

SUPPLEMENTARY DATA

Supplementary Table 1. Effect of the *GIPR* rs10423928 on metabolic phenotypes in the studied cohorts.

Clinical characteristics of the studied cohorts.

Study	Cohort	Number (M,%)	Age (yrs) / Duration diabetes (yrs)	Diabetes, N (%)	BMI (kg/m ²)	Fasting P-glucose (mmol/l)	2hr P-glucose (mmol/l)
I	PPP-Botnia	4654 (53.6)	47.9 ± 15.2	-	26.2 ± 4.3	5.26 ± 0.56	5.19 ± 1.55
II	BPS basal	2770 (54.4)	44.9 ± 14.2	-	25.6 ± 4.1	5.54 ± 0.58	6.22 ± 1.53
	follow-up		52.7 ± 14.7	138 (5.0)	26.7 ± 4.3	5.41 ± 0.72	6.18 ± 2.17
III	Incretin clamps	47 (100)	21.7 ± 0.7	-	23.4 ± 3.0	5.68 ± 0.36	-
IV	MPP basal	16,061 (64.9)	45.5 ± 6.9	-	24.3 ± 3.3	5.45 ± 0.56	6.39 ± 1.65
	follow-up		69.0 ± 5.6	2063 (12.8)	27.1 ± 4.1	5.77 ± 1.29	-
V	MDC	28,449 (39.5)	58.1 ± 7.6	874 (3.1)	25.8 ± 4.0	5.85 ± 1.56	-
VI	METSIM	5513 (100)	57.5 ± 7.0	1058 (13.4)	27.3 ± 4.2	5.96 ± 1.13	6.47 ± 2.45
VII	GENFIEV	861 (43.0)	49.4 ± 11	121 (14)	29.0 ± 5.3	5.4 ± 0.9	7.8 ± 2.7
VIII	Verona Newly Diagnosed Type 2 Diabetes Study	483 (68.3)	58.0 ± 9.9	483 (100)	30.1 ± 5.1	7.26 ± 1.82	13.45 ± 4.22
IX	Low birth weight cohort	118 (100)	24.0 ± 2.0	-	23.6 ± 3.0	5.39 ± 0.50	-
X	Steno-Twins	287 (48.4)	73.7 ± 5.2	47 (16.4)	26.2 ± 4.3	5.93 ± 1.44	8.49 ± 4.29
XI	EUGENE	277 (46.6)	35.4 ± 6.3	-	26.2 ± 5.0	5.20 ± 0.44	6.21 ± 1.38

Abbreviations. Data are means ± SD or, if not normally distributed, as median [interquartile range]. LBM = lean body mass. ISI = insulin sensitivity index¹. CIR = corrected insulin response to glucose at 30 min during OGTT². DI = disposition index³. FPIR=first phase insulin response during IVGTT. AIR = acute insulin response during frequently-sampled intravenous glucose tolerance test. GIP = glucose-dependent insulinotropic polypeptide

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Study I. PPP-Botnia							
Phenotype	Number	Genotypes			Additive model		
		TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		27.6					
Number	4532	2374	1814	344			
Age (yrs)	4527	48.2 ± 15.1	47.7 ± 15.3	47.5 ± 15.3	-0.210	0.348	0.55
BMI (kg/m²)	4531	26.4 ± 4.4	26.2 ± 4.2	25.7 ± 4.0	-0.233	0.098	0.017
BMI (kg/m²) †	2825	26.6 ± 4.3	26.3 ± 4.2	25.7 ± 4.3	-0.271	0.124	0.029
Weight (kg)	4531	76.9 ± 15.1	76.0 ± 14.6	75.3 ± 14.4	-0.645	0.306	0.035
Waist (cm)	4508	88.9 ± 13.0	88.2 ± 12.6	87.6 ± 12.2	-0.351	0.256	0.17
LBM (kg)	2859	54.3 ± 11.0	53.5 ± 10.7	53.9 ± 10.9	-0.183	0.173	0.29
Fasting P-glucose (mmol/l)	4532	5.26 ± 0.57	5.25 ± 0.55	5.21 ± 0.57	-0.012	0.013	0.36
30 min P-glucose (mmol/l)	4497	8.26 ± 1.62	8.23 ± 1.61	8.23 ± 1.62	0.012	0.036	0.75
120 min P-glucose (mmol/l)	4502	5.15 ± 1.55	5.21 ± 1.55	5.23 ± 1.61	0.075	0.035	0.031
Fasting insulin (mU/l)	4467	5.36 [4.24]	5.29 [4.05]	5.40 [4.31]	-0.003	0.012	0.82
30 min insulin (mU/l)	4363	52.4 [40.8]	47.9 [37.5]	45.2 [33.7]	-0.055	0.013	4.6x10⁻⁵
30 min insulin (mU/l)*	4363	52.4 [40.8]	47.9 [37.5]	45.2 [33.7]	-0.056	0.013	2.2x10⁻⁵
120 min insulin (mU/l)	4339	23.7 [26.7]	23.6 [24.7]	22.8 [20.7]	-0.006	0.019	0.74
120 min insulin (mU/l) *	4339	23.7 [26.7]	23.6 [24.7]	22.8 [20.7]	-0.133	0.015	0.026
ISI	4279	8.05 [6.23]	8.21 [6.14]	8.58 [6.59]	0.019	0.012	0.13
CIR (mU×l/mmol²)	4358	155 [166]	145 [148]	147 [151]	-0.064	0.018	0.00051
CIR (mU×l/mmol²) †	2738	162 [174]	153 [151]	149 [169]	-0.075	0.023	0.001
DI (mU³/l³)	4278	1,217 [1,333]	1,144 [1,286]	1,198 [1,260]	-0.047	0.020	0.016
DI (mU³/l³) †	2698	1,266 [1,437]	1,175 [1,321]	1,277 [1,362]	-0.075	0.025	0.002
Fasting proinsulin (pmol/l)	927	8.90 [4.80]	9.30 [5.10]	9.80 [5.60]	0.024	0.057	0.67
120 min proinsulin (pmol/l)	903	32.9 [21.6]	32.1 [22.2]	36.2 [25.4]	0.007	0.031	0.83
Fasting glucagon (pg/ml)	1018	72.0 [28.0]	69.0 [25.0]	71.0 [30.0]	-0.028	0.014	0.053
120 min glucagon (pg/ml)	989	67.0 [24.0]	68.0 [24.0]	63.5 [24.0]	-0.003	0.014	0.86

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Fasting GIP (pg/ml)	3011	32.6 [22.5]	30.2 [21.8]	27.6 [22.0]	-0.071	0.015	3.1x10⁻⁶
120 min GIP (pg/ml)	2958	182 [110]	173 [104]	153 [97]	-0.066	0.013	8.3x10⁻⁷
Triglycerides (mmol/l)	4373	1.09 [0.76]	1.06 [0.72]	1.08 [0.78]	0.017	0.011	0.12
HDL-cholesterol (mmol/l)	4373	1.40 ± 0.39	1.40 ± 0.38	1.38 ± 0.40	-0.016	0.008	0.046
Cholesterol (mmol/l)	4373	5.33 ± 1.05	5.31 ± 1.05	5.32 ± 1.18	0.001	0.024	0.98
APOA1 (mg/l)	144	129 ± 21	127 ± 20	126 ± 13	-1.741	2.578	0.50
APOB (mg/l)	144	97.0 ± 27.1	98.6 ± 26.4	95.7 ± 21.1	1.157	3.241	0.72

* = data adjusted for glucose levels at each time point respectively.

† = data adjusted for fasting GIP levels.

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Study II. BPS (Botnia prospective study)							
Phenotype		Genotypes			Additive model		
Baseline	Number	TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		27.3					
Number	2255	1182	913	160			
Age (yrs)	2255	45.4 ± 13.6	45.5 ± 13.5	44.9 ± 13.4	-0.024	0.444	0.96
BMI (kg/m ²)	2250	25.6 ± 3.9	25.5 ± 3.8	25.8 ± 4.1	-0.001	0.128	0.996
Weight (kg)	2362	74.3 ± 13.6	73.9 ± 13.6	75.0 ± 14.8	-0.021	0.185	0.91
Waist (cm)	1807	86.6 ± 11.3	86.2 ± 11.5	87.2 ± 12.5	0.176	0.372	0.64
LBM (kg)	2309	54.6 ± 10.6	54.1 ± 10.5	55.0 ± 12.2	-0.097	0.185	0.60
Fasting P-glucose (mmol/l)	2255	5.55 ± 0.57	5.49 ± 0.56	5.53 ± 0.59	-0.028	0.019	0.14
30 min P-glucose (mmol/l)	2255	8.35 ± 1.59	8.33 ± 1.69	8.54 ± 1.70	0.043	0.053	0.41
60 min P-glucose (mmol/l)	2250	7.66 ± 2.13	7.68 ± 2.23	7.89 ± 2.19	0.074	0.069	0.29
120 min P-glucose (mmol/l)	2255	6.06 ± 1.44	6.18 ± 1.49	6.35 ± 1.50	0.130	0.048	0.0069
Fasting insulin (mU/l)	2255	4.41 [2.90]	4.25 [2.90]	4.40 [2.70]	-0.009	0.016	0.57
Fasting insulin (mU/l) *	2255	4.41 [2.90]	4.25 [2.90]	4.40 [2.70]	-0.006	0.016	0.71
30 min insulin (mU/l)	2255	35.9 [37.9]	35.3 [35.1]	34.4 [32.6]	-0.051	0.022	0.020
30 min insulin (mU/l) *	2255	35.9 [37.9]	35.3 [35.1]	34.4 [32.6]	-0.055	0.022	0.010
60 min insulin (mU/l)	2248	44.8 [41.0]	36.3 [35.0]	36.8 [36.0]	-0.048	0.022	0.032
60 min insulin (mU/l) *	2248	44.8 [41.0]	36.3 [35.0]	36.8 [36.0]	-0.060	0.020	0.0039
120 min insulin (mU/l)	2255	25.0 [32.1]	25.3 [29.0]	24.9 [29.5]	-0.012	0.026	0.66
120 min insulin (mU/l) *	2255	25.0 [32.1]	25.3 [29.0]	24.9 [29.5]	-0.052	0.022	0.016
HbA1c	1636	5.40 [0.60]	5.39 [0.50]	5.30 [0.50]	-0.004	0.003	0.29
ISI	2255	8.11 [6.00]	8.44 [6.17]	8.17 [6.39]	0.027	0.017	0.11
CIR (mU×l/mmol²)	2255	114 [131]	109 [122]	96.7 [103]	-0.058	0.026	0.029

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DI (mU ³ /l ³)	2255	896 [983]	877 [1,059]	717 [896]	-0.030	0.027	0.26
Leptin (µg/l)							
men	485	4.11 [3.92]	3.84 [3.25]	3.34 [2.19]	-0.052	0.014	0.00027
women	536	13.98 [11.11]	14.08 [12.44]	16.26 [14.22]	0.005	0.014	0.70
Triglycerides (mmol/l)	2185	1.07 [0.68]	1.07 [0.70]	1.01 [0.78]	-0.009	0.015	0.55
HDL-cholesterol (mmol/l)	2178	1.38 ± 0.33	1.38 ± 0.33	1.36 ± 0.31	-0.010	0.011	0.33
Cholesterol (mmol/l)	2185	5.62 ± 1.18	5.46 ± 1.09	5.39 ± 1.05	-0.115	0.036	0.0015
APOA1 (mg/l)	2184	139 ± 23	139 ± 22	137 ± 22	-0.685	0.748	0.36
APOB (mg/l)	2182	92.0 ± 22.8	89.7 ± 22.1	89.9 ± 23.7	-1.065	0.711	0.13
FPIR (from IVGTT)	643	238 [206]	223 [212]	241 [268]	0.020	0.020	0.31
Follow-up	Number	TT	TA	AA	BETA	SE	P Value (dominant)
Number	2255	1182	913	160			
Age (yrs)	2255	53.3 ± 14.1	53.3 ± 14.0	52.3 ± 14.0	-0.349	0.482	0.47
BMI (kg/m ²)	2194	26.6 ± 4.1	26.6 ± 4.1	26.9 ± 4.4	0.130	0.141	0.36
Weight (kg)	2309	76.6 ± 14.1	76.6 ± 14.4	78.4 ± 15.9	0.037	0.194	0.85
Waist (cm)	1748	90.6 ± 11.5	91.0 ± 11.9	91.6 ± 11.5	0.706	0.404	0.08
LBM (kg)	2038	55.0 ± 11.0	54.9 ± 11.0	56.0 ± 13.0	0.035	0.217	0.87
Fasting P-glucose (mmol/l)	2255	5.31 ± 0.58	5.29 ± 0.55	5.30 ± 0.55	-0.014	0.019	0.46
30 min P-glucose (mmol/l)	2255	8.48 ± 1.76	8.61 ± 1.84	8.51 ± 1.61	0.058	0.059	0.32
60 min P-glucose (mmol/l)	2249	7.81 ± 2.43	7.98 ± 2.56	7.93 ± 2.46	0.109	0.080	0.18
120 min P-glucose (mmol/l)	2255	5.77 ± 1.69	5.89 ± 1.73	6.20 ± 1.64	0.171	0.056	0.0024
Fasting insulin (mU/l)	2254	7.09 [6.00]	7.33 [6.50]	7.09 [6.10]	0.031	0.019	0.11
Fasting insulin (mU/l) *	2254	7.09 [6.00]	7.33 [6.50]	7.09 [6.10]	0.033	0.019	0.08
30 min insulin (mU/l)	2255	54.6 [43.4]	52.3 [43.8]	47.8 [36.6]	-0.054	0.020	0.0070
30 min insulin (mU/l) *	2255	54.6 [43.4]	52.3 [43.8]	47.8 [36.6]	-0.057	0.020	0.0045
60 min insulin (mU/l)	2235	57.7 [51.0]	55.2 [47.0]	49.1 [39.0]	-0.059	0.021	0.0055
60 min insulin (mU/l) *	2235	57.7 [51.0]	55.2 [47.0]	49.1 [39.0]	-0.069	0.020	0.00063
120 min insulin (mU/l)	2255	30.3 [35.1]	30.0 [35.8]	30.9 [29.4]	0.035	0.027	0.20

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120 min insulin (mU/l)*	2255	30.3 [35.1]	30.0 [35.8]	30.9 [29.4]	-0.013	0.022	0.56
HbA1c	352	5.50 [0.60]	5.50 [0.70]	5.50 [0.70]	0.000	0.007	0.97
ISI	2255	5.72 [4.83]	5.50 [4.89]	5.83 [5.56]	-0.002	0.019	0.91
CIR (mU×l/mmol²)	2255	150 [167]	138 [151]	132 [130]	-0.080	0.027	0.0034
DI (mU³/l³)	2254	846 [1,137]	740 [1,020]	806 [916]	-0.081	0.030	0.0063
Triglycerides (mmol/l)	2102	1.19 [0.75]	1.18 [0.78]	1.15 [0.88]	0.011	0.016	0.49
HDL-cholesterol (mmol/l)	2093	1.33 ± 0.35	1.32 ± 0.36	1.31 ± 0.33	-0.008	0.012	0.52
Cholesterol (mmol/l)	2102	5.50 ± 1.08	5.41 ± 1.07	5.38 ± 1.04	-0.058	0.037	0.12
APOA1 (mg/l)	2092	137 ± 23	136 ± 23	135 ± 23	1.008	0.797	0.21
APOB (mg/l)	1459	102 ± 26	99 ± 25	98 ± 25	-2.032	0.877	0.021
Non-converters, N (%)	2550	1337 (52.4)	1026 (40.2)	187 (7.3)			
Converters to T2D, N (%)	128	65 (50.8)	49 (38.3)	14 (10.9)			
OR (95% CI), <i>P</i> value		1.13 (0.86-1.50), 0.38					
OR (95% CI), <i>P</i> value †		1.12 (0.84-1.48), 0.45					

* = data adjusted for glucose levels at each time point respectively. Odds ratio for the risk of T2D are from logistic regression adjusted for age, gender and † for BMI.

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Study III. Incretin clamps				
Phenotype	Genotypes		P value (t-test)	P value adjusted for body weight
	TT	TA/AA		
Risk (A) allele frequency, %	20.2			
Number	30	17		
Age (yrs)	21.7 ± 0.7	21.8 ± 0.9	0.67	
Birth weight (g)	3312 ± 106	3513 ± 154	0.28	
Fasting P-glucose (mmol/l)	5.72 ± 0.07	5.61 ± 0.09	0.34	0.44
Fasting P-insulin (pmol/l)	37.58 ± 3.65	32.21 ± 3.54	0.34	0.42
Height (cm)	183.42 ± 1.30	183.76 ± 2.13	0.88	0.99
Weight (kg)	81.17 ± 1.93	74.65 ± 1.54	0.025	0.019
BMI (kg/m ²)	24.15 ± 0.56	22.20 ± 0.58	0.029	0.032

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Study IV. MPP							
Phenotype		Genotypes			Additive model		
Baseline	Number	TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		22.3					
Number	15318	9260	5290	768			
Age (yrs)	15318	45.4 ± 6.9	45.4 ± 6.9	45.6 ± 6.9	0.108	0.080	0.18
BMI (kg/m²)	15312	24.3 ± 3.3	24.2 ± 3.3	24.0 ± 3.0	-0.148	0.044	0.00080
Weight (kg)	15312	72.8 ± 12.0	72.4 ± 12.1	71.9 ± 10.8	-0.487	0.143	0.00065
Fasting P-glucose (mmol/l)	15314	5.45 ± 0.56	5.45 ± 0.56	5.44 ± 0.54	-0.003	0.007	0.66
40' min P-glucose (mmol/l)	2239	9.97 ± 1.85	10.0 ± 1.98	9.64 ± 1.89	-0.031	0.066	0.64
120 min P-glucose (mmol/l)	8451	6.34 ± 1.63	6.42 ± 1.68	6.55 ± 1.68	0.109	0.028	7.9x10⁻⁵
Fasting insulin (mU/l)	2981	7.00 [9.00]	8.00 [9.00]	8.00 [9.00]	0.013	0.021	0.52
Fasting insulin (mU/l) *	2981	7.00 [9.00]	8.00 [9.00]	8.00 [9.00]	0.014	0.020	0.51
40 min insulin (mU/l)	1556	91.0 [67.0]	83.0 [53.0]	80.0 [43.0]	-0.069	0.021	0.00085
40 min insulin (mU/l) *	1556	91.0 [67.0]	83.0 [53.0]	80.0 [43.0]	-0.063	0.020	0.0020
120 min insulin (mU/l)	2734	26.0 [34.0]	26.0 [33.0]	22.0 [25.3]	0.028	0.027	0.31
120 min insulin (mU/l) *	2729	26.0 [34.0]	26.0 [33.0]	22.0 [25.3]	-0.001	0.02	0.97
ISI	2718	9.22 [9.48]	8.67 [9.42]	9.96 [10.99]	-0.020	0.021	0.35
CIR (mU×l/mmol ²)	1547	155 [133]	139 [119]	155 [148]	-0.021	0.028	0.45
DI (mU ³ /l ³)	1530	1,327 [1,558]	1,210 [1,263]	1,538 [1,655]	-0.045	0.035	0.20
Triglycerides (mmol/l)	15294	1.09 [0.71]	1.10 [0.70]	1.06 [0.71]	0.000	0.006	0.97
Cholesterol (mmol/l)	15300	5.63 ± 1.04	5.61 ± 1.03	5.58 ± 1.03	-0.022	0.014	0.11
APOA1(mg/l)	4967	133 ± 26	133 ± 26	132 ± 24	-0.552	0.617	0.37
Follow-up							
Age (yrs)	13,291	68.9 ± 5.6	69.0 ± 5.6	69.0 ± 5.5	0.106	0.082	0.20
BMI (kg/m²)	13,225	26.1 ± 4.0	26.7 ± 3.9	26.7 ± 4.0	-0.167	0.058	0.0039
Weight (kg)	13,230	78.6 ± 13.8	77.9 ± 13.7	78.1 ± 13.4	-0.508	0.179	0.0046
Waist (cm)	13,226	94.1 ± 11.8	93.4 ± 11.8	93.6 ± 11.4	-0.533	0.153	0.0005
Fasting P-glucose (mmol/l)	13,220	5.47 ± 0.54	5.46 ± 0.54	5.44 ± 0.53	-0.008	0.006	0.45
Triglycerides (mmol/l)	13,218	1.10 [0.7]	1.10 [0.6]	1.10 [0.6]	-0.009	0.007	0.19
Cholesterol (mmol/l)	13,220	5.68 ± 1.07	5.66 ± 1.06	5.57 ± 1.06	-0.034	0.015	0.026

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Non-converters, N (%)	13,292	8034 (60.4)	4592 (34.5)	666 (5.0)			
Converters to T2D, N (%)	2026	1226 (60.5)	698 (34.5)	102 (5.0)			
OR (95% CI), <i>P</i> value		0.995 (0.92-1.08), 0.90					
OR (95% CI), <i>P</i> value **		1.03 (0.95-1.12), 0.51					

* = data adjusted for glucose levels at each time point respectively. Odds ratio for the risk of T2D are from logistic regression adjusted for age, gender and ** for BMI.

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Study V. MDC							
Phenotype		Genotypes			Additive model		
	Number	TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		22.4					
Number (M/F)	24883	5765/9180	3374/5353	488/723			
Age (yrs)	24883	58.0 ± 7.7	58.1 ± 7.7	57.9 ± 7.6	-0.016	0.083	0.85
BMI (kg/m²)	24849	25.7 ± 4.0	25.6 ± 3.9	25.3 ± 3.7	-0.185	0.042	9.9x10⁻⁶
Height (cm)	24850	168.6 ± 8.9	168.7 ± 8.8	168.7 ± 8.7	-0.003	0.066	0.96
Weight (kg)	24849	73.4 ± 13.6	73.0 ± 13.4	72.3 ± 13.1	-0.512	0.127	5.3x10⁻⁵
Body fat%	24740	26.9 ± 7.0	26.7 ± 6.9	26.4 ± 6.7	-0.188	0.053	4.1x10⁻⁴
Fat weight (kg)	24738	19.8 ± 6.8	19.5 ± 6.7	19.1 ± 6.3	-0.286	0.070	4.1x10⁻⁵
Lean body weight (kg)	24738	53.0 ± 11.0	52.9 ± 10.9	52.6 ± 10.8	-0.211	0.072	0.004
Waist (cm)	24842	84.0 ± 14.3	83.5 ± 12.8	83.7 ± 25.9	-0.378	0.132	0.004
Fasting P-glucose (mmol/l)	4830	5.65 ± 0.84	5.65 ± 0.94	5.61 ± 0.67	-0.013	0.021	0.53
Fasting insulin (mU/l)	4666	6.00 [5.00]	6.00 [5.00]	7.00 [5.00]	-0.271	0.193	0.16
Triglycerides (mmol/l)	4836	1.16 [0.73]	1.13 [0.69]	1.17 [0.88]	-0.024	0.018	0.18

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Study VI. METSIM							
Phenotype		Genotypes			Additive model		
	Number	TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		21.7					
Number		3420	1918	253			
Age (yrs)	5591	57.8 ± 6.8	57.6 ± 6.7	57.9 ± 6.4	-0.116	0.115	0.46
BMI (kg/m ²)	5591	26.9 ± 3.8	26.7 ± 3.7	26.9 ± 3.7	-0.136	0.087	0.12
Weight (kg)	5588	83.1 ± 13.1	82.6 ± 16.6	83.2 ± 13.5	-0.313	0.298	0.29
Waist (cm)	5586	97.6 ± 10.7	97.1 ± 10.3	97.7 ± 10.7	-0.236	0.244	0.33
Fasting P-glucose (mmol/L)	5591	5.71 ± 0.49	5.68 ± 0.49	5.66 ± 0.49	-0.023	0.011	0.035
30 min P-glucose (mmol/l)	5575	8.81 ± 1.45	8.72 ± 1.48	8.77 ± 1.46	-0.061	0.033	0.066
120 min P-glucose (mmol/l)	5591	6.03 ± 1.68	6.11 ± 1.69	6.22 ± 1.67	0.111	0.037	0.003
Fasting insulin (mU/l)	5587	6.30 [5.90]	6.30 [5.50]	6.50 [5.68]	-0.005	0.011	0.66
Fasting insulin (mU/l) *	5587	6.30 [5.90]	6.30 [5.50]	6.50 [5.68]	0.001	0.010	0.91
30 min insulin (mU/l)	5564	54.0 [48.6]	49.6 [44.0]	51.0 [49.5]	-0.052	0.013	6.0 × 10⁻⁵
30 min insulin (mU/l) *	5564	54.0 [48.6]	49.6 [44.0]	51.0 [49.5]	-0.049	0.013	1.3 × 10⁻⁴
120 min insulin (mU/l)	5585	34.7 [43.8]	33.9 [42.3]	35.1 [40.2]	0.009	0.018	0.62
120 min insulin (mU/l) *	5585	34.7 [43.8]	33.9 [42.3]	35.1 [40.2]	-0.025	0.014	0.079
CIR (mU×l/mmol ²)	5563	134 [133]	128 [119]	127 [148]	-0.029	0.016	0.071
ISI	5559	6.14 [5.28]	6.36 [5.52]	6.35 [5.36]	0.021	0.012	0.080
DI (mU ³ /l ³)	5559	754 [733]	778 [798]	741 [706]	-0.008	0.016	0.62

* = data adjusted for glucose levels at each time point respectively.

SUPPLEMENTARY DATA

Study VII. GENFIEV							
Phenotype	Number	Genotypes			Additive model		
		TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		18.6					
Number	861	568	266	27	--	--	--
Age (yrs)	832	49.5±11.3	48.9±11.3	49±11.3			0.8
BMI (kg/m ²)	814	29.18±5.38	29.00±4.96	28.59±6.99	-0.236	0.34 4	0.5
Weight (kg)	814	82.30±37.4	80.84±15.24	78.31±19.1	-1.64	2.06	0.4
Waist (cm)	798	100.16±13.8	99.72±14.07	99.33±15.18	-0.38	0.9	0.6
Fasting P-glucose (mmol/l)	802	5.5±0.9	5.4±0.9	5.2±0.9	0.14	1.08	0.8
30 min P-glucose (mmol/l)	801	9.0±2.0	9.1±1.8	9.0±2.0	2.5	2.1	0.2
120 min P-glucose (mmol/l)	802	7.8±2.8	7.9±2.6	7.5±2.0	1.7	2.9	0.57
Fasting insulin (mU/l)	804	10.0[6.8-15.1]	10.2[6.8-15.8]	10.4[7.8-15.0]	0.024	0.03 4	0.4
Fasting c-peptide (ng/ml)	797	2.31±1.21	2.28±1.07	2.62±1.07	0.07	0.07	0.3
30 min c-peptide (ng/ml)	798	5.68±2.69	5.67±2.83	5.75±1.79	0.027	0.17 2	0.8
120 min c-peptide (ng/ml)	801	8.53±4.03	8.65±4.23	9.18±3.18	0.284	0.25 7	0.2
HOMA-IR (mU×mmol/l ²)	783	2.38[1.57-3.70]	2.44[1.52-3.71]	2.50[1.74-3.39]	0.019	0.03 7	0.5
Insulinogenic index (ng/[mmol*l ²])	783	0.049[0.029-0.076]	0.044[0.028-0.071]	0.041[0.028-0.057]	-0.095	0.05 3	0.07
DI (ng/[mmol²*mU])	780	0.021[0.010-0.038]	0.018[0.009-0.033]	0.016[0.011-0.032]	-0.130	0.06 5	0.046
HbA1c	731	5.7±0.57	5.71±0.55	5.58±0.45	0.014	0.03 6	0.7

SUPPLEMENTARY DATA

Triglycerides (mmol/l)	737	1.6±1.2	1.6±1.0	1.5±0.8	0.05	0.03	0.1
HDL-cholesterol (mmol/l)	730	1.3±0.4	1.37±0.4	1.33±0.3	0.29	0.93	0.7
Total Cholesterol (mmol/l)	739	5.3±1.0	5.5±1.0	5.3±0.7	3.07	2.59 4	0.2
LDL-cholesterol (mmol/l)	610	3.4±0.9	3.5±1.0	3.3±0.6	3.8	2.69 3	0.1
Basal Insulin secretion (pmol/m ² BSA/min) ⁴⁻⁷	736	96.17[68.63-125.86]	94.37[69.72-131.77]	104.10[87.62-122.77]	0.024	0.03	0.4
Derivative control (1st phase) [(pmol/m ² BSA) (mM/min)] ⁴⁻⁷	736	1124.8[639.2-1794.7]	1083.3[627.0-1903.0]	1046.7[700.1-1860.7]	0.023	0.06	0.7
Dose-response curve (pmol/min/m ²)							
isr_4	736	98.9[70.1-129.9]	96.7[70.8-134.8]	104.1[89.9-122.7]	0.014	0.03	0.6
isr_5.5	736	140.4[95.7-205.6]	141.3[92.9-195.9]	155.5[122.7-199.9]	-0.016	0.03	0.6
isr_8	736	362.6[250.5-548.3]	369.3[239.2-504.4]	417.9[268.3-495.5]	-0.009	0.04	0.8
isr_11	736	670.1[471.9-986.1]	677.3[451.6-935.4]	728.7[478.7-868.8]	-0.011	0.04	0.8

SUPPLEMENTARY DATA

Study VIII. Verona Newly Diagnosed Type 2 Diabetes Study							
		Genotypes			Additive model (dominant)		
Phenotype	Number	TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		19.6					
Number	491	320	150	21	11.6	14	0.40
Age (yrs)	491	57.7±10.1	58.6 ± 9.7	57.4 ± 10.9	0.4	0.8	0.56
BMI (kg/m ²)	491	29.4 [26.5-33.0]	29.4 [26.4-32.8]	29.3 [25.7-35.5]	-0.2	0.4	0.58
Weight (kg)	491	80 [73-93]	82 [72.5-92]	80 [71-103]	0.05	1.3	0.96
LBM (kg)	391	53.6 ± 9.7	53.7 ± 9.2	55.9 ± 14.5	1.8	0.6	0.005
Fasting P-glucose (mmol/l)	471	7.1 ± 1.7	7.4 ± 1.9	7.5 ± 2.6	0.3	0.1	0.059
30 min P-glucose (mmol/l)	458	11.6 ± 2.6	12.2 ± 2.7	11.7 ± 2.8	0.3	0.2	0.12
120 min P-glucose (mmol/l)	466	13.2 ± 4.2	14.3 ± 4.1	13.7 ± 4.4	0.8	0.3	0.034
Fasting insulin (mU/l)	423	11.1 [7.6-16.4]	11.9 [7.5-16.2]	12.3 [8.5-19.5]	0.04	0.04	0.3
30 min insulin (mU/l)	416	30.1 [18.9-44.4]	27.4 [17.8-43.2]	33.9 [16.9-47.7]	-0.3	0.05	0.56
120 min insulin (mU/l)	425	63 [38.1-102.7]	64.2 [38.7-94.6]	63.8 [40.1-105.4]	-0.05	0.06	0.4
Insulinogenic Index (mU/mmol)	409	4.02 (2.16-6.54)	3.10 (1.65-5.75)	3.10 (2.39-6.40)	-0.48 (-0.64)	0.24 (0.29)	0.06 (0.03)
CIR _{30'} (mU×l/mmol ²)	413	0.35 (0.20 – 0.59)	0.29 (0.17-0.49)	0.40 (0.21-0.59)	-0.05 (-0.07)	0.04 (0.04)	0.14 (0.06)
CIR_{120'} (mU×l/mmol²)	424	0.62 (0.26 – 1.59)	0.43 (0.21-1.03)	0.72 (0.28-1.52)	-0.18 (-0.24)	0.07 (0.09)	0.017 (0.008)
HbA1c	448	6.7 [6.1-7.5]	6.7 [6.1-7.6]	6.7 [6.3-7.5]	0.01	0.01	0.37
Adiponectin (µg/ml)	323	6.1 [4.5-8.9]	6.9 [4.9-9.6]	7.3 [6.0-7.7]	0.007	0.042	0.86
men	224	5.4 [4-7.9]	5.9 [3.9-7.6]	7.1 [5.2-7.6]	0.01	0.05	0.82
women	99	8.1 [6.6-10.6]	9.1 [7-10.5]	8 [6.5-9.7]	-0.01	0.06	0.87
Triglycerides (mmol/l)	455	1.4 [1-2]	1.4 [1.1-2]	1.2 [1-1.8]	-0.04	0.04	0.40
HDL-cholesterol (mmol/l)	452	1.1 [0.9-1.4]	1.1 [1-1.4]	1.1 [1-1.3]	0.01	0.02	0.60
Cholesterol (mmol/l)	454	5 [4.3-5.6]	4.9 [4.3-5.6]	5 [4.6-5.4]	-0.008	0.01	0.63

SUPPLEMENTARY DATA

APOA1 (mg/l)	399	1.3 [1.1-1.5]	1.3 [1.2-1.5]	1.3 [1.2-1.6]	0	0.02	0.98
APOB (mg/l)	399	1 [0.8-.2]	1 [0.8-1.1]	1 [0.9-1.1]	-0.03	0.03	0.34
Derivative control (1st phase) [(pmol/m²BSA) (mM/min)]⁴⁻⁷	448	529.3 (66.8-1015)	345.8 (0-837)	296.9 (0-1174)	-118.3 (-158.7)	57.9 (69.9)	0.042 (0.023)
Stimulus-response curve (pmol/min/m² BSA)⁴⁻⁷							
ISR at glucose=5.5 mM	448	163.4±70.7	160.6±63.2	168.5±63.3			0.093 (0.033)
ISR at glucose=8.0 mM		233.6±130.5	211.7±108.1	238.6±102.2			
ISR at glucose=11.0 mM		380.7±234.6	334.6±204.8	373.9±163.2			
ISR at glucose=15.0 mM		609.1±398.8	528.8±364.2	565.4±276.3			
ISR at glucose=20.0 mM		901.3±623.4	777.7±577.6	805.6±432.8			
L Ox basal (mg/min/BSA)	354	39.9±16.7	38.8±17.3	37.2±16.1	-0.14	1.5	0.93
L Ox clamp (mg/min/BSA)	334	33.6±14.5	32.5±16.4	31.3±13.1	-0.33	1.4	0.8
Delta L Ox	333	-5.6±12.2	-6.2±11	-6.4±8.3	-0.43	1.1	0.7
G Ox basal (mg/min/BSA)	354	50.9±35.9	49.3±33.3	53.1±47	-0.8	3.4	0.8
G Ox clamp (mg/min/BSA)	337	59.6±35.3	59±34.3	71.7±43	1.5	3.4	0.66
Delta G Ox	335	7.6±33	9.6±29.5	18±24.2	2.8	3	0.35
EER basal (cal/min/BSA)	355	660.4 [612.4-721]	647.5 [592.6-700.2]	665.2 [581.5-736.4]	0.004	0.01	0.7
EER clamp (cal/min/BSA)	339	637 [590-693]	625.4 [575.9-673.7]	644.1 [560.1-721.3]	0.007	0.01	0.5
Delta EER (cal/min/BSA)	336	-28.1±42	-22.7±36.5	-1.8±60.5	8.2 (7.2)	3.9 (4.65)	0.039 (0.12)

SUPPLEMENTARY DATA

Study IX. Low birth weight cohort			
Phenotype	Genotypes		<i>P</i> value
	TT	TA/AA	
Risk (A) allele frequency, %	20.3		
Number	74	44	
Anthropometrics			
Height (cm)	182.0 ± 7.0	182.2 ± 7.1	0.881
Weight (kg)	79.9 ± 11.1	75.3 ± 8.6	0.016
BMI (kg/m ²)	24.1 ± 3.0	22.8 ± 2.9	0.024
Birth weight (g)	3265 ± 656	3401 ± 651	0.302
Fasting P-glucose (mmol/l)	5.36 ± 0.50	5.42 ± 0.52	0.466
Fasting P-insulin (pmol/l)	34.2 ± 18.0	30.9 ± 15.8	0.338
HbA1c (%)	5.15 ± 0.25	5.17 ± 0.33	0.376
HOMA- IR	8.32 ± 4.90	7.51 ± 3.94	0.374
DXA			
Fat percentage (%)	20.9 ± 7.1	19.3 ± 6.9	0.306
Bone mass trunk (g)	1043 ± 221	1002 ± 148	0.332
Fat mass trunk (g)	8213 ± 4201	7854 ± 3640	0.642
Lean mass trunk (g)	27627 ± 3018	26368 ± 2757	0.014
Bone mass total	3273 ± 458	3211 ± 367	0.510
Fat mass total (g)	16238 ± 7736	15282 ± 6721	0.473
Lean mass total (g)	59836 ± 6525	56953 ± 5698	0.006
Cholesterols			
Total cholesterol (mmol/l)	4.12 ± 0.86	3.97 ± 0.84	0.377
HDL (mmol/l)	1.24 ± 0.32	1.28 ± 0.27	0.499
LDL (mmol/l)	2.35 ± 0.77	2.28 ± 0.72	0.615
VLDL (mmol/l)	0.49 ± 0.25	0.43 ± 0.17	0.135
Triglycerides (mmol/l)	1.13 ± 0.81	0.91 ± 0.37	0.091
Free fatty acides (mmol/l)	416 ± 207	373 ± 166	0.323
Glycerol turnover (n:24; n:14)			
Rate of appearance (basal)	3.44 ± 1.67	3.26 ± 2.45	0.785

SUPPLEMENTARY DATA

Study X. Steno-Twins							
Phenotype	Number	Genotypes			Additive model (dominant)		
		TT	TA	AA	BETA	SE	P Value
Risk (A) allele frequency, %		27.7					
Number	287	148	119	20			
IGT/T2D (N)	121	64	47	10	-	-	0.72
Age (yrs)		74.1 ± 4.8	73.1 ± 5.4	74.2 ± 5.8	-0.463	0.490	0.35
Height (cm)	286	166 ± 8	167 ± 10	163 ± 9	-0.383	0.612	0.53
Weight (kg)	285	73.4 ± 13.8	72.9 ± 12.4	65.7 ± 13.2	-1.351	1.283	0.29
Waist (cm)	239	91.9 ± 11.4	91.6 ± 10.5	86.7 ± 13.7	-1.428	1.095	0.19
BMI (kg/m ²)	285	26.5 ± 4.7	26.0 ± 3.6	25.0 ± 4.6	-0.356	0.455	0.44
Fasting P-glucose (mmol/l)	239	5.68 ± 0.58	5.52 ± 0.47	5.53 ± 0.42	-0.099 (-0.134)	0.053 (0.07)	0.063 (0.057)
30 min P-glucose (mmol/l)	237	9.18 ± 1.62	9.08 ± 1.47	8.50 ± 1.46	-0.143	0.185	0.44
120 min P-glucose (mmol/l)	239	7.12 ± 1.62	6.84 ± 1.69	7.37 ± 1.48	0.008	0.179	0.97
Fasting insulin (pmol/l)	238	45 [32]	43 [30]	41 [34]	-0.073	0.053	0.17
30 min insulin (pmol/l)	238	354 [284]	268 [177]	303 [139]	-0.104 (-0.166)	0.058 (0.071)	0.076 (0.019)
30 min insulin (pmol/l) *	238	354 [284]	268 [177]	303 [139]	-0.089 (-0.147)	0.057 (0.07)	0.12 (0.035)
120 min insulin pmol/l)	238	309 [276]	238 [197]	264 [234]	-0.113 (-0.18)	0.072 (0.092)	0.12 (0.051)
120 min insulin (pmol/l) *	238	309 [276]	238 [197]	264 [234]	-0.124 (-0.17)	0.059 (0.075)	0.034 (0.024)
HOMA-IR	284	2.22 ± 2.35	1.70 ± 0.99	1.57 ± 0.73	-0.088	0.058	0.13

* = data adjusted for glucose levels at each time point respectively. Analyses for glucose, insulin levels during OGTT and HOMA-IR are performed only in non-diabetic individuals.

SUPPLEMENTARY DATA

Study XI. EUGENE					
Phenotype	Number	Genotypes			Additive model
		TT	TA	AA	<i>P</i> Value
Risk (A) allele frequency, %			21.1		
Number	277	175	87	15	
IGT/T2D (N)	33/0	18/0	13/0	2/0	
Age (yrs)	277	35.2 ± 6.2	35.1 ± 6.6	38.6 ± 5.1	0.12
Height (cm)	277	172.3 ± 9.3	173.0 ± 8.3	170.5 ± 8.5	0.57
Weight (kg)	277	77.7 ± 16.8	79.1 ± 16.5	76.7 ± 15.1	0.76
BMI (kg/m ²)	273	26.2 ± 5.1	26.3 ± 4.9	26.2 ± 5.0	0.99
Fasting P-glucose (mmol/l)	277	5.20 ± 0.45	5.20 ± 0.46	5.15 ± 0.33	0.89
30 min P-glucose (mmol/l)	276	7.72 ± 1.34	7.88 ± 1.48	7.23 ± 1.16	0.23
120 min P-glucose (mmol/l)	277	6.14 ± 1.41	6.37 ± 1.34	6.20 ± 1.20	0.43
Fasting insulin (mU/l)	275	9.15 ± 4.15	9.93 ± 5.59	8.77 ± 3.59	0.69
30 min insulin (mU/l)	273	55.56 ± 33.22	57.34 ± 32.88	41.25 ± 34.19	0.018
120 min insulin (mU/l)	275	44.96 ± 35.19	50.91 ± 42.02	43.08 ± 35.03	0.49
HOMA-IR	275	2.14 ± 1.06	2.34 ± 1.45	2.03 ± 0.91	0.72

SUPPLEMENTARY DATA

Supplementary Table 2. Correlations between GIP in plasma and metabolic phenotypes in the PPP-Botnia study in relation to *GIPR* genotypes.

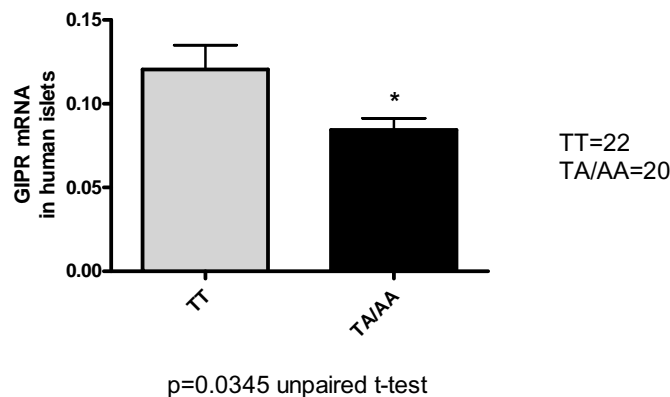
		TT N=1478		TA N=1127		AA N=227	
		Fasting GIP	GIP 120 min	Fasting GIP	GIP 120 min	Fasting GIP	GIP 120 min
Fasting GIP (pg/ml)	R^2	-	0.342	-	0.347	-	0.454
	P	-	<0.0001	-	<0.0001	-	<0.0001
BMI (kg/m ²)	R^2	0.048	-0.036	0.110	-0.033	0.025	-0.011
	P	0.064	0.17	<0.0001	0.27	0.71	0.86
Weight (kg)	R^2	0.163	-0.128	0.126	-0.172	0.152	-0.111
	P	<0.0001	<0.0001	<0.0001	<0.0001	0.001	0.016
Fasting glucose (mmol/l)	R^2	0.056	-0.199	-0.046	-0.110	-0.014	-0.167
	P	0.030	<0.0001	0.12	<0.0001	0.83	0.001
Glucose 30 (mmol/l)	R^2	0.088	-0.146	0.143	-0.123	0.046	-0.109
	P	0.001	<0.0001	<0.0001	<0.0001	0.50	0.10
Glucose 120 (mmol/l)	R^2	-0.057	0.136	0.019	0.155	-0.005	0.116
	P	0.028	<0.0001	0.53	<0.0001	0.94	0.080
Fasting insulin (mU/l)	R^2	0.062	-0.059	0.141	-0.034	-0.104	-0.122
	P	0.017	0.025	<0.0001	0.26	0.12	0.07
Insulin 30 (mU/l)	R^2	0.142	0.032	0.115	0.015	-0.057	-0.055
	P	<0.0001	0.23	<0.0001	0.61	0.40	0.41
Insulin 120 (mU/l)	R^2	-0.004	0.262	0.067	0.238	-0.045	0.168
	P	0.88	<0.0001	0.027	<0.0001	0.51	0.012
ISI	R^2	-0.071	-0.007	-0.151	-0.019	0.097	0.073
	P	0.007	0.79	<0.0001	0.53	0.15	0.28
CIR	R^2	0.052	0.136	-0.034	0.102	-0.098	0.0000
	P	0.048	<0.0001	0.26	0.001	0.15	0.99
Disposition index	R^2	-0.017	0.110	-0.121	0.077	-0.042	0.054
	P	0.51	<0.0001	<0.0001	0.011	0.54	0.42

SUPPLEMENTARY DATA

References:

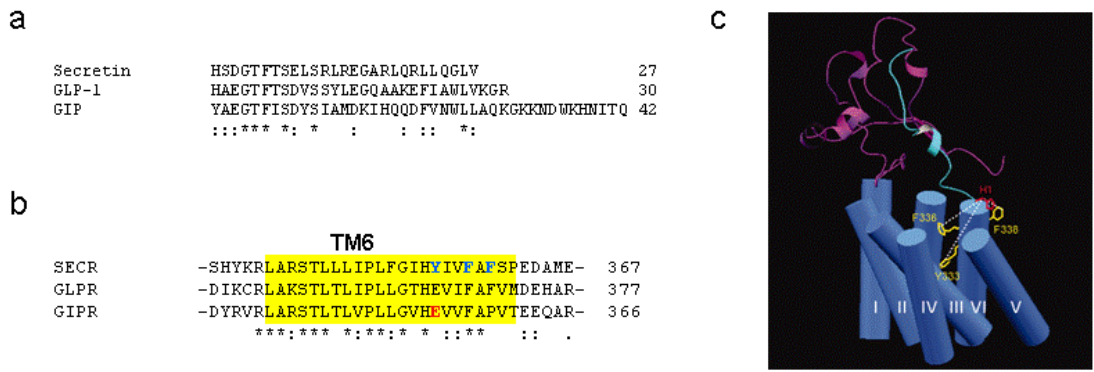
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Supplementary Figure 1. Carriers of the *GIPR* SNP had decreased *GIPR* mRNA (*GIPR* mRNA without adjustment for *PDX1*).



SUPPLEMENTARY DATA

Supplementary Figure 2. Comparison of G protein-coupled receptors.



A. Alignment of the peptide hormones secretin, GLP-1 and GIP. B. Alignment of the sequence containing TM6 (yellow box) in secretin receptor (SECR), GLP-1 receptor (GLPR) and GIP receptor (rs10423928 G allele). The variant position Glu/Gln354 in *GIPR* is colored red. The blue residues in SECR have been cross-linked to the N-terminus of bound secretin. C. Model showing the transmembrane helix arrangement of SECR and indicating the positions of residues which can be cross-linked to secretin (after M. Dong et al., JBC 2004).