**Supplementary Table S1: SNP quality assessment tests for Hardy-Weinberg equilibrium (HWE)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | Gene (functional consequence) | Minor/Major alleles | MAF | Genotype counts | Observed heterozygous | Expected heterozygous | P-value  HWE |
| rs1748197 | DOCK7 (intronic) | A/G | 0.355 | 40/119/121 | 0.425 | 0.458 | 0.241 |
| rs12130333 | DOCK7-ATG4C (intergenic) | T/C | 0.146 | 10/62/209 | 0.220 | 0.249 | 0.057 |

**Supplementary Table S2: Clinical characteristics of the study cohort as per gender-wise distribution@.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Traits** | **Male participants (Mean±SD)** | **Female participants (Mean±SD)** | **P-value$ (for differences in mean values between male and female participants)** |
| Age (in years) | 46.62±12.44 | 45.95±12.37 | 0.654 |
| Height (in meter) | 1.72±0.065 | 1.59±0.06 | <2.2e-16 |
| Weight (in kg) | 89.07±14.62 | 75.33±14.86 | 3.48e-13 |
| BMI (kg/m2) | 30.12±4.71 | 29.77±5.53 | 0.569 |
| WC (in cm) | 104.76±11.43 | 95.30±13.31 | 1.01e-06 |
| HDL (in mmol/l) | 1.05±0.249 | 1.32±0.32 | 6.75e-13 |
| TC (in mmol/l) | 5.25±1.19 | 5.52±1.24 | 0.0701 |
| LDL (in mmol/l) | 3.48±1.22 | 3.53±1.11 | 0.728 |
| Non-HDL (inmmol/l) | 4.19±1.21 | 4.13±1.16 | 0.654 |
| TG (in mmol/l) | 1.39±0.635 | 1.08±0.52 | 3.73e-05 |
| FPG (in mmol/l) | 6.11±1.41 | 5.51±1.00 | 2.9e-04 |
| HbA1c (%) | 6.54±1.34 | 6.12±1.22 | 0.012 |
| Irisin (ng/ml) | 564.39±179 | 550.92±202 | 0.602 |
| IL7 (pg/ml)**@** | 13.93±6.03 | 12.67±5.48 | 0.171 |
| IL13 (pg/ml) | 10.46±4.48 | 9.06±5.03 | 0.067 |
| Insulin (pg/ml) | 15.85±11.87 | 14.14±12.04 | 0.320 |
| c-peptide (pg/ml) | 2.49±1.52 | 2.79±1.86 | 0.262 |
| ANGPTL3 (ng/ml) | 36.65±9.51 | 37.98±10.82 | 0.364 |
| TNFa (pg/ml) | 125.48±32.25 | 129.45±32.14 | 0.429 |
| Obese status | 63 (obese):62 (non obese) | 72 (obese):81 (non obese) | 0.664 |
| Diabetes status | 60 (diabetic): 65 (non-diabetic) | 60 (diabetic):93(non-diabetic) | 0.177 |
| Anti-diabetic medication | 49 (med):76 (no med) | 52 (no med):100 | 0.463 |
| Lipid lowering medication | 44(med):81 | 44(med):108 | 0.325 |

**@,** The values for TC, and LDL were adjusted for lipid lowering medication by adopting procedures used in [Liu, D., Peloso, G., Yu, H. *et al.* Exome-wide association study of plasma lipids in >300,000 individuals. *Nat Genet* **49,** 1758–1766 (2017). https://doi.org/10.1038/ng.3977]: TC\_adjusted=TC/0.8; and LDL\_adjusted=LDL/0.7. The nonHDL was calculated by subtracting HDL from adjusted TC.

**Supplementary Table S3: Differences in the levels of c-peptide and irisin between individuals with reference homozygous genotypes and those with carrier genotypes at each of the two study variants.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trait** | **SNP** | **(Mean±SD) in individuals with reference homozygous genotypes**  **(rs1748197:GG; rs12130333:CC)** | **(Mean±SD) in individuals with carrier genotypes**  **(rs1748197:GA+AA; rs12130333:CT+TT)** | **P-value$ (for differences in mean values between individuals having reference genotypes and carrier genotypes.** |
| c-peptide | rs1748197 | 3.155±1.819 | 2.25±1.55 | 0.0015 |
| rs12130333 | 2.91±1.79 | 1.94±1.27 | 0.0003 |
|  |  |  |  |  |
| Irisin | rs1748197 | 599.45±192.83 | 524.9±186.7 | 0.027 |
| rs12130333 | 573.29±191.33 | 509.37±188.64 | 0.085 |

$, Student’s t-test was used for quantitative variables.

**Supplementary Table S4: Results of association tests for the two study variants with phenotype traits, using genetic model based on additive mode of inheritance.** Association tests were adjusted for age, sex (Regular correction) and further confounders of diabetes medication (DM) and lipid lowering medication (LLM). Significant P-values passing the threshold for multiple testing (P-value ≤0.003 = 0.05/17) and significant P*emp*-value≤0.05 are high-lighted in bold & italics font.Associations with P-values ≤0.05 are highlighted in bold font.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Traits** | **SNP with effect allele** | **Correction** | **Sample size** | **Beta** | **P-value** | **Empirical P-value (**P*emp*-value) |
| c-peptide | rs1748197 | R | 160 | -0.6976 | ***0.000127*** | ***0.00679*** |
|  |  | DM | 160 | -0.6944 | ***0.000161*** | ***0.00939*** |
|  |  | LLM | 160 | -0.6964 | ***0.000138*** | ***0.00739*** |
|  | rs12130333 | R | 161 | -0.9002 | ***0.00032*** | ***0.0154*** |
|  |  | R+DM | 161 | -0.8991 | ***0.000335*** | ***0.0174*** |
|  |  | R+LLM | 161 | -0.9117 | ***0.000288*** | ***0.0167*** |
|  |  |  |  |  |  |  |
| Irisin | rs1748197 | R | 217 | -63.1 | ***0.000299*** | ***0.0149*** |
|  |  | DM | 216 | -67.78 | ***9.58E-05*** | ***0.0047*** |
|  |  | LLM | 216 | -63 | ***0.000357*** | ***0.0184*** |
|  | rs12130333 | R | 218 | -72.61 | ***0.002135*** | 0.0979 |
|  |  | R+DM | 217 | -70.87 | ***0.002436*** | 0.1184 |
|  |  | R+LLM | 217 | -74.3 | ***0.001806*** | 0.0898 |
|  |  |  |  |  |  |  |
| TG | rs1748197 | R | 257 | -0.07759 | 0.1235 | 0.9989 |
|  |  | DM | 256 | -0.1008 | **0.04564** | 0.8984 |
|  |  | LLM | 256 | -0.08852 | 0.08188 | 0.9853 |
|  | rs12130333 | R | 258 | -0.1369 | **0.03926** | 0.8709 |
|  |  | R+DM | 257 | -0.132 | **0.04434** | 0.8917 |
|  |  | R+LLM | 257 | -0.1334 | **0.04469** | 0.8991 |
|  |  |  |  |  |  |  |
| FPG | rs1748197 | R | 239 | -0.05879 | 0.5645 | 1 |
|  |  | DM | 238 | -0.1421 | 0.1395 | 0.9995 |
|  |  | LLM | 238 | -0.07696 | 0.4457 | 1 |
|  | rs12130333 | R | 239 | -0.06309 | 0.6295 | 1 |
|  |  | R+DM | 238 | -0.09334 | 0.4424 | 1 |
|  |  | R+LLM | 238 | -0.07927 | 0.5372 | 1 |
|  |  |  |  |  |  |  |
| HbA1c | rs1748197 | R | 251 | 0.1714 | 0.1094 | 0.9958 |
|  |  | DM | 250 | 0.03895 | 0.6681 | 1 |
|  |  | LLM | 250 | 0.1411 | 0.1676 | 0.9997 |
|  | rs12130333 | R | 252 | -0.09417 | 0.5011 | 1 |
|  |  | R+DM | 251 | -0.1285 | 0.2672 | 1 |
|  |  | R+LLM | 251 | -0.09992 | 0.4505 | 1 |
|  |  |  |  |  |  |  |
| HDL | rs1748197 | R | 257 | 0.003359 | 0.8989 | 1 |
|  |  | DM | 256 | 0.01511 | 0.5664 | 1 |
|  |  | LLM | 256 | 0.01106 | 0.6766 | 1 |
|  | rs12130333 | R | 258 | 0.0582 | 0.09481 | 0.9926 |
|  |  | R+DM | 257 | 0.05328 | 0.1207 | 0.9986 |
|  |  | R+LLM | 257 | 0.05558 | 0.1088 | 0.9969 |
|  |  |  |  |  |  |  |
| nonHDL | rs1748197 | R | 256 | -0.2321 | 0.0257 | 0.7363 |
|  |  | DM | 256 | -0.2417 | 0.0208 | 0.6565 |
|  |  | LLM | 256 | -0.2577 | 0.0113 | 0.4375 |
|  | rs12130333 | R | 257 | -0.1641 | 0.2344 | 1 |
|  |  | R+DM | 257 | -0.1603 | 0.2461 | 1 |
|  |  | R+LLM | 257 | -0.1555 | 0.2486 | 1 |
|  |  |  |  |  |  |  |
| LDL**@** | rs1748197 | R | 266 | -0.1032 | 0.3132 | 1 |
|  |  | DM | 265 | -0.116 | 0.2594 | 1 |
|  |  | LLM | 265 | -0.129 | 0.1944 | 1 |
|  | rs12130333 | R | 267 | 7.08E-05 | 0.999 | 1 |
|  |  | R+DM | 266 | 0.00088 | 0.994 | 1 |
|  |  | R+LLM | 266 | 0.0087 | 0.946 | 1 |
|  |  |  |  |  |  |  |
| TC**@** | rs1748197 | R | 270 | -0.1397 | 0.1831 | 0.999 |
|  |  | DM | 269 | -0.146 | 0.1666 | 0.999 |
|  |  | LLM | 269 | -0.163 | 0.1134 | 0.999 |
|  | rs12130333 | R | 271 | 0.0145 | 0.9157 | 1 |
|  |  | R+DM | 270 | 0.0156 | 0.9097 | 1 |
|  |  | R+LLM | 270 | 0.0186 | 0.8901 | 1 |
|  |  |  |  |  |  |  |
| Weight | rs1748197 | R | 271 | -0.847 | 0.5094 | 1 |
|  |  | DM | 270 | -1.423 | 0.2598 | 1 |
|  |  | LLM | 270 | -1.269 | 0.3155 | 1 |
|  | rs12130333 | R | 272 | -2.25 | 0.182 | 1 |
|  |  | R+DM | 271 | -2.135 | 0.1928 | 1 |
|  |  | R+LLM | 271 | -2.142 | 0.1932 | 1 |
|  |  |  |  |  |  |  |
| BMI | rs1748197 | R | 275 | -0.5333 | 0.2292 | 1 |
|  |  | DM | 274 | -0.771 | 0.07754 | 0.9833 |
|  |  | LLM | 274 | -0.7136 | 0.102 | 0.9963 |
|  | rs12130333 | R | 276 | -0.9555 | 0.09993 | 0.9943 |
|  |  | R+DM | 275 | -0.9042 | 0.1099 | 0.9974 |
|  |  | R+LLM | 275 | -0.9168 | 0.1063 | 0.9974 |
|  |  |  |  |  |  |  |
| Waist circumference | rs1748197 | R | 177 | -0.9137 | 0.4845 | 1 |
|  |  | DM | 177 | -1.681 | 0.1732 | 0.9998 |
|  |  | LLM | 177 | -1.383 | 0.2642 | 1 |
|  | rs12130333 | R | 177 | -2.191 | 0.2181 | 1 |
|  |  | R+DM | 177 | -2.335 | 0.1619 | 0.9996 |
|  |  | R+LLM | 177 | -2.637 | 0.1173 | 0.9986 |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

**@,** The values for TC, and LDL were adjusted for lipid lowering medication by adopting procedures used in [Liu, D., Peloso, G., Yu, H. *et al.* Exome-wide association study of plasma lipids in >300,000 individuals. *Nat Genet* **49,** 1758–1766 (2017). https://doi.org/10.1038/ng.3977]: TC\_adjusted=TC/0.8; and LDL\_adjusted=LDL/0.7. The nonHDL was calculated by subtracting HDL from adjusted TC.

**Supplementary Table S5: Evaluation of the association signals relating to c-peptide and irisin in the sub-cohorts of entirely diabetic individuals and of entirely non-diabetic individuals.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Traits** | **SNP** | **Correction** | **Beta** | **p-value** | **Empirical P-value (P*emp*-value)** |
| **Sub-cohort of diabetes individuals** | | | | | |
| c-peptide | rs1748197 | R | -0.809 | 0.0012 | 0.0732 |
|  | rs12130333 | R | -0.709 | 0.039 | 0.863 |
| irisin | rs1748197 | R | -103.9 | 0.00011 | 0.0054 |
|  | rs12130333 | R | -115.3 | 0.0022 | 0.106 |
| **Sub-cohort of diabetes individuals** | | | | | |
| c-peptide | rs1748197 | R | -0.517 | 0.0614 | 0.955 |
|  | rs12130333 | R | -1.169 | 0.0019 | 0.104 |
| irisin | rs1748197 | R | -28.08 | 0.194 | 1 |
|  | rs12130333 | R | -34.12 | 0.231 | 1 |

**Supplementary Table S6: Logistic regression analysis for impact of the two study variants on the disease status of the study participants.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Disease status** | **SNP** | **OR [CI]** | **Standard error** | **P-value** |
| Obesity | rs1748197 | 0.794 [0.56-1.12] | 0.176 | 0.191 |
| rs12130333 | 0.765 [0.48-1.21] | 0.234 | 0.253 |
| Diabetes | rs1748197 | 1.23 [0.84-1.78] | 0.189 | 0.274 |
| rs12130333 | 1.01 [0.62-1.64] | 0.248 | 0.967 |
| Hypertension | rs1748197 | 1.004 [0.66-1.52] | 0.211 | 0.983 |
| rs12130333 | 0.621 [0.348-1.11] | 0.295 | 0.106 |

**Supplementary Table S7: Power Calculation for the association of the rs1748197\_A variant (MAF=0.35) and rs12130333\_T variant (MAF=0.15) with c-peptide and Irisin.** Calculations for “gene only” hypothesis were performed using additive genetic model (AA versus AG versus GG for rs1748197; TT versus TC versus CC for rs12130333); calculations for “gene-environment GxE” hypothesis were performed using dominant genetic model (AA versus (AG+GG) for rs1748197; TT versus TC+CC for rs12130333).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Frequency | Marginal Rsq | Sample Size | Expected (±) effect size considering “Gene only” hypothesis (response variable) for c-peptide | Expected (±) effect size considering “Gene only” hypothesis (response variable) for Irisin | Expected (±) effect size considering GXE hypothesis (Irisin and E=TG) |
| 0.15 | 0.001 | 7845 | 0.1083 | 12.039 | 20.40 |
|  | 0.006 | 1304 | 0.2652 | 29.491 | 49.96 |
|  | 0.011 | 710 | 0.3591 | 39.931 | 67.65 |
|  | 0.016 | 487 | 0.4331 | 48.159 | 81.60 |
|  | 0.021 | 370 | 0.4962 | 55.173 | 93.48 |
|  | 0.026 | 298 | 0.5521 | 61.391 | 104.02 |
|  | 0.031 | 249 | 0.6028 | 67.034 | 113.58 |
|  | 0.036 | 214 | 0.6496 | 72.238 | 122.40 |
|  | 0.041 | 187 | 0.6933 | 77.092 | 130.62 |
|  | 0.046 | 167 | 0.7344 | 81.657 | 138.35 |
|  |  |  |  |  |  |
| 0.35 | 0.001 | 7845 | 0.0811 | 9.013 | 15.27 |
|  | 0.006 | 1304 | 0.1985 | 22.078 | 37.41 |
|  | 0.011 | 710 | 0.2688 | 29.893 | 50.65 |
|  | 0.016 | 487 | 0.3242 | 36.053 | 61.08 |
|  | 0.021 | 370 | 0.3714 | 41.304 | 69.98 |
|  | 0.026 | 298 | 0.4133 | 45.958 | 77.87 |
|  | 0.031 | 249 | 0.4513 | 50.183 | 85.03 |
|  | 0.036 | 214 | 0.4863 | 54.079 | 91.63 |
|  | 0.041 | 187 | 0.5190 | 57.713 | 97.78 |
|  | 0.046 | 167 | 0.5498 | 61.131 | 103.57 |