Supplementary Figure 1.

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A

PPARG P12A

PA/AA

r=0.62

PP

r=0.57

B

Log AUC ins$_{OGTT}$

Log GIP 120 min (pg/ml)
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.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotypes</th>
<th>Converters n (%)</th>
<th>Non-converters n (%)</th>
<th>OR (95%CI) P</th>
<th>Converters n (%)</th>
<th>Non-converters n (%)</th>
<th>OR (95%CI) P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malmoe Prospective study</td>
<td></td>
<td>Botnia Prospective Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7903146</td>
<td>CC</td>
<td>637 (45.9)</td>
<td>3102 (56.2)</td>
<td>1</td>
<td>82 (54.7)</td>
<td>1603 (64.4)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>634 (45.6)</td>
<td>2051 (37.1)</td>
<td>1.57 (1.37-1.80)</td>
<td>10 x 10^-11</td>
<td>58 (38.7)</td>
<td>796 (32.0)</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>118 (8.5)</td>
<td>368 (6.7)</td>
<td>1.47 (1.15-1.89)</td>
<td>0.002</td>
<td>10 (6.7)</td>
<td>92 (3.7)</td>
</tr>
<tr>
<td></td>
<td>CC vs. CT/TT</td>
<td>752 (54.1)</td>
<td>2419 (43.8)</td>
<td>1.58 (1.38-1.81)</td>
<td>5 x 10^-12</td>
<td>68 (45.3)</td>
<td>888 (35.6)</td>
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<td>T</td>
<td>870 (31.3)</td>
<td>2787 (25.2)</td>
<td>1.35 (1.23-1.48)</td>
<td>1.4 x 10^-11</td>
<td>78 (26.0)</td>
<td>980 (19.7)</td>
</tr>
<tr>
<td>rs12255372</td>
<td>GG</td>
<td>596 (44.8)</td>
<td>2803 (53.2)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>616 (46.2)</td>
<td>2073 (39.4)</td>
<td>1.42 (1.23-1.63)</td>
<td>8.3 x 10^-7</td>
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<tr>
<td></td>
<td>TT</td>
<td>120 (9.0)</td>
<td>392 (7.4)</td>
<td>1.44 (1.13-1.84)</td>
<td>0.003</td>
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</tr>
<tr>
<td></td>
<td>GG vs. GT/TT</td>
<td>736 (55.3)</td>
<td>2465 (46.8)</td>
<td>1.42 (1.24-1.62)</td>
<td>2.1 x 10^-7</td>
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<tr>
<td></td>
<td>T</td>
<td>856 (32.0)</td>
<td>2857 (27.1)</td>
<td>1.27 (1.16-1.40)</td>
<td>2.7 x 10^-7</td>
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Supplementary Table 1B. The combination of alleles of TCF7L2 SNPs rs7903146 and rs1088540 in the Botnia study.

<table>
<thead>
<tr>
<th>rs1088540</th>
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<td>CC</td>
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<tr>
<td>TT</td>
<td></td>
</tr>
<tr>
<td>GG</td>
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</tr>
<tr>
<td>GA</td>
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</tr>
<tr>
<td>AA</td>
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<table>
<thead>
<tr>
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<th>rs7903146</th>
</tr>
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<tbody>
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<tr>
<td></td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>TT</td>
</tr>
<tr>
<td>GG</td>
<td>128</td>
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<td>GA</td>
<td>653</td>
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<td>AA</td>
<td>869</td>
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<td>CT</td>
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<td>GA</td>
<td>587</td>
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<tr>
<td>AA</td>
<td>2</td>
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</table>

The T allele of rs7903146 and G allele of rs1088540 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.

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

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 Malmo and Botnia prospective studies.

<table>
<thead>
<tr>
<th></th>
<th>Malmo</th>
<th></th>
<th>Botnia</th>
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<tbody>
<tr>
<td></td>
<td>CC</td>
<td>CT</td>
<td>TT</td>
<td>CT/TT</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>46.5±5.8 (3739)</td>
<td>46.5±5.8 (2685)</td>
<td>46.0±5.9 (486)</td>
<td>46.4±5.8 (3171)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5±3.5 (3737)</td>
<td>24.5±3.4 (2685)</td>
<td>24.4±3.3 (486)</td>
<td>24.5±3.4 (3170)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>4.9±0.5 (3739)</td>
<td>4.9±0.5 (2685)</td>
<td>4.9±0.5 (486)</td>
<td>4.9±0.5 (3171)</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>2hr glucose</td>
<td>5.8±1.5 (2249)</td>
<td>5.8±1.5 (1613)</td>
<td>5.9±1.6 (275)</td>
<td>5.8±1.5 (1888)</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>10.2±5.3 (557)</td>
<td>9.2±5.5 (413)</td>
<td>9.5±4.9 (68)</td>
<td>9.3±5.5 (481)</td>
</tr>
<tr>
<td>(mU/mmol)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Disposition index</td>
<td>8.1±6.2 (557)</td>
<td>7.2±5.4 (413)</td>
<td>7.1±6.2 (68)</td>
<td>7.1±5.5 (481)</td>
</tr>
<tr>
<td>(mU/l²)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>HOMA (mmol · mU/l²)</td>
<td>1.9±1.5 (840)</td>
<td>2.1±2.9 (592)</td>
<td>2.2±2.2 (104)</td>
<td>2.1±2.8 (696)</td>
</tr>
<tr>
<td>Leptin (µg/l)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Men</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Women</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NGT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>45.4±5.3 (2863)</td>
<td>45.4±5.2 (2003)</td>
<td>44.9±5.2 (352)</td>
<td>45.3±5.2 (2355)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2±3.3 (2862)</td>
<td>24.2±3.2 (2003)</td>
<td>24.2±3.1 (351)</td>
<td>24.2±3.2 (2354)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>4.8±0.4 (2863)</td>
<td>4.8±0.4 (2003)</td>
<td>4.8±0.4 (352)</td>
<td>4.8±0.4 (2355)</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>2hr glucose</td>
<td>5.0±1.0 (1515)</td>
<td>5.0±1.0 (1054)</td>
<td>5.0±1.0 (169)</td>
<td>5.0±1.0 (1223)</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>10.4±5.3 (420)</td>
<td>9.5±5.4 (289)</td>
<td>9.8±4.7 (42)</td>
<td>9.5±5.3 (331)</td>
</tr>
<tr>
<td>(mU/mmol)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Disposition index</td>
<td>8.9±6.5 (420)</td>
<td>7.9±5.6 (289)</td>
<td>8.3±7.1 (42)</td>
<td>8.0±5.8 (331)</td>
</tr>
<tr>
<td>(mU/l²)</td>
<td>24.2</td>
<td>24.5</td>
<td>24.4</td>
<td>24.5</td>
</tr>
<tr>
<td>HOMA (mmol · mU/l²)</td>
<td>1.6±1.2 (620)</td>
<td>2.0±3.2 (415)</td>
<td>1.9±1.9 (71)</td>
<td>2.0±3.0 (486)</td>
</tr>
<tr>
<td>Leptin (µg/l)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IFG/IGT</td>
<td>Age (yrs)</td>
<td>BMI (kg/m²)</td>
<td>Fasting glucose (mmol/l)</td>
<td>2hr glucose (mmol/l)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>50.3±5.9 (876)</td>
<td>25.4±3.9 (875)</td>
<td>5.2±0.5 (876)</td>
<td>7.3±1.1 (734)</td>
</tr>
<tr>
<td></td>
<td>49.9±6.0 (682)</td>
<td>25.5±3.7 (682)</td>
<td>5.2±0.5 (682)</td>
<td>7.3±1.2 (559)</td>
</tr>
<tr>
<td></td>
<td>48.9±6.4 (134)</td>
<td>24.9±3.8 (134)</td>
<td>5.3±0.5 (134)</td>
<td>7.4±1.3 (106)</td>
</tr>
<tr>
<td></td>
<td>49.7±6.1 (816)</td>
<td>25.4±3.7 (816)</td>
<td>5.2±0.5 (816)</td>
<td>7.3±1.2 (665)</td>
</tr>
<tr>
<td></td>
<td>48.9±12.9 (396)</td>
<td>27.2±4.6 (395)</td>
<td>6.0±0.6 (395)</td>
<td>7.9±1.4 (392)</td>
</tr>
<tr>
<td></td>
<td>49.1±13.1 (231)</td>
<td>27.5±4.1 (228)</td>
<td>6.0±0.6 (229)</td>
<td>8.1±1.4 (222)</td>
</tr>
<tr>
<td></td>
<td>48.0±15.0 (29)</td>
<td>25.6±4.2 (29)</td>
<td>5.9±0.7 (29)</td>
<td>8.2±1.6 (29)</td>
</tr>
<tr>
<td></td>
<td>49.0±13.3 (26)</td>
<td>27.3±4.2 (257)</td>
<td>6.0±0.6 (258)</td>
<td>8.1±1.4 (251)</td>
</tr>
</tbody>
</table>

*P=0.002 between CC, CT and TT; and P=0.0006 between CC vs. CT/TT
bP=0.02 between CC, CT and TT; and P=0.005 between CC vs. CT/TT
cP=0.02 between CC, CT and TT; and P=0.006 between CC vs. CT/TT
dP=0.02 between CC vs. CT/TT
eP=0.004 between CC, CT and TT
fP=0.006 between CC, CT and TT; and P=0.002 between CC vs. CT/TT
gP=1.9x10⁻⁵ between CC, CT and TT; and P=2.6x10⁻⁵ between CC vs. CT/TT
hP=0.02 between CC, CT and TT
iP=0.005 between CC, CT and TT; and P=0.006 between CC vs. CT/TT
jP=0.006 between CC, CT and TT; and P=0.004 between CC vs. CT/TT
kP=0.02 between CC, CT and TT; and P=0.009 between CC vs. CT/TT
lP=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.

<table>
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<tr>
<th></th>
<th>HapA</th>
<th>HapAB</th>
<th>HapB</th>
</tr>
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<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>45.1±13.6 (1453)</td>
<td>44.9±13.8 (555)</td>
<td>45.9±14.0 (330)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7±4.2 (1449)</td>
<td>25.8±3.7 (553)</td>
<td>25.5±4.2 (326)</td>
</tr>
<tr>
<td>Fasting P-glucose (mmol/l)</td>
<td>5.5±0.6 (1453)</td>
<td>5.6±0.6 (555)</td>
<td>5.6±0.6 (330)</td>
</tr>
<tr>
<td>2hr P-glucose (mmol/l)</td>
<td>6.1±1.5 (1413)</td>
<td>6.3±1.5 (536)</td>
<td>6.4±1.6 (323)</td>
</tr>
<tr>
<td>Insulinogenic index (mU/mmol)</td>
<td>5.4±4.3 (1395)</td>
<td>5.0±3.9 (527)</td>
<td>5.2±3.9 (315)</td>
</tr>
<tr>
<td>Disposition index (mU²/l²)</td>
<td>4.8±3.7 (1395)</td>
<td>4.4±3.6 (527)</td>
<td>4.6±3.6 (315)</td>
</tr>
<tr>
<td>HOMA (mmol · mU/l²)</td>
<td>1.3±1.0 (1453)</td>
<td>1.3±0.8 (555)</td>
<td>1.4±1.0 (330)</td>
</tr>
<tr>
<td>Leptin (µg/l)</td>
<td>Men: 4.7±3.1 (285)</td>
<td>5.3±3.9 (136)</td>
<td>5.6±3.4 (53)</td>
</tr>
<tr>
<td></td>
<td>Women: 15.8±10.1 (318)</td>
<td>18.0±12.4 (103)</td>
<td>17.0±12.7 (74)</td>
</tr>
<tr>
<td><strong>NGT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>43.6±13.7 (1107)</td>
<td>43.6±13.9 (405)</td>
<td>44.2±14.1 (240)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2±3.9 (1103)</td>
<td>25.2±3.5 (403)</td>
<td>24.9±3.7 (236)</td>
</tr>
<tr>
<td>Fasting P-glucose (mmol/l)</td>
<td>5.4±0.5 (1107)</td>
<td>5.4±0.5 (405)</td>
<td>5.4±0.5 (240)</td>
</tr>
<tr>
<td>2hr P-glucose (mmol/l)</td>
<td>5.6±1.0 (1069)</td>
<td>5.7±1.0 (389)</td>
<td>5.7±1.0 (233)</td>
</tr>
<tr>
<td>Insulinogenic index (mU/mmol)</td>
<td>5.3±4.2 (1058)</td>
<td>5.0±4.0 (383)</td>
<td>5.3±3.9 (228)</td>
</tr>
<tr>
<td>Disposition index (mU²/l²)</td>
<td>5.2±3.8 (1058)</td>
<td>4.8±3.9 (383)</td>
<td>5.2±3.8 (228)</td>
</tr>
<tr>
<td>HOMA (mmol · mU/l²)</td>
<td>1.2±0.7 (1107)</td>
<td>1.2±0.6 (405)</td>
<td>1.2±0.9 (240)</td>
</tr>
<tr>
<td>Leptin (µg/l)</td>
<td>Men: 4.4±3.2 (199)</td>
<td>4.5±2.6 (90)</td>
<td>5.5±3.7 (38)</td>
</tr>
<tr>
<td></td>
<td>Women: 14.0±7.7 (232)</td>
<td>16.3±10.5 (75)</td>
<td>15.1±9.4 (52)</td>
</tr>
<tr>
<td><strong>IFG/IGT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>49.9±12.3 (346)</td>
<td>48.4±13.1 (150)</td>
<td>50.6±12.8 (90)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2±4.6 (346)</td>
<td>27.2±3.8 (150)</td>
<td>27.2±4.8 (90)</td>
</tr>
<tr>
<td>Fasting P-glucose (mmol/l)</td>
<td>6.0±0.6 (346)</td>
<td>6.0±0.6 (150)</td>
<td>6.0±0.6 (90)</td>
</tr>
<tr>
<td>2hr P-glucose (mmol/l)</td>
<td>7.9±1.4 (344)</td>
<td>8.0±1.3 (147)</td>
<td>8.3±1.5 (90)</td>
</tr>
<tr>
<td>Insulinogenic index (mU/mmol)</td>
<td>5.6±4.5 (337)</td>
<td>4.9±3.7 (144)</td>
<td>4.7±4.1 (87)</td>
</tr>
<tr>
<td>Disposition index (mU²/l²)</td>
<td>3.5±3.1 (337)</td>
<td>3.3±2.3 (144)</td>
<td>3.0±2.2 (87)</td>
</tr>
<tr>
<td>HOMA (mmol · mU/l²)</td>
<td>1.9±1.4 (346)</td>
<td>1.7±1.1 (150)</td>
<td>1.9±1.3 (90)</td>
</tr>
<tr>
<td>Leptin (µg/l)</td>
<td>Men: 5.4±2.6 (69)</td>
<td>7.0±5.2 (46)</td>
<td>5.7±2.7 (15)</td>
</tr>
<tr>
<td></td>
<td>Women: 20.6±13.7 (86)</td>
<td>22.7±15.7 (28)</td>
<td>21.6±17.7 (22)</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th></th>
<th>rs7903146</th>
<th>Haplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT</td>
<td>HapA</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>63.1 ± 7.3</td>
<td>61.5 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>(51)</td>
<td>(28)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>27.1 ± 3.6</td>
<td>24.9 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>(51)</td>
<td>(28)</td>
</tr>
<tr>
<td><strong>E8G basal</strong></td>
<td>5.4 ± 0.5</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>(mU/l)</td>
<td>(51)</td>
<td>(29)</td>
</tr>
<tr>
<td><strong>AIR</strong> (mmol/l)</td>
<td>36.3 ± 19.1</td>
<td>33.1 ± 16.3</td>
</tr>
<tr>
<td></td>
<td>(47)</td>
<td>(23)</td>
</tr>
<tr>
<td>**AIR2 (mmol/l)</td>
<td>110.9 ± 67.0</td>
<td>106.4 ± 55.6</td>
</tr>
<tr>
<td></td>
<td>(47)</td>
<td>(23)</td>
</tr>
<tr>
<td>**AIR3 (mmol/l)</td>
<td>148.0 ± 81.1</td>
<td>136.7 ± 75.1</td>
</tr>
<tr>
<td></td>
<td>(47)</td>
<td>(23)</td>
</tr>
<tr>
<td><strong>E8G basal</strong></td>
<td>2.8 ± 0.3</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>(mg.lbm⁻¹.min⁻¹)</td>
<td>(25)</td>
<td>(13)</td>
</tr>
<tr>
<td><strong>AIR</strong> (mmol/l)</td>
<td>5.3 ± 2.3</td>
<td>6.3 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>(35)</td>
<td>(18)</td>
</tr>
</tbody>
</table>

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

*P<0.05 between CC, CT/TT carriers; and for comparison between HapA, HapAB and HapB

*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.

<table>
<thead>
<tr>
<th>rs7903146 Haplotypes</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>CT/TT</th>
<th>HapA</th>
<th>HapAB</th>
<th>HapB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>45.6±12.6 (373)</td>
<td>47.6±12.8 (211)</td>
<td>48.0±14.1 (23)</td>
<td>47.7±12.9 (234)</td>
<td>45.5±12.5 (342)</td>
<td>46.8±13.9 (142)</td>
<td>49.2±11.4 (83)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>25.8±3.8 (373)</td>
<td>26.1±4.0 (211)</td>
<td>25.3±3.4 (23)</td>
<td>26.0±3.9 (234)</td>
<td>25.8±3.8 (342)</td>
<td>26.0±4.0 (142)</td>
<td>25.8±3.5 (83)</td>
</tr>
<tr>
<td><strong>Fasting glucose (mmol/l)</strong></td>
<td>5.4±0.7 (374)</td>
<td>5.5±0.6 (211)</td>
<td>5.4±0.5 (23)</td>
<td>5.5±0.6 (234)</td>
<td>5.4±0.7 (342)</td>
<td>5.6±0.6 (142)</td>
<td>5.4±0.6 (83)</td>
</tr>
<tr>
<td><strong>2-hr glucose (mmol/l)</strong></td>
<td>6.0±1.7 (373)</td>
<td>6.0±1.6 (210)</td>
<td>6.2±1.5 (23)</td>
<td>6.0±1.6 (233)</td>
<td>6.0±1.6 (343)</td>
<td>6.1±1.6 (141)</td>
<td>5.9±1.6 (83)</td>
</tr>
<tr>
<td><strong>Incretin effect</strong></td>
<td>47.6±7.3292.6 (364)</td>
<td>5989.8±3997.6 (206)</td>
<td>5006.6±2099.7 (23)</td>
<td>5609.2±3855.6 (229)</td>
<td>5577.7±3241.7 (335)</td>
<td>6113.6±4304.9 (137)</td>
<td>5102.9±2619.6 (83)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>1068.4±707.0 (251)</td>
<td>1146.5±774.7 (145)</td>
<td>921.0±381.8 (16)</td>
<td>1124.1±747.3 (161)</td>
<td>1061.9±707.2 (228)</td>
<td>1169.4±777.7 (95)</td>
<td>1010.2±657.0 (60)</td>
</tr>
<tr>
<td><strong>Fasting glucose (mmol/l)</strong></td>
<td>6.1±3.1 (245)</td>
<td>5.5±2.4 (142)</td>
<td>5.2±1.5 (16)</td>
<td>5.5±2.3 (158)</td>
<td>6.2±3.2 (223)</td>
<td>5.5±2.2 (92)</td>
<td>5.6±2.5 (60)</td>
</tr>
<tr>
<td><strong>Incretin effect</strong></td>
<td>79.7±9.8 (245)</td>
<td>78.8±8.3 (142)</td>
<td>78.8±7.0 (16)</td>
<td>78.8±8.1 (158)</td>
<td>79.9±8.8 (223)</td>
<td>79.0±8.1 (92)</td>
<td>78.7±8.6 (60)</td>
</tr>
</tbody>
</table>

**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) |
| **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) | 4.9±0.3 (176) | 5.0±0.3 (61) | 4.9±0.3 (38) |
| **Incretin effect**  | 1517.0±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) |
| **BMI**              | 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) |
| **Fasting glucose (mmol/l)** | 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) |
| **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) | 6.6±1.6 (80) | 6.3±1.5 (45) |
| **Incretin effect**  | 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) |
| **BMI**              | 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) |
| **Fasting glucose (mmol/l)** | 6.7±3.2 (137) | 5.3±2.0 (88) | 5.1±1.7 (10) | 5.2±1.9 (98) | 6.7±3.2 (125) | 5.4±2.0 (56) | 5.0±1.8 (36) |
| **Incretin effect**  | 81.5±8.9 (137) | 78.4±7.9 (88) | 77.8±8.4 (10) | 78.3±7.9 (98) | 81.8±8.6 (125) | 79.1±8.0 (56) | 77.3±8.2 (36) |
Data mean ± SD. Fasting glycemia was based upon median of fasting p-glucose (FPG) = 5.4 mmol/l. Incretin effect = \(100\% \times \frac{\text{AUC}_{\text{ins OGGT}} - \text{AUC}_{\text{ins IVGTT}}}{\text{AUC}_{\text{ins OGGT}}}\).

\[\text{aP=0.04 between CC, CT and TT carriers and P=0.01 for CC vs CT/TT carriers}\]
\[\text{bP=0.0004 between CC, CT and TT carriers and P=8.8e-05 for CC vs CT/TT carriers}\]
\[\text{cP=0.01 between CC, CT and TT carriers and P=0.003 for CC vs CT/TT carriers}\]
\[\text{dP=0.03 between HapA, HapAB and HapB}\]
\[\text{eP=0.02 between HapA, HapAB and HapB; P=0.002 for HapA vs HapB}\]
\[\text{fP=0.03 between HapA, HapAB and HapB}\]
\[\text{gP=0.0003 between HapA, HapAB and HapB; P=0.001 for HapA vs HapB}\]
\[\text{hP=0.004 between HapA, HapAB and HapB; P=0.005 for HapA vs HapB}\]
Supplementary Table 5. Glucagon and GIP concentrations during OGTT according to TCF7L2 rs7903146 from the Botnia study.

<table>
<thead>
<tr>
<th></th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>CT/TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>148</td>
<td>137</td>
<td>21</td>
<td>158</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>52.8 ± 11.7</td>
<td>53.3 ± 10.3</td>
<td>53.2 ± 9.9</td>
<td>53.3 ± 10.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 3.9</td>
<td>26.3 ± 3.6</td>
<td>27.6 ± 5.9</td>
<td>26.4 ± 4.0</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.1 ± 0.5</td>
<td>5.2 ± 0.6</td>
<td>5.0 ± 0.4</td>
<td>5.2 ± 0.5</td>
</tr>
<tr>
<td>2 hr glucose (mmol/l)</td>
<td>4.9 ± 1.2</td>
<td>4.8 ± 1.2</td>
<td>5.0 ± 1.2</td>
<td>4.8 ± 1.2</td>
</tr>
<tr>
<td>HOMA (mmol · mU/l²)</td>
<td>1.6 ± 1.7</td>
<td>1.3 ± 0.7</td>
<td>1.3 ± 0.8</td>
<td>1.3 ± 0.8</td>
</tr>
<tr>
<td>Fasting glucagon (pg/ml)</td>
<td>80.0 ± 24.8</td>
<td>79.1 ± 29.6</td>
<td>73.6 ± 35.0</td>
<td>78.4 ± 30.3</td>
</tr>
<tr>
<td>2 hr glucagon (pg/ml)</td>
<td>74.0 ± 23.3</td>
<td>72.8 ± 27.3</td>
<td>71.7 ± 24.1</td>
<td>72.7 ± 26.8</td>
</tr>
<tr>
<td>Fasting GIP (pg/ml)</td>
<td>34.0 ± 3.8 (28)</td>
<td>42.6 ± 5.1 (29)</td>
<td>35.1 ± 3.0 (21)</td>
<td>39.5 ± 3.3 (50)</td>
</tr>
<tr>
<td>2hr GIP (pg/ml)</td>
<td>172.4 ± 12.2 (28)</td>
<td>179.4 ± 19.1 (29)</td>
<td>225.8 ± 19.6 (21)</td>
<td>198.9 ± 14.0 (50)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th><em>TCF7L2</em> gene expression (p-value;N)</th>
<th>Insulin gene expression (p-value;N)</th>
<th>Glucagon (p-value;N)</th>
<th>Insulin (p-value;N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>TCF7L2</em> gene</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin gene</td>
<td>0.76 (0.001;15)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td>0 (1;13)</td>
<td>0.18 (0.55;13)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.26 (0.4;12)</td>
<td>-0.14 (0.67;12)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SI</td>
<td>-0.63 (0.02;13)</td>
<td>-0.35 (0.24;13)</td>
<td>0.10 (0.70;15)</td>
<td>-0.48 (0.08;14)</td>
</tr>
</tbody>
</table>

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