**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.
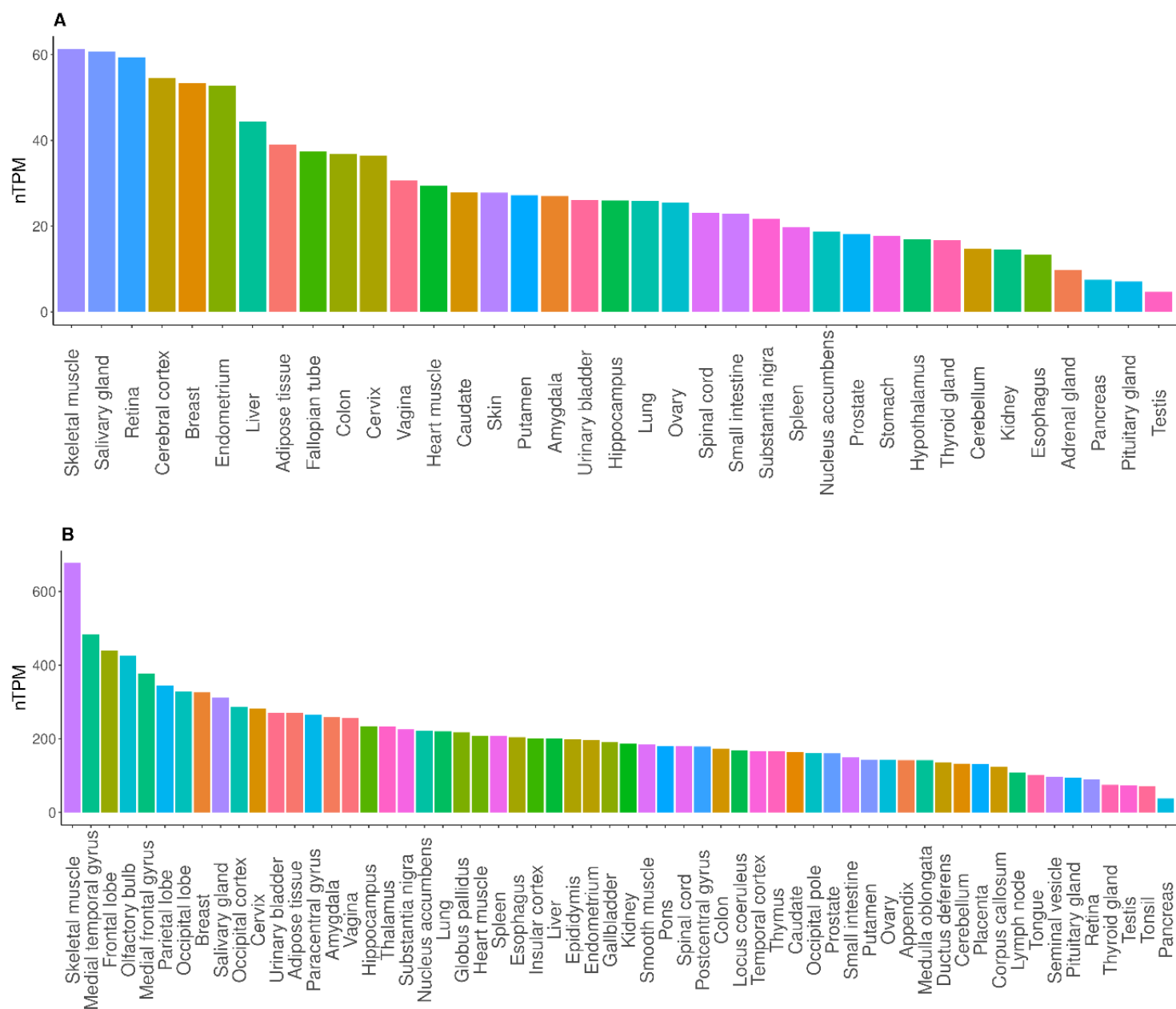
Supplementary Figure 2 displays the expression of PIK3R1 across various tissues, as illustrated in the **A**) GTEx and **B**) FANTOM5 datasets from 2023. Notably, the highest levels of expression are observed in skeletal muscles, brain cells, and reproductive organs of both males and females, as well as in the liver, heart, and adipose tissues.
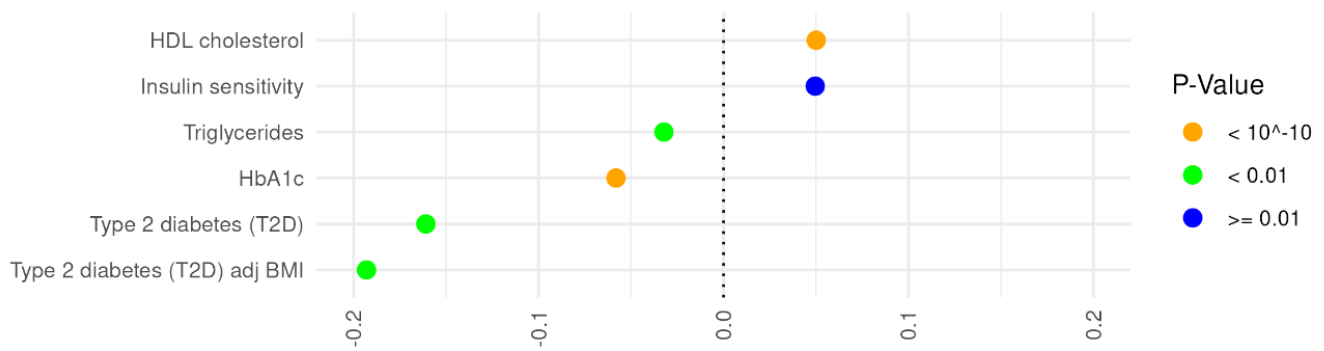
Phenotype	Beta	P-Value	EffectiveSampleSize
HDL cholesterol	0.0501000	2.250e-15	1406470
HbA1c	-0.0581000	2.570e-11	438069
Type 2 diabetes (T2D) adj BMI	-0.1929781	1.480e-07	220608
Triglycerides	-0.0322000	2.700e-07	1418760
Type 2 diabetes (T2D)	-0.1608732	6.590e-07	340908
Insulin sensitivity	0.0496000	6.857e-01	2765

Supplementary Figure 3 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.