

Supplementary Note

Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways

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Supplementary Table Legends

Supplementary Table 1 - Study characteristics

Supplementary Tables 2a-e Follow-up and adjusted model results for genome-wide associations with each trait

a) BMI-adjusted results and follow-up only (i.e. all studies excluding those in the original discovery) results for novel SNPs for FG. b) for FI. c) for FI with BMI-adjustment and d) for 2hGlu SNPs. e) Full results for all known MAGIC glycemc loci (FG,FI, 2hGlu, proinsulin) and respective look-ups for the traits investigated in this study (FG/FI/2hGlu) and adjustment conditions (with/without BMI adjustment).

Supplementary Tables 3a-c Gene-based analyses results

The gene region is shown along with the *P*-value for the gene as well as the most significant SNP in the region and its respective *P*-value. Novel regions are those which were previously unidentified in conventional SNP-based analyses (or more than 500kb from lead SNPs) a) results from gene-based analyses for FG.. b) FI(BMI-adjusted) results. c) 2hGlu results.

Supplementary Table 4 Fine-mapping results

For each known FG-, FI- and 2hGlu-associated locus, we show the previous lead SNP and the most significant SNP in the region with the higher SNP density available on the Metabochip. The chromosome and position of the new loci as well as the effect size and *P*-value are shown. Loci where another SNP was markedly more significant than the previous lead are shown in **bold** and regional plots are shown in Supplementary Figure 6.

Supplementary Tables 5a-c GRAIL genome-wide loci connectivity results

Results from GRAIL analyses amongst established genome-wide loci are shown, and the relative connectivity between loci and respective *P*-value is shown for a) FG, b) FI (BMI-adjusted) and c) 2hGlu

Supplementary Tables 6a-c GRAIL results for established Vs suggestively associated loci

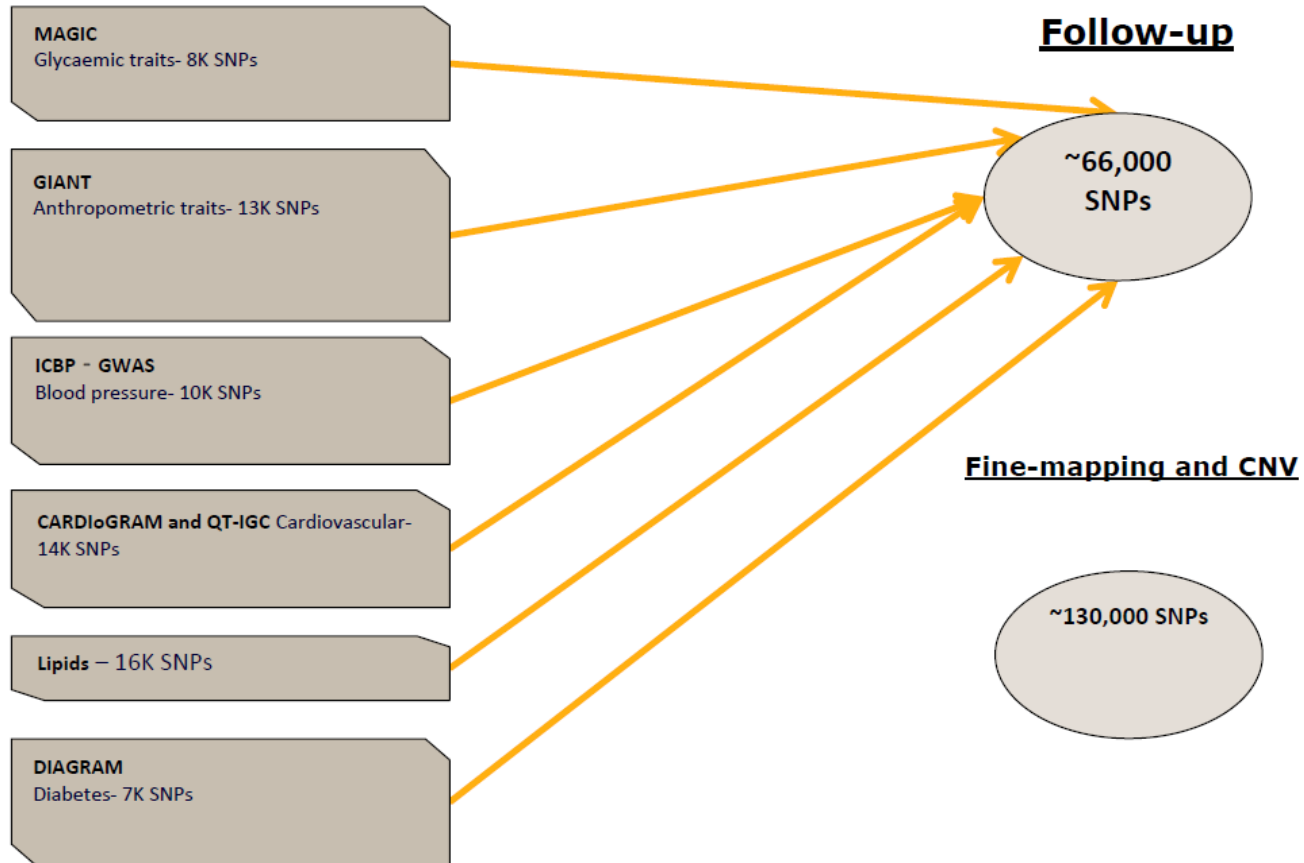
Results from GRAIL analyses between established genome-wide and borderline ($P < 0.0005$) loci and the relative connectivity between loci and respective *P*-value is shown for a) FG, b) FI (BMI-adj) and c) 2hGlu

Supplementary Table 7 Directional consistency of associations between discovery and follow-up studies

The number of SNPs nominated to the Metabochip for follow-up of particular traits by each consortium is shown, alongside the number of SNPs where $P < 0.05$ in follow-up studies. The number of those SNPs showing consistent direction is also shown, as well as the *P*-value for the binomial test comparing this number to the null expectation (50%). In addition, the *q*-value from FDR analyses at $P = 0.05$ is also shown.

Supplementary Figures

Supplementary Figure 1

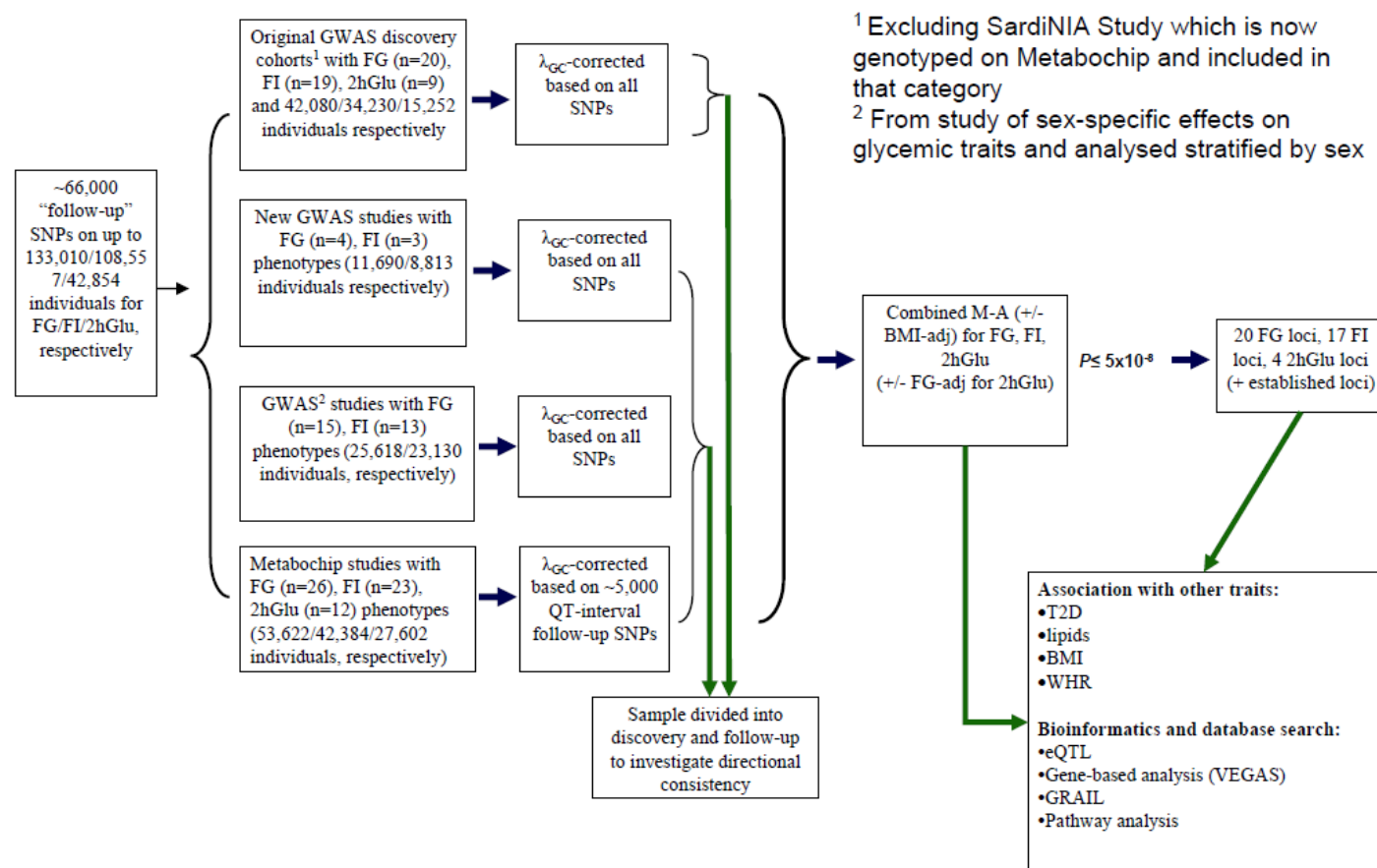


Supplementary Figure 1 MetaboChip design

Consortia and the number of SNPs they submitted to be followed-up using the MetaboChip are shown.

Supplementary Figure 2

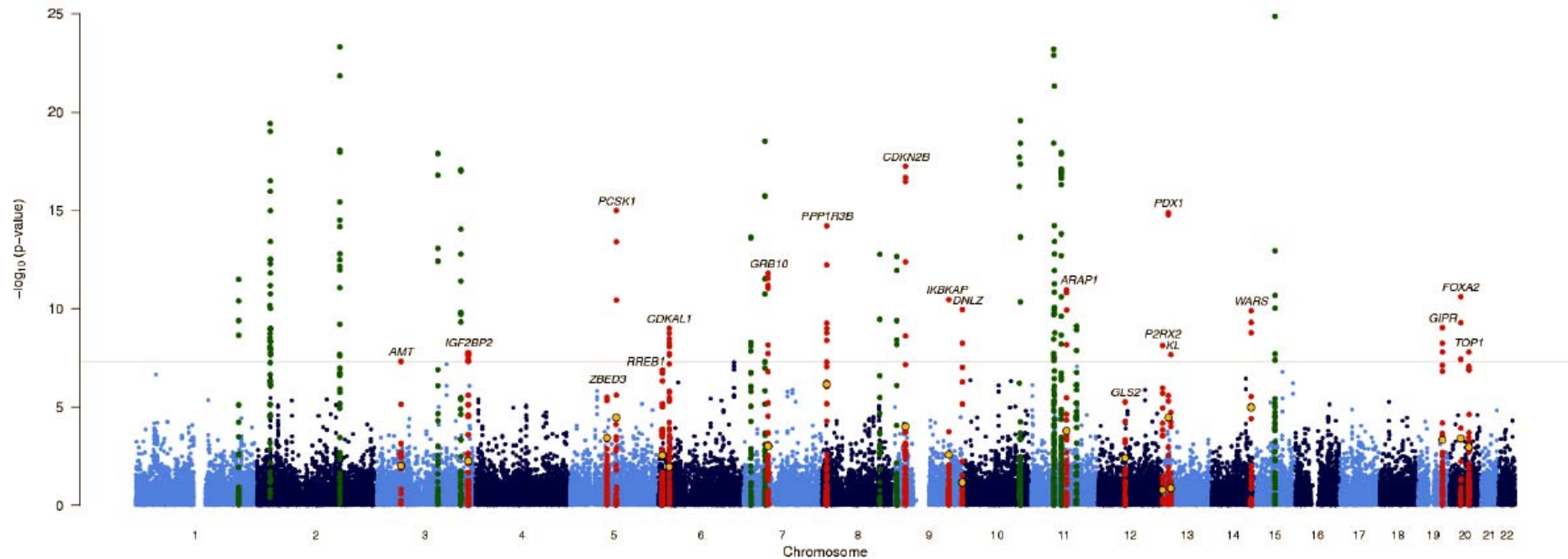
MAGIC MetaboChip Study Design



Supplementary Figure 2 MAGIC MetaboChip Study Design

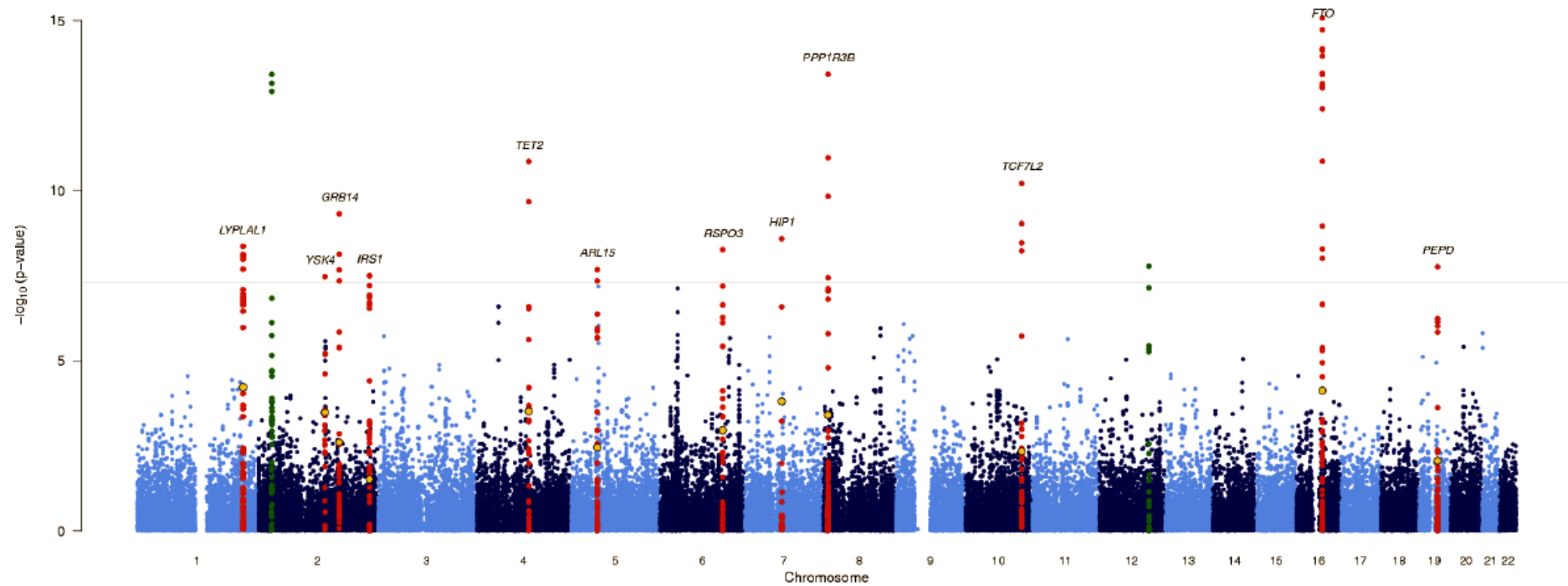
The overall design for the follow-up of ~66,000 SNPs is shown above.

Supplementary Figure 3a



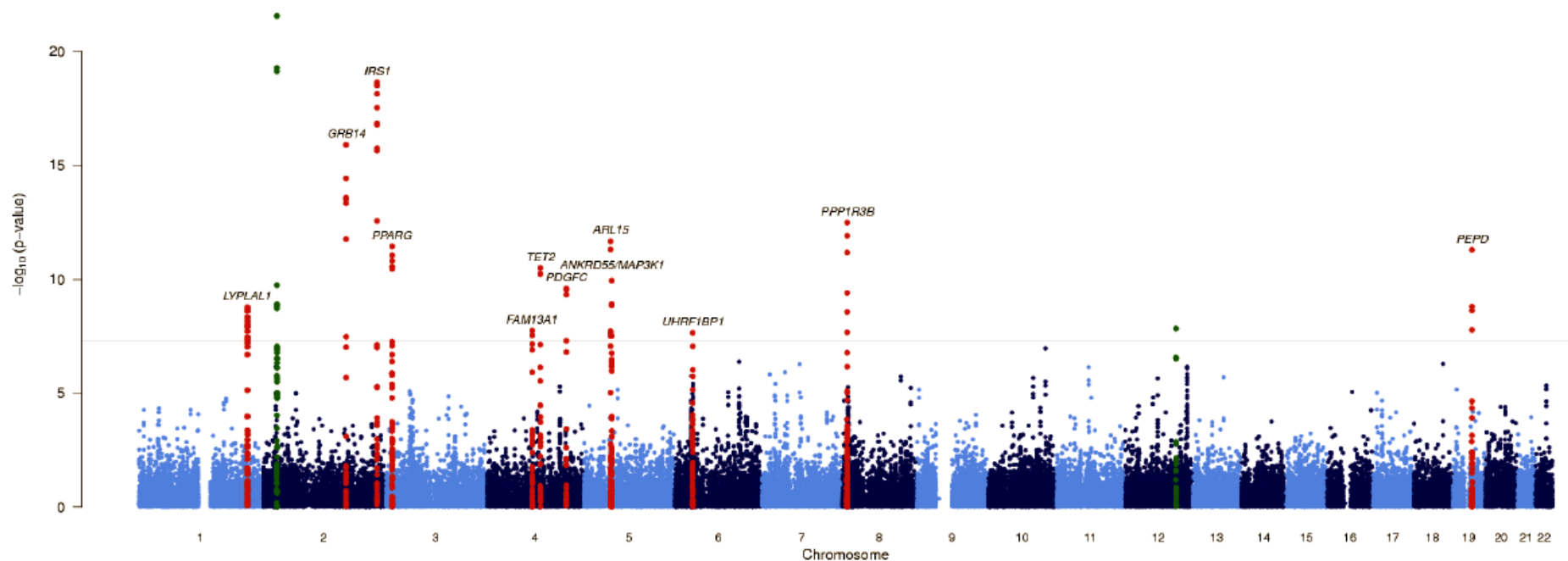
Supplementary Figure 3a. Manhattan plot of Fasting Glucose associations. Points shown in yellow mark the P -value for these SNPs for association with FG in the original discovery meta-analysis². Novel lead SNPs ($\pm 500\text{kb}$) are highlighted red, and known loci in green. P -values were cropped at $P < 1 \times 10^{-25}$. *ZBED3*, *RREB1* and *GLS2* were genome-wide significant only after adjustment for BMI, but are also highlighted red above.

Supplementary Figure 3b



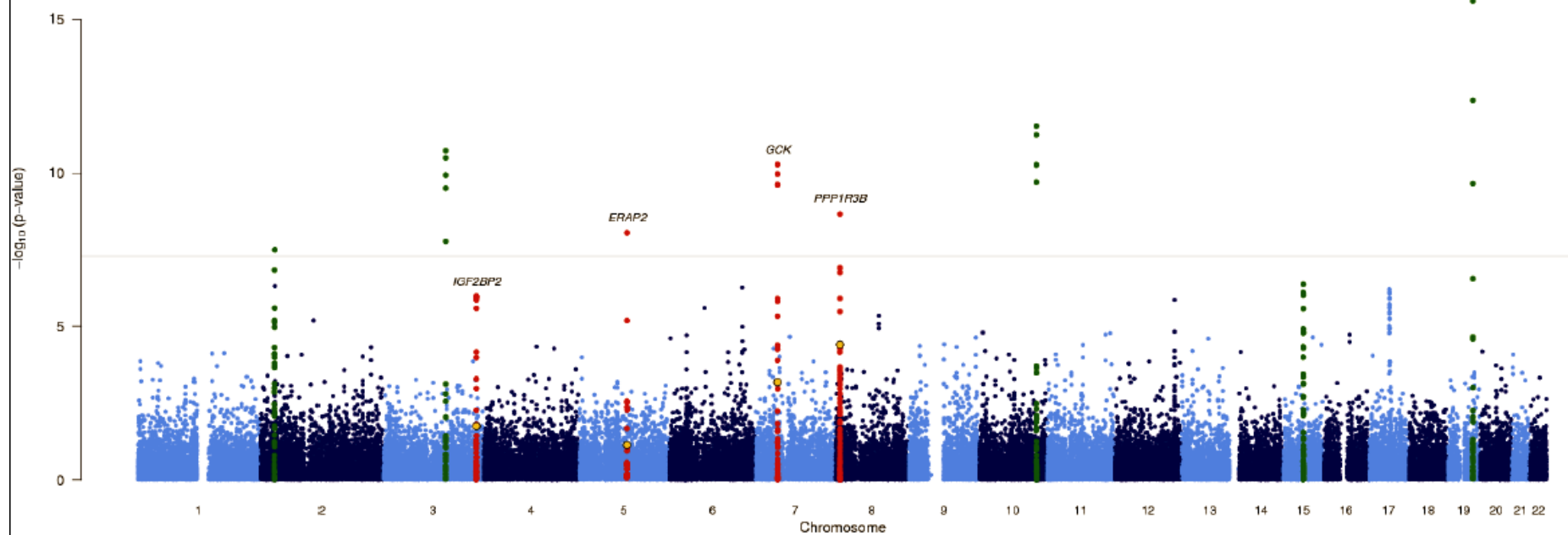
Supplementary Figure 3b Manhattan plot of Fasting Insulin associations. Novel lead SNPs ($\pm 500\text{kb}$) are highlighted red, and known loci in green. Points shown in yellow mark the P -value for these SNPs for association with FI in the original discovery meta-analysis²

Supplementary Figure 3c



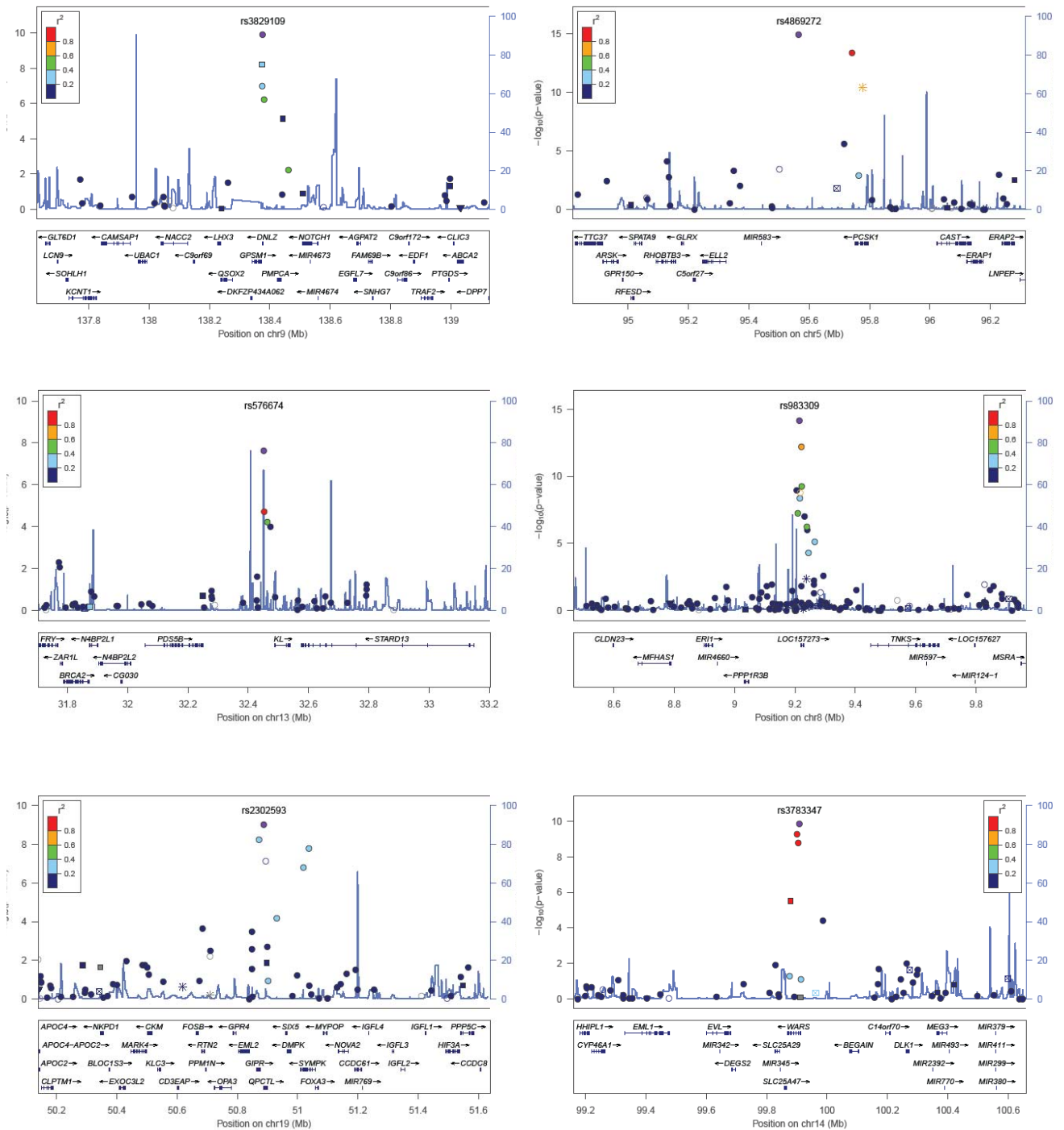
Supplementary Figure 3c Manhattan plot of Fasting Insulin (adjusted for BMI) associations. Novel lead SNPs ($\pm 500\text{kb}$) are highlighted red, and known loci in green. Points shown in yellow mark the P -value for these SNPs for association with FI in the original discovery meta-analysis²

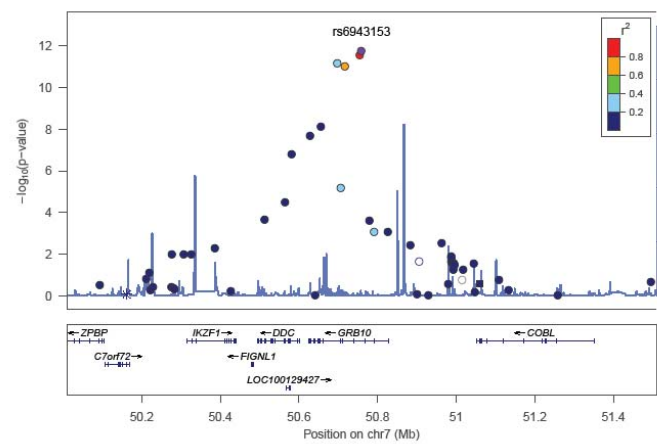
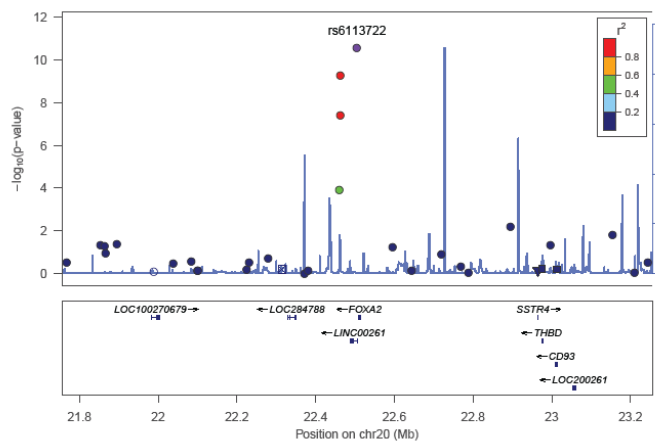
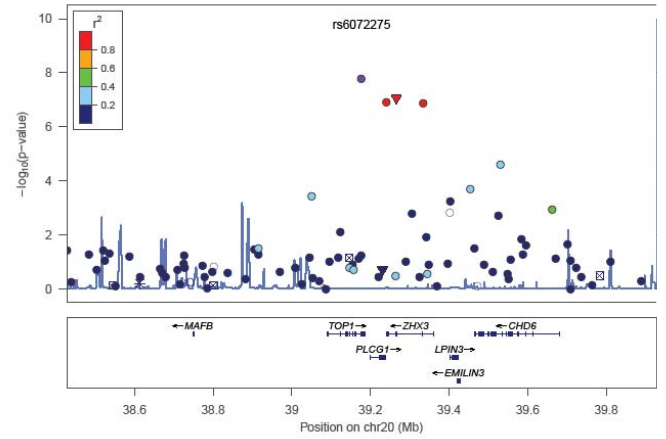
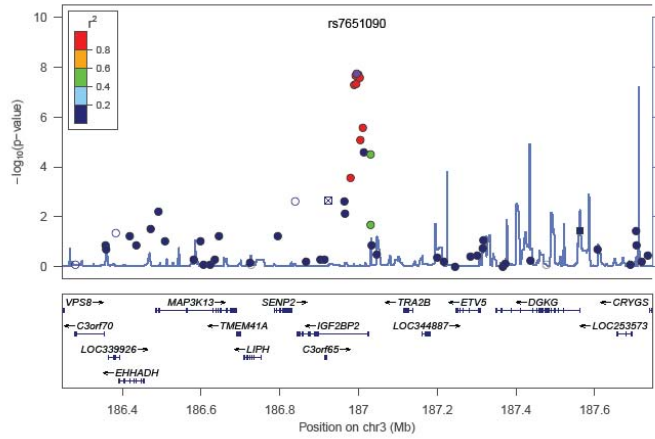
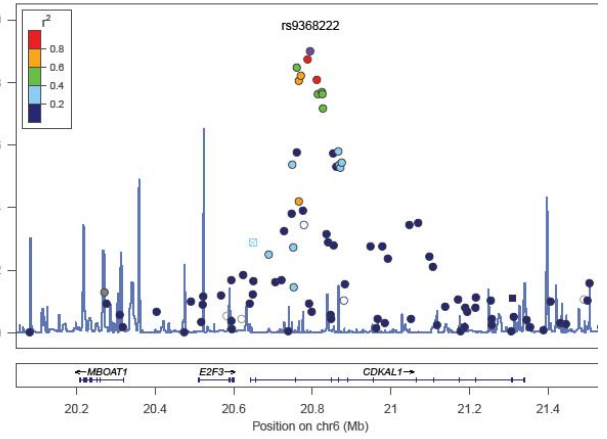
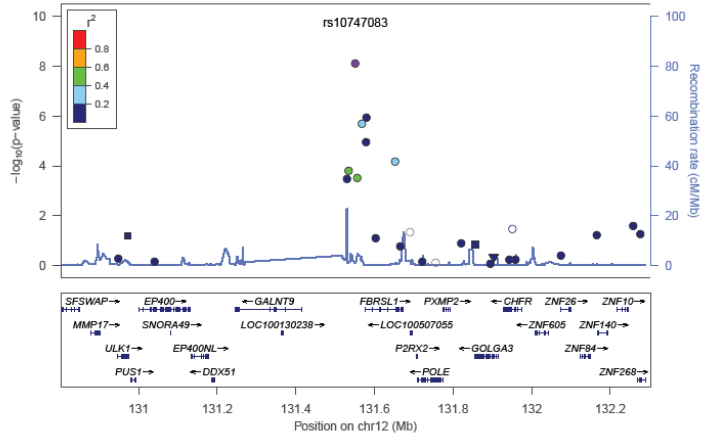
Supplementary Figure 3d

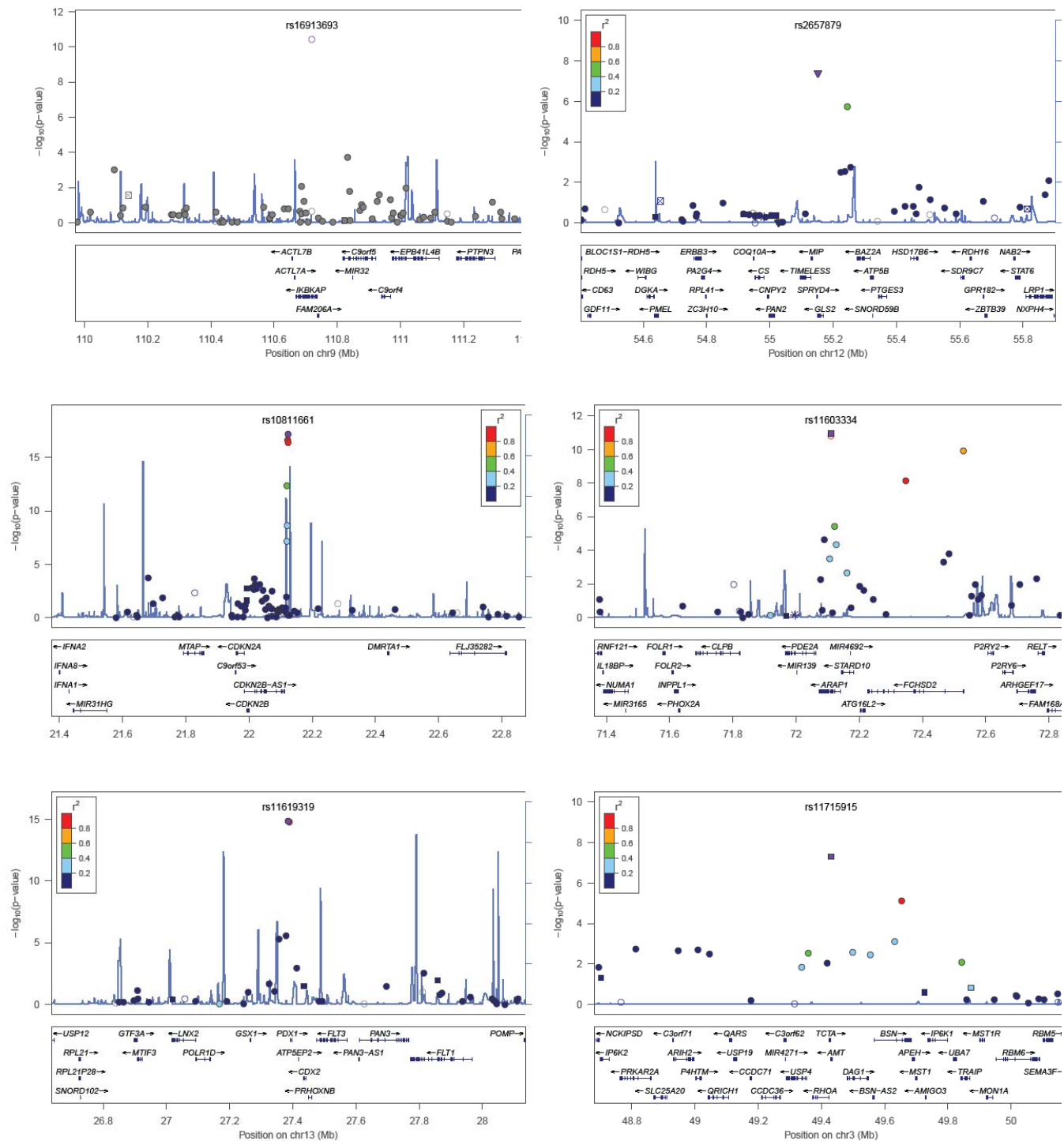


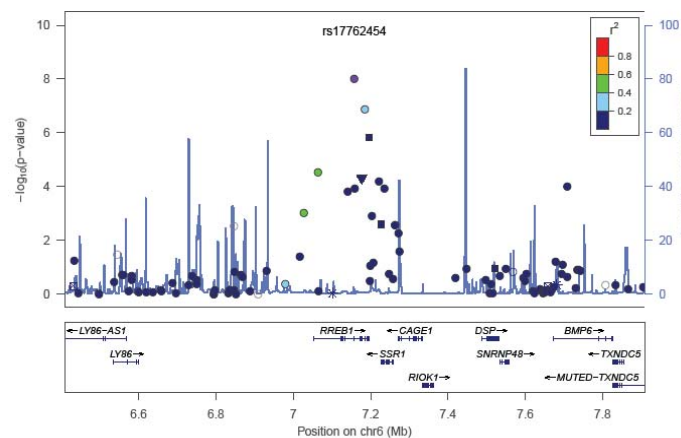
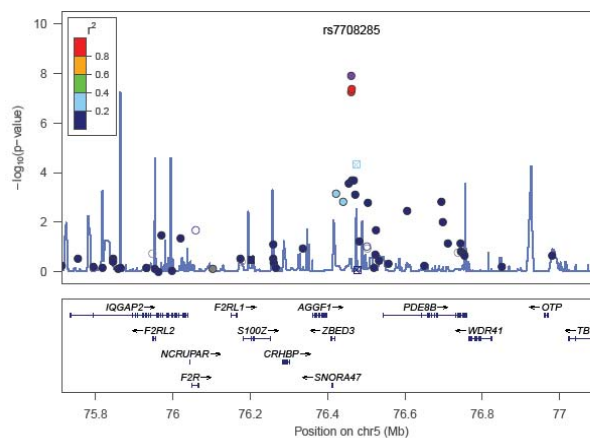
Supplementary Figure 3d Manhattan plot of 2-h Glucose associations. Novel lead SNPs ($\pm 500\text{kb}$) are highlighted red, and known loci in green. Points shown in yellow mark the P -value for these SNPs for association with 2hGlu in the original discovery meta-analysis³

Supplementary Figure 4a

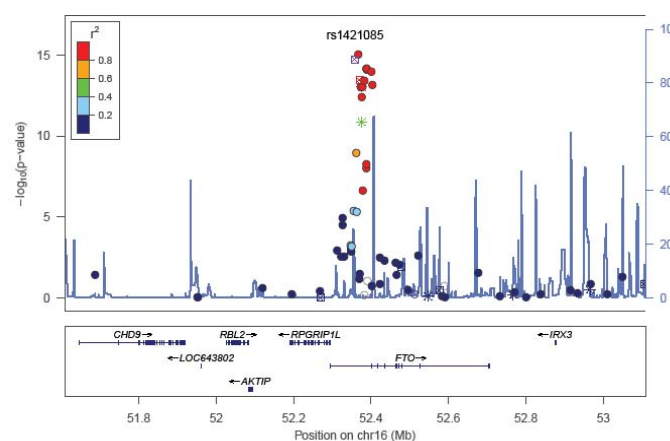
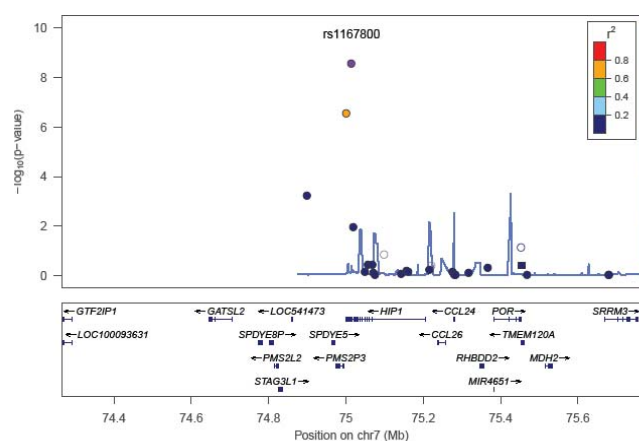
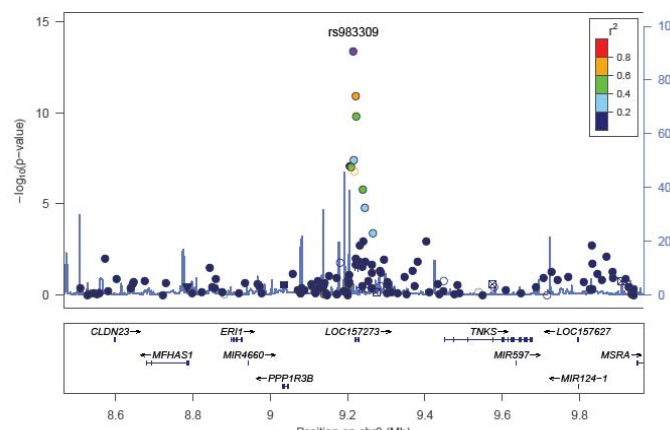
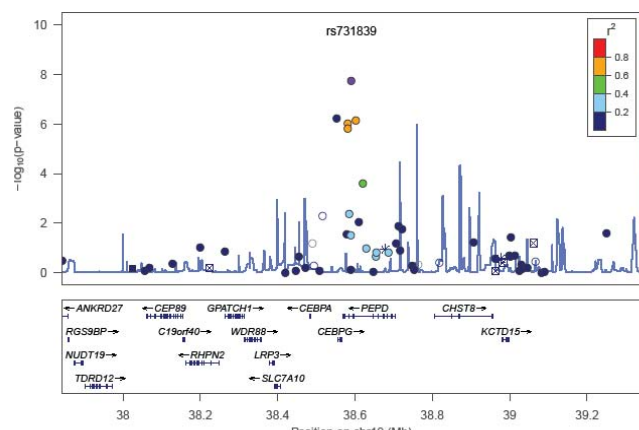


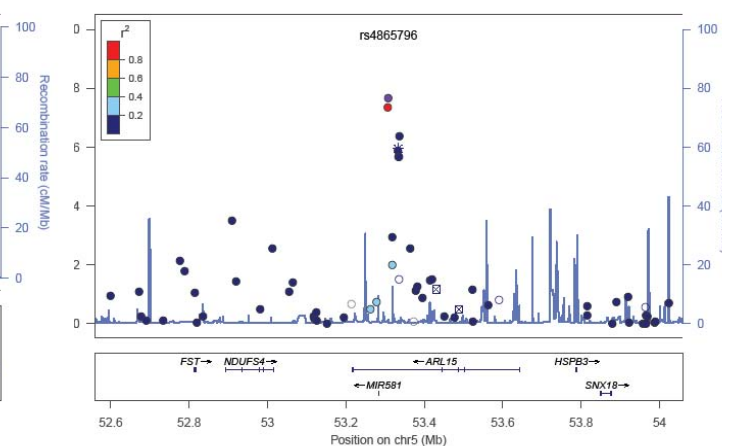
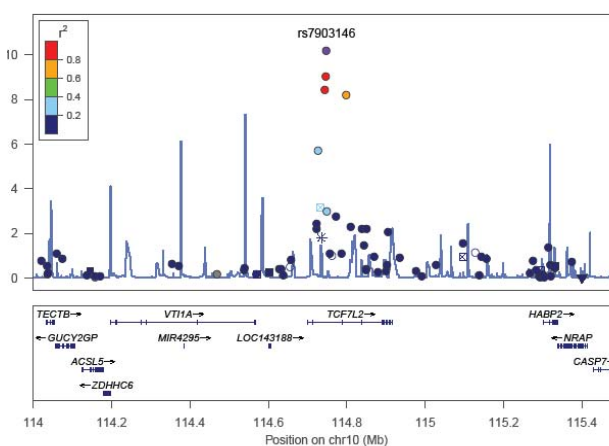
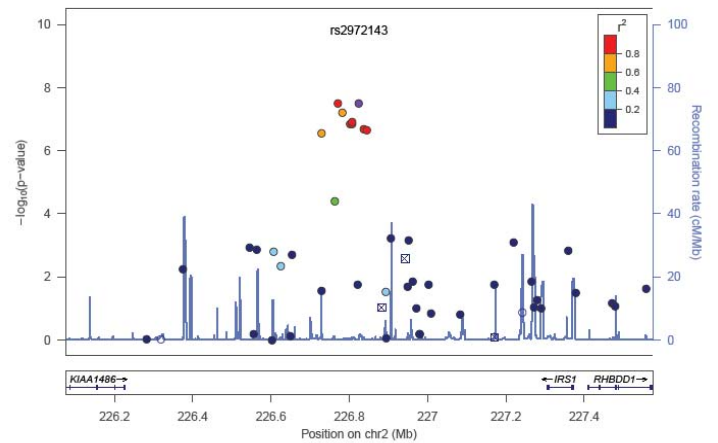
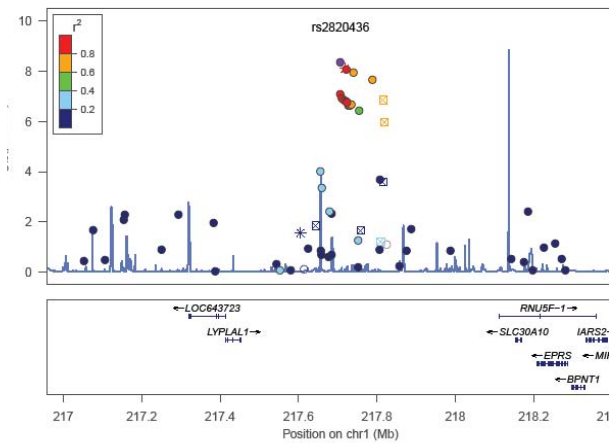
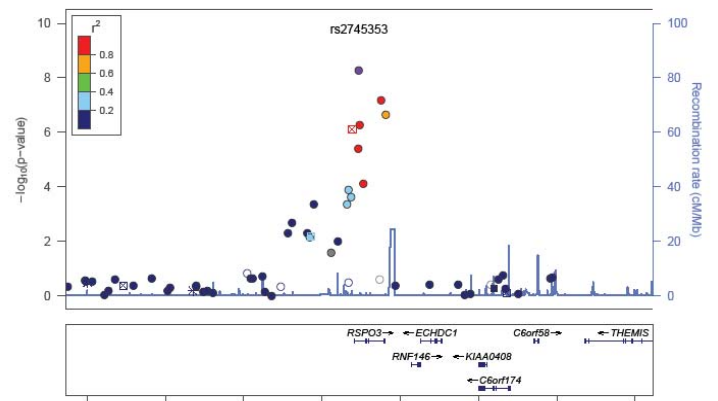
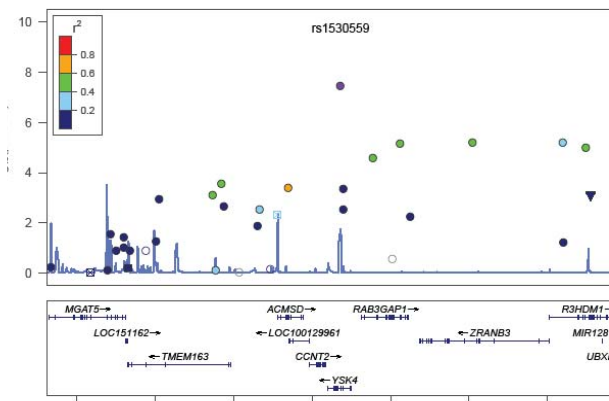


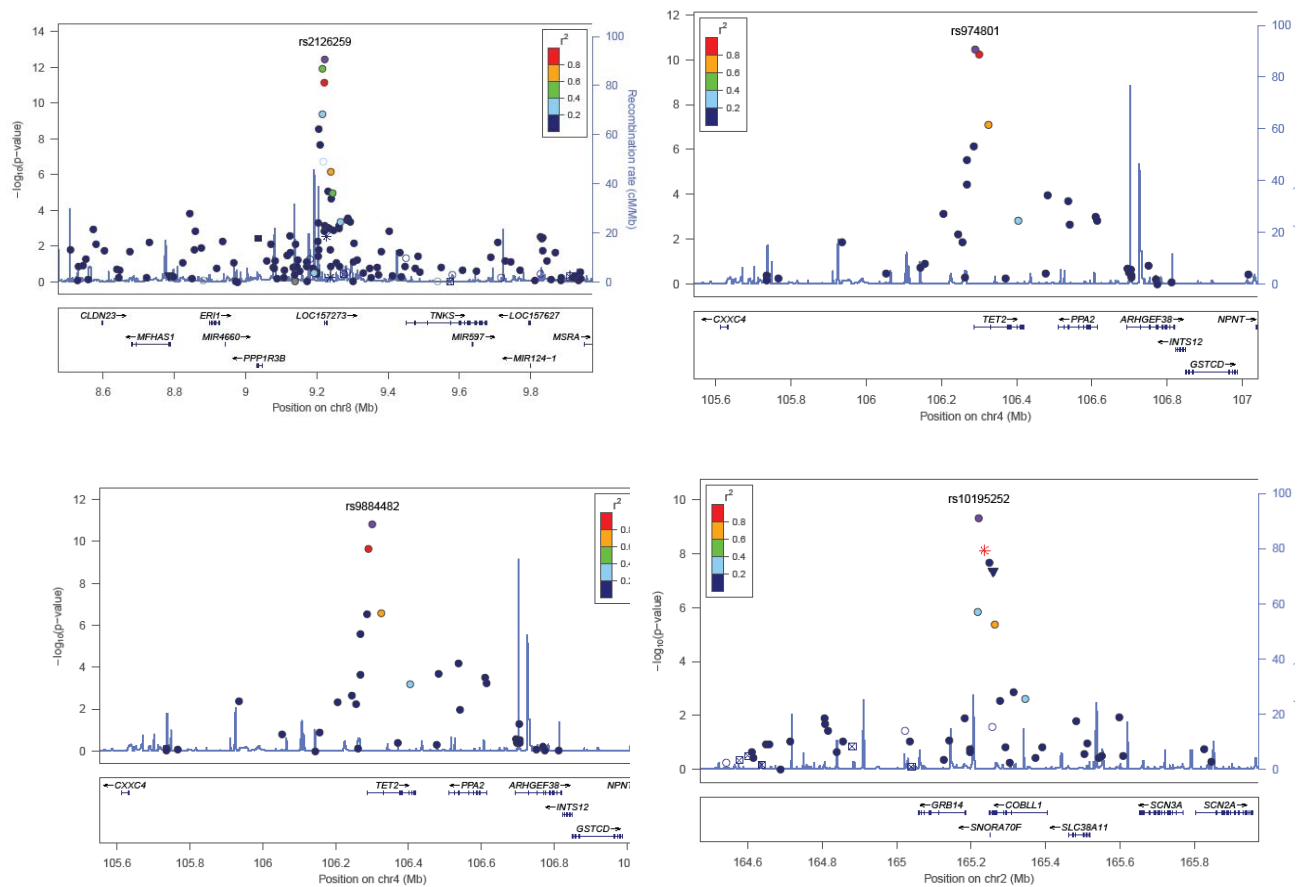




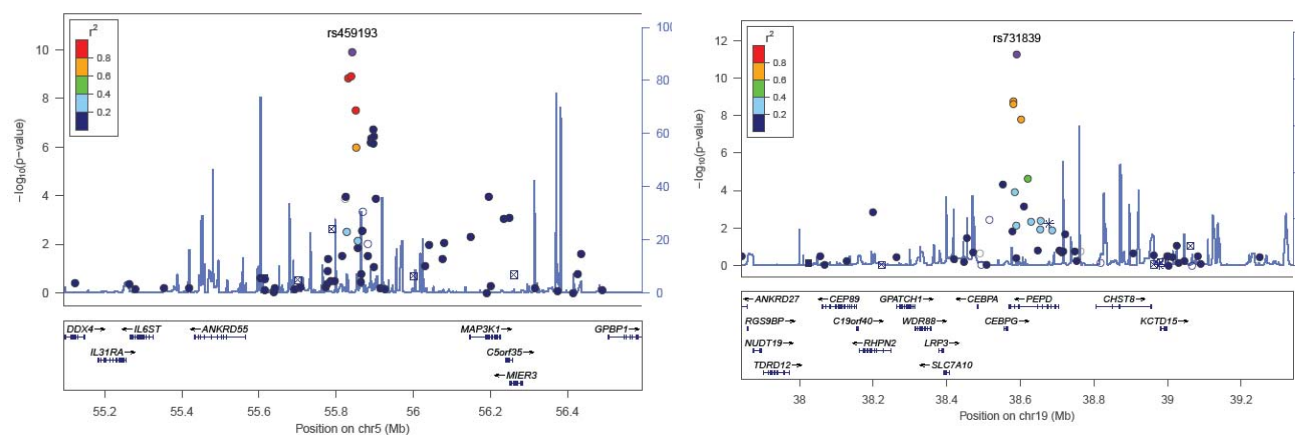
Supplementary Figure 4b

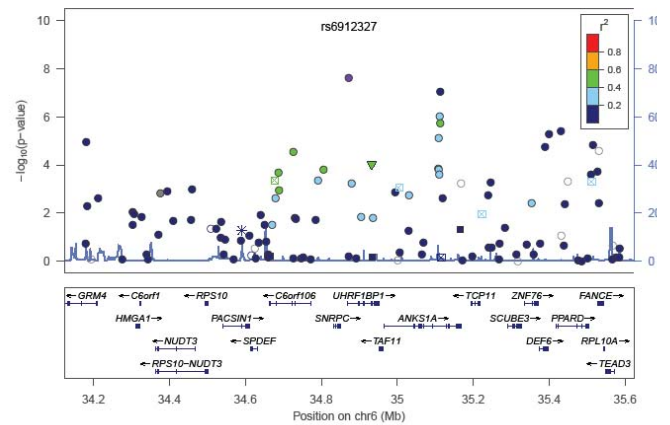
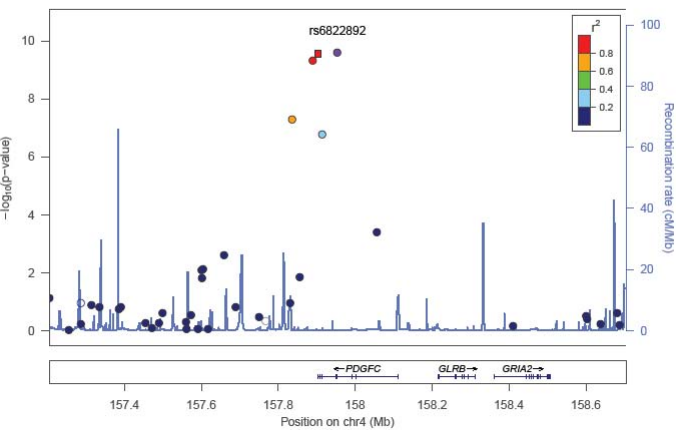
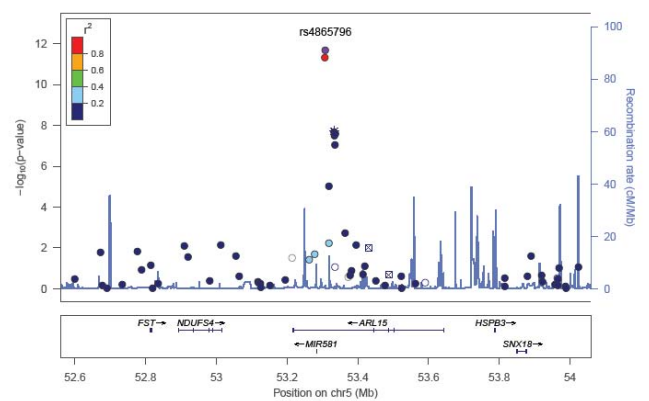
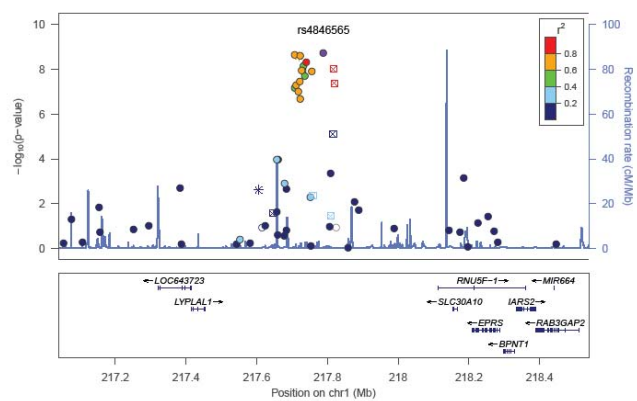
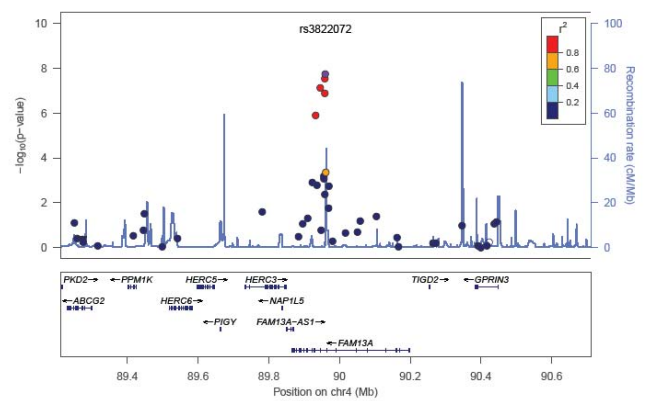
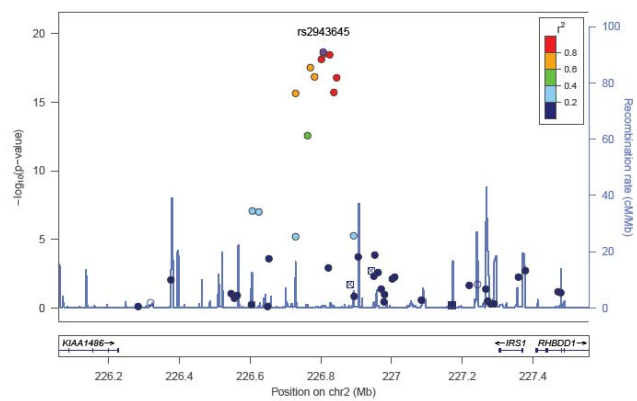


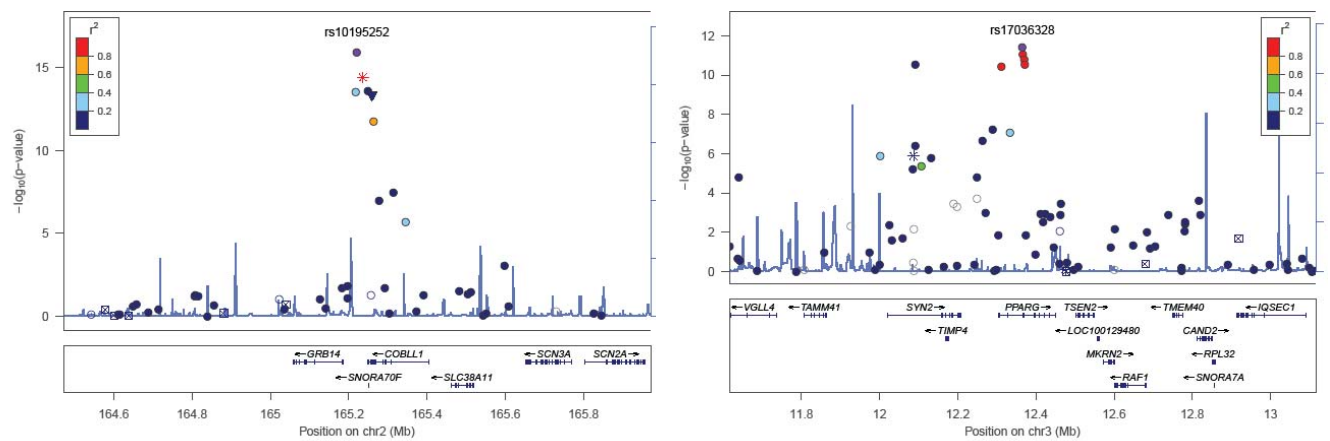




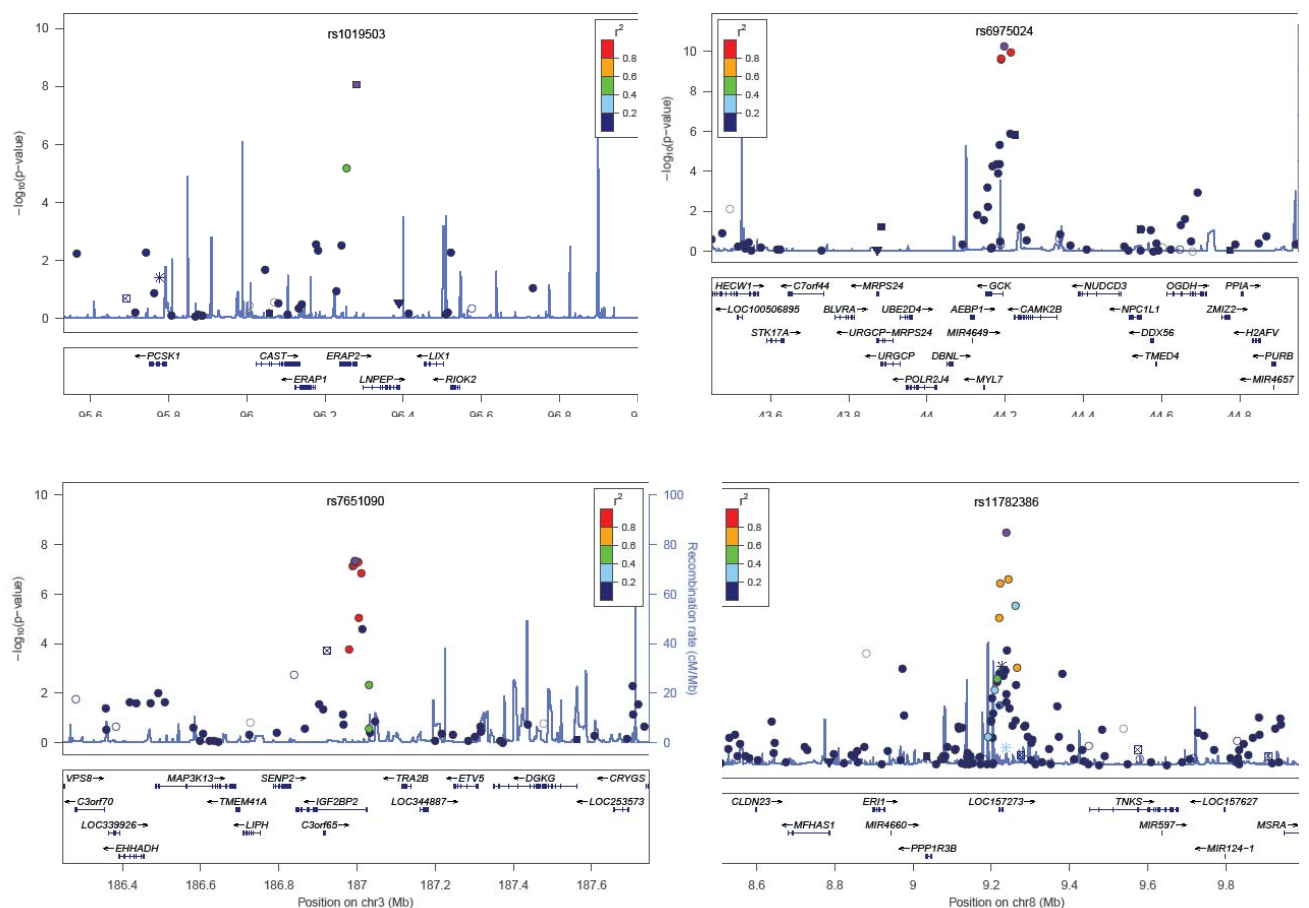
Supplementary Figure 4c







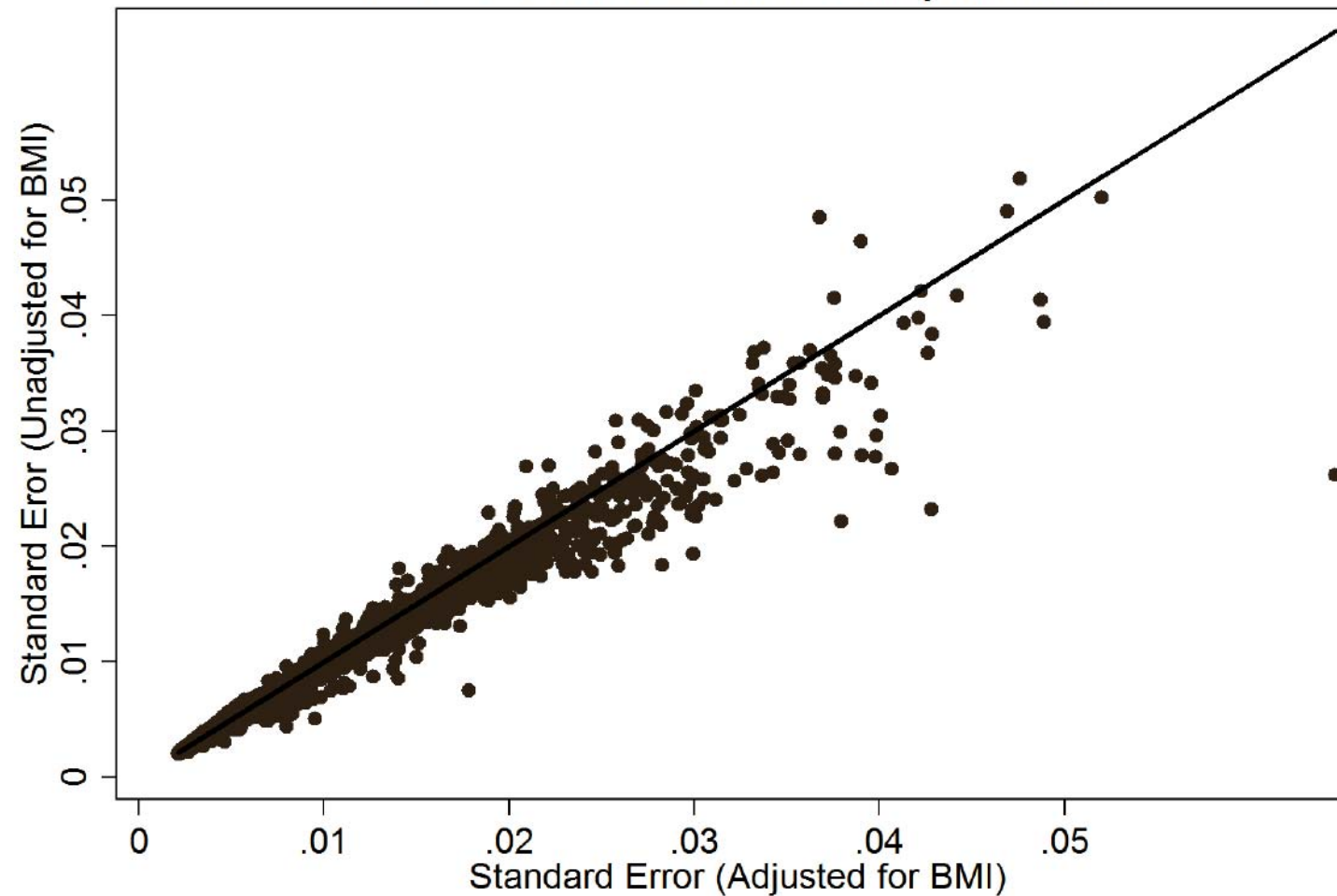
Supplementary Figure 4d



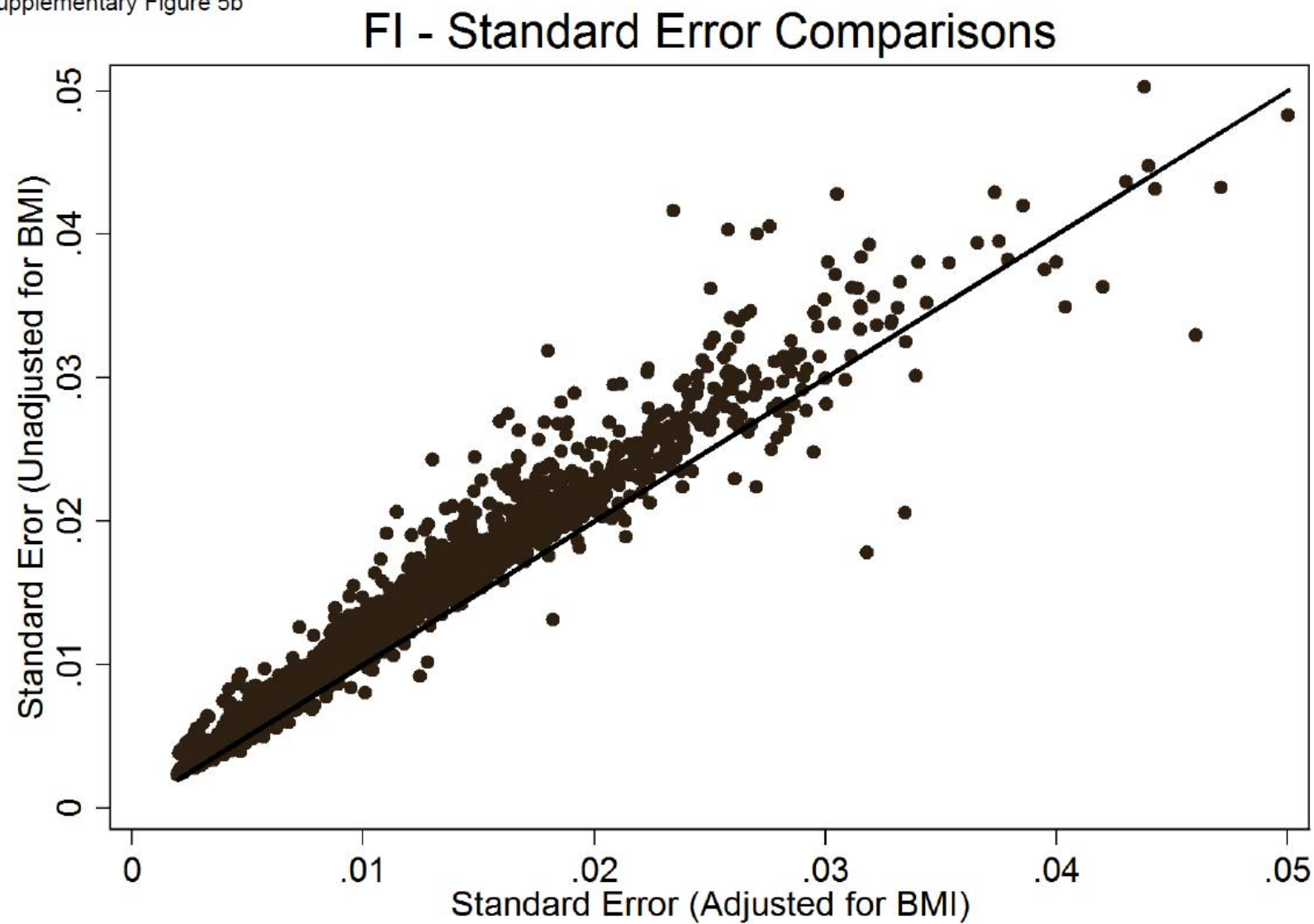
Supplementary Figure 4a-d Regional plots for novel glycemic loci

a) FG, b) FI, c) FI(adjusted for BMI), d) 2hGlu

FG - Standard Error Comparisons

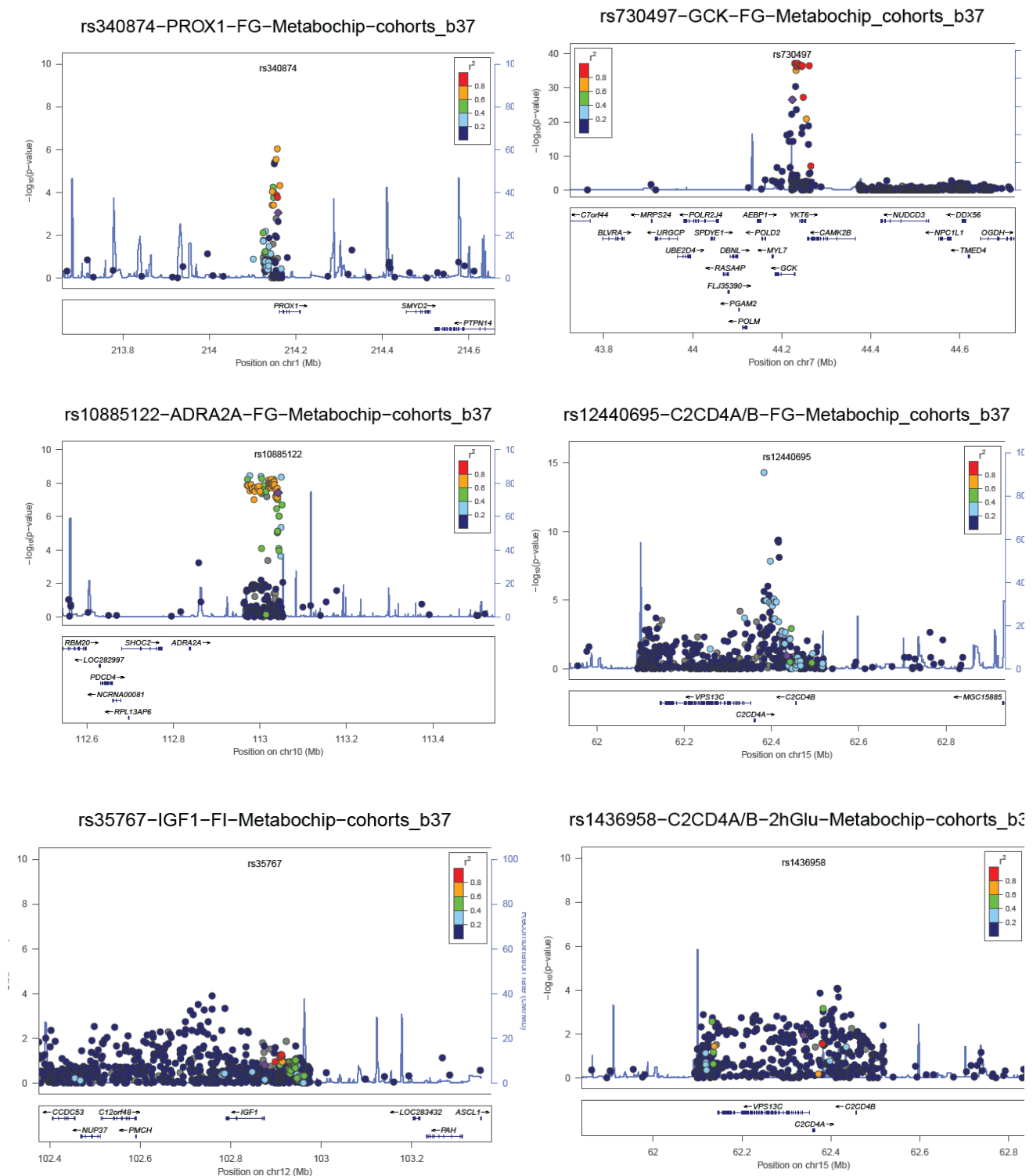


Supplementary Figure 5a Comparison of standard errors of FG effect estimates All ~66,000 SNPs are shown for models unadjusted (uniform) and adjusted for BMI.



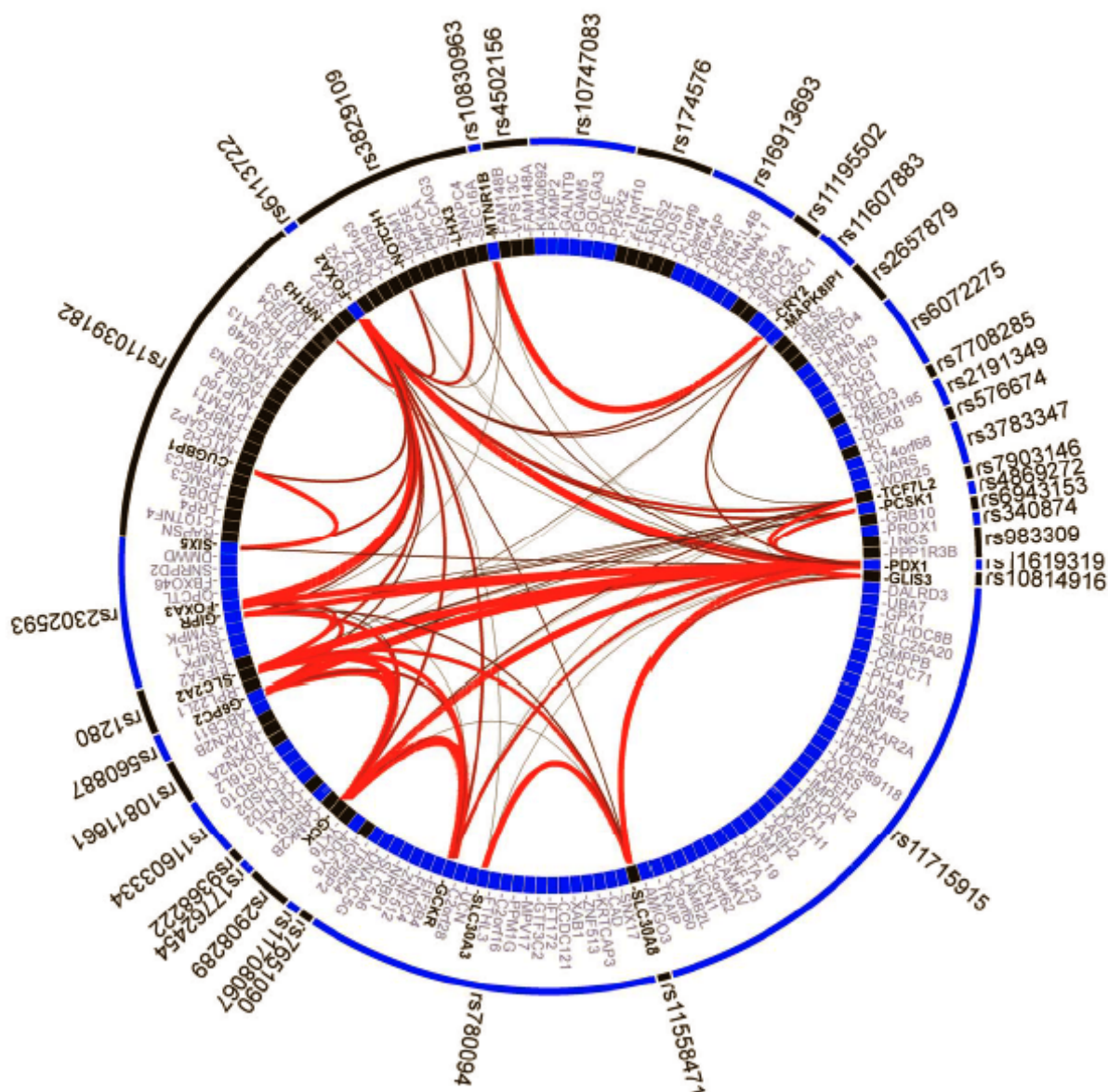
Supplementary Figure 5b Comparison of standard errors of FI effect estimates All ~66,000 SNPs are shown for models unadjusted (uniform) and adjusted for BMI.

Supplementary Figure 6



Supplementary Figure 6 Regional plots of fine-mapping data for FG at *PROX1*, *GCK*, *ADRA2A*, *VPS13C/C2CD4A/B*, and for FI at *IGF1* as well as *VPS13C/C2CD4A/B* for 2hGlu. Previous lead SNPs are shown in purple, and it can be seen that a number of SNPs are more significant than that previously considered to be the lead. New lead SNPs are shown in Supplementary Table 4.

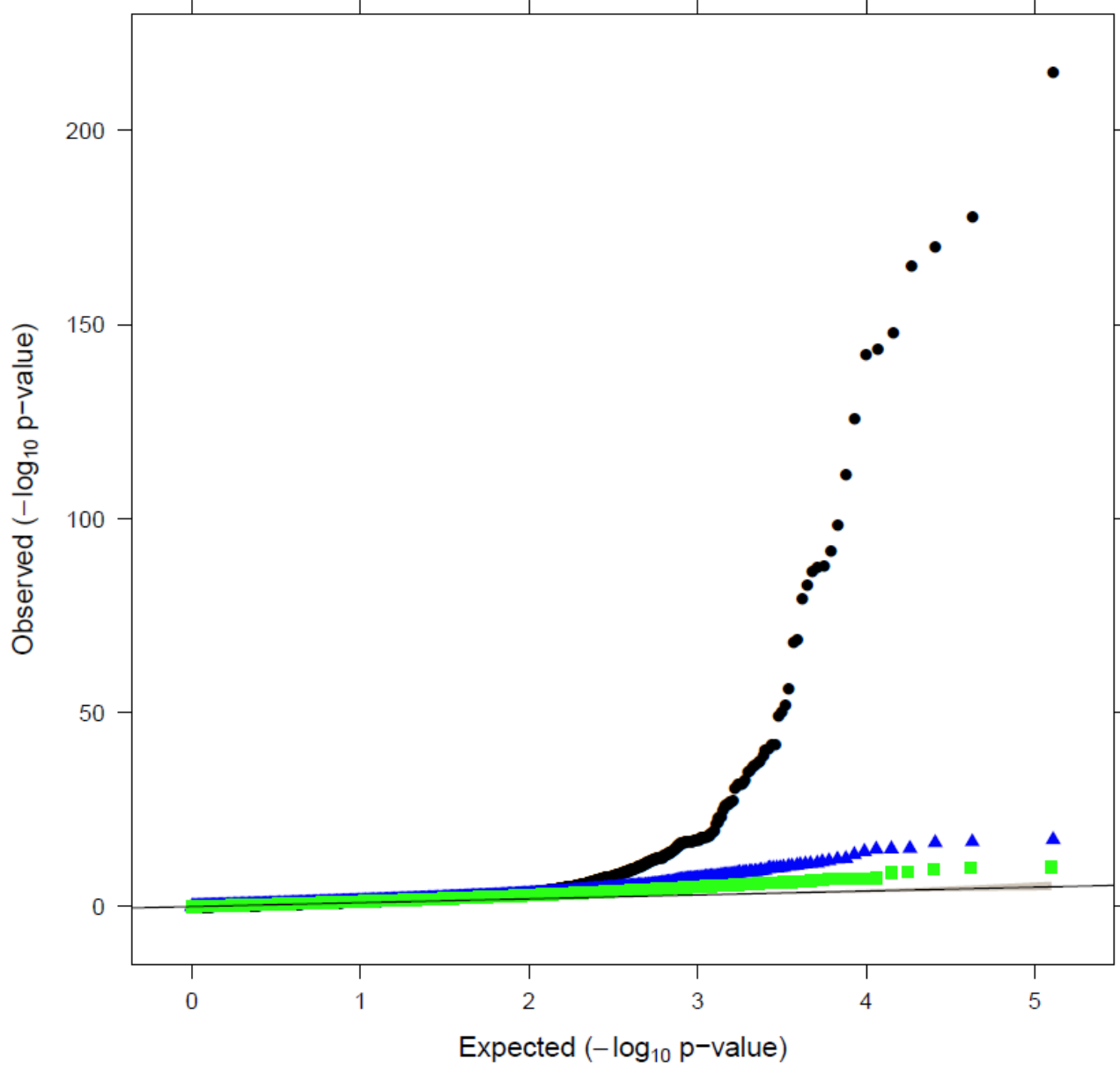
Supplementary Figure 7



Supplementary Figure 7 - GRAIL Connectivity plot for FG Each genome-wide locus for FG is plotted and significant connections ($P < 0.05$) based on pubmed abstracts (pre-2007) shown as red lines.

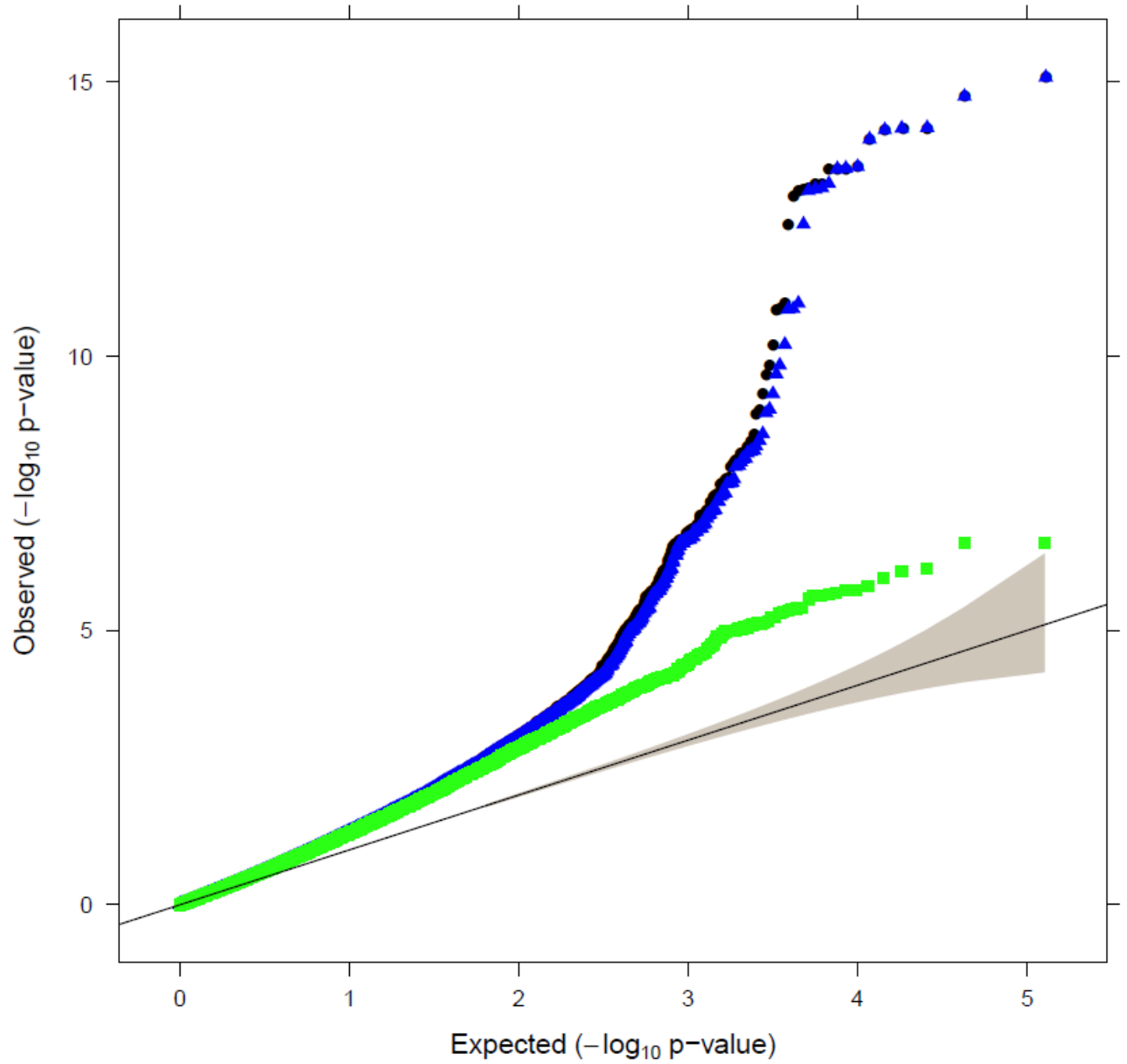
Fasting Glucose

Supplementary Figure 8a



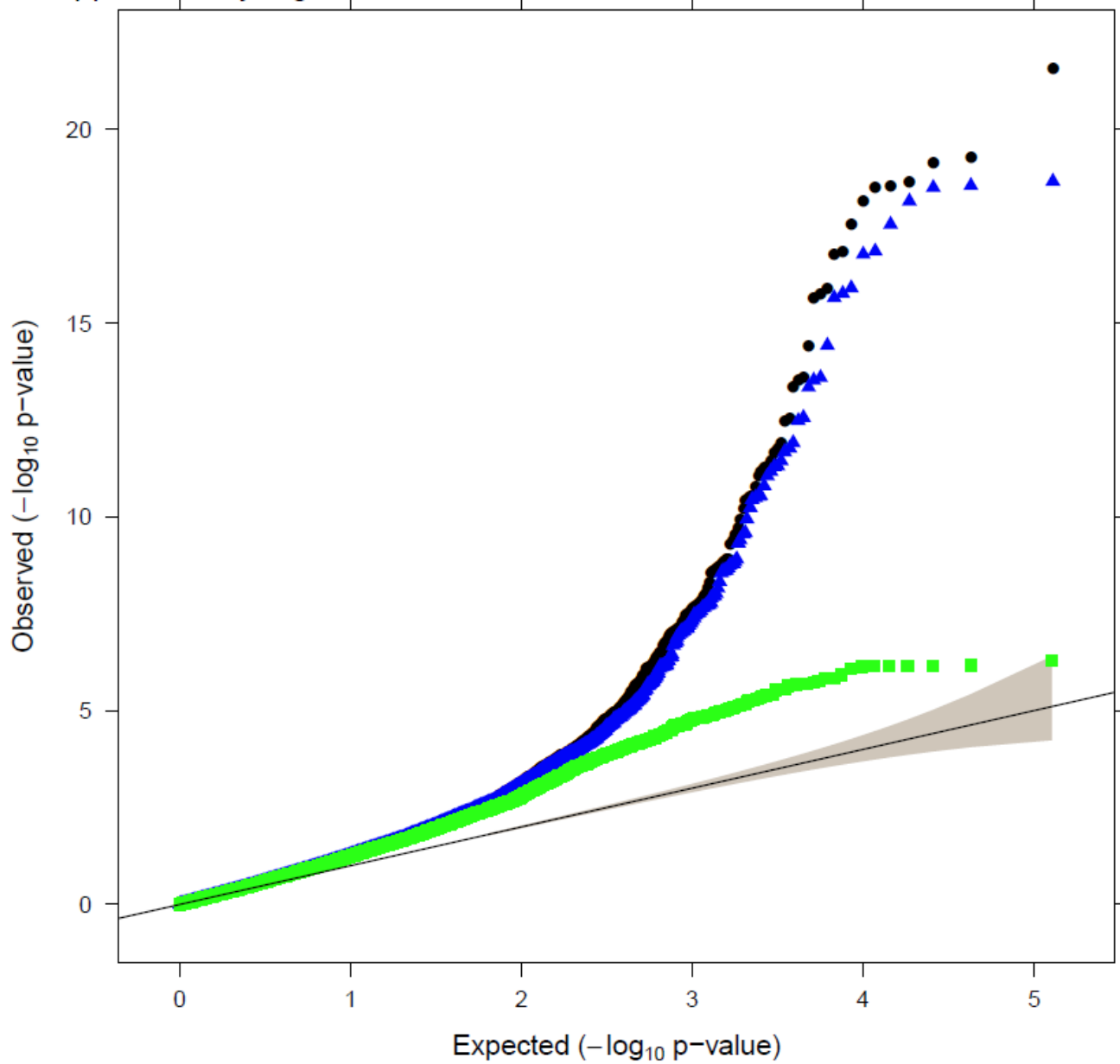
Fasting Insulin

Supplementary Figure 8b

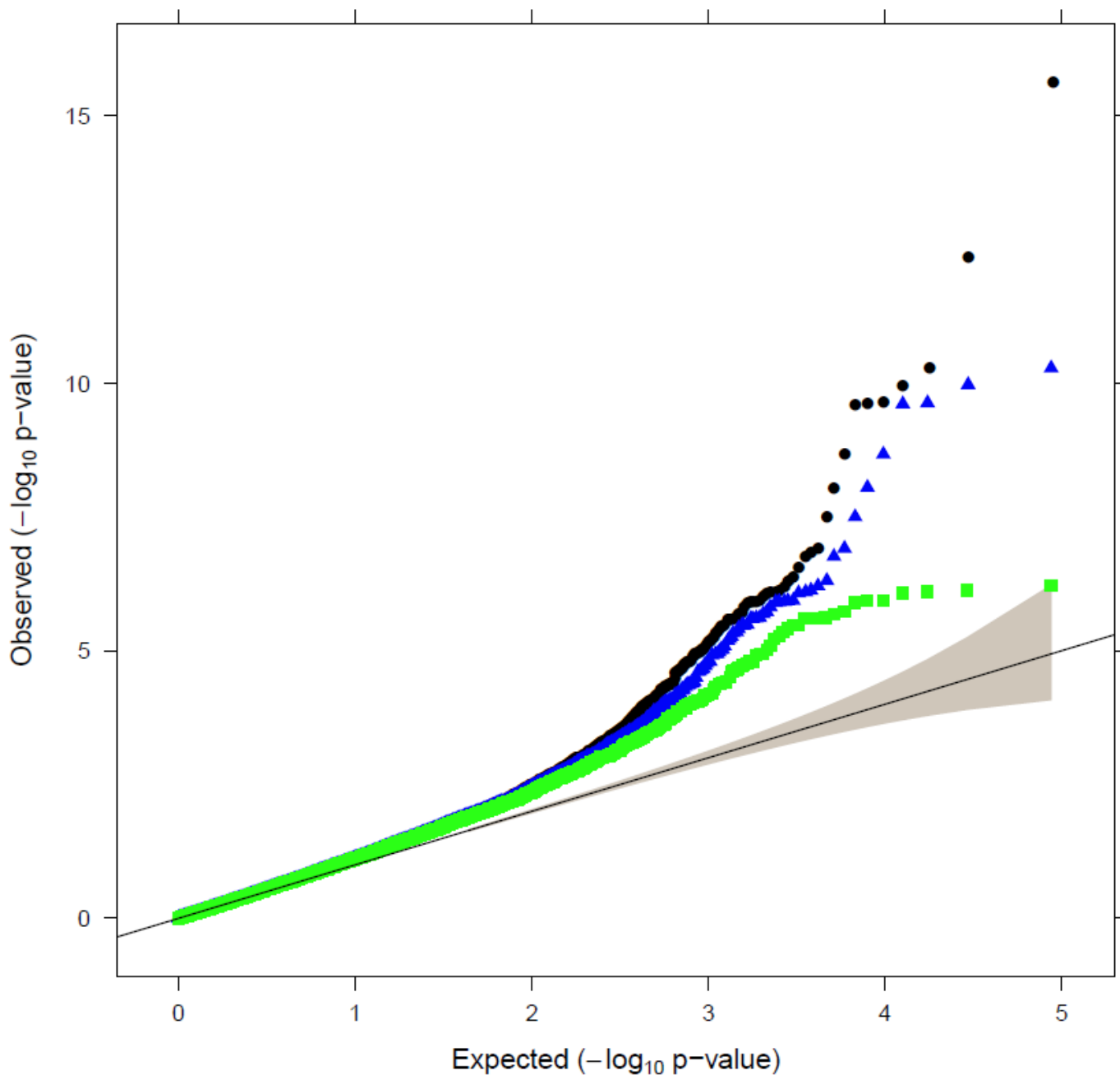


Fasting Insulin adj. BMI

Supplementary Figure 8c

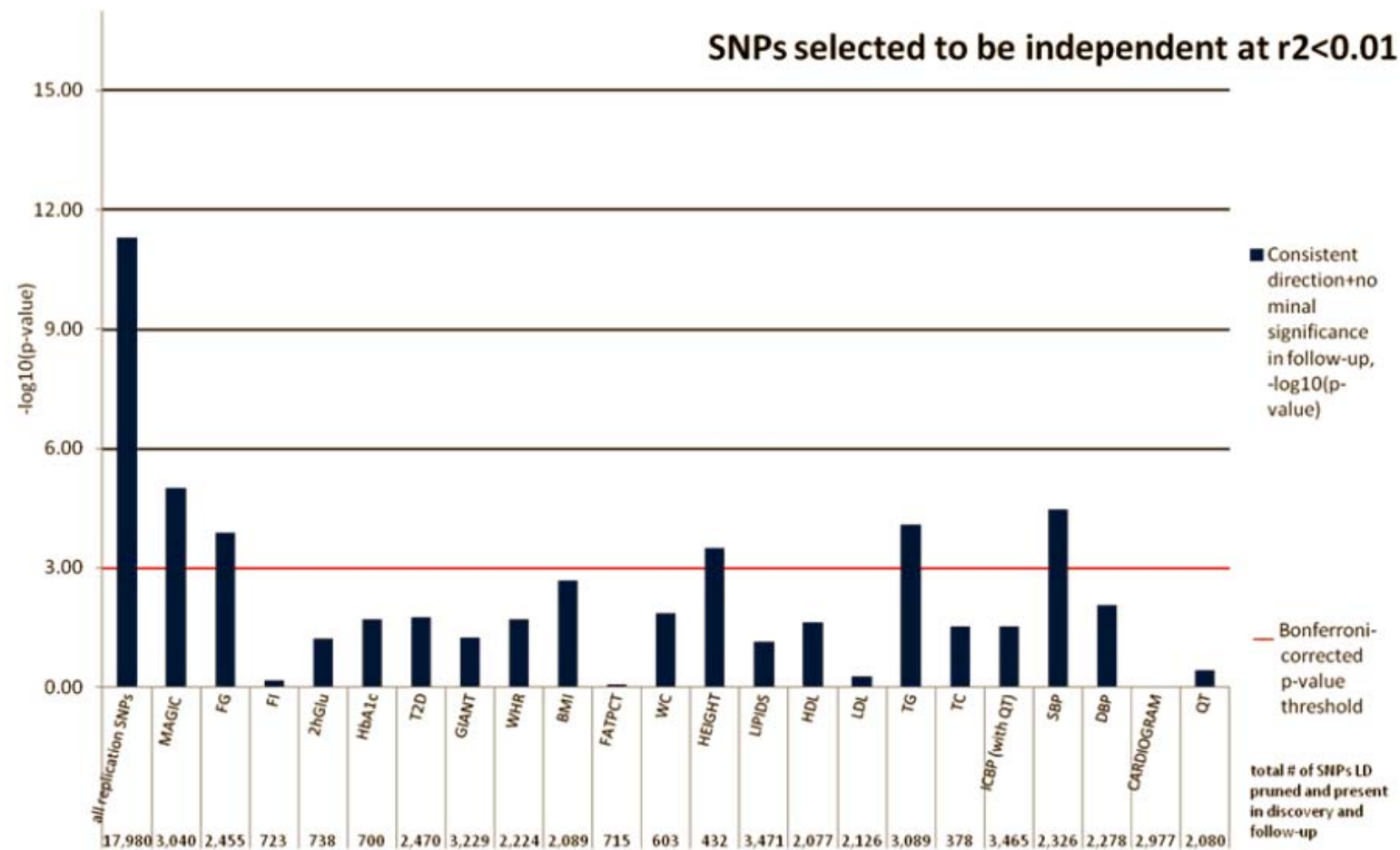


Supplementary Figure 8d 2-hr Glucose



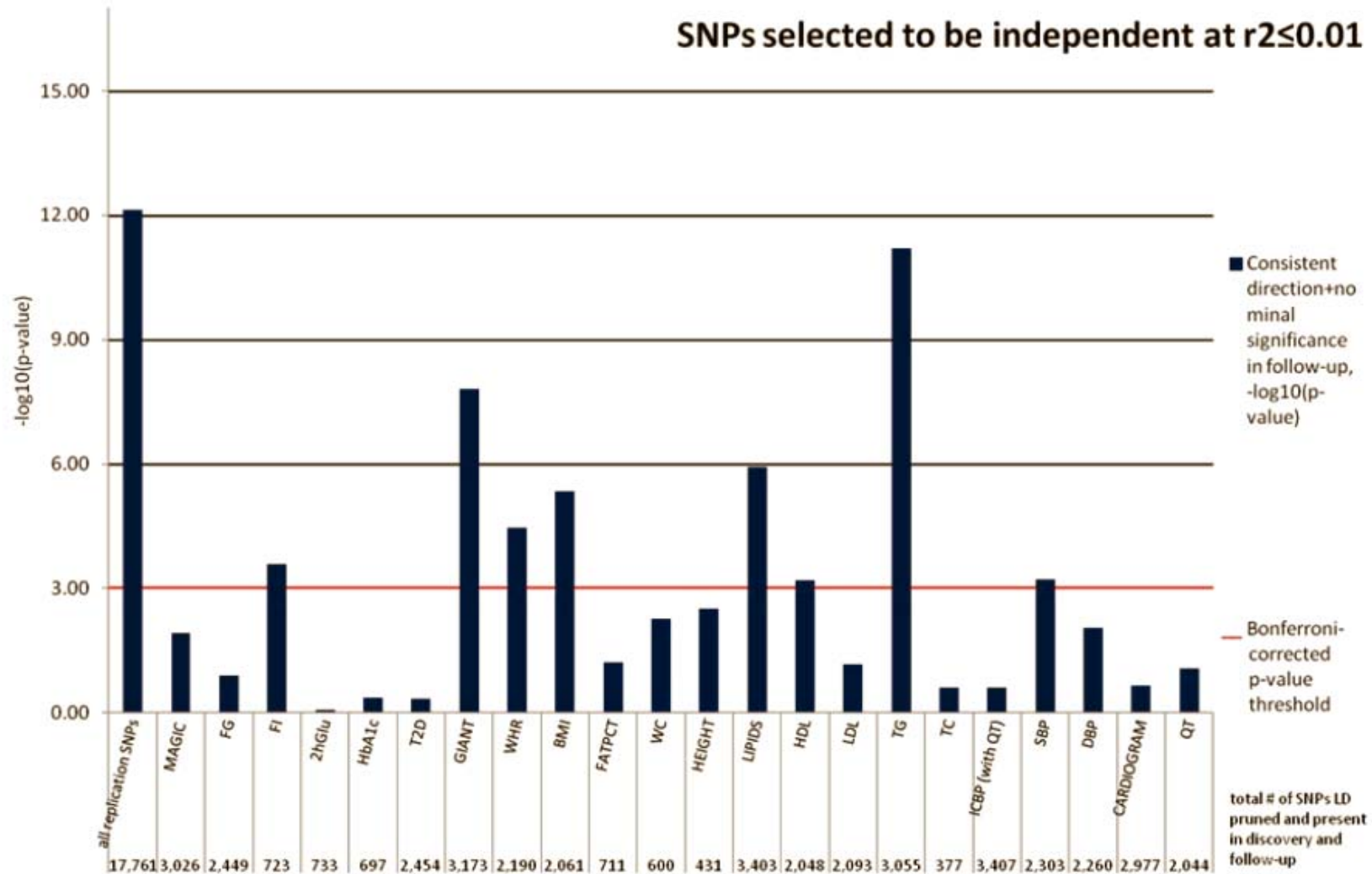
Supplementary Figure 8a-d QQ plots of Metabochip follow-up SNPs Black dots show all Metabochip follow-up SNPs, Blue triangles show observed associations after removal of previously established signals while green squares shows observed associations after removal of all genome-wide significant SNPs. a) FG, b) FI, c) FI(adjusted for BMI), d) 2hGlu

Supplementary Figure 9a: FG



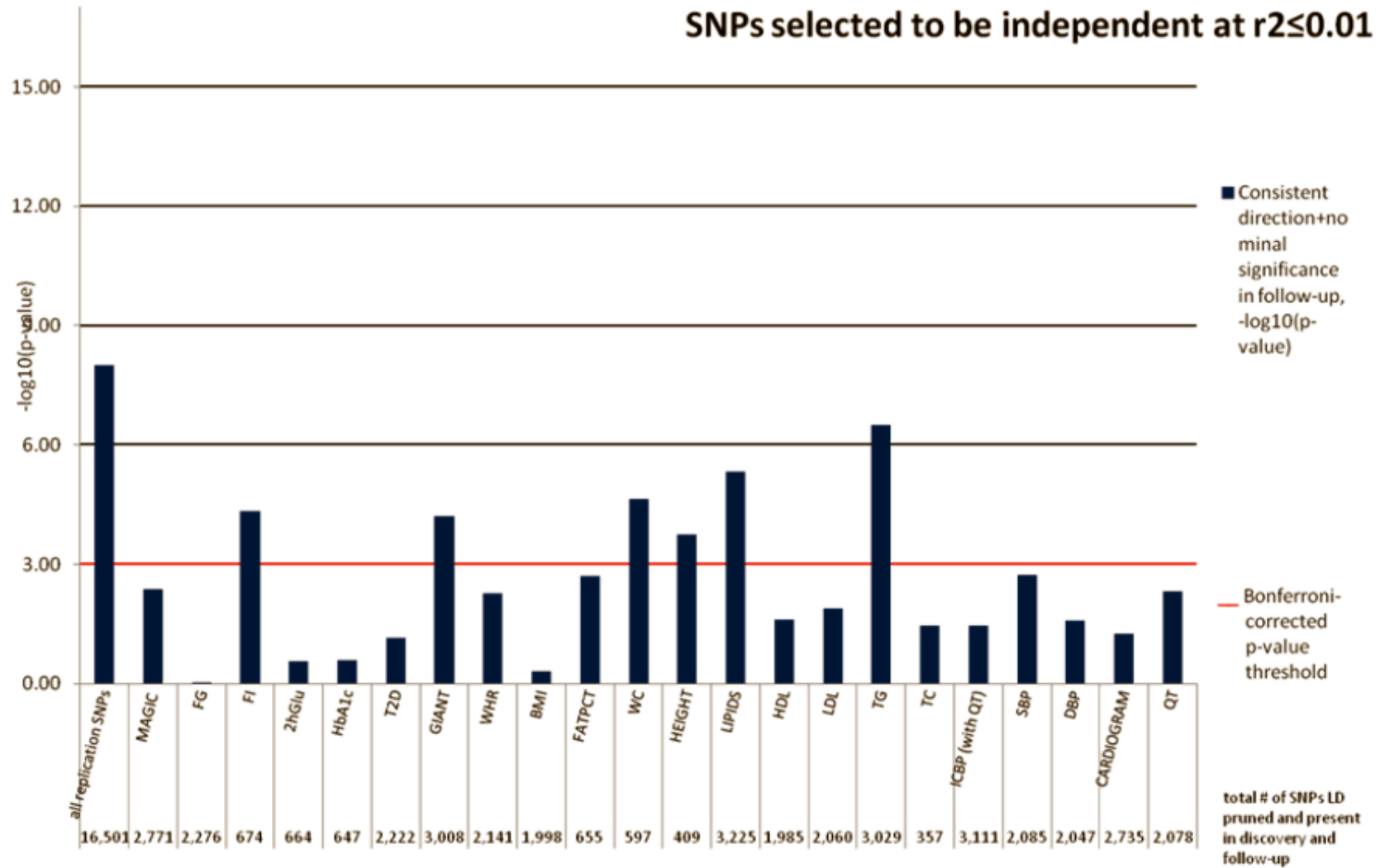
Supplementary Figure 9a FG association directional consistency. SNP lists submitted by each consortium are detailed on the x-axis and $-\log_{10}$ p-values on the y-axis for the binomial tests of consistent direction and nominal significance ($P < 0.05$) in follow-up studies..

Supplementary Figure 9b: FI



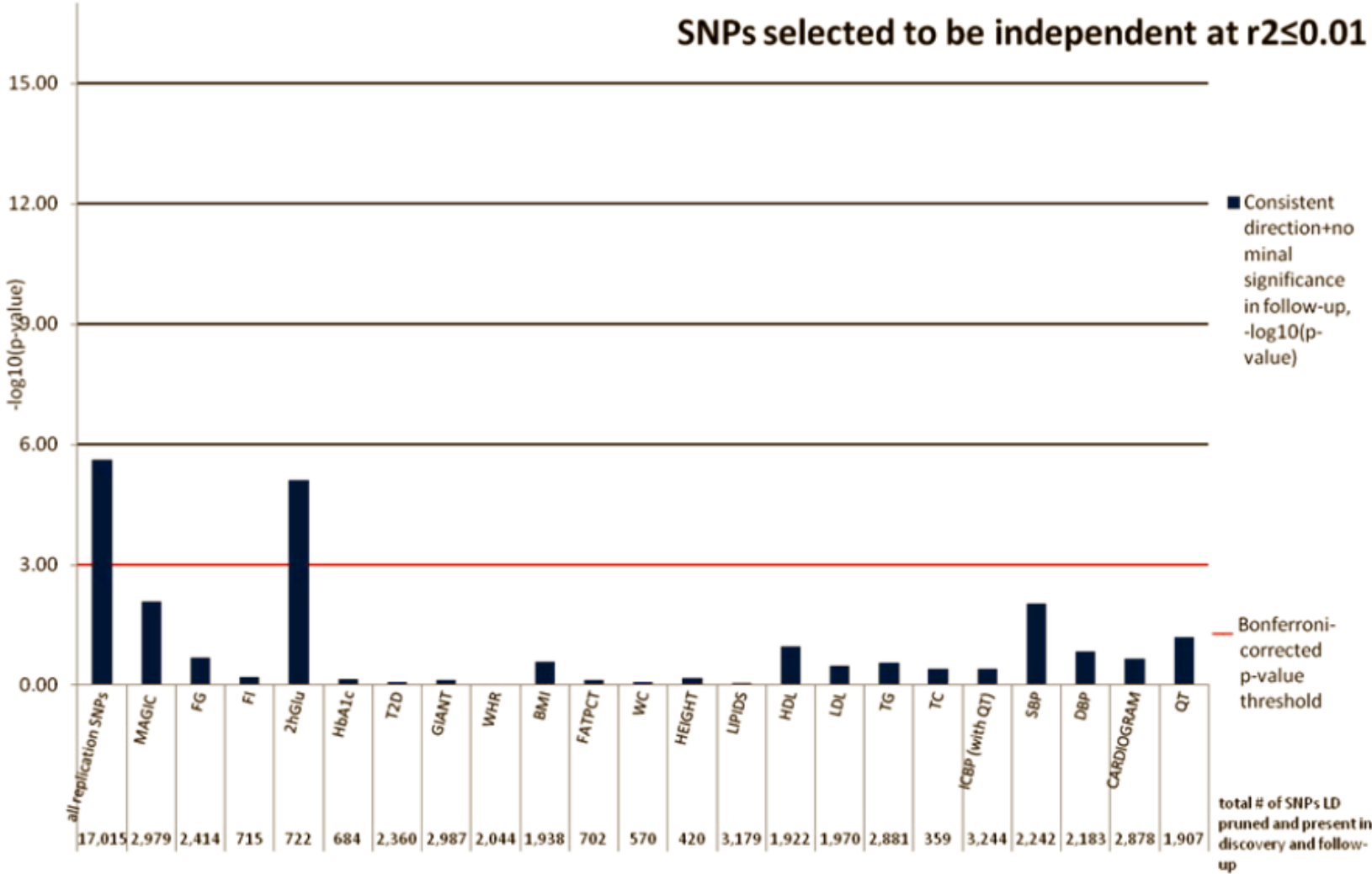
Supplementary Figure 9b FI association directional consistency. SNP lists submitted by each consortium are detailed on the x-axis and $-\log_{10}$ p-values on the y-axis for the binomial tests of consistent direction and nominal significance ($P < 0.05$) in follow-up studies..

Supplementary Figure 9c: FladjBMI

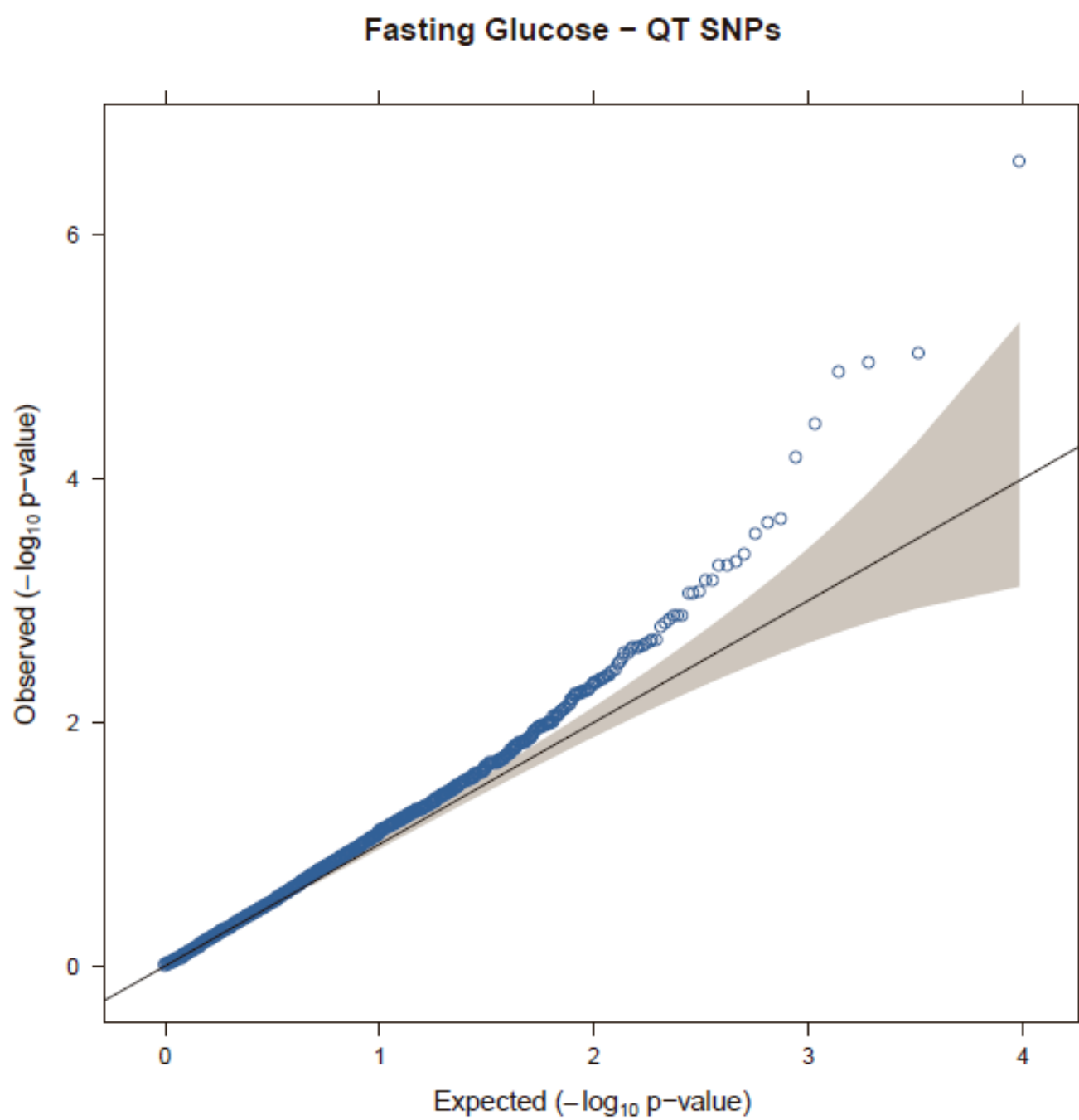


Supplementary Figure 9c FI (BMI-adjusted) association directional consistency. SNP lists submitted by each consortium are detailed on the x-axis and $-\log_{10} p$ values on the y-axis for the binomial tests of consistent direction and nominal significance ($P < 0.05$) in follow-up studies..

Supplementary Figure 9d: 2hGlu

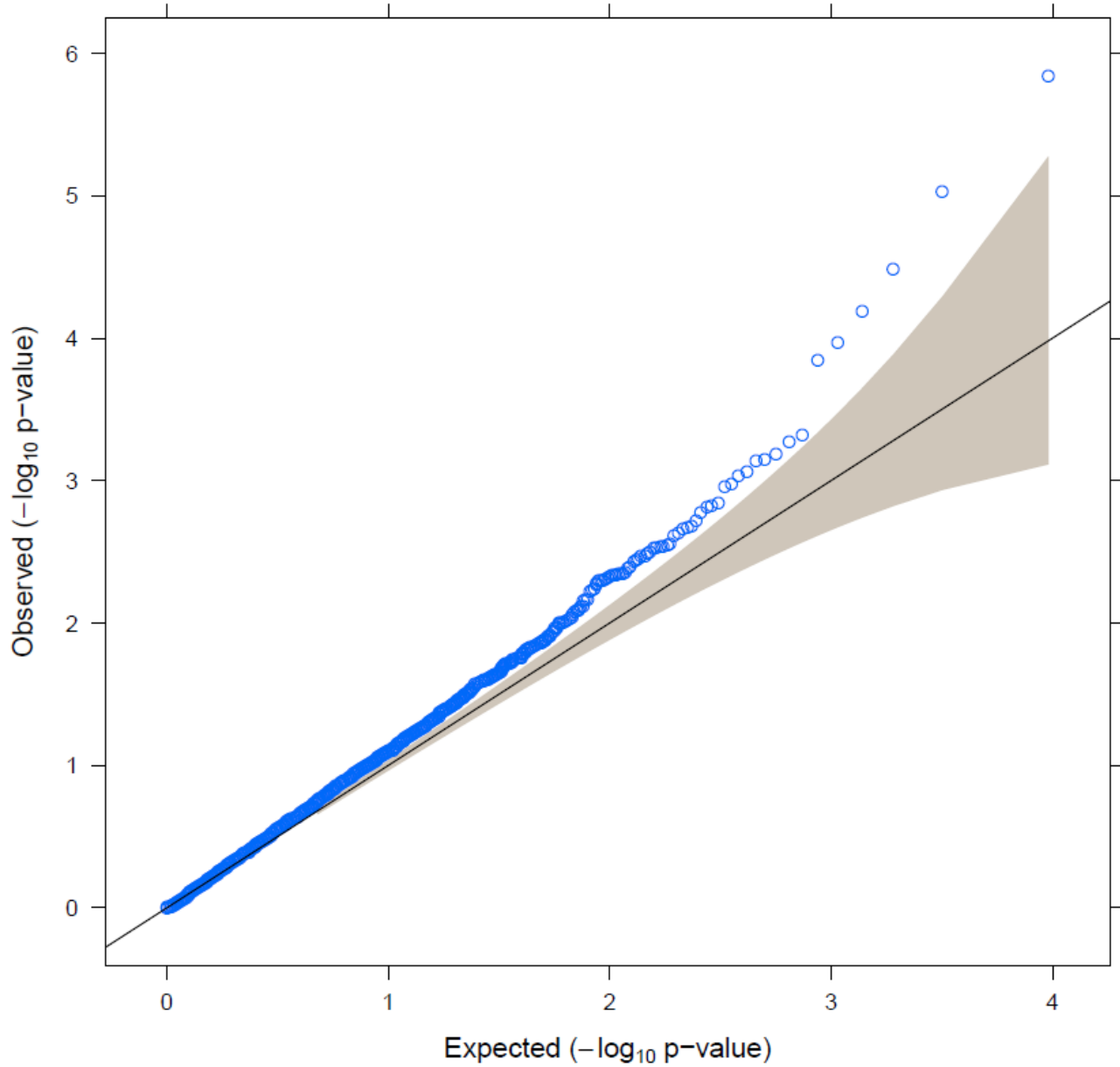


Supplementary Figure 9d 2hGlu association directional consistency. SNP lists submitted by each consortium are detailed on the x-axis and $-\log_{10}$ p-values on the y-axis for the binomial tests of consistent direction and nominal significance ($P < 0.05$) in follow-up studies..



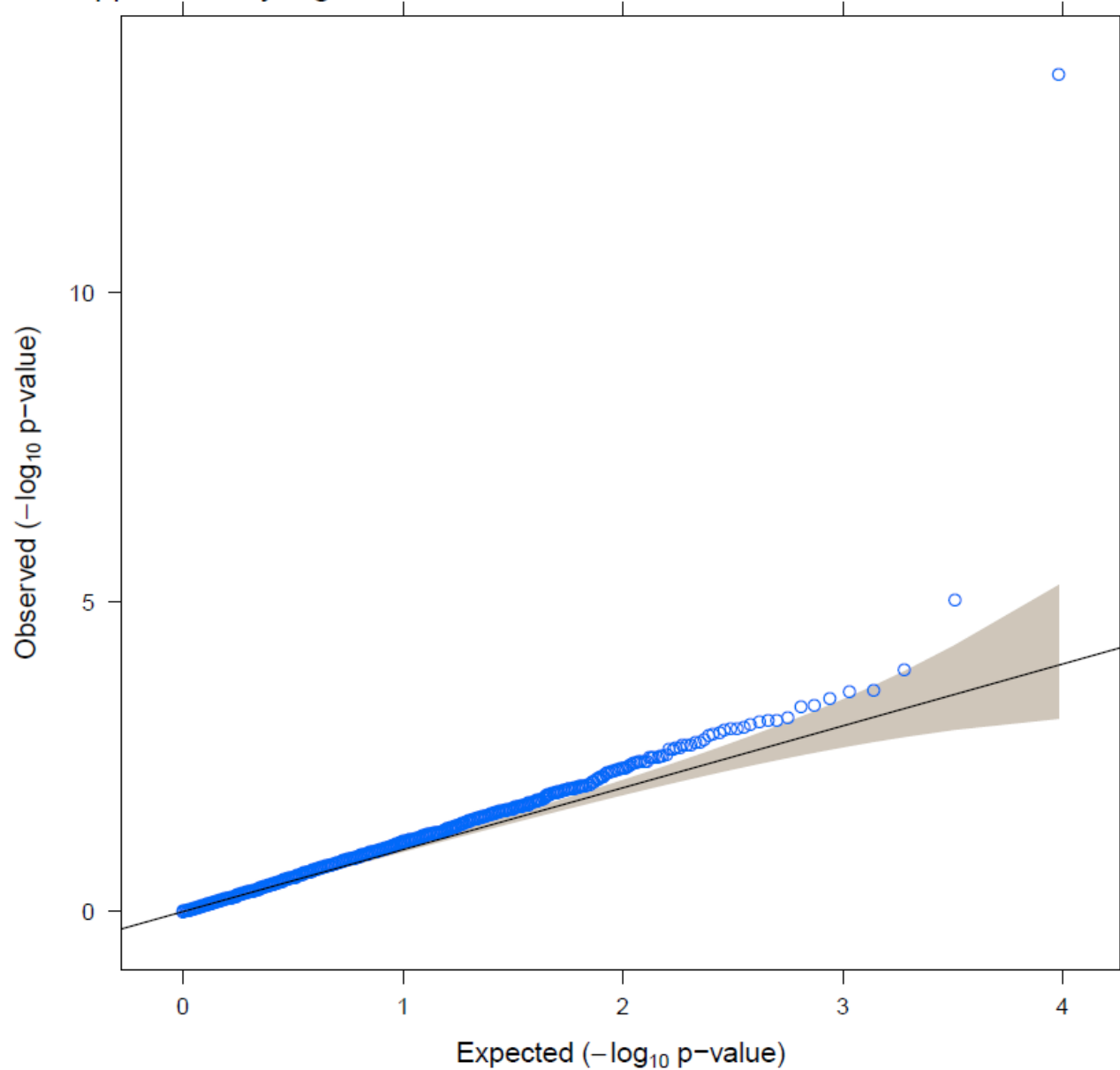
Fasting Insulin - QT SNPs

Supplementary Figure 10b



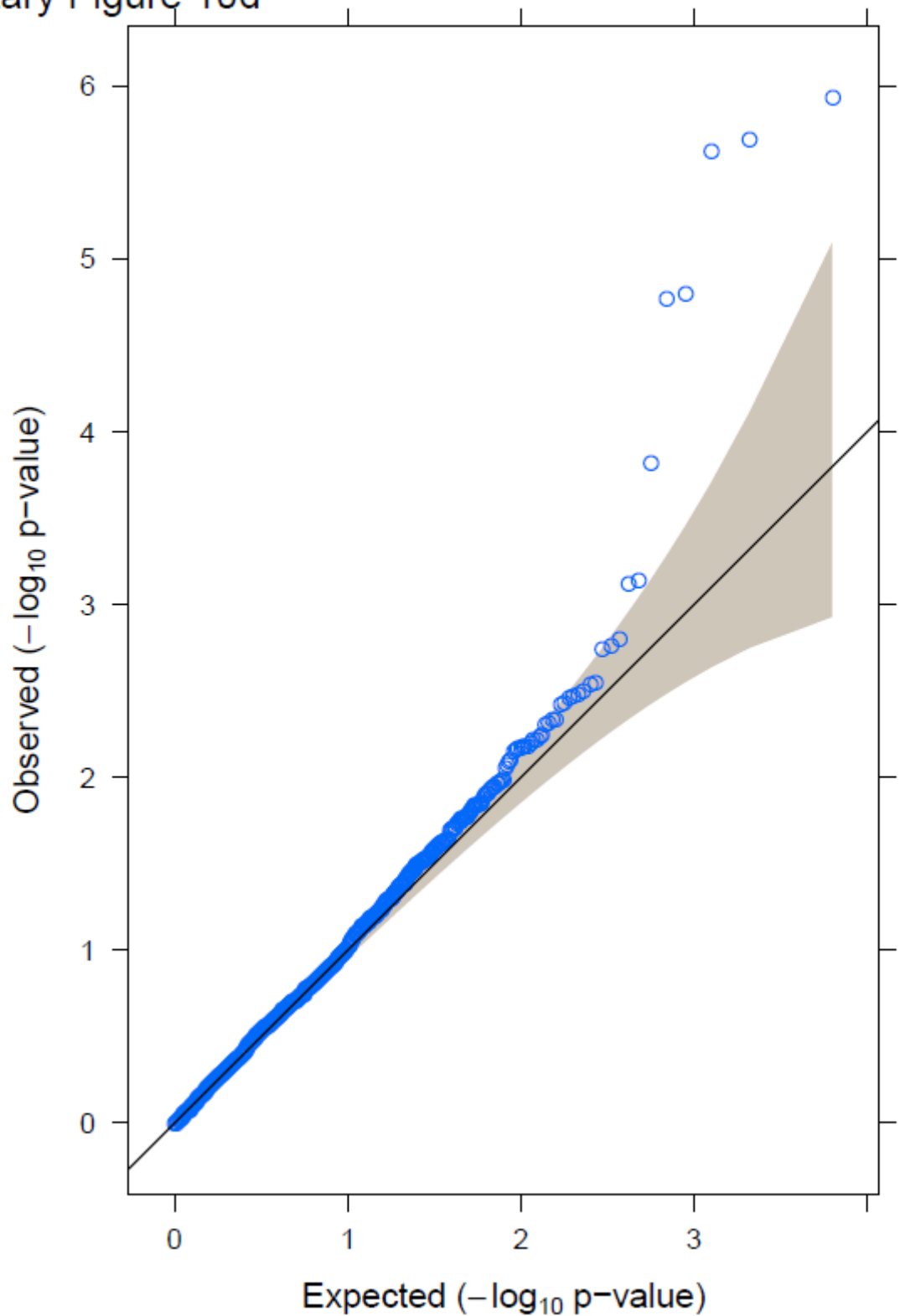
Fasting Insulin adj. BMI – QT SNPs

Supplementary Figure 10c



2-hr Glucose – QT SNPs

Supplementary Figure 10d



Supplementary Figure 10a-d - QQ plots for SNPs selected to follow-up QT-interval associations
a) FG, b) FI, c) FI(adjusted for BMI), d) 2hGlu

Reference List

1. Morris, A.P. *et al.* Large-scale association analysis of the "MetaboChip" provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* (2012).
2. Dupuis, J. *et al.* New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat. Genet.* **42**, 105-116 (2010).
3. Saxena, R. *et al.* Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nat. Genet.* **42**, 142-148 (2010).