Supplementary Figure 1.

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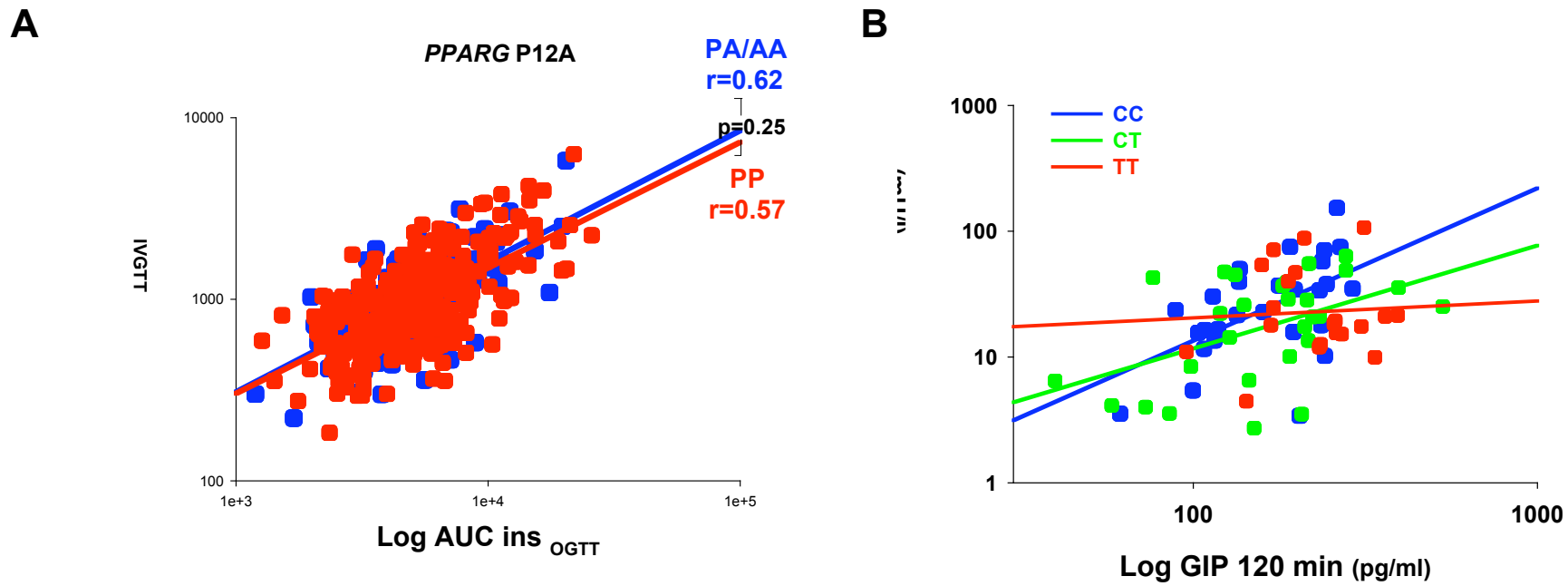

Supplementary Figure 2.

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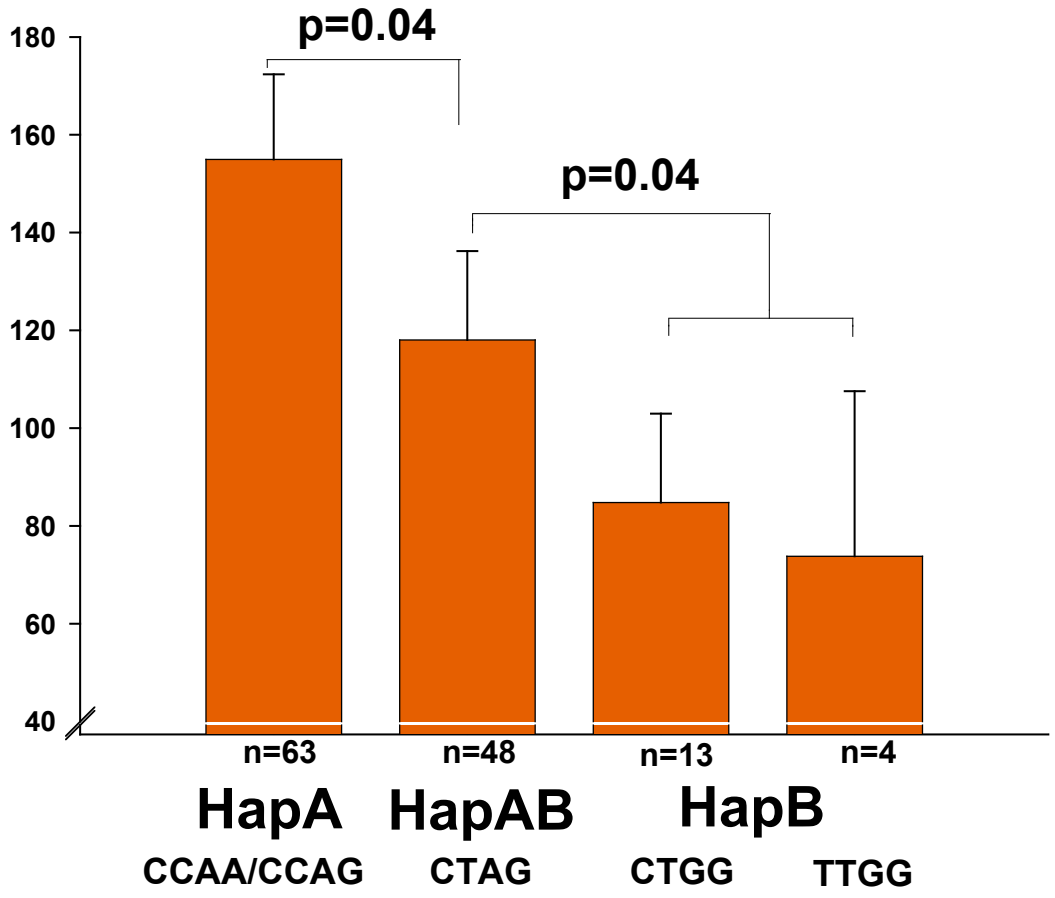

Supplementary Figure 1. (A) Correlation between the area under the insulin curve during oral (OGTT) and intravenous (IVGTT) glucose tolerance test according to *PPARG* P12A polymorphism (Botnia cohort, N=403). (B) Correlation between 2hr GIP (pg/ml) and glucagon (pg/ml) concentrations (Botnia PPP cohort, N=78). Blue lines represent non-risk PA/AA and red lines risk PP genotype carriers of *PPARG* P12A polymorphism.

Supplementary Figure 2. Acute insulin response to arginine at 28 mmol/l of glucose in carriers of *TCF7L2* haplotypes of SNPs rs7903146 and rs1088540: HapA (CCAA and/or CCAG), Hap AB (CTAG) and the two HapB possibilities (CTGG and TTGG) in subjects with IGT/T2D. Bars represent mean ± SE.

Supplementary information.

Supplementary Table 1A. Risk of developing T2D according to *TCF7L2* rs7903146 and rs12255372 in the prospective studies.

SNP	Genotypes	Converters n (%)	Non-converters n (%)	OR (95%CI) *P*	Converters n (%)	Non-converters n (%)	OR (95%CI) *P*
	Malmoe Prospective study				**Botnia Prospective Study**		
rs7903146	CC	637 (45.9)	3102 (56.2)	1	82 (54.7)	1603 (64.4)	1
	CT	634 (45.6)	2051 (37.1)	1.57 (1.37-1.80) 1.0×10^{-11}	58 (38.7)	796 (32.0)	1.48 (1.04-2.12) 0.03
	TT	118 (8.5)	368 (6.7)	1.47 (1.15-1.89) 0.002	10 (6.7)	92 (3.7)	3.17 (1.54-6.52) 0.002
	CC vs. CT/TT	752 (54.1)	2419 (43.8)	1.58 (1.38-1.81) 5×10^{-12}	68 (45.3)	888 (35.6)	1.61 (1.14-2.27) 0.007
	T	870 (31.3)	2787 (25.2)	1.35 (1.23-1.48) 1.4×10^{-11}	78 (26.0)	980 (19.7)	1.43 (1.10-1.87) 0.01
rs12255372	GG	596 (44.8)	2803 (53.2)	1			
	GT	616 (46.2)	2073 (39.4)	1.42 (1.23-1.63) 8.3×10^{-7}			
	TT	120 (9.0)	392 (7.4)	1.44 (1.13-1.84) 0.003			
	GG vs. GT/TT	736 (55.3)	2465 (46.8)	1.42 (1.24-1.62) 2.1×10^{-7}			
	T	856 (32.0)	2857 (27.1)	1.27 (1.16-1.40) 2.7×10^{-7}			

Supplementary Table 1B. The combination of alleles of *TCF7L2* SNPs rs7903146 and rs1088540 in the Botnia study.

	rs7903146		
rs1088540	CC	CT	TT
GG	128	248	97
GA	653	587	0
AA	869	2	0

The T allele of rs7903146 and G allele of rs10885406 are in almost complete LD (D'=0.99, r^2=1).

Supplementary Table 1C. Risk of developing T2D according to *TCF7L2* SNPs rs7903146 and rs1088540 haplotypes in the Botnia prospective study.

Haplotypes	Genotypes	Converters n (%)	Non-converters n (%)	OR (95%CI) *P*
HapA	CCAA/CCAG	79 (53.7)	1437 (59.2)	1
HapAB	CTAG	35 (23.8)	552 (22.7)	1.22 (0.80-1.86) 0.4
HapB	CTGG	21 (14.3)	225 (9.3)	1.62 (0.97-2.72) 0.07
	TTGG	10 (6.8)	87 (3.6)	3.02 (1.47-6.18) 0.003
Neither A nor B	CCGG	2 (1.4)	126 (5.2)	0.30 (0.07-1.24) 0.1
HapA vs others		118 (78.1)	1989 (81.8)	0.73 (0.48-1.10) 0.13

The combination of allele C of SNP rs7903146 and allele A of rs10885406 was designated Hap A, the combination of alleles C or T of rs7903146 and A from rs10885406 Hap AB and combination of T allele of rs7903146 and G allele of rs10885406 as Hap B.

Supplementary Table 2A. Insulin secretion during OGTT according to *TCF7L2* rs7903146 genotypes in the Malmoe and Botnia prospective studies.

	Malmoe				**Botnia**			
	CC	CT	TT	CT/TT	CC	CT	TT	CT/TT
				All				
Age (yrs)	46.5±5.8 (3739)	46.5±5.8 (2685)	46.0±5.9 (486)	46.4±5.8 (3171)	44.9±14.1 (1690)	45.1±14.2 (856)	44.1±15.4 (102)	45.0±14.3 (958)
BMI (kg/m^2)	24.5±3.5 (3737)	24.5±3.4 (2685)	24.4±3.3 (485)	24.5±3.4 (3170)	**25.6±4.2 (1681)**	**25.9±4.0 (846)**	**24.2±3.5 (101)**	**25.7±4.0 (947)**
Fasting glucose (mmol/l)	4.9±0.5 (3739)	4.9±0.5 (2685)	4.9±0.5 (486)	4.9±0.5 (3171)	**5.5±0.6 (1689)**	**5.6±0.6 (855)**	**5.6±0.5 (101)**	**5.6±0.6 (956)**
2hr glucose (mmol/l)	5.8±1.5 (2249)	5.8±1.5 (1613)	5.9±1.6 (275)	5.8±1.5 (1888)	**6.1±1.5 (1615)**	**6.4±1.5 (815)**	**6.5±1.6 (98)**	**6.4±1.5 (913)**
Insulinogenic index (mU/mmol)	**10.2±5.3 (557)**	**9.2±5.5 (413)**	**9.5±4.9 (68)**	**9.3±5.5 (481)** [a]	5.4±4.3 (1545)	5.1±4.0 (762)	4.6±3.3 (92)	5.0±3.9 (854)
Disposition index (mU^2/l^2)	**8.1±6.2 (557)**	**7.2±5.4 (413)**	**7.1±6.2 (68)**	**7.1±5.5 (481)** [b]	4.8±3.8 (1545)	4.5±3.6 (762)	4.3±3.7 (92)	4.5±3.6 (854)
HOMA (mmol · mU/l^2)	1.9±1.5 (840)	2.1±2.9 (592)	2.2±2.2 (104)	2.1±2.8 (696)	1.3±1.0 (1607)	1.4±0.9 (800)	1.3±1.0 (97)	1.4±0.9 (897)
Leptin (μg/l)								
Men	-	-	-	-	4.7-3.1 (296)	5.4-3.8 (176)	5.0-2.9 (15)	5.4-3.7 (191)
Women	-	-	-	-	15.7-10.0 (353)	18.2-13.0 (163)	13.5-6.3 (20)	17.7-12.6 (183
				NGT				
Age (yrs)	45.4±5.3 (2863)	45.4±5.2 (2003)	44.9±5.2 (352)	45.3±5.2 (2355)	43.4±14.0(1294)	43.6±14.3 (625)	42.5±15.4 (73)	43.5±14.4 (698
BMI (kg/m^2)	24.2±3.3 (2862)	24.2±3.2 (2003)	24.2±3.1 (351)	24.2±3.2 (2354)	**25.1±3.9 (1286)**	**25.3±3.7 (618)**	**23.7±3.1 (72)**	**25.1±3.7 (690)**
Fasting glucose (mmol/l)	4.8±0.4 (2863)	4.8±0.4 (2003)	4.8±0.4 (352)	4.8±0.4 (2355)	**5.4±0.5 (1294)**	**5.4±0.5 (626)**	**5.5±0.4 (72)**	**5.4±0.5 (698)**
2hr glucose (mmol/l)	5.0±1.0 (1515)	5.0±1.0 (1054)	5.0±1.0 (169)	5.0±1.0 (1223)	**5.6±1.1 (1223)**	**5.7±1.0 (593)**	**5.8±0.9 (69)**	**5.7±1.0 (662)**
Insulinogenic index (mU/mmol)	**10.4±5.3 (420)**	**9.5±5.4 (289)**	**9.8±4.7 (42)**	**9.5±5.3 (331)** [c]	5.3±4.3 (1181)	5.1±4.0 (555)	5.2±3.6 (65)	5.1±4.0 (620)
Disposition index (mU^2/l^2)	**8.9±6.5 (420)**	**7.9±5.6 (289)**	**8.3±7.1 (42)**	**8.0±5.8 (331)** [d]	5.2±3.9 (1181)	4.9±3.9 (555)	5.1±4.0 (65)	5.0±3.9 (620)
HOMA (mmol · mU/l^2)	1.6±1.2 (620)	2.0±3.2 (415)	1.9±1.9 (71)	2.0±3.0 (486)	1.2±0.7 (1234)	1.2±0.7 (584)	1.3±0.9 (70)	1.2±0.8 (654)
Leptin (μg/l)								
Men	-	-	-	-	4.5±3.2 (234)	4.7±3.0 (118)	5.3±3.3 (10)	4.8±3.0 (128)
Women	-	-	-	-	13.9±7.8 (255)	16.0±10.6 (118)	14.2±6.6 (14)	15.8±10.2 (132

	IFG/IGT							
Age (yrs)	50.3±5.9 (876)	49.9±6.0 (682)	48.9±6.4 (134)	49.7±6.1 (816)	50.1±12.9 (396)	49.1±13.1 (231)	48.0±15.0 (29)	49.0±13.3 (260
BMI (kg/m^2)	25.4±3.9 (875)	25.5±3.7 (682)	24.9±3.8 (134)	25.4±3.7 (816)	27.2±4.6 (395)	27.5±4.1 (228)	25.6±4.2 (29)	27.3±4.2 (257
Fasting glucose (mmol/l)	5.2±0.5 (876)	5.2±0.5 (682)	5.3±0.5 (134)	5.2±0.5 (816)	6.0±0.6 (395)	6.0±0.6 (229)	5.9±0.7 (29)	6.0±0.6 (258)
2hr glucose (mmol/l)	7.3±1.1 (734)	7.3±1.2 (559)	7.4±1.3 (106)	7.3±1.2 (665)	**7.9±1.4 (392)**	**8.1±1.4 (222)**	**8.2±1.6 (29)**	**8.1±1.4 (251)**
Insulinogenic index (mU/mmol)	9.6±5.3 (137)	8.7±5.9 (124)	9.1±5.1 (26)	8.8±5.8 (150)	**5.5±4.4 (364)**	**5.0±3.9 (207)**	**3.2±2.0 (27)**	**4.8±3.8 (234)**
Disposition index (mU^2/l^2)	5.5±4.1 (137)	5.4±4.3 (124)	5.0±3.3 (26)	5.3±4.2 (150)	3.5±3.1 (364)	3.3±2.4 (207)	2.6±1.6 (27)	3.2±2.3 (234)
HOMA (mmol · mU/l^2)	2.5±2.0 (220)	2.4±1.8 (177)	2.7±2.6 (33)	2.5±2.0 (210)	1.9±1.4 (373)	1.8±1.2 (216)	1.5±1.0 (27)	1.8±1.2 (243)
Leptin (μg/l)								
Men	-	-	-	-	5.5±2.6 (62)	6.7±4.8 (58)	4.6±2.3 (5)	6.6±4.7 (63)
Women	-	-	-	-	20.4±13.3 (98)	23.9±16.8 (45)	11.8±5.8 (6)	22.5±16.4 (51

[a]P=0.002 between CC, CT and TT; and P=0.0006 between CC vs. CT/TT
[b]P=0.02 between CC, CT and TT; and P=0.005 between CC vs. CT/TT
[c]P=0.02 between CC, CT and TT; and P=0.006 between CC vs. CT/TT
[d]P=0.02 between CC vs. CT/TT
[e]P=0.004 between CC, CT and TT
[f]P=0.006 between CC, CT and TT; and P=0.002 between CC vs. CT/TT
[g]P=1.9×10^{-5} between CC, CT and TT; and P=2.6×10^{-5} between CC vs. CT/TT
[h]P=0.02 between CC, CT and TT
[i]P=0.005 between CC, CT and TT; and P=0.006 between CC vs. CT/TT
[j]P=0.006 between CC, CT and TT; and P=0.004 between CC vs. CT/TT
[k]P=0.02 between CC, CT and TT; and P=0.009 between CC vs. CT/TT
[l]P=0.006 between CC, CT and TT; and P=0.03 between CC vs. CT/TT

Supplementary Table 2B. Insulin secretion during OGTT according to *TCF7L2* haplotypes of rs7903146 and rs10885406 in the Botnia prospective study at baseline.

	HapA	HapAB	HapB
	All		
Age (yrs)	45.1±13.6 (1453)	44.9±13.8 (555)	45.9±14.0 (330)
BMI (kg/m^2)	25.7±4.2 (1449)	25.8±3.7 (553)	25.5±4.2 (326)
Fasting P-glucose (mmol/l)	**5.5±0.6 (1453)**	**5.6±0.6 (555)**	**5.6±0.6 (330)** [a]
2hr P-glucose (mmol/l)	**6.1±1.5 (1413)**	**6.3±1.5 (536)**	**6.4±1.6 (323)** [b]
Insulinogenic index (mU/mmol)	5.4±4.3 (1395)	5.0±3.9 (527)	5.2±3.9 (315)
Disposition index (mU^2/l^2)	4.8±3.7 (1395)	4.4±3.6 (527)	4.6±3.6 (315)
HOMA (mmol · mU/l^2)	1.3±1.0 (1453)	1.3±0.8 (555)	1.4±1.0 (330)
Leptin (μg/l)			
Men	4.7±3.1 (258)	5.3±3.9 (136)	5.6±3.4 (53)
Women	15.8±10.1 (318)	18.0±12.4 (103)	17.0±12.7 (74)
	NGT		
Age (yrs)	43.6±13.7 (1107)	43.6±13.9 (405)	44.2±14.1 (240)
BMI (kg/m^2)	25.2±3.9 (1103)	25.2±3.5 (403)	24.9±3.7 (236)
Fasting P-glucose (mmol/l)	**5.4±0.5 (1107)**	**5.4±0.5 (405)**	**5.4±0.5 (240)** [a]
2hr P-glucose (mmol/l)	**5.6±1.0 (1069)**	**5.7±1.0 (389)**	**5.7±1.0 (233)** [a]
Insulinogenic index (mU/mmol)	5.3±4.2 (1058)	5.0±4.0 (383)	5.3±3.9 (228)
Disposition index (mU^2/l^2)	5.2±3.8 (1058)	4.8±3.9 (383)	5.2±3.8 (228)
HOMA (mmol · mU/l^2)	1.2±0.7 (1107)	1.2±0.6 (405)	1.2±0.9 (240)
Leptin (μg/l)			
Men	4.4±3.2 (199)	4.5±2.6 (90)	5.5±3.7 (38)
Women	14.0±7.7 (232)	16.3±10.5 (75)	15.1±9.4 (52)
	IFG/IGT		
Age (yrs)	49.9±12.3 (346)	48.4±13.1 (150)	50.6±12.8 (90)
BMI (kg/m^2)	27.2±4.6 (346)	27.2±3.8 (150)	27.2±4.8 (90)
Fasting P-glucose (mmol/l)	6.0±0.6 (346)	6.0±0.6 (150)	6.0±0.6 (90)
2hr P-glucose (mmol/l)	**7.9±1.4 (344)**	**8.0±1.3 (147)**	**8.3±1.5 (90)** [a]
Insulinogenic index (mU/mmol)	**5.6±4.5 (337)**	**4.9±3.7 (144)**	**4.7±4.1 (87)** [a]
Disposition index (mU^2/l^2)	**3.5±3.1 (337)**	**3.3±2.3 (144)**	**3.0±2.2 (87)** [c]
HOMA (mmol · mU/l^2)	1.9±1.4 (346)	1.7±1.1 (150)	1.9±1.3 (90)
Leptin (μg/l)			
Men	5.4±2.6 (59)	7.0±5.2 (46)	5.7±2.7 (15)
Women	20.6±13.7 (86)	22.7±15.7 (28)	21.6±17.7 (22)

Data are mean ± SD.
Hap A=allele C of rs7903146 and allele A of rs10885406
Hap AB=alleles C or T of rs7903146 and allele A of rs10885406
Hap B= T allele of rs7903146 and G allele of rs10885406
[a]P<0.04 between HapA, HapAB and HapB
[b]P=0.0004 between HapA, HapAB and HapB
[C]P=0.04 HapA vs. HapB

Supplementary Table 3. Insulin secretion during glucose arginine stimulation test according to *TCF7L2* rs7903146 genotypes and haplotypes of SNPs rs7903146 and rs10885406.

	rs7903146				**Haplotypes**		
NGT							
	CC	CT	TT	CT/TT	HapA	HapAB	HapB
Age (yrs)	63.1 ± 7.3 (51)	62.6 ± 7.8 (22)	57.7 ± 1.4 (6)	61.5 ± 8.7 (28)	62.8 ± 7.7 (45)	60.6 ± 9.5 (13)	63.0 ± 7.9 (16)
BMI (kg/m^2)	**27.1 ± 3.6 (51)**	**24.5 ± 3.5 (22)**	**26.0 ± 4.4 (6)**	**24.9 ± 3.7 (28) [a]**	**27.5 ± 3.5 (45)**	**24.6 ± 3.7 (13)**	**25.6 ± 3.1(16) [a]**
Fasting P-glucose (mmol/l)	5.4 ± 0.5 (51)	5.4 ± 0.8 (23)	5.2 ± 0.3 (6)	5.3 ± 0.7 (29)	5.4 ± 0.5 (45)	5.4 ± 0.9 (14)	5.3 ± 0.5 (16)
AIR$_{5mmol/l}$ (mU/l)	36.3 ± 19.1 (47)	32.0 ± 18.3 (17)	36.4 ± 9.1 (6)	33.1 ± 16.3 (23)	37.0 ± 19.2 (44)	34.1 ± 23.0 (10)	32.2 ± 9.2 (14)
AIR$_{14mmmol/l}$ (mU/l)	110.9 ± 67.0 (47)	97.9 ± 45.2 (17)	130.6 ± 78.2 (6)	106.4 ± 55.6 (23)	113.2 ± 68.2 (44)	94.1 ± 41.5 (10)	113.4 ± 62.7 (14)
AIR$_{28mmmol/l}$ (mU/l)	148.0 ± 81.1 (47)	137.9 ± 76.7 (17)	130.7 ± 76.9 (6)	136.1 ± 75.1 (23)	151.2 ± 82.4 (44)	132.6 ± 64.4 (10)	134.2 ± 83.2 (14)
AIR slope	8.1 ± 6.0 (47)	7.3 ± 4.2 (17)	12.1 ± 12.2 (6)	8.6 ± 7.2 (23)	8.3 ± 6.1 (44)	6.5 ± 3.7 (10)	9.8 ± 8.5 (14)
EGP basal (mg.lbmkg^{-1}.min^{-1})	2.8 ± 0.3 (25)	2.7 ± 0.3 (11)	2.7 ± 0.1 (2)	2.7 ± 0.3 (13)	2.8 ± 0.3 (22)	2.7 ± 0.4 (6)	2.6 ± 0.2 (9)
Glucose uptake (mg.lbmkg^{-1}.min^{-1})	5.3 ± 2.3 (35)	6.3 ± 2.3 (18)	6.1 ± 2.8 (3)	6.3 ± 2.3 (21)	6.4 ± 2.5 (29)	8.2 ± 2.7 (10)	7.3 ± 2.4 (13)
IFG/IGT/T2D							
Age (yrs)	64.0 ± 5.5 (69)	64.0 ± 6.7 (76)	64.6 ± 2.4 (4)	64.1 ± 6.5 (80)	64.0 ± 5.6 (66)	63.8 ± 7.3 (58)	65.4 ± 1.9 (20)
BMI (kg/m^2)	27.7 ± 3.8 (69)	26.8 ± 3.1 (74)	30.1± 3.9 (4)	27.0 ± 3.2 (78)	27.8 ± 3.8 (66)	26.8 ± 3.0 (57)	27.8 ± 3.8 (19)
Fasting P-glucose (mmol/l)	7.8 ± 3.2 (68)	9.0 ± 3.8 (77)	10.3 ± 3.5 (4)	9.1 ± 3.8 (81)	7.8 ± 3.3 (65)	8.9 ± 3.8 (59)	9.6 ± 3.7 (20)
AIR$_{5mmol/l}$ (mU/l)	39.2 ± 25.3 (63)	32.0 ± 21.0 (62)	36.9 ± 18.5 (4)	32.3 ± 20.8 (66)	39.8 ± 25.8 (60)	33.0 ± 22.2 (47)	32.4 ± 16.5 (17)
AIR$_{14mmmol/l}$ (mU/l)	**85.5 ± 70.3 (63)**	**67.5 ± 60.8 (63)**	**52.6 ± 45.6 (4)**	**66.6 ± 59.8 (67) [a]**	86.2 ± 71.6 (60)	71.0 ± 63.3 (48)	57.7 ± 51.0 (17)
AIR$_{28mmmol/l}$ (mU/l)	**155.0 ± 138.2 (63)**	**108.8 ± 115.1 (63)**	**73.8 ± 67.5 (4)**	**106.7 ± 112.8 (67) [b]**	**158.0 ± 140.7 (60)**	**118.0 ± 126.0 (48)**	**82.2 ± 64.0 (17) [a]**
AIR slope	5.2 ± 6.3 (62)	3.4 ± 6.9 (58)	1.6 ± 3.6 (4)	3.2 ± 6.7 (62)	5.2 ± 6.4 (59)	3.3 ± 7.6 (44)	3.3 ± 4.2 (16)
EGP basal (mg.lbmkg^{-1}.min^{-1})	**2.8 ± 0.3 (36)**	**3.2 ± 0.9 (39)**	**3.2 ± 0.8 (3)**	**3.2 ± 0.8 (42) [a]**	**2.8 ± 0.3 (34)**	**3.1 ± 0.9 (28)**	**3.2 ± 0.8 (13) [a]**
Glucose uptake (mg.lbmkg^{-1}.min^{-1})	4.7 ± 2.3 (61)	5.1 ± 2.5 (61)	2.8 ± 0.4 (3)	5.0 ± 2.5 (64)	4.6 ± 2.3 (59)	5.3 ± 2.5 (48)	4.1 ± 2.4 (15)

Data mean ± SD.

Hap A=allele C of rs7903146 and allele A of rs10885406

Hap AB=alleles C or T of rs7903146 and allele A of rs10885406

Hap B= T allele of rs7903146 and G allele of rs10885406

[a]P<0.05 between CC, CT/TT carriers; and for comparision between HapA, HapAB and HapB

[b]P<0.01 between CC, CT/TT carriers

Supplementary Table 4. Estimates of incretin effect from insulin response to OGTT and IVGTT according to *TCF7L2* rs7903146 genotypes and haplotypes in the Botnia study.

	rs7903146				**Haplotypes**		
	CC	CT	TT	CT/TT	HapA	HapAB	HapB
All							
Age (yrs)	45.6±12.6 (373)	47.6±12.8 (211)	48.0±14.1 (23)	47.7±12.9 (234)	45.5±12.5 (342)	46.8±13.9 (142)	49.2±11.4 (83)
BMI	25.8±3.8 (373)	26.1±4.0 (211)	25.3±3.4 (23)	26.0±3.9 (234)	25.8±3.8 (342)	26.0±4.0 (142)	25.8±3.5 (83)
Fasting glucose (mmol/l)	5.4±0.7 (374)	5.5±0.6 (211)	5.4±0.5 (23)	5.5±0.6 (234)	5.4±0.7 (343)	5.6±0.6 (142)	5.4±0.6 (83)
2-hr glucose (mmol/l)	6.0±1.7 (373)	6.0±1.6 (210)	6.2±1.5 (23)	6.0±1.6 (233)	6.0±1.6 (343)	6.1±1.6 (141)	5.9±1.6 (83)
$AUC_{ins\ OGTT}$	5572.7±3292.6 (364)	5898.8±3997.6 (206)	5006.6±2099.7 (23)	5809.2±3855.6 (229)	5577.7±3241.7 (335)	6113.6±4304.9 (137)	5102.9±2619.6 (83)
$AUC_{ins\ IVGTT}$	1068.4±707.0 (251)	1146.5±774.7 (145)	921.0±381.8 (16)	1124.1±747.3 (161)	1061.9±707.2 (228)	1169.4±777.7 (95)	1010.2±657.0 (60)
$AUC_{ins\ OGTT}$ / $AUC_{ins\ IVGTT}$	6.1±3.1 (245)	5.5±2.4 (142)	5.2±1.5 (16)	5.5±2.3 (158)	6.2±3.2 (223)	5.5±2.2 (92)	5.6±2.5 (60)
Incretin effect	79.7±9.8 (245)	78.8±8.3 (142)	78.8±7.0 (16)	78.8±8.1 (158)	79.9±9.8 (223)	79.0±8.1 (92)	78.7±8.6 (60)
Normoglycemia (FPG <5.4 mmol/l)							
Age (yrs)	43.7±12.6 (189)	47.2±12.4 (91)	47.9±16.0 (10)	47.3±12.7 (101)	43.7±12.5 (175)	46.0±13.1 (61)	49.4±12.4 (38) [d]
BMI	25.2±3.4 (189)	25.1±3.9 (91)	25.2±2.9 (10)	25.1±3.8 (101)	25.2±3.4 (175)	25.3±4.1 (61)	24.6±3.3 (38)
Fasting glucose (mmol/l)	4.9±0.3 (190)	5.0±0.3 (91)	5.0±0.3 (10)	5.0±0.3 (101) [a]	4.9±0.3 (176)	5.0±0.3 (61)	4.9±0.3 (38)
2-hr glucose (mmol/l)	5.4±1.5 (190)	5.5±1.5 (90)	5.4±1.2 (10)	5.5±1.4 (100)	5.4±1.5 (176)	5.6±1.4 (60)	5.3±1.4 (38)
$AUC_{ins\ OGTT}$	5137.0±3259.6 (185)	5611.6±4709.2 (88)	5444.7±2282.5 (10)	5594.6±4514.0 (98)	5149.3±3257.7 (172)	6143.4±5572.9 (58)	4799.8±2076.4 (38)
$AUC_{ins\ IVGTT}$	1115.7±788.8 (109)	1038.4±891.2 (55)	814.6±292.4 (6)	1016.4±852.4 (61)	1112.3±796.1 (99)	1189.0±1043.9 (36)	756.3±346.2 (24) [e]
$AUC_{ins\ OGTT}$ / $AUC_{ins\ IVGTT}$	5.5±2.9 (108)	6.0±3.0 (54)	5.3±1.1 (6)	5.9±2.8 (60)	5.6±3.0 (98)	5.6±2.6 (35)	6.4±3.2 (24)
Incretin effect	77.3±10.4 (108)	79.6±8.9 (54)	80.4±4.2 (6)	79.7±8.5 (60)	77.3±10.7 (98)	78.7±8.3 (35)	80.9±8.9 (24)
Hyperglycemia (FPG >5.4 mmol/l)							
Age (yrs)	47.6±12.3 (184)	47.9±13.2 (120)	48.1±13.0 (13)	47.9±13.1 (133)	47.5±12.2 (167)	47.3±14.6 (80)	49.1±10.7 (45)
BMI	26.4±4.0 (184)	26.9±3.8 (120)	25.4±3.9 (13)	26.7±3.9 (133)	**26.5±4.1 (167)**	**26.6±3.9 (80)**	**26.7±3.5 (45)** [f]
Fasting glucose (mmol/l)	6.0±0.4 (184)	5.9±0.4 (120)	5.7±0.3 (13)	5.9±0.4 (133)	6.0±0.4 (167)	6.0±0.5 (80)	5.8±0.4 (45)
2-hr glucose (mmol/l)	6.6±1.6 (183)	6.3±1.6 (120)	6.8±1.5 (13)	6.4±1.6 (133)	6.6±1.6 (167)	6.4±1.6 (80)	6.3±1.5 (45)
$AUC_{ins\ OGTT}$	6023.0±3274.8 (179)	6112.9±3376.6 (118)	4±669.6±1972.8 (13)	5969.7±3287.6 (131)	6029.8±3172.2 (163)	6113.8±3114.7 (78)	5359.0±3002.8 (45)
$AUC_{ins\ IVGTT}$	1032.2±637.6 (142)	1212.6±691.1 (90)	984.9±428.2 (10)	1189.8±671.3 (100)	1023.2±631.1 (129)	1163.5±570.8 (58)	1179.5±758.4 (36)
$AUC_{ins\ OGTT}$ / $AUC_{ins\ IVGTT}$	**6.7±3.2 (137)**	**5.3±2.0 (88)**	**5.1±1.7 (10)**	**5.2±1.9 (98)** [b]	**6.7±3.2 (125)**	**5.4±2.0 (56)**	**5.0±1.8 (36)** [g]
Incretin effect	**81.5±8.9 (137)**	**78.4±7.9 (88)**	**77.8±8.4 (10)**	**78.3±7.9 (98)** [c]	**81.8±8.6 (125)**	**79.1±8.0 (56)**	**77.3±8.2 (36)** [h]

Data mean ± SD. Fasting glycemia was based upon median of fasting p-glucose (FPG) = 5.4 mmol/l. Incretin effect = $100\%*(AUC_{ins\ OGTT}-AUC_{ins\ IVGTT})/AUC_{ins\ OGTT}$.

[a]P=0.04 between CC, CT and TT carriers and P=0.01 for CC vs CT/TT carriers
[b]P=0.0004 between CC, CT and TT carriers and P=8.8e-05 for CC vs CT/TT carriers
[c]P=0.01 between CC, CT and TT carriers and P=0.003 for CC vs CT/TT carriers
[d]P=0.03 between HapA, HapAB and HapB
[e]P=0.02 between HapA, HapAB and HapB; P=0.002 for HapA vs HapB
[f]P=0.03 between HapA, HapAB and HapB
[g]P=0.0003 between HapA, HapAB and HapB; P=0.001 for HapA vs HapB
[h]P=0.004 between HapA, HapAB and HapB; P=0.005 for HapA vs HapB

Supplementary Table 5. Glucagon and GIP concentrations during OGTT according to *TCF7L2* rs7903146 from the Botnia study.

	CC	**CT**	**TT**	**CT/TT**
Number	148	137	21	158
Age (yrs)	52.8 ± 11.7	53.3 ± 10.3	53.2 ± 9.9	53.3 ± 10.2
BMI (kg/m^2)	26.7 ± 3.9	26.3 ± 3.6	27.6 ± 5.9	26.4 ± 4.0
Fasting glucose (mmol/l)	5.1 ± 0.5	5.2 ± 0.6	5.0 ± 0.4	5.2 ± 0.5
2 hr glucose (mmol/l)	4.9 ± 1.2	4.8 ± 1.2	5.0 ± 1.2	4.8 ± 1.2
HOMA ($mmol \cdot mU/l^2$)	1.6 ± 1.7	1.3 ± 0.7	1.3 ± 0.8	1.3 ± 0.8
Fasting glucagon (pg/ml)	80.0 ± 24.8	79.1 ± 29.6	73.6 ± 35.0	78.4 ± 30.3
2 hr glucagon (pg/ml)	74.0 ± 23.3	72.8 ± 27.3	71.7 ± 24.1	72.7 ± 26.8
Fasting GIP (pg/ml)	34.0 ± 3.8 (28)	42.6 ± 5.1 (29)	35.1 ± 3.0 (21)	39.5 ± 3.3 (50)
2hr GIP(pg/ml)	172.4 ± 12.2 (28)	179.4 ± 19.1 (29)	225.8 ± 19.6 (21)	198.9 ± 14.0 (50)

Data mean ± SD.

Supplementary Table 6. Univariate correlations between *TCF7L2* and insulin gene mRNA as well as (total) amount of insulin and glucagon secretion in human islets.

	***TCF7L2* gene expression (p-value;N)**	**Insulin gene expression (p-value;N)**	**Glucagon (p-value;N)**	**Insulin (p-value;N)**
***TCF7L2* gene expression**	-	-	-	-
Insulin gene expression	**0.76 (0.001;15)**	-		
Glucagon	0 (1;13)	0.18 (0.55;13)	-	-
Insulin	0.26 (0.4;12)	-0.14 (0.67;12)	-	-
SI	**-0.63 (0.02;13)**	-0.35 (0.24;13)	0.10 (0.70;15)	-0.48 (0.08;14)

SI= Stimulation Index estimates glucose-stimulated insulin release after normalization for total insulin content.