

Supplementary Materials and Methods

Genetics of fasting indices of glucose homeostasis using GWIS unravels tight relationships with inflammation markers

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MAGIC studies (subset) contributing to each primary phenotype meta-analysis

FG: AGES, ALSPAC, AMISH, ARIC, ASCOT, BLSA, BSN, CHS, COLAUS, CROATIA, DECODE, DGI, ERF, FAMHS, FENLAND, FHS, FRENCHADULTCONTROL, FRENCHADULTTOBESE, FRENCHYOUNGCONTROL, FRENCHYOUNGOBESE, FUSION, GENOA, GENOMEUTWINS, HABC, HEALTH2000, INCHIANTI, KORA, KORCULA, LIFELINES, NFBC66, ORCADES, PREVEND, PROCARDIS, RS, SARDINIA, SORBS, SPLIT, SUVIMAX, TWINSUK, TYROL.

FI: AGES, ALSPAC, AMISH, ARIC, BLSA, BSN, CHS, COLAUS, CROATIA, DECODE, DGI, ERF, FAMHS, FENLAND, FHS, FRENCHADULTCONTROL, FRENCHADULTTOBESE, FRENCHYOUNGOBESE, FUSION, GENOA, GENOMEUTWINS, HABC, HEALTH2000, INCHIANTI, KORCULA, NFBC66, ORCADES, PREVEND, PROCARDIS, RS, SARDINIA, SORBS, TWINSUK.

Fasting Glucose (FG) and Fasting Insulin (FI) GWAS and pre-GWIS quality control

(QC)

Summary statistics for FG and FI GWAS meta-analyses were obtained with permission of MAGIC (the Meta-Analyses of Glucose and Insulin-related traits Consortium). For detailed description of the above-mentioned cohorts, genotyping, imputation and QC on the individual study level see (*Lagou et al., manuscript in preparation, www.magicinvestigators.org*). In the individual samples FG and FI were measured in mmol/L and pmol/L respectively. Before performing a GWAS FI was natural logarithm transformed. Genotyping was performed on either Illumina or Affymetrix platforms and imputed to the HapMap II CEU reference panel¹. Studies, genotyped on specifically designed

arrays, such as Metabochip were excluded. Meta-analysis was performed in the software GWAMA².

We started with 2,728,451 SNPs for FG and 2,717,287 SNPs for FI, which passed QC in the separate GWAS. First, we compared allele frequencies between HapMap II CEU¹ and separate FG and FG analysis results. SNPs with allele frequency differences more than 20% were excluded from each study results (66 for FG and 36 for FI). Second, we selected 2,715,654 overlapped SNPs and checked them for reference allele concordance and frequency. 2,715,004 SNPs had concordant alleles and 647 SNPs had swapped reference and not reference allele. We aligned 647 alleles, their beta coefficients and frequencies. 3 SNPs were flipped by strand, we excluded them from the analysis. SNPs, which had an allele frequency difference between the GWASs of FG and FI of more than 10% were excluded (N = 4,299). The resulting set contained 2,711,352 SNPs. Data management and analyses were performed in R version 3.2.5³, easyQC software⁴ was used to compare FG/FI SNP frequencies with HapMap II CEU reference set¹.

GWIS of HOMA-B and HOMA-IR

Throughout the Supplementary Materials and Methods we will refer to the previous meta-analysis of HOMA-B/-IR⁵ as ‘published’ and the results of the present study and analyses as to ‘inferred’ meta-analysis of HOMA-B/-IR.

Allele effect estimates

The GWIS-inferred⁶ effect estimates (β s) for HOMA-B and HOMA-IR for SNP_i , $i=1,\dots,M$ were calculated using the following formulae:

$$\beta_{HOMA-B/-IR} = AF1 \times \beta_1 + AF2 \times \beta_2, [1]$$

AF1 and AF2 are relative population frequencies and β_1 and β_2 are HOMA-B/-IR functions (main text formulas [3,4]) evaluated for 1 and 2 copies of effect allele respectively. For both HOMA-B/-IR AF1 and AF2 are the same:

$$AF1 = \frac{2 \times p \times (1-p)}{2 \times p \times (1-p) + p^2}, [2]$$

$$AF2 = \frac{p^2}{2 \times p \times (1-p) + p^2}, [3]$$

where p is the effect allele frequency, calculated as a weighted mean of FG and FI effect allele frequencies, expressed as:

$$p = \frac{N1 \times EAF_{FI} + N2 \times EAF_{FG}}{N1 + N2}, [4]$$

where $N1$ and $N2$ are the sample sizes of FI and FG respectively for SNP_i .

For HOMA-B β_1 and β_2 for each SNP_i are represented by:

$$\beta_1 = \ln \frac{20 \times \frac{e^{(M_{FI} + \beta_{FI})}}{6.945}}{(M_{FG} + \beta_{FG}) - 3.5} - \ln \frac{20 \times \frac{e^{M_{FI}}}{6.945}}{M_{FG} - 3.5}, [5]$$

$$\beta_2 = (\ln \frac{20 \times \frac{e^{(M_{FI} + 2 \times \beta_{FI})}}{6.945}}{(M_{FG} + 2 \times \beta_{FG}) - 3.5} - \ln \frac{20 \times \frac{e^{M_{FI}}}{6.945}}{M_{FG} - 3.5}) / 2, [6]$$

For HOMA-IR β_1 and β_2 for each SNP_i are represented by:

$$\beta_1 = \ln \frac{(M_{FG} + \beta_{FG}) \times \frac{e^{(M_{FI} + \beta_{FI})}}{6.945}}{22.5} - \ln \frac{M_{FG} \times \frac{e^{M_{FI}}}{6.945}}{22.5}, [7]$$

$$\beta_2 = (\ln \frac{(M_{FG} + 2 \times \beta_{FG}) \times \frac{e^{(M_{FI} + 2 \times \beta_{FI})}}{6.945}}{22.5} - \ln \frac{M_{FG} \times \frac{e^{M_{FI}}}{6.945}}{22.5}) / 2, [8]$$

$M_{FG/FI}$ are the estimated population means (5.252857 mmol/l and 60.40195 pmol/l for FG/FI respectively) computed as mean of means across meta-analyses studies (from which mean estimates were available). $M_{FG/FI}$ are used instead of intercept terms in GWIS⁶. $\beta_{FG/FI}$ are the effect estimates for a SNP_i from GWAS meta-analyses of FG and FI respectively. During calculation of β values 35 SNPs

resulted in missing values (NAs) for HOMA-B because the logarithm of negative value is not defined.

Standard errors

For the calculation of the standard errors (SEs) of the GWIS-inferred⁶ summary statistics of HOMA-B/-IR we used the Delta method implemented in R package *msm* to account for the estimated sample overlap⁷. We estimated the sample overlap between FG and FI by using two strategies: 1) ‘Global’, assuming the sample overlap is the same across all SNPs. In this case cross-trait LDSC⁸ intercept from FG and FI genetic correlation analysis (before the GWIS QC) reflects the sample overlap between FG and FI meta-analyses and could be used as a correction factor while calculating SEs. 2) ‘Local’, assuming varying sample overlap across SNPs. To compute the cross-trait LDSC⁸ intercept per each SNP we performed the following steps:

- a) We run the LDSC⁸ between FG and FI to obtain the LDSC intercept. The latter is represented by the formulae

$$gcov_int = \frac{N_s \times r}{\sqrt{N_1 \times N_2}}, [9]$$

where N_s =samples overlap, r is the phenotypic correlation between the two traits and N_1 and N_2 are the sample sizes for traits 1 and 2 (here FI and FG) from each meta-analysis. The same estimate of $gcov_int$ was used as correction factor when assuming ‘global’ sample overlap ($gcov_int = 0.2606$).

- b) In order to compute ‘local’ $gcov_int_i$ for each SNP_i using formula [9] we would need to know N_{s_i} , N_{1_i} and N_{2_i} per each SNP_i as well as phenotypic correlation between FG and FI (r). N_{1_i} and N_{2_i} are known. N_{s_i} is the unknown sample overlap for each SNP_i and therefore we approximated it as $\min(N_{1_i}, N_{2_i})$.

As only summary statistics were available and we were not able to estimate phenotypic correlation r from the actual phenotype data, we rearranged formula [9] to derive r from LDSC intercept as follows:

$$r = gcov_int \times \sqrt{N_1 \times N_2} / N_s, [10]$$

where $gcov_int$ is the cross-trait LDSC intercept from step a), $N_1=minimum$ sample size for FI, and $N_2=minimum$ sample size for FG meta-analyses across all SNPs. Note, N_1 and N_2 were obtained after an initial run with LDSC⁸, which removes SNPs with low N and suggests reliable minimum values for the traits ($N_1 < 42727.3333333$, $N_2 < 58876.6666667$). As sample overlap between FG and FI is unknown, we approximated $N_s = \min(N_1, N_2)$,

c) Finally, we calculated a vector of cross-trait LDSC intercepts $gcov_int_i$ per SNP_i $i=1,\dots,M$ using the same formulae [9] adjusted for each SNP_i as follows:

$$gcov_int_i = \frac{Ns_i \times r}{\sqrt{N1_i \times N2_i}}, [11],$$

where we used the estimated phenotypic correlation r from the previous step b). The values of computed cross-trait intercept vector ranged from 0.02846 to 0.3059 with the mean=0.2634 and median=0.2606.

Sample size

We approximated a sample size for each SNP_i of the inferred HOMA-B/-IR meta-analysis results, as a geometric mean between FG (N_1) and FI (N_2) sample sizes:

$$N = \sqrt{N_1 \times N_2}, [12]$$

Post-GWIS HOMA-B/-IR QC

We computed the genetic correlation r_g between published and inferred HOMA-B/-IR (both 'global' or 'local' corrected versions) using LDSC⁸ (the expectation,

when the same trait is analyzed, is that the genetic correlation equals 1) and found similar results (**Table S9**). The comparison of summary statistics distributions between published and inferred HOMAs demonstrated that standard errors (SEs) decreased in current analyses compared to the previously determined validating the fact that GWIS results gain in power over previous GWAS efforts (**Figures S8 - S18**)⁵. We also compared the distribution of summary statistics of the two versions of inferred and published HOMA-B/-IR aiming to select ‘global’ or ‘local’ corrected version. The distribution between the ‘global’ and ‘local’ correction versions of HOMA-B/-IR results were also very similar (**Figures S8 - S19**), therefore we proceeded with the ‘local’ correction as it is assumed to be more precise. However, to re-iterate we did not observe a difference between ‘global’ and ‘local’ correction approaches in current analysis and given the similarity of summary statistics they both could have been used in further analysis (**Figure S19**).

From genetic correlation analysis the LDSC intercepts for inferred HOMA-B/-IR summary statistics were also available (**Table S9**). The LDSC intercepts were estimated as 1.0493/1.033 for HOMA-B/-IR ‘local’ corrections, confirming the gain in power in GWIS did not arise from inflation due to imprecise approximation. However, as LDSC intercepts exceeded 1 and could indicate residual population stratification or misspecification of the sample overlap, we additionally adjusted SEs for excess in the LDSC intercept:

$$SE_{adj} = \frac{\sqrt{(SE \times \sqrt{N})^2 \times intercept}}{\sqrt{N}}, [13]$$

where for a particular SNP_i SE is the standard error from inferred HOMA-B/-IR summary statistics, N is the sample size and $(SE \times \sqrt{N})^2$ is the variance. P-values were computed based on chi-square distribution with 1 degree of freedom.

The comparison of variants with low N and MAF between the published and inferred GWAS showed a marginally lower concordance between SEs for low N and MAF (**Figures S9, S13-S15, S18**) confirming it is sensible to apply QC filters for minimal sample size and MAF. As difference in SEs between inferred and published meta-analysis results gets larger when N decreases (**Figures S13-S15,S18**) we excluded SNPs with low N (278,542/278,577 SNPs with N<35,000 for HOMA-B/-IR, among which 113/113 were filtered out based on MAF<0.01 filter). The total number of SNPs after QC was 2,432,775 for HOMA-B/-IR. LocusZoom⁹ was used to build region plots for the established loci (**Figures S20-S21**).

Effects of established T2D, FG/FI and HbA1c loci on HOMA-B/-IR

We plotted the effects of HOMA-B/-IR at established T2D, FG/FI and HbA1c loci in Figure 2. Effects of HOMA-B/-IR SNPs were aligned to the risk allele of either T2D, FG/FI or HbA1c SNPs. If loci between T2D and FG/FI overlapped, but SNPs did not, we selected one SNP per locus. First, we considered loci from previous efforts^{10,11}, then added novel 1000G detected loci from the two recent T2D studies^{12,13} and HbA1c¹⁴. For SNPs, which were not present in HOMA-B/-IR results, we obtained the proxies via LDlink ($R^2 > 0.9$)¹⁵.

Table S1. Comparison of HOMA-B effects across genome-wide significant loci between inferred and published GWAS

SNP	CHR	Locus name	Alleles (effect / other)	HOMA-B inferred		HOMA-B published	
				Effect (SE), p-value	N	Alleles (effect / other)	Effect (SE), p-value
rs560887	2	<i>G6PC2</i>	C/T	-0.046 (0.0033), 4.74×10 ⁻⁴⁶	75,173	T/C	0.040 (0.0036), 7.67×10 ⁻²⁹
rs11708067	3	<i>ADCY5</i>	A/G	-0.024 (0.0038), 2.50×10 ⁻¹⁰	75,227	A/G	-0.016 (0.0043), 1.77×10 ⁻⁰⁴
rs10258074	7	<i>DGKB</i>	A/T	0.019 (0.0031), 2.55×10 ⁻¹⁰	75,202	A/T	0.022 (0.0033), 2.99×10 ⁻¹¹
rs3757840	7	<i>GCK</i>	G/T	0.02 (0.0033), 1.98×10 ⁻⁰⁹	64,352	T/G	-0.017 (0.0038), 7.96×10 ⁻⁰⁶
rs3802177	8	<i>SLC30A8</i>	G/A	-0.021 (0.0036), 2.55×10 ⁻⁰⁹	68,044	A/G	0.016 (0.0038), 1.96×10 ⁻⁰⁵
rs7034200	9	<i>GLIS3</i>	A/C	-0.019 (0.003), 2.96×10 ⁻¹⁰	74,669	A/C	-0.016 (0.0033), 1.67×10 ⁻⁰⁶
rs7903146	10	<i>TCF7L2</i>	C/T	0.03 (0.0034), 7.41×10 ⁻¹⁹	75,212	T/C	-0.020 (0.0038), 1.39×10 ⁻⁰⁷
rs10830963	11	<i>MTNR1B</i>	C/G	0.039 (0.0038), 9.34×10 ⁻²⁵	68,612	C/G	0.039 (0.0040), 8.60×10 ⁻²³
rs1552224	11	<i>ARAP1</i>	C/A	0.025 (0.004), 4.28×10 ⁻¹⁰	75,207	A/C	-0.017 (0.0043), 9.39×10 ⁻⁰⁵
rs174555	11	<i>FADS1-2-3</i>	T/C	-0.021 (0.0033), 8.97×10 ⁻¹¹	75,237	T/C	-0.015 (0.0034), 1.32×10 ⁻⁰⁵
rs5029909	20	<i>FOXA2</i>	C/T	-0.044 (0.0079), 2.70×10 ⁻⁰⁸	68,584	T/C	0.032 (0.0092), 4.84×10 ⁻⁰⁴

Table S2. Comparison of HOMA-IR effects across genome-wide significant loci between inferred and published GWAS

SNP	CHR	Locus name	Alleles (effect / other)	HOMA-IR inferred		HOMA-IR published	
				Effect (SE), p-value	N	Alleles (effect / other)	Effect (SE), p-value
rs2605101	1	<i>LYPLAL1/</i> <i>SLC30A10</i>	A/T	0.019 (0.0034), 3.78×10^{-8}	75,238	A/T	0.016 (0.0042), 1.24×10^{-4}
rs780093	2	<i>GCKR</i>	C/T	0.024 (0.0032), 1.06×10^{-13}	75,226	T/C	-0.019 (0.0040), 1.31×10^{-6}
rs10224545	7	<i>PER4</i>	T/C	-0.031 (0.0056), 2.60×10^{-8}	71,951	T/C	-0.015 (0.0069), 2.51×10^{-2}
rs4240624	8	<i>PPP1R3B</i>	A/G	-0.035 (0.0055), 2.73×10^{-10}	68,617	A/G	-0.021 (0.0066), 1.66×10^{-3}
rs2114912	12	<i>IGF1</i>	T/G	0.026 (0.0044), 3.08×10^{-9}	74,634	T/G	0.026 (0.0053), 1.33×10^{-6}

Table S3. Meta-analyses summary statistics sources

	Reference	Year	Phenotype	Sample Size	Ancestry
1	Pattaro, C., Teumer, A., Gorski, M., Chu, A. Y., Li, M., Mijatovic, V., ... & Taliun, D. (2016). Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. <i>Nature communications</i> , 7.	2015	Estimated glomerular filtration rate based on serum creatinine (eGFRcrea) all/non-DM/DM, cystatin C (eGFRcys) all, chronic kidney disease (CKD) all	133,413 (eGFRcrea all), 118,448 (eGFRcrea non-DM), 11,522 (eGFRcrea DM), 32,834 (eGFRcys), 117,165 (CKD)	European
2	Dehghan, A., Dupuis, J., Barbalic, M., Bis, J. C., Eiriksdottir, G., Lu, C., ... & Baumert, J. (2011). Meta-analysis of genome-wide association studies in > 80 000 subjects identifies multiple loci for C-reactive protein levels. <i>Circulation</i> , 123(7), 731-738.	2010	C-Reactive Protein (CRP)	66,185	European
3	Huang, J., Sabater-Lleal, M., Asselbergs, F. W., Tregouet, D., Shin, S. Y., Ding, J., ... & Smith, N. L. (2012). Genome-wide association study for circulating levels of PAI-1 provides novel insights into its regulation. <i>Blood</i> , 120(24), 4873-4881.	2012	Plasminogen Activator Inhibitor 1 (PAI-1)	19,599	European
4	Dastani, Z., Hivert, M. F., Timpson, N., Perry, J. R., Yuan, X., Scott, R. A., ... & Fuchsberger, C. (2012). Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. <i>PLoS Genet</i> , 8(3), e1002607.	2012	Adiponectin (ADIP)	29,347	European
5	Paré, G., Ridker, P. M., Rose, L., Barbalic, M., Dupuis, J., Dehghan, A., ... & Chasman, D. I. (2011). Genome-wide association analysis of soluble ICAM-1 concentration reveals novel associations at the NFKBIK, PNPLA3, RELA, and SH2B3 loci. <i>PLoS Genet</i> , 7(4), e1001374.	2011	Intercellular Adhesion molecule 1 (ICAM-1)	22,435	North American women, Caucasian
6	Nalls, M. A., Couper, D. J., Tanaka, T., Van Rooij, F. J., Chen, M. H., Smith, A. V., ... & Wood, A. R. (2011). Multiple loci are associated with white blood cell phenotypes. <i>PLoS Genet</i> , 7(6), e1002113.	2011	White Blood Cell Counts (WBC)	19,509	European

Table S3. Continued

	Reference	Year	Phenotype	Sample Size	Ancestry
7	Schunkert, H., König, I. R., Kathiresan, S., Reilly, M. P., Assimes, T. L., Holm, H., ... & Absher, D. (2011). Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. <i>Nature genetics</i> , 43(4), 333-338.	2011	Coronary Artery Disease (CAD)	22,233 cases and 64,762 controls	European
8	Prokopenko, I., Poon, W., Mägi, R., Prasad, R., Salehi, S. A., Almgren, P., ... & Stančáková, A. (2014). A central role for GRB10 in regulation of islet function in man. <i>PLoS Genet</i> , 10(4), e1004235.	2014	Corrected Insulin Response (CIR), ratio of the area under the curve for insulin and glucose (AUCins/AUCglu), disposition index (DI), insulin at 30 min (Ins30), incremental insulin at 30 min (Increm30), insulin response adjusted for BMI (Ins30adjBMI), area under the curve of insulin levels during OGTT (AUCIns).	5,318 CIR, 4,789 CIRadjISI, 4,213 AUCins/AUCglu, 5,130 DI, 4,483 Ins30, 4,447 Increm30, 4,483 Ins30adjBMI, 4,324 AUCIns.	European
9	Strawbridge, R. J., Dupuis, J., Prokopenko, I., Barker, A., Ahlvist, E., Rybin, D., ... & Nica, A. (2011). Genome-wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type 2 diabetes. <i>Diabetes</i> , 60(10), 2624-2634.	2011	Fasting Proinsulin	10,701	European
10	Soranzo, N., Sanna, S., Wheeler, E., Gieger, C., Radke, D., Dupuis, J., ... & Sandhu, M. S. (2010). Common variants at 10 genomic loci influence hemoglobin A1C levels via glycemic and nonglycemic pathways. <i>Diabetes</i> , 59(12), 3229-3239.	2010	Hemoglobin A1C	46,368	European
11	Saxena, R., Hivert, M. F., Langenberg, C., Tanaka, T., Pankow, J. S., Vollenweider, P., ... & Kao, W. L. (2010). Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. <i>Nature genetics</i> , 42(2), 142-148.	2009	2hr glucose	15,234	European

Table S3. Continued

	Reference	Year	Phenotype	Sample Size	Ancestry
12	Newton-Cheh, C., Johnson, T., Gateva, V., Tobin, M. D., Bochud, M., Coin, L., ... & Papadakis, K. (2009). Genome-wide association study identifies eight loci associated with blood pressure. <i>Nature genetics</i> , 41(6), 666-676.	2008	Systolic and Diastolic blood pressure (SBP/DBP)	34,433	European
13	Shungin, D., Winkler, T. W., Croteau-Chonka, D. C., Ferreira, T., Locke, A. E., Mägi, R., ... & Workalemahu, T. (2015). New genetic loci link adipose and insulin biology to body fat distribution. <i>Nature</i> , 518(7538), 187-196.	2015	HIP, WHR, WC	≈ 210,088	European
14	Morris, A. P., Voight, B. F., Teslovich, T. M., Ferreira, T., Segre, A. V., Steinhorsdottir, V., ... & Prokopenko, I. (2012). Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. <i>Nature genetics</i> , 44(9), 981.	2012	T2D	12,171 cases and 56,862 controls	European
15	Walford, G. A., Gustafsson, S., Rybin, D., Stančáková, A., Chen, H., Liu, C. T., ... & Mägi, R. (2016). Genome-wide association study of the modified Stumvoll Insulin Sensitivity Index identifies BCL2 and FAM19A2 as novel insulin sensitivity loci. <i>Diabetes</i> , db160199.	2016	ISI	16,753	European
16	Teslovich, T. M., Musunuru, K., Smith, A. V., Edmondson, A. C., Stylianou, I. M., Koseki, M., ... & Johansen, C. T. (2010). Biological, clinical and population relevance of 95 loci for blood lipids. <i>Nature</i> , 466(7307), 707-713.	2010	TG, HDL-C, LDL-C, TC	Maximum sample size 100,184 for TC, 95,454 for LDL-C, 99,900 for HDL-C and 96,598 for TG	European
17	Locke, A. E., Kahali, B., Berndt, S. I., Justice, A. E., Pers, T. H., Day, F. R., ... & Croteau-Chonka, D. C. (2015). Genetic studies of body mass index yield new insights for obesity biology. <i>Nature</i> , 518(7538), 197-206.	2015	BMI	234,069	European
18	Shungin, D., Winkler, T. W., Croteau-Chonka, D. C., Ferreira, T., Locke, A. E., Mägi, R., ... & Workalemahu, T. (2015). New genetic loci link adipose and insulin biology to body fat distribution. <i>Nature</i> , 518(7538), 187-196.	2015	WHR, WC, HIP	≈ 210,088	European

Table S4. 1000G summary statistics imputation results

SNP	CHR	Locus name	Alleles (effect / other)	Effect (SE), p-value	N	P-value (imputed)	New lead variant (imputed)	P-value of the new lead variant	LD with new lead variant, R ²	Distance from lead variant, bp
HOMA-B										
rs560887	2	<i>G6PC2</i>	C/T	-0.046 (0.0033), 4.74×10 ⁻⁴⁶	75,173	4.74×10 ⁻⁴⁶	rs580670	2.35×10 ⁻⁴⁷	0.7009	12,973
rs11708067	3	<i>ADCY5</i>	A/G	-0.024 (0.0038), 2.50×10 ⁻¹⁰	75,227	2.50×10 ⁻¹⁰	-	-	-	-
rs10258074	7	<i>DGKB</i>	A/T	0.019 (0.0031), 2.55×10 ⁻¹⁰	75,202	2.04×10 ⁻⁰⁹	rs2191349	5.41×10 ⁻¹⁰	0.9881	93
rs3757840	7	<i>GCK</i>	G/T	0.02 (0.0033), 1.98×10 ⁻⁰⁹	64,352	1.98×10 ⁻⁰⁹	-	-	-	-
rs3802177	8	<i>SLC30A8</i>	G/A	-0.021 (0.0036), 2.55×10 ⁻⁰⁹	68,044	2.55×10 ⁻⁰⁹	rs35859536	9.48×10 ⁻¹⁰	0.9854	6,450
rs7034200	9	<i>GLIS3</i>	A/C	-0.019 (0.003), 2.96×10 ⁻¹⁰	74,669	2.96×10 ⁻¹⁰	rs57884925	2.85×10 ⁻¹⁰	0.9685	3,931
rs7903146	10	<i>TCF7L2</i>	C/T	0.03 (0.0034), 7.41×10 ⁻¹⁹	75,212	7.41×10 ⁻¹⁹	rs10659211	6.76×10 ⁻²²	0.9103	24,232
rs10830963	11	<i>MTNR1B</i>	C/G	0.039 (0.0038), 9.34×10 ⁻²⁵	68,612	2.73×10 ⁻¹⁵	rs10830956	5.23×10 ⁻²¹	0.7217	27,697
rs1552224	11	<i>ARAP1[STAR D10]</i>	C/A	0.025 (0.004), 4.28×10 ⁻¹⁰	75,207	4.28×10 ⁻¹⁰	rs11603349	5.82×10 ⁻¹¹	0.9313	27,596
rs174555	11	<i>FADS1/2/3</i>	T/C	-0.021 (0.0033), 8.97×10 ⁻¹¹	75,237	8.97×10 ⁻¹¹	-	-	-	-
rs5029909	20	<i>FOXA2</i>	C/T	-0.044 (0.0079), 2.70×10 ⁻⁰⁸	68,584	2.70×10 ⁻⁰⁸	-	-	-	-

Table S4. Continued

SNP	CHR	Locus name	Alleles (effect / other)	Effect (SE), p-value	N	P-value (imputed)	New lead variant (imputed)	P-value of the new lead variant	LD with new lead variant, R ²	Distance from lead variant, bp
HOMA-IR										
rs2605101	1	<i>LYPLAL1/SLC30A10</i>	A/T	0.019 (0.0034), 3.78×10^{-8}	75,238	3.46×10^{-7}	rs6669360	5.41×10^{-8}	0.5529	3,443
rs780093	2	<i>GCKR</i>	C/T	0.024 (0.0032), 1.06×10^{-13}	75,226	1.06×10^{-13}	rs11336847	3.08×10^{-14}	0.9796	6,390
rs10224545	7	<i>PER4</i>	T/C	-0.031 (0.0056), 2.60×10^{-8}	71,951	2.60×10^{-8}	-	-	-	-
rs4240624	8	<i>PPP1R3B</i>	A/G	-0.035 (0.0055), 2.73×10^{-10}	68,617	2.73×10^{-10}	-	-	-	-
rs2114912	12	<i>IGF1</i>	T/G	0.026 (0.0044), 3.08×10^{-9}	74,634	3.08×10^{-9}	-	-	-	-

Table S5. Established T2D loci with their effect, standard errors (SE), significance (P), sample size (N) and minor allele frequency (MAF) in HOMA-B/-IR GWIS.

rsID	LOCUS	EA	NEA	HOMA-B, effect (SE, P)	HOMA-IR, effect (SE, P)	N	MAF
rs10146997	<i>NRXN3</i>	G	A	0.0108 (0.004, 3.57e-03)	0.0128 (0.004, 9.87e-04)	75216	0.21
rs10203174	<i>THADA</i>	C	T	-0.0209 (0.005, 5.43e-05)	-0.0084 (0.005, 1.24e-01)	75198	0.1
rs10229583	<i>PAX4</i>	G	A	0.0013 (0.004, 7.15e-01)	-0.0032 (0.004, 3.94e-01)	75194	0.24
rs10401969	<i>CILP2</i>	C	T	-3e-04 (0.007, 9.66e-01)	0.0099 (0.007, 1.69e-01)	68635	0.07
rs10507349	<i>RNF6</i>	G	A	0.0045 (0.004, 2.08e-01)	-0.0024 (0.004, 5.33e-01)	75173	0.23
rs1061810	<i>HSD17B12</i>	A	C	0.0029 (0.003, 3.97e-01)	0.0059 (0.004, 1.05e-01)	75185	0.29
rs10758593	<i>GLIS3</i>	A	G	-0.0183 (0.003, 1.90e-09)	-0.0072 (0.003, 2.55e-02)	75203	0.42
rs10811661	<i>CDKN2A/B</i>	T	C	-0.0125 (0.004, 2.11e-03)	0.0034 (0.004, 4.39e-01)	68591	0.18
rs10830963	<i>MTNR1B</i>	G	C	-0.039 (0.004, 9.34e-25)	0.0184 (0.004, 4.40e-06)	68612	0.29
rs10842994	<i>KLHDC5</i>	C	T	-0.0025 (0.004, 5.15e-01)	7e-04 (0.004, 8.60e-01)	75225	0.21
rs10886471	<i>GRK5</i>	C	T	0.0051 (0.003, 1.05e-01)	-2e-04 (0.003, 9.43e-01)	75137	0.5
rs10923931	<i>NOTCH2</i>	T	G	-0.0053 (0.005, 2.81e-01)	1e-04 (0.005, 9.83e-01)	73038	0.11
rs11063069	<i>CCND2</i>	G	A	-0.0025 (0.004, 5.65e-01)	0.0037 (0.005, 4.08e-01)	75147	0.22
rs1111875	<i>HHEX/IDE</i>	C	T	-0.0066 (0.003, 2.88e-02)	-0.003 (0.003, 3.51e-01)	75236	0.43
rs11123406	<i>BCL2L11</i>	T	C	2e-04 (0.003, 9.60e-01)	7e-04 (0.003, 8.40e-01)	75235	0.37
rs1116357	<i>CCDC85A</i>	G	A	0.0029 (0.003, 3.43e-01)	0.0045 (0.003, 1.60e-01)	75228	0.49
rs11257655	<i>CDC123/CAMK1D</i>	T	C	-0.0067 (0.004, 7.83e-02)	0.0029 (0.004, 4.67e-01)	68554	0.22
rs11603334	<i>ARAP1</i>	G	A	-0.0246 (0.004, 8.24e-10)	-0.0074 (0.004, 8.08e-02)	75206	0.16
rs11634397	<i>ZFAND6</i>	G	A	-0.0015 (0.003, 6.47e-01)	-6e-04 (0.004, 8.59e-01)	75237	0.36
rs11708067	<i>ADCY5</i>	A	G	-0.0239 (0.004, 2.50e-10)	-0.0072 (0.004, 7.12e-02)	75227	0.21
rs1182443	<i>MNX1</i>	G	A	-0.012 (0.004, 2.85e-03)	-0.0019 (0.004, 6.55e-01)	74533	0.21
rs12242953	<i>VPS26A</i>	G	A	-0.0016 (0.006, 8.03e-01)	-0.0045 (0.007, 5.03e-01)	75224	0.07
rs12427353	<i>HNF1A(TCF1)</i>	G	A	-0.0048 (0.004, 2.14e-01)	-0.0053 (0.004, 1.90e-01)	75196	0.21
rs12454712	<i>BCL2</i>	T	C	0.0171 (0.006, 2.00e-03)	0.0157 (0.006, 8.15e-03)	47310	0.36
rs12497268	<i>PSMD6</i>	G	C	-0.005 (0.004, 2.08e-01)	0.0056 (0.004, 1.84e-01)	75220	0.19
rs12571751	<i>ZMIZ1</i>	A	G	6e-04 (0.003, 8.38e-01)	4e-04 (0.003, 8.95e-01)	75228	0.47
rs12681990	<i>KCNU1</i>	C	T	0.0052 (0.004, 2.28e-01)	0.011 (0.005, 1.50e-02)	74652	0.17
rs12899811	<i>PRC1</i>	G	A	-0.0016 (0.003, 6.32e-01)	0.0043 (0.003, 2.18e-01)	75232	0.31
rs12970134	<i>MC4R</i>	A	G	0.0078 (0.003, 2.46e-02)	0.0111 (0.004, 2.41e-03)	75198	0.25
rs13233731	<i>KLF14</i>	G	A	0.0037 (0.003, 2.23e-01)	0.0083 (0.003, 9.03e-03)	75215	0.48
rs13389219	<i>GRB14</i>	A	C	0.0109 (0.003, 4.41e-04)	0.0135 (0.003, 3.67e-05)	75225	0.41
rs1359790	<i>SPRY2</i>	G	A	-0.0135 (0.003, 7.09e-05)	-0.0095 (0.004, 8.14e-03)	75098	0.27
rs1421085	<i>FTO</i>	C	T	0.0145 (0.003, 3.56e-06)	0.0174 (0.003, 1.38e-07)	75230	0.42
rs1496653	<i>UBE2E2</i>	A	G	-0.0116 (0.004, 1.21e-03)	-0.0082 (0.004, 3.05e-02)	75149	0.22
rs163184	<i>KCNQ1</i>	G	T	-0.0074 (0.003, 2.15e-02)	0.0021 (0.003, 5.35e-01)	75153	0.5
rs16927668	<i>PTPRD</i>	T	C	-0.0032 (0.004, 3.95e-01)	-0.004 (0.004, 3.13e-01)	75216	0.21
rs17106184	<i>FAF1</i>	G	A	-0.0076 (0.005, 1.55e-01)	-5e-04 (0.006, 9.26e-01)	75236	0.09
rs17168486	<i>DGKB</i>	T	C	-0.018 (0.004, 1.08e-05)	0.0089 (0.004, 3.82e-02)	71882	0.18
rs1727313	<i>MPHOSPH9</i>	C	T	0.0026 (0.004, 4.84e-01)	0.0037 (0.004, 3.36e-01)	75227	0.21

rs17301514	<i>ST64GAL1</i>	A	G	-0.0065 (0.006, 3.01e-01)	-0.0014 (0.007, 8.37e-01)	56174	0.12
rs17791513	<i>TLE4(CHCHD9)</i>	A	G	-0.0042 (0.006, 4.78e-01)	-0.0016 (0.006, 7.94e-01)	64543	0.07
rs17867832	<i>GCC1</i>	T	G	-0.0064 (0.005, 2.41e-01)	-0.0084 (0.006, 1.44e-01)	68915	0.09
rs1799884	<i>GCK</i>	T	C	-0.0236 (0.004, 2.32e-08)	0.0208 (0.004, 3.30e-06)	68074	0.16
rs1801282	<i>PPARG</i>	C	G	0.0158 (0.005, 5.23e-04)	0.0186 (0.005, 1.09e-04)	75233	0.12
rs1861612	<i>DNER</i>	T	C	2e-04 (0.003, 9.60e-01)	0.0044 (0.003, 1.69e-01)	75238	0.45
rs2007084	<i>AP3S2</i>	G	A	-0.0021 (0.007, 7.57e-01)	-4e-04 (0.007, 9.52e-01)	60850	0.09
rs2023681	<i>MTMR3/HORMAD2</i>	G	A	-0.001 (0.005, 8.54e-01)	0.007 (0.006, 2.22e-01)	75239	0.09
rs2050188	<i>HLA-DRB5</i>	T	C	0.0065 (0.003, 5.07e-02)	0.0074 (0.003, 3.39e-02)	75159	0.36
rs2244020	<i>HLA-B</i>	G	A	-0.0029 (0.003, 3.70e-01)	0.0019 (0.003, 5.80e-01)	72272	0.38
rs2261181	<i>HMG A2</i>	T	C	-0.0041 (0.005, 4.25e-01)	0.0011 (0.005, 8.39e-01)	75234	0.09
rs2292626	<i>PLEKHA1</i>	C	T	0.0016 (0.003, 6.07e-01)	-0.0023 (0.003, 4.66e-01)	75238	0.49
rs2296172	<i>MACF1</i>	G	A	0.0019 (0.004, 6.04e-01)	0.0075 (0.004, 5.16e-02)	74891	0.21
rs2334499	<i>DUSP8</i>	T	C	-0.0039 (0.003, 2.05e-01)	-0.0032 (0.003, 3.36e-01)	75192	0.41
rs243088	<i>BCL11A</i>	T	A	-9e-04 (0.003, 7.78e-01)	0.0039 (0.003, 2.32e-01)	74640	0.46
rs2447090	<i>SRR</i>	A	G	-0.0015 (0.003, 6.42e-01)	-0.0053 (0.003, 1.26e-01)	64307	0.38
rs2796441	<i>TLE1</i>	G	A	0.0036 (0.003, 2.75e-01)	0.0029 (0.004, 4.12e-01)	75210	0.39
rs2867125	<i>TMEM18</i>	C	T	0.0063 (0.004, 1.12e-01)	0.0127 (0.004, 2.53e-03)	75232	0.17
rs2925979	<i>CMIP</i>	T	C	1e-04 (0.003, 9.69e-01)	0.0042 (0.004, 2.41e-01)	75189	0.3
rs2943640	<i>IRS1</i>	C	A	0.0127 (0.003, 4.74e-05)	0.0153 (0.003, 3.78e-06)	75218	0.37
rs3132524	<i>POU5F1/TCF19</i>	G	A	0.0026 (0.003, 4.56e-01)	0.0031 (0.004, 3.95e-01)	75230	0.25
rs329122	<i>PHF15</i>	A	G	-0.0057 (0.003, 7.12e-02)	-0.005 (0.003, 1.31e-01)	75233	0.42
rs340874	<i>PROX1</i>	C	T	-0.0123 (0.003, 7.52e-05)	-0.002 (0.003, 5.47e-01)	75167	0.47
rs3802177	<i>SLC30A8</i>	G	A	-0.0212 (0.004, 2.55e-09)	7e-04 (0.004, 8.46e-01)	68044	0.31
rs3812547	<i>GPSM1</i>	A	G	-0.0152 (0.004, 7.06e-04)	-0.0036 (0.005, 4.45e-01)	46507	0.36
rs4299828	<i>ZFAND3</i>	A	G	6e-04 (0.004, 8.65e-01)	-6e-04 (0.004, 8.89e-01)	75230	0.2
rs4430796	<i>HNF1B(TCF2)</i>	G	A	-0.0093 (0.004, 2.06e-02)	-0.009 (0.004, 3.49e-02)	54542	0.47
rs4458523	<i>WFS1</i>	G	T	-0.0049 (0.003, 1.09e-01)	1e-04 (0.003, 9.64e-01)	75192	0.41
rs4502156	<i>C2CD4A</i>	T	C	-0.0086 (0.003, 5.88e-03)	0.0054 (0.003, 1.01e-01)	75192	0.43
rs459193	<i>ANKRD55</i>	G	A	0.009 (0.003, 9.41e-03)	0.0185 (0.004, 4.76e-07)	75230	0.25
rs4865796	<i>ARL15</i>	A	G	0.0082 (0.003, 1.16e-02)	0.0112 (0.003, 1.14e-03)	75232	0.32
rs516946	<i>ANK1</i>	C	T	-0.0115 (0.003, 9.63e-04)	-0.0074 (0.004, 4.28e-02)	75161	0.25
rs5215	<i>KCNJ11</i>	C	T	0.0012 (0.003, 7.04e-01)	-0.005 (0.003, 1.24e-01)	75155	0.39
rs576674	<i>KL</i>	G	A	-0.0147 (0.005, 1.48e-03)	-0.0028 (0.005, 5.68e-01)	68623	0.16
rs6017317	<i>HNF4A</i>	G	T	-0.011 (0.004, 5.01e-03)	-0.01 (0.004, 1.53e-02)	75224	0.17
rs6723108	<i>TMEM163</i>	T	G	-0.0076 (0.003, 1.49e-02)	-0.0114 (0.003, 5.39e-04)	75045	0.45
rs6795735	<i>ADAMTS9</i>	C	T	-0.0026 (0.003, 4.00e-01)	0.0022 (0.003, 5.05e-01)	75229	0.43
rs6808574	<i>LPP</i>	C	T	-0.0034 (0.003, 2.69e-01)	0.0044 (0.003, 1.78e-01)	75205	0.4
rs6813195	<i>TMEM154</i>	C	T	-0.0075 (0.004, 3.76e-02)	-0.0119 (0.004, 1.82e-03)	68582	0.29
rs6878122	<i>ZBED3</i>	G	A	-0.0028 (0.004, 4.52e-01)	0.0057 (0.004, 1.47e-01)	67346	0.27
rs7177055	<i>HMG20A</i>	A	G	-0.0031 (0.003, 3.49e-01)	0.0051 (0.004, 1.48e-01)	75233	0.29
rs7202877	<i>BCAR1</i>	T	G	-0.0067 (0.005, 1.75e-01)	0.0035 (0.005, 5.02e-01)	75181	0.1
rs7258890	<i>GIPR</i>	C	T	-0.0027 (0.004, 4.71e-01)	6e-04 (0.004, 8.81e-01)	75223	0.29
rs731839	<i>PEPD</i>	G	A	0.0118 (0.003, 2.79e-04)	0.016 (0.003, 3.30e-06)	75142	0.33
rs7403531	<i>RASGRP1</i>	T	C	-0.0053 (0.004, 1.52e-01)	0.0019 (0.004, 6.21e-01)	75215	0.23
rs7569522	<i>RBMS1</i>	A	G	5e-04 (0.003, 8.77e-01)	0.0053 (0.003, 1.17e-01)	68569	0.45

rs7651090	<i>IGF2BP2</i>	G	A	-0.011 (0.003, 9.68e-04)	-0.0015 (0.004, 6.78e-01)	68594	0.31
rs7674212	<i>CISD2</i>	G	T	-0.0047 (0.003, 1.29e-01)	-9e-04 (0.003, 7.76e-01)	75187	0.42
rs780094	<i>GCKR</i>	C	T	8e-04 (0.003, 7.86e-01)	0.0238 (0.003, 1.47e-13)	75208	0.39
rs7845219	<i>TP53INP1</i>	T	C	-0.0076 (0.003, 1.15e-02)	-4e-04 (0.003, 9.06e-01)	75229	0.5
rs7903146	<i>TCF7L2</i>	T	C	-0.0303 (0.003, 7.41e-19)	-0.0134 (0.004, 1.93e-04)	75212	0.3
rs791595	<i>MIR129-LEP</i>	A	G	-0.0025 (0.004, 5.34e-01)	0.0033 (0.004, 4.47e-01)	68626	0.18
rs7955901	<i>TSPAN8/LGR5</i>	C	T	-0.0055 (0.003, 7.04e-02)	-0.0012 (0.003, 7.02e-01)	75232	0.45
rs7985179	<i>MIR17HG</i>	T	A	0.0079 (0.004, 2.41e-02)	0.0114 (0.004, 2.18e-03)	75239	0.25
rs8090011	<i>LAMA1</i>	G	C	-0.0024 (0.003, 4.70e-01)	-6e-04 (0.003, 8.58e-01)	67134	0.37
rs825476	<i>CCDC92</i>	T	C	0.006 (0.003, 4.49e-02)	0.0065 (0.003, 4.00e-02)	75233	0.42
rs849135	<i>JAZF1</i>	G	A	-0.005 (0.003, 9.63e-02)	-0.0028 (0.003, 3.83e-01)	75225	0.49
rs9309245	<i>ASB3</i>	G	C	0.001 (0.003, 7.47e-01)	-4e-04 (0.003, 9.14e-01)	75236	0.34
rs9368222	<i>CDKAL1</i>	A	C	-0.0156 (0.003, 2.98e-06)	-0.0064 (0.004, 7.00e-02)	75205	0.28
rs9502570	<i>SSR1/RREB1</i>	A	G	0.0116 (0.004, 1.20e-03)	0.0023 (0.004, 5.45e-01)	75168	0.26
rs9648716	<i>BRAF</i>	T	A	-0.0103 (0.005, 3.60e-02)	-0.0072 (0.005, 1.62e-01)	75214	0.11
rs9674498	<i>GLP2R</i>	G	T	0.0038 (0.003, 2.41e-01)	0.0076 (0.003, 2.64e-02)	75226	0.31
rs9940149	<i>ITFG3</i>	G	A	-0.0036 (0.004, 3.84e-01)	-2e-04 (0.004, 9.67e-01)	68628	0.17

Table S6. Established FG/FI loci with their effect, standard errors (SE), significance (P), sample size (N) and minor allele frequency (MAF) in HOMA-B/-IR GWIS.

rsID	LOCUS	EA	NEA	Associated phenotype	HOMA-B, effect (SE, P)	HOMA-IR, effect (SE, P)	N	MAF
rs10195252	<i>COBLL1/GRB14</i>	T	C	FI	0.0106 (0.003, 5.86e-04)	0.0135 (0.003, 3.19e-05)	75199	0.41
rs10747083	<i>P2RX2</i>	A	G	FG	-0.0062 (0.004, 7.86e-02)	0.0046 (0.004, 2.22e-01)	74820	0.33
rs10758593	<i>GLIS3</i>	A	G	FG	-0.0183 (0.003, 1.90e-09)	-0.0072 (0.003, 2.55e-02)	75203	0.42
rs10811661	<i>CDKN2A/B</i>	T	C	FG	-0.0125 (0.004, 2.11e-03)	0.0034 (0.004, 4.39e-01)	68591	0.18
rs10830963	<i>MTNR1B</i>	G	C	FG	-0.039 (0.004, 9.34e-25)	0.0184 (0.004, 4.40e-06)	68612	0.29
rs10885122	<i>ADRA2A</i>	G	T	FG	-0.0245 (0.005, 4.10e-07)	-0.0034 (0.005, 5.10e-01)	75220	0.11
	<i>FAM148B/VPS13C/</i>							
rs11071657	<i>C2CD4A/B</i>	A	G	FG	-0.0067 (0.003, 4.41e-02)	0.0039 (0.004, 2.63e-01)	68605	0.37
rs11603334	<i>ARAP1</i>	G	A	FG	-0.0246 (0.004, 8.24e-10)	-0.0074 (0.004, 8.08e-02)	75206	0.16
rs11605924	<i>CRY2</i>	A	C	FG	-0.0135 (0.003, 7.21e-06)	0.0037 (0.003, 2.42e-01)	75188	0.48
rs11619319	<i>PDX1</i>	G	A	FG	-0.0165 (0.004, 6.13e-06)	-0.002 (0.004, 6.07e-01)	75224	0.22
rs1167800	<i>HIP1</i>	A	G	FI	0.0148 (0.003, 1.79e-05)	0.0162 (0.004, 8.01e-06)	62225	0.45
rs11708067	<i>ADCY5</i>	A	G	FG	-0.0239 (0.004, 2.50e-10)	-0.0072 (0.004, 7.12e-02)	75227	0.21
rs11715915	<i>AMT</i>	C	T	FG	0.0012 (0.003, 7.28e-01)	0.0109 (0.004, 1.92e-03)	73791	0.31
rs11920090	<i>SLC2A2</i>	T	A	FG	-0.0174 (0.004, 8.07e-05)	0.0017 (0.005, 7.10e-01)	75238	0.13
rs13179048	<i>PCSK1</i>	C	A	FG	-0.0088 (0.003, 6.77e-03)	0.0067 (0.003, 5.21e-02)	75214	0.31
rs1371614	<i>DPYSL5</i>	T	C	FG	-0.0064 (0.004, 7.06e-02)	0.0047 (0.004, 2.12e-01)	75135	0.25
rs1421085	<i>FTO</i>	C	T	FI	0.0145 (0.003, 3.56e-06)	0.0174 (0.003, 1.38e-07)	75230	0.42
rs1483121	<i>OR4S1</i>	G	A	FG	-0.0097 (0.005, 4.10e-02)	0.0061 (0.005, 2.31e-01)	62728	0.14
rs1530559	<i>YSK4</i>	A	G	FI	0.01 (0.003, 4.24e-03)	0.0143 (0.004, 9.81e-05)	75236	0.46
rs17168486	<i>DGKB</i>	T	C	FG	-0.018 (0.004, 1.08e-05)	0.0089 (0.004, 3.82e-02)	71882	0.18
rs174550	<i>FADS1</i>	T	C	FG	-0.0197 (0.003, 4.67e-10)	-0.0051 (0.003, 1.26e-01)	75237	0.34
rs1799884	<i>GCK</i>	T	C	FG	-0.0236 (0.004, 2.32e-08)	0.0208 (0.004, 3.30e-06)	68074	0.16
rs2657879	<i>GLS2</i>	G	A	FG	-0.0029 (0.004, 4.81e-01)	0.0056 (0.004, 2.05e-01)	68622	0.18
rs2745353	<i>RSP03</i>	T	C	FI	0.0154 (0.003, 4.53e-07)	0.0136 (0.003, 2.41e-05)	75223	0.49
rs2785980	<i>LYPLAL1</i>	T	C	FI	0.012 (0.003, 1.82e-04)	0.0162 (0.003, 1.77e-06)	75231	0.33
rs2943640	<i>IRS1</i>	C	A	FI	0.0127 (0.003, 4.74e-05)	0.0153 (0.003, 3.78e-06)	75218	0.37
rs340874	<i>PROX1</i>	C	T	FG	-0.0123 (0.003, 7.52e-05)	-0.002 (0.003, 5.47e-01)	75167	0.47
rs35767	<i>IGF1</i>	G	A	FI	0.0187 (0.004, 1.09e-05)	0.0226 (0.005, 5.57e-07)	68021	0.16
rs3783347	<i>WARS</i>	G	T	FG	-0.0073 (0.004, 6.24e-02)	0.0045 (0.004, 2.77e-01)	75170	0.21
rs3802177	<i>SLC30A8</i>	G	A	FG	-0.0212 (0.004, 2.55e-09)	7e-04 (0.004, 8.46e-01)	68044	0.31
rs3829109	<i>DNLZ</i>	G	A	FG	-0.0108 (0.005, 2.06e-02)	4e-04 (0.005, 9.37e-01)	59012	0.29
rs4646949	<i>C6orf107/UHFR1BP1</i>	T	G	FI	0.0122 (0.003, 4.77e-04)	0.0161 (0.004, 1.14e-05)	75217	0.26
rs4691380	<i>PDGFC</i>	C	T	FI	0.0109 (0.003, 7.62e-04)	0.0139 (0.003, 4.63e-05)	75234	0.33
rs4841132	<i>PPP1R3B</i>	A	G	FG/FI	0.0165 (0.005, 1.37e-03)	0.0342 (0.005, 3.22e-10)	75219	0.09
rs4865796	<i>ARL15</i>	A	G	FI	0.0082 (0.003, 1.16e-02)	0.0112 (0.003, 1.14e-03)	75232	0.32
rs560887	<i>G6PC2</i>	C	T	FG	-0.0465 (0.003, 4.74e-46)	0.0047 (0.003, 1.74e-01)	75173	0.3
rs576674	<i>KL</i>	G	A	FG	-0.0147 (0.005, 1.48e-03)	-0.0028 (0.005, 5.68e-01)	68623	0.16
rs6048205	<i>FOXA2</i>	A	G	FG	-0.0398 (0.007, 3.12e-08)	-0.0077 (0.008, 3.10e-01)	70262	0.06

rs6072275	<i>TOP1</i>	A	G	FG	-0.0071 (0.004, 8.19e-02)	0.0078 (0.004, 6.88e-02)	75235	0.16
rs6450057	<i>PELO</i>	C	T	FI	0.0089 (0.003, 3.61e-03)	0.0089 (0.003, 5.90e-03)	75204	0.44
rs6943153	<i>GRB10</i>	T	C	FG	0.0043 (0.003, 1.80e-01)	0.0137 (0.003, 4.93e-05)	75221	0.32
rs7258890	<i>GIPR</i>	C	T	FG	-0.0027 (0.004, 4.71e-01)	6e-04 (0.004, 8.81e-01)	75223	0.29
rs731839	<i>PEPD</i>	G	A	FI	0.0118 (0.003, 2.79e-04)	0.016 (0.003, 3.30e-06)	75142	0.33
rs7651090	<i>IGF2BP2</i>	G	A	FG	-0.011 (0.003, 9.68e-04)	-0.0015 (0.004, 6.78e-01)	68594	0.31
rs780094	<i>GCKR</i>	C	T	FG/FI	8e-04 (0.003, 7.86e-01)	0.0238 (0.003, 1.47e-13)	75208	0.39
rs7903146	<i>TCF7L2</i>	T	C	FG	-0.0303 (0.003, 7.41e-19)	-0.0134 (0.004, 1.93e-04)	75212	0.3
rs7944584	<i>MADD</i>	A	T	FG	-0.0148 (0.003, 2.20e-05)	0.0032 (0.004, 3.82e-01)	75201	0.28
rs9368222	<i>CDKAL1</i>	A	C	FG	-0.0156 (0.003, 2.98e-06)	-0.0064 (0.004, 7.00e-02)	75205	0.28
rs9502570	<i>SSR1/RREB1</i>	A	G	FG	0.0116 (0.004, 1.20e-03)	0.0023 (0.004, 5.45e-01)	75168	0.26
rs9884482	<i>TET2</i>	C	T	FI	0.013 (0.003, 4.61e-05)	0.0141 (0.003, 2.84e-05)	71820	0.39

Table S7. Established HbA1c loci with their effect, standard errors (SE), significance (P), sample size (N) and minor allele frequency (MAF) in HOMA-B/-IR GWIS.

rsID	LOCUS	EA	NEA	Classification	HOMA-B, effect (SE, P)	HOMA-IR, effect (SE, P)	N	MAF
rs1046896	<i>FN3KRP</i>	T	C	Unclassified	9e-04 (0.003, 7.83e-01)	0.0039 (0.003, 2.64e-01)	75225	0.32
rs10774625	<i>ATXN2</i>	G	A	Erythrocytic	-0.0038 (0.003, 2.17e-01)	-0.0023 (0.003, 4.93e-01)	75185	0.48
rs10823343	<i>HK1</i>	A	G	Unclassified	-0.0067 (0.004, 8.17e-02)	-0.0049 (0.004, 2.27e-01)	68494	0.26
rs10830963	<i>MTNR1B</i>	G	C	Glycemic	-0.039 (0.004, 9.34e-25)	0.0184 (0.004, 4.40e-06)	68612	0.29
rs11086054	<i>MYO9B</i>	A	T	Unclassified	0.003 (0.003, 3.81e-01)	0.0051 (0.004, 1.64e-01)	68574	0.31
rs11224302	<i>CNTN5</i>	C	T	Erythrocytic	0.001 (0.005, 8.42e-01)	-0.0053 (0.005, 3.28e-01)	75221	0.11
rs11248914	<i>ITFG3</i>	T	C	Erythrocytic	-7e-04 (0.003, 8.20e-01)	0.0013 (0.003, 6.94e-01)	75218	0.34
rs11558471	<i>SLC30A8</i>	A	G	Glycemic	-0.0197 (0.003, 3.12e-09)	0.001 (0.004, 7.84e-01)	74470	0.31
rs11603334	<i>ARAP1</i>	G	A	Glycemic	-0.0246 (0.004, 8.24e-10)	-0.0074 (0.004, 8.08e-02)	75206	0.16
rs11619319	<i>PDX1</i>	G	A	Glycemic	-0.0165 (0.004, 6.13e-06)	-0.002 (0.004, 6.07e-01)	75224	0.22
rs11708067	<i>ADCY5</i>	A	G	Glycemic	-0.0239 (0.004, 2.50e-10)	-0.0072 (0.004, 7.12e-02)	75227	0.21
rs11964178	<i>C6orf183</i>	A	G	Erythrocytic	0.005 (0.003, 1.02e-01)	0.0055 (0.003, 8.71e-02)	75210	0.43
rs12132919	<i>TMEM79</i>	A	C	Erythrocytic	0.0021 (0.003, 5.42e-01)	-6e-04 (0.004, 8.73e-01)	75194	0.29
rs12621844	<i>FOXN2</i>	T	C	Unclassified	0.0036 (0.003, 2.45e-01)	0.0076 (0.003, 2.16e-02)	75228	0.39
rs13134327	<i>FREM3</i>	A	G	Glycemic	-0.0079 (0.003, 1.54e-02)	-0.0021 (0.003, 5.48e-01)	75206	0.32
rs13387347	<i>G6PC2</i>	T	C	Glycemic	-0.012 (0.003, 1.35e-04)	-0.002 (0.003, 5.41e-01)	74615	0.45
rs1467311	<i>KLF4</i>	G	A	Unclassified	0.0022 (0.003, 4.90e-01)	-0.001 (0.003, 7.62e-01)	75221	0.34
rs1558902	<i>FTO</i>	A	T	Unclassified	0.0145 (0.003, 3.26e-06)	0.0173 (0.003, 1.49e-07)	75230	0.42
rs17256082	<i>SCRN3</i>	C	T	Unclassified	-0.0018 (0.003, 5.83e-01)	-0.0018 (0.003, 6.00e-01)	75180	0.37
rs174577	<i>FADS2</i>	C	A	Glycemic	-0.019 (0.003, 2.58e-09)	-0.0046 (0.003, 1.71e-01)	75226	0.34
rs17509001	<i>ATAD2B</i>	C	T	Unclassified	0.0071 (0.005, 1.21e-01)	0.0099 (0.005, 3.95e-02)	75234	0.13
rs17533903	<i>MYO9B</i>	A	G	Erythrocytic	0.0032 (0.004, 4.47e-01)	0.003 (0.004, 4.98e-01)	70516	0.22
rs17747324	<i>TCF7L2</i>	C	T	Glycemic	-0.0328 (0.004, 2.71e-17)	-0.0138 (0.004, 7.50e-04)	75196	0.23
rs1800562	<i>HFE</i>	G	A	Erythrocytic	1e-04 (0.007, 9.89e-01)	-0.0025 (0.007, 7.26e-01)	68618	0.05
rs198846	<i>HFE</i>	G	A	Erythrocytic	0.0024 (0.004, 5.91e-01)	0.0033 (0.005, 4.85e-01)	75197	0.14
rs2073285	<i>TMC6</i>	C	T	Unclassified	-0.0019 (0.005, 6.86e-01)	-0.0021 (0.005, 6.64e-01)	46186	0.2
rs2110073	<i>PHB2</i>	T	C	Unclassified	0.0123 (0.005, 2.06e-02)	0.0126 (0.006, 2.48e-02)	71133	0.09
rs2191349	<i>DGKB</i>	T	G	Glycemic	-0.0187 (0.003, 5.41e-10)	0.002 (0.003, 5.39e-01)	75224	0.47
rs2237896	<i>KCNQ1</i>	G	A	Glycemic	-0.0144 (0.008, 5.69e-02)	-0.0057 (0.008, 4.79e-01)	68615	0.05
rs2375278	<i>SYF2</i>	A	G	Unclassified	-0.0092 (0.004, 3.65e-02)	-0.0076 (0.005, 9.83e-02)	61698	0.17
rs2383208	<i>MTAP</i>	A	G	Glycemic	-0.0145 (0.004, 2.22e-04)	0.002 (0.004, 6.28e-01)	75164	0.18
rs2408955	<i>SENP1</i>	T	G	Erythrocytic	-0.0038 (0.003, 2.05e-01)	-0.0032 (0.003, 3.09e-01)	74663	0.48
rs267738	<i>CERS2</i>	T	G	Unclassified	-0.0134 (0.004, 3.35e-04)	-0.0067 (0.004, 8.88e-02)	73633	0.21
rs282587	<i>ATP11A</i>	G	A	Unclassified	-0.0036 (0.005, 4.40e-01)	7e-04 (0.005, 8.92e-01)	74667	0.13
rs3782123	<i>BET1L</i>	C	A	Unclassified	7e-04 (0.004, 8.47e-01)	0.0043 (0.004, 2.61e-01)	70242	0.31
rs3824065	<i>GCK</i>	C	T	Glycemic	-0.0143 (0.003, 9.94e-06)	0.0102 (0.003, 2.82e-03)	75053	0.45
rs4607517	<i>GCK</i>	A	G	Glycemic	-0.0242 (0.004, 4.07e-09)	0.0205 (0.004, 2.07e-06)	74674	0.17
rs4737009	<i>ANK1</i>	A	G	Erythrocytic	-0.0087 (0.004, 2.08e-02)	-0.0039 (0.004, 3.25e-01)	75215	0.24
rs4745982	<i>HK1</i>	T	G	Erythrocytic	0.0103 (0.011, 3.57e-01)	0.0026 (0.012, 8.24e-01)	45217	0.08

rs4783565	<i>CDH3</i>	A	G	Erythrocytic	-0.0067 (0.004, 5.96e-02)	-0.0057 (0.004, 1.33e-01)	75158	0.28
rs4820268	<i>TMPRSS6</i>	G	A	Erythrocytic	0.0042 (0.003, 1.89e-01)	0.0069 (0.003, 4.25e-02)	68613	0.44
rs4894799	<i>FNDC3B</i>	A	G	Unclassified	0.0079 (0.003, 1.09e-02)	0.0098 (0.003, 2.97e-03)	75232	0.37
rs560887	<i>G6PC2</i>	C	T	Glycemic	-0.0465 (0.003, 4.74e-46)	0.0047 (0.003, 1.74e-01)	75173	0.3
rs576674	<i>KL</i>	G	A	Glycemic	-0.0147 (0.005, 1.48e-03)	-0.0028 (0.005, 5.68e-01)	68623	0.16
rs579459	<i>ABO</i>	C	T	Glycemic	-0.0045 (0.004, 2.19e-01)	0.0019 (0.004, 6.27e-01)	75225	0.22
rs592423	<i>CITED2</i>	A	C	Erythrocytic	0.0032 (0.003, 3.10e-01)	0.0067 (0.003, 4.40e-02)	68554	0.45
rs6474359	<i>ANK1</i>	T	C	Unclassified	0.0036 (0.01, 7.06e-01)	-0.0024 (0.01, 8.09e-01)	63710	0.03
rs6980507	<i>SLC20A2</i>	A	G	Erythrocytic	-8e-04 (0.003, 7.93e-01)	-0.0017 (0.003, 6.06e-01)	68628	0.39
rs7040409	<i>C9orf47</i>	C	G	Erythrocytic	0.0039 (0.007, 5.65e-01)	6e-04 (0.007, 9.33e-01)	68611	0.06
rs7616006	<i>SYN2</i>	A	G	Erythrocytic	0.0013 (0.003, 6.76e-01)	0.0016 (0.003, 6.29e-01)	75207	0.43
rs7756992	<i>CDKAL1</i>	G	A	Glycemic	-0.0151 (0.003, 5.03e-06)	-0.0063 (0.003, 7.30e-02)	75227	0.28
rs8192675	<i>SLC2A2</i>	T	C	Glycemic	-0.0134 (0.003, 5.51e-05)	-3e-04 (0.003, 9.28e-01)	75239	0.3
rs837763	<i>CDT1</i>	T	C	Erythrocytic	-0.0051 (0.004, 1.58e-01)	-0.0037 (0.004, 3.33e-01)	55770	0.44
rs857691	<i>SPTA1</i>	T	C	Erythrocytic	0.0014 (0.003, 6.85e-01)	0.002 (0.004, 5.71e-01)	75226	0.26
rs9604573	<i>GAS6</i>	T	C	Unclassified	0.0113 (0.004, 2.05e-03)	0.0084 (0.004, 2.99e-02)	68889	0.26
rs9818758	<i>USP4</i>	A	G	Unclassified	0.0012 (0.004, 7.54e-01)	-0.0073 (0.004, 6.99e-02)	75235	0.19
rs9914988	<i>ERAL1</i>	A	G	Erythrocytic	0 (0.004, 9.93e-01)	0.0034 (0.004, 3.93e-01)	75213	0.19

Table S8. Genetic correlations (r_g) between derived HOMA-B and HOMA-IR and 13 glycaemic, 17 cardiometabolic traits, 5 inflammation markers, and T2D, including their standard errors (SEs), z-statistics and p-values (p indicates p-value, yielded by LD Score regression, p_{fdr} indicates p-value, obtained after correction for multiple testing). Asterisk (*) indicates adjustment for BMI in primary GWAS meta-analysis. Table also reports SNP-heritability (h^2) and LD Score intercept (Intercept) for the phenotypes with their corresponding SEs.

T2D	T2D	HOMA-B					HOMA-IR					SNP- h^2			
		Genetic Correlation					Genetic Correlation					h^2	se	Intercept	se
		r_g	se	z	p	p_{fdr}	r_g	se	z	p	p_{fdr}				
Glycaemic Traits	Fasting Glucose (FG)	-0.32	0.14	-2.34	0.02	0.05	0.49	0.08	6.33	2.45×10^{-10}	1.37×10^{-9}	0.09	0.02	1.02	0.01
	Fasting Insulin (FI)	0.80	0.04	18.12	2.40×10^{-73}	8.77×10^{-72}	0.98	0.005	202.87	<0.001	<0.001	0.06	0.01	1.04	0.01
	HbA1c	-0.02	0.13	-0.16	0.87	0.93	0.28	0.11	2.61	8.9×10^{-3}	0.024	0.06	0.01	1.00	0.01
	Fasting Proinsulin (FPI)	0.03	0.17	0.16	0.87	0.93	0.22	0.12	1.89	0.06	0.12	0.20	0.09	0.98	0.01
	Insulin Sensitivity Index (ISI)	-0.90	0.19	-4.67	2.97×10^{-6}	1.20×10^{-5}	-1.04	0.18	-5.83	5.56×10^{-9}	2.71×10^{-8}	0.10	0.03	0.99	0.01
	Insulin Sensitivity Index (ISI)*	-0.60	0.16	-3.82	1.00×10^{-4}	3.32×10^{-4}	-0.63	0.13	-4.76	1.91×10^{-6}	8.18×10^{-6}	0.12	0.03	0.98	0.01
	Disposition Index (DI)	0.26	0.24	1.07	0.28	0.45	-0.26	0.25	-1.04	0.30	0.45	0.12	0.09	1.00	0.01
	Corrected Insulin Response (CIR) adjusted for Insulin Sensitivity Index (ISI)	0.56	0.46	1.24	0.22	0.37	0.04	0.29	0.14	0.89	0.93	0.07	0.10	1.01	0.01
	Corrected Insulin Response (CIR)	0.53	0.26	2.04	0.04	0.09	0.15	0.22	0.68	0.50	0.61	0.13	0.09	1.00	0.01
	Incr30	0.55	0.35	1.56	0.12	0.23	0.56	0.36	1.54	0.12	0.23	0.10	0.10	1.01	0.01
	AUC for insulin	0.98	1.32	0.74	0.46	0.60	0.83	1.13	0.73	0.47	0.60	0.05	0.11	1.01	0.01
	Ins30*	0.97	0.80	1.21	0.23	0.38	0.57	0.54	1.06	0.29	0.45	0.06	0.09	1.01	0.01
	2 hour Glucose*	0.05	0.15	0.32	0.75	0.84	0.06	0.14	0.41	0.69	0.78	0.11	0.03	0.99	0.01

Table S8. Continued

		HOMA-B					HOMA-IR					SNP-h ²			
		Genetic Correlation					Genetic Correlation								
		r _g	se	z	p	p _{fdr}	r _g	se	z	p	p _{fdr}	h ²	se	Intercept	se
Lipids	Triglycerides (TG)	0.35	0.07	5.34	9.23×10 ⁻⁸	4.21×10 ⁻⁷	0.42	0.10	4.01	6.12×10 ⁻⁵	2.13×10 ⁻⁴	0.15	0.03	0.86	0.02
	High Density Lipoprotein Cholesterol (HDL-C)	-0.36	0.08	-4.23	2.34×10 ⁻⁵	8.98×10 ⁻⁵	-0.53	0.08	-6.76	1.39×10 ⁻¹¹	9.20×10 ⁻¹¹	0.11	0.02	0.93	0.04
	Low Density Lipoprotein Cholesterol (LDL-C)	0.15	0.08	1.74	0.08	0.17	0.09	0.08	1.11	0.27	0.43	0.09	0.02	0.96	0.04
	Total Cholesterol (TC)	0.09	0.07	1.27	0.20	0.37	0.005	0.07	0.07	0.94	0.95	0.12	0.02	0.93	0.03
Obesity	Hip Circumference (HIP)	0.39	0.06	6.55	5.82×10 ⁻¹¹	3.54×10 ⁻¹⁰	0.53	0.06	9.16	5.06×10 ⁻²⁰	4.61×10 ⁻¹⁹	0.15	0.01	0.75	0.01
	Waist Circumference (WC)	0.52	0.06	9.26	2.14×10 ⁻²⁰	2.23×10 ⁻¹⁹	0.70	0.05	14.06	6.44×10 ⁻⁴⁵	1.57×10 ⁻⁴³	0.14	0.01	0.74	0.01
	Waist to Hip Ratio (WHR)	0.50	0.06	8.70	3.32×10 ⁻¹⁸	2.69×10 ⁻¹⁷	0.66	0.05	12.65	1.16×10 ⁻³⁶	2.11×10 ⁻³⁵	0.10	0.01	0.83	0.01
	BMI	0.43	0.05	8.63	6.15×10 ⁻¹⁸	4.49×10 ⁻¹⁷	0.62	0.05	12.43	1.73×10 ⁻³⁵	2.52×10 ⁻³⁴	0.14	0.01	0.65	0.01
T2D complications	Systolic Blood Pressure (SBP)	-0.08	0.11	-0.68	0.50	0.61	0.10	0.10	0.94	0.35	0.51	0.11	0.02	0.95	0.01
	Diastolic Blood Pressure (DBP)	-0.11	0.12	-0.98	0.33	0.48	0.01	0.10	0.05	0.96	0.96	0.13	0.02	0.94	0.01
	Hypertension (HTN)	-0.01	0.13	-0.09	0.92	0.95	0.16	0.13	1.24	0.21	0.37	0.15	0.03	0.96	0.01
	Coronary Artery Disease (CAD)	0.09	0.10	0.86	0.39	0.55	0.19	0.10	1.89	0.06	0.12	0.07	0.01	1.03	0.01
	eGFR creatinine Diabetes Mellitus	-0.09	0.18	-0.52	0.60	0.71	0.03	0.18	0.19	0.85	0.93	0.09	0.04	1.00	0.01
	eGFR creatinine non Diabetes Mellitus	-0.05	0.06	-0.79	0.43	0.59	-0.05	0.07	-0.70	0.49	0.61	0.11	0.01	0.98	0.01
	eGFR creatinine all	-0.05	0.06	-0.78	0.43	0.59	-0.04	0.07	-0.53	0.59	0.71	0.11	0.01	0.98	0.01
	eGFR cystatin C all	-0.31	0.13	-2.49	0.01	0.03	-0.27	0.11	-2.34	0.02	0.05	0.16	0.07	0.95	0.01
	Chronic Kidney Disease (CKD)	0.31	0.14	2.23	0.03	0.06	0.23	0.14	1.59	0.11	0.22	0.02	0.01	1.02	0.01

Table S8. Continued

	HOMA-B					HOMA-IR					SNP-h ²				
	Genetic Correlation					Genetic Correlation					h ²	se	Intercept	se	
	r _g	se	z	p	p _{fdr}	r _g	se	z	p	p _{fdr}					
Inflammation	White Blood Cell counts (WBC)	0.14	0.19	0.74	0.46	0.60	0.23	0.18	1.26	0.21	0.37	0.05	0.02	1.00	0.01
	ICAM-1	0.14	0.17	0.82	0.41	0.58	0.03	0.17	0.16	0.88	0.93	0.74	0.50	1.04	0.03
	C-Reactive Protein (CRP)	0.28	0.09	3.25	1.20×10 ⁻³	3.65×10 ⁻³	0.33	0.11	3.16	1.60×10 ⁻³	4.67×10 ⁻³	0.13	0.03	1.00	0.02
	PAI-1	0.78	0.23	3.36	8.00×10 ⁻⁴	2.54×10 ⁻³	0.92	0.23	4.01	6.13×10 ⁻⁵	2.13×10 ⁻⁴	0.06	0.03	1.00	0.01
	ADIPONECTIN	-0.24	0.11	-2.16	0.03	0.07	-0.30	0.10	-2.85	4.40×10 ⁻³	0.012	0.11	0.02	0.96	0.01

Table S9. Genetic correlation (r_g) between inferred and published HOMA-B and HOMA-IR, the LD score regression intercepts, SNP-heritability and their standard errors (SE).

	Published	Inferred Global Correction	Inferred Local Correction
HOMA-B			
r_g (SE), p-value	-	1.12 (0.07), 4.30×10^{-66}	1.14 (0.07), 2.22×10^{-56}
Intercept (SE)	0.99 (0.007)	1.043 (0.008)	1.05 (0.008)
h^2 (SE)	0.08 (0.014)	0.058 (0.01)	0.055 (0.01)
HOMA-IR			
r_g (SE), p-value	-	1.18 (0.07), 3.58×10^{-58}	1.18 (0.07), 1.40×10^{-58}
Intercept (SE)	1.003 (0.007)	1.03 (0.008)	1.03 (0.008)
h^2 (SE)	0.07 (0.01)	0.059 (0.008)	0.060 (0.008)

Figure S1. Manhattan Plots of published meta-analysis results

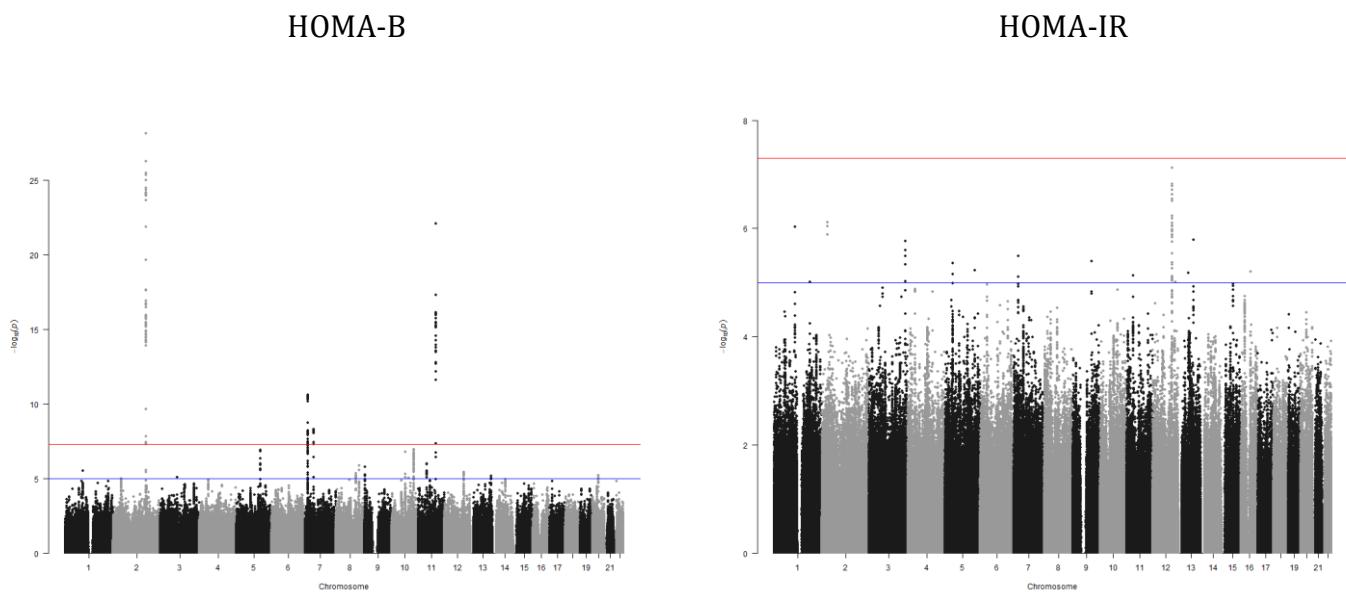


Figure S2. Manhattan Plots of inferred meta-analysis results

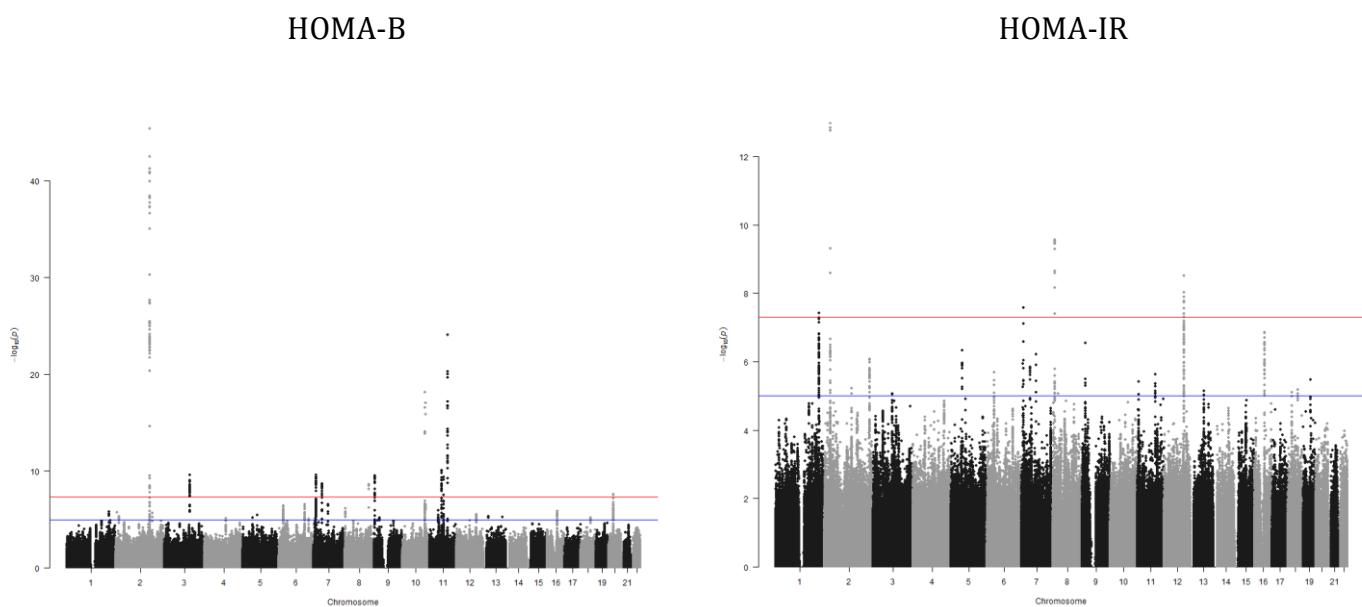


Figure S3. QQ plots of published meta-analysis results

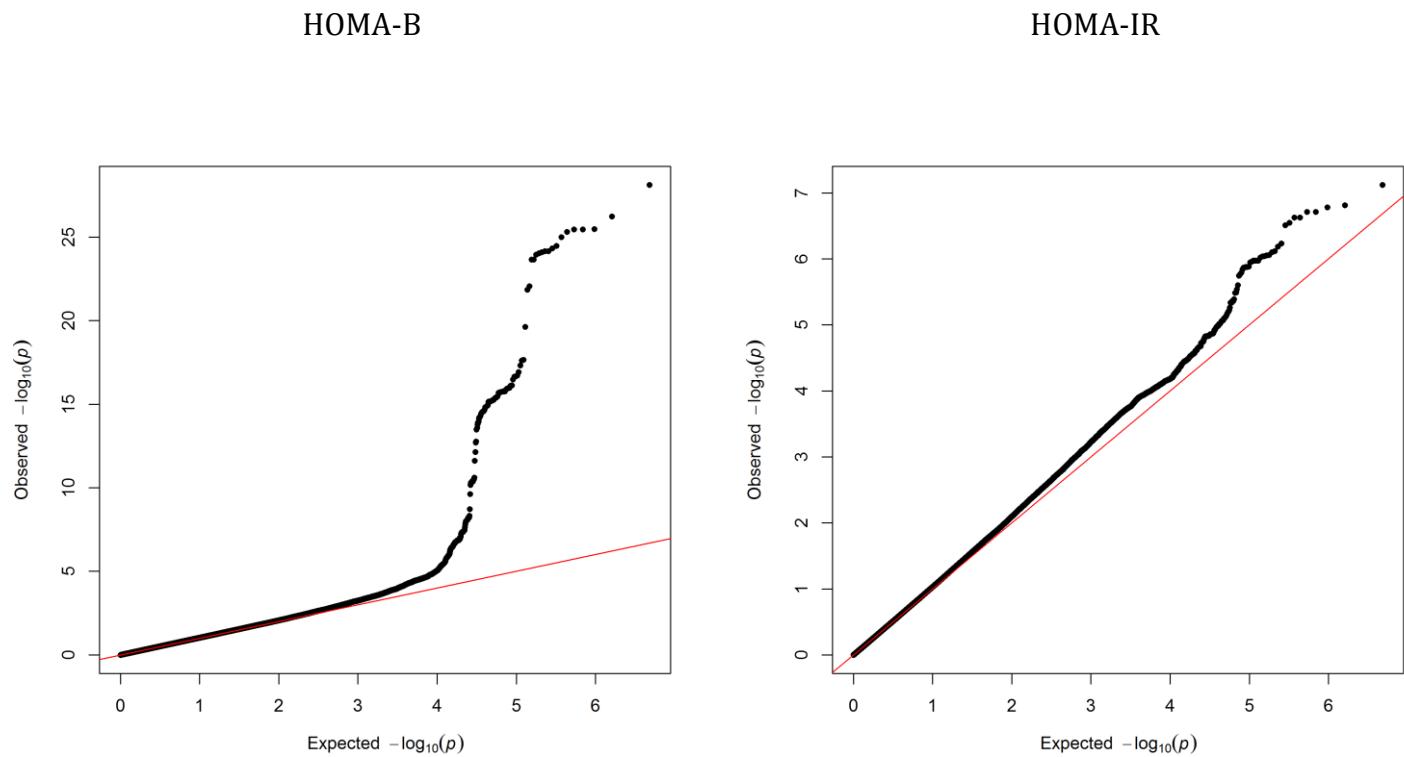


Figure S4. QQ plots of inferred meta-analysis results

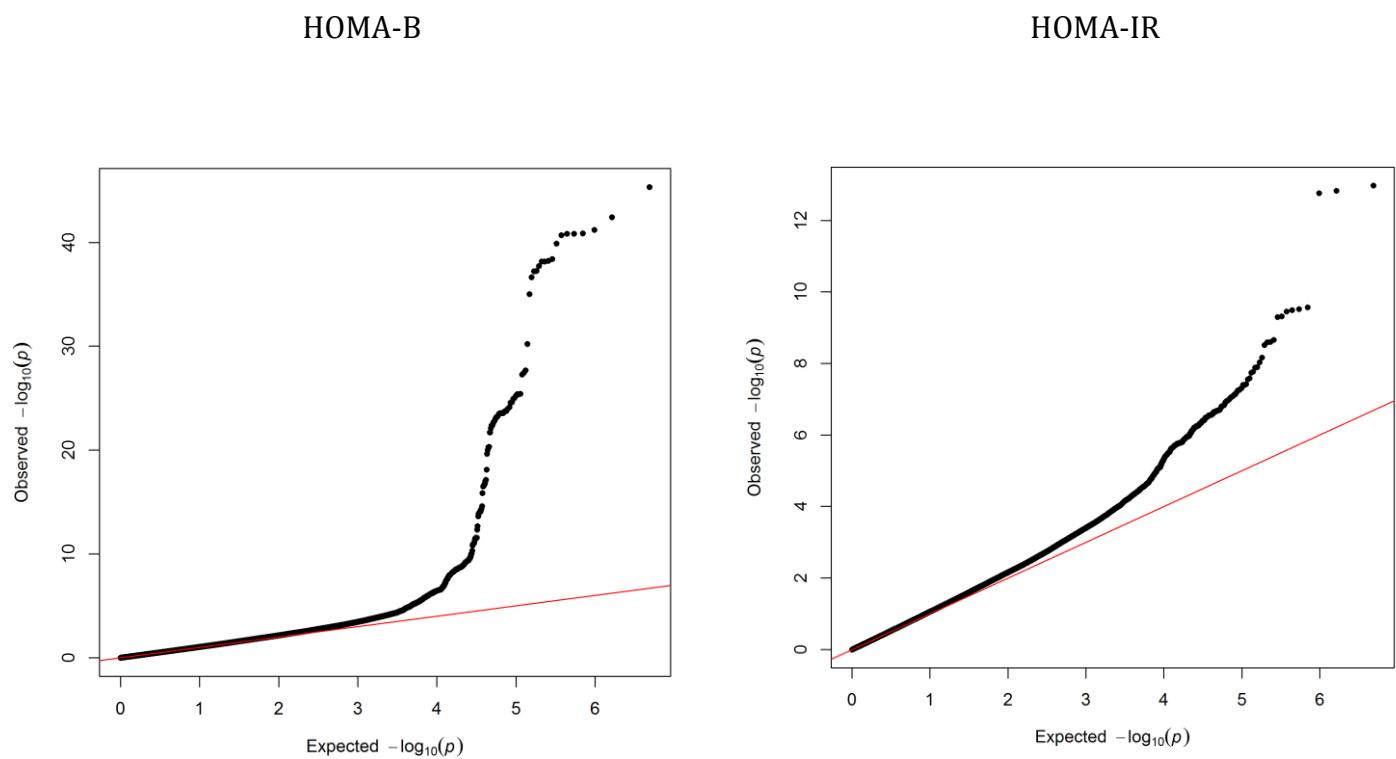


Figure S5. Manhattan and QQ plots, showing GWIS results for HOMA-B (a)/-IR (b).

Novel loci are highlighted in purple/red colour. The X-axis denotes chromosome and base-pair positions of SNPs against $-\log_{10}(P)$ plotted on the Y-axis. The red horizontal line indicates genome-wide significance level ($P < 5 \times 10^{-8}$), and the blue line represents suggestive significance level ($P < 1 \times 10^{-5}$). HOMA-B/IR GWAS significant loci are labelled by the name of nearest gene, established FG(a)/FI(b) loci are also represented in blue/green colour, respectively.

a) HOMA-B

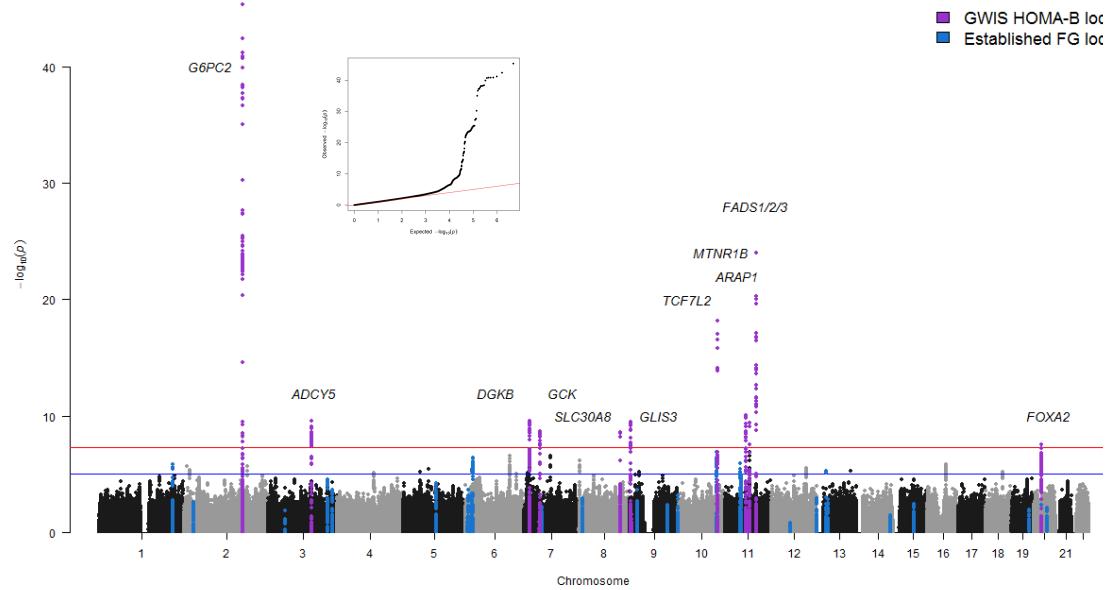


Figure S5. Continued

b) HOMA-IR

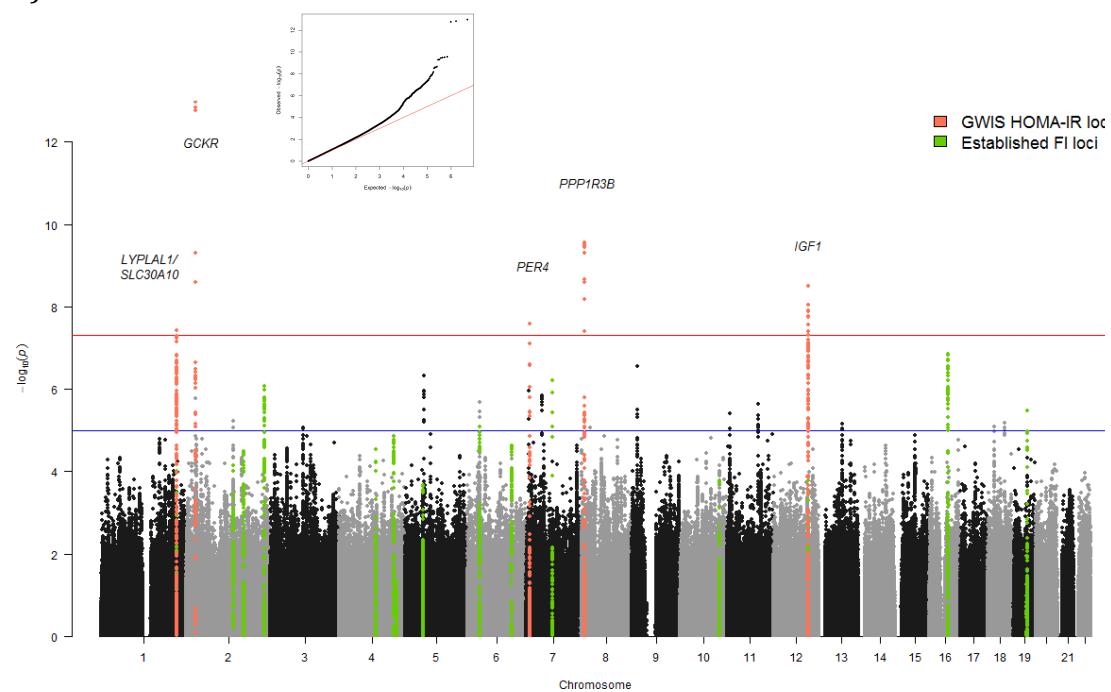


Figure S6. FG (a) and FI (b) average estimates from each participating cohort, plotted against $-\log_{10}(P)$ for each HOMA-B/-IR locus lead SNP that was genome-wide significant in main analysis. The horizontal line indicates genome-wide significance level ($P < 5 \times 10^{-8}$). Vertical lines indicate the FG/FI means and dashed lines indicate 1SDs from either of FG/FI means.

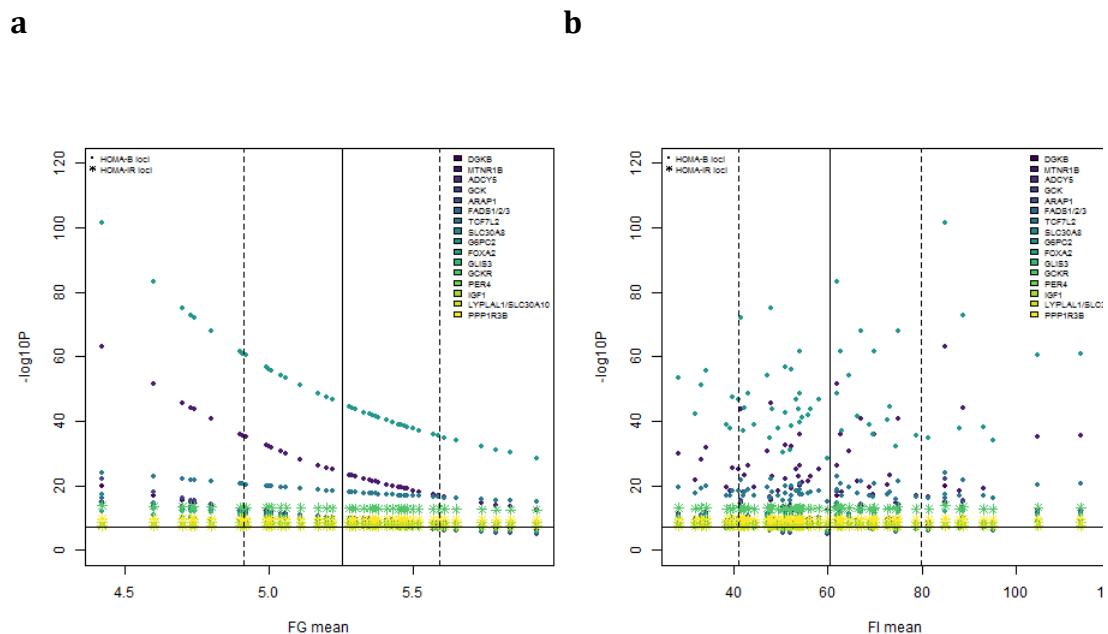


Figure S7.

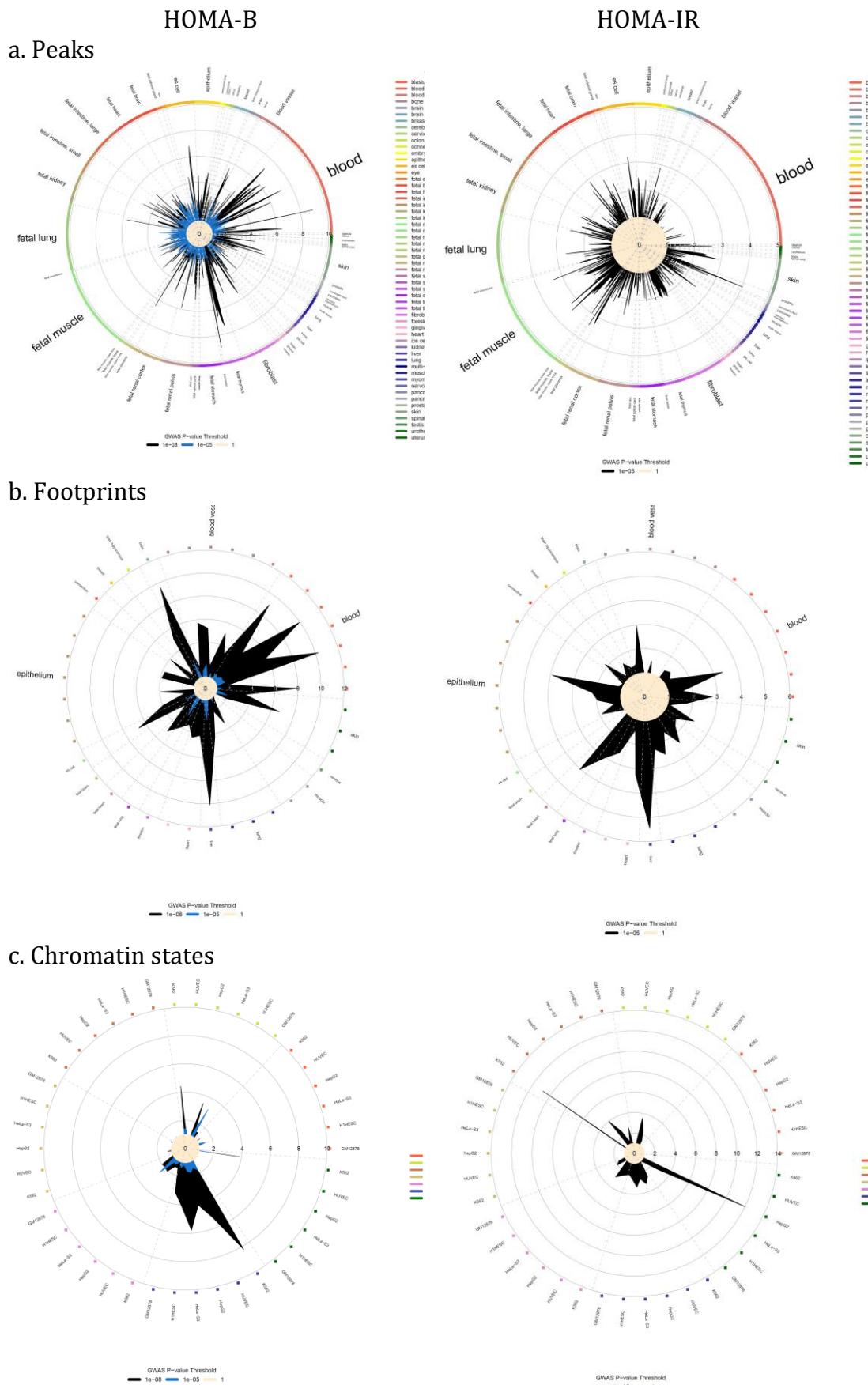
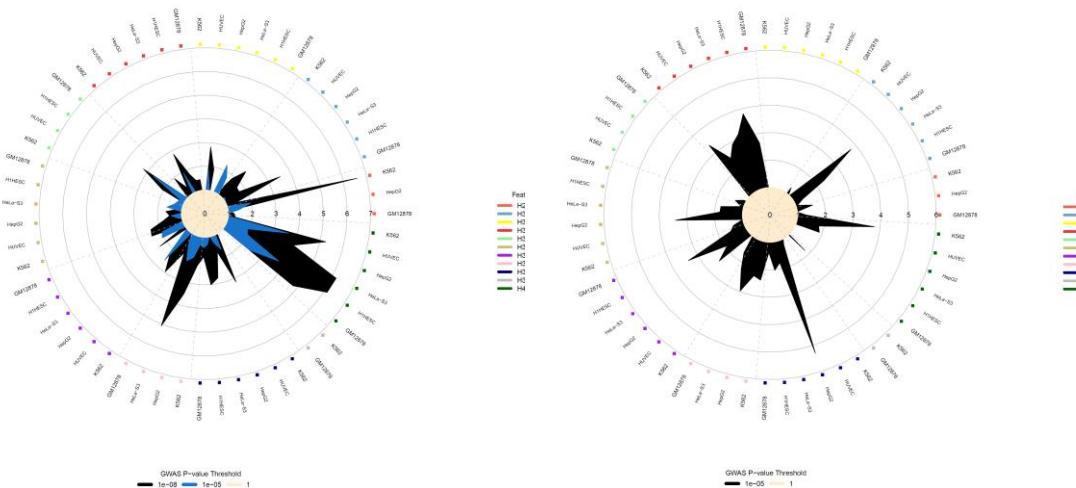


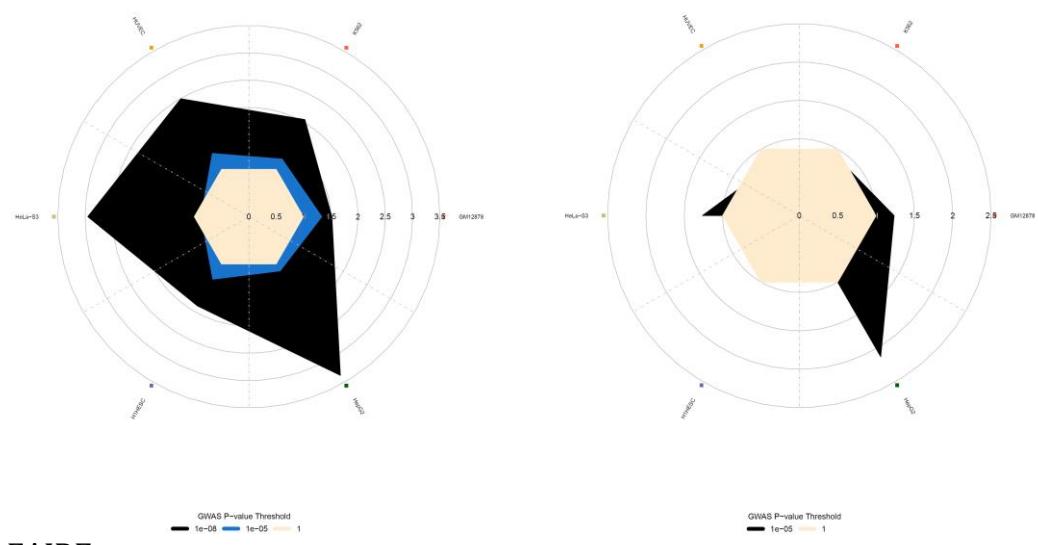
Figure S7. Continued.

HOMA-B

d. Histone modifications



e. TFBS



f. FAIRE

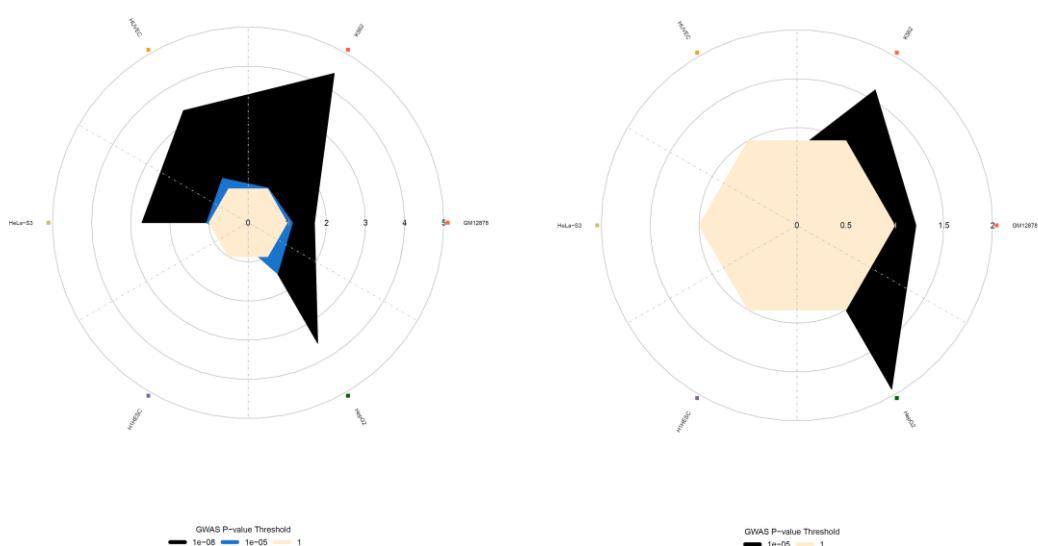


Figure S8. Effect size, $-\log_{10}P$ and SE comparison between published and inferred meta-analysis results for ‘global’ (dark color) and ‘local’ (light color) correction.

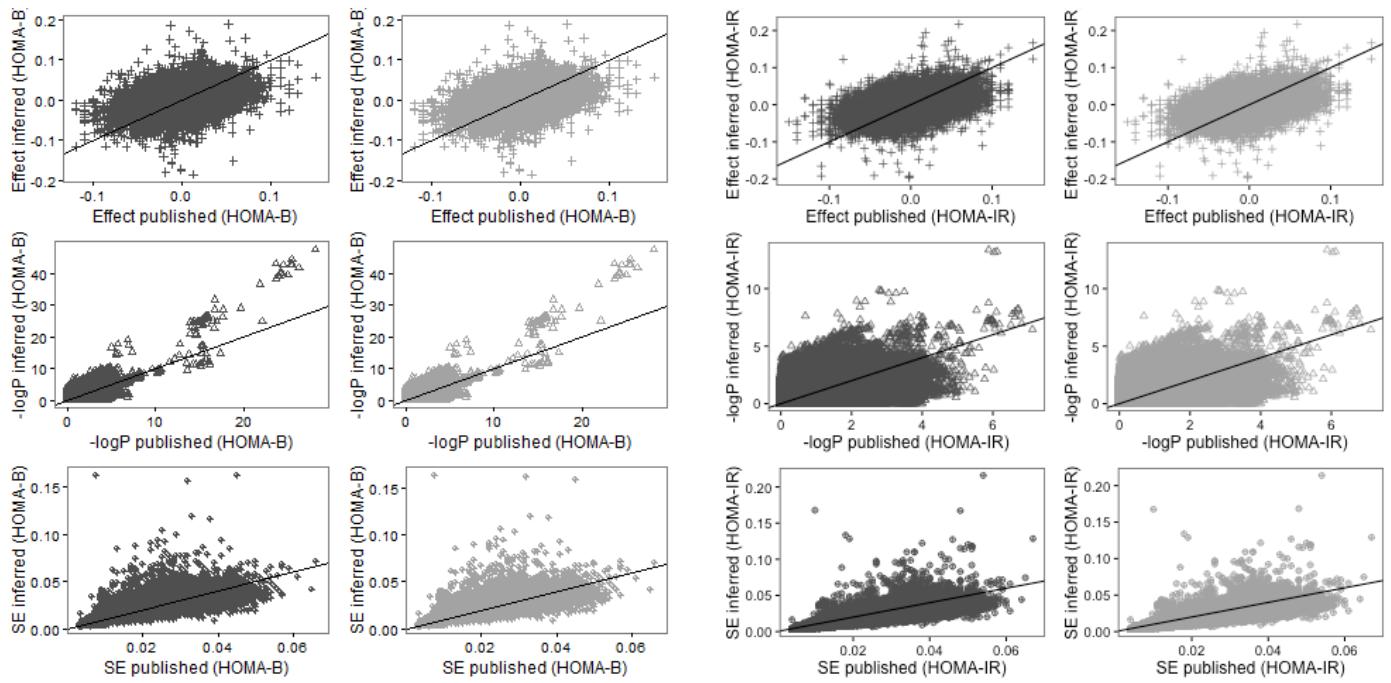


Figure S9. Difference in SE, effect size and Z-score plotted against N for ‘global’ (dark color) and ‘local’ (light color) correction.

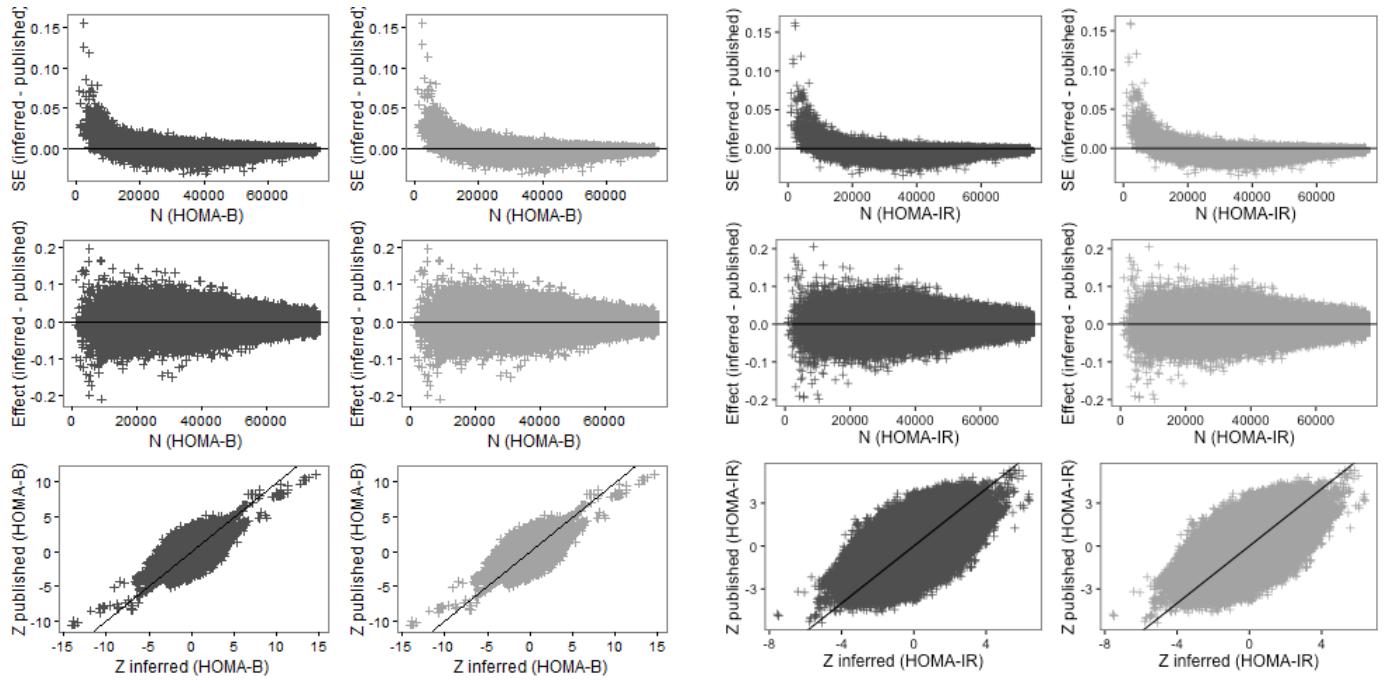


Figure S10. Distributions of the difference between inferred and published meta-analysis SE, for all SNPs (left) and for SNPs with smaller difference (right)

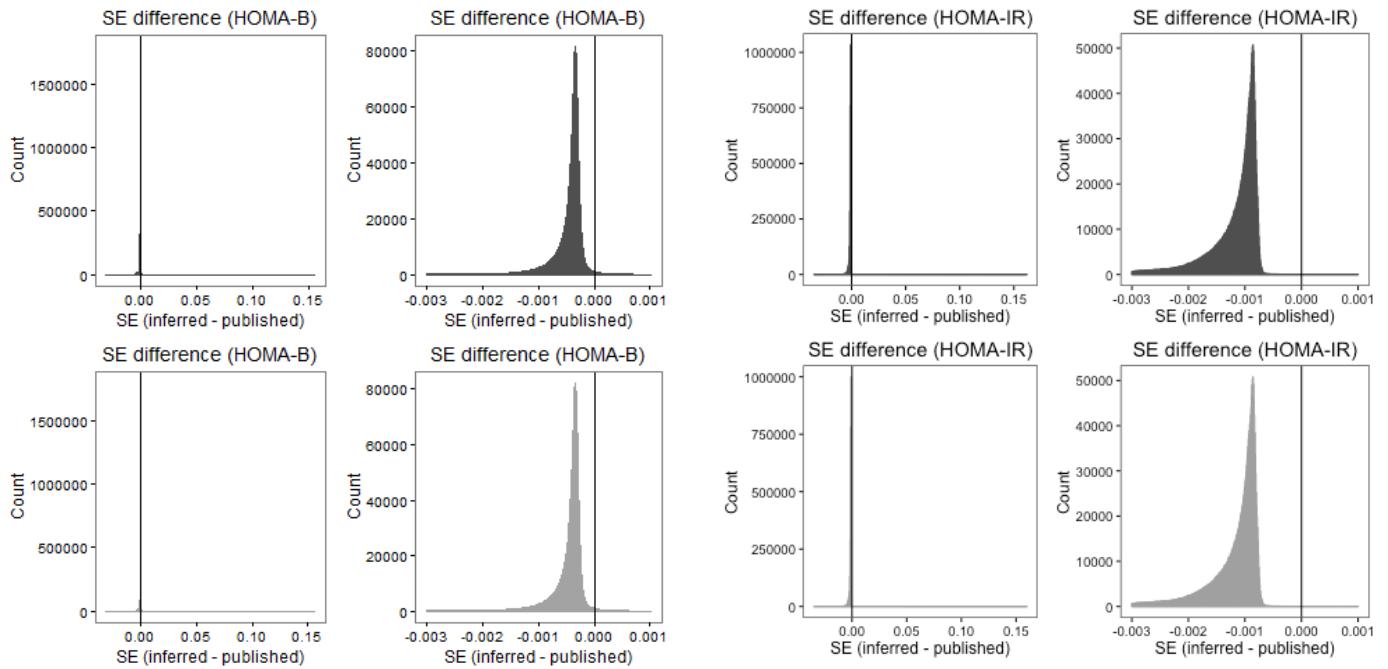


Figure S11. Distributions of the difference between inferred and published meta-analysis effect sizes, for all SNPs (left) and for SNPs with smaller difference (right)

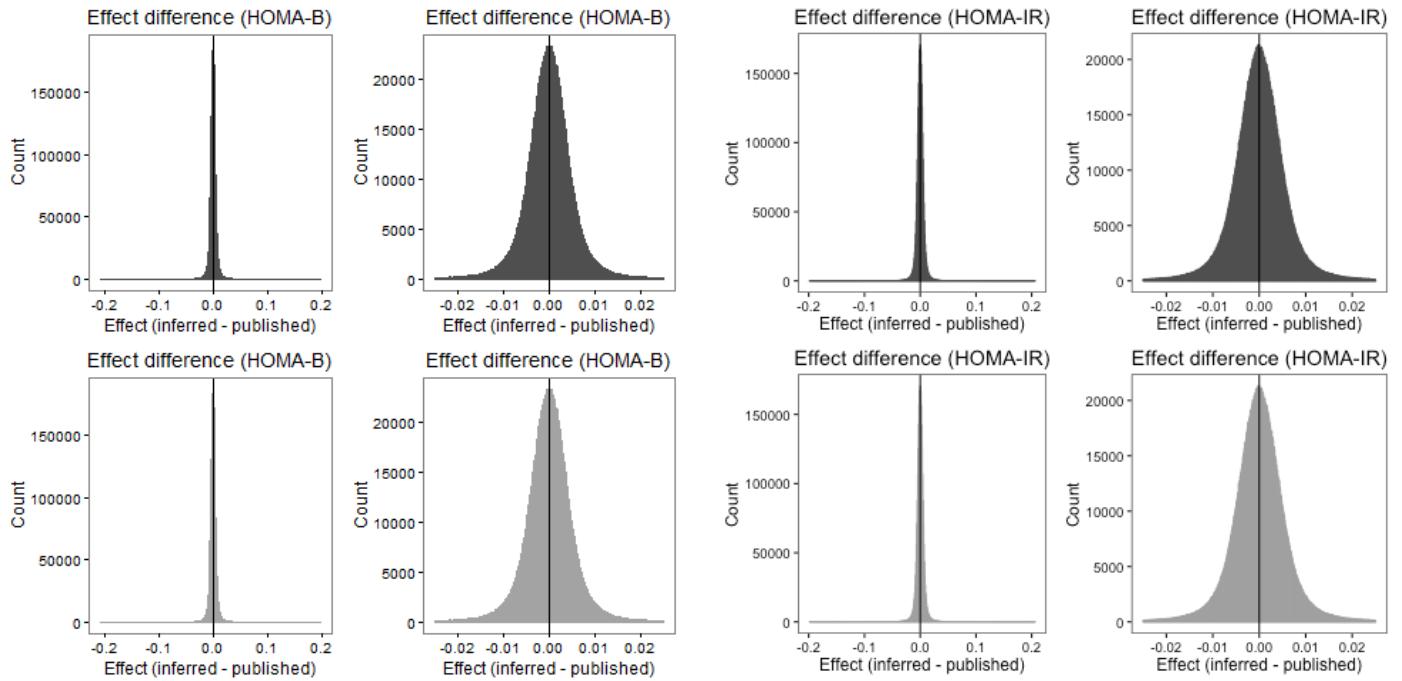


Figure S12. Distributions of the difference between inferred and published meta-analysis Z scores and difference in effect sizes plotted against difference in SE's for 'global' (dark color) and 'local' (light color) versions.

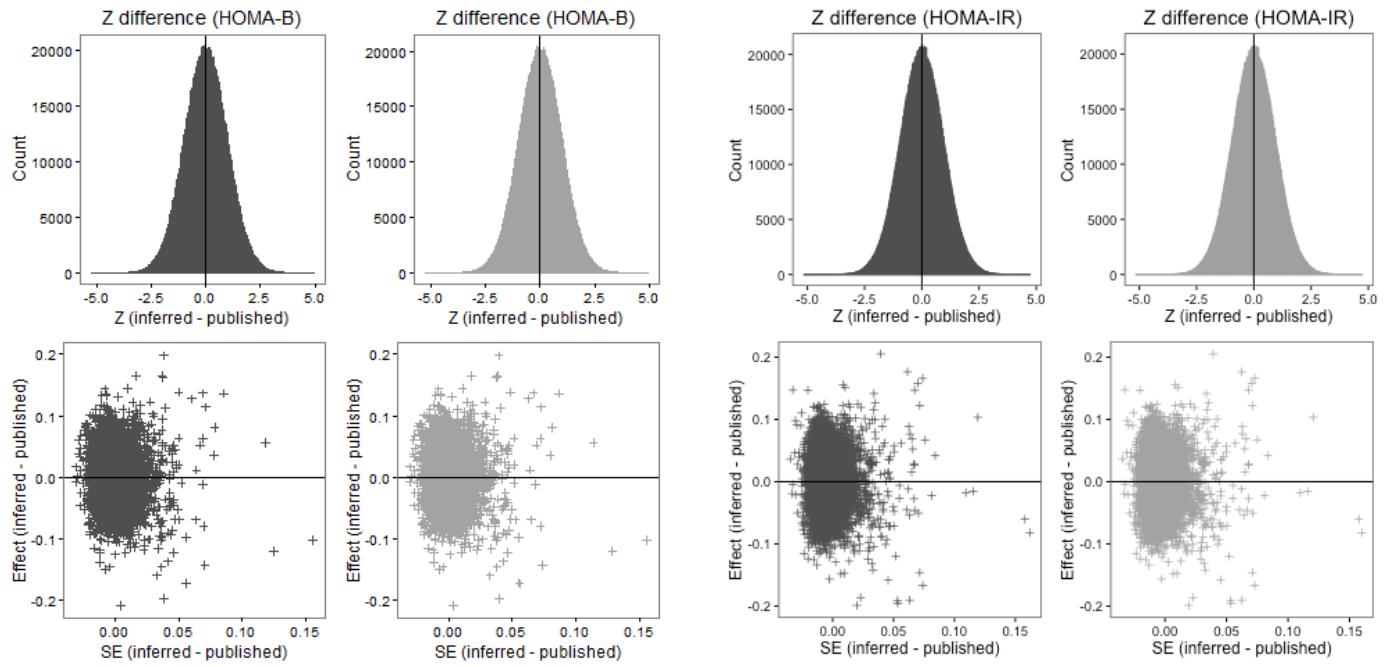


Figure S13. SE differences plotted against MAF in published and inferred meta-analysis for 'global' (dark color) and 'local' (light color) correction

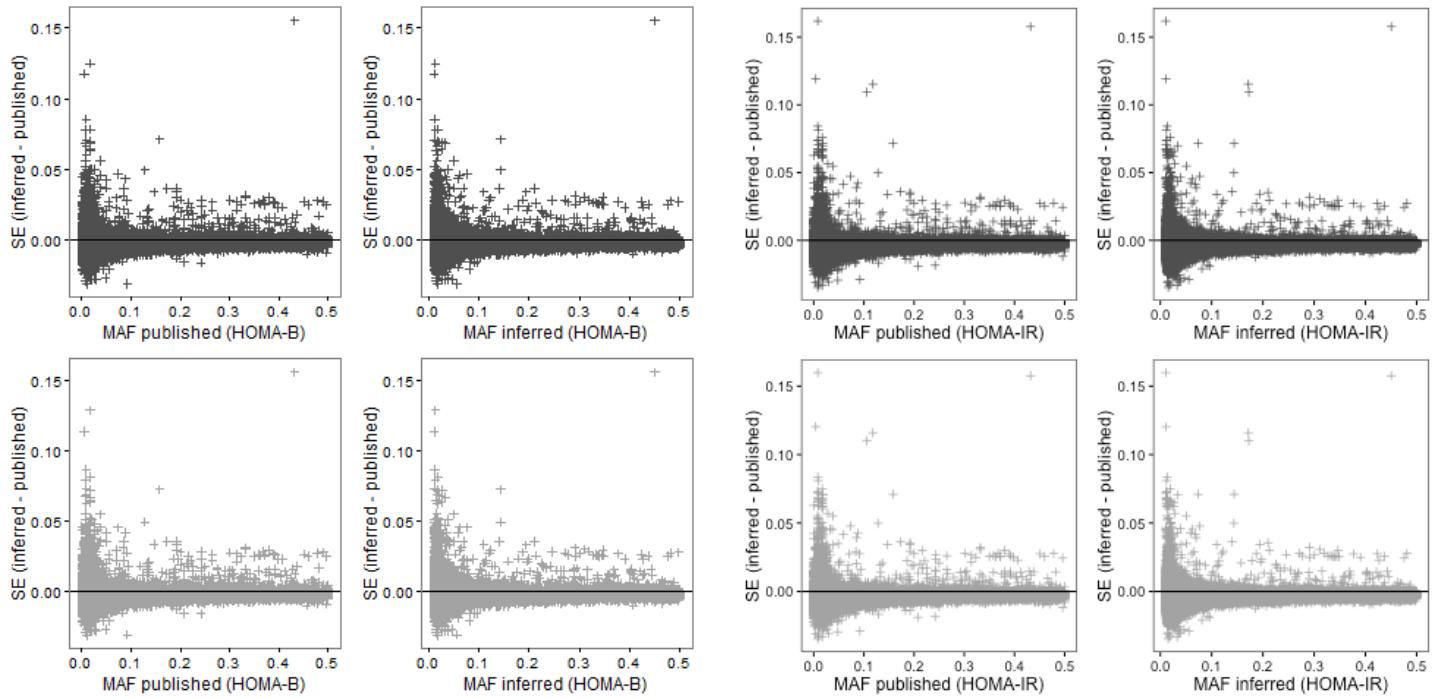


Figure S14. Difference in SE (left) and effect sizes (right) between inferred and published GWAS plotted against N. Dashed line indicated difference in SE < -0.003. Datasets are filtered with N > 35,000 and MAF > 0.01

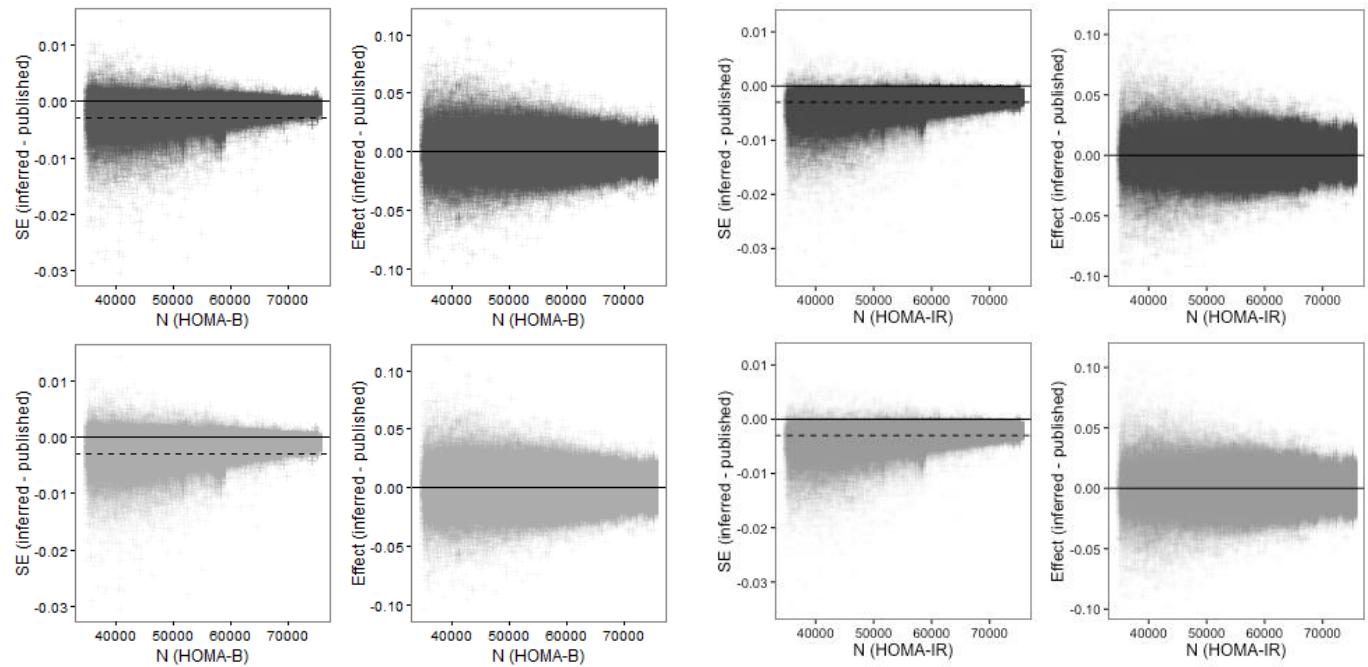


Figure S15. Difference in SE between inferred and published GWAS plotted against SE published (left) and inferred (right). Dashed line indicated difference in SE < -0.003. Datasets are filtered with N > 35,000 and MAF > 0.01

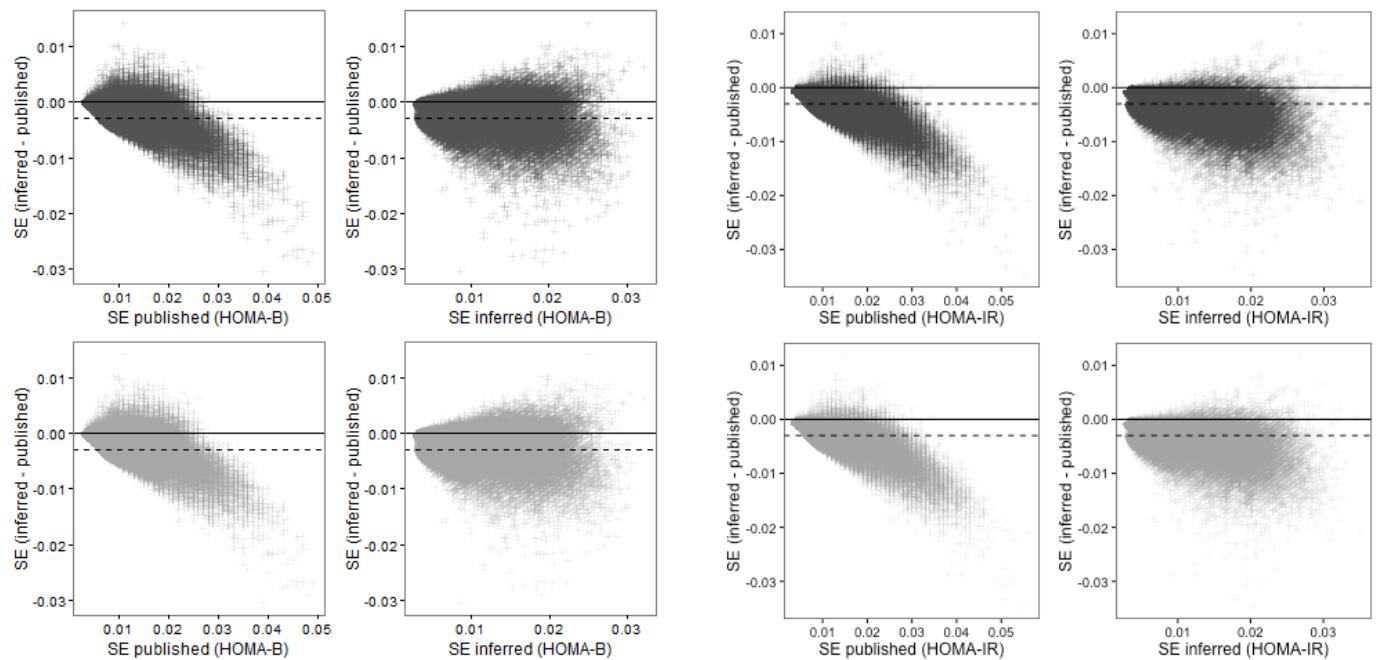


Figure S16. $-\log_{10}P$ of inferred against published meta-analysis results plotted for all SNPs (left) and SNPs, which SE difference between inferred and published GWAS less than -0.003 (right).

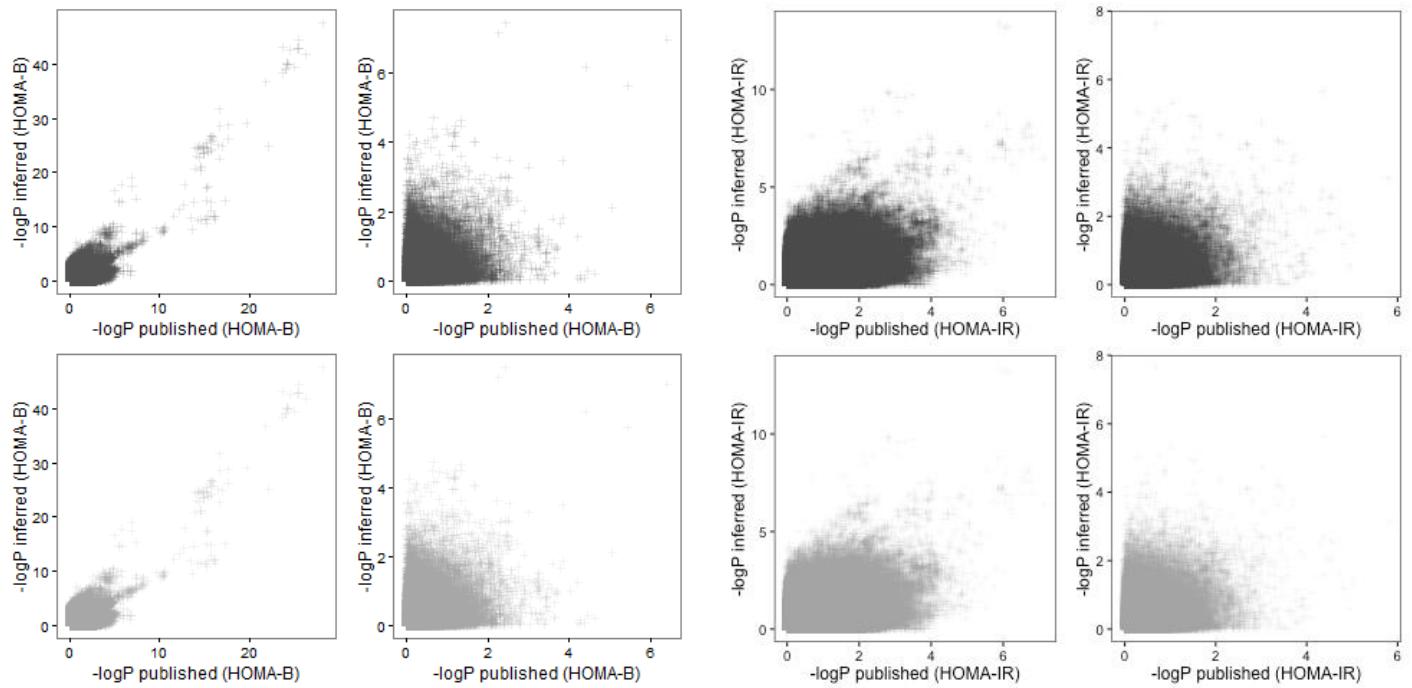


Figure S17. Effect size of inferred against published meta-analysis results plotted for all SNPs (left) and SNPs, which SE difference between inferred and published GWAS less than -0.003 (right).

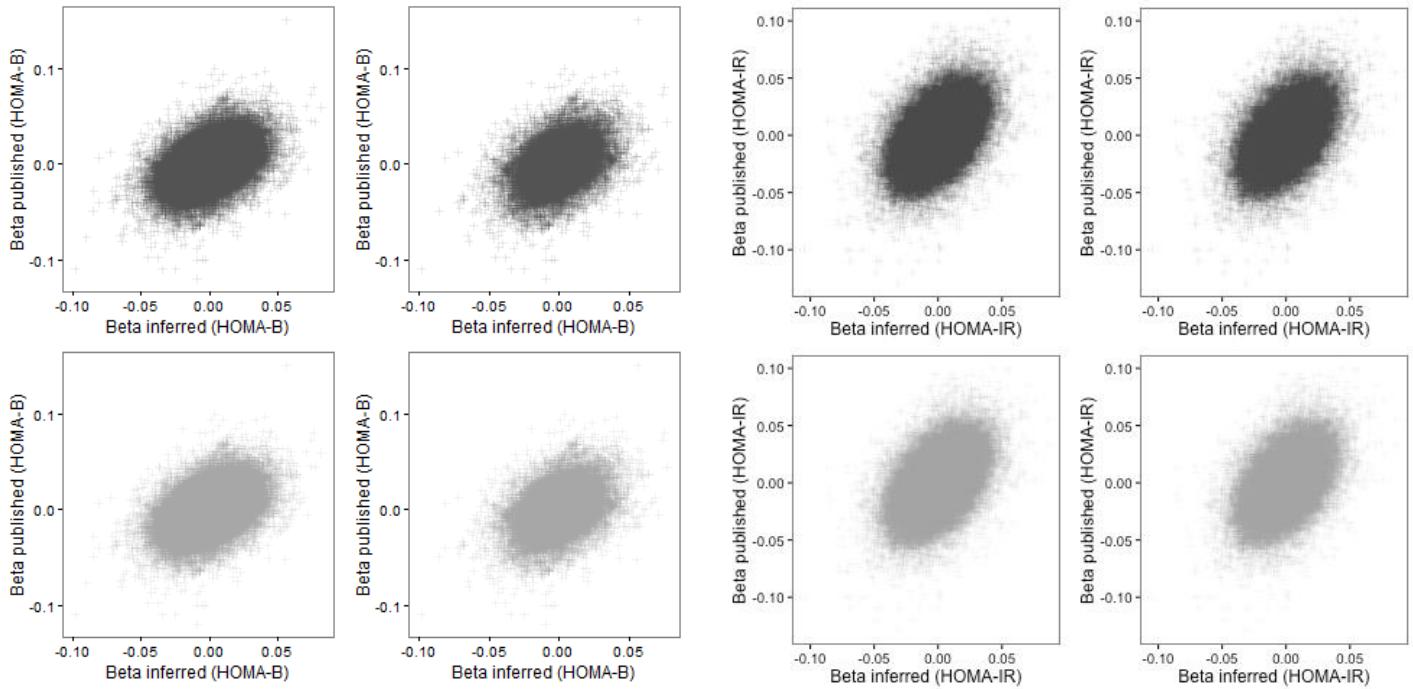


Figure S18. Distribution of SE's of the published (upper panel) and inferred (lower panel) results stratified by SE difference < -0.003. Low (light gray) vs. large (dark gray) SEs difference between inferred and published GWAS.

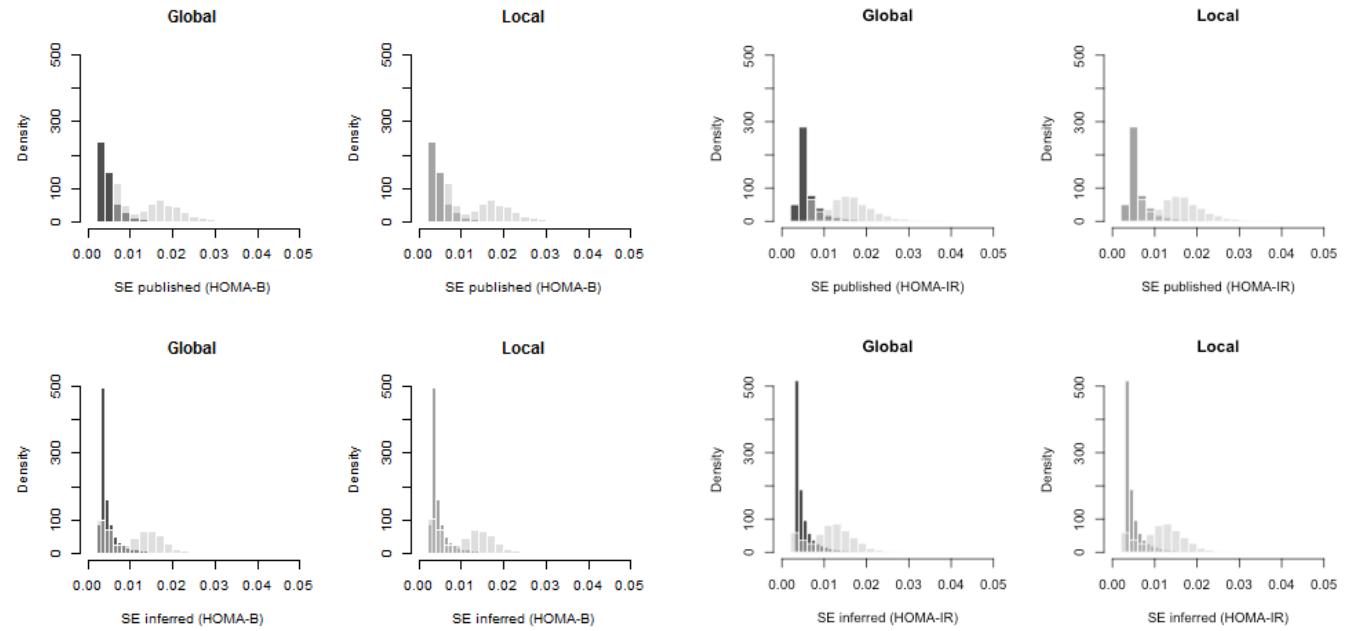


Figure S19. Comparison of SE's and effect sizes between 'global' and 'local' correction versions. Upper panel represent the whole dataset, whereas lower panel represent the dataset filtered with $N > 35,000$ and $MAF > 0.01$.

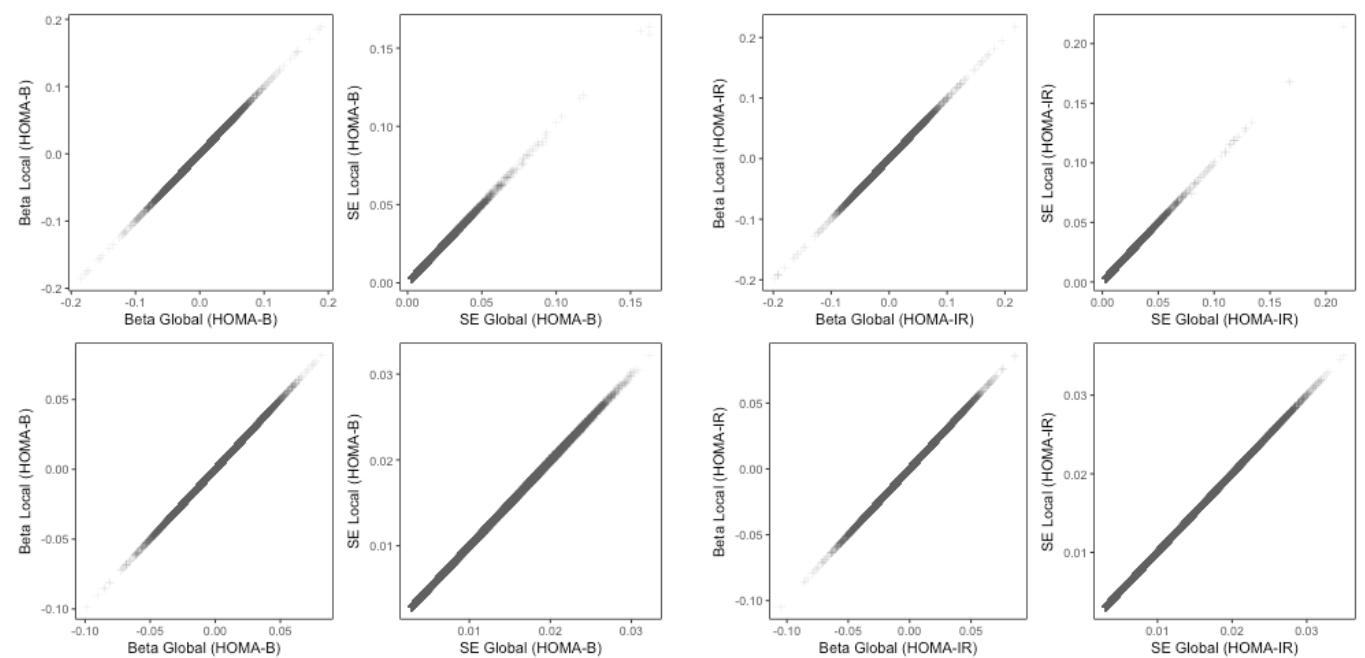
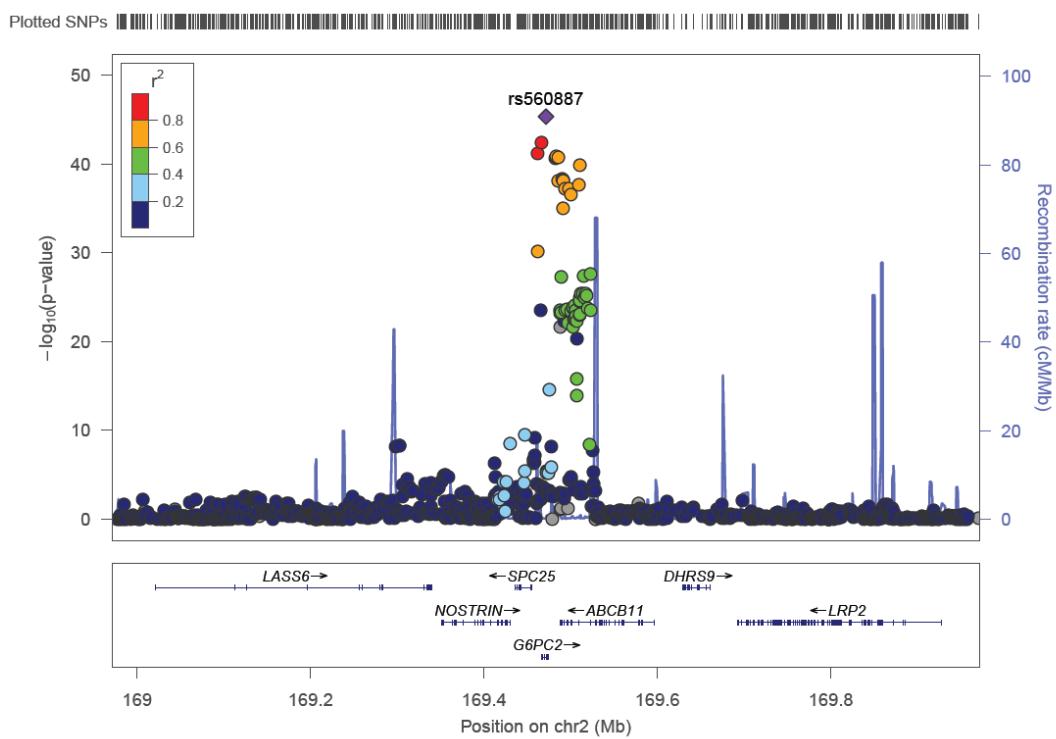
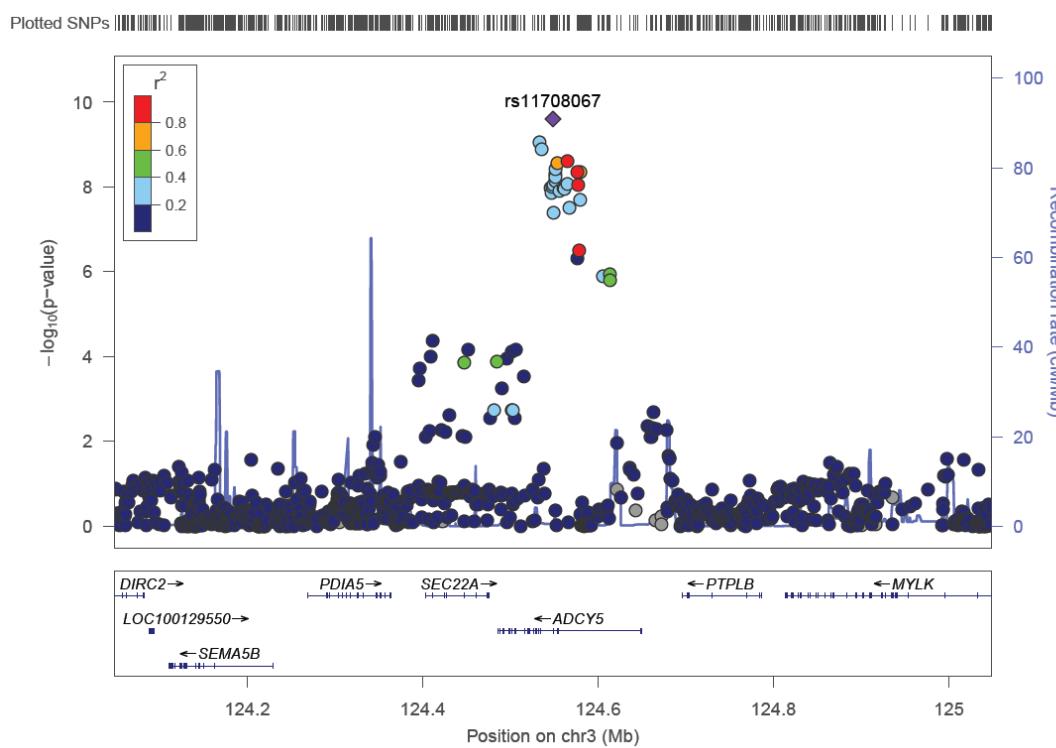


Figure S20. Region plots for each of the leading SNPs in HOMA-B GWIS results

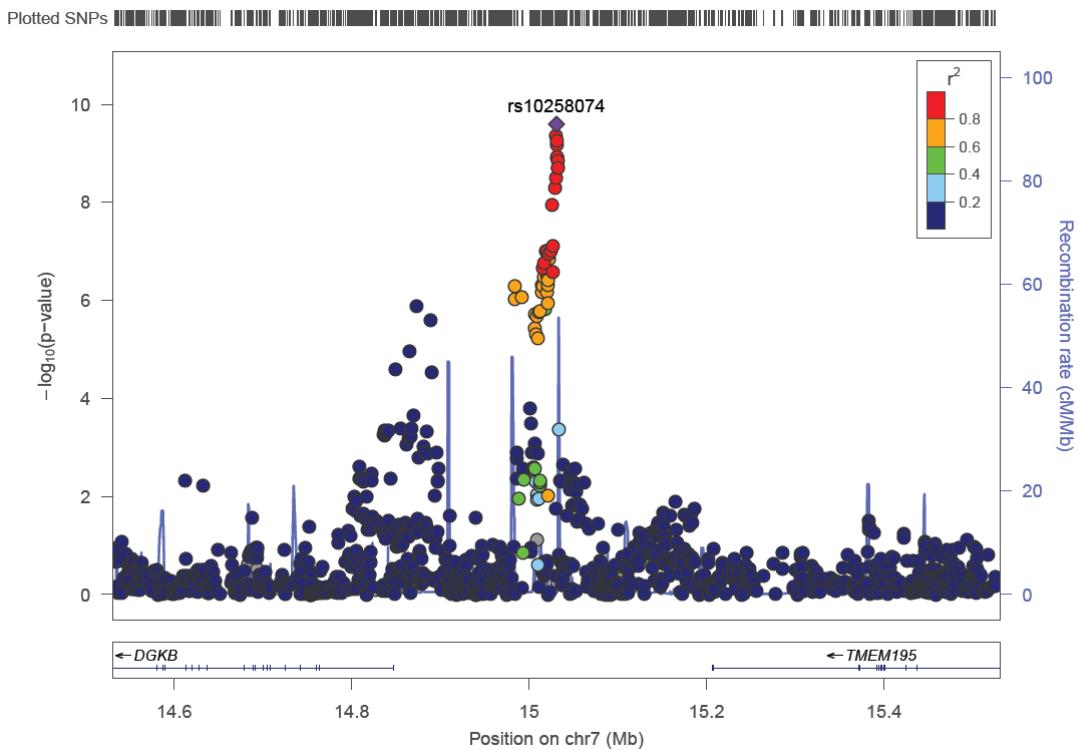
a



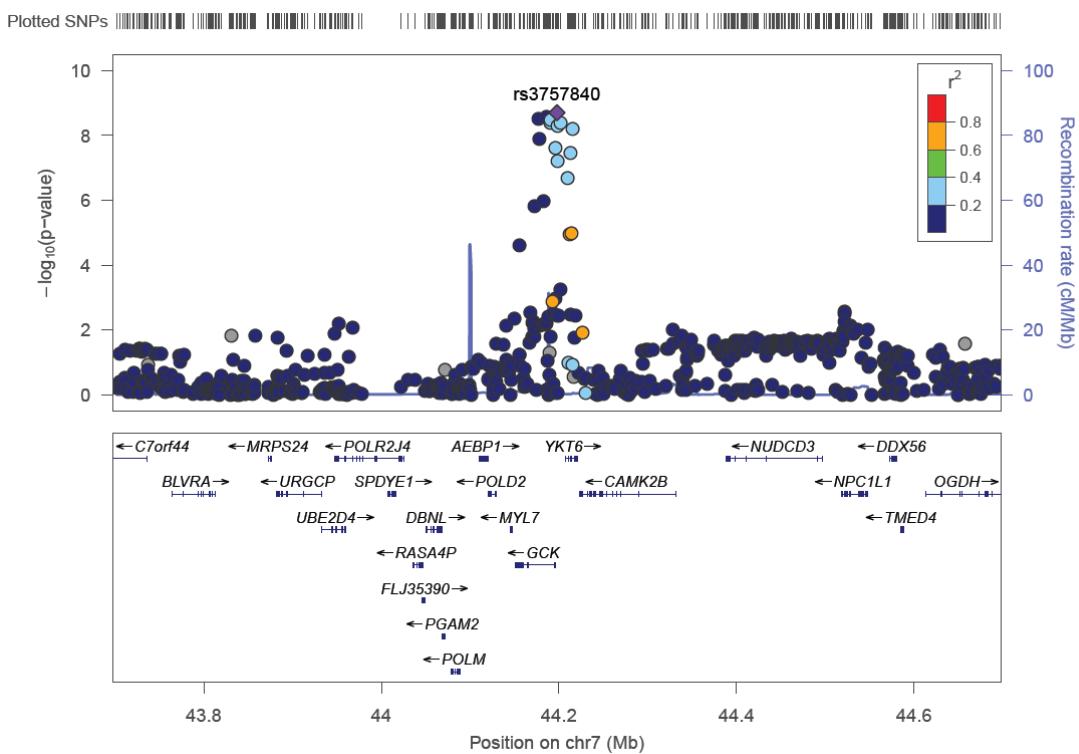
b

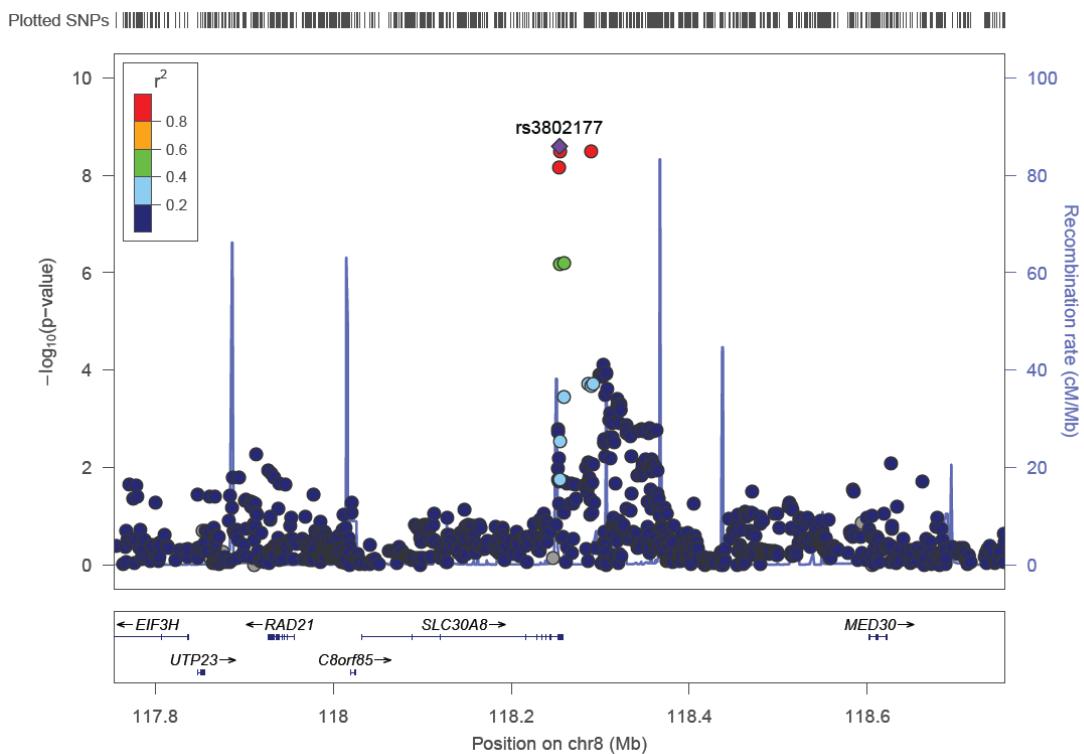
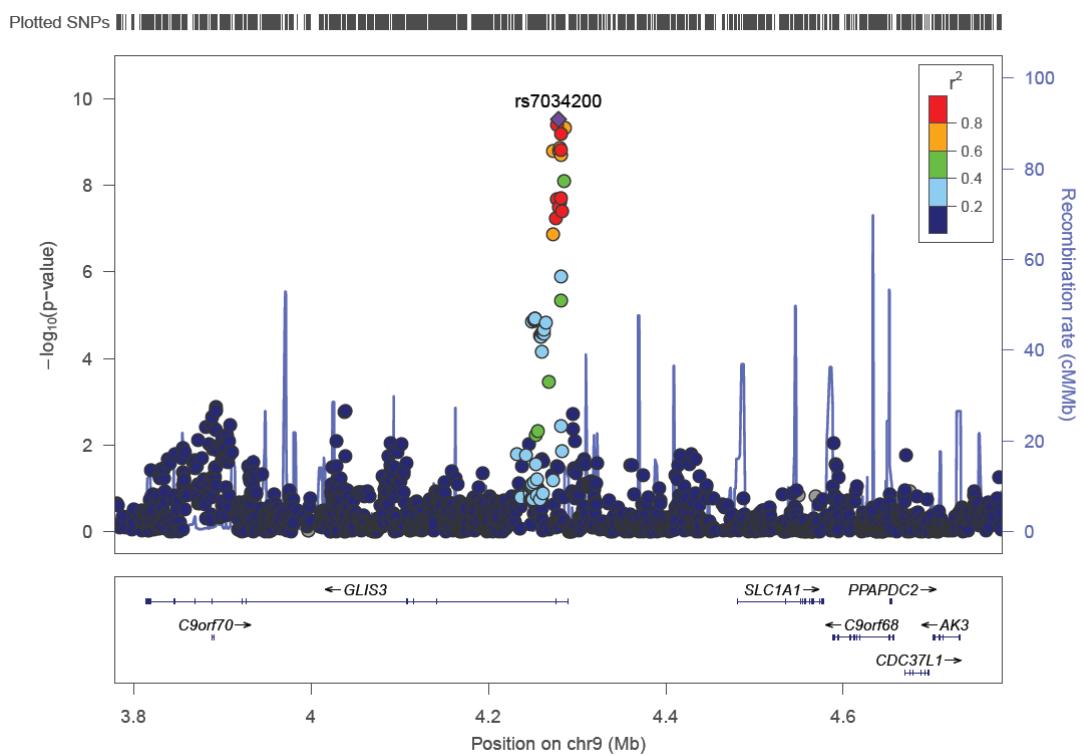


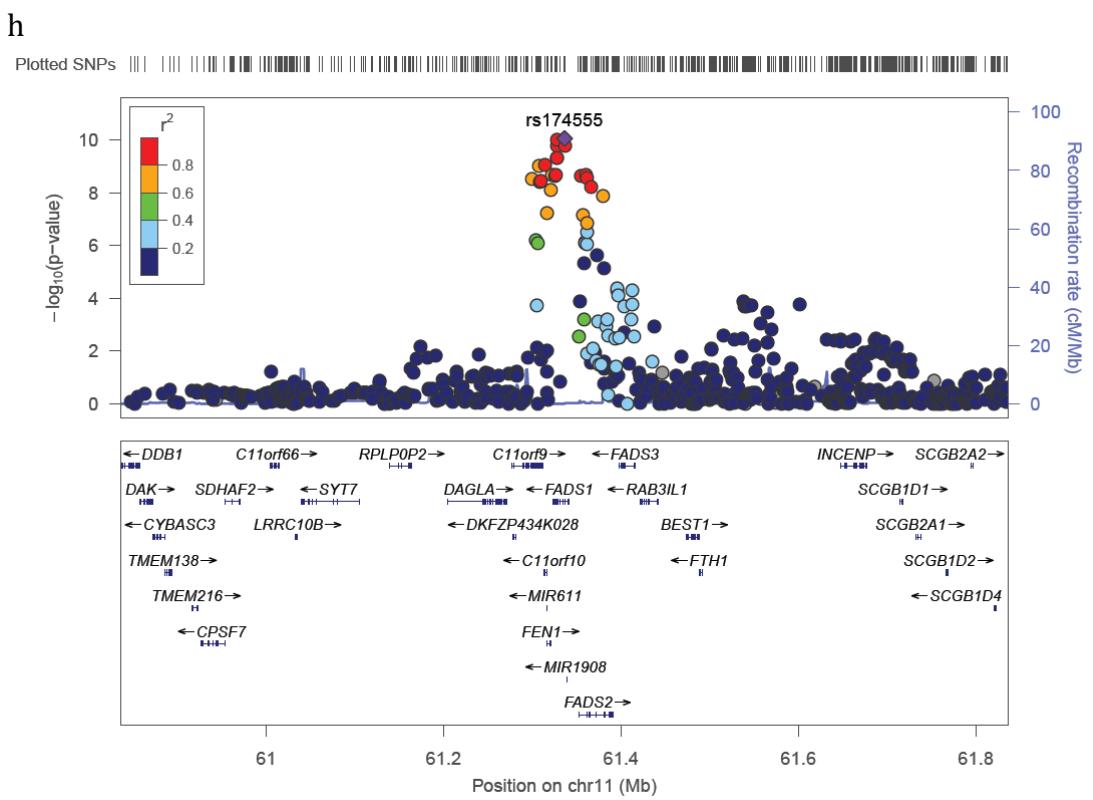
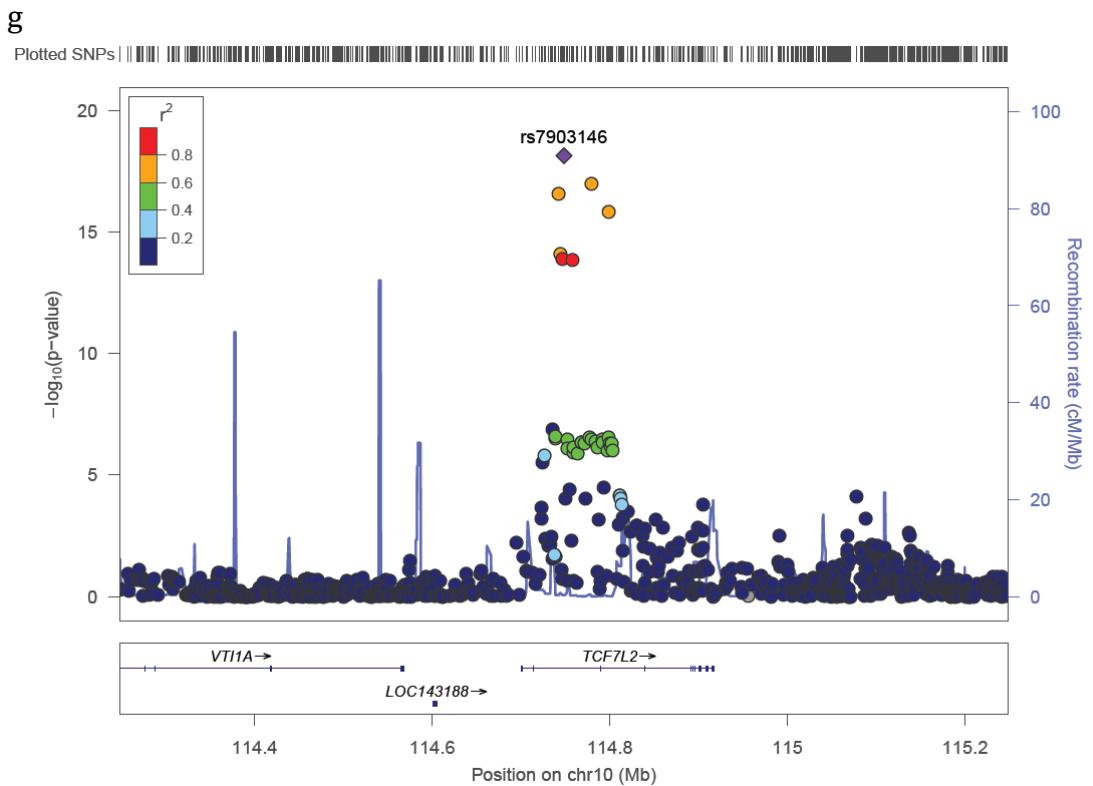
C



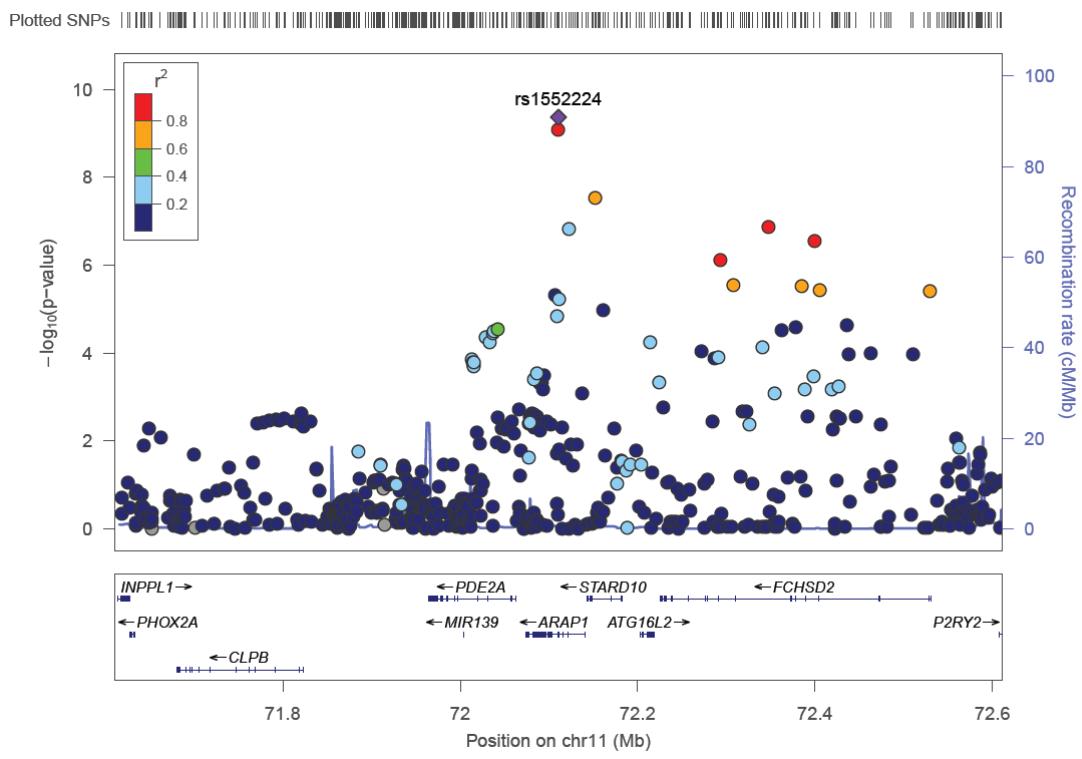
d



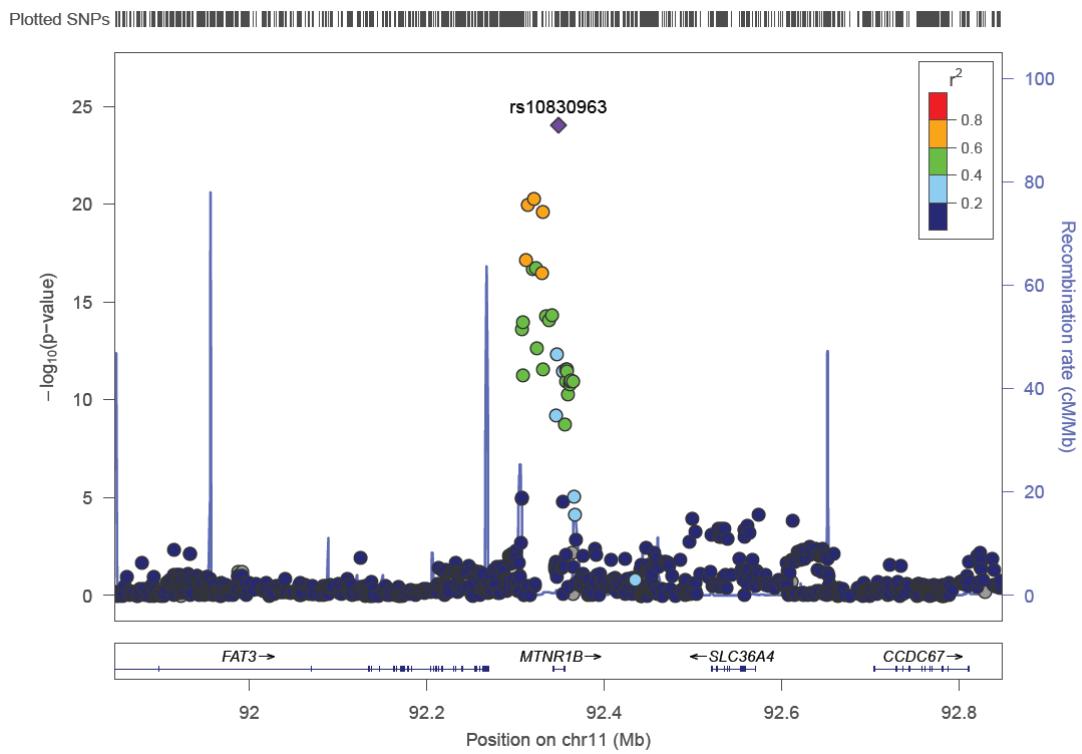
e**f**



i



j



k

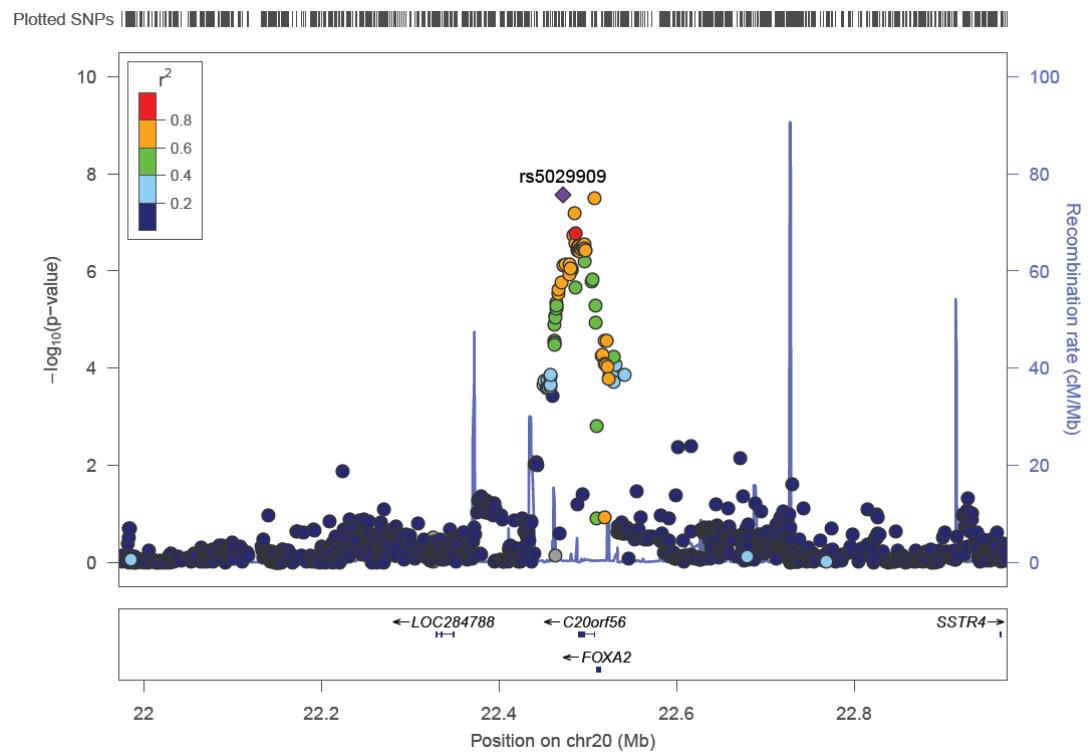
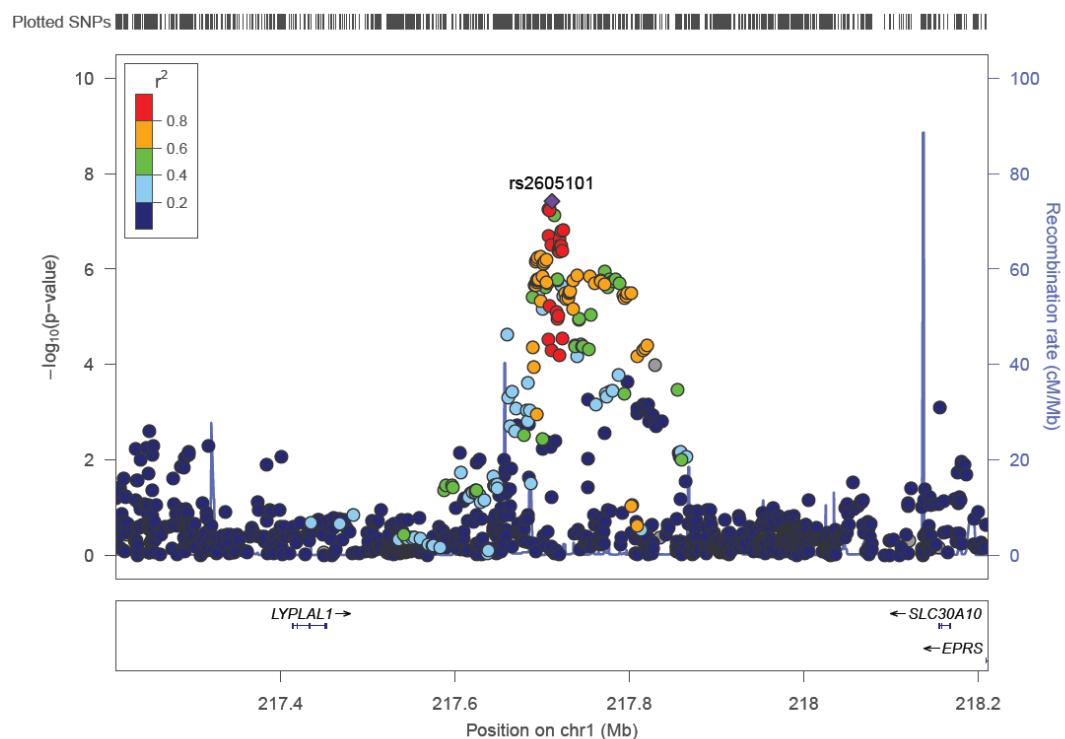
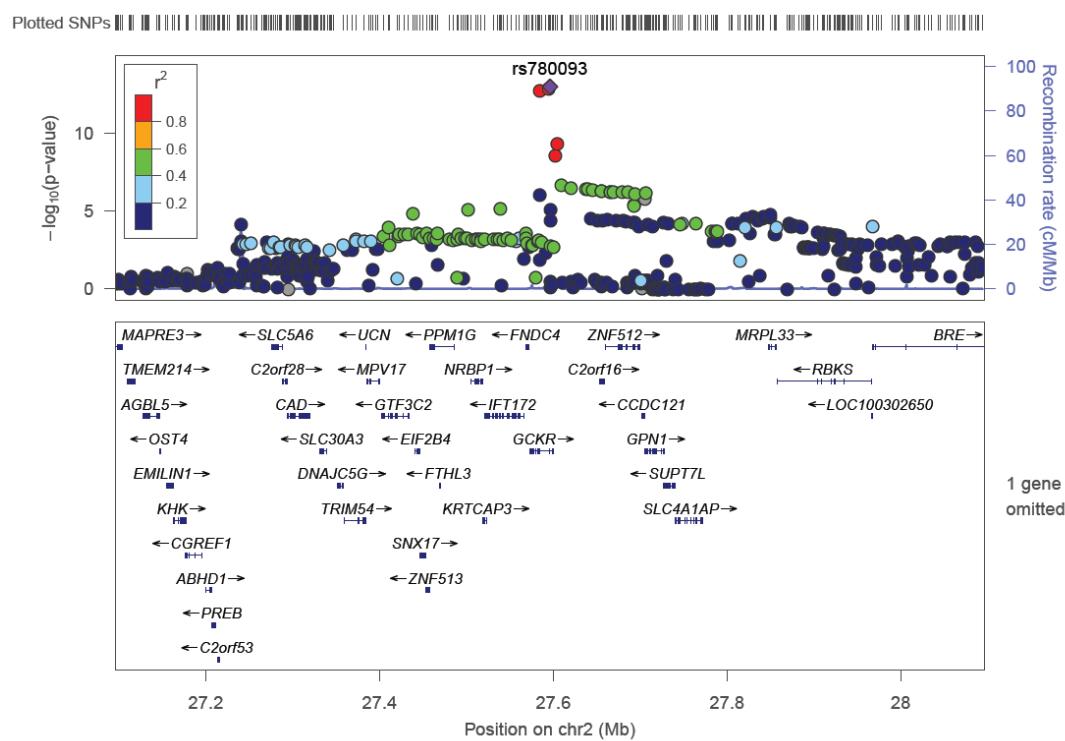


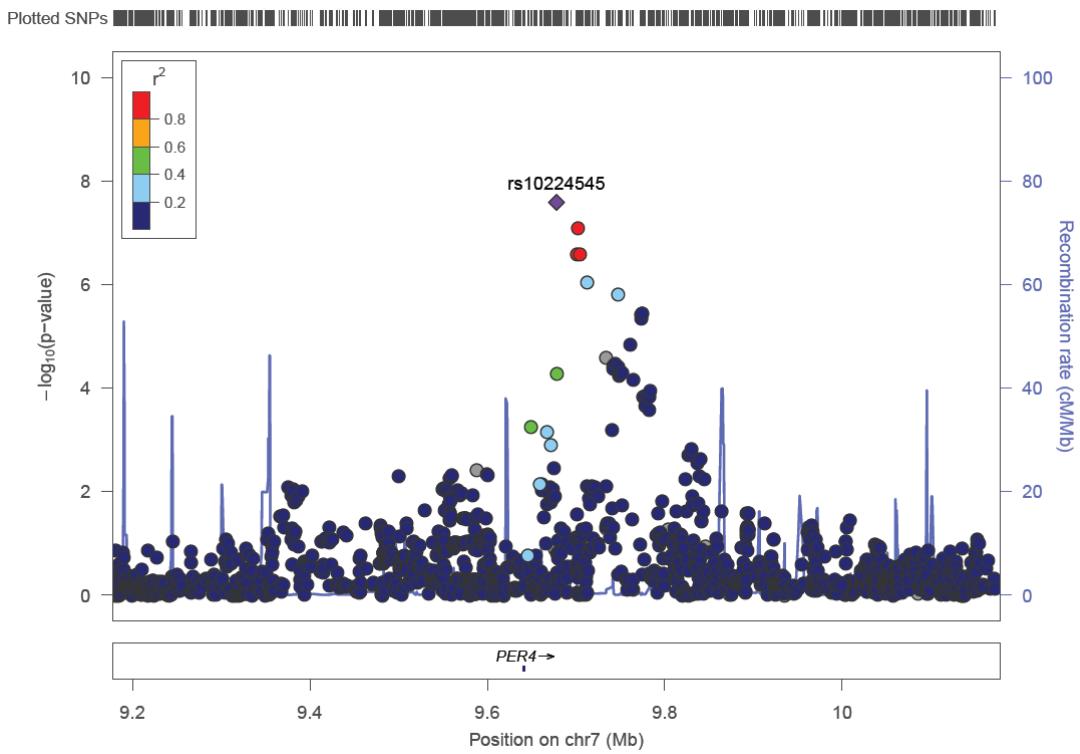
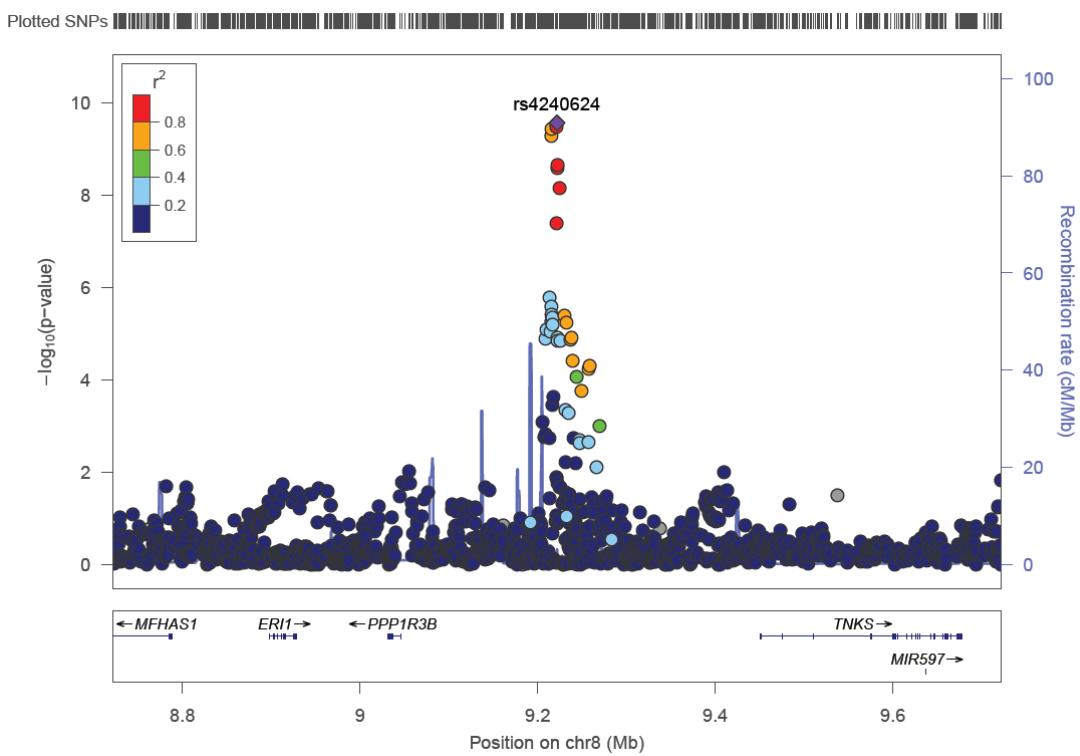
Figure S21. Region plots for each of the leading SNPs in HOMA-IR GWIS results.

a

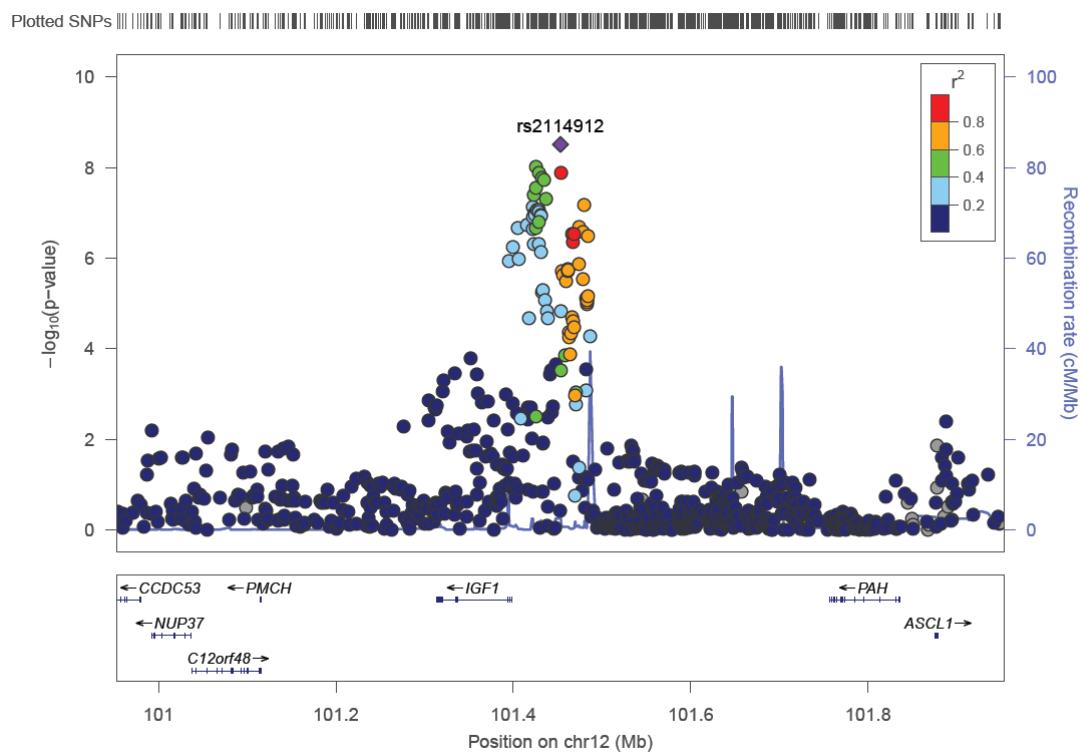


b



C**d**

e



MAGIC (the Meta-Analyses of Glucose and Insulin-related traits

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