Supplemental Table 1. Characteristics of the cohort.

	Hoorn*1		Utrecht*2,3		NTR*4	Germany*5	
	IGT	NGT	IGT	NGT	IGT	NGT	IGT
n	137	64	12	116	7	81	32
Sex (male/female)	64/73	15/49	4/8	58/58	0/7	33/48	14/18
Age (years)	60.5±8.6	45.9±6.4	49.5±7.7	31.5±6.5	31.2±3.2	36.7±12.6	45.9±13.3
BMI (kg m^{-2})	28.1±4.0	25.8±3.8	26.7±4.1	24.2±3.5	24.5±3.3	25.0±5.8	26.8±4.5
FPG (mmol/l)	6.3±0.7	4.6±0.4	5.1±0.4	4.6±0.4	4.6±0.6	5.0±0.6	5.5±0.7
FPI (pmol/l)	62 (46-91)	30 (24-42)	66 (42-78)	34 (27-51)	39 (29-60)	40 (30-60)	58 (39-95)
First-phase GSIS (pmol/l)	587 (378-895)	885 (644-1217)	678 (461-909)	814 (589-1162)	795 (693-1210)	667 (522-1148)	524 (416-922)
Second-phase GSIS (pmol/l)	255 (176-354)	260 (191-365)	251 (186-307)	218 (162-358)	217 (210-434)	229 (147-343)	196 (145-294)
ISI (μmol min^{-1} kg^{-1} $pmol^{-1}$ l^{-1})	0.11 (0.07-0.17)	0.19 (0.13-0.29)	0.11 (0.08-0.26)	0.23 (0.15-0.32)	0.12 (0.11-0.18)	0.15 (0.09-0.22)	0.11 (0.06-0.15)
DI (μmol min^{-1} kg^{-1})	65 (42-92)	172 (103-238)	72 (55-128)	180 (140-234)	138 (82-151)	109 (71-166)	62 (45-80)

Data are mean± SD, median (interquartile range) or *n*. *Original population from which the cohort originated [1-5]. FPG: fasting plasma glucose; FPI: fasting plasma insulin; GSIS: glucose-stimulated insulin secretion; ISI: insulin sensitivity index; DI: disposition index.

[1] Ruige JB, Dekker JM, Nijpels G, Popp-Snijders C, Stehouwer CD, Kostense PJ, et al. Hyperproinsulinaemia in impaired glucose tolerance is associated with a delayed insulin response to glucose. Diabetologia. 1999 Feb;42(2):177-80.

[2] van Haeften TW, Dubbeldam S, Zonderland ML, Erkelens DW. Insulin secretion in normal glucose-tolerant relatives of type 2 diabetic subjects. Assessments using hyperglycemic glucose clamps and oral glucose tolerance tests. Diabetes Care. 1998 Feb;21(2):278-82.

[3] van Haeften TW, Pimenta W, Mitrakou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, et al. Disturbances in beta-cell function in impaired fasting glycemia. Diabetes. 2002 Feb;51 Suppl 1:S265-70.

[4] Simonis-Bik AM, Eekhoff EM, Diamant M, Boomsma DI, Heine RJ, Dekker JM, et al. The heritability of HbA1c and fasting blood glucose in different measurement settings. Twin Res Hum Genet. 2008 Dec;11(6):597-602.

[5] Fritsche A, Madaus A, Renn W, Tschritter O, Teigeler A, Weisser M, et al. The prevalent Gly1057Asp polymorphism in the insulin receptor substrate-2 gene is not associated with impaired insulin secretion. J Clin Endocrinol Metab. 2001 Oct;86(10):4822-5.

Supplemental Table 2. Major inclusion criteria of the study cohort.

Cohort	Reference	Ethnicity	Age	Relatedness	Glucometabolic State	FDR T2DM
Hoorn	*1*	Caucasian	45-74	Unrelated	IGT	No
Utrecht	*2*	Caucasian	NA	Unrelated	NGT	Yes
	3	Caucasian	NA	Unrelated	NGT/IGT	No
NTR	*4*	Caucasian	20-50	Same sex twins and siblings	NGT and IGT	No
Tubingen	*5*	Caucasian	NA	Unrelated	NGT and IGT	No

Glucometabolic state was determined following an OGTT. FDR T2DM: first degree relative of patient with type 2 diabetes mellitus; IGT: impaired glucose tolerance; NA: not applicable; NTR: Netherlands Twin Registry; NGT: normal glucose tolerance.

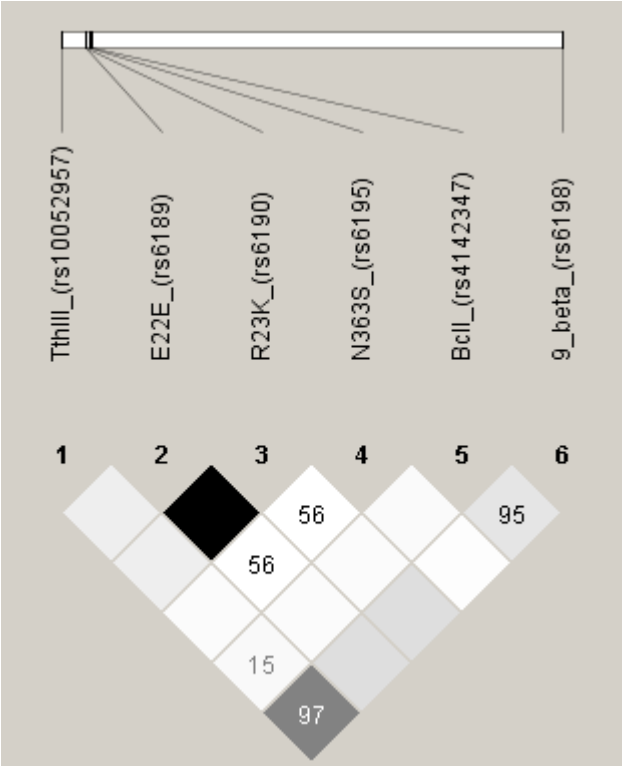
[1] Ruige JB, Dekker JM, Nijpels G, Popp-Snijders C, Stehouwer CD, Kostense PJ, et al. Hyperproinsulinaemia in impaired glucose tolerance is associated with a delayed insulin response to glucose. Diabetologia. 1999 Feb;42(2):177-80.
[2] van Haeften TW, Dubbeldam S, Zonderland ML, Erkelens DW. Insulin secretion in normal glucose-tolerant relatives of type 2 diabetic subjects. Assessments using hyperglycemic glucose clamps and oral glucose tolerance tests. Diabetes Care. 1998 Feb;21(2):278-82.
[3] van Haeften TW, Pimenta W, Mitrakou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, et al. Disturbances in beta-cell function in impaired fasting glycemia. Diabetes. 2002 Feb;51 Suppl 1:S265-70.
[4] Simonis-Bik AM, Eekhoff EM, Diamant M, Boomsma DI, Heine RJ, Dekker JM, et al. The heritability of HbA1c and fasting blood glucose in different measurement settings. Twin Res Hum Genet. 2008 Dec;11(6):597-602.
[5] Fritsche A, Madaus A, Renn W, Tschritter O, Teigeler A, Weisser M, et al. The prevalent Gly1057Asp polymorphism in the insulin receptor substrate-2 gene is not associated with impaired insulin secretion. J Clin Endocrinol Metab. 2001 Oct;86(10):4822-5.

Supplemental Table 3. Insulin response according to *NR3C1* haplotype in women and men.

		Women					Men			
Haplotype	n	First-phase GSIS (pmol/l)	Second-phase GSIS (pmol/l)	ISI (μmol min^{-1} kg^{-1} $pmol^{-1}$ l^{-1})	DI (μmol min^{-1} kg^{-1}	n	1^{st}-phase GSIS (pmol/l)	2^{nd}-phase GSIS (pmol/l)	ISI (μmol min^{-1} kg^{-1} $pmol^{-1}$ l^{-1})	DI (μmol min^{-1} kg^{-1}
Haplotype 1										
0	80	802 (721-892)	269 (245-294)	0.13 (0.11-0.15)	105 (94-118)	44	651 (552-768)	227 (200-257)	0.15 (0.12-0.18)	98 (86-116)
1	108	754 (693-821)	246 (227-267)	0.14 (0.13-0.16)	107 (98-116)	92	719 (641-807)	254 (233-276)	0.15 (0.14-0.17)	108 (96-123)
2	52	694 (625-772)	229 (205-257)	0.15 (0.13-0.16)	102 (91-115)	33	677 (570-804)	260 (226-300)	0.14 (0.12-0.17)	99 (83-119)
P		0.06	0.03	0.18	0.75		0.68	0.12	0.83	0.86
Haplotype 2										
0	148	716 (665-771)	240 (224-256)	0.14 (0.13-0.15)	100 (93-108)	114	706 (636-783)	245 (225-267)	0.15 (0.14-0.17)	106 (95-119)
1	81	811 (745-883)	263 (240-288)	0.14 (0.13-0.16)	112 (102-123)	53	660 (569-767)	245 (220-274)	0.15 (0.13-0.18)	101 (86-119)
2	11	937 (687-1278)	292 (238-357)	0.14 (0.09-0.21)	122 (92-163)	2	923 (763-1115)	418 (362-482)	0.06 (0.05-0.07)	79 (59-106)
P		0.02	0.03	0.74	0.04		0.65	0.54	0.71	0.45
Haplotype 3										
0	163	730 (684-780)	247 (232-264)	0.14 (0.13-0.15)	104 (97-111)	126	698 (634-768)	250 (232-269)	0.15 (0.13-0.17)	104 (93-116)
1	73	807 (720-904)	252 (229-278)	0.13 (0.12-0.15)	108 (95-122)	37	654 (537-797)	246 (212-284)	0.16 (0.13-0.19)	102 (83-125)
2	4	889 (731-1081)	306 (183-512)	0.12 (0.06-0.21)	109 (72-165)	6	835 (689-1012)	232 (200-270)	0.16 (0.09-0.26)	117 (88-156)
P		0.08	0.51	0.30	0.58		0.98	0.63	0.70	0.87
Haplotype 4										
0	189	756 (711-804)	253 (238-268)	0.14 (0.13-0.15)	104 (97-111)	124	711 (645-784)	258 (241-278)	0.15 (0.13-0.17)	106 (95-118)
1	47	781 (681-895)	241 (218-268)	0.15 (0.13-0.17)	113 (98-130)	40	633 (535-748)	215 (188-246)	0.16 (0.13-0.19)	99 (84-116)
2	4	488 (312-762)	198 (131-300)	0.14 (0.09-0.20)	70 (45-109)	5	772 (541-1101)	257 (186-355)	0.13 (0.07-0.25)	98 (66-145)
P		0.58	0.23	0.37	0.96		0.45	0.06	0.95	0.44
Haplotype 5										
0	223	767 (724-813)	248 (235-263)	0.14 (0.13-0.15)	108 (101-115)	161	696 (637-760)	249 (232-267)	0.15 (0.13-0.17)	103 (94-114)
1	17	614 (515-760)	264 (226-308)	0.11 (0.09-0.14)	74 (62-88)	8	658 (553-783)	229 (191-274)	0.20 (0.14-0.29)	118 (91-154)
P		0.02	0.47	0.04	**0.0001**		0.53	0.38	0.13	0.33
Haplotype 6										
0	231	764 (722-808)	248 (235-262)	0.14 (0.13-0.15)	106 (100-113)	155	690 (632-754)	249 (232-266)	0.15 (0.14-0.17)	104 (94-114)
1	9	518 (386-694)	294 (205-420)	0.10 (0.08-0.14)	68 (51-90)	14	751 (595-947)	240 (210-274)	0.14 (0.10-0.17)	106 (78-144)
P		**0.011**	0.36	0.04	**0.003**		0.49	0.62	0.49	0.87

For the haplotypes dummy variables indicating 0, 1 and 2 copies of each haplotype allele are shown. Data are estimated means (95% CI) unless otherwise indicated. All variables were log transformed before analysis. *P* values were computed for additive models using linear generalized estimating equations, which takes into account the family relatedness when computing the standard errors. First- and second-phase GSIS were adjusted for study center, family relatedness, glucose tolerance status, age, BMI and ISI. ISI and DI were adjusted for study center, family relatedness, glucose tolerance status, age and BMI. GSIS: glucose-stimulated insulin secretion; ISI: insulin sensitivity index.

Supplementary Figure 1



Pairwise Linkage Disequilibrium (LD) values between the SNP quantified using r^2 in the Haploview program are indicated. Black color indicates full linkage disequilibrium, lower shades of gray indicate lower LD and white color indicates no LD.