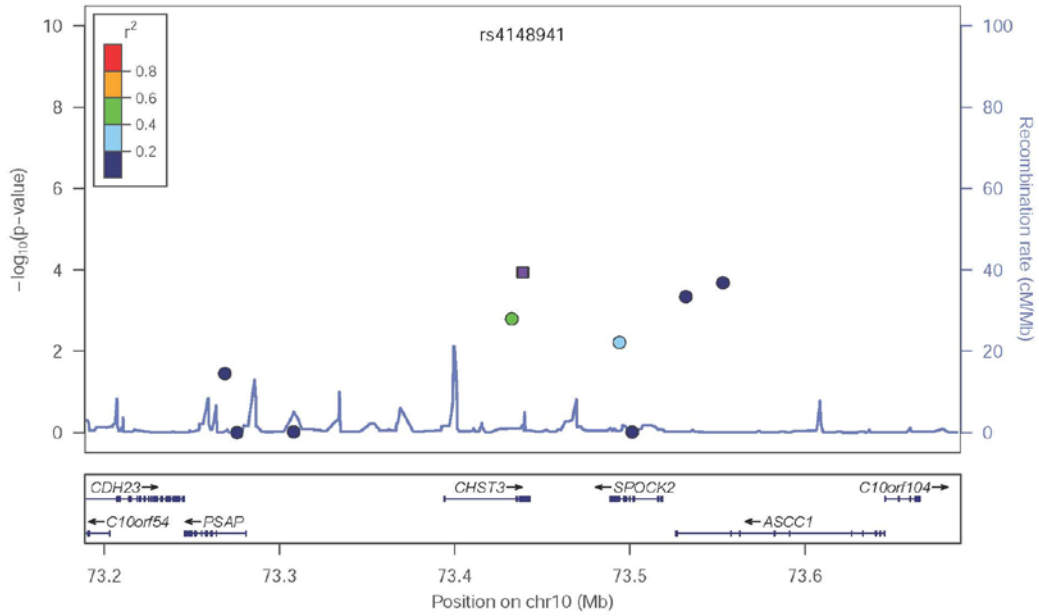
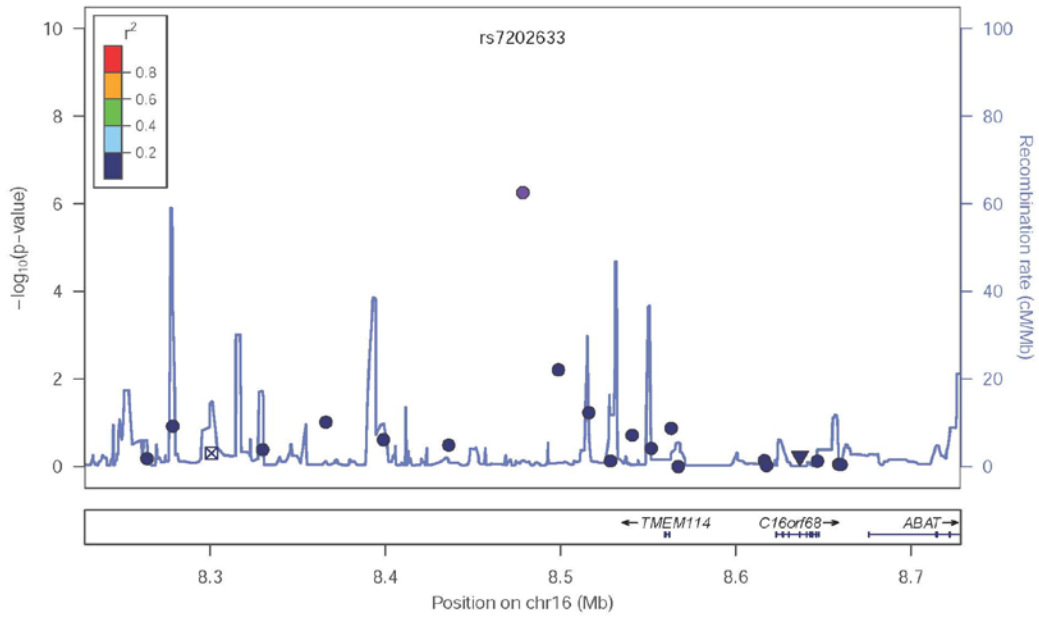
**Supplementary Figure 1.** Quantile-Quantile plot for GLP-1 stimulated insulin secretion during hyperglycemic clamps of SNPs in loci previously associated with QT interval.



Quantile-Quantile plot for GLP-1 stimulated insulin secretion during hyperglycemic clamps of SNPs in loci previously associated with QT interval (4;5). The genomic inflation factor was 1.014. Grey areas indicate the 95% confidence interval.

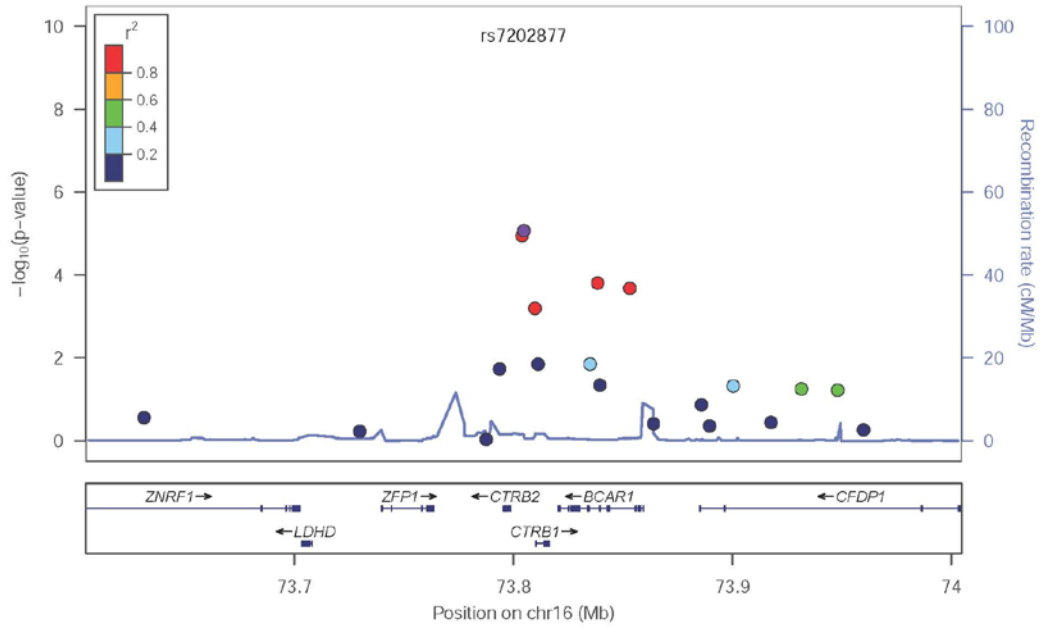
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**Supplementary Figure 2.** Regional plots of the loci associated with GLP-1 stimulated insulin secretion using the additive model.

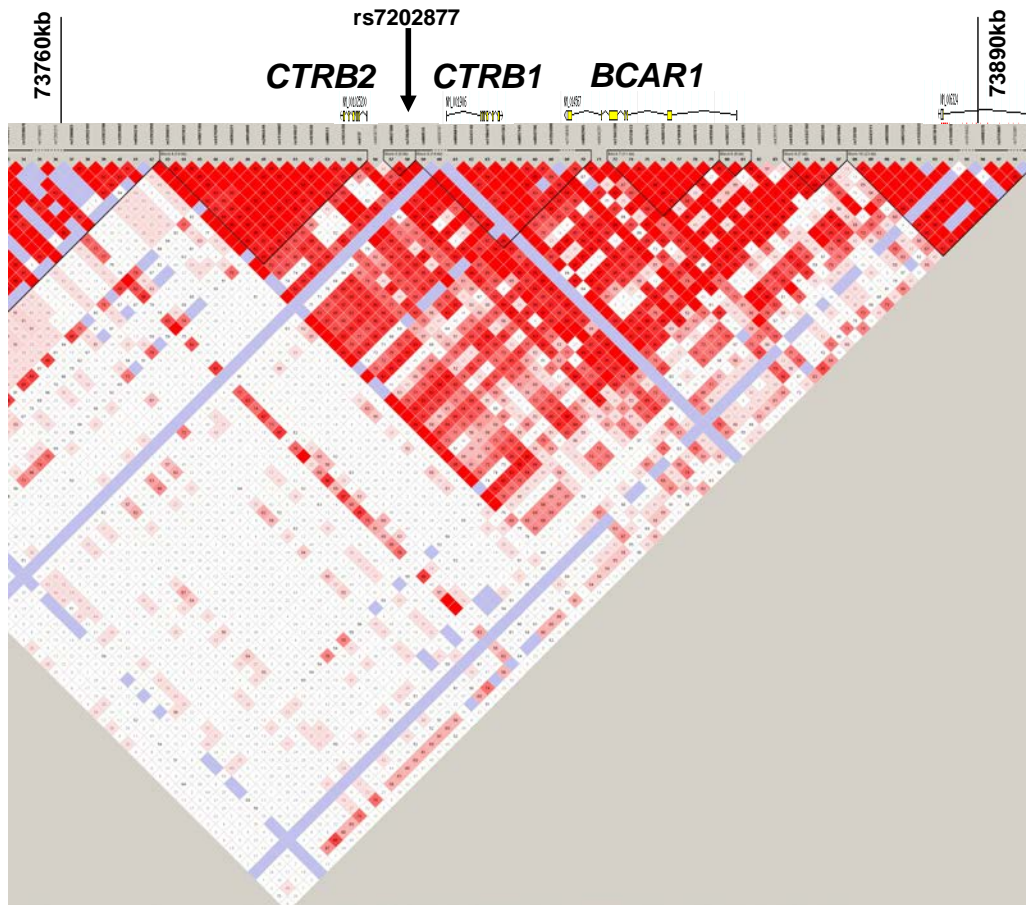




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Supplementary Figure 3. LD plot of the chromosome 16q23.1 region.



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Linkage disequilibrium plot showing  $D'$  prime in the region surrounding rs7202877 in CEU+TSI participants using HAPMAP phase III (release 2) data. Bright red indicates  $D'=1$  while, lighter shades of red indicate  $D' < 1$  but  $> 0$ , white indicates  $D'=0$ . The arrow indicates the position of rs7202877

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