

| Variable                                                      | UKB study<br>(N=428,719) | GHS study<br>(N=121,061) | MCPS study<br>(N=95,846) |
|---------------------------------------------------------------|--------------------------|--------------------------|--------------------------|
| Age, mean (SD) in years                                       | 57 (8)                   | 53 (17)                  | 52 (13)                  |
| Women, N (%)                                                  | 232,553 (54)             | 73,769 (61)              | 65,330 (68)              |
| Body mass index, mean (SD)<br>in kg/m <sup>2</sup>            | 27.4 (4.8)               | 31.1 (7.3)               | 29.1 (5.1)               |
| Body weight, mean (SD) in<br>kg                               | 78 (16)                  | 88 (23)                  | 70 (14)                  |
| Body mass index WHO<br>categories, N (%)                      |                          |                          |                          |
| Underweight<br>( $< 18.5$ kg/m <sup>2</sup> )                 | 2,089 (0.49)             | 994 (0.82)               | 499 (0.52)               |
| Healthy weight<br>( $18.5$ to $< 25$ kg/m <sup>2</sup> )      | 140,175 (32.70)          | 23,784 (19.65)           | 18,599 (19.41)           |
| Overweight<br>( $25$ to $< 30$ kg/m <sup>2</sup> )            | 182,564 (42.58)          | 35,787 (29.56)           | 40,672 (42.43)           |
| Obesity, non-severe<br>( $30$ to $< 40$ kg/m <sup>2</sup> )   | 95,928 (22.37)           | 46,067 (38.05)           | 33,203 (34.64)           |
| Severe obesity<br>( $\geq 40$ kg/m <sup>2</sup> )             | 7,963 (1.86)             | 14,429 (11.92)           | 2,873 (3.00)             |
| Blood pressure, mean (SD) in<br>mmHg                          |                          |                          |                          |
| Systolic                                                      | 138 (19)                 | 124 (11)                 | 127 (17)                 |
| Diastolic                                                     | 82 (11)                  | 74 (7)                   | 83 (10)                  |
| Low-density lipoprotein<br>cholesterol, mean (SD) in<br>mg/dL | 138 (34)                 | 107 (29)                 | Not measured             |
| Triglycerides, median (IQR)<br>in mg/dL                       | 132 (93, 191)            | 124 (90, 172)            | Not measured             |

Figure 1

SUBSTITUTE SHEET (RULE 26)

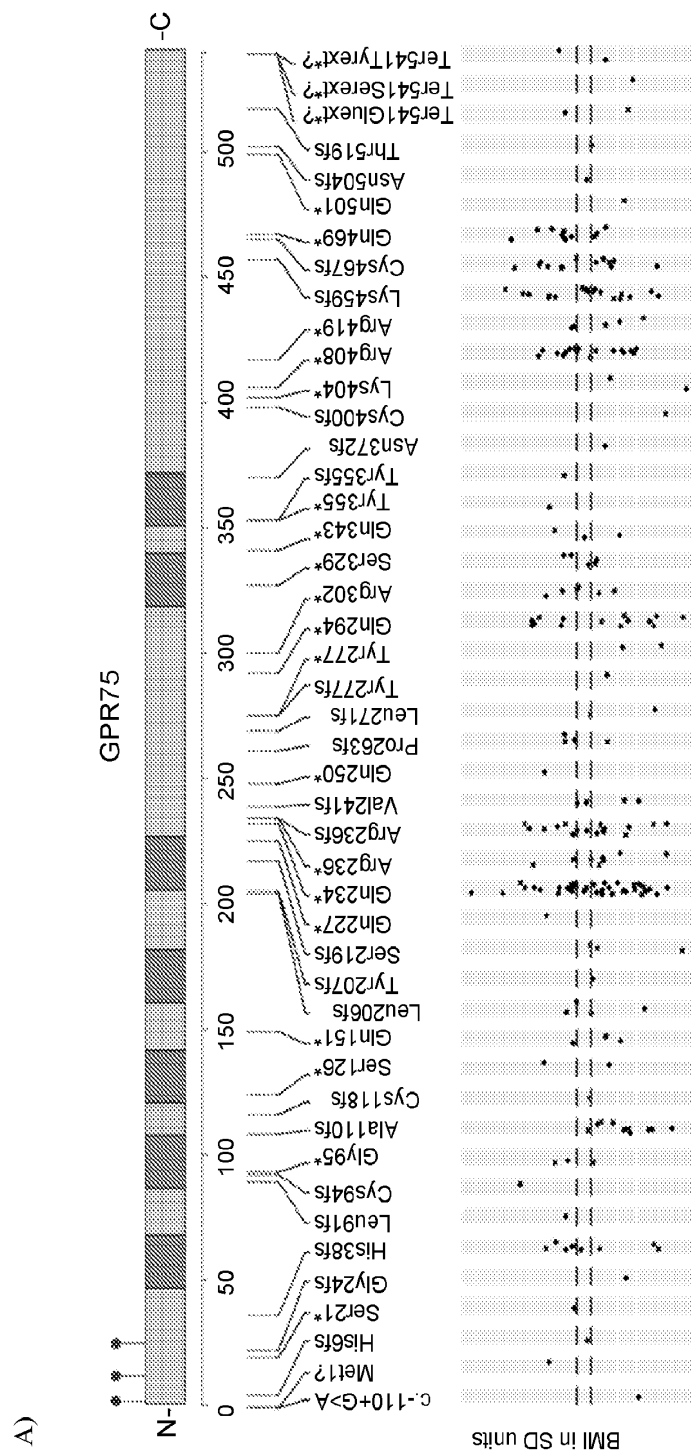
| Gene  | Genetic exposure, variant type; allele frequency cut-off in % | Study | Beta (95% CI) per allele in SD units of BMI | p       | AAF, fraction of 1 | Genotype counts, RR RA AA genotypes |
|-------|---------------------------------------------------------------|-------|---------------------------------------------|---------|--------------------|-------------------------------------|
| GPR75 | pLOF; AAF < 1%                                                | UKB   | -0.34<br>(-0.49, -0.19)                     | 6.6E-06 | 0.0002             | 428,572 147 0                       |
| GPR75 | pLOF; AAF < 1%                                                | MCPS  | -0.48<br>(-0.82, -0.13)                     | 7.1E-03 | 0.0002             | 95,816 30 0                         |
| GPR75 | pLOF; AAF < 1%                                                | GHS   | -0.27<br>(-0.52, -0.02)                     | 3.6E-02 | 0.0002             | 121,010 51 0                        |

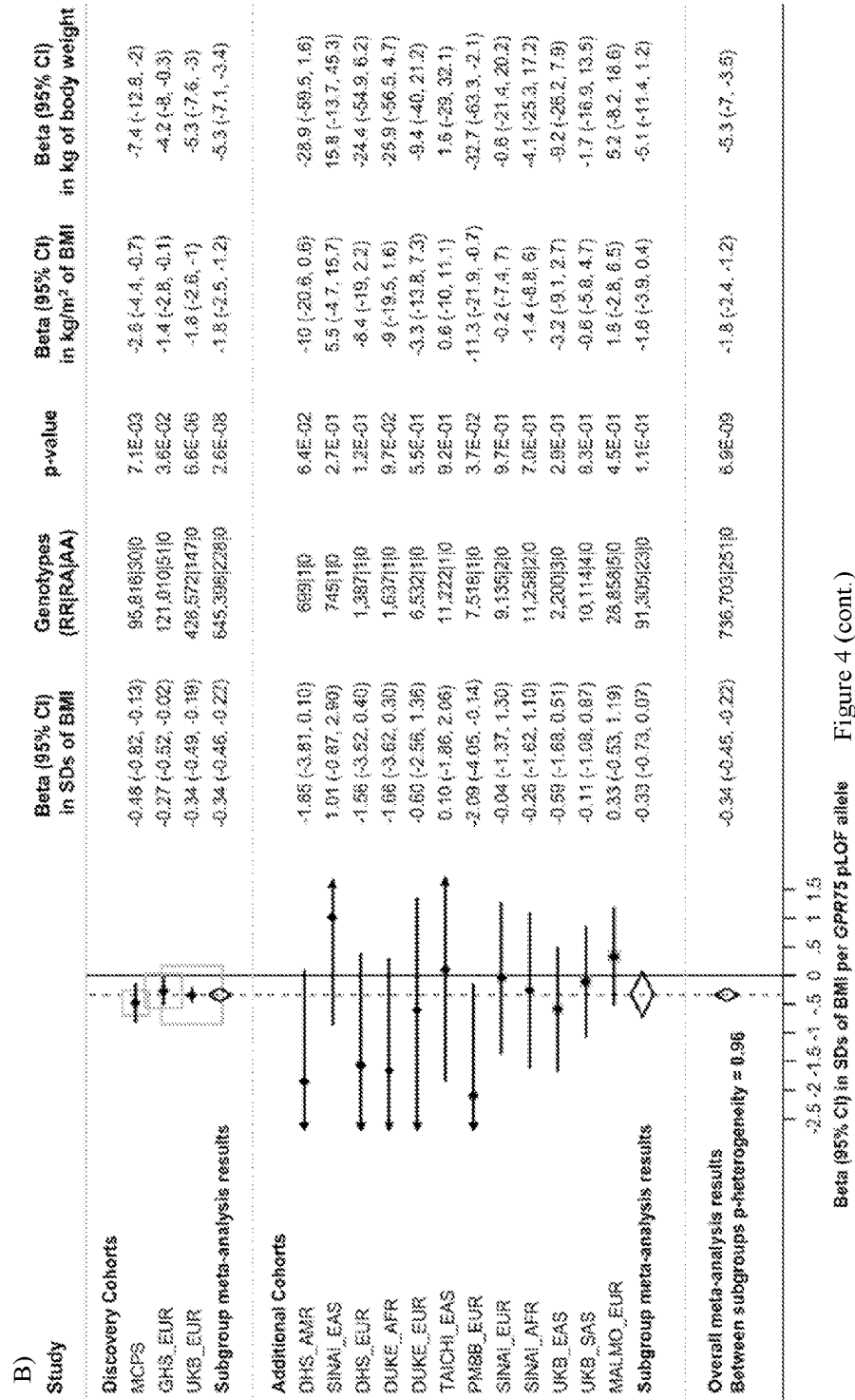
Figure 2

| Gene  | Genomic Coordinates | Genetic exposure, variant type; frequency cut-off in % | Beta (95% CI) per allele in SD units of BMI | p                     |
|-------|---------------------|--------------------------------------------------------|---------------------------------------------|-----------------------|
| GPR75 | 2: 53853133         | pLOF; AAF < 1%                                         | -0.34<br>(-0.46, -0.22)                     | 2.6×10 <sup>-08</sup> |

| Gene  | AAF, fraction of 1 | Genotype counts, RR RA AA genotypes | Beta (95% CI) per allele in kg/m <sup>2</sup> units of BMI | Beta (95% CI) per allele in kgs of body weight | Beta (95% CI) per allele in lbs of body weight |
|-------|--------------------|-------------------------------------|------------------------------------------------------------|------------------------------------------------|------------------------------------------------|
| GPR75 | 0.0002             | 645,398 228 0                       | -1.8<br>(-2.5, -1.2)                                       | -5.3<br>(-7.1, -3.4)                           | -11.6<br>(-15.7, -7.5)                         |

Figure 3





| Genetic exposure,<br>variant type; frequency<br>cutoff in % | Group                                 | Beta (95% CI)<br>per allele in<br>SD units of<br>BMI | Beta (95% CI)<br>per allele in<br>kg/m <sup>2</sup> units<br>of BMI | P       | AAF,<br>fraction<br>of 1 | Genotype<br>counts,<br>RR RA AA<br>genotypes | P-value for<br>heterogeneity in<br>effect estimates<br>between groups |
|-------------------------------------------------------------|---------------------------------------|------------------------------------------------------|---------------------------------------------------------------------|---------|--------------------------|----------------------------------------------|-----------------------------------------------------------------------|
| GPR75 pLOF; AAF < 1%                                        | Age ≤<br>median<br>value in<br>cohort | -0.33<br>(-0.50, -0.17)                              | -1.80<br>(-2.70, -0.89)                                             | 1.0E-04 | 0.0002                   | 331,175   117   0                            | 0.93                                                                  |
|                                                             | Age ><br>median<br>value in<br>cohort | -0.35<br>(-0.52, -0.18)                              | -1.90<br>(-2.80, -0.95)                                             | 7.8E-05 | 0.0002                   | 314,223   111   0                            |                                                                       |
| GPR75 pLOF; AAF < 1%                                        | Men                                   | -0.35<br>(-0.55, -0.16)                              | -1.90<br>(-3.00, -0.86)                                             | 3.5E-04 | 0.0002                   | 273,885   89   0                             | 0.91                                                                  |
|                                                             | Women                                 | -0.33<br>(-0.49, -0.18)                              | -1.80<br>(-2.60, -0.97)                                             | 2.4E-05 | 0.0002                   | 371,513   139   0                            |                                                                       |

Figure 5

| Gene  | Genetic exposure, variant type; allele frequency cut-off in % | Per-allele OR (95% CI) for obesity | P       | AAF, fraction of 1 | Genotype counts (cases), RR   RA   AA genotypes | Genotype counts (controls), RR   RA   AA genotypes |
|-------|---------------------------------------------------------------|------------------------------------|---------|--------------------|-------------------------------------------------|----------------------------------------------------|
| GPR75 | pLOF; AAF < 1%                                                | 0.46<br>(0.31, 0.67)               | 6.9E-05 | 0.0002             | 200.613   45   0                                | 186.335   94   0                                   |

Figure 6

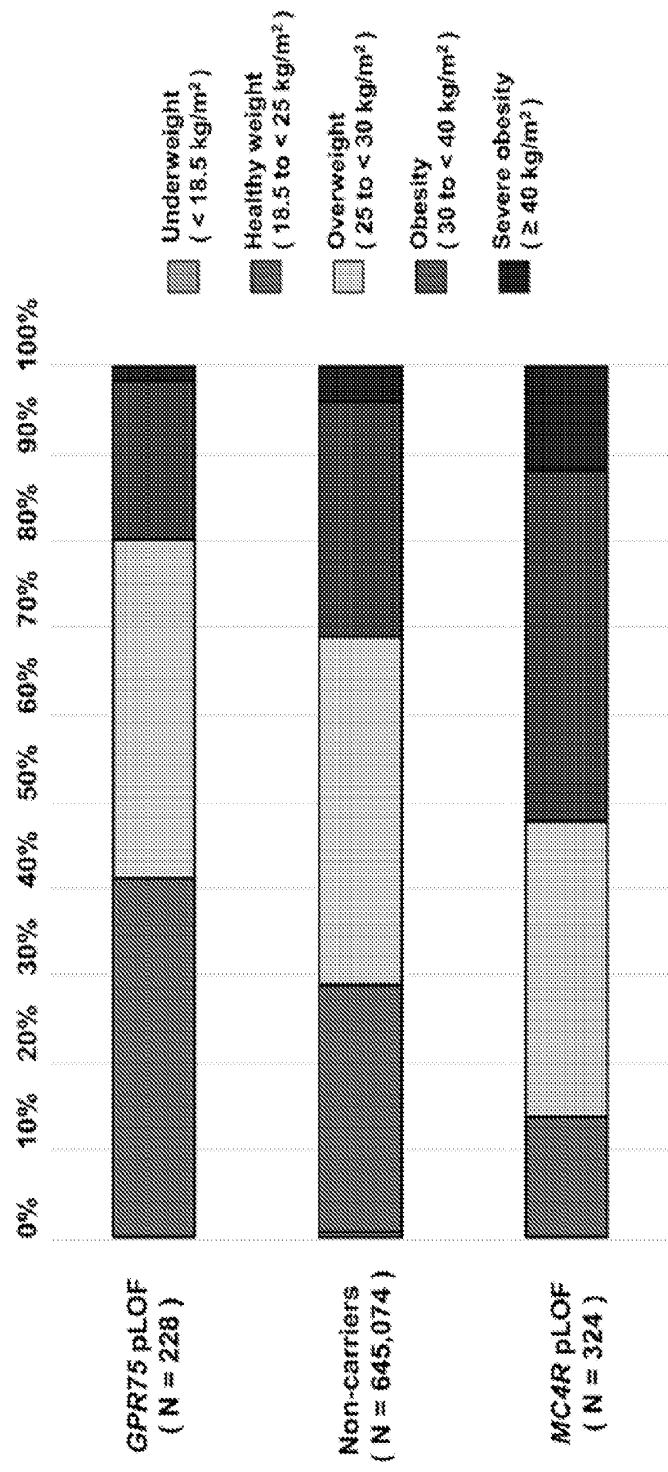


Figure 7

| Genetic exposure, variant type; frequency cutoff in % | Outcome                                                                                                                                                                                                | AAF, fraction of 1 | OR (95% CI) per allele | P       | Genotype counts (cases), RR   RA   AA genotypes | Genotype counts (controls), RR   RA   AA genotypes |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------------------|---------|-------------------------------------------------|----------------------------------------------------|
| GPR75 pLOF; AAF < 1%                                  | Responded "Thinner" to multiple choice question: "When you were 10 years old, compared to average would you describe yourself as: thinner, plumper, about average, do not know, prefer not to answer?" | 1.7E-04            | 1.66<br>(1.18, 2.34)   | 3.9E-03 | 141,442   62   0                                | 282,026   82   0                                   |

Figure 8

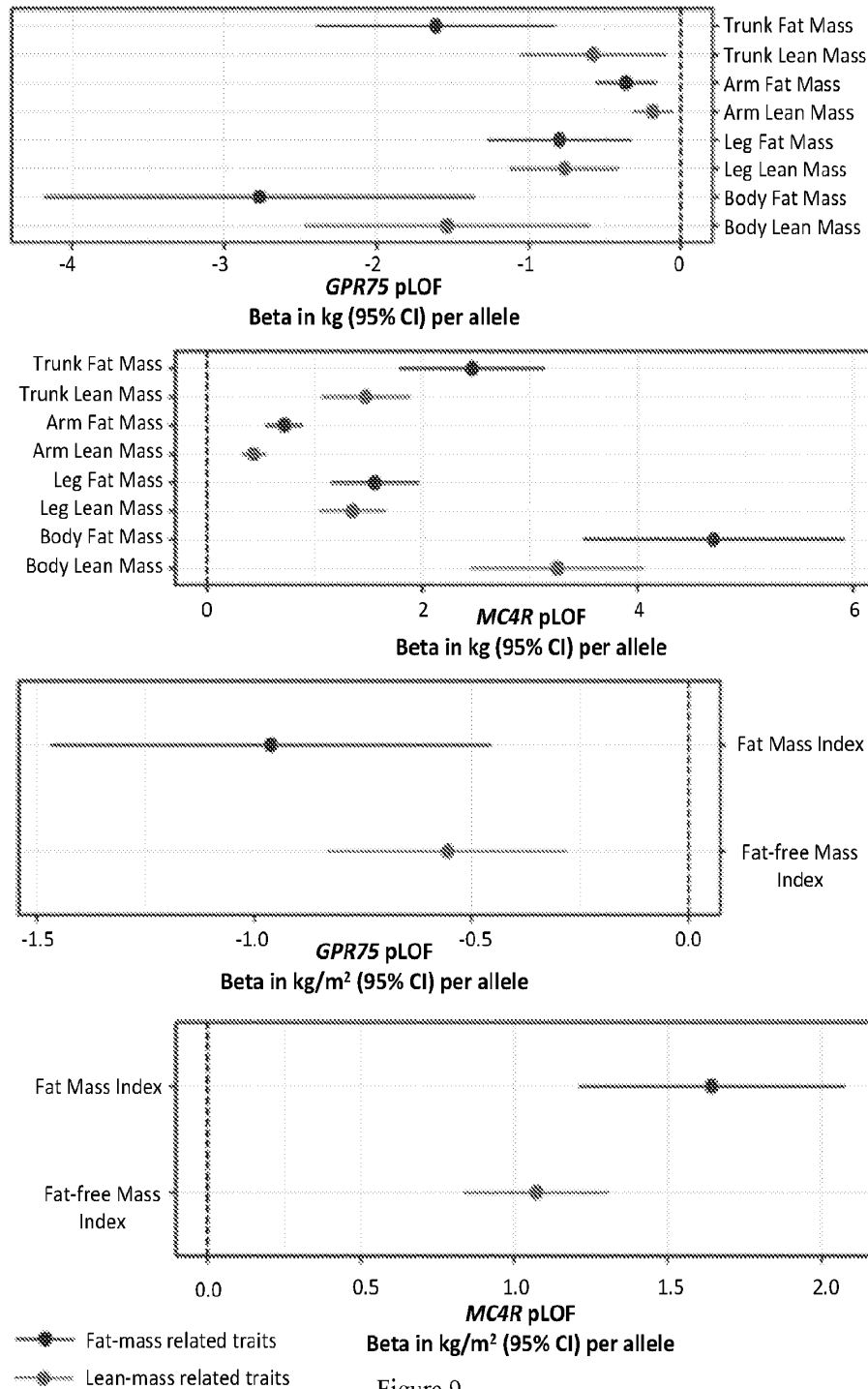


Figure 9

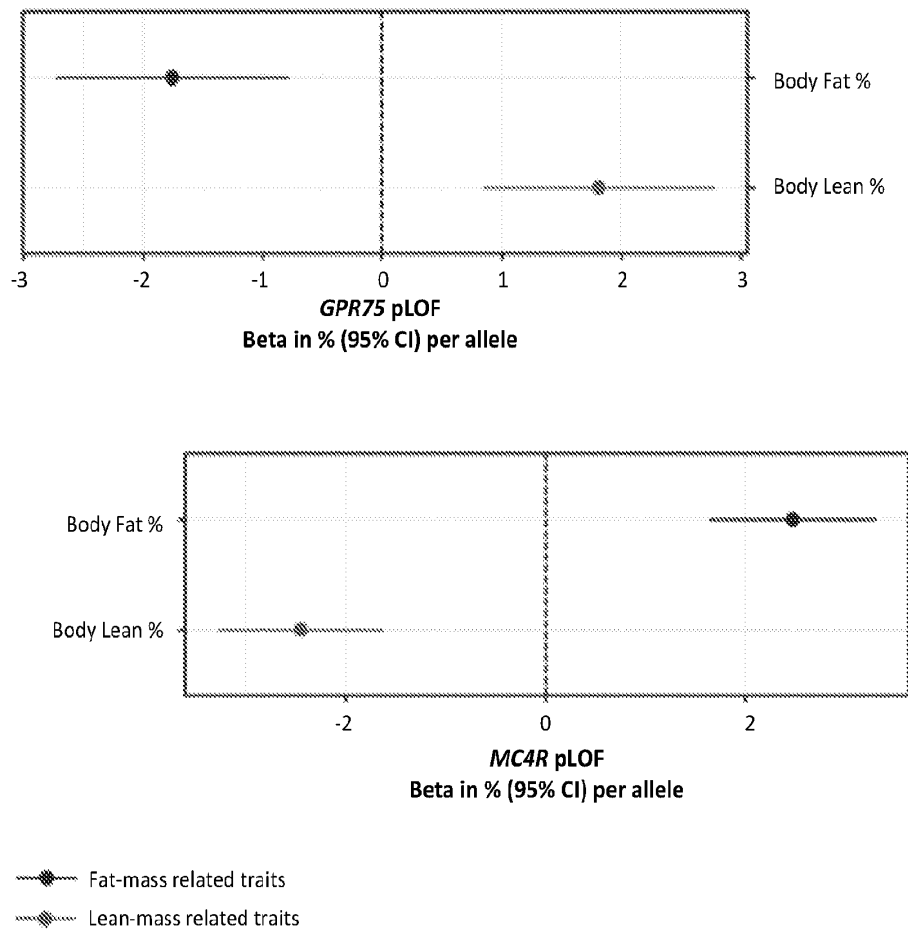


Figure 9 (cont.)

| Exposure                                          | Outcome,<br>clinical unit             | Beta in SDs<br>or odds<br>ratio (95%<br>CI) per<br>allele | p       | Allele counts<br>participants (or<br>disease cases<br>for binary<br>traits),<br>RR RA AA | Allele<br>counts<br>controls,<br>RR RA <br>AA | Beta in<br>clinical units<br>(95% CI) per<br>allele |
|---------------------------------------------------|---------------------------------------|-----------------------------------------------------------|---------|------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------|
| GPR75<br>pLOF<br>genetic<br>variants,<br>AAF < 1% | Glucose <sup>a</sup> ,<br>mg/dL       | -0.04                                                     | 5.8E-01 | 461,056 162 0                                                                            | -                                             | -0.9                                                |
|                                                   |                                       | (-0.19, 0.11)                                             |         |                                                                                          |                                               | (-4.1, 2.3)                                         |
|                                                   | HbA1c, %                              | -0.06                                                     | 3.5E-01 | 574,999 191 0                                                                            | -                                             | -0.06                                               |
|                                                   |                                       | (-0.19, 0.07)                                             |         |                                                                                          |                                               | (-0.17, 0.06)                                       |
|                                                   | AST <sup>a</sup> , U/L                | -0.01                                                     | 9.0E-01 | 515,532 182 0                                                                            | -                                             | -0.1                                                |
|                                                   |                                       | (-0.15, 0.13)                                             |         |                                                                                          |                                               | (-1.4, 1.3)                                         |
|                                                   | ALT <sup>a</sup> , U/L                | -0.11                                                     | 1.2E-01 | 518,135 182 0                                                                            | -                                             | -1.5                                                |
|                                                   |                                       | (-0.25, 0.03)                                             |         |                                                                                          |                                               | (-3.4, 0.4)                                         |
|                                                   | Triglycerides <sup>a</sup> ,<br>mg/dL | -0.05                                                     | 4.4E-01 | 501,508 178 0                                                                            | -                                             | -4.8                                                |
|                                                   |                                       | (-0.19, 0.08)                                             |         |                                                                                          |                                               | (-16.7, 7.2)                                        |
|                                                   | HDL-C <sup>a</sup> , mg/dL            | 0.19                                                      | 6.3E-03 | 467,058 167 0                                                                            | -                                             | 2.9                                                 |
|                                                   |                                       | (0.05, 0.33)                                              |         |                                                                                          |                                               | (0.8, 4.9)                                          |
|                                                   | LDL-C <sup>a</sup> , mg/dL            | -0.02                                                     | 7.9E-01 | 500,249 177 0                                                                            | -                                             | -0.6                                                |
|                                                   |                                       | (-0.15, 0.12)                                             |         |                                                                                          |                                               | (-5.2, 3.9)                                         |
|                                                   | Systolic blood<br>pressure,<br>mmHg   | -0.03                                                     | 5.8E-01 | 622,080 222 0                                                                            | -                                             | -0.6                                                |
|                                                   |                                       | (-0.15, 0.08)                                             |         |                                                                                          |                                               | (-2.7, 1.5)                                         |
|                                                   | Diastolic blood<br>pressure,<br>mmHg  | -0.03                                                     | 6.5E-01 | 618,264 222 0                                                                            | -                                             | -0.3                                                |
|                                                   |                                       | (-0.15, 0.1)                                              |         |                                                                                          |                                               | (-1.6, 1)                                           |
|                                                   | Waist-to-hip<br>ratio, ratio<br>units | -0.13                                                     | 8.0E-02 | 525,809 177 0                                                                            | -                                             | -0.011                                              |
|                                                   |                                       | (-0.27, 0.01)                                             |         |                                                                                          |                                               | (-0.024, 0.001)                                     |
|                                                   | Type 2<br>diabetes                    | 0.92                                                      | 7.3E-01 | 63,468 24 0                                                                              | 549,770<br> 191 0                             | -                                                   |
|                                                   |                                       | (0.59, 1.45) <sup>b</sup>                                 |         |                                                                                          |                                               | -                                                   |

Figure 10

SUBSTITUTE SHEET (RULE 26)



| Variant (CPRA)                          | AAF     | cDNA change HGVS                     | Protein change HGVS   | Affected exon | In genotyping array | In raw imputed data | Imputation quality INFO score, fraction of 1 <sup>a</sup> |
|-----------------------------------------|---------|--------------------------------------|-----------------------|---------------|---------------------|---------------------|-----------------------------------------------------------|
| 2:5385313<br>4:T:G                      | 2.3E-06 | c.1623A>C                            | p.Ter541Tyrex<br>t*?  | Exon 2        | No                  | No                  | -                                                         |
| 2:5385313<br>5:T:G                      | 1.2E-06 | c.1622A>C                            | p.Ter541Serex<br>t*?  | Exon 2        | No                  | No                  | -                                                         |
| 2:5385313<br>6:A:C                      | 2.3E-06 | c.1621T>G                            | p.Ter541Glutex<br>t*? | Exon 2        | No                  | No                  | -                                                         |
| 2:5385320<br>0:GGT:G                    | 7.6E-06 | c.1555_1556<br>delAC                 | p.Thr519fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:5385324<br>5:GT:G                     | 1.2E-06 | c.1511delA                           | p.Asn504fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:5385325<br>6:G:A                      | 1.2E-06 | c.1501C>T                            | p.Gln501*             | Exon 2        | No                  | No                  | -                                                         |
| 2:5385335<br>2:G:A                      | 1.3E-05 | c.1405C>T                            | p.Gln469*             | Exon 2        | No                  | No                  | -                                                         |
| 2:5385335<br>4:CCA:C                    | 5.4E-05 | c.1401_1402<br>delTG                 | p.Cys467fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:5385338<br>2:TG:T                     | 1.8E-05 | c.1374delC                           | p.Lys459fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:5385350<br>2:T:A                      | 5.8E-06 | c.1255A>T                            | p.Arg419*             | Exon 2        | No                  | No                  | -                                                         |
| 2:5385353<br>5:G:A                      | 1.4E-05 | c.1222C>T                            | p.Arg408*             | Exon 2        | No                  | No                  | -                                                         |
| 2:5385354<br>7:T:A                      | 1.0E-05 | c.1210A>T                            | p.Lys404*             | Exon 2        | No                  | No                  | -                                                         |
| 2:5385356<br>0:G:GA                     | 1.2E-06 | c.1196dupT                           | p.Cys400fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:5385364<br>1:GTT:G                    | 9.0E-06 | c.1114_1115<br>delAA                 | p.Asn372fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:5385368<br>0:CAATTC<br>AAACTGGT<br>:C | 1.2E-06 | c.1064_1076<br>delACCAAGTT<br>TGAATT | p.Tyr355fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:5385369<br>2:G:T                      | 1.2E-06 | c.1065C>A                            | p.Tyr355*             | Exon 2        | No                  | No                  | -                                                         |

Figure 12

| Variant (CPRA)     | AAF     | cDNA change HGVS | Protein change HGVS | Affected exon | In genotyping array | In raw imputed data                                           | Imputation quality INFO score, fraction of 1 <sup>a</sup> |
|--------------------|---------|------------------|---------------------|---------------|---------------------|---------------------------------------------------------------|-----------------------------------------------------------|
| 2:53853730:G:A     | 3.5E-06 | c.1027C>T        | p.Gln343*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53853771:G:C     | 2.1E-05 | c.986C>G         | p.Ser329*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53853853:G:A     | 5.1E-06 | c.904C>T         | p.Arg302*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53853877:G:A     | 7.3E-05 | c.880C>T         | p.Gln294*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53853926:G:T     | 1.8E-05 | c.831C>A         | p.Tyr277*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53853927:T:TA    | 1.2E-06 | c.829dupT        | p.Tyr277fs          | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53853946:G:GT    | 2.3E-06 | c.810_811insA    | p.Leu271fs          | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53853967:TGG:T   | 4.7E-06 | c.788_789delCC   | p.Pro263fs          | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53854009:G:A     | 1.2E-06 | c.748C>T         | p.Gln250*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53854037:A:AG    | 4.7E-06 | c.719dupC        | p.Val241fs          | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53854045:ACTTT:A | 1.7E-05 | c.708_711delAAAG | p.Arg236fs          | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53854051:T:A     | 9.3E-06 | c.706A>T         | p.Arg236*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53854057:G:A     | 2.9E-05 | c.700C>T         | p.Gln234*           | Exon 2        | No                  | Yes, but excluded after QC due to very low imputation quality | 0.007                                                     |
| 2:53854078:G:A     | 5.2E-06 | c.679C>T         | p.Gln227*           | Exon 2        | No                  | No                                                            | -                                                         |
| 2:53854099:CAG:C   | 3.5E-06 | c.656_657delCT   | p.Ser219fs          | Exon 2        | No                  | No                                                            | -                                                         |

Figure 12 (cont.)

SUBSTITUTE SHEET (RULE 26)

| Variant (CPRA)                    | AAF     | cDNA change HGVS        | Protein change HGVS | Affected exon | In genotyping array | In raw imputed data | Imputation quality INFO score, fraction of 1 <sup>a</sup> |
|-----------------------------------|---------|-------------------------|---------------------|---------------|---------------------|---------------------|-----------------------------------------------------------|
| 2:53854<br>135:CAT<br>:C          | 1.2E-06 | c.620_621del<br>AT      | p.Tyr207fs          | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>137:TAG<br>AG:T        | 1.7E-05 | c.616_619del<br>CTCT    | p.Leu206fs          | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>306:G:A                | 1.2E-05 | c.451C>T                | p.Gln151*           | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>380:G:C                | 2.1E-06 | c.377C>G                | p.Ser126*           | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>409:A:A<br>G           | 7.6E-06 | c.347dupC               | p.Cys118fs          | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>421:ACT<br>ACTGG:<br>A | 1.2E-05 | c.329_335del<br>CCAGTAG | p.Ala110fs          | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>474:C:A                | 1.2E-05 | c.283G>T                | p.Gly95*            | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>476:C:C<br>A           | 1.2E-06 | c.280dupT               | p.Cys94fs           | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>485:AG:<br>A           | 1.2E-06 | c.271delC               | p.Leu91fs           | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>644:TG:<br>T           | 4.2E-05 | c.112delC               | p.His38fs           | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>685:TC:T               | 5.2E-06 | c.71delG                | p.Gly24fs           | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>695:G:T                | 1.2E-06 | c.62C>A                 | p.Ser21*            | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>740:TG:<br>T           | 1.2E-06 | c.16delC                | p.His6fs            | Exon 2        | No                  | No                  | -                                                         |
| 2:53854<br>755:A:G                | 9.0E-06 | c.2T>C                  | p.Met1?             | Exon 2        | No                  | No                  | -                                                         |
| 2:53859<br>827:C:T                | 1.2E-06 | c.-110+1G>A             | -                   | Exon 1        | No                  | No                  | -                                                         |

Figure 12 (cont.)

SUBSTITUTE SHEET (RULE 26)

| Gene | Genetic exposure, variant type; frequency cutoff in % | AAF, fraction of 1 | Beta (95% CI) per allele in SD units of BMI | Beta (95% CI) per allele in kg/m <sup>2</sup> units of BMI | p    | Genotype counts, RR   RA   AA genotypes |
|------|-------------------------------------------------------|--------------------|---------------------------------------------|------------------------------------------------------------|------|-----------------------------------------|
| ASB3 | pLOF; AAF < 1%                                        | 0.00015            | -0.037<br>(-0.17, 0.091)                    | -0.2<br>(-0.9, 0.49)                                       | 0.57 | 645,432   194   0                       |
| ASB3 | pLOF plus any missense; AAF < 0.1%                    | 0.00467            | -0.0081<br>(-0.031, 0.015)                  | -0.044<br>(-0.17, 0.082)                                   | 0.50 | 639,601   6,023   2                     |
| ASB3 | pLOF plus any missense; AAF < 1%                      | 0.01375            | -0.0069<br>(-0.021, 0.0068)                 | -0.037<br>(-0.11, 0.037)                                   | 0.33 | 627,913   17,677   36                   |
| ASB3 | pLOF plus deleterious missense (5/5); AAF < 0.1%      | 0.00015            | -0.037<br>(-0.17, 0.091)                    | -0.2<br>(-0.9, 0.49)                                       | 0.57 | 645,432   194   0                       |
| ASB3 | pLOF plus deleterious missense (5/5); AAF < 1%        | 0.00015            | -0.037<br>(-0.17, 0.091)                    | -0.2<br>(-0.9, 0.49)                                       | 0.57 | 645,432   194   0                       |
| ASB3 | pLOF plus deleterious missense (1/5); AAF < 0.1%      | 0.00355            | -0.019<br>(-0.045, 0.0079)                  | -0.1<br>(-0.25, 0.042)                                     | 0.17 | 641,041   4,583   2                     |
| ASB3 | pLOF plus deleterious missense (1/5); AAF < 1%        | 0.01150            | -0.011<br>(-0.026, 0.0039)                  | -0.059<br>(-0.14, 0.021)                                   | 0.15 | 630,803   14,798   25                   |

Figure 13

| Gene       | Genetic exposure, variant type; frequency cutoff in % | AAF, fraction of 1 | Beta (95% CI) per allele in SD units of BMI | Beta (95% CI) per allele in kg/m <sup>2</sup> units of BMI | p    | Genotype counts, RR   RA   AA genotypes |
|------------|-------------------------------------------------------|--------------------|---------------------------------------------|------------------------------------------------------------|------|-----------------------------------------|
| GPR75-ASB3 | pLOF; AAF < 1%                                        | 0.00015            | -0.039<br>(-0.17, 0.088)                    | -0.21<br>(-0.89, 0.47)                                     | 0.55 | 645,426   200   0                       |
| GPR75-ASB3 | pLOF plus any missense; AAF < 0.1%                    | 0.00497            | -0.0096<br>(-0.032, 0.013)                  | -0.052<br>(-0.17, 0.071)                                   | 0.41 | 639,208   6,416   2                     |
| GPR75-ASB3 | pLOF plus any missense; AAF < 1%                      | 0.01565            | -0.0012<br>(-0.014, 0.012)                  | -0.0065<br>(-0.076, 0.063)                                 | 0.85 | 625,469   20,110   47                   |
| GPR75-ASB3 | pLOF plus deleterious missense (5/5); AAF < 0.1%      | 0.00015            | -0.039<br>(-0.17, 0.088)                    | -0.21<br>(-0.89, 0.47)                                     | 0.55 | 645,426   200   0                       |
| GPR75-ASB3 | pLOF plus deleterious missense (5/5); AAF < 1%        | 0.00015            | -0.039<br>(-0.17, 0.088)                    | -0.21<br>(-0.89, 0.47)                                     | 0.55 | 645,426   200   0                       |
| GPR75-ASB3 | pLOF plus deleterious missense (1/5); AAF < 0.1%      | 0.00385            | -0.02<br>(-0.046, 0.0056)                   | -0.11<br>(-0.25, 0.03)                                     | 0.13 | 640,655   4,969   2                     |
| GPR75-ASB3 | pLOF plus deleterious missense (1/5); AAF < 1%        | 0.01319            | -0.0045<br>(-0.019, 0.0096)                 | -0.024<br>(-0.1, 0.052)                                    | 0.53 | 628,634   16,956   36                   |

Figure 13 (cont.)

| Genetic exposure, variant type; frequency cutoff in % | Additional covariates adjusted for in the analysis in addition to standard covariates*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Beta (95% CI) per allele in SD units of BMI | Beta (95% CI) per allele in kg/m <sup>2</sup> units of BMI | P       | AAF, fraction of 1 | Genotype counts, RR   RA   AA genotypes |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------|---------|--------------------|-----------------------------------------|
| GPR75 pLOF; AAF < 1%                                  | ASB3 pLOF (AAF < 1%); ASB3 pLOF plus any missense (AAF < 0.1%); ASB3 pLOF plus any missense (AAF < 1%); ASB3 pLOF plus deleterious missense (5/5) (AAF < 0.1%); ASB3 pLOF plus deleterious missense (5/5) (AAF < 1%); ASB3 pLOF plus deleterious missense (1/5) (AAF < 0.1%); ASB3 pLOF plus deleterious missense (1/5) (AAF < 1%); GPR75-ASB3 pLOF (AAF < 1%); GPR75-ASB3 pLOF plus any missense (AAF < 0.1%); GPR75-ASB3 pLOF plus any missense (AAF < 1%); GPR75-ASB3 pLOF plus deleterious missense (5/5) (AAF < 0.1%); GPR75-ASB3 pLOF plus deleterious missense (5/5) (AAF < 1%); GPR75-ASB3 pLOF plus deleterious missense (1/5) (AAF < 0.1%); GPR75-ASB3 pLOF plus deleterious missense (1/5) (AAF < 1%) | -0.34<br>(-0.46, -0.22)                     | -1.85<br>(-2.50, -1.19)                                    | 3.1E-08 | 0.00018            | 645,398   228   0                       |
| GPR75 pLOF; AAF < 1%                                  | 26 common variants associated with BMI at the locus in Europeans (listed in Table S9)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -0.34<br>(-0.46, -0.22)                     | -1.85<br>(-2.50, -1.19)                                    | 3.1E-08 | 0.00018            | 645,398   228   0                       |

Figure 14

| Variant (CPRA) | dbSNP rsID  | AAF   | PPA   | Sentinel<br>variant in<br>credible set | Nearest gene      |
|----------------|-------------|-------|-------|----------------------------------------|-------------------|
| 2:53634252:A:G | rs59428052  | 0.147 | 0.304 | Yes                                    | ASB3,GPR75-ASB3   |
| 2:53899622:C:A | rs805422    | 0.431 | 0.063 | No                                     | PSME4             |
| 2:53966056:T:C | rs805343    | 0.524 | 0.047 | No                                     | PSME4             |
| 2:53965962:A:G | rs805342    | 0.523 | 0.046 | No                                     | PSME4             |
| 2:53893683:G:A | rs805412    | 0.415 | 0.045 | No                                     | PSME4             |
| 2:53812428:C:G | rs2287347   | 0.092 | 0.039 | No                                     | ERLEC1,GPR75-ASB3 |
| 2:53813267:A:G | rs6545368   | 0.092 | 0.026 | No                                     | ERLEC1,GPR75-ASB3 |
| 2:53965020:G:A | rs805341    | 0.522 | 0.024 | No                                     | PSME4             |
| 2:53921194:C:A | rs805330    | 0.431 | 0.022 | No                                     | PSME4             |
| 2:53807744:G:T | rs6724214   | 0.092 | 0.021 | No                                     | ERLEC1,GPR75-ASB3 |
| 2:53938709:G:T | rs805361    | 0.438 | 0.02  | No                                     | PSME4             |
| 2:53934885:C:T | rs805358    | 0.439 | 0.015 | No                                     | PSME4             |
| 2:53907915:C:T | rs805318    | 0.44  | 0.01  | No                                     | PSME4             |
| 2:54051530:T:C | rs7590846   | 0.374 | 0.007 | No                                     | ACYP2             |
| 2:54051448:C:G | rs1559037   | 0.373 | 0.006 | No                                     | ACYP2             |
| 2:54052186:A:G | rs1833497   | 0.375 | 0.005 | No                                     | ACYP2             |
| 2:54052992:A:C | rs1862122   | 0.375 | 0.005 | No                                     | ACYP2             |
| 2:53899904:C:T | rs805423    | 0.482 | 0.005 | No                                     | PSME4             |
| 2:53995028:C:A | rs7591431   | 0.361 | 0.004 | No                                     | ACYP2             |
| 2:53958004:A:G | rs805335    | 0.49  | 0.004 | No                                     | PSME4             |
| 2:54053847:A:G | rs7558126   | 0.374 | 0.004 | No                                     | ACYP2             |
| 2:53733092:C:T | rs114272138 | 0.022 | 0.003 | No                                     | ASB3,GPR75-ASB3   |
| 2:53822332:G:A | rs3095756   | 0.412 | 0.002 | No                                     | GPR75-ASB3        |
| 2:53720820:C:A | rs77601694  | 0.022 | 0.002 | No                                     | ASB3,GPR75-ASB3   |
| 2:53822111:G:A | rs2542577   | 0.412 | 0.002 | No                                     | GPR75-ASB3        |
| 2:53821221:G:A | rs2542575   | 0.412 | 0.002 | No                                     | GPR75-ASB3        |

Figure 15

SUBSTITUTE SHEET (RULE 26)

| Variant (CPRA) | Annotation        | Nonsynonymous variants in LD<br>( $R^2 > 0.8$ ) | $R^2$ with<br>nonsynonymous<br>variant |
|----------------|-------------------|-------------------------------------------------|----------------------------------------|
| 2:53634252:A:G | intergenic        | None                                            |                                        |
| 2:53899622:C:A | intronic          | None                                            |                                        |
| 2:53966056:T:C | intronic          | None                                            |                                        |
| 2:53965962:A:G | intronic          | None                                            |                                        |
| 2:53893683:G:A | synonymous        | None                                            |                                        |
| 2:53812428:C:G | intronic;intronic | None                                            |                                        |
| 2:53813267:A:G | intronic;intronic | None                                            |                                        |
| 2:53965020:G:A | intronic          | None                                            |                                        |
| 2:53921194:C:A | intronic          | None                                            |                                        |
| 2:53807744:G:T | intronic          | None                                            |                                        |
| 2:53938709:G:T | intronic          | None                                            |                                        |
| 2:53934885:C:T | intronic          | None                                            |                                        |
| 2:53907915:C:T | intronic          | None                                            |                                        |
| 2:54051530:T:C | intronic          | None                                            |                                        |
| 2:54051448:C:G | intronic          | None                                            |                                        |
| 2:54052186:A:G | intronic          | None                                            |                                        |
| 2:54052992:A:C | intronic          | None                                            |                                        |
| 2:53899904:C:T | synonymous        | None                                            |                                        |
| 2:53995028:C:A | intronic          | None                                            |                                        |
| 2:53958004:A:G | intronic          | None                                            |                                        |
| 2:54053847:A:G | intronic          | None                                            |                                        |
| 2:53733092:C:T | intronic          | 2:53765485:G:C,2:53765485:G:C                   | 0.83,0.83                              |
| 2:53822332:G:A | intergenic        | None                                            |                                        |
| 2:53720820:C:A | intronic;intronic | 2:53765485:G:C,2:53765485:G:C                   | 0.83,0.83                              |
| 2:53822111:G:A | intergenic        | None                                            |                                        |
| 2:53821221:G:A | intergenic        | None                                            |                                        |

Figure 15 (cont.)

SUBSTITUTE SHEET (RULE 26)

| Variant (CPRA) | Nonsynonymous variant effect | Gene for nonsynonymous change | Sentinel eQTL in LD ( $R^2 > 0.8$ ) |
|----------------|------------------------------|-------------------------------|-------------------------------------|
| 2:53634252:A:G |                              |                               | None                                |
| 2:53899622:C:A |                              |                               | None                                |
| 2:53966056:T:C |                              |                               | None                                |
| 2:53965962:A:G |                              |                               | None                                |
| 2:53893683:G:A |                              |                               | None                                |
| 2:53812428:C:G |                              |                               | None                                |
| 2:53813267:A:G |                              |                               | None                                |
| 2:53965020:G:A |                              |                               | None                                |
| 2:53921194:C:A |                              |                               | None                                |
| 2:53807744:G:T |                              |                               | None                                |
| 2:53938709:G:T |                              |                               | None                                |
| 2:53934885:C:T |                              |                               | None                                |
| 2:53907915:C:T |                              |                               | None                                |
| 2:54051530:T:C |                              |                               | None                                |
| 2:54051448:C:G |                              |                               | None                                |
| 2:54052186:A:G |                              |                               | None                                |
| 2:54052992:A:C |                              |                               | None                                |
| 2:53899904:C:T |                              |                               | None                                |
| 2:53995028:C:A |                              |                               | None                                |
| 2:53958004:A:G |                              |                               | None                                |
| 2:54053847:A:G |                              |                               | None                                |
| 2:53733092:C:T | missense,missense            | ASB3,GPR75-ASB3               | None                                |
| 2:53822332:G:A |                              |                               | None                                |
| 2:53720820:C:A | missense,missense            | ASB3,GPR75-ASB3               | None                                |
| 2:53822111:G:A |                              |                               | None                                |
| 2:53821221:G:A |                              |                               | None                                |

Figure 15 (cont.)

SUBSTITUTE SHEET (RULE 26)

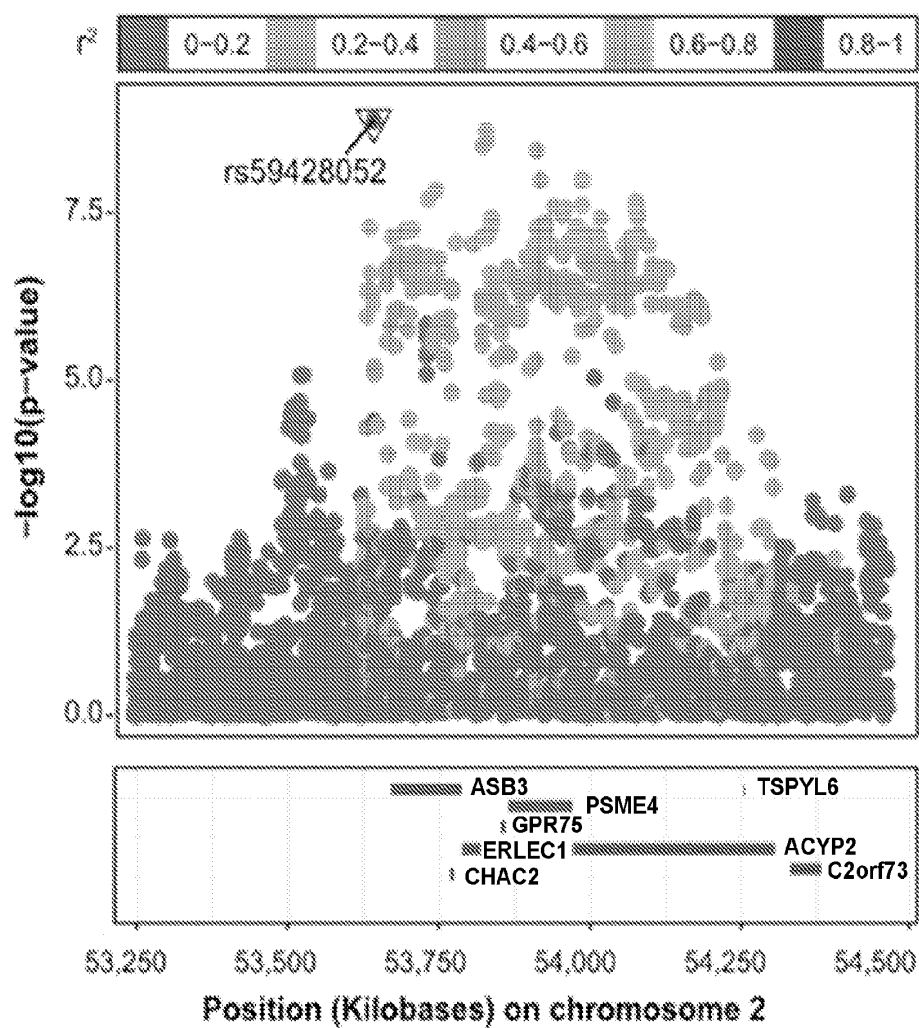


Figure 16

SUBSTITUTE SHEET (RULE 26)

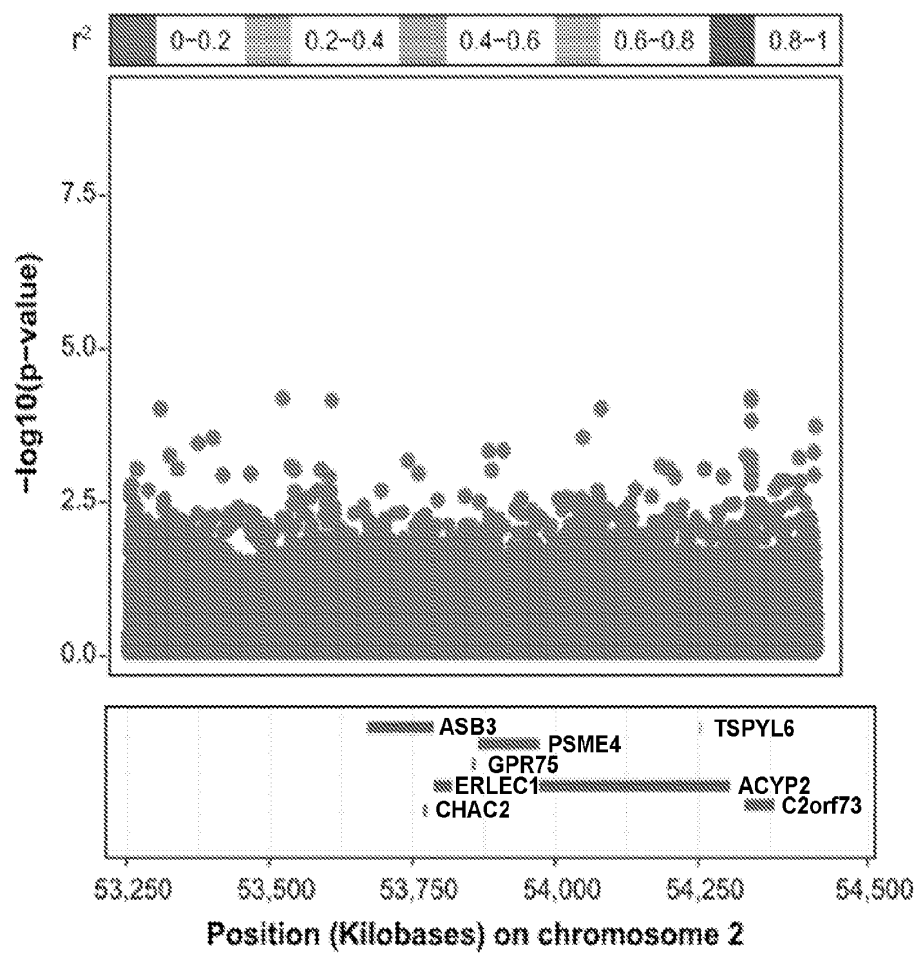


Figure 16 (cont.)

SUBSTITUTE SHEET (RULE 26)

| Exposure                                  | Excluded genetic variants                   | Number of genetic variants left in the analysis | Beta (95% CI) per allele in SD units of BMI | p       |
|-------------------------------------------|---------------------------------------------|-------------------------------------------------|---------------------------------------------|---------|
| GPR75 pLOF genetic variants with AAF < 1% | None (main analysis as reported in Table 1) | 46                                              | -0.34 (-0.46, -0.22)                        | 2.6E-08 |
|                                           | 2:53853134:T:G                              | 45                                              | -0.34 (-0.46, -0.22)                        | 2.5E-08 |
|                                           | 2:53853135:T:G                              | 45                                              | -0.33 (-0.45, -0.22)                        | 3.9E-08 |
|                                           | 2:53853136:A:C                              | 45                                              | -0.34 (-0.45, -0.22)                        | 3.9E-08 |
|                                           | 2:53853200:GGT:G                            | 45                                              | -0.34 (-0.46, -0.22)                        | 3.0E-08 |
|                                           | 2:53853245:GT:G                             | 45                                              | -0.34 (-0.46, -0.22)                        | 2.7E-08 |
|                                           | 2:53853256:G:A                              | 45                                              | -0.33 (-0.45, -0.22)                        | 3.9E-08 |
|                                           | 2:53853352:G:A                              | 45                                              | -0.36 (-0.49, -0.24)                        | 4.9E-09 |
|                                           | 2:53853354:CCA:C                            | 45                                              | -0.36 (-0.48, -0.24)                        | 8.1E-09 |
|                                           | 2:53853382:TG:T                             | 45                                              | -0.35 (-0.48, -0.23)                        | 3.6E-08 |
|                                           | 2:53853502:T:A                              | 45                                              | -0.33 (-0.45, -0.21)                        | 7.0E-08 |
|                                           | 2:53853535:G:A                              | 45                                              | -0.34 (-0.47, -0.22)                        | 5.5E-08 |
|                                           | 2:53853547:T:A                              | 45                                              | -0.33 (-0.45, -0.21)                        | 8.4E-08 |
|                                           | 2:53853560:G:GA                             | 45                                              | -0.33 (-0.45, -0.21)                        | 6.2E-08 |

Figure 17

SUBSTITUTE SHEET (RULE 26)

| Exposure                                         | Excluded genetic variants    | Number of genetic variants left in the analysis | Beta (95% CI) per allele in SD units of BMI | p       |
|--------------------------------------------------|------------------------------|-------------------------------------------------|---------------------------------------------|---------|
| <i>GPR75</i> pLOF genetic variants with AAF < 1% | 2:53853641:GTT:G             | 45                                              | -0.34 (-0.46, -0.22)                        | 2.8E-08 |
|                                                  | 2:53853680:CAATTCAAAC TGGT:C | 45                                              | -0.34 (-0.46, -0.22)                        | 2.4E-08 |
|                                                  | 2:53853692:G:T               | 45                                              | -0.34 (-0.46, -0.22)                        | 1.9E-08 |
|                                                  | 2:53853730:G:A               | 45                                              | -0.34 (-0.46, -0.22)                        | 2.3E-08 |
|                                                  | 2:53853771:G:C               | 45                                              | -0.34 (-0.46, -0.22)                        | 2.2E-08 |
|                                                  | 2:53853853:G:A               | 45                                              | -0.34 (-0.46, -0.22)                        | 2.2E-08 |
|                                                  | 2:53853877:G:A               | 45                                              | -0.33 (-0.45, -0.21)                        | 1.2E-07 |
|                                                  | 2:53853926:G:T               | 45                                              | -0.33 (-0.45, -0.21)                        | 5.9E-08 |
|                                                  | 2:53853927:T:TA              | 45                                              | -0.34 (-0.46, -0.22)                        | 3.0E-08 |
|                                                  | 2:53853946:G:GT              | 45                                              | -0.33 (-0.45, -0.21)                        | 5.4E-08 |
|                                                  | 2:53853967:TGG:T             | 45                                              | -0.34 (-0.46, -0.22)                        | 1.9E-08 |
|                                                  | 2:53854009:G:A               | 45                                              | -0.34 (-0.46, -0.22)                        | 2.1E-08 |
|                                                  | 2:53854037:A:AG              | 45                                              | -0.33 (-0.45, -0.21)                        | 4.6E-08 |
|                                                  | 2:53854045:ACTTT:A           | 45                                              | -0.34 (-0.46, -0.21)                        | 1.0E-07 |

Figure 17 (cont.)

SUBSTITUTE SHEET (RULE 26)

| Exposure                                         | Excluded genetic variants | Number of genetic variants left in the analysis | Beta (95% CI) per allele in SD units of BMI | p       |
|--------------------------------------------------|---------------------------|-------------------------------------------------|---------------------------------------------|---------|
| <i>GPR75</i> pLOF genetic variants with AAF < 1% | 2:53854051:T:A            | 45                                              | -0.33 (-0.45, -0.21)                        | 8.5E-08 |
|                                                  | 2:53854057:G:A            | 45                                              | -0.34 (-0.47, -0.2)                         | 4.7E-07 |
|                                                  | 2:53854078:G:A            | 45                                              | -0.34 (-0.46, -0.22)                        | 1.7E-08 |
|                                                  | 2:53854099:CAG:C          | 45                                              | -0.33 (-0.45, -0.21)                        | 8.9E-08 |
|                                                  | 2:53854135:CAT:C          | 45                                              | -0.34 (-0.46, -0.22)                        | 3.0E-08 |
|                                                  | 2:53854137:TAGAG:T        | 45                                              | -0.34 (-0.46, -0.22)                        | 3.3E-08 |
|                                                  | 2:53854306:G:A            | 45                                              | -0.34 (-0.46, -0.22)                        | 3.1E-08 |
|                                                  | 2:53854380:G:C            | 45                                              | -0.34 (-0.46, -0.22)                        | 2.3E-08 |
|                                                  | 2:53854409:A:AG           | 45                                              | -0.34 (-0.46, -0.22)                        | 2.7E-08 |
|                                                  | 2:53854421:ACTACTGG:A     | 45                                              | -0.31 (-0.43, -0.19)                        | 7.2E-07 |
|                                                  | 2:53854474:C:A            | 45                                              | -0.34 (-0.46, -0.22)                        | 1.8E-08 |
|                                                  | 2:53854476:C:CA           | 45                                              | -0.34 (-0.46, -0.23)                        | 1.4E-08 |
|                                                  | 2:53854485:AG:A           | 45                                              | -0.34 (-0.46, -0.22)                        | 2.3E-08 |
|                                                  | 2:53854644:TG:T           | 45                                              | -0.34 (-0.46, -0.21)                        | 5.6E-08 |
|                                                  | 2:53854685:TC:T           | 45                                              | -0.34 (-0.45, -0.22)                        | 3.5E-08 |

Figure 17 (cont.)

| Exposure                                         | Excluded genetic variants                                                                   | Number of genetic variants left in the analysis | Beta (95% CI) per allele in SD units of BMI | p       |
|--------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------|---------|
| <i>GPR75</i> pLOF genetic variants with AAF < 1% | 2:53854695:G:T                                                                              | 45                                              | -0.34 (-0.46, -0.22)                        | 2.3E-08 |
|                                                  | 2:53854740:TG:T                                                                             | 45                                              | -0.34 (-0.46, -0.22)                        | 2.6E-08 |
|                                                  | 2:53854755:A:G                                                                              | 45                                              | -0.34 (-0.46, -0.22)                        | 2.1E-08 |
|                                                  | 2:53859827:C:T                                                                              | 45                                              | -0.33 (-0.45, -0.21)                        | 4.9E-08 |
|                                                  | 5 variants associated with body mass index (Ala110fs, Ser219fs, Gln234*, Cys400fs, Lys404*) | 41                                              | -0.26 (-0.39, -0.12)                        | 2.2E-04 |

Figure 17 (cont.)

| Gene                                            | Genetic exposure,<br>variant type | Description                                  | AAF, fraction of 1 | Beta (95% CI)<br>per allele in SD<br>units of BMI | p       |
|-------------------------------------------------|-----------------------------------|----------------------------------------------|--------------------|---------------------------------------------------|---------|
| 2:53853547:T:A; <i>GPR75</i><br>Lys404*         | 404* allele                       | Single variant<br>exome analysis<br>(AAF<1%) | 1.0E-05            | -1.77<br>(-3.12, -0.43)                           | 9.5E-03 |
| 2:53853560:G:GA; <i>GPR75</i><br>Cys400fs       | 400fs allele                      | Single variant<br>exome analysis<br>(AAF<1%) | 1.2E-06            | -2.25<br>(-4.04, -0.47)                           | 1.3E-02 |
| 2:53854057:G:A; <i>GPR75</i><br>Gln234*         | 234* allele                       | Single variant<br>exome analysis<br>(AAF<1%) | 2.9E-05            | -0.35<br>(-0.64, -0.06)                           | 1.8E-02 |
| 2:53854099:CAG:C; <i>GPR75</i><br>Ser219fs      | 219fs allele                      | Single variant<br>exome analysis<br>(AAF<1%) | 3.5E-06            | -1.16<br>(-2.19, -0.13)                           | 2.8E-02 |
| 2:53854421:ACTACTGG:A;<br><i>GPR75</i> Ala110fs | 110fs allele                      | Single variant<br>exome analysis<br>(AAF<1%) | 1.2E-05            | -0.99<br>(-1.55, -0.42)                           | 6.2E-04 |

Figure 18

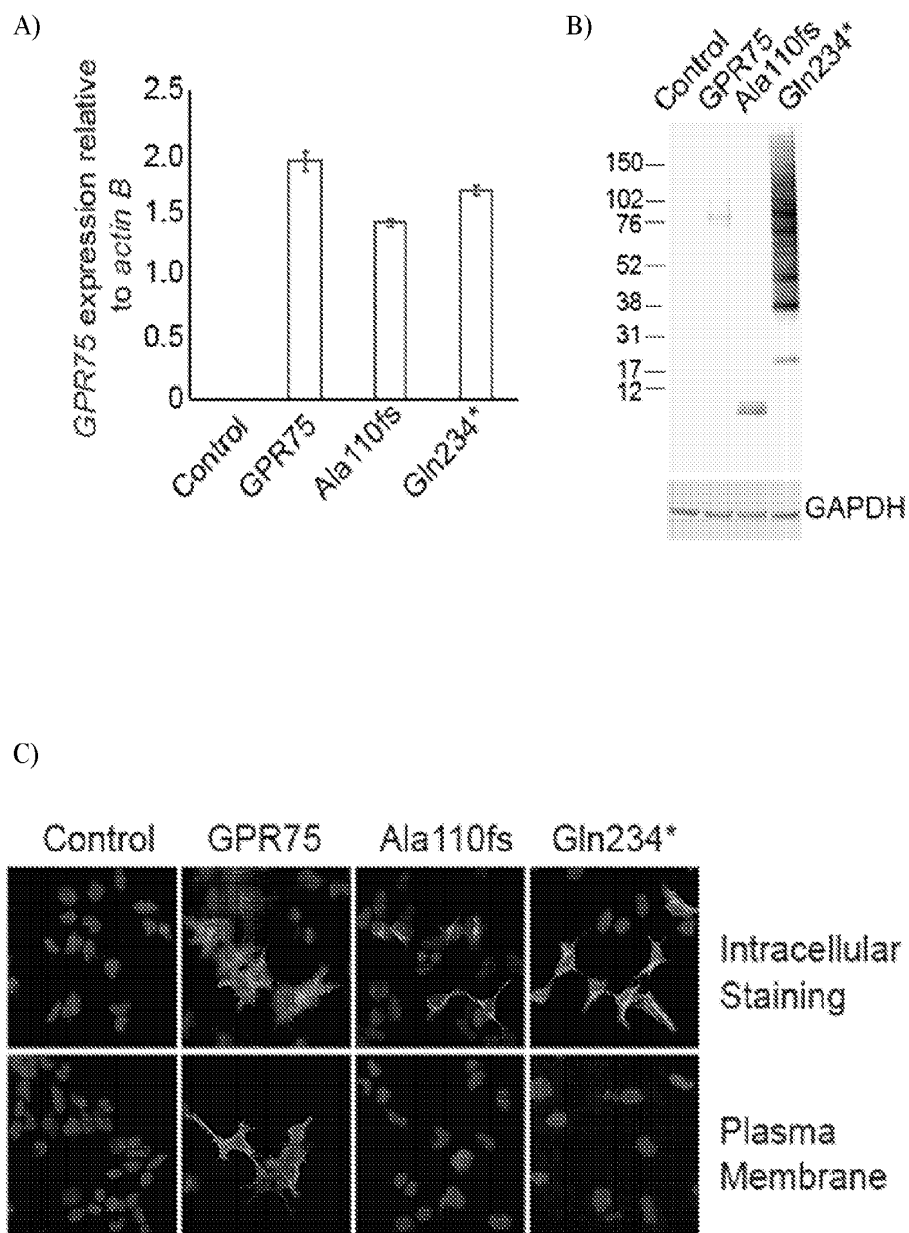


Figure 19

SUBSTITUTE SHEET (RULE 26)

D)

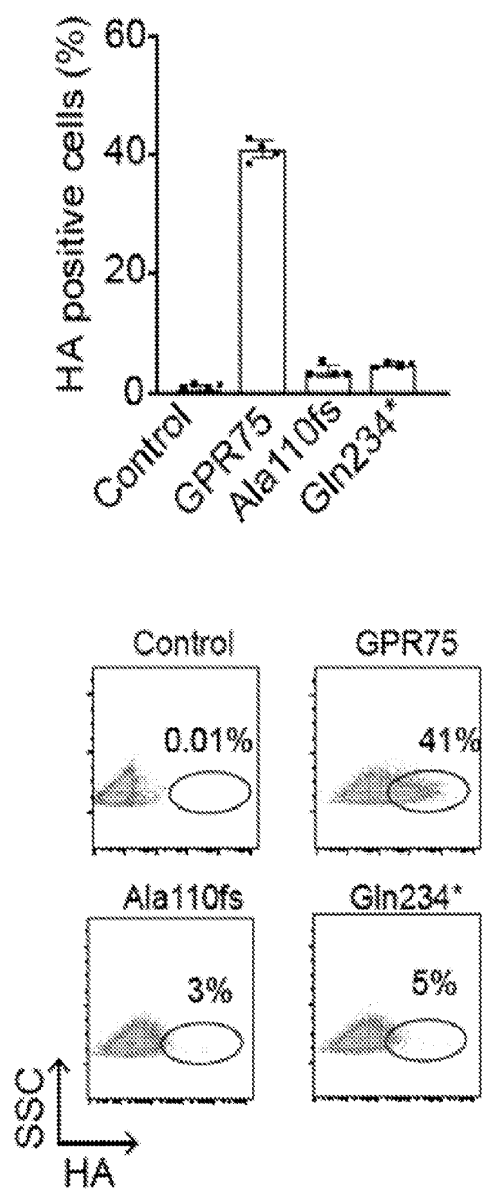


Figure 19 (cont.)

| Exposure                                                                 | Number of variant sites | Beta (95% CI) per allele in SD units of BMI | p       | AAF, fraction of 1 | Genotype counts, RR   RA   AA genotypes | Beta (95% CI) per allele in kg/m <sup>2</sup> units of BMI |
|--------------------------------------------------------------------------|-------------------------|---------------------------------------------|---------|--------------------|-----------------------------------------|------------------------------------------------------------|
| N-terminal variants – truncation <i>before</i> last intracellular domain | 32                      | -0.38<br>(-0.53, -0.23)                     | 4.1E-07 | 0.00012            | 645,477   149   0                       | -2.1 (-2.9, -1.3)                                          |
| C-terminal variants – truncation <i>within</i> last intracellular domain | 14                      | -0.26<br>(-0.46, -0.06)                     | 0.012   | 0.00006            | 645,547   79   0                        | -1.4 (-2.5, -0.3)                                          |
| N-terminal variants – truncation <i>before</i> last 100 amino acids      | 37                      | -0.4<br>(-0.54, -0.26)                      | 6.4E-09 | 0.00014            | 645,450   176   0                       | -2.2 (-2.9, -1.4)                                          |
| C-terminal variants – truncation <i>within</i> last 100 amino acids      | 9                       | -0.13<br>(-0.38, 0.12)                      | 0.32    | 0.00004            | 645,574   52   0                        | -0.7 (-2.1, 0.7)                                           |

Figure 20

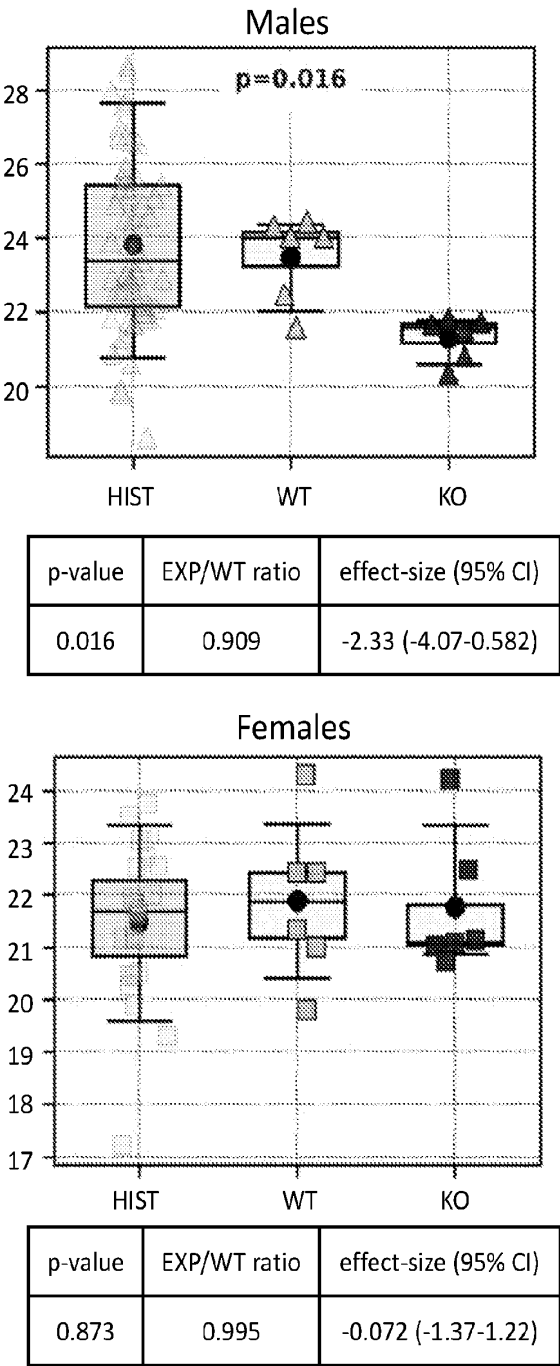


Figure 21

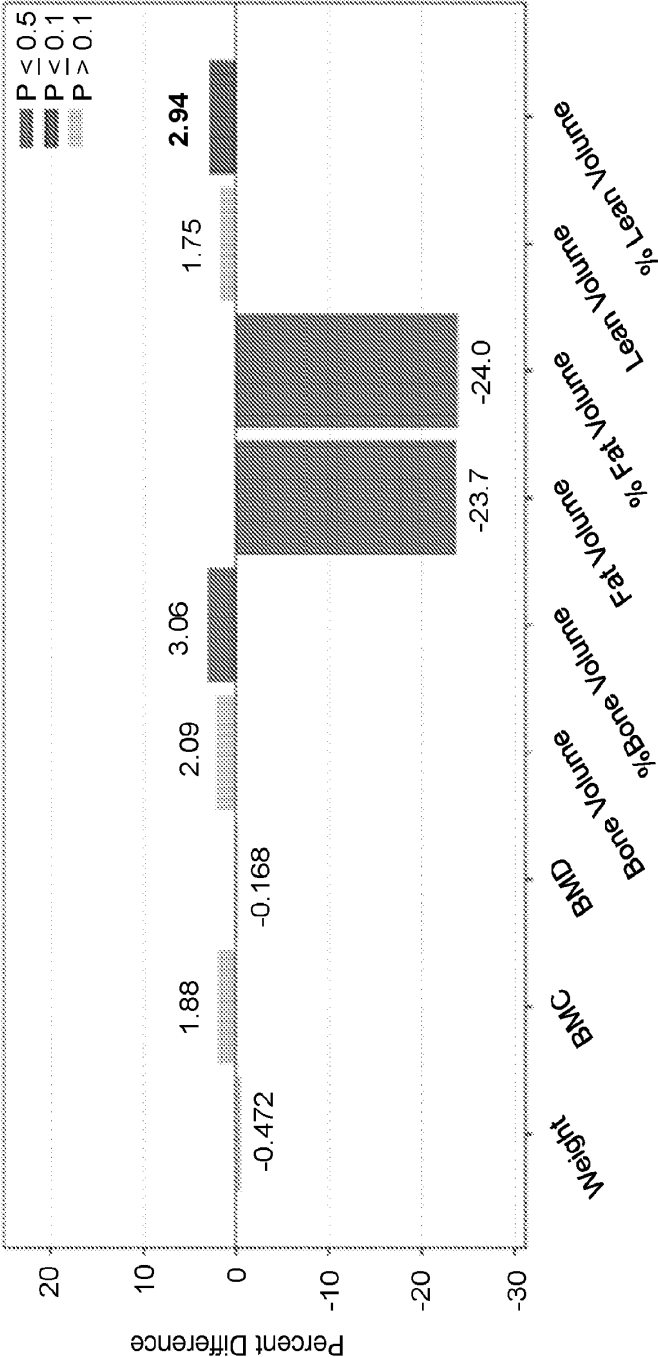


Figure 22

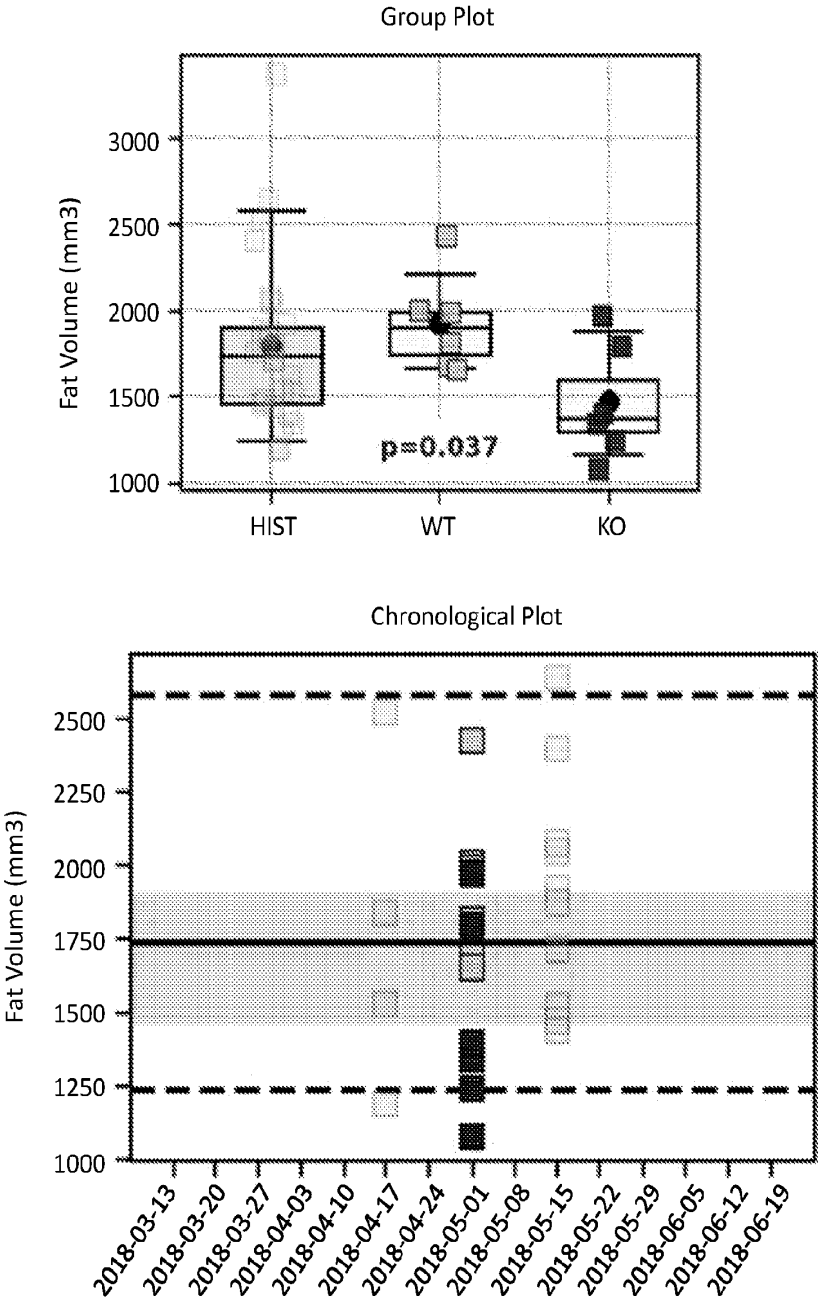


Figure 23

Fat Volume (mm3)

| group | n  | mean | std | p05  | med. | P95  |
|-------|----|------|-----|------|------|------|
| WT    | 6  | 1926 | 285 | 1666 | 1900 | 2212 |
| KO    | 6  | 1469 | 340 | 1160 | 1368 | 1879 |
| HIST  | 26 | 1799 | 496 | 1239 | 1736 | 2578 |

| p-value | EXP/WT ratio | effect-size (95% CI) |
|---------|--------------|----------------------|
| 0.037   | 0.763        | -1.45 (-2.94-0.032)  |

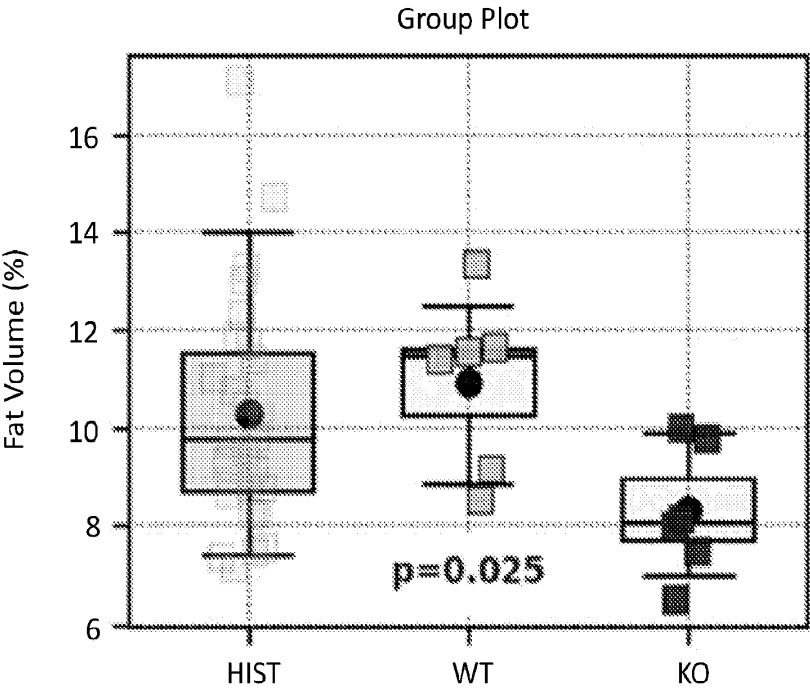
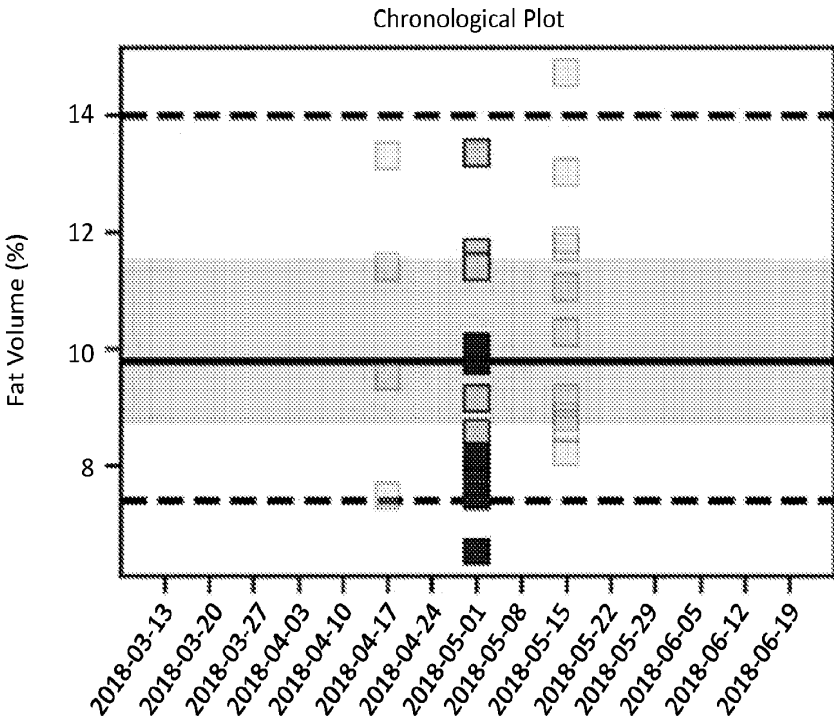


Figure 23 (cont.)



| group | n  | mean | std  | p05  | med. | P95  |
|-------|----|------|------|------|------|------|
| WT    | 6  | 10.9 | 1.78 | 8.85 | 11.5 | 12.5 |
| KO    | 6  | 8.32 | 1.36 | 6.98 | 8.06 | 9.91 |
| HIST  | 26 | 10.3 | 2.41 | 7.41 | 9.79 | 14.0 |

| p-value | EXP/WT ratio | effect-size (95% CI) |
|---------|--------------|----------------------|
| 0.025   | 0.760        | -1.66 (-3.20--0.118) |

Figure 23 (cont.)

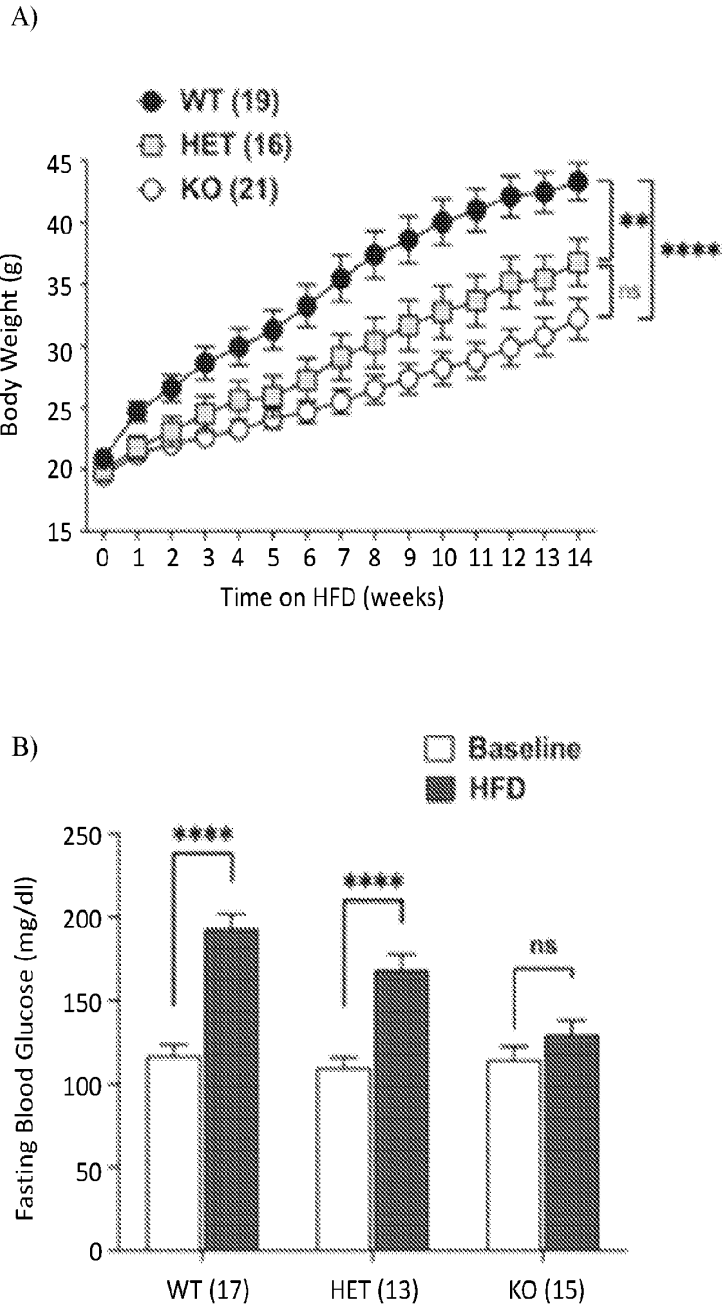


Figure 24

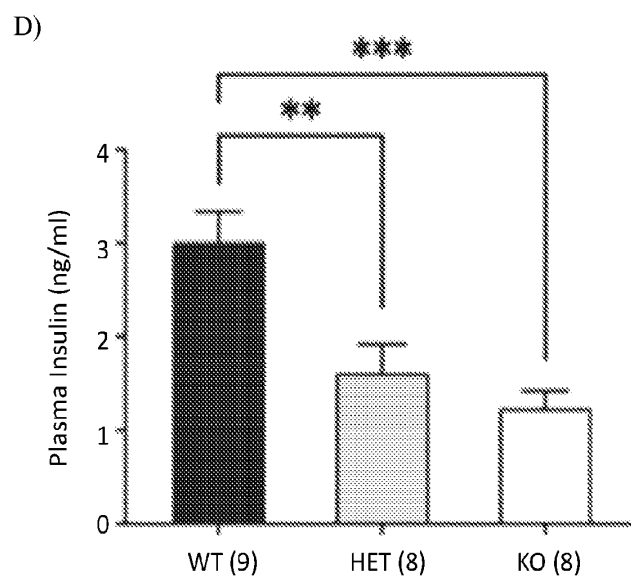
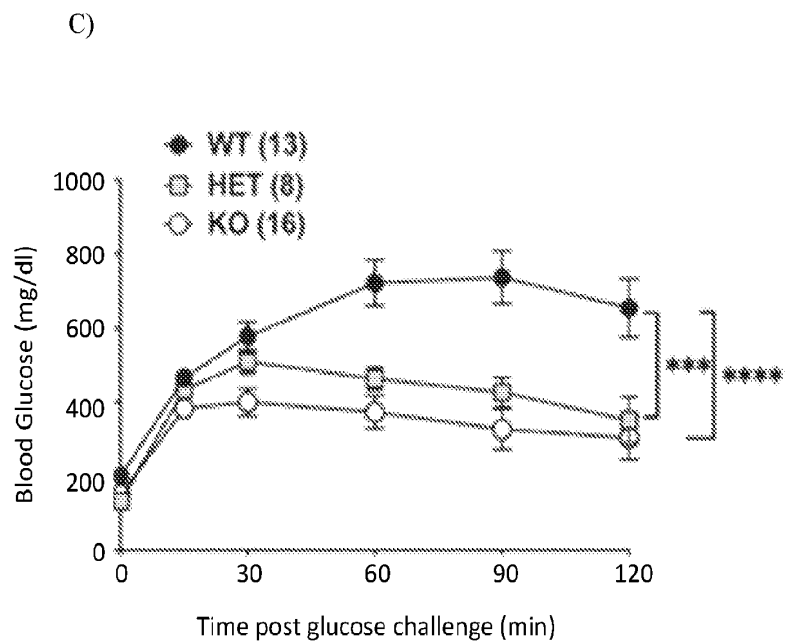
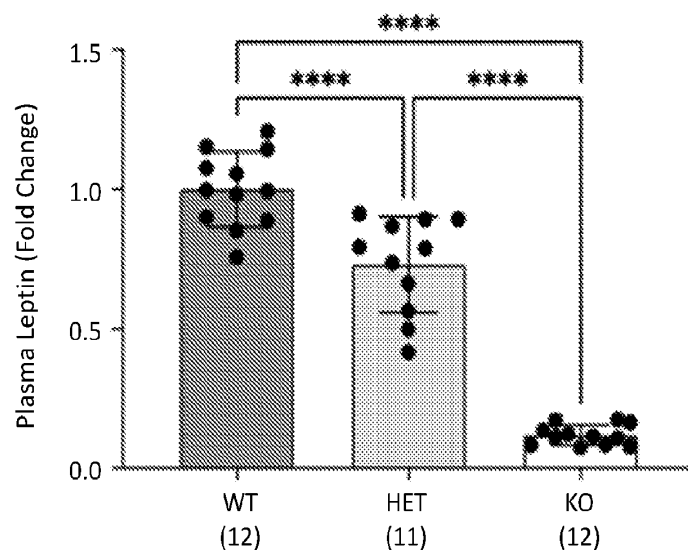


Figure 24 (cont.)

SUBSTITUTE SHEET (RULE 26)

A)



B)

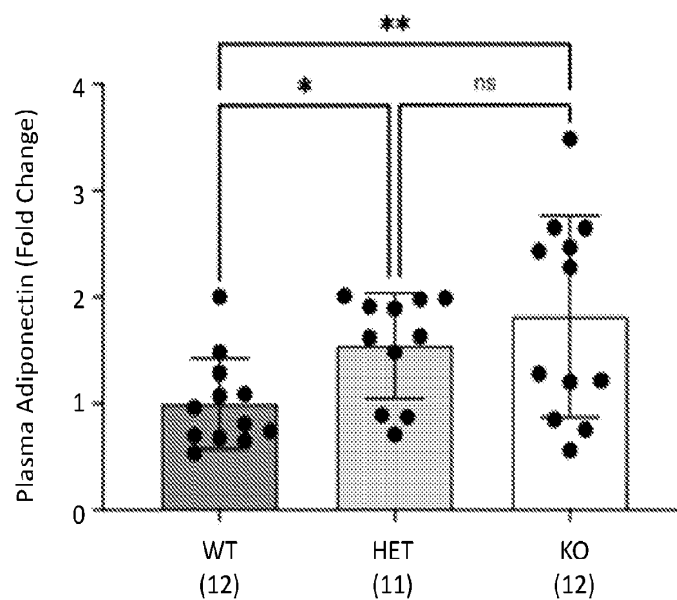


Figure 25

SUBSTITUTE SHEET (RULE 26)

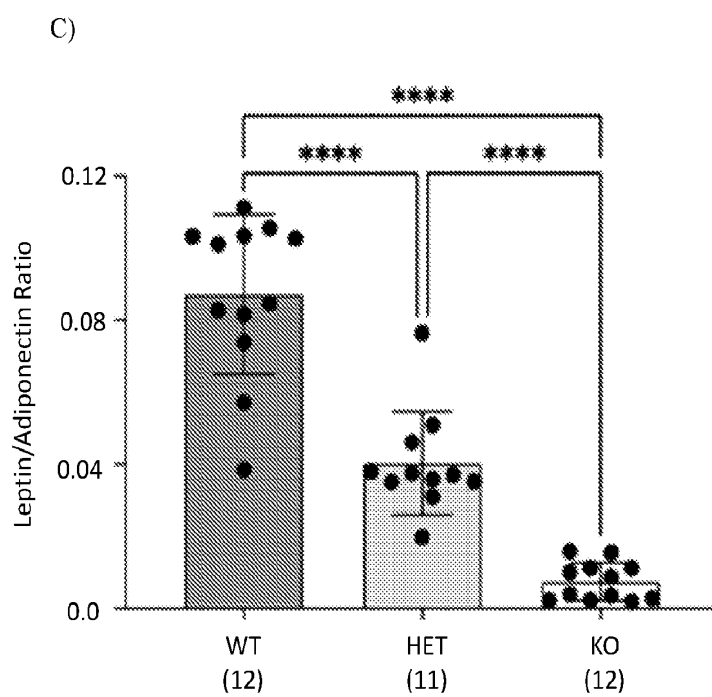


Figure 25 (cont.)

A)

● Gpr75<sup>+/+</sup> + HFD      ■ Gpr75<sup>+/-</sup> + HFD      ▲ Gpr75<sup>-/-</sup> + HFD

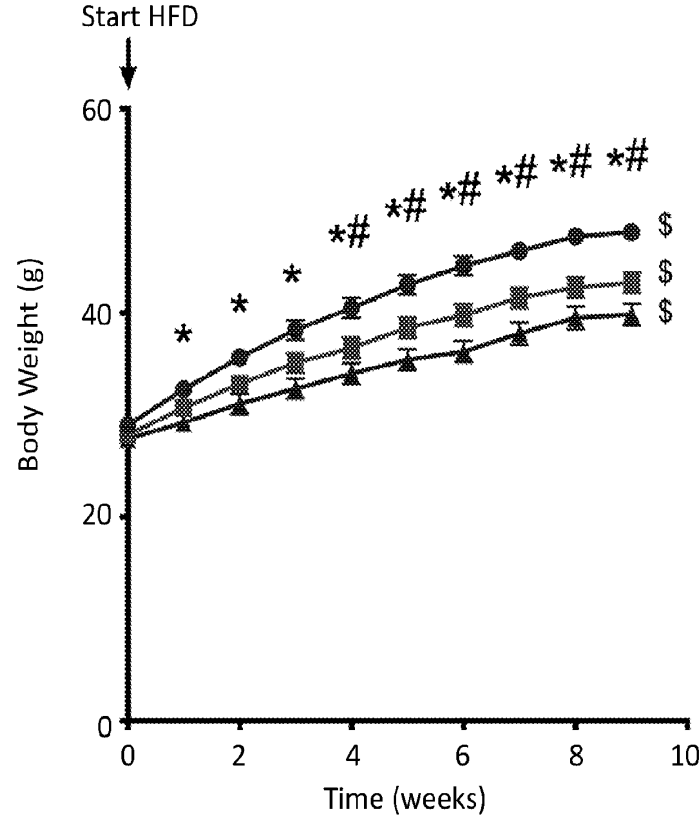


Figure 26

B)

◆ Gpr75<sup>+/+</sup> + HFD    ■ Gpr75<sup>+/-</sup> + HFD    ▲ Gpr75<sup>-/-</sup> + HFD

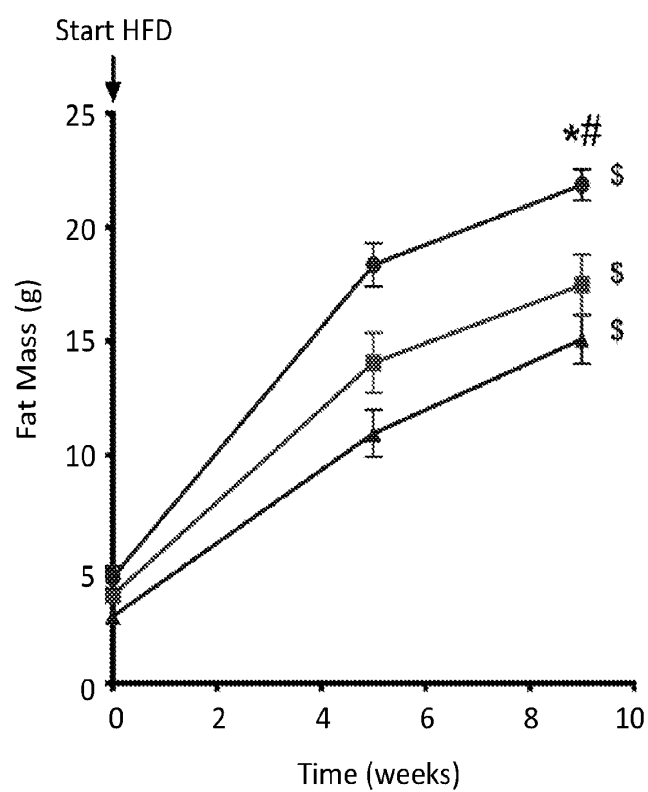


Figure 26 (cont.)

SUBSTITUTE SHEET (RULE 26)

B)

◆ Gpr75<sup>+/+</sup> + HFD    ■ Gpr75<sup>+/-</sup> + HFD    ▲ Gpr75<sup>-/-</sup> + HFD

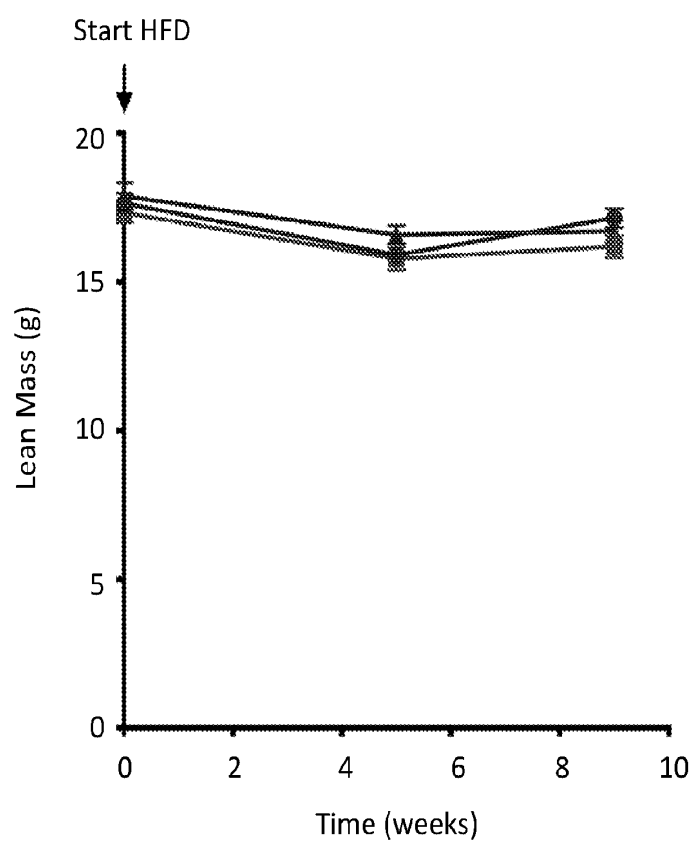


Figure 26 (cont.)

SUBSTITUTE SHEET (RULE 26)

B)

◆ Gpr75<sup>+/+</sup> + HFD    ■ Gpr75<sup>+/-</sup> + HFD    ▲ Gpr75<sup>-/-</sup> + HFD

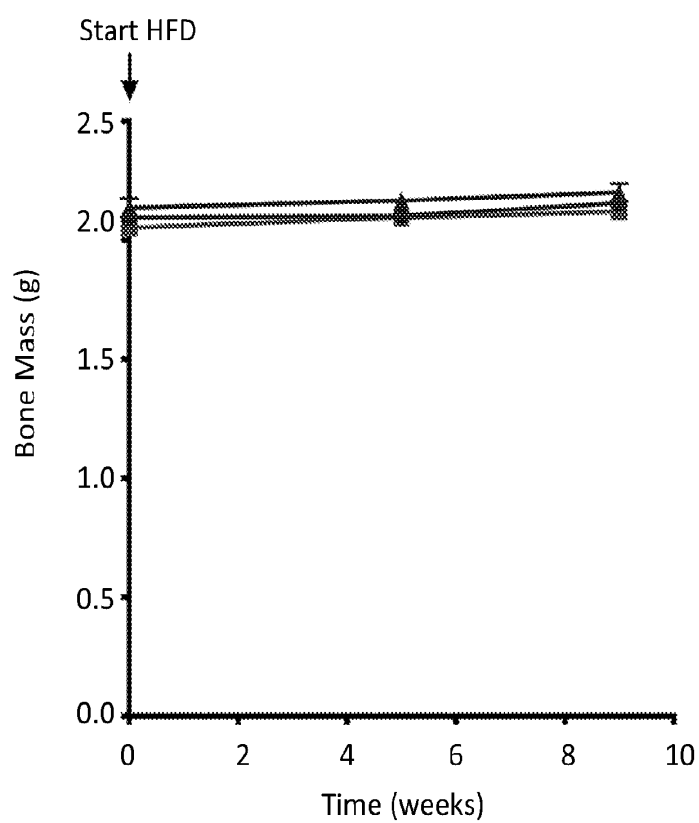


Figure 26 (cont.)

SUBSTITUTE SHEET (RULE 26)

C)

● Gpr75<sup>+/+</sup> + HFD    ■ Gpr75<sup>+/-</sup> + HFD    ▲ Gpr75<sup>-/-</sup> + HFD

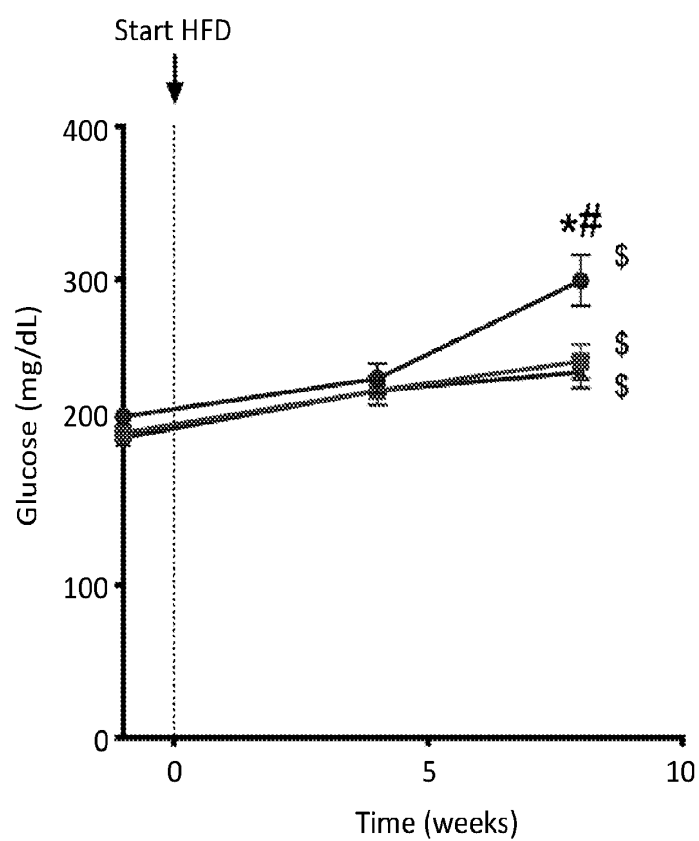


Figure 26 (cont.)

SUBSTITUTE SHEET (RULE 26)

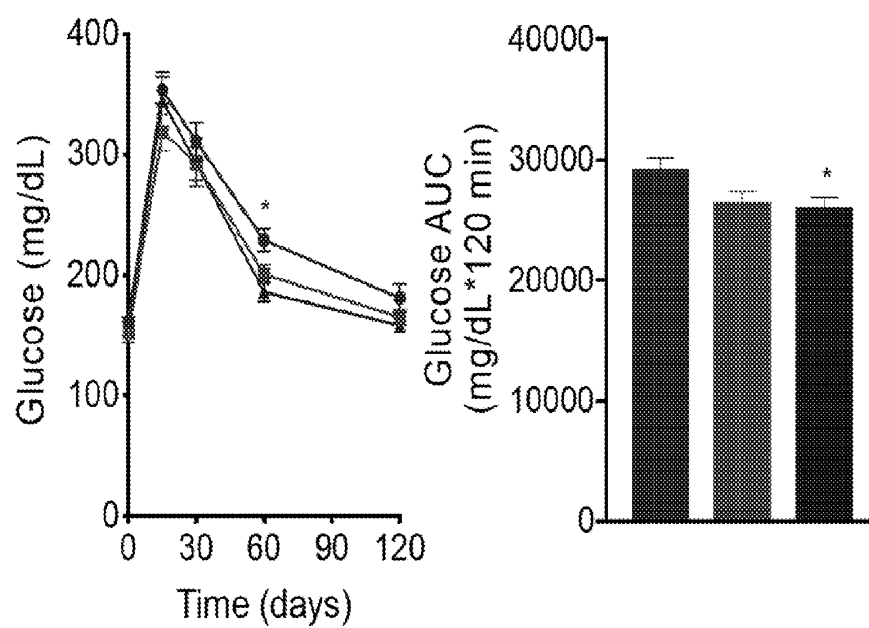


Figure 27