**TABLE 1** Discovery and replication meta-analyses for all SNPs taken into replication

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model of adjustment |  |  |  |  |  |  |  | **Discovery** (n░=░38,292) | **Replication** (n░=░47,227) | **Combined** (n░=░85,519) |
|  | SNP ID |  | Chr | Position | Gene | A1/A2 | AF 1 | Beta | SE | P-value | Beta | SE | P-value | Beta | SE | P-value | I2 |
| (Model 1) | rs9991501 |  | 4 | 88,477,507 | HSD17B11 | T/C | 0.04 | -0.65 | 0.13 | 1.7E-06 | -0.36 | 0.10 | 5.5E-04 | -0.46 | 0.08 | **1.6E-08** | 6 |
| (Model 1) | rs9936385 |  | 16 | 52,376,670 | FTO | T/C | 0.63 | -0.38 | 0.04 | **1.0E-19** | -0.28 | 0.04 | 4.5E-13 | -0.32 | 0.03 | **1.8E-30** | 38 |
| (Model 1) | rs10871777 |  | 18 | 56,002,743 | MC4R | A/G | 0.75 | -0.28 | 0.05 | **4.1E-10** | -0.27 | 0.04 | 4.2E-10 | -0.28 | 0.03 | **1.0E-18** | 11 |
| (Model 1) | rs2385539 |  | 2 | 220,075,197 | GMPPA | C/G | 0.62 | 0.24 | 0.05 | 7.3E-07 | 0.05 | 0.04 | 1.8E-01 | 0.13 | 0.03 | 3.2E-05 | 18 |
| (Model 1) | rs6796318 | [1](#tb1fn1) | 3 | 32,276,790 | CMTM8 | A/G | 0.09 | 0.30 | 0.06 | 2.7E-07 | 0.02 | 0.15 | 9.2E-01 | 0.27 | 0.06 | 1.38E-06 | 14 |
| (Model 1) | rs9641123 |  | 7 | 93,035,668 | CALCR | C/G | 0.40 | 0.24 | 0.04 | **4.6E-09** | 0.08 | 0.04 | 2.2E-02 | 0.15 | 0.03 | 2.6E-08 | 17 |
| (Model 1) | rs902634 | [1](#tb1fn1) | 10 | 133,793,941 | C10orf39 | A/G | 0.30 | 0.21 | 0.04 | 1.5E-06 | -0.09 | 0.10 | 3.6E-01 | 0.16 | 0.04 | 4.5E-05 | 16 |
| (Model 2) | rs9991501 |  | 4 | 88,477,507 | HSD17B11 | T/C | 0.04 | -0.70 | 0.13 | **2.5E-08** | -0.34 | 0.10 | 4.9E-04 | -0.48 | 0.08 | **7.3E-10** | 6 |
| (Model 2) | rs9936385 |  | 16 | 52,376,670 | FTO | T/C | 0.61 | -0.28 | 0.04 | **6.3E-13** | -0.21 | 0.04 | **2.8E-09** | -0.24 | 0.03 | **2.4E-20** | 33 |
| (Model 2) | rs10871777 |  | 18 | 56,002,743 | MC4R | A/G | 0.76 | -0.22 | 0.04 | 2.7E-07 | -0.20 | 0.04 | 3.1E-07 | -0.21 | 0.03 | **4.2E-13** | 10 |
| (Model 2) | rs733381 |  | 22 | 38,999,594 | TNRC6B | A/G | 0.79 | 0.22 | 0.04 | 2.6E-07 | 0.17 | 0.04 | 2.7E-05 | 0.20 | 0.03 | **4.6E-11** | 9 |
| (Model 2) | rs2999156 |  | 1 | 113,048,650 | RHOC | C/G | 0.56 | -0.19 | 0.04 | 2.4E-07 | 0.02 | 0.04 | 6.7E-01 | -0.08 | 0.03 | 1.2E-03 | 14 |
| (Model 2) | rs2385539 |  | 2 | 220,075,197 | GMPPA | C/G | 0.63 | 0.21 | 0.04 | 2.2E-06 | 0.06 | 0.04 | 9.5E-02 | 0.12 | 0.03 | 1.8E-05 | 21 |
| (Model 2) | rs464553 |  | 6 | 34,423,057 | NUDT3 | T/G | 0.20 | 0.21 | 0.04 | 2.1E-06 | 0.12 | 0.04 | 7.0E-03 | 0.16 | 0.03 | 1.6E-07 | 23 |
| (Model 2) | rs9641123 |  | 7 | 93,035,668 | CALCR | C/G | 0.43 | 0.21 | 0.04 | **2.8E-08** | 0.08 | 0.03 | 2.2E-02 | 0.14 | 0.03 | 7.6E-08 | 19 |
| (Model 2) | rs6944616 | [1](#tb1fn1) | 7 | 133,739,304 | AKR1B1 | T/G | 0.29 | -0.19 | 0.04 | 2.2E-06 | -0.06 | 0.10 | 5.7E-01 | -0.17 | 0.04 | 4.4E-06 | 16 |
| (Model 2) | rs2515418 |  | 8 | 6,355,630 | ANGPT2 | A/G | 0.44 | 0.18 | 0.04 | 8.8E-07 | 0.07 | 0.03 | 5.1E-02 | 0.12 | 0.02 | 1.7E-06 | 16 |
| (Model 2) | rs11214913 |  | 11 | 113,624,353 | ZBTB16 | A/C | 0.12 | -0.30 | 0.06 | 1.8E-06 | -0.07 | 0.05 | 1.8E-01 | -0.16 | 0.04 | 5.2E-05 | 24 |
| (Model 2) | rs899926 | [1](#tb1fn1) | 15 | 82,364,495 | ADAMTSL3 | A/G | 0.47 | -0.19 | 0.04 | 1.7E-07 | 0.52 | -0.01 | 8.6E-01 | 0.52 | -0.16 | 9.3E-07 | 17 |
| (Model 2) | rs17834425 |  | 17 | 2,062,021 | SMG6 | T/C | 0.17 | 0.25 | 0.05 | 3.8E-07 | 0.11 | 0.05 | 2.2E-02 | 0.18 | 0.03 | 2.0E-07 | 12 |
| (Model 3) | rs2943656 |  | 2 | 226,830,162 | IRS1 | A/G | 0.37 | -0.17 | 0.03 | 2.5E-07 | -0.13 | 0.03 | 8.0E-06 | -0.14 | 0.02 | **1.5E-11** | 14 |
| (Model 3) | rs9991501 |  | 4 | 88,477,507 | HSD17B11 | T/C | 0.04 | -0.61 | 0.11 | **2.9E-08** | -0.26 | 0.08 | 1.9E-03 | -0.39 | 0.07 | **5.8E-09** | 7 |
| (Model 3) | rs2287926 |  | 5 | 82,851,164 | VCAN | A/G | 0.13 | 0.24 | 0.05 | 8.6E-07 | 0.15 | 0.04 | 8.5E-04 | 0.19 | 0.03 | **7.5E-09** | 7 |
| (Model 3) | rs4842924 |  | 15 | 82,378,611 | ADAMTSL3 | T/C | 0.52 | -0.17 | 0.03 | 1.4E-07 | -0.08 | 0.03 | 3.9E-03 | -0.12 | 0.02 | **1.4E-08** | 23 |
| (Model 3) | rs9936385 |  | 16 | 52,376,670 | FTO | T/C | 0.61 | -0.17 | 0.03 | 1.1E-06 | -0.11 | 0.03 | 1.6E-04 | -0.14 | 0.02 | **1.4E-09** | 33 |
| (Model 3) | rs2999156 |  | 1 | 113,048,650 | RHOC | C/G | 0.56 | -0.17 | 0.03 | 4.0E-07 | 0.00 | 0.03 | 9.3E-01 | -0.09 | 0.02 | 1.7E-04 | 12 |
| (Model 3) | rs4404708 | [1](#tb1fn1) | 5 | 119,680,527 | PRR16 | A/G | 0.37 | -0.18 | 0.04 | 1.9E-06 | 0.03 | 0.07 | 7.0E-01 | -0.14 | 0.03 | 4.3E-05 | 15 |
| (Model 3) | rs10223402 |  | 6 | 116,004,392 | FRK | A/G | 0.17 | 0.24 | 0.05 | 4.1E-07 | 0.04 | 0.04 | 3.4E-01 | 0.12 | 0.03 | 6.2E-05 | 19 |
| (Model 3) | rs7795758 |  | 7 | 133,751,491 | AKR1B1 | T/G | 0.73 | 0.17 | 0.04 | 1.9E-06 | 0.00 | 0.03 | 9.4E-01 | 0.08 | 0.02 | 8.6E-04 | 14 |
| (Model 3) | rs9641123 |  | 7 | 93,035,668 | CALCR | C/G | 0.43 | 0.17 | 0.03 | 4.8E-07 | 0.06 | 0.03 | 3.3E-02 | 0.11 | 0.02 | 9.8E-07 | 21 |
| (Model 3) | rs1028883 |  | 13 | 73,006,588 | KLF12 | T/G | 0.43 | -0.16 | 0.03 | 3.2E-07 | -0.04 | 0.03 | 2.0E-01 | -0.10 | 0.02 | 8.8E-06 | 20 |

1Replication number only 6927 (Due to limited resources, five of the sGWS signals were replicated only in the cohorts available for in-silico replication). AF░=░Allele frequency. Bold *P*░<░5\*10−8. I2 is the measure of heterogeneity.

Model 1: no adjustment for fat mass; Model 2: adjustment for fat mass as a % of body mass; Model 3: adjustment for fat mass in kg.

**TABLE 2** Comparison of Models for GWS hits

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | Whole Body lean Mass |
|  |  |  |  |  |  | **Model 1** (n░=░85,519) |  |  | **Model 2** (n░=░85,519) |  |  | **Model 3** (n░=░85,519) |  |  |
| SNP ID | Chr | Position | Gene | A1/A2 | AF 1 | Beta | SE | P-value | Beta | SE | P-value | Beta | SE | P-value |
| rs2943656 | 2 | 226,830,162 | IRS1 | A/G | 0.37 | -0.04 | 0.03 | 9.1E-02 | -0.11 | 0.02 | 7.4E-06 | -0.14 | 0.02 | **1.5E-11** |
| rs9991501 | 4 | 88,477,507 | HSD17B11 | T/C | 0.04 | -0.46 | 0.08 | **1.6E-08** | -0.48 | 0.08 | **7.3E-10** | -0.39 | 0.07 | **5.8E-09** |
| rs2287926 | 5 | 82,851,164 | VCAN | A/G | 0.13 | 0.12 | 0.04 | 3.2E-03 | 0.17 | 0.04 | 6.2E-06 | 0.19 | 0.03 | **7.5E-09** |
| rs4842924 | 15 | 82,378,611 | ADAMTSL3 | T/C | 0.52 | -0.08 | 0.03 | 2.3E-03 | -0.12 | 0.02 | 9.7E-07 | -0.12 | 0.02 | **1.4E-08** |
| rs9936385 | 16 | 52,376,670 | FTO | T/C | 0.61 | -0.32 | 0.03 | **1.8E-30** | -0.24 | 0.03 | **2.4E-20** | -0.14 | 0.02 | **1.4E-09** |
| rs10871777 | 18 | 56,002,743 | MC4R | A/G | 0.76 | -0.28 | 0.03 | **1.0E-18** | -0.21 | 0.03 | **4.2E-13** | -0.12 | 0.03 | 6.2E-07 |
| rs733381 | 22 | 38,999,594 | TNRC6B | A/G | 0.79 | 0.19 | 0.03 | **5.2E-09** | 0.20 | 0.03 | **4.6E-11** | 0.15 | 0.03 | **5.5E-09** |

AF░=░Allele frequency. Bold *P*░<░5\*10−8.

Model 1: not adjusted for fat, Model 2 - adjusted for fat mass as a % of body mass, Model 3 adjusted for fat mass in kg.

**TABLE 3** Associations of lean mass increasing alleles with metabolic phenotypes

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | Cross phenotype |  |
| SNP | LM IA | Gene | Effect in M1 | M1/M3 ratio % | Type of locus | %Fat | BMI | CAD | DM | Insulin | HOMA-IR | Trig | Chol | LDL | HDL | Summary (Metabolism) |
| rs9936385 | C | FTO | Yes | 234 | Sumo Wrestler | **++** | **++** | **+** | **++** | **++** | **++** | **++** | **0** | **0** | **--** | Adverse metabolic profile |
| rs10871777 | G | MC4R | Yes | 222 | Sumo Wrestler | **++** | **++** | **0** | **++** | **+** | **+** | **++** | **0** | **0** | **--** |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| rs733381 | A | TNRC6B | Yes | 125 | Intermediate | **0** | **++** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **-** | No metabolic phenotype |
| rs9991501 | C | HSD17B11 | Yes | 120 | Intermediate | **0** | **0** | **0** | **?** | **0** | **0** | **?** | **?** | **?** | **?** |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| rs2287926 | A | VCAN | Yes | 64 | Body Builder | **0** | **0** | **0** | **?** | **-** | **0** | **--** | **0** | **0** | **+** | Metabolic protection |
| rs4842924 | C | ADAMTSL3 | Yes | 67 | Body Builder | **--** | **0** | **0** | **-** | **0** | **0** | **0** | **0** | **0** | **++** |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| rs2943656 | G | IRS1 | No | NA | Indirect/Fat locus | **--** | **--** | **++** | **++** | **+** | **+** | **++** | **0** | **0** | **--** | Adverse metabolic profile |

+ nominal significant increase,░+░+░multiple testing corrected significant increase, - nominal significant decrease, -- multiple testing corrected significant decrease, 0 No significant effect. ?░=░not included. The threshold for a statistically significant association with Bonferroni correction for 10 traits is *P*░=░0.005 (0.05/10). CAD░=░coronary artery disease, DM diabetes mellitus, Trig░=░tryglicerides, Chol░=░Cholesterol. For further details see **Supplemental Table 7**.

NA░=░not applicable as no effect in M1. LM IA░=░Lean Mass Increasing Allele. M1░=░Model 1 not adjusted for fat, M3░=░Model 3 adjusted for fat mass(kg).

Model 1/Model 3 ratio: a measure of the degree of attenuation of the LM association after fat mass adjustment.

**TABLE 4** Associations of lean mass increasing alleles with musculoskeletal phenotypes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | Cross phenotype |
| SNP | LM IA | Gene | Effect in M1 | M1/M3 ratio % | Type of locus | Grip Strength | FN-BMD | LS-BMD | Fx |
| rs9936385 | C | FTO | Yes | 234 | Sumo Wrestler | **0** | **0** | **0** | **--** |
| rs10871777 | G | MC4R | Yes | 222 | Sumo Wrestler | **0** | **0** | **0** | **0** |
| rs733381 | A | TNRC6B | Yes | 125 | Intermediate | **++** | **0** | **--** | **+** |
| rs9991501 | C | HSD17B11 | Yes | 120 | Intermediate | **0** | **0** | **+** | **0** |
| rs2287926 | A | VCAN | Yes | 64 | Body Builder | **0** | **0** | **0** | **0** |
| rs4842924 | C | ADAMTSL3 | Yes | 67 | Body Builder | **++** | **0** | **0** | **0** |
| rs2943656 | G | IRS1 | No | NA | Indirect/Fat locus | **0** | **0** | **0** | **0** |

+ nominal significant increase,░+░+░multiple testing corrected significant increase, - nominal significant decrease, -- multiple testing corrected significant decrease, 0 No significant effect. The threshold for a statistically significant association with Bonferroni correction for 4 traits is *P*░=░0.0125 (0.05/4). For further details see Supplemental Table 8.

NA░=░not applicable as no effect in M1. LM IA░=░Lean Mass Increasing Allele. M1░=░Model 1 not adjusted for fat, M3░=░Model 3 adjusted for fat mass in kg. BMD░=░bone mineral density, FN░=░femoral neck, LS░=░lumbar spine, Fx░=░fracture

*Model 1*/*Model 3* ratio: a measure of the degree of attenuation of the LM association after fat mass adjustment.

**TABLE 5** Genetic correlations of lean mass phenotype with other traits and conditions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait |  | Model 1 | Model 2 | Model 3 |
|  |  | rg | p | rg | p | rg | p |
| **Obesity** | BMI | 0.96 | **1.1E-91** | 0.76 | **1.2E-53** | 0.49 | **3.3E-24** |
|  | Childhood obesity | 0.60 | **1.4E-19** | 0.47 | **4.4E-13** | 0.30 | **2.6E-06** |
|  | Extreme bmi | 0.98 | **4.8E-40** | 0.76 | **4.1E-26** | 0.51 | **9.4E-13** |
|  | Overweight | 0.93 | **2.1E-70** | 0.72 | **1.3E-43** | 0.46 | **1.1E-16** |
|  | waist-to-hip ratio | 0.48 | **4.1E-20** | 0.29 | **3.3E-09** | 0.15 | **4.0E-03** |
|  | Body fat | 0.45 | **3.7E-13** | 0.17 | **1.2E-02** | -0.16 | **1.4E-02** |
| **Carbohydrate** | Type 2 Diabetes | 0.27 | **1.0E-04** | 0.18 | **1.0E-02** | 0.10 | 1.9E-01 |
|  | Fasting glucose | 0.21 | **4.9E-03** | 0.20 | **4.6E-03** | 0.15 | **3.6E-02** |
|  | Fasting insulin | 0.48 | **2.2E-09** | 0.28 | **2.0E-04** | 0.20 | **1.1E-02** |
|  | Fasting proinsulin | 0.35 | **9.8E-03** | 0.21 | 9.6E-02 | 0.05 | 7.1E-01 |
|  | HbA1C | 0.19 | **4.3E-02** | 0.15 | 1.0E-01 | 0.08 | 3.5E-01 |
|  | HOMA-IR | 0.48 | **8.2E-06** | 0.33 | **5.0E-04** | 0.26 | **8.7E-03** |
| **Lipid** | Triglycerides | 0.15 | **6.5E-03** | 0.12 | **2.3E-02** | 0.08 | 1.8E-01 |
|  | Total Cholesterol | -0.14 | **1.8E-02** | -0.17 | **3.0E-03** | -0.20 | **6.0E-04** |
|  | HDL cholesterol | -0.40 | **7.5E-11** | -0.35 | **4.6E-09** | -0.28 | **2.2E-06** |
|  | LDL cholesterol | -0.05 | 4.4E-01 | -0.10 | 1.1E-01 | -0.16 | 1.9E-02 |
| **Cardiovascular** | CAD | 0.08 | 1.7E-01 | 0.07 | 2.0E-01 | 0.02 | 7.3E-01 |
| **Musculoskeletal** | FN-BMD | 0.15 | **9.5E-03** | 0.11 | **4.3E-02** | 0.12 | **2.9E-02** |
|  | LS-BMD | 0.14 | **2.4E-02** | 0.15 | **1.8E-02** | 0.17 | **8.9E-03** |
|  | Grip Strength | 0.16 | 1.1E-01 | 0.2704 | **4.4E-03** | 0.2797 | **3.6E-03** |
| **Reproductive** | Age at Menarche | -0.36 | **2.9E-18** | -0.32 | **1.9E-15** | -0.24 | **1.9E-08** |
|  | Age at Menopause | -0.11 | 7.0E-02 | -0.04 | 4.7E-01 | 0.05 | 3.8E-01 |

rg░=░genetic correlation. Bold *P*░<░0.05.

CAD - coronary artery disease; BMD░=░bone mineral density. FN░=░Femoral neck, LS░=░Lumbar spine.