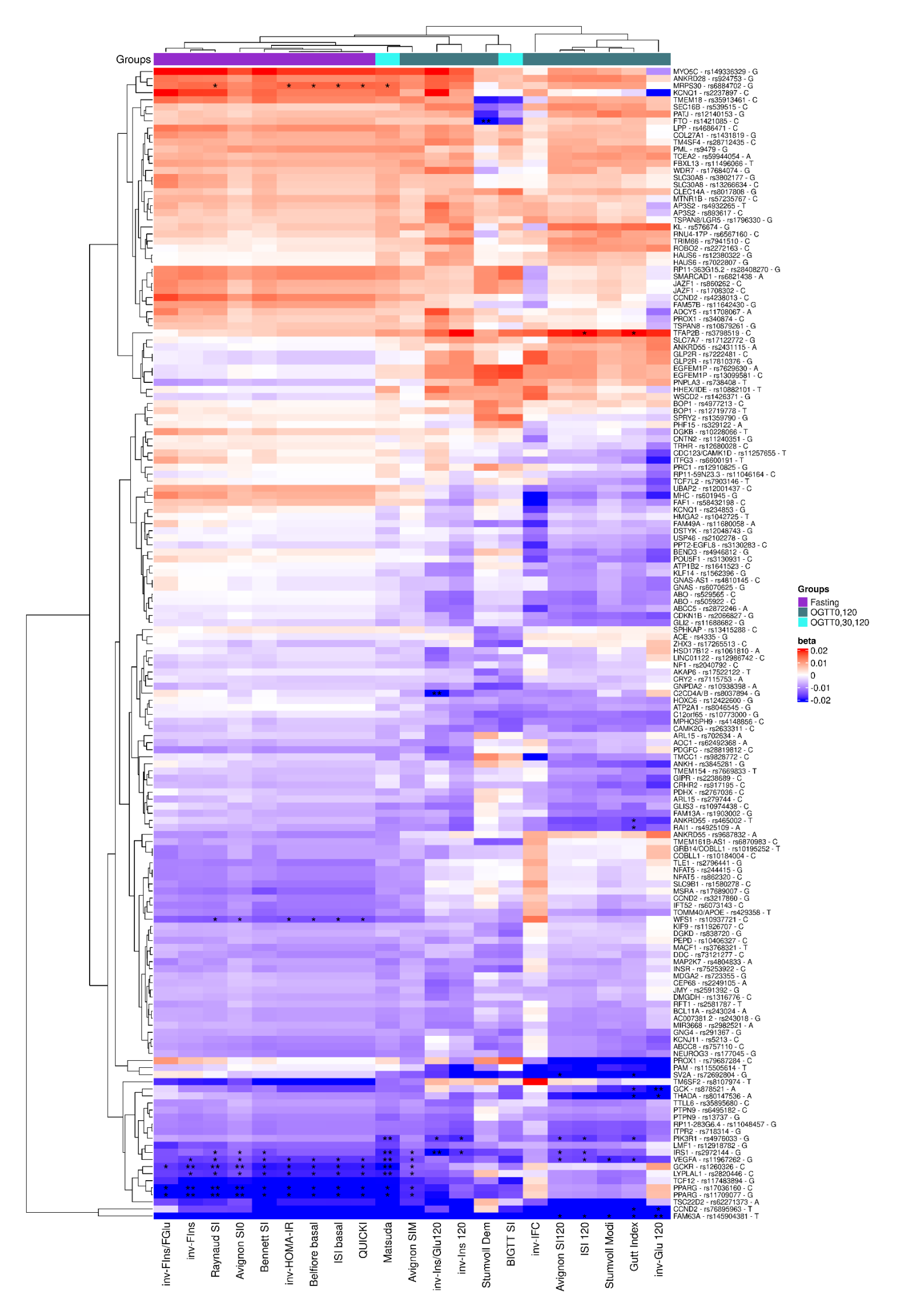
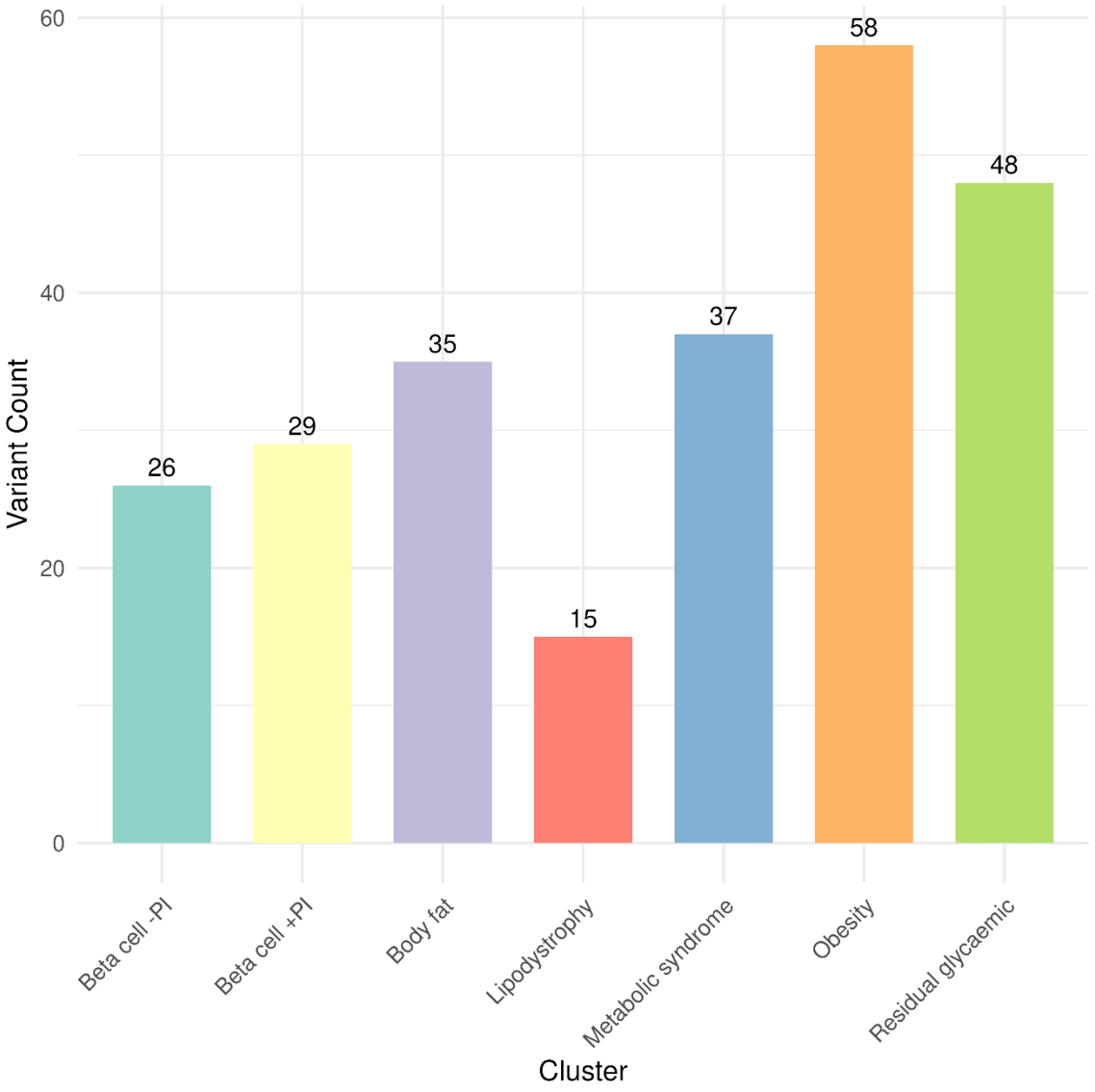
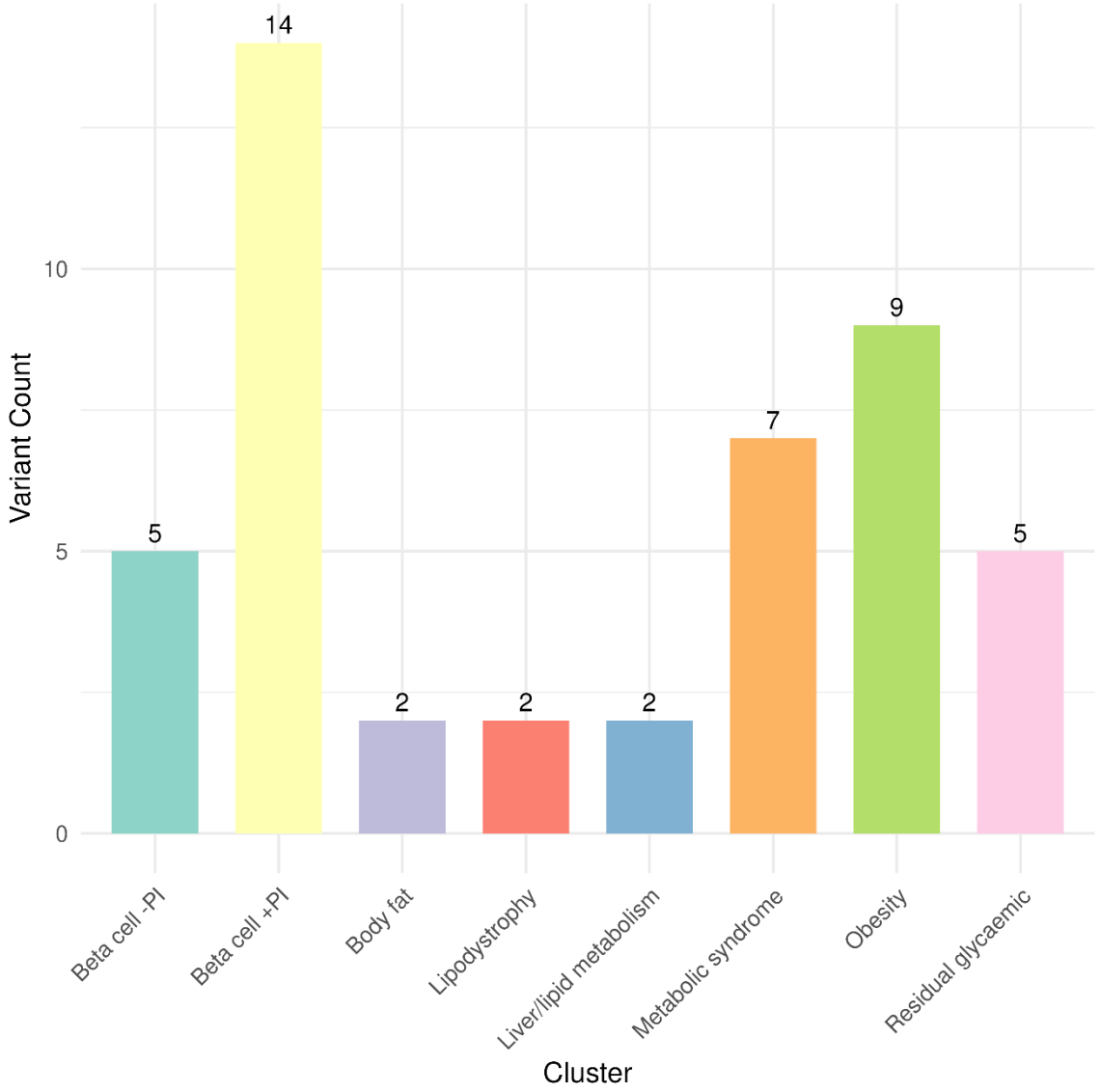

Groups
MYO5C - rs149336329 - G
ANKRD28 - rs924753 - G
MRPS30 - rs6884702 - G
KCNQ1 - rs2237897 - C
TMEM18 - rs35913461 - C
SEC16B - rs539515 - C
PATJ - rs12140153 - G
FTO - rs1421085 - C
LPP - rs4686471 - C
COL27A1 - rs1431819 - G
TM4SF4 - rs28712435 - C
PML - rs9479 - G
TCEA2 - rs59944054 - A
FBXL13 - rs11496066 - T
WDR7 - rs17684074 - G
SLC30A8 - rs3802177 - G
SLC30A8 - rs13266634 - C
CLEC14A - rs8017808 - G
MTNR1B - rs57235767 - C
AP3S2 - rs4932265 - T
AP3S2 - rs893617 - C
TSPAN8/LGR5 - rs1796330 - G
KL - rs576674 - G
RNU4-17P - rs6567160 - C
TRIM66 - rs7941510 - C
ROBO2 - rs2272163 - C
HAUS6 - rs12380322 - G
HAUS6 - rs7022807 - G
RP11-363G15.2 - rs28408270 - G
SMARCAD1 - rs6821438 - A
JAZF1 - rs860262 - C
JAZF1 - rs1708302 - C
CCND2 - rs4238013 - C
FAM57B - rs11642430 - G
ADCY5 - rs11708067 - A
PROX1 - rs340874 - C
TSPAN8 - rs10879261 - G
TFAP2B - rs3798519 - C
SLC7A7 - rs17122772 - G
ANKRD55 - rs2431115 - A
GLP2R - rs7222481 - C
GLP2R - rs17810376 - G
EGFEM1P - rs7629630 - A
EGFEM1P - rs13099581 - C
PNPLA3 - rs738408 - T
HHEX/IDE - rs10882101 - T
WSCD2 - rs1426371 - G
BOP1 - rs4977213 - C
BOP1 - rs12719778 - T
SPRY2 - rs1359790 - G
PHF15 - rs329122 - A
DGKB - rs10228066 - T
CNTN2 - rs11240351 - G
TRHR - rs12680028 - C
CDC123/CAMK1D - rs11257655 - T
ITFG3 - rs6600191 - T
PRC1 - rs12910825 - G
RP11-59N23.3 - rs11046164 - C
TCF7L2 - rs7903146 - T
UBAP2 - rs12001437 - C
MHC - rs601945 - G
FAF1 - rs58432198 - C
KCNQ1 - rs234853 - G
HMGA2 - rs1042725 - T
FAM49A - rs11680058 - A
DSTYK - rs12048743 - G
USP46 - rs2102278 - G
PPT2-EGFL8 - rs3130283 - C
BEND3 - rs4946812 - G
POU5F1 - rs3130931 - C
ATP1B2 - rs1641523 - C
KLF14 - rs1562396 - G
GNAS-AS1 - rs4810145 - C
GNAS - rs6070625 - G
ABO - rs529565 - C
ABO - rs505922 - C
ABCC5 - rs2872246 - A
CDKN1B - rs2066827 - G
GLI2 - rs11688682 - G
SPHKAP - rs13415288 - C
ACE - rs4335 - G
ZHX3 - rs17265513 - C
HSD17B12 - rs1061810 - A
LINC01122 - rs12986742 - C
NF1 - rs2040792 - C
AKAP6 - rs17522122 - T
CRY2 - rs7115753 - A
GNPDA2 - rs10938398 - A
C2CD4A/B - rs8037894 - G
HOXC6 - rs12422600 - G
ATP2A1 - rs8046545 - G
C12orf65 - rs10773000 - G
MPHOSPH9 - rs4148856 - C
CAMK2G - rs2633311 - C
ARL15 - rs702634 - A
AOC1 - rs62492368 - A
PDGFC - rs28819812 - C
TMCC1 - rs9828772 - C
ANKH - rs3845281 - G
TMEM154 - rs7669833 - T
GIPR - rs2238689 - C
CRHR2 - rs917195 - C
PDHX - rs2767036 - C
ARL15 - rs279744 - C
GLIS3 - rs10974438 - C
FAM13A - rs1903002 - G
ANKRD55 - rs465002 - T
RAI1 - rs4925109 - A
ANKRD55 - rs9687832 - A
TMEM161B-AS1 - rs6870983 - C
GRB14/COBLL1 - rs10195252 - T
COBLL1 - rs10184004 - C
TLE1 - rs2796441 - G
NFAT5 - rs244415 - G
NFAT5 - rs862320 - C
SLC9B1 - rs1580278 - C
MSRA - rs17689007 - G
CCND2 - rs3217860 - G
IFT52 - rs6073143 - C
TOMM40/APOE - rs429358 - T
WFS1 - rs10937721 - C
KIF9 - rs11926707 - C
DGKD - rs838720 - G
PEPD - rs10406327 - C
MACF1 - rs3768321 - T
DDC - rs73121277 - C
MAP2K7 - rs4804833 - A
INSR - rs75253922 - C
MDGA2 - rs723355 - G
CEP68 - rs2249105 - A
JMY - rs2591392 - G
DMGDH - rs1316776 - C
RFT1 - rs2581787 - T
BCL11A - rs243024 - A
AC007381.2 - rs243018 - G
MIR3668 - rs2982521 - A
GNG4 - rs291367 - G
KCNJ11 - rs5213 - C
ABCC8 - rs757110 - C
NEUROG3 - rs177045 - G
PROX1 - rs79687284 - C
PAM - rs115505614 - T
SV2A - rs72692904 - G
TM6SF2 - rs8107974 - T
GCK - rs878521 - A
THADA - rs80147536 - A
TTLL6 - rs35895680 - C
PTPN9 - rs6495182 - C
PTPN9 - rs13737 - G
RP11-283G6.4 - rs11048457 - G
ITPR2 - rs718314 - G
PIK3R1 - rs4976033 - G
LMF1 - rs12918782 - G
IRS1 - rs2972144 - G
VEGFA - rs11967262 - G
GCKR - rs1260326 - C
LYPLAL1 - rs2820446 - C
TCF12 - rs117483894 - G
PPARG - rs17036160 - C
PPARG - rs11709077 - G
TSC22D2 - rs62271373 - A
CCND2 - rs76895963 - T
FAM63A - rs145904381 - T
inv-FIns/FGlu
inv-FIns
Raynaud SI
Avignon SI0
Bennett SI
inv-HOMA-IR
Belfiore basal
ISI basal
QUICKI
Matsuda
Avignon SIM
inv-Ins/Glu120
inv-Ins 120
Stumvoll Dem
BIGTT SI
inv-IFC
Avignon SI120
ISI 120
Stumvoll Modi
Gutt Index
inv-Glu 120
Groups
Fasting
OGTT0,120
OGTT0,30,120
beta
0.02
0.01
0
-0.01
-0.02

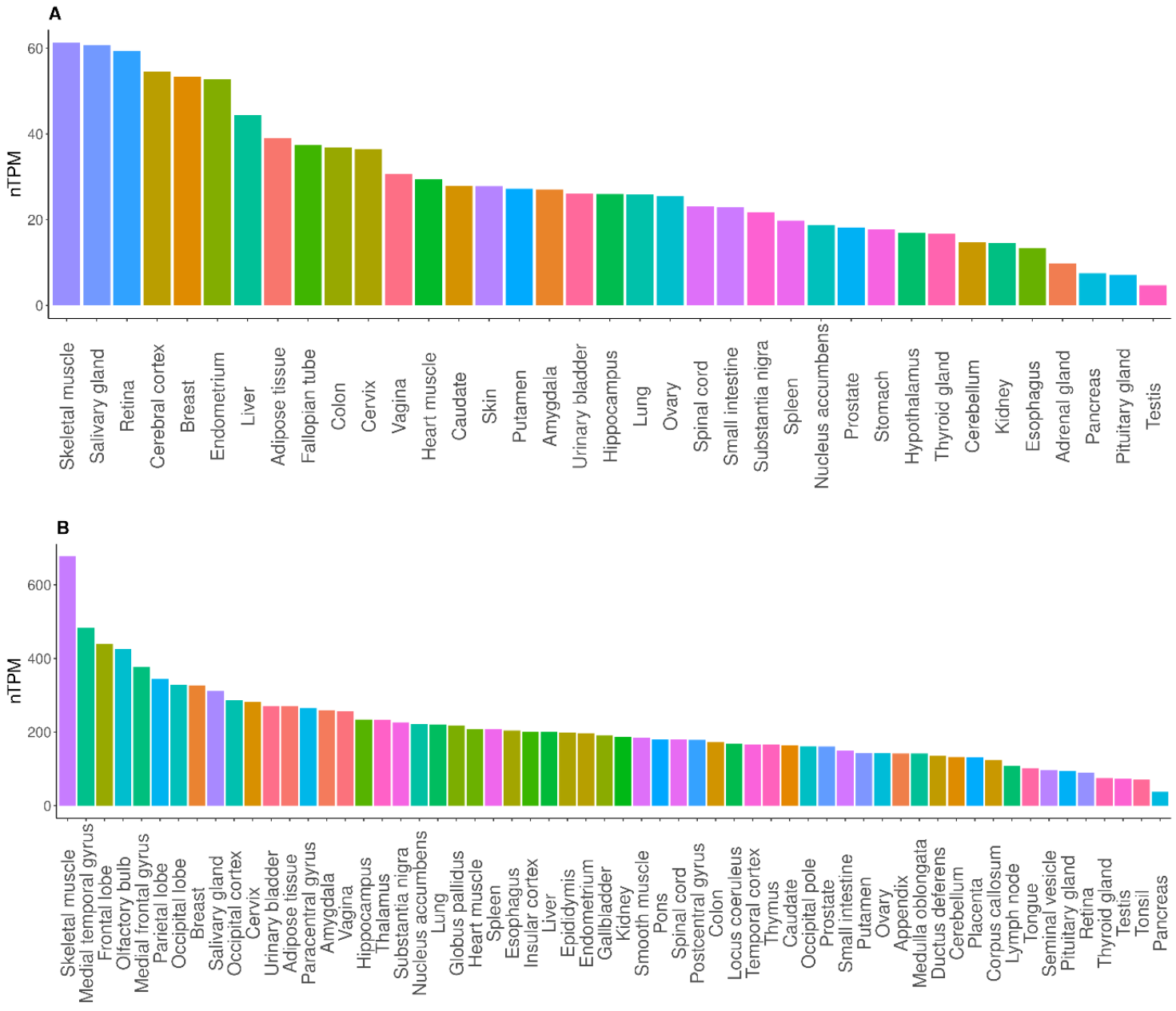
Supplementary Figure 1. The effect of T2D-associated risk alleles on IS indices. The figure displays association between IS indices and 163 T2D-associated variants with MAF > 1% and with a p-value of < 0.05 with at least one index. All effects are for T2D-risk increasing allele. The x-axis displays the indices, and the y-axis represents the gene, variant, and T2D-risk allele. An asterisk (*) indicates an false discovery rate (FDR) of < 0.05, while two asterisks (**) denote an FDR of < 0.01.



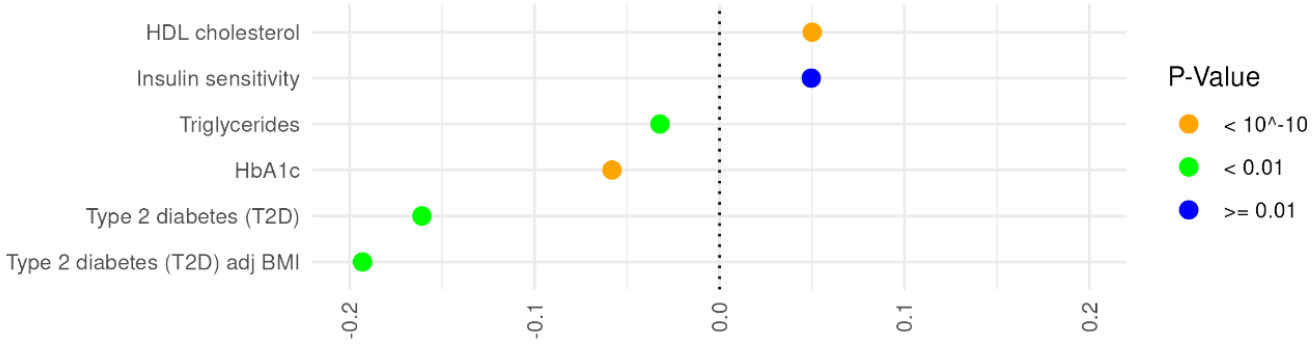
Supplementary Figure 2 illustrates the distribution of T2D-associated genetic variants that did not have a nominal association with IS indices in T2D mechanistic clusters. The y-axis represents the count of variants within each cluster, while the x-axis labels the names of clusters associated with cardiometabolic traits group. Out of the 269 variants analyzed, 248 intersected with variants for which clustering was available. The phenotypic clusters were composed of various phenotypes such as **Beta cell** –proinslin (**PI)** ((**+/-** indicate increase and decrease) + fasting glucose, + 2 h glucose, + HbA1c, -PI), **Beta cell +PI** (+ fasting glucose, + 2 h glucose, + HbA1c, +PI), **Body fat** (+ body fat, + abdominal subcutaneous adipose tissue), **Lipodystrophy** (+ fasting insulin, + waist to hip ratio, - body fat, - gluteofemoral adipose tissue, + triglycerides, + high density lipoprotiens, + blood pressure), **Metabolic syndrome** (+ fasting flucose, + fasting insulin, + waist to hip ratio, + visceral adipose tissue, − gluteofemoral adipose tissue, + triglycerides, − high density lipoproteins, + blood pressure), **Obesity** (+ body mass index, + waist to hip ratio, +body fat, + basal metabolism rate, + triglycerides, − high density lipoproteins) and **Residual glycaemic** (+ fasting glucose, + HbA1c).



Supplementary Figure 3 displays the distribution of T2D-associated genetic variants that show a nominal positive association with IS indices categorized into T2D mechanistic clusters along the x-axis. Of the 49 variants analyzed, 46 intersected with 5 out of the 8 assigned clusters of cardiometabolic traits. The phenotypic clusters were composed of various phenotypes such as **Beta cell -PI** ((**+/-** indicate increase and decrease) + fasting glucose, + 2 h glucose, + HbA1c, -PI), **Beta cell +PI** (+ fasting glucose, + 2 h glucose, + HbA1c, +PI), **Body fat** (+ body fat, + abdominal subcutaneous adipose tissue), **Lipodystrophy** (+ fasting insulin, + waist to hip ratio, - body fat, - gluteofemoral adipose tissue, + triglycerides, + high density lipoprotiens, + blood pressure), **Liver/lipid metabolism** (− low-density lipoprotein cholesterol, − total cholesterol, +liver fat, +liver biomarkers), **Metabolic syndrome** (+ fasting flucose, + fasting insulin, + waist to hip ratio, + visceral adipose tissue, − gluteofemoral adipose tissue, + triglycerides, − high density lipoproteins, + blood pressure), **Obesity** (+ body mass index, + waist to hip ratio, +body fat, + basal metabolism rate, + triglycerides, − high density lipoproteins) and **Residual glycaemic** (+ fasting glucose, + HbA1c).



Supplementary Figure 4 displays the expression of PIK3R1 across various tissues, as illustrated in the **A**) GTEx and **B**) FANTOM5 datasets from 2023. Notably, the highest levels of expression are observed in skeletal muscles, brain cells, and reproductive organs of both males and females, as well as in the liver, heart, and adipose tissues.



Phenotype	Beta	P-Value	EffectiveSampleSize
HDL cholesterol	0.0501000	2.250e-15	1406470
HbA1c	-0.0581000	2.570e-11	438069
Type 2 diabetes (T2D) adj BMI	-0.1929781	1.480e-07	220608
Triglycerides	-0.0322000	2.700e-07	1418760
Type 2 diabetes (T2D)	-0.1608732	6.590e-07	340908
Insulin sensitivity	0.0496000	6.857e-01	2765

Supplementary Figure 5 presents a phenome-wide association analysis of the *FAM63A* locus and the rs145904381 variant with cardiometabolic traits in European populations. This figure illustrates the impact of the alternative allele C, revealing a positive association with HDL cholesterol and insulin sensitivity, and a negative correlation with Type 2 Diabetes (T2D), HbA1c levels, and triglycerides. Conversely, with the risk allele T, particularly in relation to T2D and insulin sensitivity, these associations are inverted, thus reversing the direction of the effect for all the traits.