# Supplementary Information

**Genetic variant effects on gene expression in human pancreatic islets and their implications for T2D.** Viñuela, Varshney, van de Bunt, Prasad, et al.

## Index:

# Supplementary Tables

**Supplementary Table 1 | Islet eSNP overlap and enrichment in islet chromatin states.** Input included: 1% FDR eQTL SNPs, filtered for MAF >= 0.2, LD pruned to retain SNPs with LD r2 <0.8. Enrichment was run using GREGOR tool which reports one-sided P values for enrichment.

| Cell | Chromatin State | Overlap | Expected Overlap | Pval | Fold Enrichment |
|---|---|---|---|---|---|
| **Islets** | 1 Active TSS | 646 | 168.4285695 | 5.5163E-206 | 3.835453819 |
| **Islets** | 10 Active enhancer 2 | 646 | 373.7879896 | 6.36051E-45 | 1.728252426 |
| **Islets** | 11 Weak enhancer | 107 | 55.45538991 | 1.32109E-10 | 1.929478815 |
| **Islets** | 14 Bivalent poised TSS | 8 | 8.943588041 | 0.670992632 | 0.894495583 |
| **Islets** | 16 Repressed polycomb | 42 | 64.06888459 | 0.998787342 | 0.655544423 |
| **Islets** | 17 Weak repressed polycomb | 567 | 980.5626747 | 1 | 0.578239428 |
| **Islets** | 18 Quiescent low signal | 814 | 1378.784788 | 1 | 0.59037495 |
| **Islets** | 2 Weak TSS | 220 | 91.00643384 | 3.5609E-34 | 2.417411503 |
| **Islets** | 3 Flanking TSS | 31 | 9.69543573 | 2.62495E-08 | 3.197380795 |
| **Islets** | 5 Strong transcription | 533 | 226.6297053 | 3.4569E-82 | 2.351854093 |
| **Islets** | 6 Weak transcription | 2212 | 1508.922102 | 7.2111E-124 | 1.465947114 |
| **Islets** | 8 Genic enhancer | 19 | 8.659541481 | 0.001354008 | 2.194111552 |
| **Islets** | 9 Active enhancer 1 | 29 | 14.55833157 | 0.000483652 | 1.991986503 |
| **Islets** | stretch enhancer | 279 | 178.2337579 | 2.76187E-13 | 1.565360026 |

**Supplementary Table 2 | T2D GWAS overlap and enrichment in Islet chromatin states.** Input included: T2D GWAS lead SNPs LD pruned to retain SNPs with LD r2 <0.2. Enrichment was run using GREGOR tool which reports one-sided P values for enrichment.

| Trait | Tissue | Chromatin State | Overlap | Expected Overlap | Pval | Fold Enrichment |
|---|---|---|---|---|---|---|
| **T2D** | Islets | 1 Active TSS | 83 | 36.75071553 | 5.98278E-15 | 2.258459429 |
| **T2D** | Islets | 10 Active enhancer 2 | 148 | 68.08416513 | 4.19572E-25 | 2.173780052 |
| **T2D** | Islets | 11 Weak enhancer | 33 | 15.02336156 | 7.49315E-06 | 2.196578967 |
| **T2D** | Islets | 14 Bivalent poised TSS | 4 | 2.897756572 | 0.329040071 | 1.3803782 |
| **T2D** | Islets | 16 Repressed polycomb | 14 | 14.48682595 | 0.590580855 | 0.966395265 |
| **T2D** | Islets | 17 Weak repressed polycomb | 97 | 130.7152207 | 0.999946431 | 0.742071195 |
| **T2D** | Islets | 18 Quiescent low signal | 142 | 176.804994 | 0.999953803 | 0.803144735 |
| **T2D** | Islets | 2 Weak TSS | 41 | 21.91059464 | 3.22446E-05 | 1.871240862 |
| **T2D** | Islets | 3 Flanking TSS | 4 | 2.616307877 | 0.265935301 | 1.528872055 |
| **T2D** | Islets | 5 Strong transcription | 54 | 36.73682051 | 0.001115897 | 1.469914904 |
| **T2D** | Islets | 6 Weak transcription | 231 | 164.6976275 | 9.78215E-14 | 1.402570295 |
| **T2D** | Islets | 8 Genic enhancer | 2 | 1.664686213 | 0.500115358 | 1.201427623 |
| **T2D** | Islets | 9 Active enhancer 1 | 10 | 4.005432849 | 0.006917117 | 2.496609075 |
| **T2D** | Islets | stretch enhancer | 84 | 31.15435816 | 1.52255E-18 | 2.696251984 |

**Supplementary Table 3 | Islet eSNP overlap and enrichment in ATAC-seq peaks within Islet chromatin states.** Input included: 1% FDR eQTL SNPs, filtered for MAF >= 0.2, LD pruned to retain SNPs with LD r2 <0.8. Enrichment was run using GREGOR tool which reports one-sided P values for enrichment. GREGOR LD R2 threshold = 0.99.

| Tissue | Chromatin State | Overlap | Expected Overlap | Pval |
|---|---|---|---|---|
| **Islets** | 1_Active_TSS | 529 | 126.7956399 | 2.60E-181 |
| **Islets** | 10_Active_enhancer_2 | 243 | 127.6952763 | 3.96E-22 |
| **Islets** | 11_Weak_enhancer | 8 | 6.679353733 | 0.35314905 |
| **Islets** | 14_Bivalent_poised_TSS | 3 | 3.166393089 | 0.61434421 |
| **Islets** | 16_Repressed_polycomb | 2 | 2.211965007 | 0.65024766 |
| **Islets** | 17_Weak_repressed_polycomb | 23 | 22.49119298 | 0.48560423 |
| **Islets** | 18_Quiescent_low_signal | 47 | 45.79505585 | 0.44852934 |
| **Islets** | 2_Weak_TSS | 78 | 27.00452726 | 1.79E-16 |
| **Islets** | 3_Flanking_TSS | 15 | 4.329971958 | 4.04E-05 |
| **Islets** | 5_Strong_transcription | 3 | 1.763515067 | 0.25810763 |
| **Islets** | 6_Weak_transcription | 99 | 73.82695003 | 0.0021955 |
| **Islets** | 8_Genic_enhancer | 1 | 0.374846627 | 0.31699116 |
| **Islets** | 9_Active_enhancer_1 | 7 | 6.054394149 | 0.40246364 |
| **Islets** | all atac-seq_peaks | 905 | 390.0891585 | 4.59E-142 |
| **Islets** | stretchEnhancer | 93 | 56.19877741 | 2.85E-06 |
| **Islets** | typicalEnhancer | 35 | 17.33145902 | 9.25E-05 |

**Supplementary Table 4 | Islet eSNP enrichment in TF footprint-motifs and motif directionality.** Motif by name with their enrichment and directionality. eQTL fold enrichment: Islet eQTL Fold enrichment in footprint motifs. eQTL enrichment Pvalue: Pvalue for enrichment of eQTL in footprint motifs. Total eQTL: Total eQTL overlaps with footprint motifs at positions with motif information content >= 0.7. Also, either REF or ALT allele should be the most preferred based in the motif. Motif directionality: Fraction of eQTL where most preferred base is associated with increased target gene expression. HepG2 activity: MPRA Activity score in HepG2. K562 activity: MPRA Activity score in K562. Included the binomial test Pvalue and the binomial test significance.

| Motif | eQTL Fold enrichment | eQTL enrichment Pvalue | Total eQTL | Motif directionality | HepG2 activity | K562 activity | Binomial test P | Binomial test significance |
|---|---|---|---|---|---|---|---|---|
| **AP1_known3** | 3.554 | 0.000 | 5.000 | 0.600 | 0.560 | 0.675 | 1.000 | Not significant |
| **AP1_known6** | 3.206 | 0.000 | 11.000 | 0.909 | 0.614 | 0.676 | 0.012 | Significant FDR<10% |
| **ARNT_1** | 3.773 | 0.000 | 14.000 | 0.500 | 0.350 | 0.420 | 1.000 | Not significant |
| **ATF3_disc2** | 3.784 | 0.000 | 78.000 | 0.538 | 1.046 | 1.143 | 0.572 | Not significant |
| **ATF3_known4** | 2.869 | 0.000 | 12.000 | 0.500 | 0.697 | 0.601 | 1.000 | Not significant |
| **BCL_disc1** | 4.232 | 0.000 | 15.000 | 0.867 | 1.042 | 1.106 | 0.007 | Significant FDR<10% |
| **BHLHE40_known2** | 3.770 | 0.000 | 14.000 | 0.357 | 0.427 | 0.384 | 0.424 | Not significant |
| **CREB3L1_4** | 3.389 | 0.000 | 16.000 | 0.688 | 0.600 | 0.370 | 0.210 | Not significant |
| **CTCFL_disc1** | 2.990 | 0.000 | 54.000 | 0.500 | 0.235 | 0.339 | 1.000 | Not significant |
| **CTCF_disc1** | 2.622 | 0.000 | 20.000 | 0.400 | 0.088 | 0.182 | 0.503 | Not significant |
| **CTCF_disc2** | 3.004 | 0.000 | 38.000 | 0.395 | 0.239 | 0.323 | 0.256 | Not significant |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **CTCF_known2** | 2.811 | 0.000 | 28.000 | 0.464 | 0.158 | 0.282 | 0.851 | Not significant |
| **E2F_disc2** | 3.376 | 0.000 | 28.000 | 0.643 | 1.331 | 1.429 | 0.185 | Not significant |
| **E2F_known18** | 4.762 | 0.000 | 30.000 | 0.333 | 0.289 | 0.924 | 0.099 | Not significant |
| **EGR1_disc2** | 3.502 | 0.000 | 19.000 | 0.737 | 0.587 | 0.618 | 0.064 | Not significant |
| **EGR1_disc3** | 3.824 | 0.000 | 45.000 | 0.644 | 1.261 | 1.397 | 0.072 | Not significant |
| **EGR1_disc5** | 4.045 | 0.000 | 20.000 | 0.700 | 0.290 | 0.369 | 0.115 | Not significant |
| **EGR1_disc7** | 3.695 | 0.000 | 43.000 | 0.465 | 0.828 | 0.859 | 0.542 | Not significant |
| **EGR1_known1** | 3.337 | 0.000 | 44.000 | 0.568 | 0.147 | 0.331 | 0.451 | Not significant |
| **EGR1_known5** | 3.202 | 0.000 | 51.000 | 0.627 | 0.266 | 0.500 | 0.092 | Not significant |
| **EGR1_known8** | 3.565 | 0.000 | 66.000 | 0.500 | 0.241 | 0.410 | 1.000 | Not significant |
| **EGR1_known9** | 3.624 | 0.000 | 50.000 | 0.560 | 0.289 | 0.397 | 0.480 | Not significant |
| **EGR3_3** | 3.826 | 0.000 | 58.000 | 0.500 | 0.242 | 0.399 | 1.000 | Not significant |
| **EHF_1** | 3.194 | 0.000 | 10.000 | 0.900 | 1.084 | 1.202 | 0.021 | Nominally significant (P<0.05) |
| **ELF1_disc1** | 4.135 | 0.000 | 12.000 | 0.917 | 1.476 | 1.572 | 0.006 | Significant FDR<10% |
| **ELF2_1** | 2.709 | 0.000 | 28.000 | 0.571 | 0.166 | 0.157 | 0.572 | Not significant |
| **ELF3_3** | 3.614 | 0.000 | 13.000 | 0.769 | 0.728 | 0.751 | 0.092 | Not significant |
| **ELF4_1** | 3.603 | 0.000 | 11.000 | 0.909 | 1.000 | 1.095 | 0.012 | Significant FDR<10% |
| **ELF5_3** | 4.030 | 0.000 | 7.000 | 0.714 | 0.756 | 0.805 | 0.453 | Not significant |
| **ELF5_4** | 3.585 | 0.000 | 5.000 | 0.600 | 0.750 | 0.810 | 1.000 | Not significant |
| **ELK3_1** | 4.619 | 0.000 | 12.000 | 1.000 | 1.675 | 1.676 | 0.000 | Significant FDR<10% |
| **ELK3_2** | 4.362 | 0.000 | 12.000 | 0.917 | 1.675 | 1.676 | 0.006 | Significant FDR<10% |
| **ELK4_1** | 7.220 | 0.000 | 15.000 | 0.733 | 1.655 | 1.573 | 0.118 | Not significant |
| **ELK4_2** | 5.984 | 0.000 | 13.000 | 0.846 | 1.678 | 1.663 | 0.022 | Nominally significant (P<0.05) |
| **ERG_1** | 5.537 | 0.000 | 11.000 | 0.818 | 1.592 | 1.620 | 0.065 | Not significant |
| **ERG_3** | 5.435 | 0.000 | 14.000 | 0.786 | 1.597 | 1.582 | 0.057 | Not significant |
| **ERG_4** | 4.541 | 0.000 | 11.000 | 0.545 | 0.458 | 0.370 | 1.000 | Not significant |
| **ETS_1** | 2.965 | 0.000 | 20.000 | 0.750 | 0.267 | 0.280 | 0.041 | Nominally significant (P<0.05) |
| **ETS_2** | 3.487 | 0.000 | 13.000 | 0.692 | 0.132 | 0.215 | 0.267 | Not significant |
| **ETS_known1** | 2.885 | 0.000 | 16.000 | 0.688 | 0.321 | 0.299 | 0.210 | Not significant |
| **ETS_known10** | 4.241 | 0.000 | 12.000 | 0.917 | 1.401 | 1.259 | 0.006 | Significant FDR<10% |
| **ETS_known11** | 4.858 | 0.000 | 12.000 | 1.000 | 1.745 | 1.732 | 0.000 | Significant FDR<10% |
| **ETS_known13** | 4.103 | 0.000 | 22.000 | 0.545 | 0.801 | 0.992 | 0.832 | Not significant |
| **ETS_known14** | 5.656 | 0.000 | 15.000 | 0.867 | 1.674 | 1.693 | 0.007 | Significant FDR<10% |
| **ETS_known15** | 3.407 | 0.000 | 19.000 | 0.474 | 0.387 | 0.487 | 1.000 | Not significant |
| **ETS_known16** | 6.027 | 0.000 | 12.000 | 0.833 | 1.641 | 1.660 | 0.039 | Nominally significant (P<0.05) |
| **ETS_known18** | 3.836 | 0.000 | 11.000 | 0.909 | 1.609 | 1.670 | 0.012 | Significant FDR<10% |
| **ETS_known2** | 4.342 | 0.000 | 17.000 | 0.765 | 1.195 | 1.164 | 0.049 | Nominally significant (P<0.05) |
| **ETS_known3** | 4.429 | 0.000 | 13.000 | 0.769 | 0.692 | 0.633 | 0.092 | Not significant |
| **ETS_known6** | 3.467 | 0.000 | 39.000 | 0.641 | 0.749 | 0.841 | 0.108 | Not significant |
| **ETS_known7** | 4.047 | 0.000 | 15.000 | 0.933 | 0.852 | 0.963 | 0.007 | Significant FDR<10% |
| **ETS_known9** | 4.358 | 0.000 | 21.000 | 0.857 | 1.763 | 1.989 | 0.001 | Significant FDR<10% |
| **ETV1_1** | 5.359 | 0.000 | 12.000 | 0.917 | 1.626 | 1.619 | 0.006 | Significant FDR<10% |
| **ETV4_2** | 5.688 | 0.000 | 13.000 | 0.923 | 1.578 | 1.621 | 0.003 | Significant FDR<10% |
| **ETV5_1** | 5.980 | 0.000 | 15.000 | 0.867 | 1.548 | 1.560 | 0.007 | Significant FDR<10% |
| **ETV6_1** | 3.670 | 0.000 | 29.000 | 0.759 | 0.782 | 0.972 | 0.008 | Significant FDR<10% |
| **ETV6_2** | 4.714 | 0.000 | 14.000 | 0.857 | 1.031 | 1.293 | 0.013 | Significant FDR<10% |

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|---|---|---|---|---|---|---|---|---|
| **FEV_2** | 4.980 | 0.000 | 10.000 | 1.000 | 1.572 | 1.597 | 0.002 | Significant FDR<10% |
| **FLI1_1** | 6.135 | 0.000 | 13.000 | 0.846 | 1.576 | 1.618 | 0.022 | Nominally significant (P<0.05) |
| **FLI1_3** | 5.301 | 0.000 | 11.000 | 0.818 | 1.678 | 1.663 | 0.065 | Not significant |
| **FLI1_4** | 4.904 | 0.000 | 12.000 | 0.583 | 0.533 | 0.512 | 0.774 | Not significant |
| **GATA_disc3** | 2.538 | 0.000 | 14.000 | 0.286 | 0.151 | 0.143 | 0.180 | Not significant |
| **GCM_1** | 3.493 | 0.000 | 10.000 | 0.400 | 0.304 | 0.282 | 0.754 | Not significant |
| **HDAC2_disc3** | 2.692 | 0.000 | 41.000 | 0.463 | -0.627 | -0.334 | 0.755 | Not significant |
| **HDAC2_disc4** | 3.678 | 0.000 | 61.000 | 0.508 | 0.836 | 1.014 | 1.000 | Not significant |
| **HINFP_2** | 3.428 | 0.000 | 36.000 | 0.611 | 0.479 | 0.480 | 0.243 | Not significant |
| **HINFP_3** | 4.151 | 0.000 | 93.000 | 0.527 | 0.370 | 0.345 | 0.679 | Not significant |
| **KLF12_2** | 4.210 | 0.000 | 66.000 | 0.591 | 0.193 | 0.515 | 0.175 | Not significant |
| **KLF14_1** | 3.595 | 0.000 | 80.000 | 0.550 | 0.293 | 0.596 | 0.434 | Not significant |
| **MXI1_known1** | 3.639 | 0.000 | 11.000 | 0.545 | 0.233 | 0.194 | 1.000 | Not significant |
| **MYB_1** | 3.939 | 0.000 | 15.000 | 0.667 | 0.251 | 0.343 | 0.302 | Not significant |
| **MYC_known11** | 3.118 | 0.000 | 11.000 | 0.727 | 0.307 | 0.264 | 0.227 | Not significant |
| **MYC_known19** | 3.051 | 0.000 | 22.000 | 0.455 | 0.133 | 0.186 | 0.523 | Not significant |
| **MYC_known6** | 2.921 | 0.000 | 10.000 | 0.600 | 0.467 | 0.556 | 0.754 | Not significant |
| **MYOD1_3** | 2.923 | 0.000 | 27.000 | 0.370 | -0.118 | -0.099 | 0.248 | Not significant |
| **NR2C2_disc3** | 3.566 | 0.000 | 33.000 | 0.394 | 0.167 | 0.093 | 0.296 | Not significant |
| **NRF1_disc1** | 3.403 | 0.000 | 88.000 | 0.602 | 1.348 | 1.442 | 0.069 | Not significant |
| **NRF1_known1** | 3.356 | 0.000 | 35.000 | 0.514 | 1.336 | 1.432 | 1.000 | Not significant |
| **NRF1_known2** | 3.384 | 0.000 | 29.000 | 0.552 | 1.393 | 1.494 | 0.711 | Not significant |
| **PAX2_4** | 3.642 | 0.000 | 18.000 | 0.667 | 0.549 | 0.731 | 0.238 | Not significant |
| **PAX5_disc4** | 2.903 | 0.000 | 22.000 | 0.591 | 0.245 | 0.304 | 0.523 | Not significant |
| **PAX5_disc5** | 3.326 | 0.000 | 90.000 | 0.467 | 0.468 | 0.672 | 0.598 | Not significant |
| **PAX5_known5** | 3.593 | 0.000 | 18.000 | 0.667 | 0.598 | 0.731 | 0.238 | Not significant |
| **PBX3_disc1** | 5.311 | 0.000 | 8.000 | 0.625 | 0.467 | 0.619 | 0.727 | Not significant |
| **PBX3_disc3** | 3.153 | 0.000 | 39.000 | 0.487 | 0.271 | 0.265 | 1.000 | Not significant |
| **RAD21_disc1** | 2.990 | 0.000 | 49.000 | 0.429 | 0.121 | 0.205 | 0.392 | Not significant |
| **REST_disc1** | 2.944 | 0.000 | 35.000 | 0.457 | -0.917 | -0.491 | 0.500 | Not significant |
| **REST_disc3** | 3.060 | 0.000 | 31.000 | 0.355 | -0.457 | -0.278 | 0.150 | Not significant |
| **REST_known3** | 2.913 | 0.000 | 73.000 | 0.507 | -0.521 | -0.207 | 1.000 | Not significant |
| **REST_known4** | 2.708 | 0.000 | 51.000 | 0.569 | -0.752 | -0.450 | 0.401 | Not significant |
| **SETDB1_disc1** | 3.570 | 0.000 | 32.000 | 0.656 | 0.529 | 0.488 | 0.110 | Not significant |
| **SIN3A_disc1** | 3.251 | 0.000 | 24.000 | 0.667 | -0.877 | -0.455 | 0.152 | Not significant |
| **SP2_disc2** | 3.397 | 0.000 | 20.000 | 0.400 | 0.438 | 0.480 | 0.503 | Not significant |
| **SP2_disc3** | 3.000 | 0.000 | 37.000 | 0.486 | 0.357 | 0.529 | 1.000 | Not significant |
| **SPDEF_5** | 4.594 | 0.000 | 12.000 | 0.750 | 1.023 | 0.996 | 0.146 | Not significant |
| **SREBP_disc1** | 3.625 | 0.000 | 25.000 | 0.640 | -0.216 | 0.001 | 0.230 | Not significant |
| **STAT_known2** | 3.165 | 0.000 | 12.000 | 0.583 | 0.451 | 0.556 | 0.774 | Not significant |
| **TATA_disc8** | 3.277 | 0.000 | 51.000 | 0.471 | 0.909 | 0.865 | 0.576 | Not significant |
| **TFAP2_disc1** | 3.644 | 0.000 | 10.000 | 0.900 | 0.691 | 0.850 | 0.021 | Nominally significant (P<0.05) |
| **YY1_disc1** | 2.745 | 0.000 | 13.000 | 0.615 | 0.792 | 0.805 | 0.581 | Not significant |
| **YY1_known7** | 5.327 | 0.000 | 7.000 | 0.714 | 0.476 | 0.530 | 0.453 | Not significant |
| **YY2_1** | 7.136 | 0.000 | 10.000 | 0.600 | 0.900 | 0.865 | 0.754 | Not significant |
| **YY2_2** | 3.508 | 0.000 | 7.000 | 0.571 | 0.872 | 1.064 | 1.000 | Not significant |
| **ZBTB14_1** | 3.722 | 0.000 | 27.000 | 0.259 | 0.271 | 0.338 | 0.019 | Nominally significant (P<0.05) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **ZBTB14_3** | 3.611 | 0.000 | 53.000 | 0.453 | 0.664 | 0.899 | 0.583 | Not significant |
| **ZBTB6_1** | 2.635 | 0.000 | 18.000 | 0.333 | -0.086 | -0.146 | 0.238 | Not significant |
| **ZBTB7A_disc1** | 3.466 | 0.000 | 38.000 | 0.316 | 0.206 | 0.322 | 0.034 | Nominally significant (P<0.05) |
| **ZBTB7A_disc2** | 4.717 | 0.000 | 20.000 | 0.400 | 0.286 | 0.430 | 0.503 | Not significant |
| **ZNF143_known1** | 3.194 | 0.000 | 23.000 | 0.304 | 0.233 | 0.162 | 0.035 | Nominally significant (P<0.05) |

**Supplementary Table 5 | Known GWAS signals colocalizing with islets eQTLs.**

| Loci index | GWAS Locus Gene Name | GWAS Traits | GWAS SNP | Allele | eGene | Studies | InsPIRE | Details |
|---|---|---|---|---|---|---|---|---|
| **1** | ABO | Disposition index | rs505922 | C | ABO | Fadista et al. ( 2014); van de Bunt, et al. (2015) | No evidence | COLOC < 0.2, no RTC |
| **2** | ADCY5 | FGlu,T2D | rs11708067 | A | ADCY5 | Van de Bunt et al. (2015); Varshney, et al. (2017) | Replicated | |
| **3** | AMT | Fastin glucose | rs11715915 | C/T | RBM6 | Van de Bunt et al. (2015) | No evidence | Best COLOC = 0.36 (BSN-AS2); best RTC = 0.89 (CCDC51) |
| **4** | ANK1 | T2D | rs515071 | C | NKX6-3 | Varshney, et al. (2017) | Not tested ($R^2$ < 0.5) | |
| | | T2D | rs516946 | C | NKX6-3 | Varshney, et al. (2017) | | |
| | | Corrected insulin response | rs12549902 | A/G | NKX6-3 | Van de Bunt et al. (2015) | Replicated | |
| **5** | AP3S2 | T2D | rs2028299 | C | AP3S2 | Varshney, et al. (2017) | Yes (other snp, $R^2$ = 0.897) | Same loci, different lead SNPs investigated |
| | | T2D | rs2028299 | A/C | AP3S2 | Van de Bunt et al. (2015) | | |
| | | T2D | rs2028299 | C/A | AP3S2 | Fadista et al. ( 2014) | | |
| **6** | CENTD2-ARAP1 | FGlu,FGluBMIadj,Fproinsulin | rs11603334 | G | STARD10 | Varshney, et al. (2017) | Replicated | |
| | | Fasting glucose | rs11603334 | G/A | STARD10 | Van de Bunt et al. (2015) | Replicated | |
| | | T2D | rs1552224 | A/C | STARD10 | Van de Bunt et al. (2015) | Yes (other snp, $R^2$ = 0.951) | Same loci, different lead SNPs investigated |
| | | T2D | rs1552224 | A | STARD10 | Varshney, et al. (2017) | | |
| **7** | VPS13C-C2CD4AB-NLF1 | T2D | rs7172432 | A | C2CD4B | Varshney, et al. (2017) | No evidence ($R^2$ = 1) | COLOC (rs8037894) = 0.67; no RTC |
| | | FGlu | rs11071657 | A | C2CD4B | Varshney, et al. (2017) | other snp ($R^2$ < 0.5) | COLOC (rs4502156 = 0.92, $R^2$=0.33); no eQTLs in the previously reported |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | candidate |
| | | 2hGlu | rs17271305 | G | VPS13C | Varshney, et al. (2017) | Not tested | No eQTL in VPS13C |
| **8** | CDC123/CAMK1D | T2D | rs11257655 | T | CAMK1D | Varshney, et al. (2017) | Replicated | |
| | | T2D | rs11257655 | T/C | CAMK1D | Van de Bunt et al. (2015) | | |
| | | T2D | rs12779790 | G | CAMK1D | Varshney, et al. (2017) | Not tested | Different lead SNP investigated. $R^2$ with rs11257655 = 0.82 |
| | | T2D | rs10906115 | A | CAMK1D | Varshney, et al. (2017) | | Different lead SNPs investigated. $R^2$ with rs11257655 = 0.19 |
| **9** | DGKB/TMEM195 | T2D; Fasting glucose | rs2191349 | T/G | DGKB | Van de Bunt et al. (2015) | Replicated (other snp, $R^2$ = 0.979) | Same loci, different lead SNPs investigated |
| | | T2D; Fasting glucose | rs17168486 | T/C | DGKB | Van de Bunt et al. (2015) | Replicated | |
| **10** | DNLZ | FGlu | rs3829109 | G | GPSM1 | Varshney, et al. (2017) | No evidence | $R^2$ with rs11787792 = 0.67; best COLOC (INPP5E) = 0.47; RTC (SNAPC4) = 0.75 |
| | GPSM1 | T2D | rs11787792 | A | GPSM1 | Varshney, et al. (2017) | No (other snp, R2 < 0.5) | $R^2$ rs28505901 = 0.55; rs78403475 = 0.079; rs11793035 = 0.048 |
| **11** | ERAP2 | 2hGlu | rs1019503 | A | ERAP2 | Varshney, et al. (2017) | Not tested | |
| | ERAP2 | 2-hour glucose | rs1019503 | G/A | ERAP2 | Fadista et al. ( 2014) | | |
| **12** | FADS1 | Fasting | rs174550 | T/C | FADS1 | Van de Bunt et al. (2015) | Replicated | |
| | | FGlu | rs174550 | C | FADS1 | Varshney, et al. (2017) | | |
| **13** | HIP1 | FIns | rs1167800 | A | PMS2P3 | Varshney, et al. (2017) | Not tested | No eQTL in any of the candidate genes. |
| | HIP1 | FIns | rs1167800 | A | STAG3L1 | Varshney, et al. (2017) | | |
| | HIP1 | FIns | rs1167800 | A | GTF2IP1 | Varshney, et al. (2017) | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **14** | HMG20A | T2D | rs7178572 | A | HMG20A | Varshney, et al. (2017) | Replicated (other snp, $R^2$ = 0.908) | Same loci, different lead SNPs investigated |
| | | T2D | rs7177055 | A | HMG20A | Varshney, et al. (2017) | Replicated (other snp, $R^2$ = 1) | Same loci, different lead SNPs investigated |
| **15** | IGF2BP2 | 2hGluBMIadj,FGlu | rs7651090 | G | IGF2BP2 | Varshney, et al. (2017) | Replicated | |
| | | T2D | rs4402960 | T | IGF2BP2 | Varshney, et al. (2017) | Replicated (other snp, $R^2$ = 1) | Same loci, different lead SNPs investigated |
| **16** | KCNK16 | T2D | rs1535500 | T | KCNK17 | Varshney, et al. (2017) | Not tested | KCNK16 have no eQTLs. KCNK17 have two eQTLs (rs10947805, rs3807042) |
| | | T2D | rs1535500 | G/T | KCNK17 | Fadista et al. ( 2014) | | |
| **17** | KLHDC5 | T2D | rs10842994 | C | KLHL42 | Varshney, et al. (2017) | Replicated (other snp, $R^2$ = 0.979) | Same loci, different lead SNPs investigated |
| **18** | MADD | Proinsulin | rs10501320 | G | MADD | Varshney, et al. (2017) | Replicated | |
| | | Fastin glucose | rs10501320 | G/C | MADD | Van de Bunt et al. (2015) | | |
| | | Fastin glucose | rs10838687 | T/G | ACP2 | Van de Bunt et al. (2015) | Not tested | Different lead SNPs investigated. $R^2$ with rs10501320 = 0.08 |
| | | Fastin glucose | rs7944584 | A/T | MADD | Van de Bunt et al. (2015) | only RTC | Different lead SNPs investigated. $R^2$ with rs10501320 = 0.929 |
| **19** | MPHOSPH9 | T2D | rs1727313 | C | ABCB9 | Varshney, et al. (2017) | Replicated (other snp, $R^2$ = 0.921) | Same loci, different lead SNPs investigated |
| **20** | MTNR1B | FGlu,T2D | rs10830963 | G | MTNR1B | Varshney, et al. (2017) | Not tested | Gene not expressed enough for exon filters |
| | | FGlu | rs10830962 | C | MTNR1B | Varshney, et al. (2017) | | |
| | | T2D; Fasting glucose; HOMA-B; Corrected insulin reponse | rs10830963 | G/C | MTNR1B | Van de Bunt et al. (2015) | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | T2D; Fasting glucose; HOMA-B; Corrected insulin reponse | rs10830963 | C/G | MTNR1B | Fadista et al. ( 2014) | | |
| **21** | PCSK1 | Fasting glucose | rs4869272 | T/C | CTD-2260A17.2 | Van de Bunt et al. (2015) | Not tested | |
| **22** | SIX3 - SIX2 | FGlu | rs895636 | C | SIX3-AS1 | Varshney, et al. (2017) | Replicated | |
| | | FGlu | rs895636 | C | AC012354.6 | Varshney, et al. (2017) | | |
| | | FGlu | rs895636 | C | SIX3 | Varshney, et al. (2017) | | |
| | | FGlu | rs895636 | C | RP11-89K21.1 | Varshney, et al. (2017) | | |
| **23** | TMEM163 | T2D | rs6723108 | T/G | MGAT5 | Van de Bunt et al. (2015) | Not tested | eQTL in TMEM163 (rs6760237); eQTL in MGAT5 (rs6430497) |
| **24** | UBE2E2 | T2D | rs1496653 | A | UBE2E2 | Varshney, et al. (2017) | Replicated (other snp, $R^2 = 1$) | Same loci, different lead SNPs investigated |
| **25** | WARS | Fastin glucose | rs3783347 | G/T | WARS | Van de Bunt et al. (2015) | Replicated | |
| **26** | ZFAND6 | T2D | rs11634397 | G/A | LINC00927 | Van de Bunt et al. (2015) | Not tested | No eQTLs in any candidate gene |
| **27** | ZMIZ1 | T2D | rs12571751 | A/G | ZMIZ1 | Van de Bunt et al. (2015) | No evidence | COLOC < 0.04; no RTC |

**Supplementary Table 6 | Oligonucleotide primers used for the transcriptional reporter assays.**

| Primer | Sequence (5'-3') | Amplified region (hg19) |
|---|---|---|
| Haplotype A_Forward<br>Haplotype A_Reverse | GAGTTGCTGGAATGGAGGAG<br>CATGCGTCGCAATGTCTTT | chr7:15,055,310-15,056,074 |
| Haplotype B_Forward<br>Haplotype B_Reverse | TGCTAAGGCTAACCATAAACCA<br>TCAGCCAGCTGAAAGCTAGA | chr7:15,064,030-15,064,621 |

**Supplementary Table 7 | Oligonucleotide probes used for the electrophoretic mobility shift assays.**

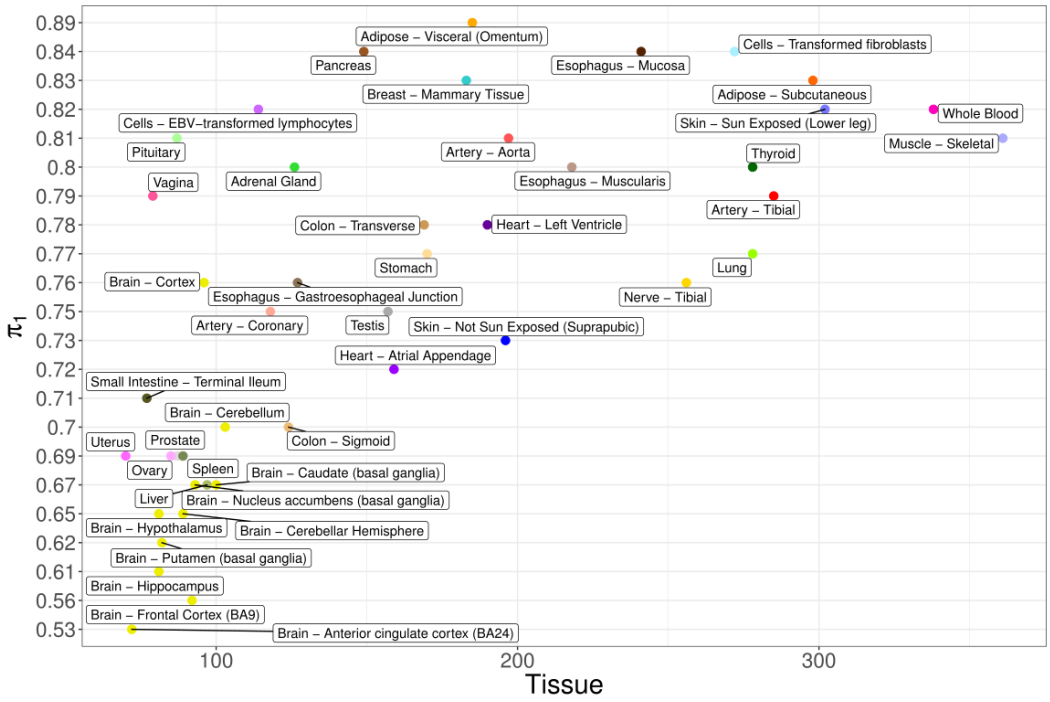
| Variant | Sequence (5'-3') ‡ | Position |
|---|---|---|
| rs10228796 | ACTGGGTT(**C/G)**TACCTTAA | chr7:15064182-15064198 |
| rs10258074 | TGGCAACC**(A/T)**GTCTCCTA | chr7:15064208-15064224 |
| rs2191348 | TTACCAAT**(G/T)**CAATACCA | chr7:15064247-15064263 |
| rs2191349 | AGGATCAT(**G/T)**TAAGACCA | chr7:15064301-15064317 |

‡Variant alleles are in bold.

# Supplementary Discussion

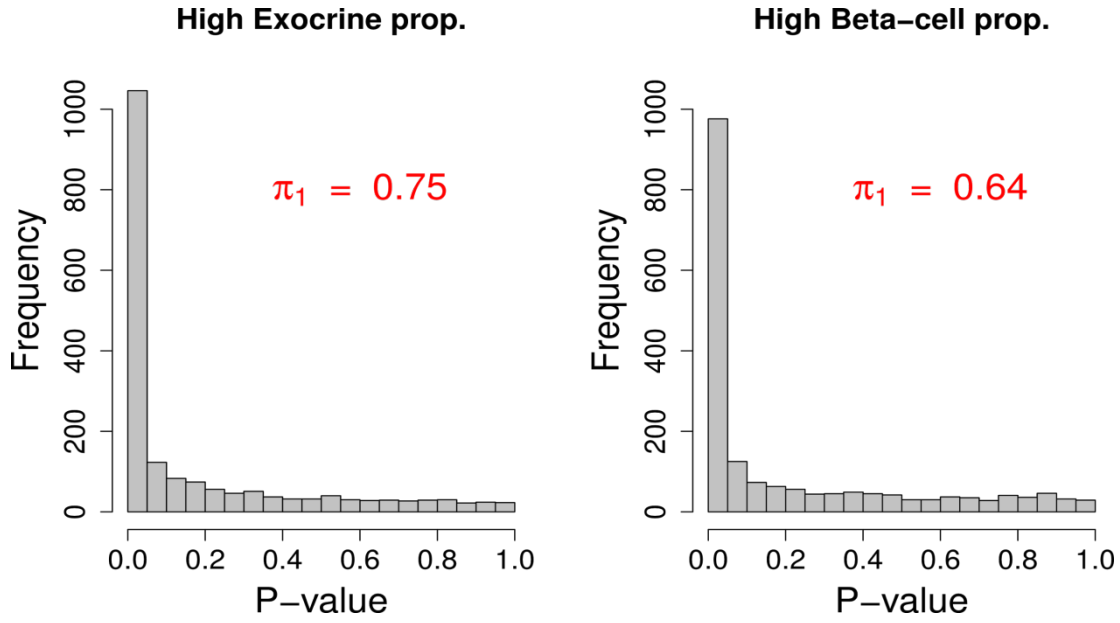
**Influence of sample size in eQTL discovery and comparison with GTEx eQTLs.**

Sample size influences eQTL discoveries, with the current knowledge indicating that larger eQTLs studies are able to find more tissue or cell specific eQTLs (Aguet, et al. 2017). Therefore, with larger samples sizes a higher absolute number of eQTLs are expected to be shared, but the percentage of shared signals is expected to be smaller. To test the influence of sample size on the discovery of shared genetic signals between our islet sample and GTEx eQTLs, we randomly selected 149 islets samples (the size of the GTEx pancreas study, performed an islet eQTL analysis and then estimated the signals shared with GTEX tissues (up to 382 samples). In the figure bellow, we observe that multiple tissues capture the same eQTLs signals as islets (N = 149), including adipose (0.89), LCLs (0.84), esophagus (0.84), and pancreas (0.84) which has the smallest sample size of the four tissues. Overall, 0.53 to 0.89 of the 149 islet samples signals were shared with GTEx tissues compared to 0.4 to 0.73 of the 420 islet samples. This supports the current expectation that larger sample size eQTLs studies will identify a larger proportion of tissue or cell specific signals.

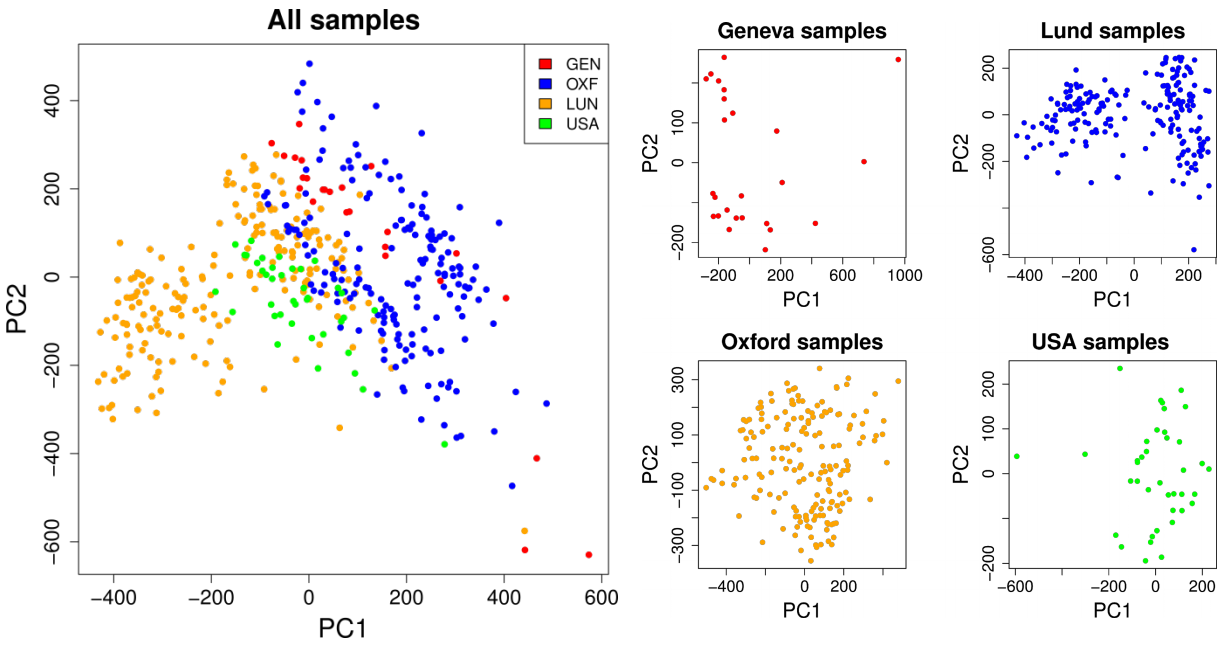


**Exocrine contamination**

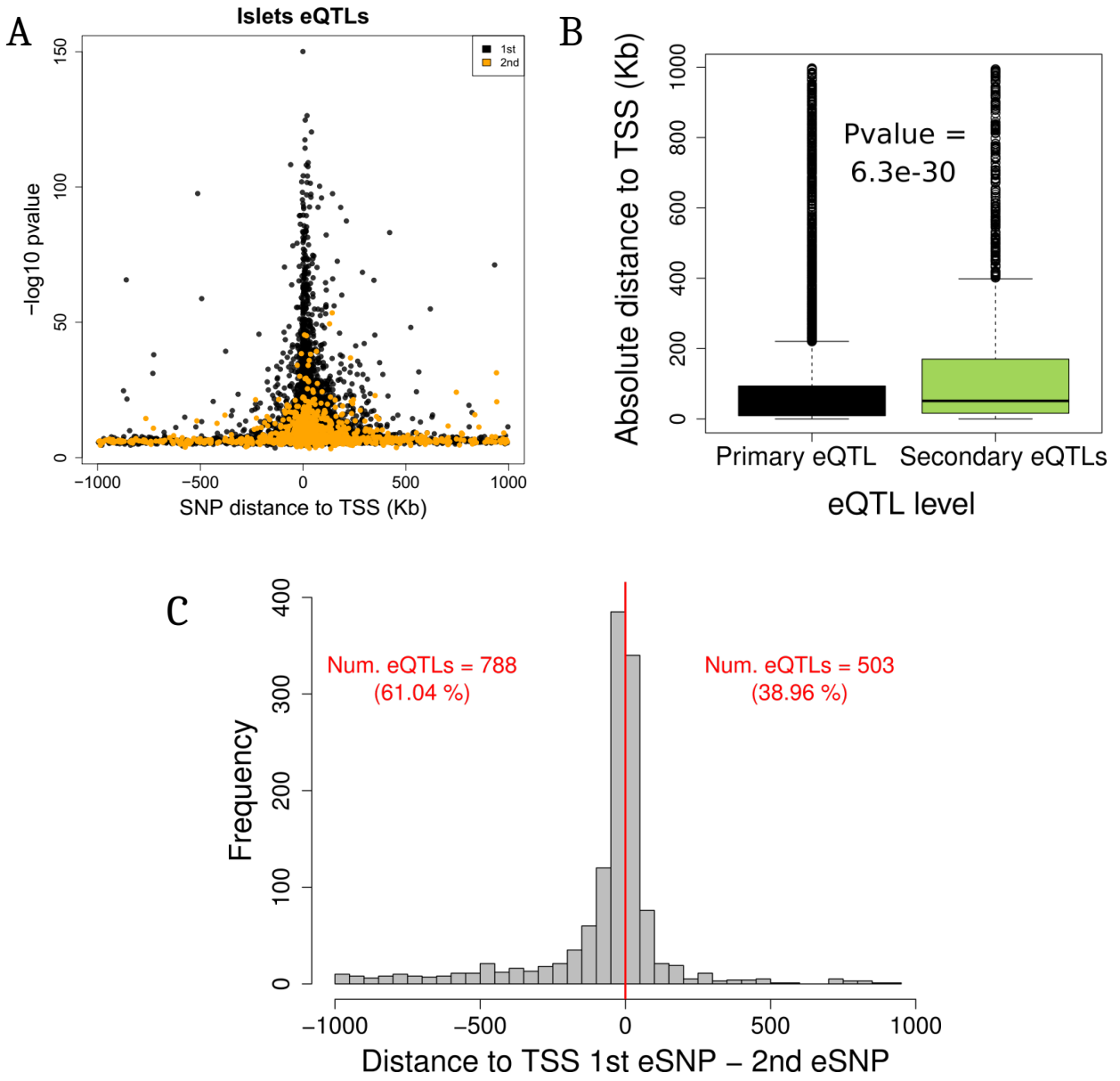
To evaluate whether some of the eQTLs attributed to pancreatic islets may reflect exocrine pancreatic contamination, we compared the sets of eQTLs identified in the InsPIRE islet samples with the highest and lowest proportions of exocrine contamination (n=100 for each) and 100 randomly-selected GTEx whole pancreas samples. The estimated signal overlap between whole pancreas and islet eQTLs was greater in islet samples with the highest exocrine contamination than with the lowest exocrine contamination ($\pi_1$ 75% vs 64%), indicating that some cell-specific effects were preserved even controlling for 25 PCs for the eQTL analysis (See Figure).



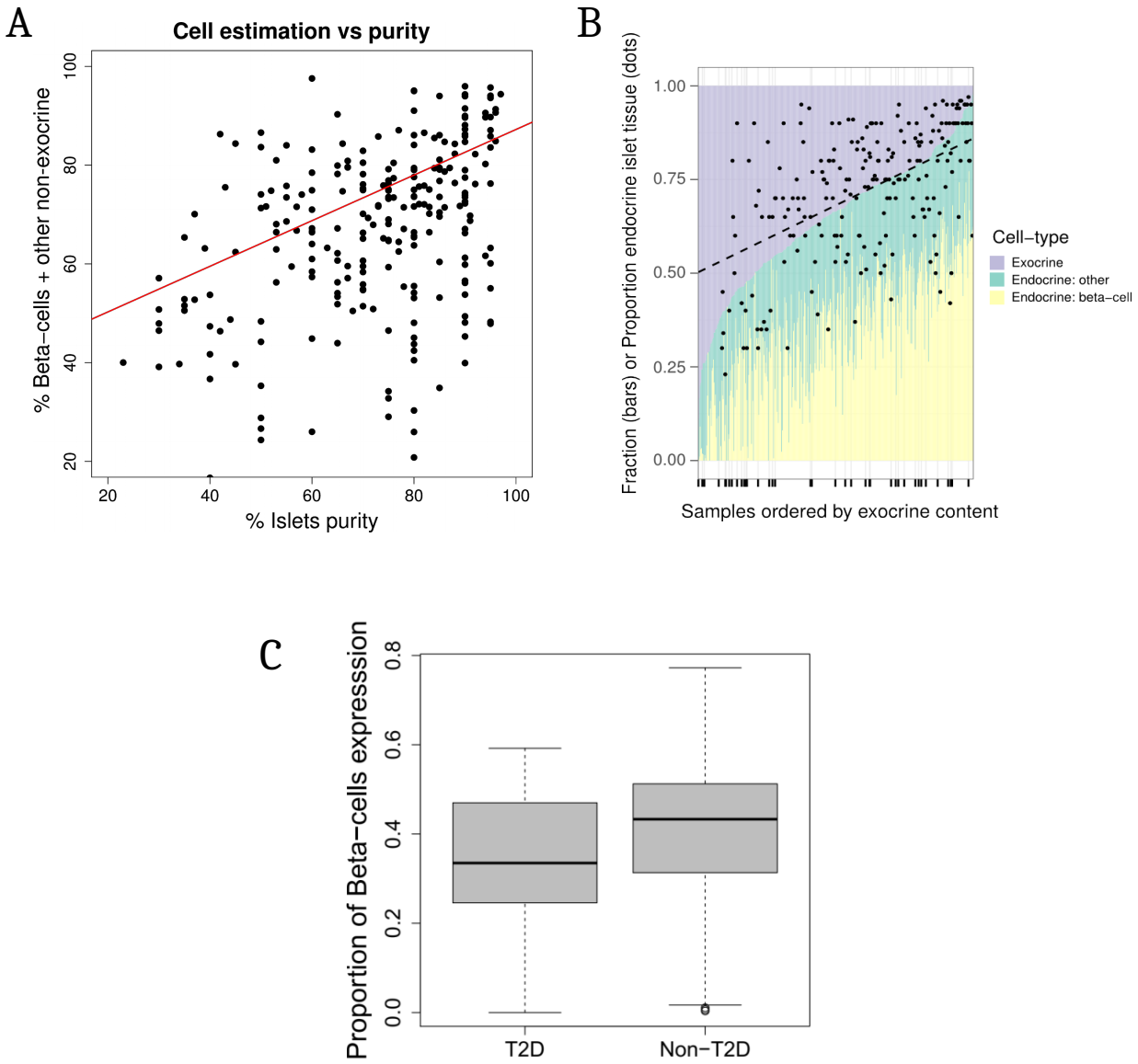
# Supplementary Figures



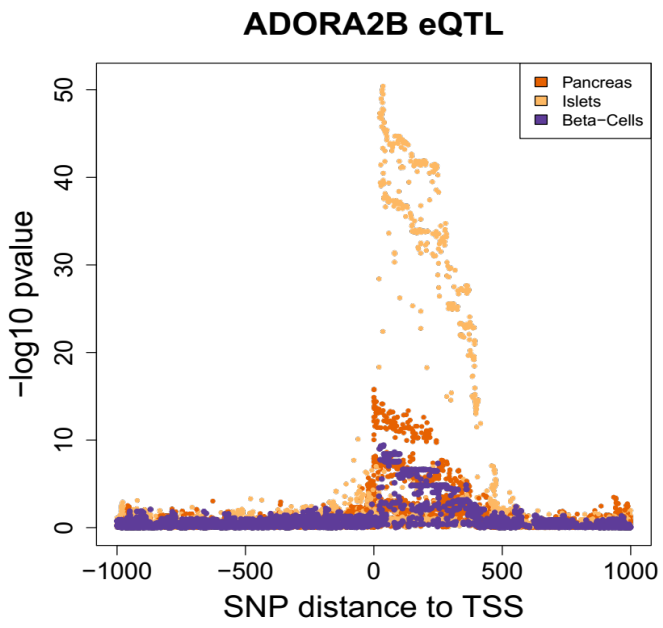

**Supplementary Figure 1 | Principal component analysis (PCA) of islets samples.** We calculate PCAs from the exon expression profiles per sample included in the InsPIRE project. Samples were re-quantified and normalized together to account for differences in the data production. The samples showed in the PCA analysis the differences due to experimental processing differences, with internal batch effects in the cases of samples from Oxford/Edmonton and Lund.



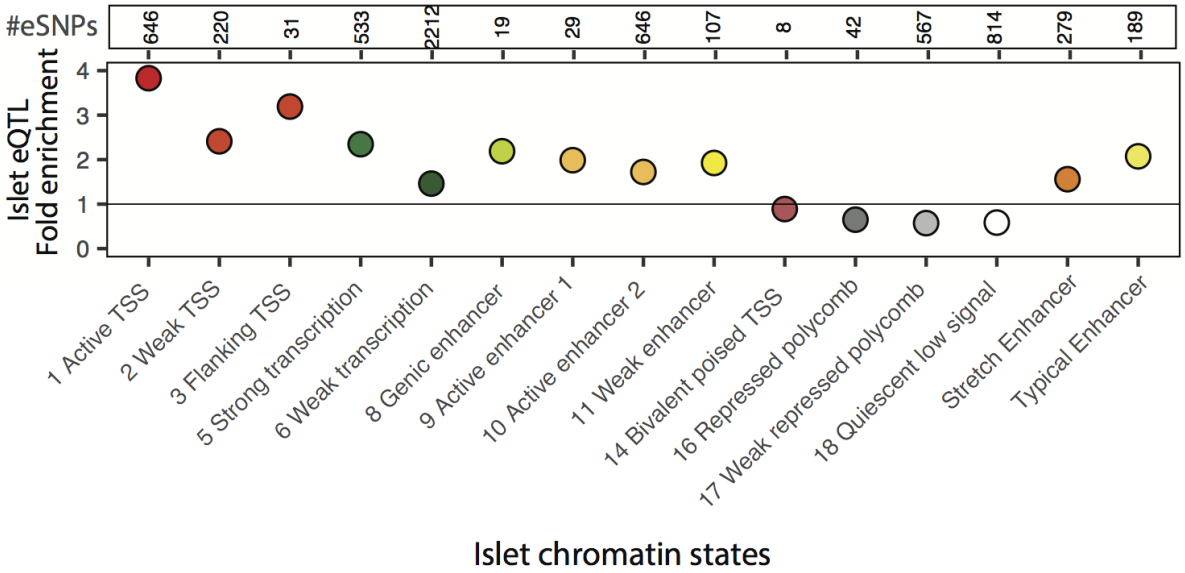

**Supplementary Figure 2 | Properties of islets eQTL. A)** –log10 p-value distribution of the lead eSNP per gene around the transcription start site (TSS) of the genes in black. Yellow values show the secondary signals discovered after conditional analysis. Both the primary and secondary sSNPs show smaller p-values around the TSS, however, the secondary signals are significantly further away from the TSS (**B**). Distance to TSS has been corrected by strand. **C)** Distance of the eSNPs around the TSS for those genes with 2 independent eQTLs (n = 1,290). The difference in the Kb distance between primary SNP (1$^{st}$) and secondary SNP (2nd SNP as the highest variance explained in expression) independent eSNPs significantly affecting the expression of the same gene is expressed in negative values (left) if the primary eSNPs is closer to the TSS than the secondary eSNPs (N = 788). Positive values identify those eGenes in which the secondary eSNP is closer to the TSS than the primary (N= 503).



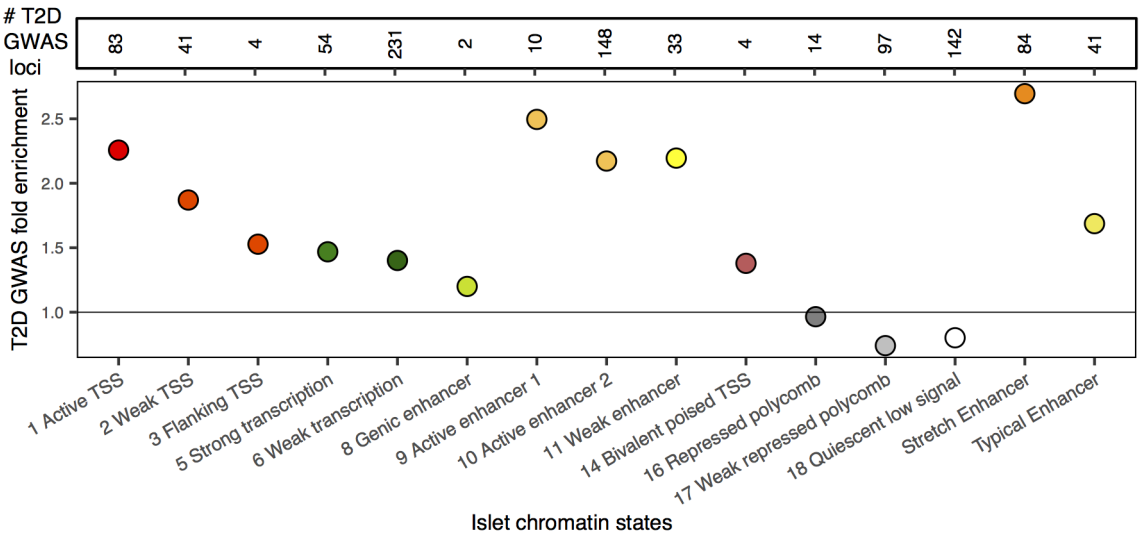

**Supplementary Figure 3 | Cell deconvolution analysis. A)** Percentage of purity for islets as measured in dithizone staining of the 253 samples compare to the estimated proportion of (beta-cells + other non-exocrine cell)/ total cell content in islets. The correlation between measured values of purity was ρ=-0.406 (p-value=1.4x10$^{-11}$). **B)** Estimates of the different types of cell considered in the 420 islets samples processed. The beta-cells proportion composition form per sample corresponded to a median of 58.8%, and 41.2% for non-beta-cell fractions. **C)** Percentage of Beta-cells expression detected in islets samples from individuals identified as diabetics (T2D), compare to non-T2D individuals.



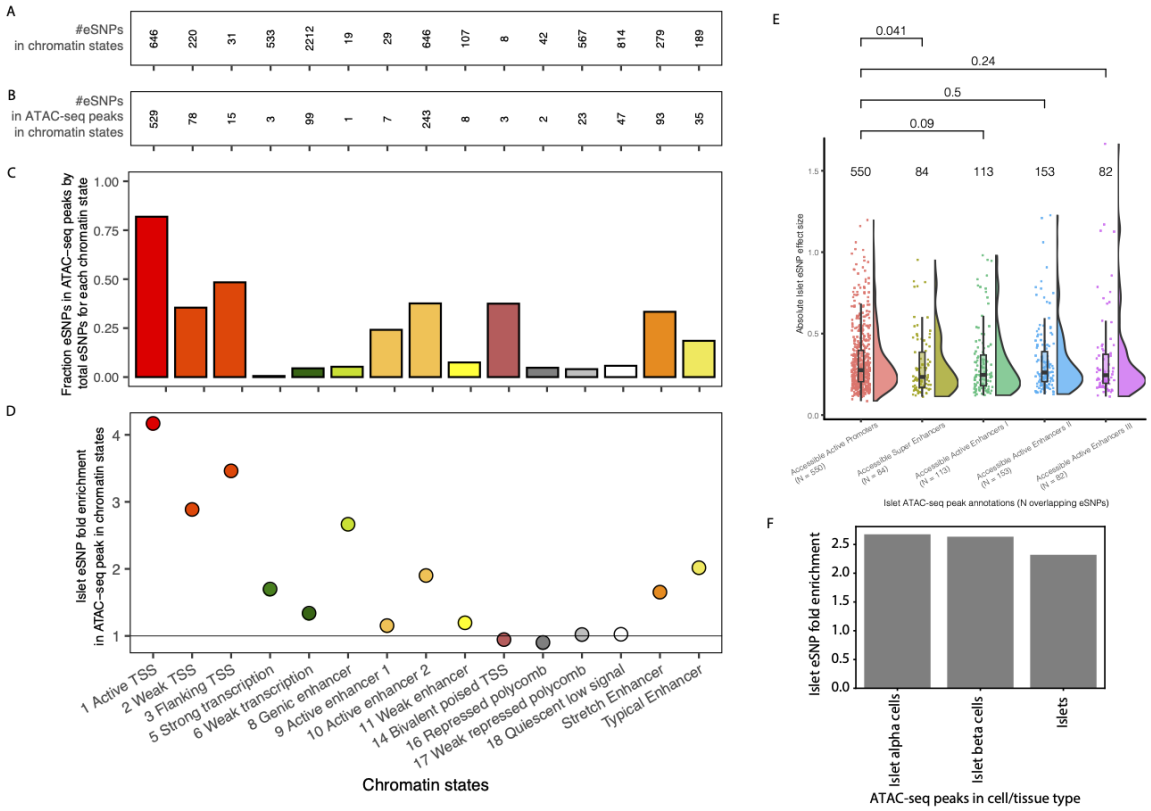

**Supplementary Figure 4 | eQTL for ADORA2B in islets, beta-cells and pancreas samples.** Each dot represent a SNPs in the cis window of ADORA2B and their distance in kb to the TSS. The y-axis shows the -log10 of the p-value for the association between a given SNP and the expression of the same exon in ADORA2B (exon ID =ENSG00000170425.3_15877177_15879060). For all tissues, at least one SNP was significant after multiple testing (FDR = 5%).



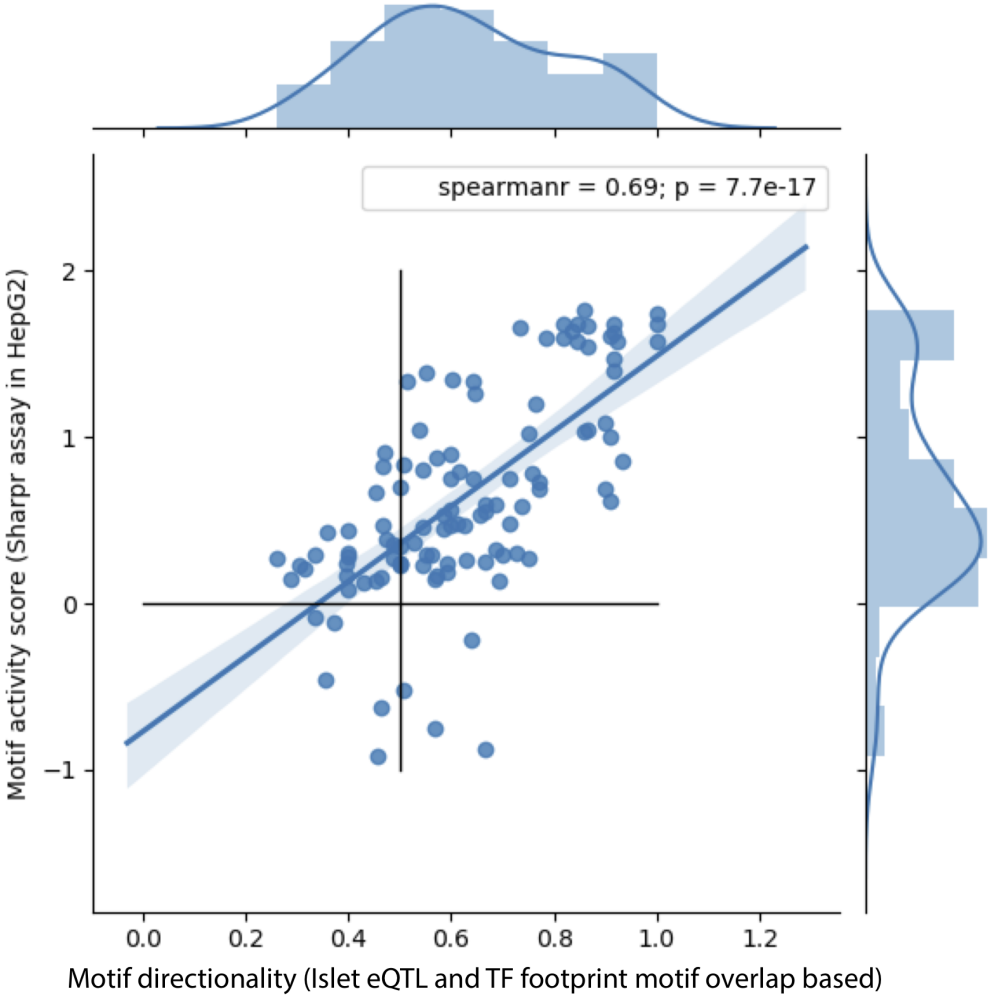

**Supplementary Figure 5 | Islet eSNP overlap and enrichment in islet chromatin states.** Top: Number of islet eSNPs (MAF>=0.2) in 13 islet chromatin states and stretch and typical enhancers. Bottom: Fold enrichment of islet eSNPs in chromatin states calculated using GREGOR [1]



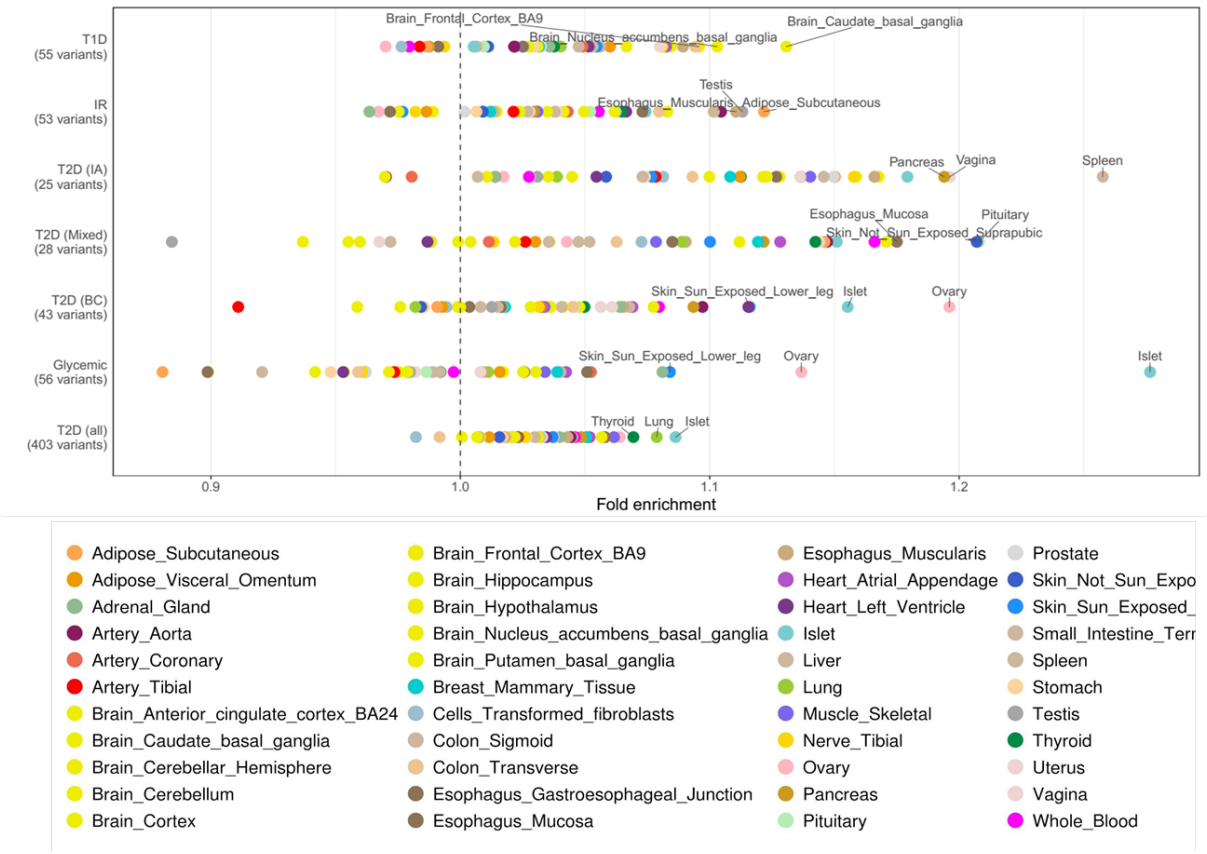

**Supplementary Figure 6 | T2D GWAS overlap and enrichment in islet chromatin states**. Top: Number of T2D GWAS loci occurring in each of the 13 islet chromatin states along with stretch and typical enhancers. Bottom: Fold enrichment of T2D GWAS in chromatin states calculated using GREGOR[1]



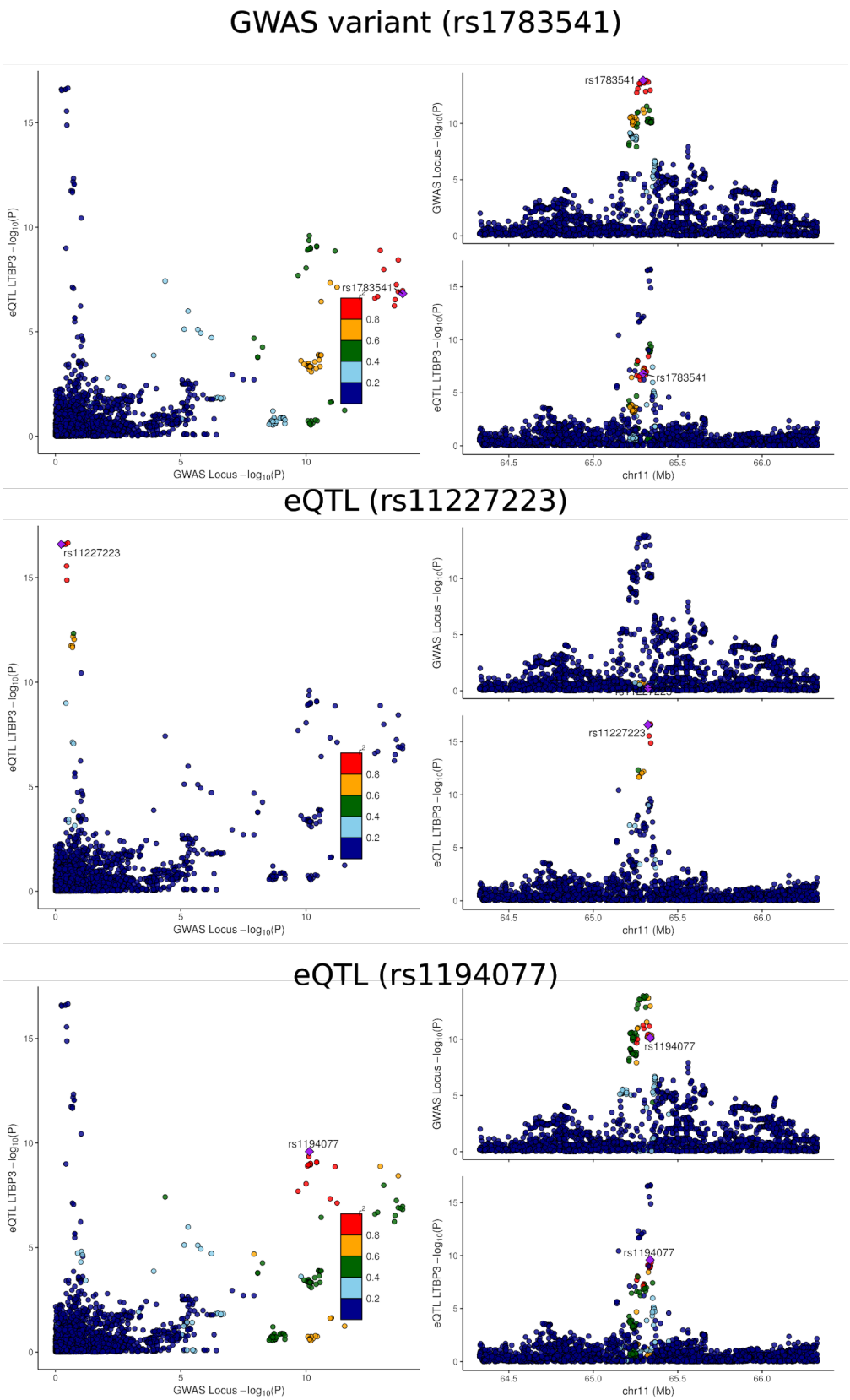

**Supplementary Figure 7 | Islet eSNP enrichment in ATAC-seq peaks . A)** Number of islet eSNPs overlapping with islet chromatin states and stretch/typical enhancers. **B)** Number of islet eSNPs in islet ATAC-seq peaks in chromatin states. **C)** Fraction of islet eSNPs in ATAC-seq peaks in each chromatin states. An eSNP overlap is considered if the eQTL lead eSNP or proxy SNP (LD r2>0.99) overlaps the feature. **D)** Fold enrichment of islet eSNPs to overlap ATAC-seq peaks within chromatin states. **E)** Absolute effect sizes for eSNPs occurring in islet ATAC-seq features such as active promoters, active enhancers I, II and III, and super enhancer segments overlapping 'robust' ATAC-seq peaks obtained from Miguel-Escalada et al. 2019. The number of eQTL overlaps in each annotation are shown in parentheses. P values are from Wilcoxon rank sum tests. **F)** Islet eSNP enrichment in ATAC-seq peaks from islets and islet alpha and beta cell clusters from the sci-ATAC-seq data from Rai et al. 2020.



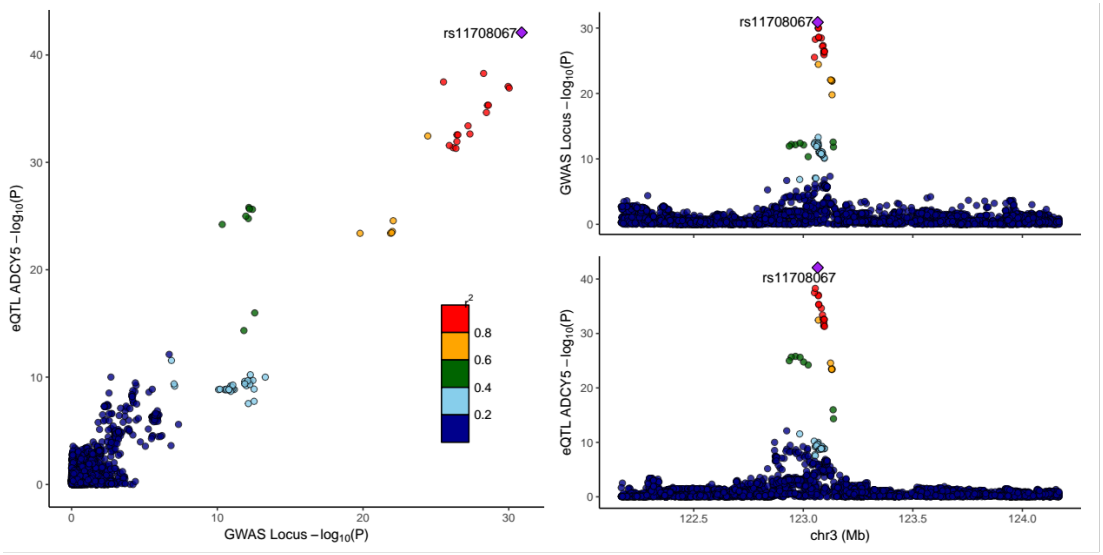

**Supplementary Figure 8 | Comparison of TF motif directionality fractions with MPRA activity scores.** Transcription factor motif activity scores from Sharpr MPRA in HepG2 vs Motif directionality fractions from islet eQTL and ATAC-seq TF footprinting data. TF Motifs that were reported to be either activating or repressive (P<0.01) from the MPRAs in both HepG2 and K562 are shown.



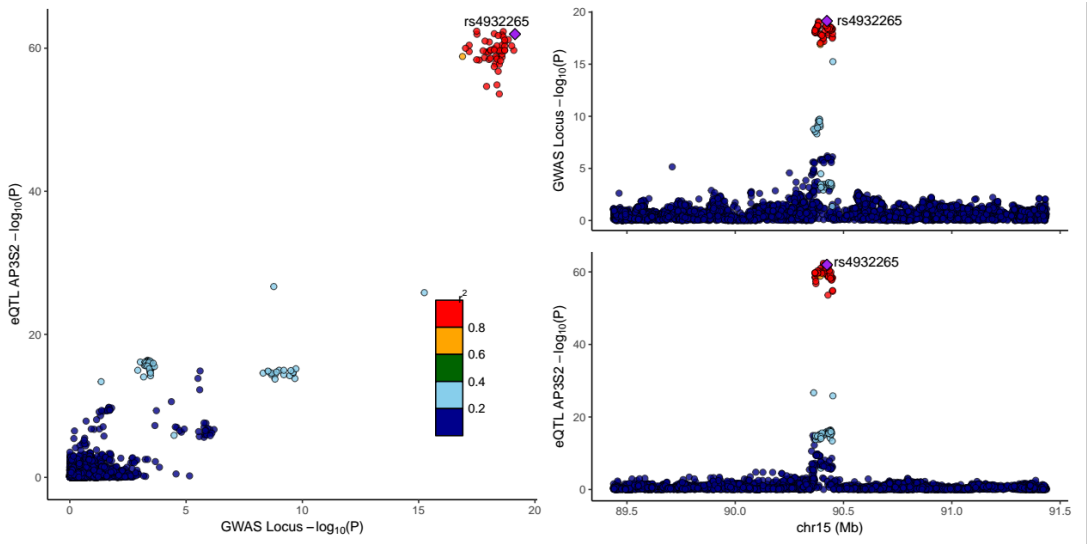

**Supplementary Figure 9 | Tissue enrichment analysis in all GTEx tissues**. Results support the conclusion show in the main figure that islets outperform other tissues for GWAS loci enrichment.



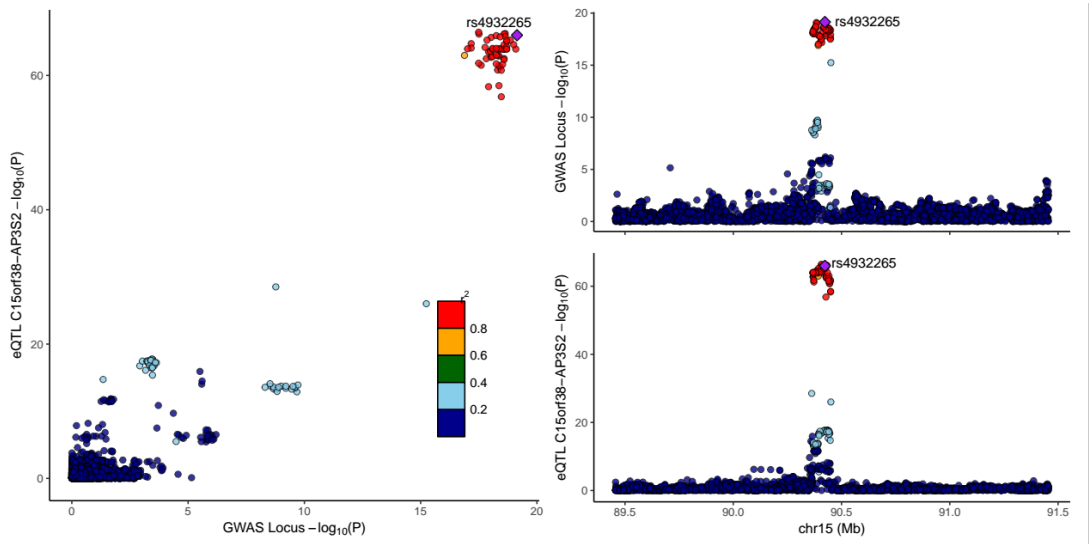

**Supplementary Figure 10 | LocusCompare plot of the eQTL for the *MAP3K11* locus.** Three LocusCompare are shown: i) Highlighting the T2D signal (rs1783541), then highlighting lead eSNP for the two eQTLs for *LTBP3*. The signal at rs1194077 appears coincident to the GWAS as reported by RTC (RTC score = 0.96), while COLOC report no colocalization with any variant.



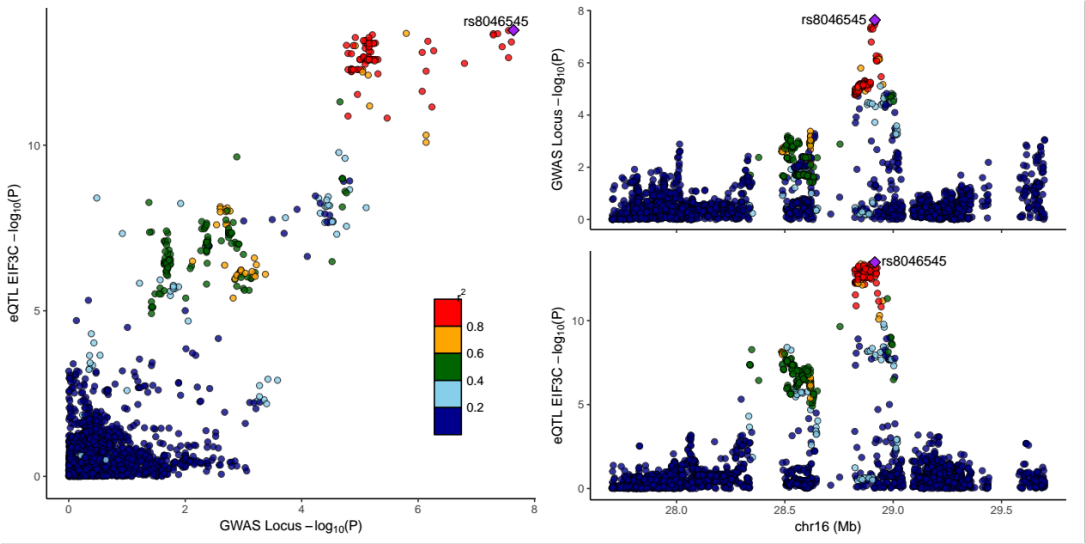

**Supplementary Figure 11.1 | LocusCompare for the eQTL in *ACDY5* and GWAS loci known as *ACDY5*.**



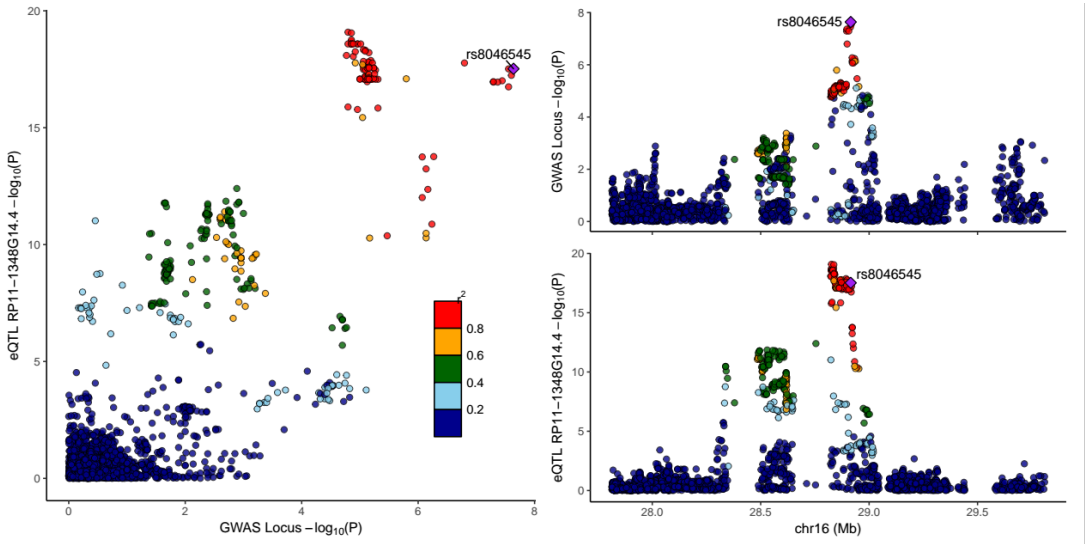

**Supplementary Figure 11.2 | LocusCompara for the eQTL in *AP3S2* and GWAS loci known as *AP3S2*.**



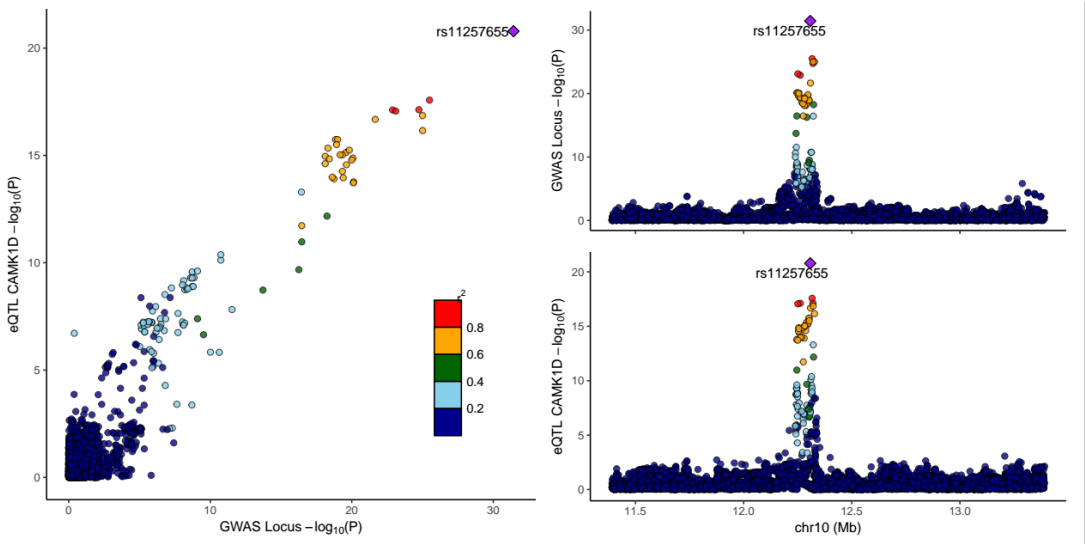

**Supplementary Figure 11.3 | LocusCompare for the eQTL in *C15orf38-AP3S2* and GWAS loci known as *AP3S2*.**



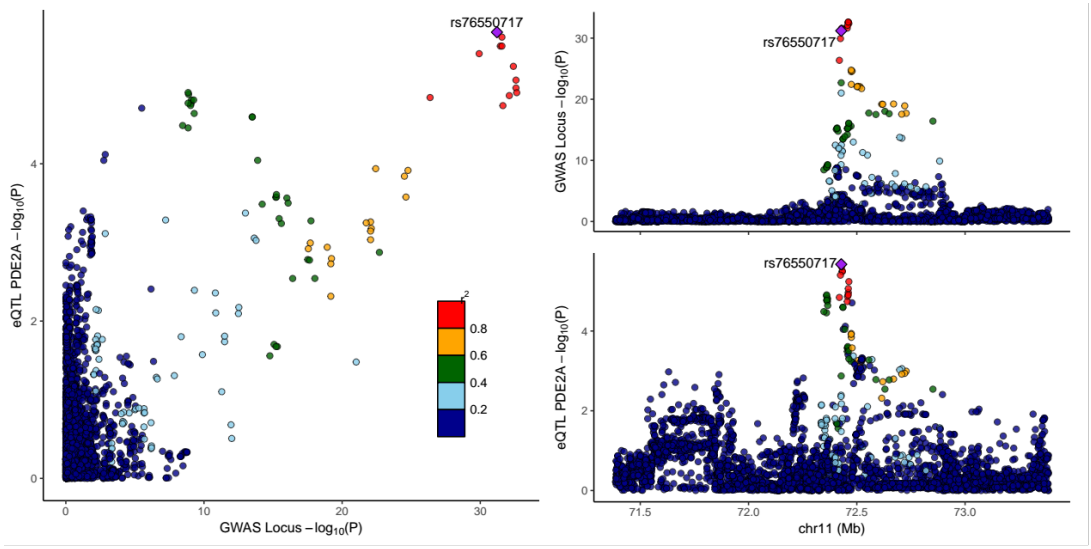

**Supplementary Figure 11.4 | LocusCompare for the eQTL in *EIF3C* and GWAS loci known as *ATP2A1*.**



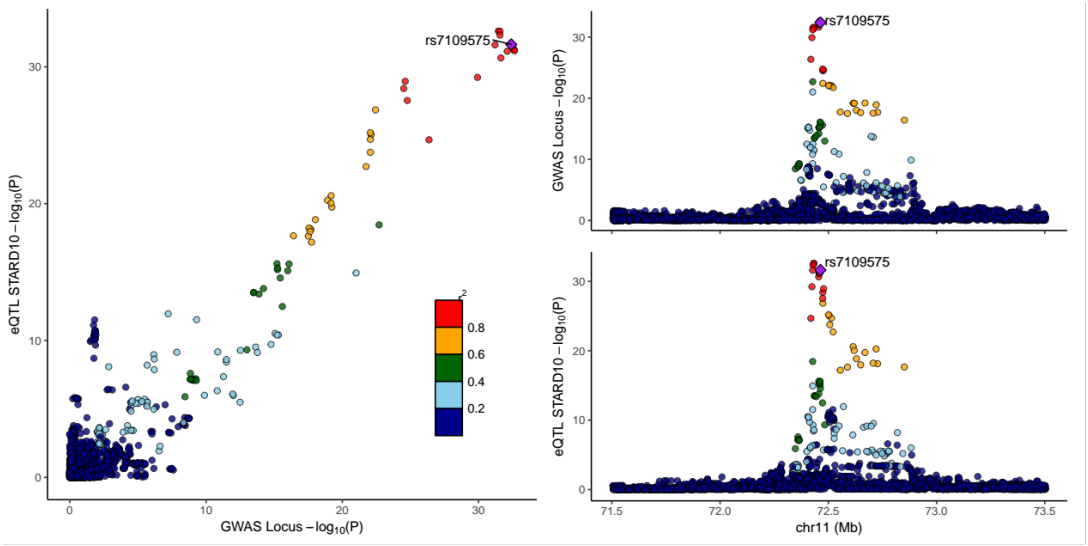

**Supplementary Figure 11.5 | LocusCompare for the eQTL in *RP11-1348G14.4* and GWAS loci known as *ATP2A1*.**



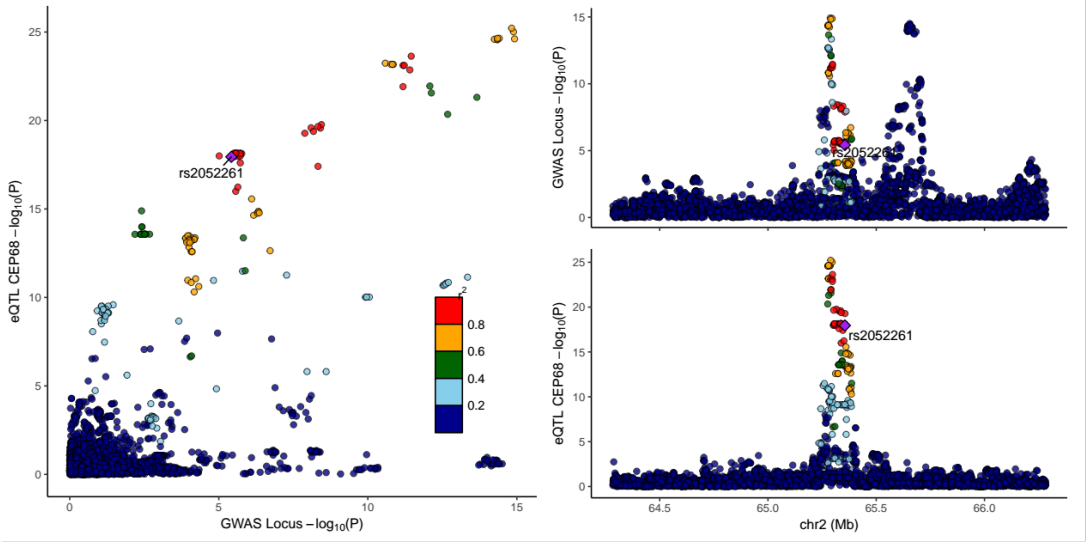

**Supplementary Figure 11.6| LocusCompare for the eQTL in *CAMK1D* and GWAS loci known as *CDC123/CAMK1D*.**



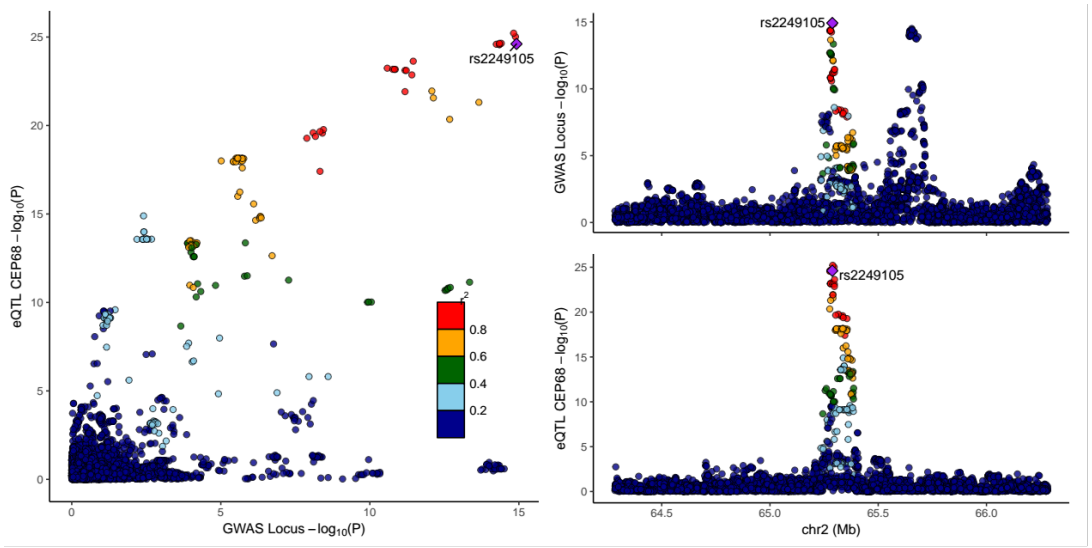

**Supplementary Figure 11.7 | LocusCompare for the eQTL in *PDE2A* and GWAS loci known as *CENTD2-ARAP1*.**



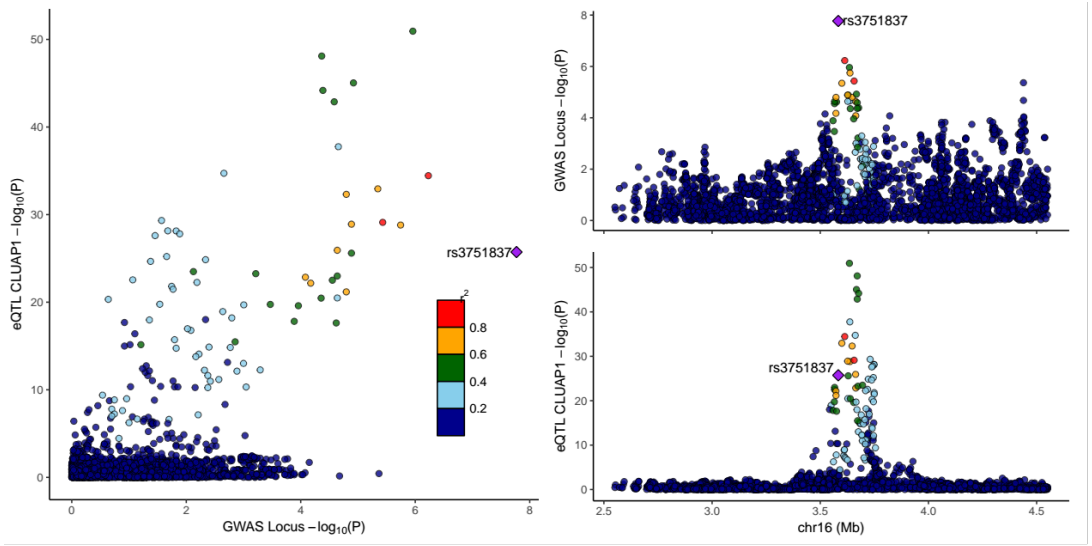

**Supplementary Figure 11.8 | LocusCompare for the eQTL in STARD10 and GWAS loci known as *CENTD2-ARAP1*.**



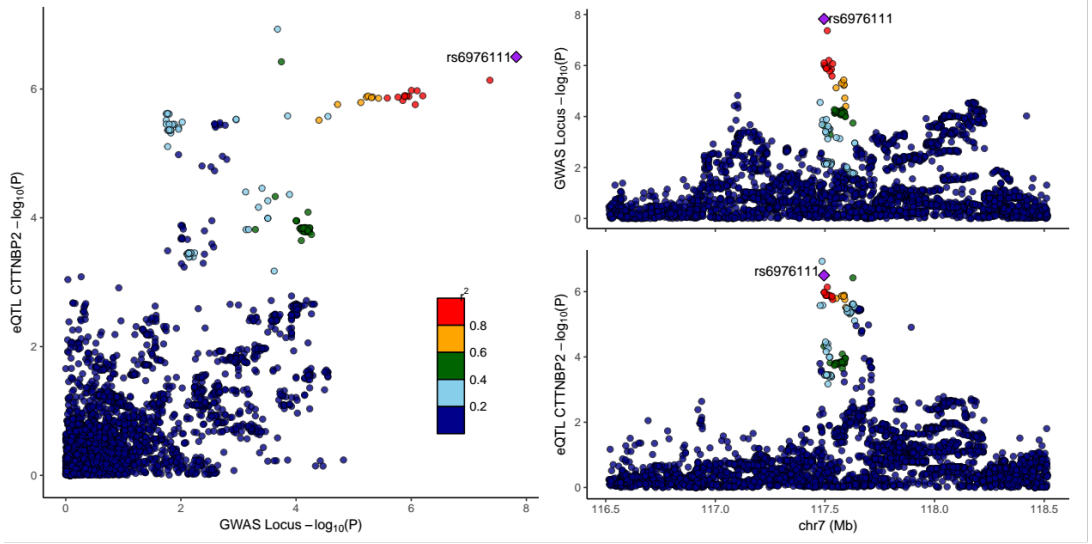

**Supplementary Figure 11.9 | LocusCompare for the eQTL in *CEP68* and a secondary GWAS loci in *CEP68*.**



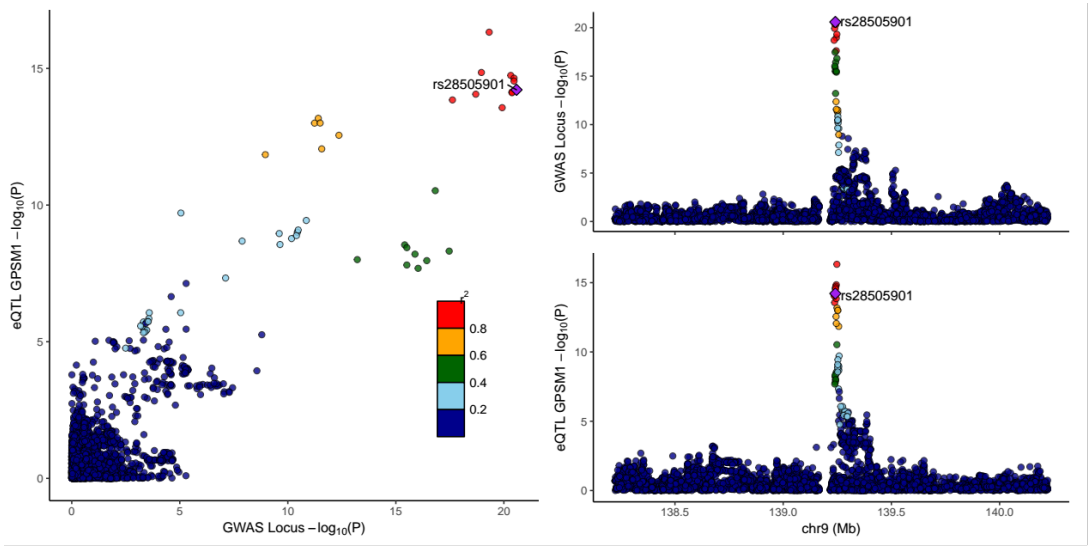

**Supplementary Figure 11.10 | LocusCompare for the eQTL in *CEP68* and a primary GWAS loci in *CEP68*.**



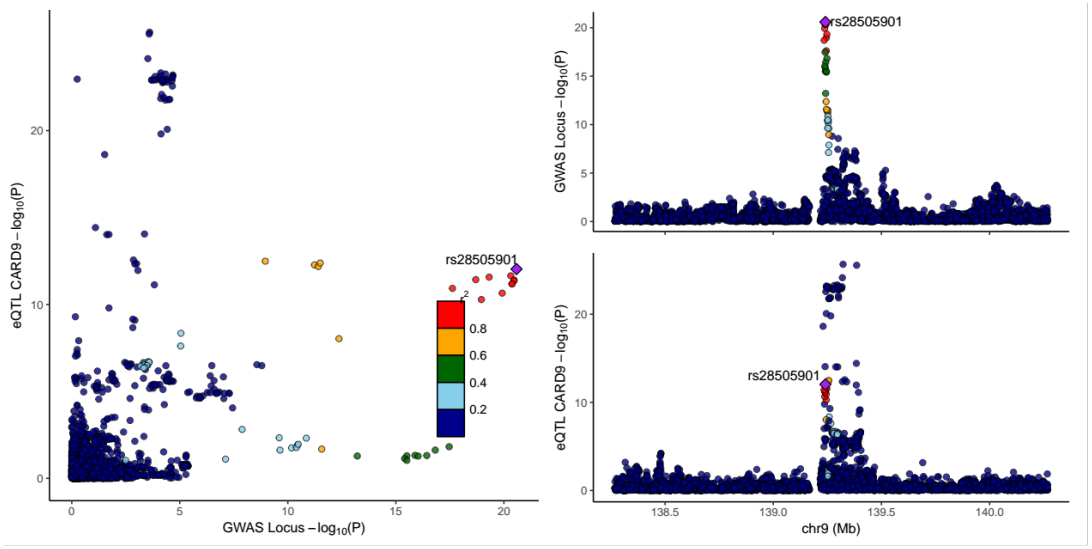

**Supplementary Figure 11.11 | LocusCompare for the eQTL in *CLUAP1* and GWAS loci known as *CLUAP1*.**



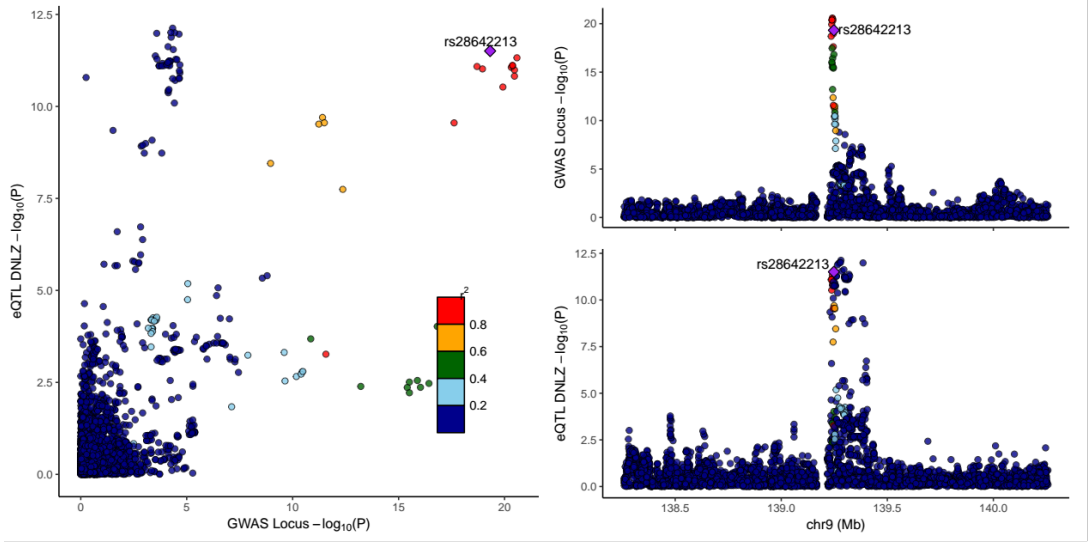

**Supplementary Figure 11.12 | LocusCompare for the eQTL in *CTTNBP2* and GWAS loci known as *CTTNBP2*.**



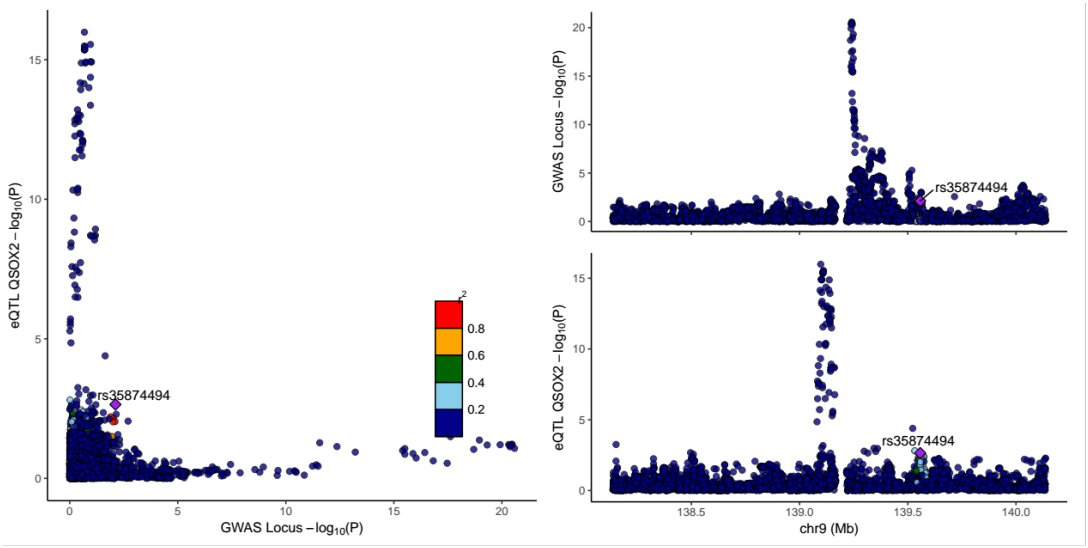

**Supplementary Figure 11.13 | LocusCompare for the eQTL in *GPSM1* and GWAS loci known as *GPSM1*.**



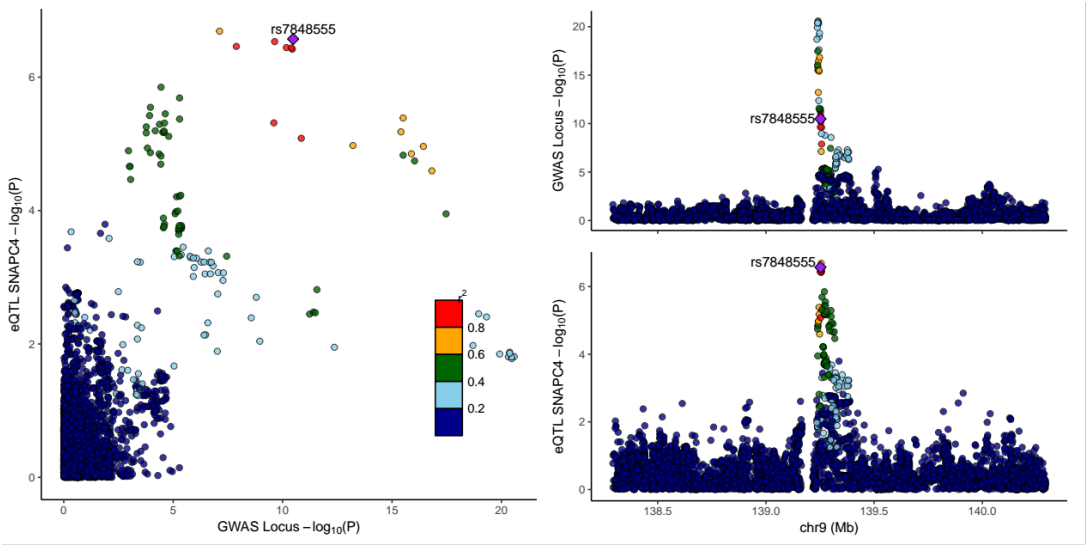

**Supplementary Figure 11.14 | LocusCompare for the eQTL in *CARD9* and GWAS loci known as *GPSM1*.**



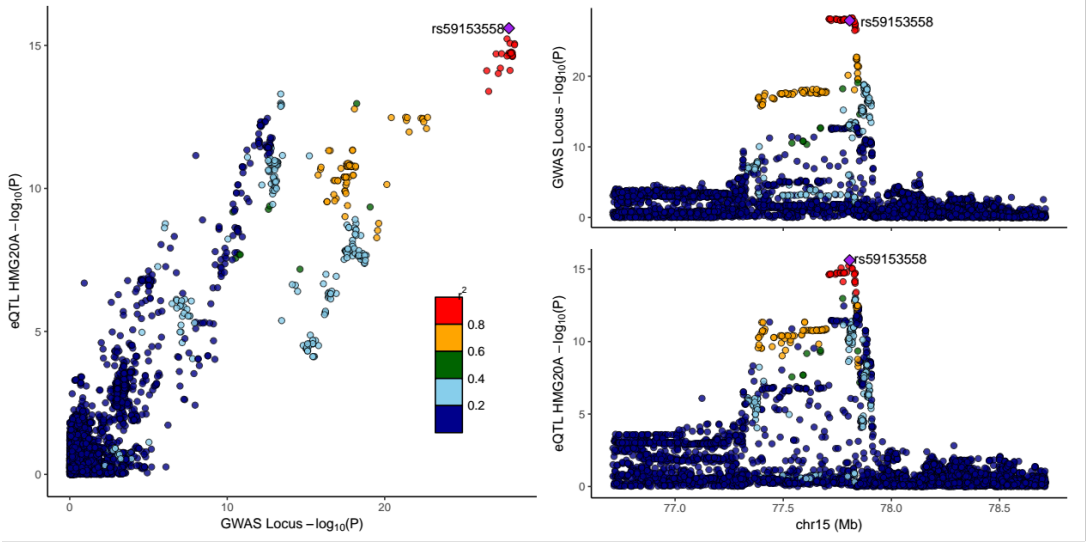

**Supplementary Figure 11.15 | LocusCompare for the eQTL in *DNLZ* and GWAS loci known as *GPSM1*.**



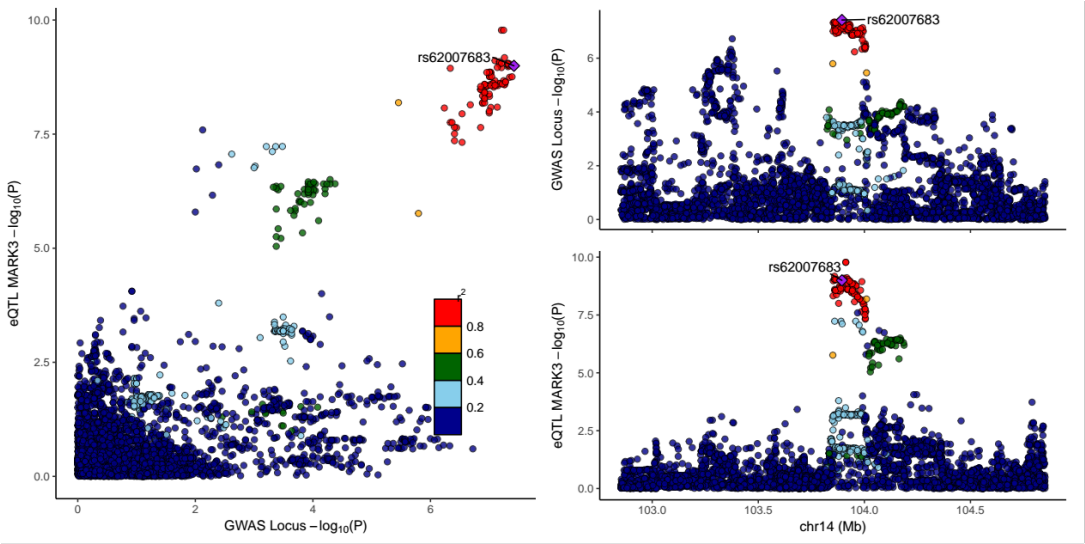

**Supplementary Figure 11.16 | LocusCompare for the eQTL in *QSOX2* and GWAS loci known as *GPSM1*.**



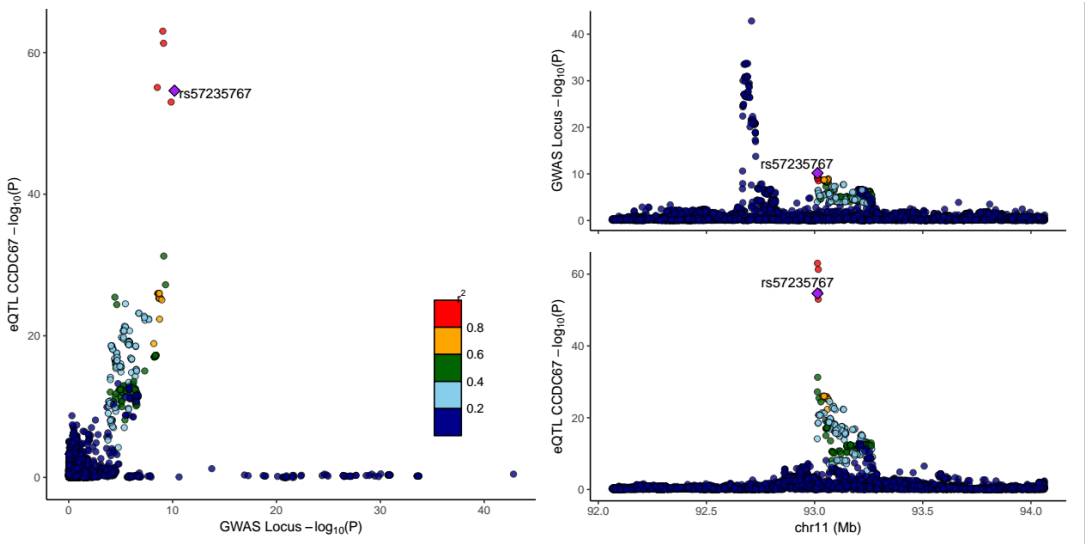

**Supplementary Figure 11.17 | LocusCompare for the eQTL in *SNAPC4* and GWAS loci known as *GPSM1*.**



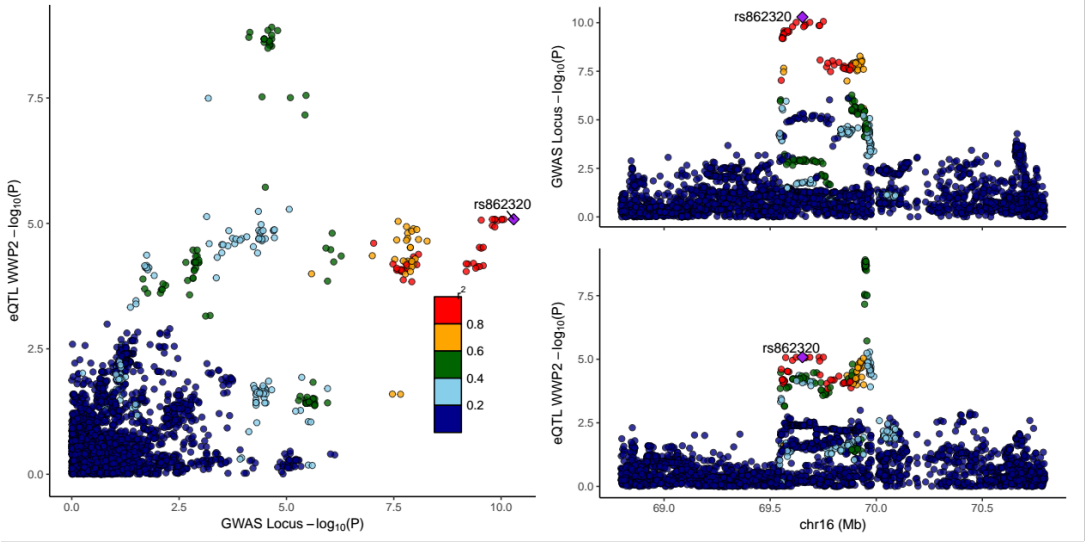

**Supplementary Figure 11.18 | LocusCompare for the eQTL in *HMG20A* and GWAS loci known as *HMG20A*.**



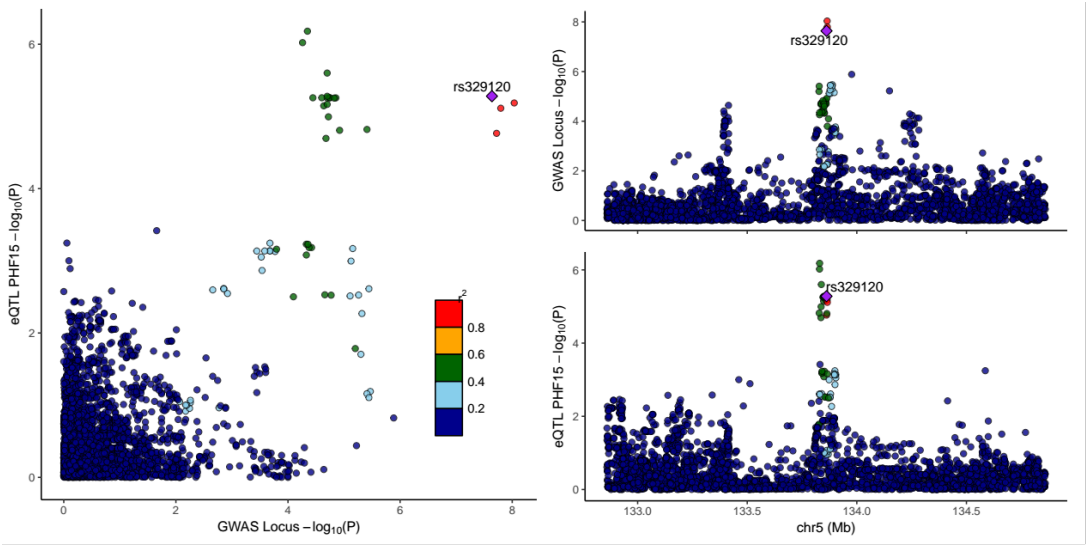

**Supplementary Figure 11.19 | LocusCompare for the eQTL in *MARK3* and GWAS loci known as *MARK3*.**



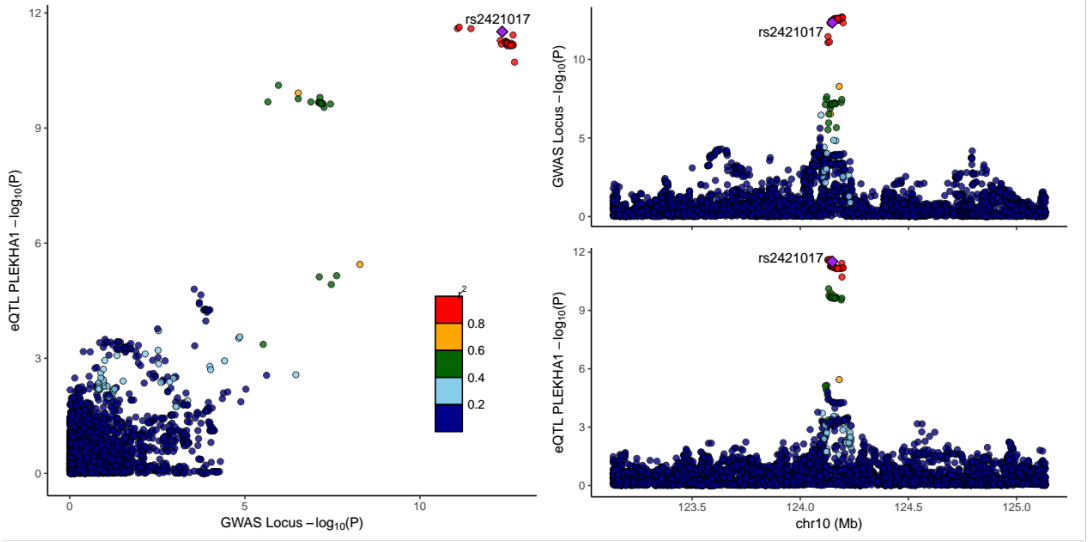

**Supplementary Figure 11.20 | LocusCompare for the eQTL in *CCDC67* and a secondary GWAS loci in *MTNR1B*.**



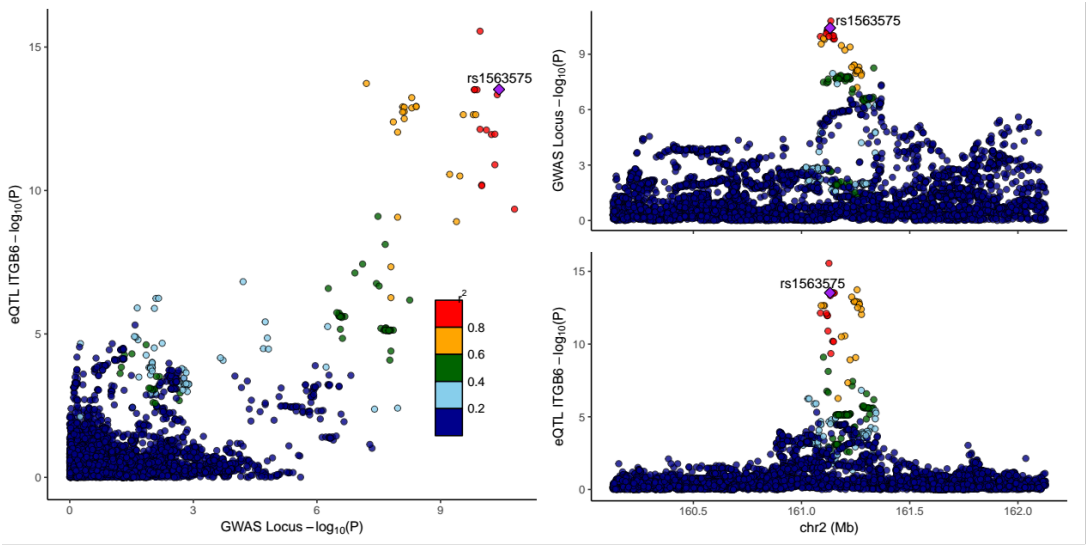

**Supplementary Figure 11.21 | LocusCompare for the eQTL in *WWP2* and GWAS loci known as *NFAT5*.**



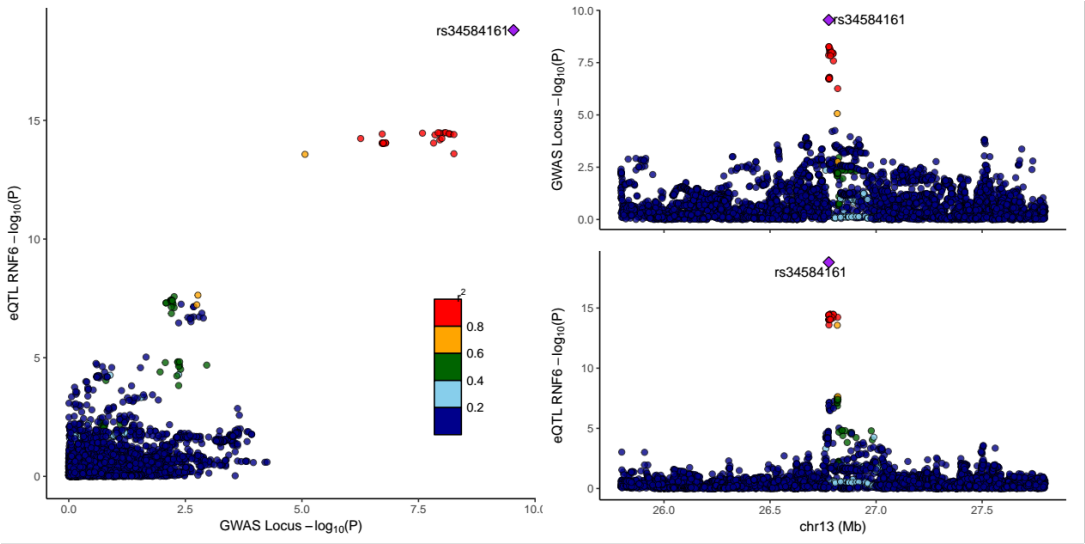

**Supplementary Figure 11.22 | LocusCompare for the eQTL in *PHF15* and GWAS loci known as *PHF15*.**



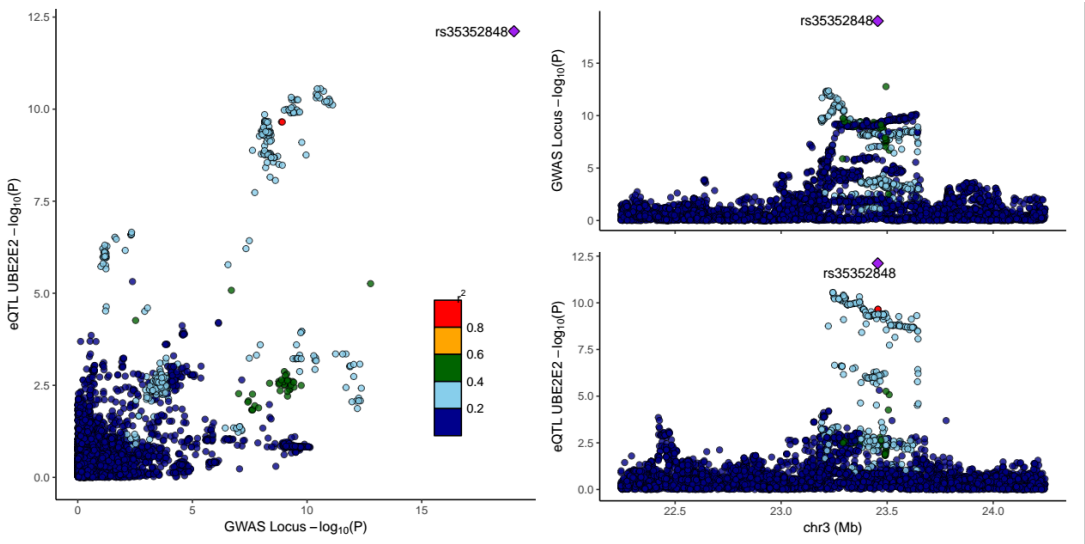

**Supplementary Figure 11.23 | LocusCompare for the eQTL in *PLEKHA1* and GWAS loci known as *PLEKHA1*.**



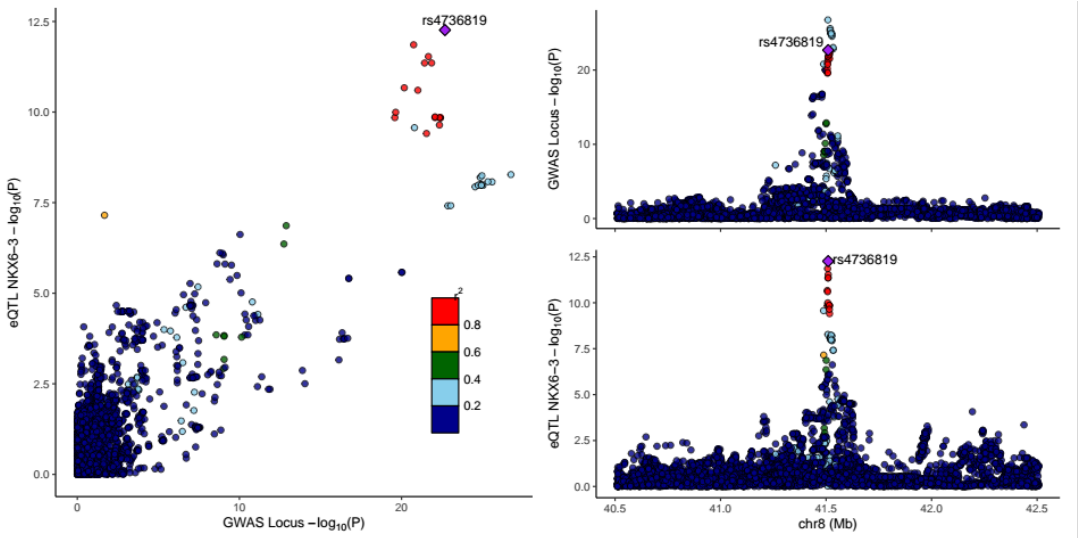

**Supplementary Figure 11.24 | LocusCompare for the eQTL in *ITGB6* and GWAS loci known as *RBMS1*.**



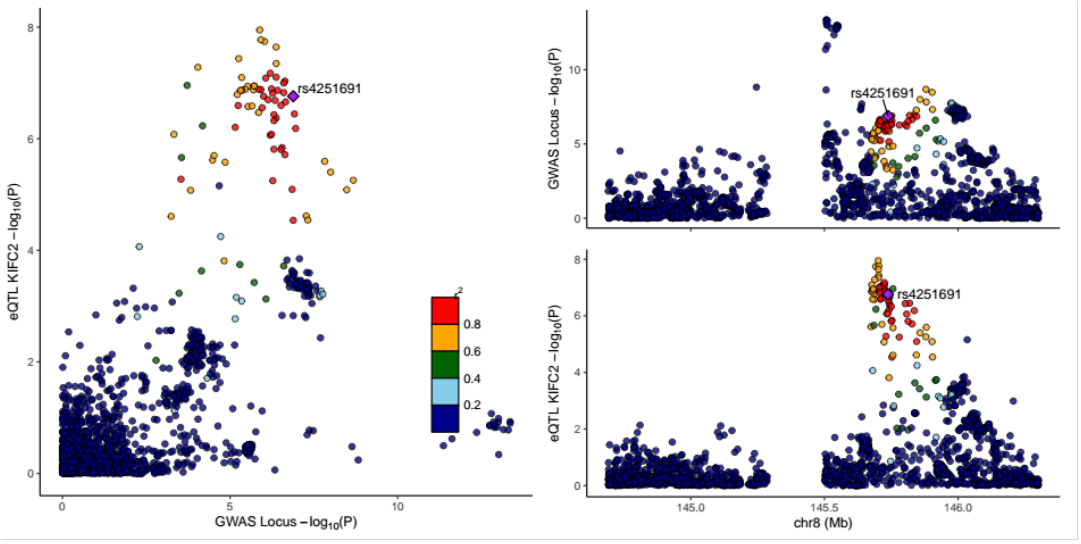

**Supplementary Figure 11.25 | LocusCompare for the eQTL in *RNF6* and GWAS loci known as *RNF6*.**



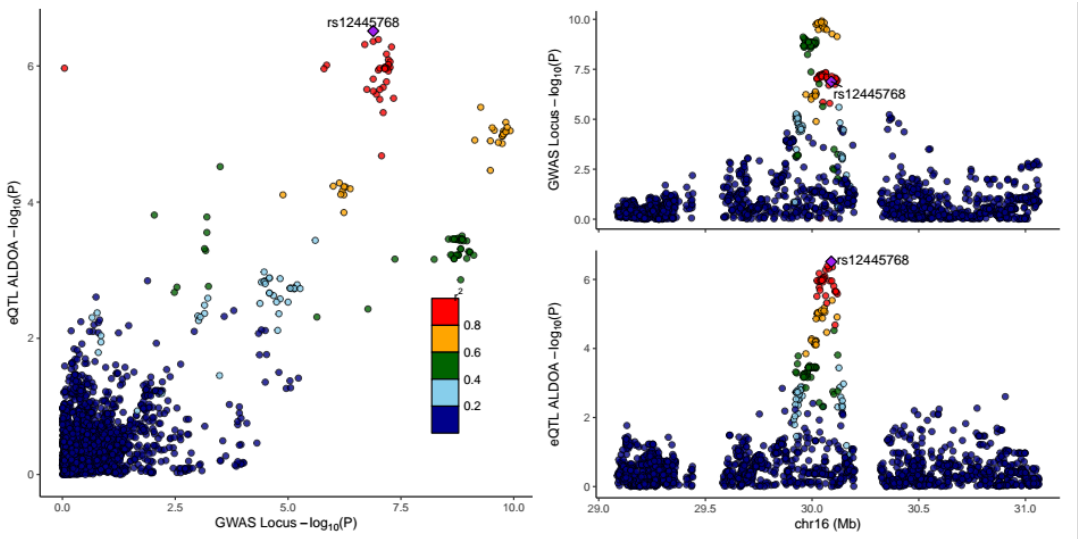

**Supplementary Figure 11.26 | LocusCompare for the eQTL in *UBE2E2* and GWAS loci known as *UBE2E2*.**



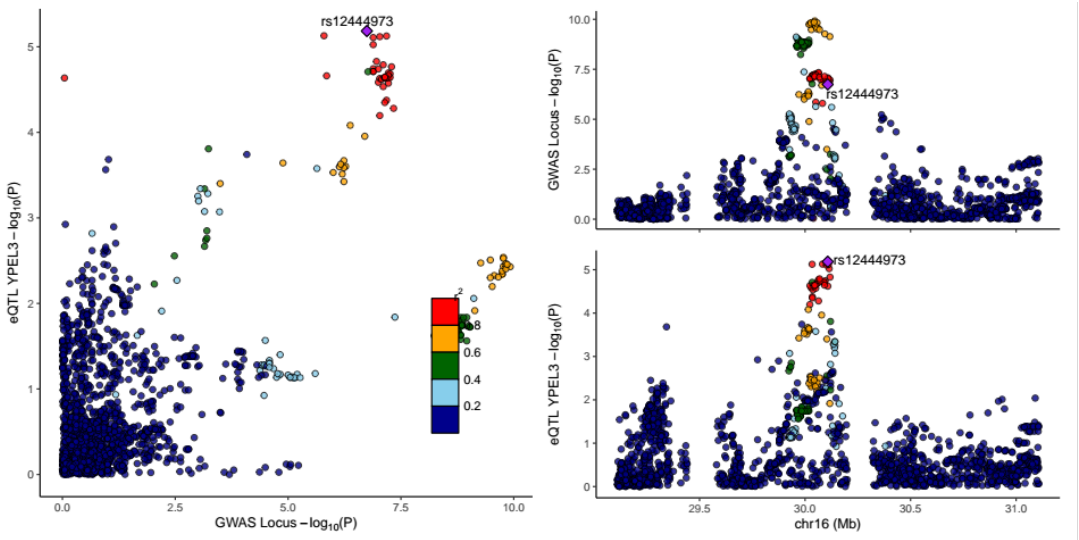

**Supplementary Figure 11.27 | LocusCompare for the eQTL in *NKX6-3* and a secondary GWAS loci in *ANK1*.**



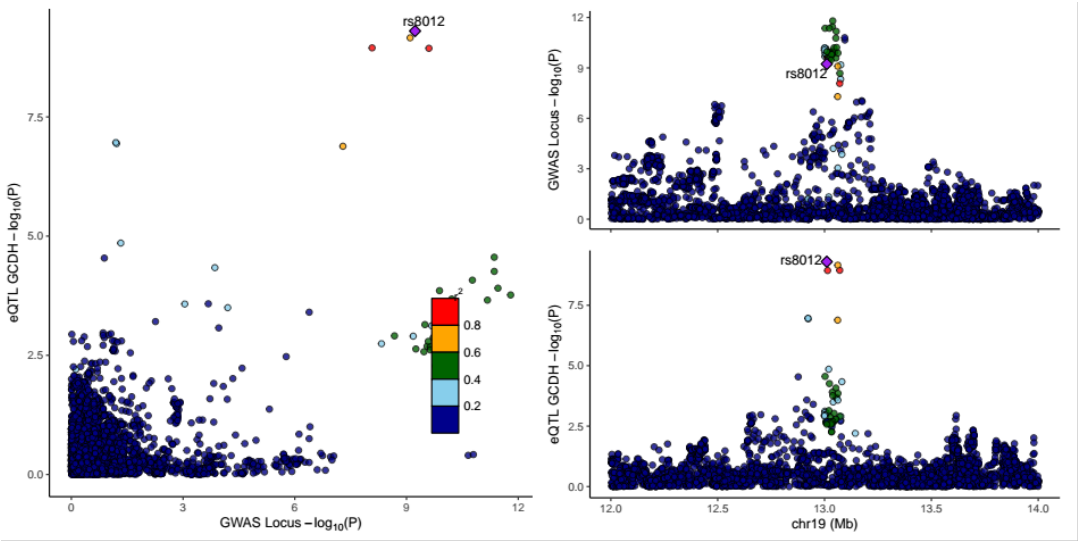

**Supplementary Figure 11.28 | LocusCompare for the eQTL in *KIFC2* and GWAS loci known as *BOP1*.**



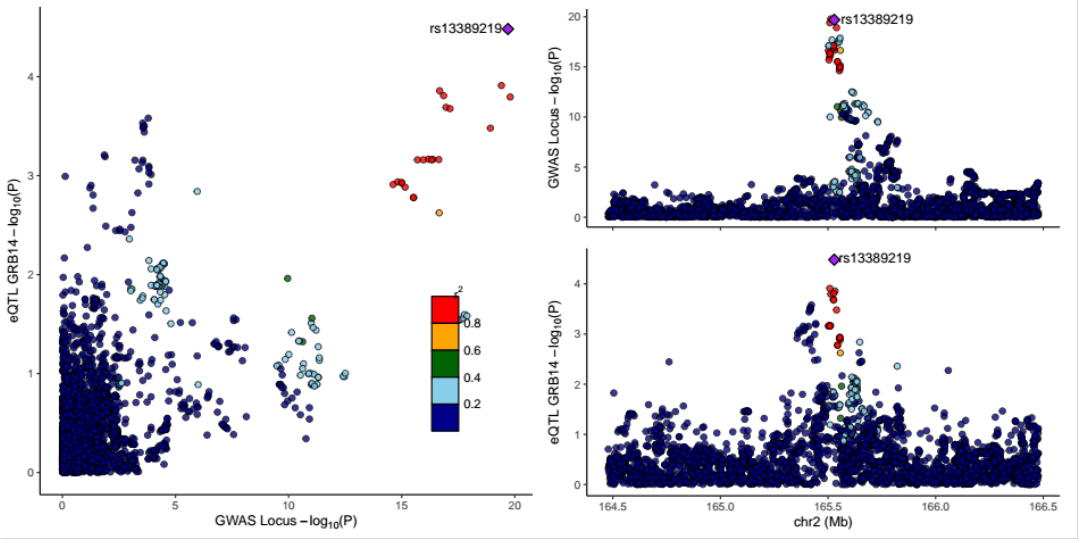

**Supplementary Figure 11.29 | LocusCompare for the eQTL in *ALDOA* and GWAS loci known as *FAM57B*.**



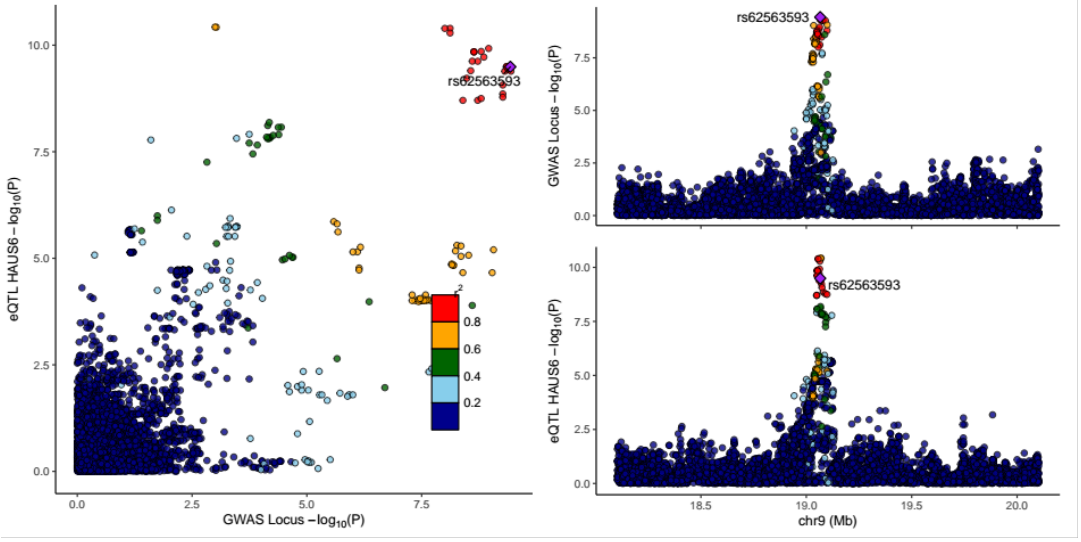

**Supplementary Figure 11.30 | LocusCompare for the eQTL in *YPEL3* and GWAS loci known as *FAM57B*.**



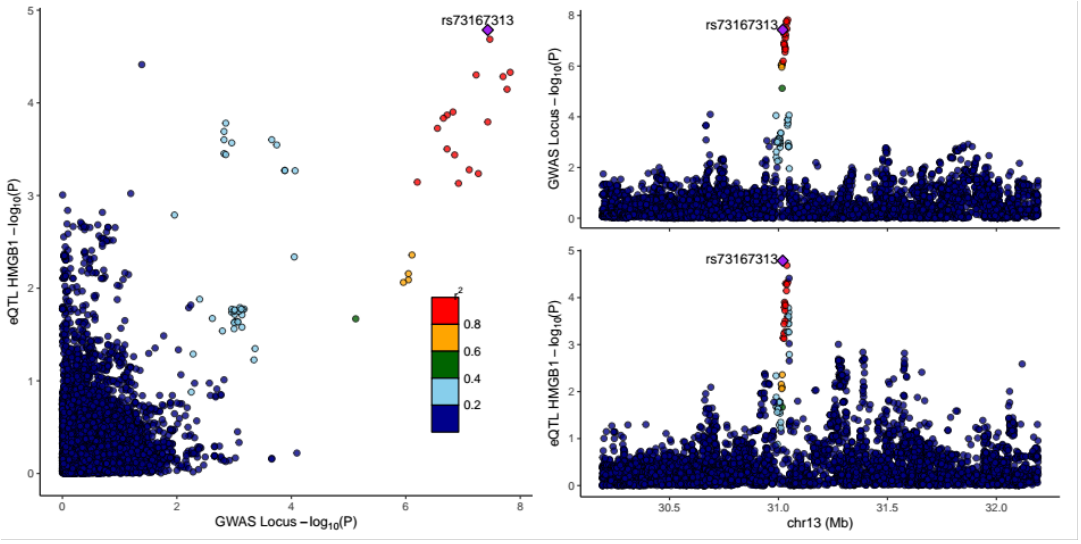

**Supplementary Figure 11.31 | LocusCompare for the eQTL in *GCDH* and GWAS loci known as *FARSA*.**



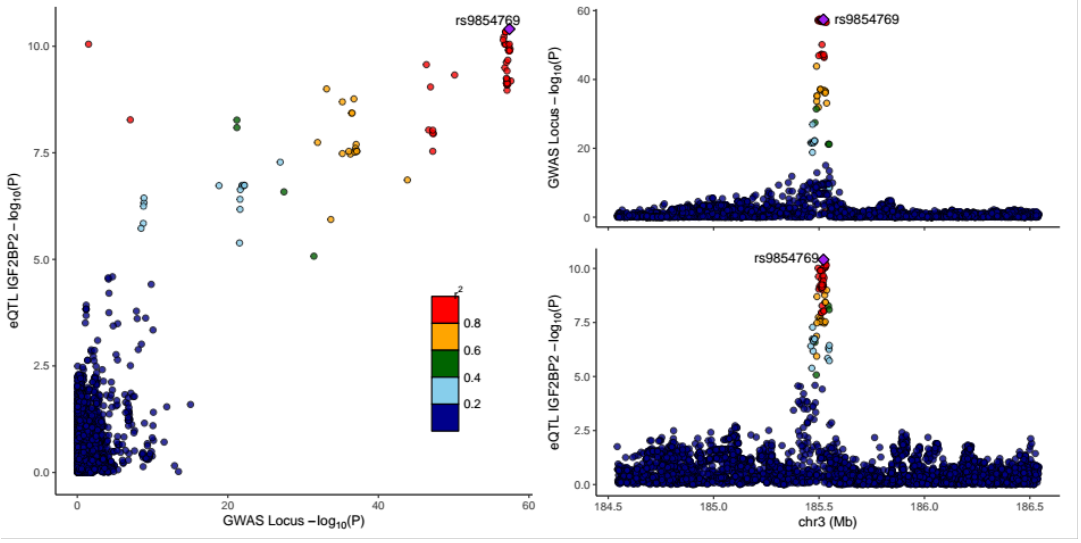

**Supplementary Figure 11.32 | LocusCompare for the eQTL in *GRB14* and GWAS loci known as *GRB14/COBLL1*.**



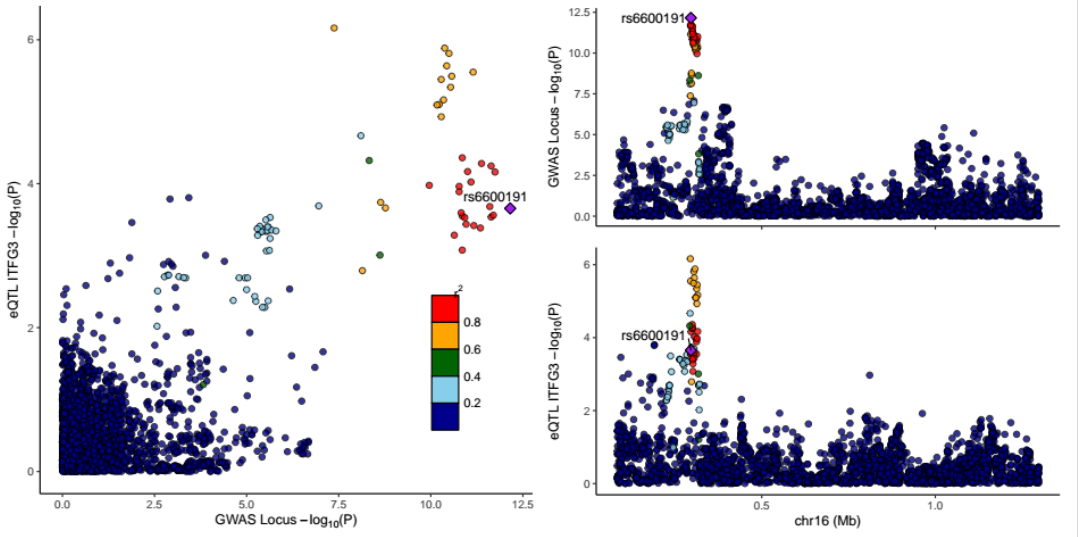

**Supplementary Figure 11.33 | LocusCompare for the eQTL in *HAUS6* and GWAS loci known as *HAUS6*.**



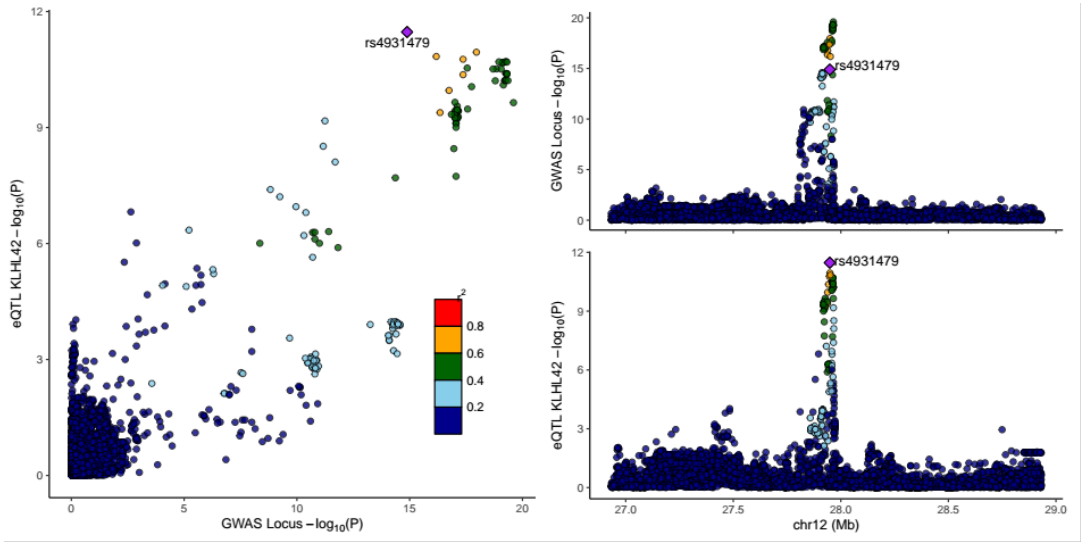

**Supplementary Figure 11.34 | LocusCompare for the eQTL in *HMGB1* and GWAS loci known as *HMGB1*.**



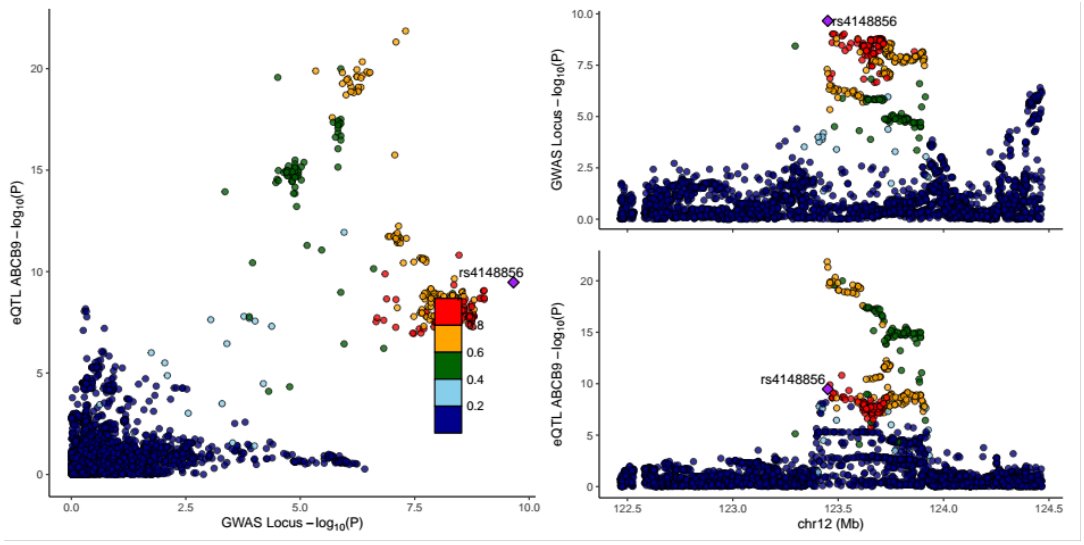

**Supplementary Figure 11.35 | LocusCompare for the eQTL in *IGF2BP2* and GWAS loci known as *IGF2BP2*.**



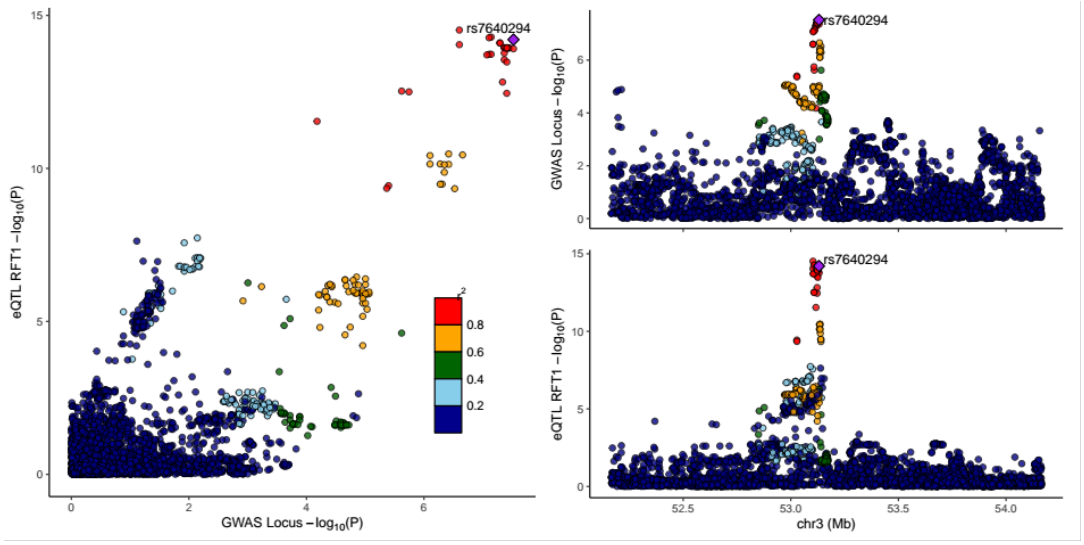

**Supplementary Figure 11.36 | LocusCompare for the eQTL in *ITFG3* and GWAS loci known as *ITFG3*.**



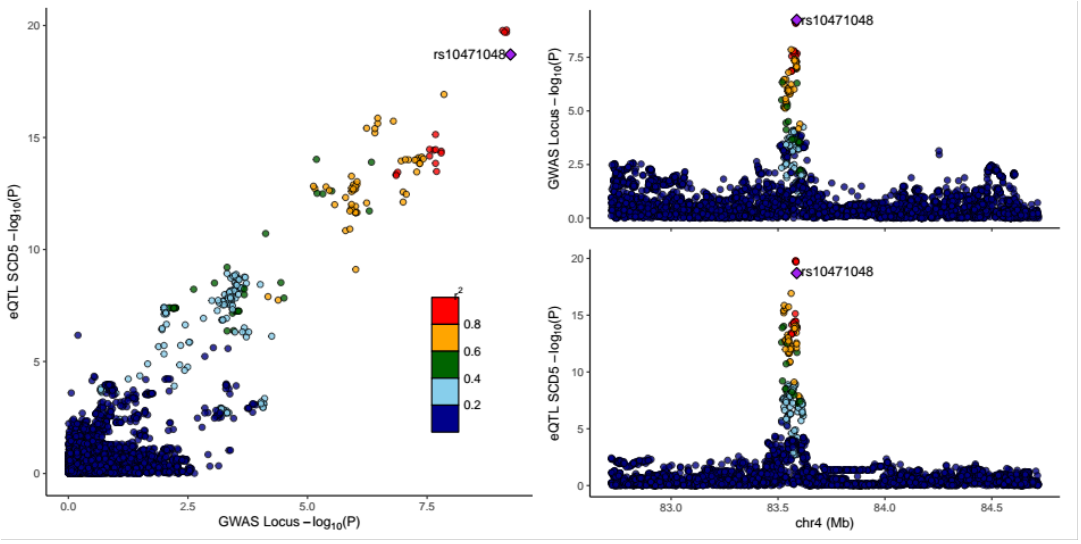

**Supplementary Figure 11.37 | LocusCompare for the eQTL in *KLHL42* and GWAS loci known as *KLHDC5*.**



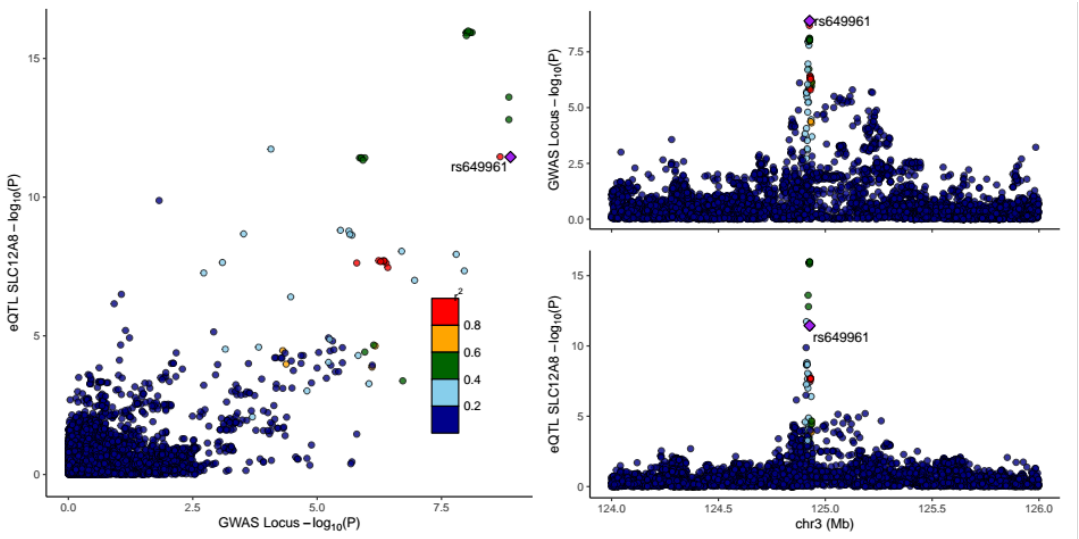

**Supplementary Figure 11.38 | LocusCompare for the eQTL in *ABCB9* and GWAS loci known as *MPHOSPH9*.**



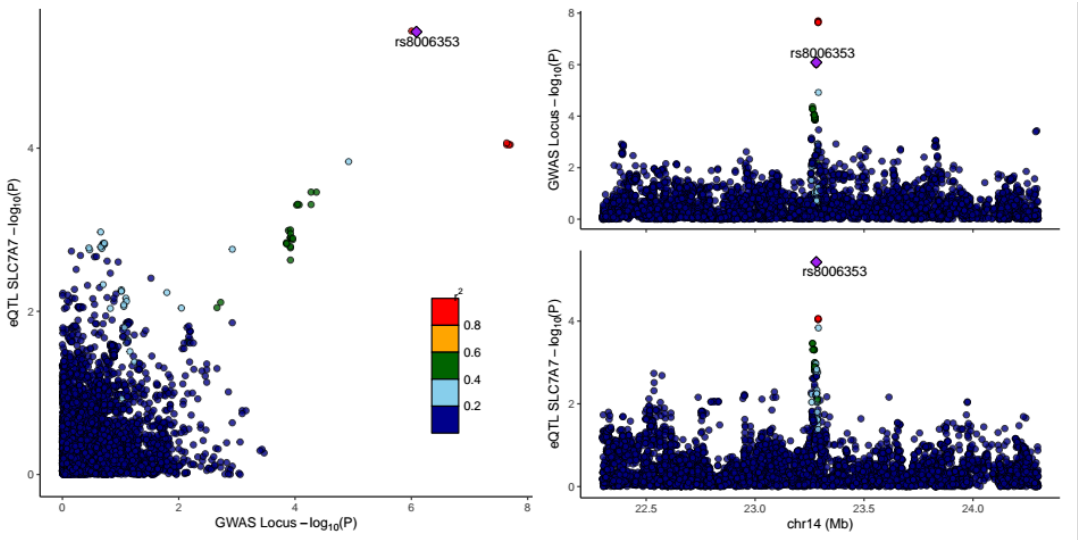

**Supplementary Figure 11.39 | LocusCompare for the eQTL in *RFT1* and GWAS loci known as *RFT1*.**



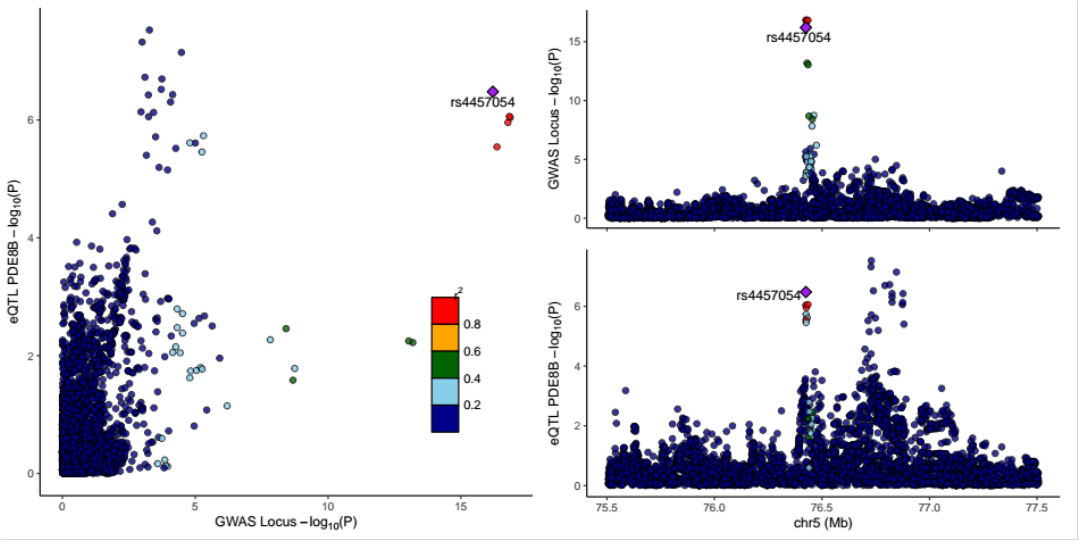

**Supplementary Figure 11.40 | LocusCompare for the eQTL in *SCD5* and GWAS loci known as *SCD5*.**



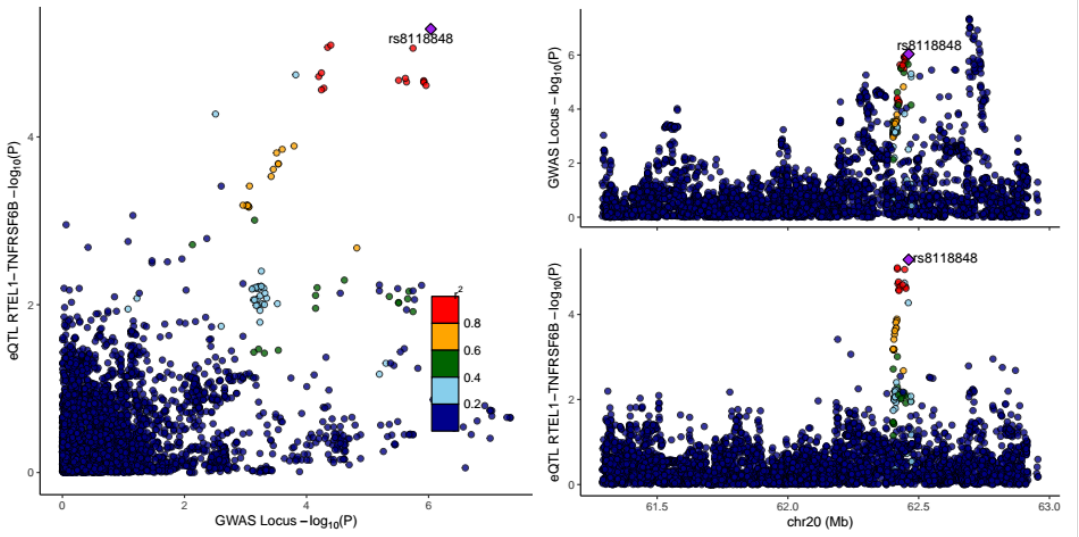

**Supplementary Figure 11.41 | LocusCompare for the eQTL in *SLC12A8* and GWAS loci known as *SLC12A8*.**



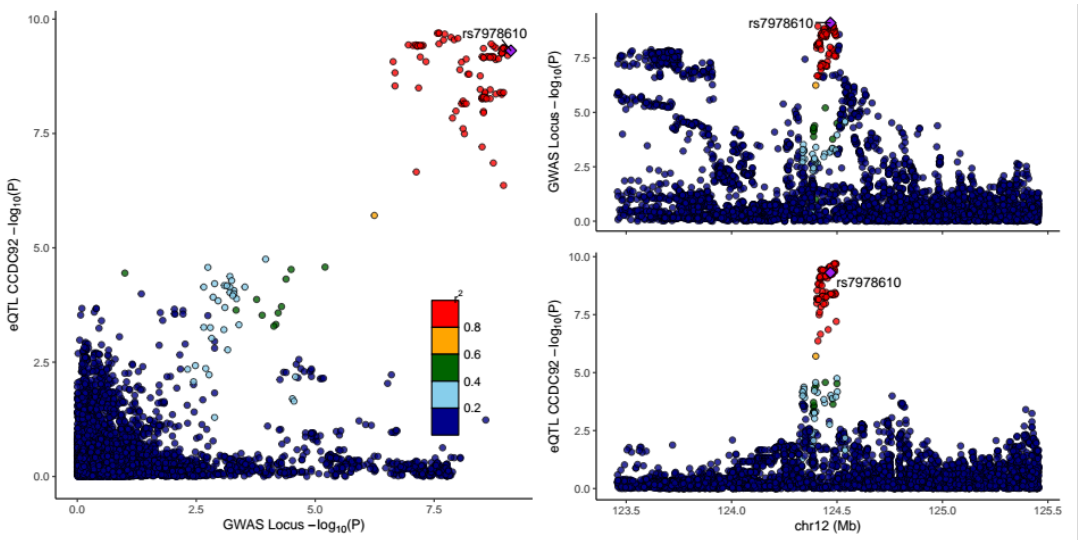

**Supplementary Figure 11.42| LocusCompare for the eQTL in *SLC7A7* and GWAS loci known as *SLC7A7*.**



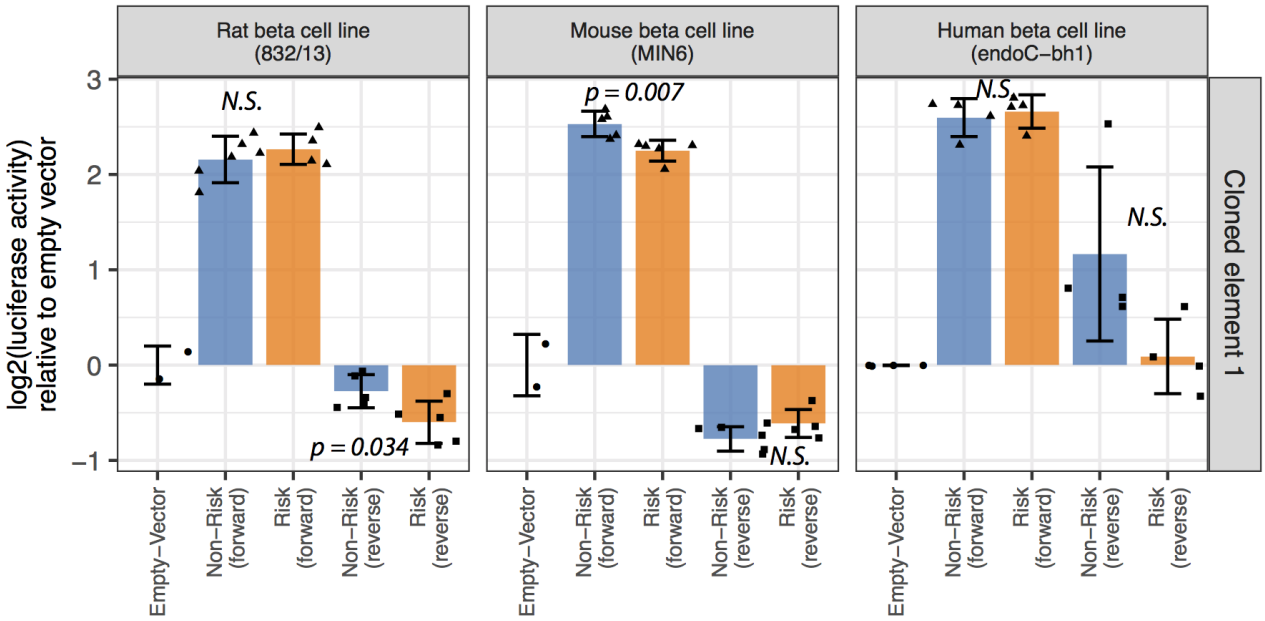

**Supplementary Figure 11.43 | LocusCompare for the eQTL in *PDE8B* and GWAS loci known as *ZBED3*.**



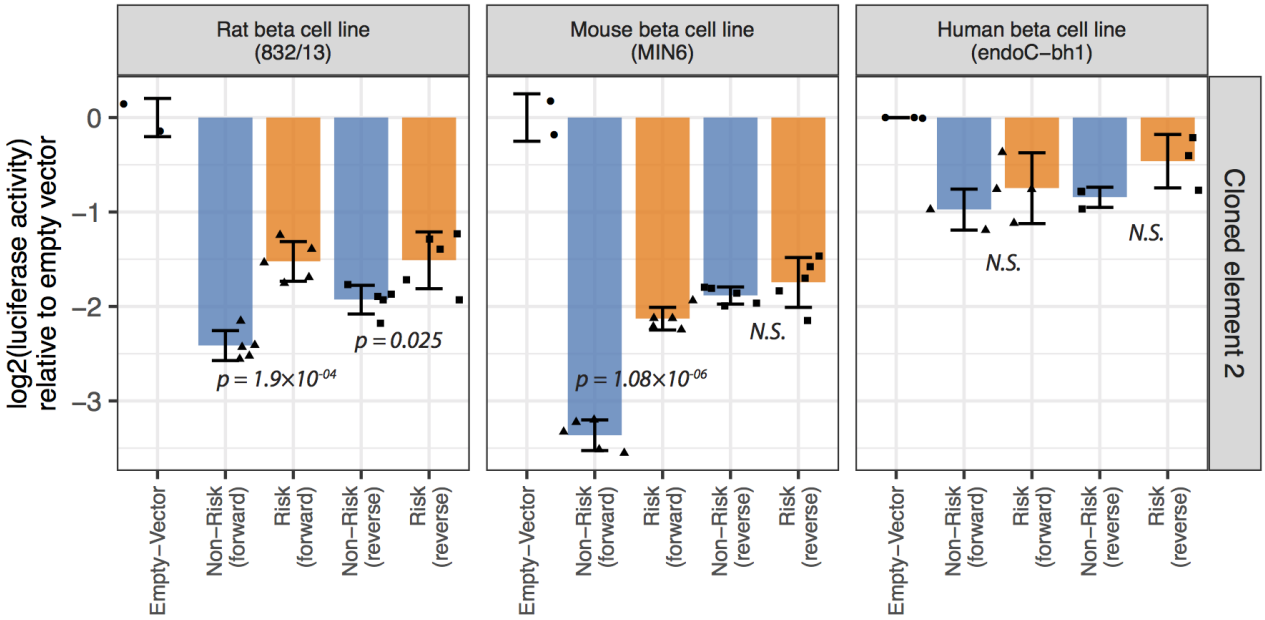

**Supplementary Figure 11.44 | LocusCompare for the eQTL in *RTEL1-TNFRSF6B* and GWAS loci known as *ZBTB46*.**



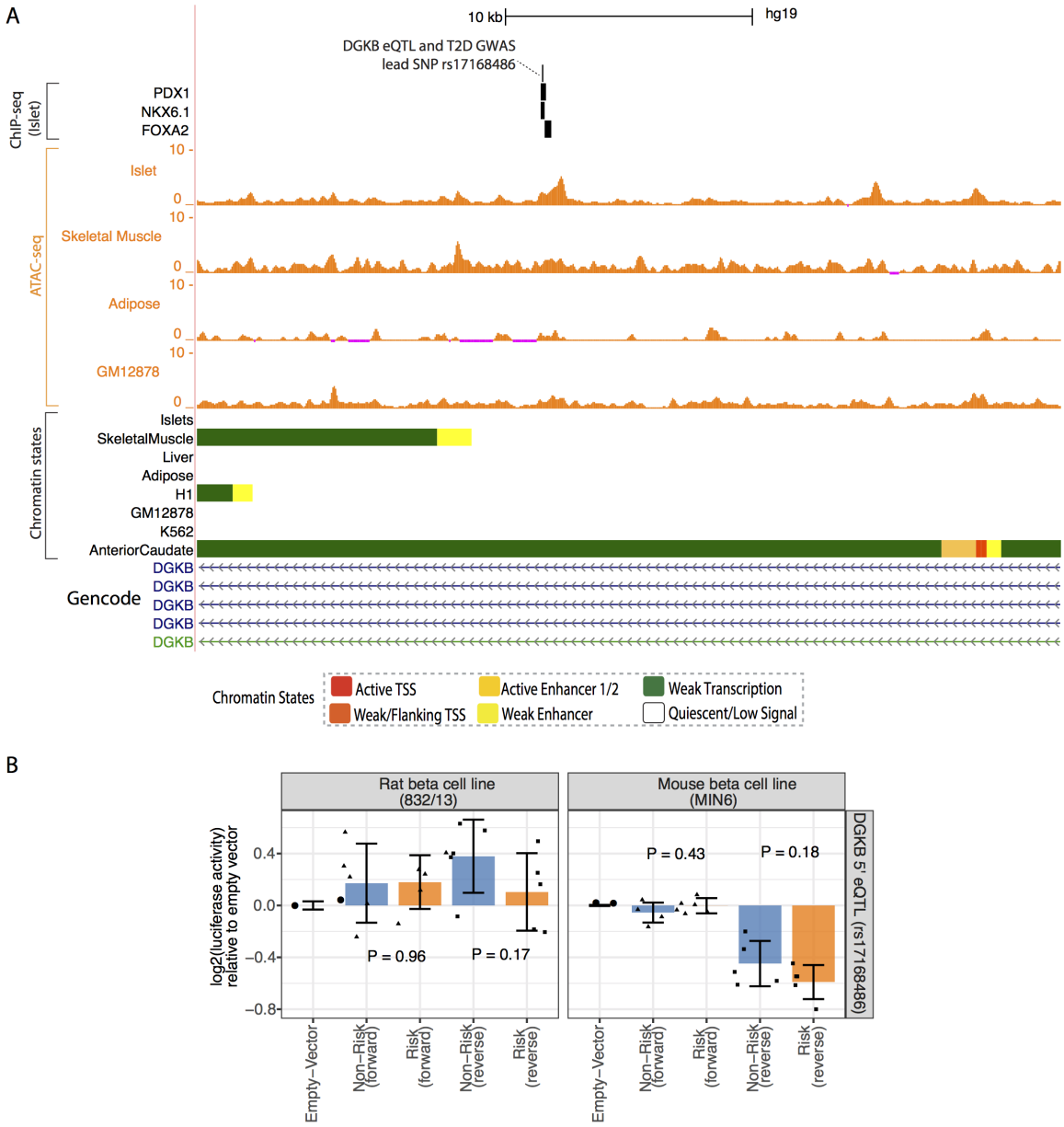

**Supplementary Figure 11.45 | LocusCompare for the eQTL in *CCDC92* and GWAS loci known as *ZNF664*.**



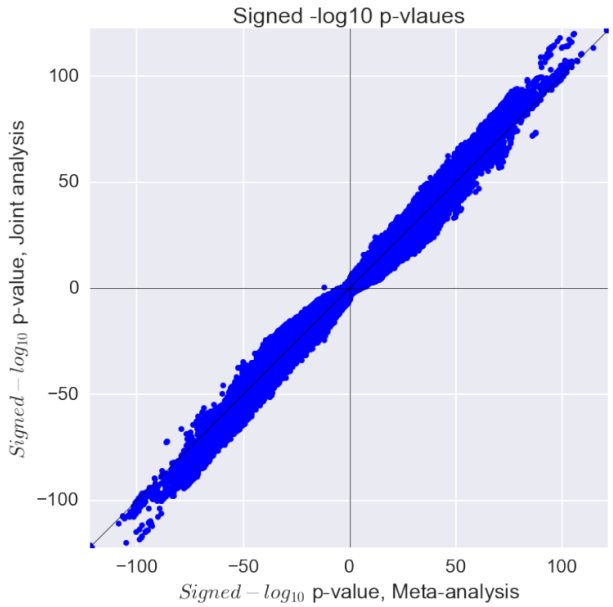

**Supplementary Figure 12 | Luciferase assay results for DGKB 3'eQTL element 1:** Log 2 Luciferase assay activities (normalized to empty vector) in rat (832/13), mouse (MIN6) and human (endoC) beta cell lines for the element 1 highlighted in green in Figure 3E. The element was cloned in both forward and reverse orientation with respect to the *DGKB* gene. P values were determined using unpaired two-sided t-tests.



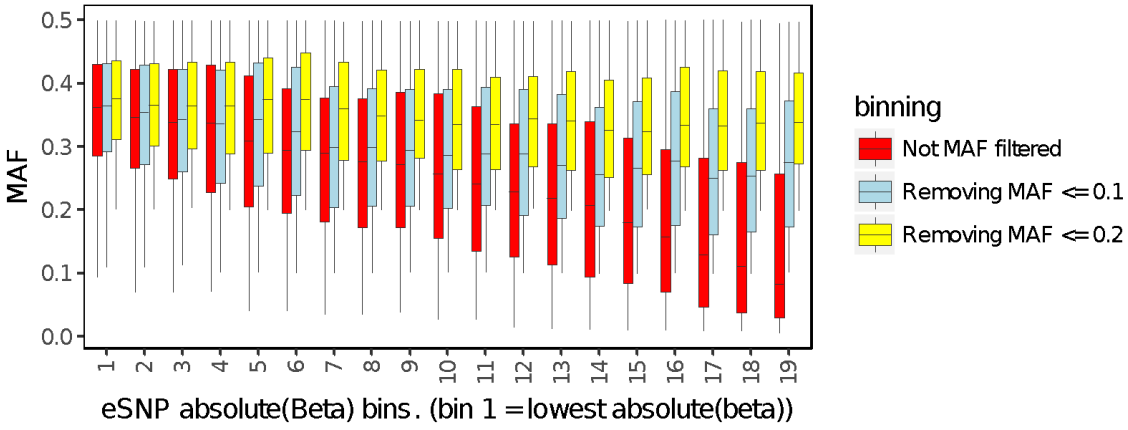

**Supplementary Figure 13 | Luciferase assay results for DGKB 3'eQTL element 2:** Log 2 Luciferase assay activities (normalized to empty vector) in rat (832/13), mouse (MIN6) and human (endoC) beta cell lines for the element 2 highlighted in blue in Figure 3E, cloned in both forward and reverse orientation with respect to the *DGKB* gene. P values were determined using unpaired two-sided t-tests.



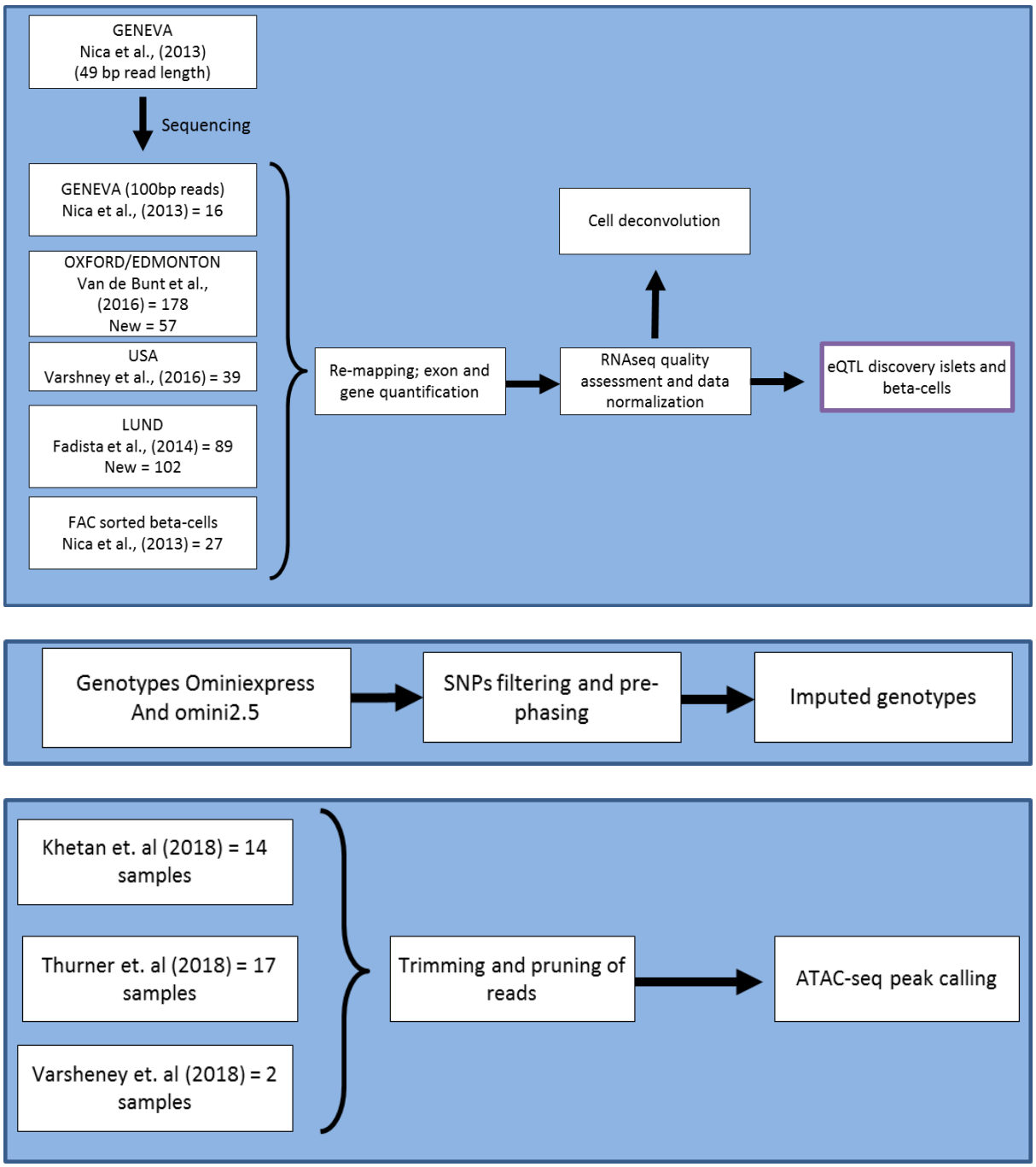

**Supplementary Figure 14 | DGKB 5' eQTL locus.** 5' eQTL (DGKB eQTL and T2D GWAS lead SNP 17168486). A: Genome browser shot of the 5' DGKB eQTL along with ChIP-seq, ATAC-seq and chromatin state profiles in islets and other tissues. B. Luciferase assay activities (normalized to empty vector) in rat (832/13) and mouse (MIN6) cell lines for the element containing the T2D GWAS and islet eQTL lead SNP (rs17168486), cloned in both forward and reverse orientation with respect to the *DGKB* gene. Differences between activities of the risk and non-risk allele containing elements were non-significant.




**Supplementary Figure 15 | Meta- vs mega-analysis.** Comparison or meta-analysis of the four studies versus join re-processing and analysis. A comparison between our joint analyses and a fixed effects meta-analysis of the four studies found highly correlated results indicating appropriate control of the differences across studies.




**Supplementary Figure 16 | MAF filtering for eSNPs.** MAF for islet eQTL eSNPs binned by absolute(beta) into equal sized, 50% overlapping bins. Bin 1 contains eSNPs with lowest absolute(beta), bin19 contains eSNPs with highest absolute(beta).




**Supplementary Figure 17 |** Diagrams showing sample and data processing.

# Supplementary References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