

SUPPLEMENTARY DATA

***TCF7L2* genotype and α -cell function in nondiabetic humans**

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Running title: *TCF7L2* genotype and islet function

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Keywords: - *TCF7L2*, insulin secretion, insulin action, glucagon, β -cell function, Disposition Index, hyperbolic correction, α -cell function, acute insulin resistance

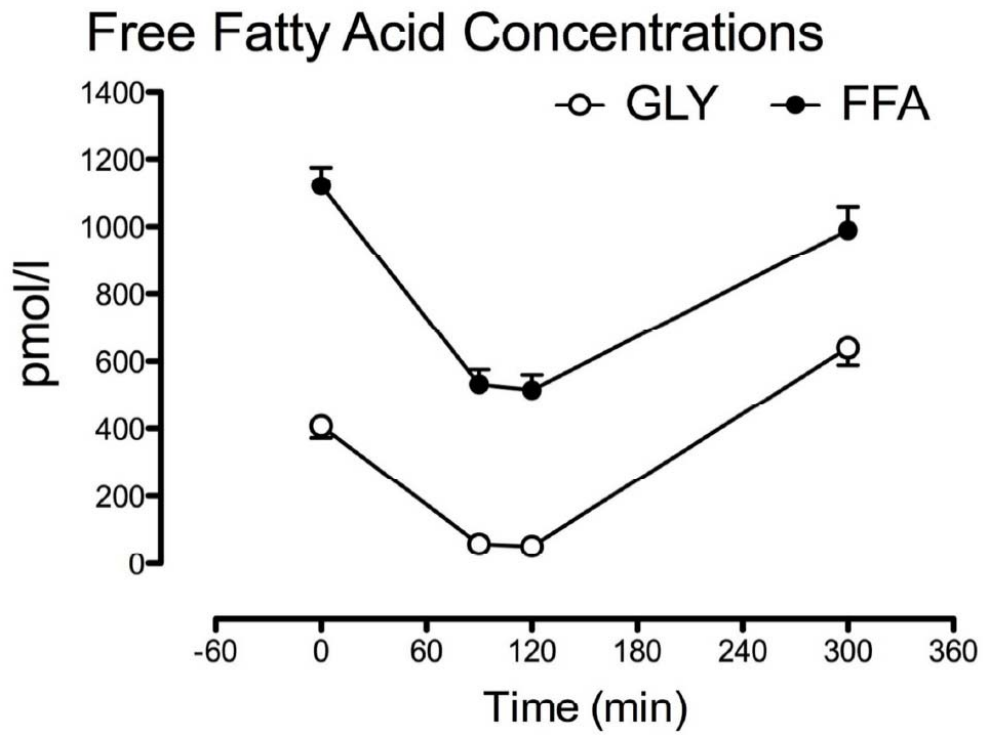
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Supplementary Table 1. Glucose, Insulin, C-Peptide and Glucagon concentrations in each genotype group. Values reported are Means \pm SEM. *P*-Value reports the result of an unpaired, two-tailed t-test.

	CC	TT	<i>P</i> -value
Screening 75g 2 hour OGTT			
Fasting Glucose (mmol/l)	5.4 \pm 0.1	5.4 \pm 0.1	0.77
Peak Glucose (mmol/l)	10.1 \pm 0.2	10.9 \pm 0.2	0.009
AAB Glucose (mmol per 2h)	356 \pm 15	431 \pm 19	0.003
Fasting Insulin (pmol/l)	30 \pm 3	26 \pm 2	0.19
Peak Insulin (pmol/l)	386 \pm 30	336 \pm 21	0.17
AAB Insulin (nmol per 2h)	23.8 \pm 1.7	22.7 \pm 1.5	0.63
Fasting C-Peptide (nmol/l)	0.68 \pm 0.03	0.69 \pm 0.03	0.90
Peak C-Peptide (nmol/l)	3.52 \pm 0.16	3.57 \pm 0.13	0.82
AAB C-Peptide (nmol per 2h)	229 \pm 10	232 \pm 9	0.84
Fasting Glucagon (ng/l)	83 \pm 3	83 \pm 2	0.85
Nadir Glucagon (ng/l)	64 \pm 2	60 \pm 2	0.12
AAB Glucagon (ng per 2h)	-1107 \pm 159	-1610 \pm 180	0.04
1g/Kg 6 hour oral glucose challenge + glycerol infusion			
Fasting Glucose (mmol/l)	5.2 \pm 0.04	5.3 \pm 0.05	0.78
Peak Glucose (mmol/l)	10.1 \pm 0.2	10.6 \pm 0.2	0.06
AAB Glucose (mmol per 6h)	368 \pm 23	406 \pm 23	0.24
Fasting Insulin (pmol/l)	29 \pm 2	30 \pm 2	0.84
Peak Insulin (pmol/l)	375 \pm 24	380 \pm 26	0.82
AAB Insulin (nmol per 6h)	204 \pm 16	214 \pm 18	0.67
Fasting C-Peptide (nmol/l)	0.67 \pm 0.02	0.71 \pm 0.03	0.28
Peak C-Peptide (nmol/l)	3.46 \pm 0.12	3.58 \pm 0.15	0.54
AAB C-Peptide (nmol per 6h)	383 \pm 19	415 \pm 23	0.29
Fasting Glucagon (ng/l)	71 \pm 3	73 \pm 3	0.62
Nadir Glucagon (ng/l)	51 \pm 2	53 \pm 2	0.52
AAB Glucagon (ng per 6h)	-1980 \pm 396	-1938 \pm 420	0.93
1g/Kg 6 hour oral glucose challenge + intralipid + heparin infusion			
Fasting Glucose (mmol/l)	5.1 \pm 0.04	5.2 \pm 0.07	0.42
Peak Glucose (mmol/l)	10.5 \pm 0.2	11.0 \pm 0.3	0.09
AAB Glucose (mmol per 6h)	522 \pm 22	554 \pm 29	0.39
Fasting Insulin (pmol/l)	39 \pm 3	39 \pm 4	0.91
Peak Insulin (pmol/l)	467 \pm 38	446 \pm 33	0.69
AAB Insulin (nmol per 6h)	285 \pm 26	274 \pm 23	0.76
Fasting C-Peptide (nmol/l)	0.78 \pm 0.03	0.81 \pm 0.04	0.56
Peak C-Peptide (nmol/l)	3.92 \pm 0.15	3.90 \pm 0.16	0.91
AAB C-Peptide (nmol per 6h)	482 \pm 23	477 \pm 26	0.97
Fasting Glucagon (ng/l)	76 \pm 3	81 \pm 3	0.25
Nadir Glucagon (ng/l)	52 \pm 2	59 \pm 2	0.04
AAB Glucagon (ng per 6h)	-3310 \pm 552	-3613 \pm 547	0.10

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Supplementary Figure 1. Free fatty acid concentrations (Panel A) during glycerol infusion (open circles) and during intralipid and heparin infusion (solid circles).



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Supplementary Table 2. Glucose, Insulin, C-Peptide and Glucagon concentrations during glycerol (Glycerol) and intralipid and heparin infusion (FFA) in each genotype group. #P-Value for an unpaired, two-tailed t-test of symmetrical percent change (Glycerol vs. FFA) in each group. The other p-values represent results of a paired, two-tailed t-test.

	CC		TT		#P-value
	Glycerol	FFA	Glycerol	FFA	
Fasting Glucose (mmol/l)	5.2 ± 0.04	5.1 ± 0.04	5.3 ± 0.05	5.2 ± 0.07	0.42
	$p < 1.0 \times 10^{-4}$		$p = 0.04$		
Peak Glucose (mmol/l)	10.1 ± 0.2	10.5 ± 0.2	10.6 ± 0.2	11.0 ± 0.3	0.79
	$p = 0.01$		$p = 0.02$		
AAB Glucose (mmol per 6h)	368 ± 23	522 ± 22	406 ± 23	554 ± 29	0.20
	$p < 1.0 \times 10^{-4}$		$p = 0.01$		
Fasting Insulin (pmol/l)	29 ± 2	39 ± 3	30 ± 2	39 ± 4	0.73
	$p < 1.0 \times 10^{-4}$		$p = 0.01$		
Peak Insulin (pmol/l)	375 ± 24	467 ± 38	380 ± 26	446 ± 33	0.67
	$p < 1.0 \times 10^{-4}$		$p = 4.0 \times 10^{-3}$		
AAB Insulin (nmol per 6h)	204 ± 16	285 ± 26	214 ± 18	274 ± 23	0.26
	$p < 1.0 \times 10^{-4}$		$p < 1.0 \times 10^{-4}$		
Fasting C-Peptide (nmol/l)	0.67 ± 0.02	0.78 ± 0.03	0.71 ± 0.03	0.81 ± 0.04	0.36
	$p < 1.0 \times 10^{-4}$		$p < 1.0 \times 10^{-4}$		
Peak C-Peptide (nmol/l)	3.46 ± 0.12	3.92 ± 0.15	3.58 ± 0.15	3.90 ± 0.16	0.31
	$p < 1.0 \times 10^{-4}$		$p = 2.0 \times 10^{-3}$		
AAB C-Peptide (nmol per 6h)	383 ± 19	482 ± 23	415 ± 23	477 ± 26	0.18
	$p < 1.0 \times 10^{-4}$		$p = 2.5 \times 10^{-4}$		
Fasting Glucagon (ng/l)	71 ± 3	76 ± 3	73 ± 3	81 ± 3	8.0×10^{-3}
	$p = 2.0 \times 10^{-3}$		$p < 1.0 \times 10^{-4}$		
Nadir Glucagon (ng/l)	51 ± 2	52 ± 2	53 ± 2	59 ± 2	0.46
	$p = 0.47$		$p < 1.0 \times 10^{-4}$		
AAB Glucagon (ng per 6h)	-1980 ± 396	-3310 ± 552	-1938 ± 420	-3613 ± 547	0.13
	$p = 8.0 \times 10^{-3}$		$p = 8.3 \times 10^{-4}$		

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Supplementary Table 3. Indices of insulin secretion and action in each genotype group. Corrected insulin secretion represents $\{(\text{Insulin}_{30\text{min}} - \text{Insulin}_{0\text{min}}) / (\text{Glucose}_{30\text{min}} - \text{Glucose}_{0\text{min}})\}$. Values reported are Means \pm SEM. *P*-Value reports the result of an unpaired, two-tailed t-test.

	CC	TT	<i>P</i> -value
Screening 75g 2 hour OGTT			
Corrected Insulin Secretion (pmol/l ÷ mmol/l)	71 \pm 7	54 \pm 5	0.03
S_i (10^{-4} dl/kg/min per $\mu\text{U/ml}$)	18 \pm 2	18 \pm 2	0.86
ϕ_{dynamic} (10^{-9})	796 \pm 51	653 \pm 42	0.03
ϕ_{static} (10^{-9} min^{-1})	46 \pm 2	41 \pm 2	0.08
ϕ (10^{-9} min^{-1})	55 \pm 3	48 \pm 2	0.03
1g/Kg 6 hour oral glucose challenge + glycerol infusion			
Corrected Insulin Secretion (pmol/l ÷ mmol/l)	72 \pm 6	61 \pm 5	0.16
S_i (10^{-4} dl/kg/min per $\mu\text{U/ml}$)	18 \pm 1	19 \pm 2	0.66
ϕ_{dynamic} (10^{-9})	717 \pm 48	617 \pm 30	0.08
ϕ_{static} (10^{-9} min^{-1})	42 \pm 2	41 \pm 2	0.44
ϕ (10^{-9} min^{-1})	55 \pm 3	50 \pm 2	0.13
1g/Kg 6 hour oral glucose challenge + intralipid + heparin infusion			
Corrected Insulin Secretion (pmol/l ÷ mmol/l)	79 \pm 7	69 \pm 6	0.29
S_i (10^{-4} dl/kg/min per $\mu\text{U/ml}$)	13 \pm 1	13 \pm 1	0.85
ϕ_{dynamic} (10^{-9})	783 \pm 52	639 \pm 39	0.02
ϕ_{static} (10^{-9} min^{-1})	42 \pm 2	36 \pm 2	0.02
ϕ (10^{-9} min^{-1})	50 \pm 3	42 \pm 2	0.02

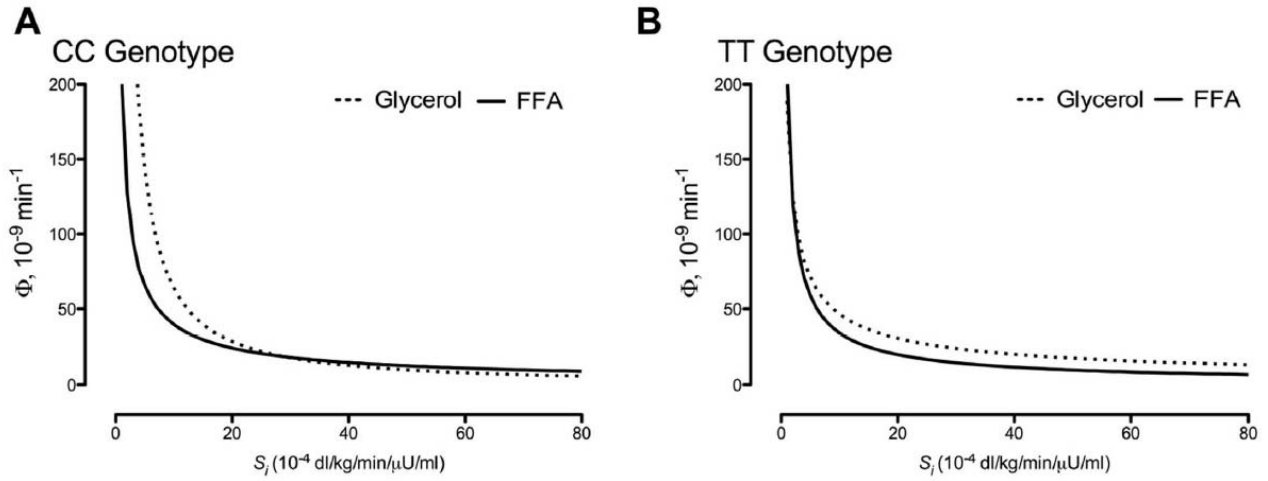
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Supplementary Table 4.Indices of insulin secretion and action during glycerol (Glycerol) and intralipid and heparin infusion (FFA) in each genotype group. [#]*P*-Value for an unpaired, two-tailed t-test of symmetrical percent change (Glycerol vs. FFA) in each group. The other *p*-values represent results of a paired, two-tailed t-test.

	CC		TT		[#] <i>P</i> -value
	Glycerol	FFA	Glycerol	FFA	
S_i (10^{-4} dl/kg/min per μ U/ml)	18 \pm 1	13 \pm 1	19 \pm 2	13 \pm 1	0.54
	$p < 1 \times 10^{-4}$		$p < 1 \times 10^{-4}$		
ϕ_{dynamic} (10^{-9})	717 \pm 48	783 \pm 52	617 \pm 30	639 \pm 39	0.65
	$p = 0.08$		$p = 0.51$		
ϕ_{static} (10^{-9} min ⁻¹)	42 \pm 2	42 \pm 2	41 \pm 2	36 \pm 2	0.05
	$p = 0.23$		$p = 3.0 \times 10^{-3}$		
ϕ (10^{-9} min ⁻¹)	55 \pm 3	50 \pm 3	50 \pm 2	42 \pm 2	0.08
	$p = 0.07$		$p = 2.9 \times 10^{-4}$		

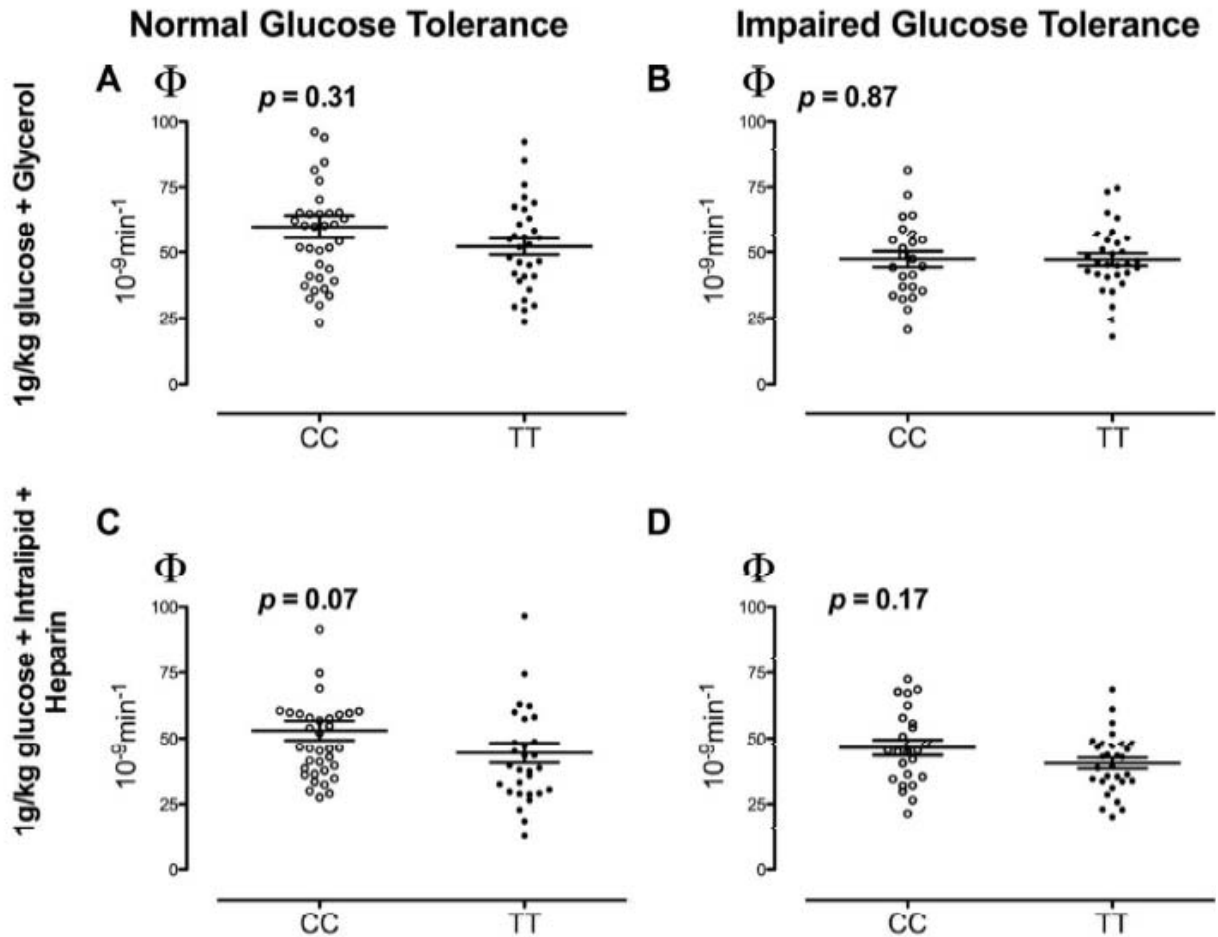
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Supplementary Figure 2. The relationship of insulin action (S_i) with β -cell responsivity (Φ) in subjects with the CC genotype at *TCF7L2* (Panel A) and in subjects with the TT genotype at *TCF7L2* (Panel B) during glycerol infusion (dashed line) and during FFA elevation (solid line).



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Supplementary Figure 3. Insulin concentrations in response to 1g/kg oral glucose challenge during glycerol (Panels A, B) and during intralipid and heparin (Panels C, D) infusion in subjects with normal (Panels A and C) and impaired (Panels B and C) glucose tolerance at the time of screening OGTT. Subjects with the CC genotype are represented by open circles and subjects with the TT genotype by solid circles. Values plotted are Means \pm SEMs. * $P < 0.05$ for a *post hoc* unpaired, two-tailed t-test.



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Supplementary Figure 4. β -cell responsivity in response to 1g/kg oral glucose challenge during glycerol (Panels A, B) and during intralipid and heparin (Panels C, D) infusion in subjects with normal (Panels A and C) and impaired (Panels B and D) glucose tolerance at the time of screening OGTT. Subjects with the CC genotype are represented by open circles and subjects with the TT genotype by solid circles.

