AMP-DCC Data Analysis Report
CAMP
Phase 1

04/17/2019 (12:41)

Prepared by: Ryan Koesterer and Maria Costanzo on behalf of Broad Institute

Contact: AMP-DCC Analysis Team (amp-dcc-dat@broadinstitute.org)

This document was generated using Loamstream [16] and the AMP-DCC Data Analysis Pipeline [17]

Contents

1 Introduction

2 Data

In order to run the data we received through our analysis pipeline in an efficient manner, the genotype arrays were each given a short code name; EX. In Table 1, we list the corresponding filename of the data set we received, the format of the file set (*note: 'bfile' refers to binary Plink format [1]*), and a liftOver [2] chain file if it was required to remap the variants to GRCh37 / hg19 coordinates

See Figure 1 for intersection counts of samples available for analysis. After applying variant filters, there were 404,854 variants remaining for analysis.

Table 1: Genotype array information

ID	Filename	Format	LiftOver
EX	boxfixSEXFill_binary_11.loamstream	bfile	N/A

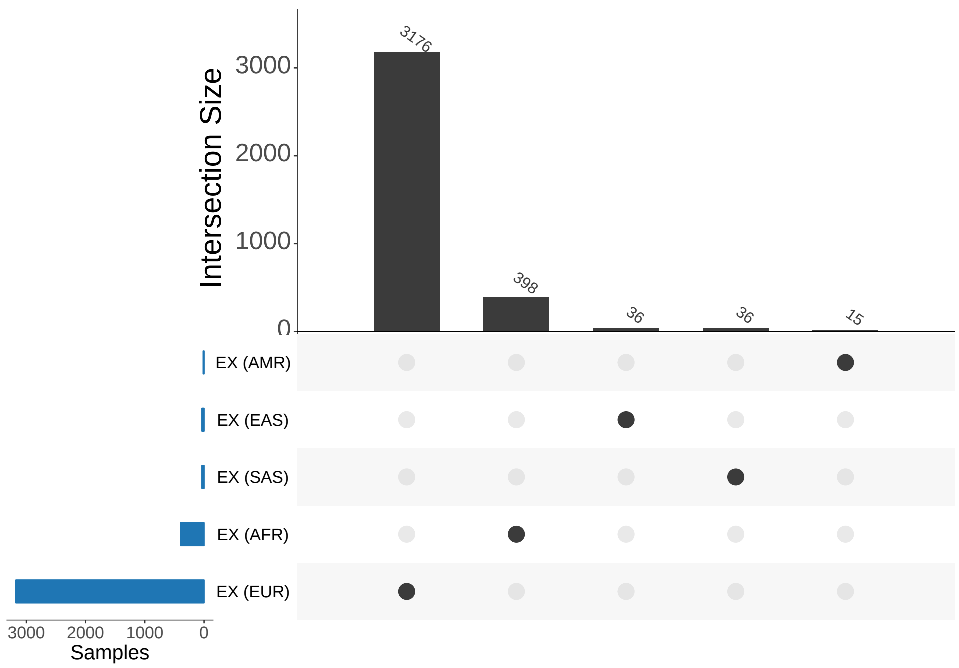


Figure 1: Samples remaining for analysis after quality control

3 Strategy

3.1 Sample structure and pipeline

The strategy we used to perform association testing can be found below. The 'ID' columns are the names used to identify each set of association test results in this document. The 'Report' columns indicate whether or not that particular set of association results will be presented in the tables and plots of the proceeding sections.

3.1.1 Cohort-level analysis

In Table 2, all of the cohorts available for analysis are defined. Each cohort was defined by a single array and one or more ancestral populations.

Table 2: Cohort-level analysis

ID	Array	Ancestry	Report
EUR	EX	EUR	NO
AFR	EX	AFR	NO

3.1.2 Meta-analysis

Table 3 defines any meta-analyses performed on the cohorts. Each cohort that was included is detailed along with the number of samples removed prior to cohort-level association testing. In order to identify samples that needed to be removed due to relatedness across cohorts, the cohorts genotypes were first merged on common variants. Then, autosomal variants with $MAF >= 0.01$ and $callrate >= 0.98$ were extracted and kinship values were calculated using King [4] with the '--kinship' flag. The reference cohort, the first one listed, maintained all of its samples. Starting from the last listed cohort, any samples shown to have some relation ($kinship >= 0.0884$) to a sample from any preceeding cohort was removed. This was continued until all cohorts subsequent to the reference cohort had been processed.

Table 3: Meta-analysis

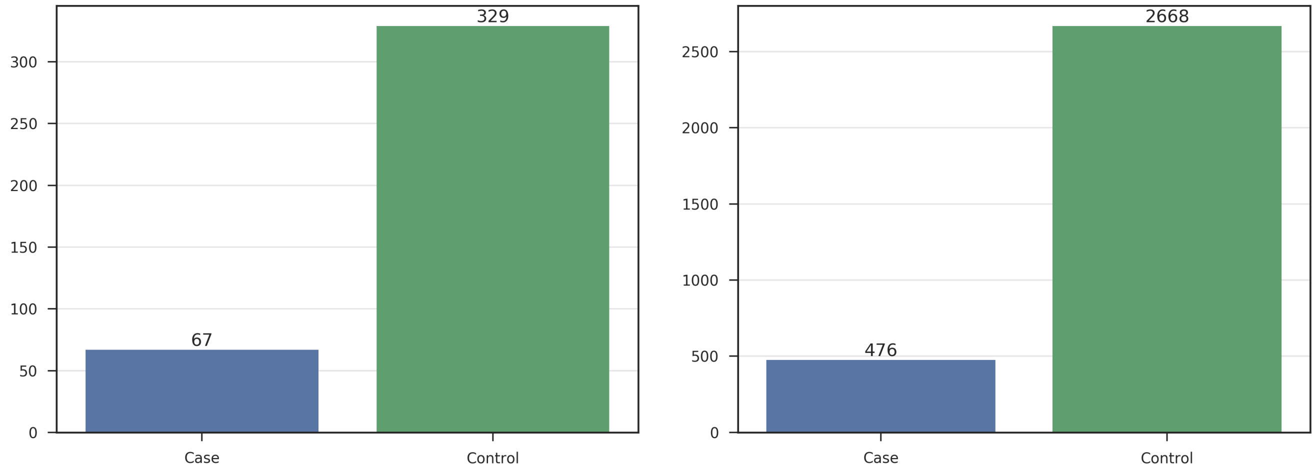
ID	Cohort	KinshipRemove	Report
META			YES
	EUR	0	
	AFR	0	

3.2 Ancestry Adjustment and Outlier Removal

Adjusting the statistical models for underlying ancestry is often crucial to reduce or eliminate Type 1 error. Often analysts include principal components of ancestry as covariates in their models as a matter of convention. In our case, we undertook a more nuanced approach. First, the top 10 PC's were calculated for each cohort using the PC-AiR method [3]. Then, the phenotype of interest was regressed on the covariates to be used in the model and all of the PC's. If the Nth PC exhibited a statistically significant p-value ($p <= 0.05$), we selected PC's $1 - N$ to be included in association testing. Once determined, any sample lying outside 6 standard deviations from the mean on any of the N PC's was marked as an outlier and removed from the sample set. This process was repeated up to a maximum of ten times until no outliers were found, resulting in more homogeneous sample sets for each particular analysis. For this project, a hard minimum of 0 PC's to be included in analysis was set by the analyst.

4 Type 2 Diabetes (T2D_HEALTH_PROVIDER)

4.1 Summary



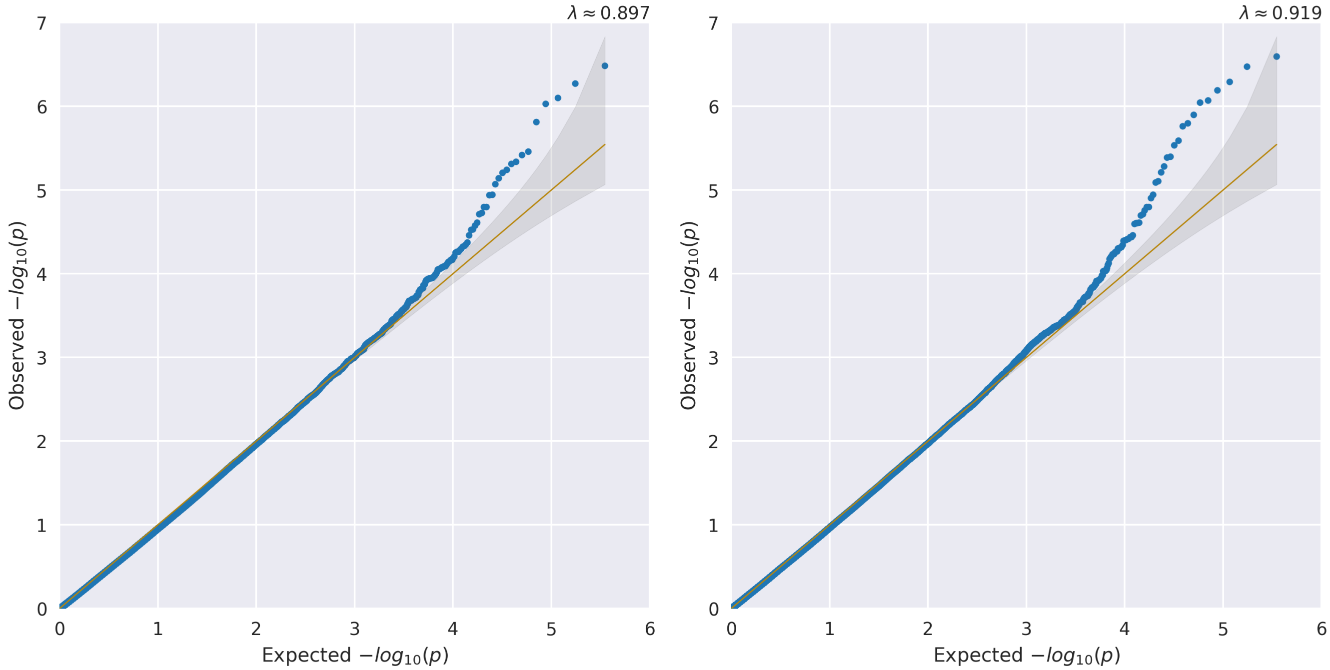
(a) AFR (b) EUR

Figure 2: Distribution of T2D_HEALTH_PROVIDER in META by cohort

Table 4: Samples with Type 2 Diabetes data summarized by cohort, transformation, and run-time adjustments

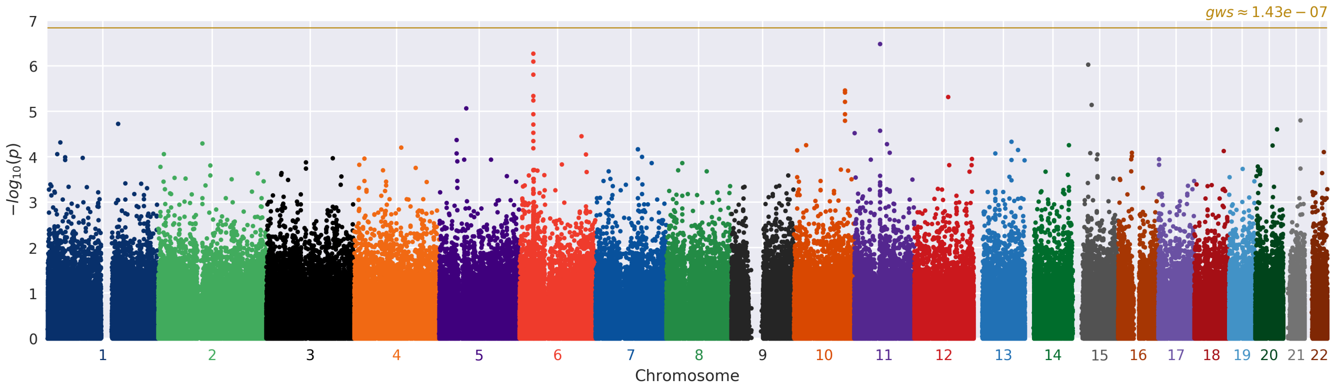
Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Case	Ctrl
META AFR	EX	AFR	-	AGE_T2D_HEALTH_PROVIDER+SEX	4	373	187	186	66	307
			-	AGE_T2D_HEALTH_PROVIDER+SEX+BMI	3	373	187	186	66	307
META EUR	EX	EUR	-	AGE_T2D_HEALTH_PROVIDER+SEX	1	3046	1853	1193	469	2577
			-	AGE_T2D_HEALTH_PROVIDER+SEX+BMI	1	3039	1850	1189	467	2572

4.2 Calibration

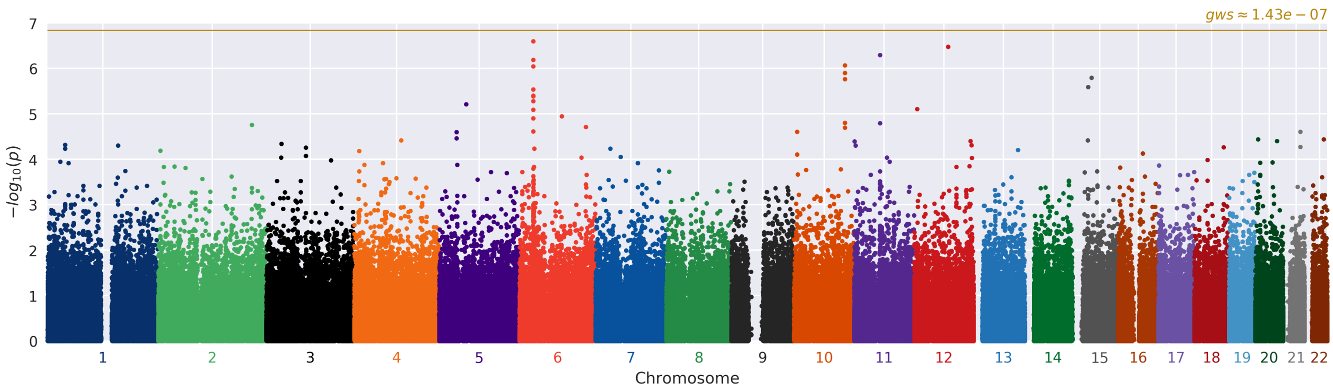


(a) Adjusted AGE_T2D_HEALTH_PROVIDER+SEX (b) Adjusted AGE_T2D_HEALTH_PROVIDER+SEX+BMI

Figure 3: QQ plots for T2D_HEALTH_PROVIDER in the META analysis



(a) Adjusted AGE_T2D_HEALTH_PROVIDER+SEX



(b) Adjusted AGE_T2D_HEALTH_PROVIDER+SEX+BMI

Figure 4: Manhattan plots for T2D_HEALTH_PROVIDER in the META analysis

4.3 Top associations

Table 5: Top variants in the META Adjusted AGE_T2D_HEALTH_PROVIDER+SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE$_{CLOSEST}$	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ$_{AVG}$	FREQ$_{MIN}$	FREQ$_{MAX}$	EFFECT	STDERR	OR	ZSCORE	P
11	58232813	rs2515350	A	G	OR5B12	++	3,419	2,040	1,379	535	2,884	0.794	0.509	0.828	0.427	$8.37 \cdot 10^{-2}$	1.533	−5.107	$3.28 \cdot 10^{-7}$
6	31253866	rs9468919	A	G	HLA-C	++	3,364	2,008	1,356	523	2,841	0.134	0.126	0.197	0.476	$9.49 \cdot 10^{-2}$	1.609	5.014	$5.33 \cdot 10^{-7}$
15	34871296	rs2879515	G	A	GOLGA8B	++	3,419	2,040	1,379	535	2,884	0.523	0.508	0.651	0.339	$6.91 \cdot 10^{-2}$	1.403	4.905	$9.34 \cdot 10^{-7}$
10	114758349	**rs7903146**	T	C	**TCF7L2**	+-	3,419	2,040	1,379	535	2,884	0.303	0.287	0.305	0.337	$7.26 \cdot 10^{-2}$	1.401	4.642	$3.46 \cdot 10^{-6}$
12	76174818	rs11180676	C	T	PHLDA1	++	3,412	2,037	1,375	533	2,879	$6.4 \cdot 10^{-2}$	$4.79 \cdot 10^{-2}$	0.196	0.595	0.13	1.813	4.572	$4.83 \cdot 10^{-6}$
15	42858891	rs1044866	T	C	HAUS2	++	3,412	2,035	1,377	534	2,878	$2.1 \cdot 10^{-2}$	$5.1 \cdot 10^{-3}$	0.15	1.012	0.226	2.752	4.489	$7.17 \cdot 10^{-6}$
5	61085552	rs6449558	C	T	ZSWIM6	++	3,419	2,040	1,379	535	2,884	0.341	0.318	0.524	0.326	$7.32 \cdot 10^{-2}$	1.385	−4.452	$8.51 \cdot 10^{-6}$
6	31318177	rs4394275	A	G	HLA-B	++	3,419	2,040	1,379	535	2,884	0.233	0.223	0.319	0.341	$7.77 \cdot 10^{-2}$	1.406	4.387	$1.15 \cdot 10^{-5}$
21	38721309	rs2835699	T	G	DYRK1A	++	3,371	2,003	1,368	530	2,841	0.405	0.395	0.484	0.31	$7.19 \cdot 10^{-2}$	1.364	−4.317	$1.58 \cdot 10^{-5}$
1	158816589	rs2188112	T	C	MNDA	++	3,417	2,039	1,378	535	2,882	0.766	0.761	0.804	0.334	$7.8 \cdot 10^{-2}$	1.396	−4.28	$1.87 \cdot 10^{-5}$
20	49036909	rs16995208	A	G	PTPN1	++	3,419	2,040	1,379	535	2,884	0.1	$8.27 \cdot 10^{-2}$	0.241	0.533	0.126	1.703	−4.219	$2.45 \cdot 10^{-5}$
11	57982896	rs2903566	T	G	OR1S2	++	3,418	2,040	1,378	534	2,884	0.432	0.312	0.447	0.288	$6.84 \cdot 10^{-2}$	1.333	4.202	$2.65 \cdot 10^{-5}$
11	1085982	rs41521548	A	G	MUC2	x+	373	187	186	66	307	$9.38 \cdot 10^{-3}$	$9.38 \cdot 10^{-3}$	$9.38 \cdot 10^{-3}$	4.183	1.002	65.529	4.175	$2.98 \cdot 10^{-5}$
6	138933559	rs4896378	G	T	NHSL1	++	3,417	2,038	1,379	534	2,883	0.34	0.298	0.681	0.306	$7.38 \cdot 10^{-2}$	1.357	4.139	$3.48 \cdot 10^{-5}$
5	39364554	rs700233	G	A	C9	++	3,419	2,040	1,379	535	2,884	0.402	0.257	0.419	0.297	$7.25 \cdot 10^{-2}$	1.346	−4.094	$4.24 \cdot 10^{-5}$
13	84629783	rs4457889	G	A	SLITRK1	++	3,419	2,040	1,379	535	2,884	0.659	0.495	0.679	0.293	$7.18 \cdot 10^{-2}$	1.34	−4.074	$4.62 \cdot 10^{-5}$
1	29139756	rs2236861	G	A	OPRD1	++	3,419	2,040	1,379	535	2,884	0.229	$9.12 \cdot 10^{-2}$	0.246	0.353	$8.67 \cdot 10^{-2}$	1.423	−4.067	$4.76 \cdot 10^{-5}$
2	99362400	rs1913621	C	T	MGAT4A	++	3,419	2,040	1,379	535	2,884	0.249	0.213	0.54	0.316	$7.78 \cdot 10^{-2}$	1.371	4.054	$5.04 \cdot 10^{-5}$
11	73787381	rs826062	G	A	C2CD3	++	3,418	2,039	1,379	535	2,883	0.492	0.469	0.68	0.278	$6.88 \cdot 10^{-2}$	1.321	−4.046	$5.2 \cdot 10^{-5}$
10	27436566	rs62622019	C	T	YME1L1	++	3,419	2,040	1,379	535	2,884	$5.66 \cdot 10^{-2}$	$5.45 \cdot 10^{-2}$	$7.37 \cdot 10^{-2}$	0.534	0.132	1.706	4.035	$5.47 \cdot 10^{-5}$

Table 6: Top variants in the META Adjusted AGE_T2D_HEALTH_PROVIDER+SEX+BMI model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE$_{CLOSEST}$	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ$_{AVG}$	FREQ$_{MIN}$	FREQ$_{MAX}$	EFFECT	STDERR	OR	ZSCORE	P
6	31253866	rs9468919	A	G	HLA-C	++	3,357	2,005	1,352	521	2,836	0.134	0.126	0.197	0.51	$9.9 \cdot 10^{-2}$	1.666	5.156	$2.52 \cdot 10^{-7}$
12	76174818	rs11180676	C	T	PHLDA1	++	3,405	2,034	1,371	531	2,874	$6.36 \cdot 10^{-2}$	$4.73 \cdot 10^{-2}$	0.196	0.696	0.136	2.006	5.104	$3.33 \cdot 10^{-7}$
11	58232813	rs2515350	A	G	OR5B12	++	3,412	2,037	1,375	533	2,879	0.794	0.509	0.829	0.439	$8.75 \cdot 10^{-2}$	1.552	−5.023	$5.09 \cdot 10^{-7}$
10	114754088	**rs7901695**	C	T	**TCF7L2**	++	3,411	2,037	1,374	533	2,878	0.337	0.325	0.437	0.363	$7.38 \cdot 10^{-2}$	1.438	4.923	$8.51 \cdot 10^{-7}$
15	42858891	rs1044866	T	C	HAUS2	++	3,405	2,032	1,373	532	2,873	$2.1 \cdot 10^{-2}$	$5.11 \cdot 10^{-3}$	0.15	1.135	0.236	3.111	4.8	$1.58 \cdot 10^{-6}$
15	34871296	rs2879515	G	A	GOLGA8B	++	3,412	2,037	1,375	533	2,879	0.523	0.507	0.651	0.339	$7.21 \cdot 10^{-2}$	1.404	4.702	$2.57 \cdot 10^{-6}$
6	31318177	rs4394275	A	G	HLA-B	++	3,412	2,037	1,375	533	2,879	0.233	0.223	0.319	0.374	$8.11 \cdot 10^{-2}$	1.454	4.613	$3.98 \cdot 10^{-6}$
5	61085552	rs6449558	C	T	ZSWIM6	++	3,412	2,037	1,375	533	2,879	0.341	0.319	0.524	0.343	$7.58 \cdot 10^{-2}$	1.409	−4.523	$6.09 \cdot 10^{-6}$
12	6666584	exm978001	G	C	NOP2	+x	3,035	1,847	1,188	467	2,568	$1.98 \cdot 10^{-3}$	$1.98 \cdot 10^{-3}$	$1.98 \cdot 10^{-3}$	3.13	0.7	22.865	4.47	$7.81 \cdot 10^{-6}$
6	94845639	rs515814	G	T	EPHA7	++	3,412	2,037	1,375	533	2,879	$4.04 \cdot 10^{-2}$	$2.78 \cdot 10^{-2}$	0.143	0.741	0.169	2.098	4.391	$1.13 \cdot 10^{-5}$
11	57982896	rs2903566	T	G	OR1S2	++	3,411	2,037	1,374	532	2,879	0.432	0.312	0.447	0.308	$7.14 \cdot 10^{-2}$	1.361	4.315	$1.6 \cdot 10^{-5}$
2	210552162	rs3768815	C	T	MAP2	++	3,412	2,037	1,375	533	2,879	0.144	0.101	0.501	0.485	0.113	1.624	−4.295	$1.75 \cdot 10^{-5}$
6	149658978	rs504985	G	T	TAB2	++	3,412	2,037	1,375	533	2,879	0.372	0.307	0.38	0.315	$7.39 \cdot 10^{-2}$	1.371	4.271	$1.95 \cdot 10^{-5}$
21	38721309	rs2835699	T	G	DYRK1A	++	3,364	2,000	1,364	528	2,836	0.405	0.395	0.484	0.317	$7.52 \cdot 10^{-2}$	1.374	−4.218	$2.46 \cdot 10^{-5}$
10	7315240	rs10905143	C	T	SFMBT2	++	3,412	2,037	1,375	533	2,879	0.491	0.49	0.501	0.302	$7.15 \cdot 10^{-2}$	1.352	4.216	$2.48 \cdot 10^{-5}$
5	39364554	rs700233	G	A	C9	++	3,412	2,037	1,375	533	2,879	0.402	0.257	0.419	0.321	$7.61 \cdot 10^{-2}$	1.378	−4.213	$2.52 \cdot 10^{-5}$
20	6209524	rs6085440	G	A	FERMT1	++	3,354	2,007	1,347	528	2,826	0.341	0.251	0.352	0.315	$7.63 \cdot 10^{-2}$	1.37	4.13	$3.63 \cdot 10^{-5}$
22	43041545	rs6002850	G	A	CYB5R3	++	3,412	2,037	1,375	533	2,879	0.277	0.264	0.387	0.323	$7.83 \cdot 10^{-2}$	1.382	4.129	$3.64 \cdot 10^{-5}$
4	105333354	rs10007721	C	A	CXXC4	++	3,412	2,037	1,375	533	2,879	0.737	0.726	0.823	0.328	$7.97 \cdot 10^{-2}$	1.389	−4.119	$3.8 \cdot 10^{-5}$
15	33879608	rs10153042	A	G	RYR3	++	3,412	2,037	1,375	533	2,879	0.38	0.369	0.472	0.308	$7.48 \cdot 10^{-2}$	1.361	−4.118	$3.83 \cdot 10^{-5}$

4.4 Previously identified risk loci

Table 7 shows statistics from the META cohort for 47 loci that were shown to be significantly associated with Type 2 Diabetes in the 2012 Nature Genetics paper by Morris et al [7]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R^2} < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R^2} >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 7 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 43 variants in both studies, 33 exhibit the same direction of effect with the known result (binomial test $p = 0.000303$).

Table 7: Top known loci in META model Adjusted AGE_T2D_HEALTH_PROVIDER+SEX (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	CASE	CTRL	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	OR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$CASE_{KNOWN}$	$CTRL_{KNOWN}$	OR_{KNOWN}	P_{KNOWN}
10	114758349	**rs7903146**	T	C	3,419	535	2,884	0.303	0.287	0.305	1.401	$3.46 \cdot 10^{-6}$	+-	TCF7L2	1	rs7903146	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.389	$1.2 \cdot 10^{-139}$
6	20679709	**rs7756992**	G	A	3,418	534	2,884	0.3	0.272	0.526	1.067	0.389	++	CDKAL1	1	rs7756992	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.167	$6.95 \cdot 10^{-35}$
9	22134094	**rs10811661**	T	C	3,403	535	2,868	0.164	$8.47 \cdot 10^{-2}$	0.173	1.163	0.109	++	CDKN2B	1	rs10811661	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.185	$3.72 \cdot 10^{-27}$
3	185511687	**rs4402960**	T	G	3,419	535	2,884	0.359	0.337	0.542	1.195	$1.25 \cdot 10^{-2}$	++	IGF2BP2	1	rs4402960	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.131	$2.39 \cdot 10^{-23}$
16	53819169	**rs9936385**	C	T	3,419	535	2,884	0.424	0.419	0.462	1.05	0.48	+-	FTO	1	rs9936385	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.129	$2.61 \cdot 10^{-23}$
8	118185025	**rs3802177**	G	A	3,419	535	2,884	0.28	0.119	0.3	1.165	$5.12 \cdot 10^{-2}$	+-	SLC30A8	1	rs3802177	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.136	$1.26 \cdot 10^{-21}$
10	94481917	**rs7923837**	G	A	3,417	535	2,882	0.361	0.101	0.393	1.096	0.203	+-	HHEX	1	rs7923837	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.113	$2.37 \cdot 10^{-18}$
7	28180556	**rs864745**	T	C	3,414	534	2,880	0.471	0.26	0.497	1.035	0.619	++	JAZF1	1	rs864745	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.099	$2.28 \cdot 10^{-16}$
4	6303022	**rs1801214**	T	C	3,419	535	2,884	0.63	0.625	0.67	1.053	0.464	+-	WFS1	1	rs1801214	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.102	$3.3 \cdot 10^{-15}$
2	227093585	**rs2943640**	C	A	3,418	535	2,883	0.681	0.656	0.887	1.164	$4.12 \cdot 10^{-2}$	++	IRS1	1	rs2943640	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.096	$2.69 \cdot 10^{-14}$
3	123065778	**rs11708067**	A	G	3,413	534	2,879	0.203	0.173	0.207	1.074	0.395	+-	ADCY5	1	rs11708067	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.113	$7.19 \cdot 10^{-14}$
10	94374377	**rs10882091**	C	T	3,419	535	2,884	0.641	0.615	0.853	1.12	0.109	++	KIF11	1	rs10882091	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.092	$8.31 \cdot 10^{-13}$
11	92673828	rs1387153	C	T	3,419	535	2,884	0.302	0.294	0.369	1.037	0.621	++	MTNR1B	1	rs1387153	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.915	$1.59 \cdot 10^{-11}$
4	6315954	**rs10804976**	T	G	3,417	535	2,882	0.559	0.516	0.564	1.067	0.347	+-	PPP2R2C	1	rs10804976	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.085	$3.77 \cdot 10^{-11}$
3	12391583	**rs2197423**	G	A	3,419	535	2,884	0.122	0.116	0.173	1.237	$4.89 \cdot 10^{-2}$	++	PPARG	1	rs2197423	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.123	$5.25 \cdot 10^{-11}$
3	64705365	**rs6795735**	C	T	3,419	535	2,884	0.502	0.463	0.823	1.034	0.636	++	ADAMTS9	1	rs6795735	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.08	$7.39 \cdot 10^{-11}$
10	80942631	rs12571751	G	A	3,419	535	2,884	0.447	0.445	0.464	1.039	0.581	++	ZMIZ1	1	rs12571751	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.928	$1.02 \cdot 10^{-10}$
11	72433098	rs1552224	C	A	3,418	534	2,884	0.117	$3.63 \cdot 10^{-2}$	0.127	1.066	0.554	+-	ARAP1	1	rs1552224	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.903	$1.79 \cdot 10^{-10}$
17	36099840	**rs11651755**	C	T	3,408	532	2,876	0.479	0.365	0.493	1.017	0.805	+-	HNF1B	1	rs11651755	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.098	$1.84 \cdot 10^{-10}$
7	14922007	rs10276674	T	C	3,419	535	2,884	0.17	0.164	0.217	1.072	0.453	++	DGKB	1	rs10276674	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.908	$2.07 \cdot 10^{-10}$
11	2858546	**rs2237897**	C	T	3,417	535	2,882	$4.71 \cdot 10^{-2}$	$3.98 \cdot 10^{-2}$	0.107	1.291	0.124	++	KCNQ1	1	rs2237897	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.215	$2.1 \cdot 10^{-10}$
8	41519248	**rs516946**	C	T	3,419	535	2,884	0.749	0.745	0.784	1.155	$7.1 \cdot 10^{-2}$	+-	ANK1	1	rs516946	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.091	$2.49 \cdot 10^{-10}$
2	43687879	**rs17030845**	C	T	3,419	535	2,884	$9.8 \cdot 10^{-2}$	$9.34 \cdot 10^{-2}$	0.135	1.112	0.36	++	THADA	1	rs17030845	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.14	$3.28 \cdot 10^{-10}$
2	227020653	**rs7578326**	A	G	3,419	535	2,884	0.357	0.347	0.444	1.151	$4.91 \cdot 10^{-2}$	++	NYAP2	1	rs7578326	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.083	$3.81 \cdot 10^{-10}$
12	27965150	**rs10842994**	C	T	3,419	535	2,884	0.18	$5.5 \cdot 10^{-2}$	0.195	1.039	0.673	++	KLHL42	1	rs10842994	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.096	$6.08 \cdot 10^{-10}$
11	17408630	**rs5215**	C	T	3,419	535	2,884	0.675	0.647	0.906	1.241	$3.06 \cdot 10^{-3}$	++	KCNJ11	1	rs5215	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.075	$8.5 \cdot 10^{-10}$
12	66192667	rs2612035	A	G	3,414	533	2,881	0.166	0.123	0.511	1.115	0.275	++	HMGA2	1	rs2612035	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.889	$2.95 \cdot 10^{-9}$
3	23454790	**rs1496653**	A	G	3,419	535	2,884	0.209	0.191	0.354	1.014	0.869	+-	UBE2E2	1	rs1496653	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.085	$3.56 \cdot 10^{-9}$
15	77832762	**rs7177055**	A	G	3,419	535	2,884	0.668	0.367	0.705	1.054	0.482	+-	HMG20A	1	rs7177055	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.077	$4.6 \cdot 10^{-9}$
11	17418477	**rs757110**	C	A	3,419	535	2,884	0.675	0.645	0.924	1.277	$8.24 \cdot 10^{-4}$	++	ABCC8	1	rs757110	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.074	$5 \cdot 10^{-9}$
9	84308948	**rs2796441**	G	A	3,419	535	2,884	0.361	0.168	0.384	1.05	0.503	++	TLE1	1	rs2796441	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.074	$5.39 \cdot 10^{-9}$
5	55806751	**rs459193**	G	A	3,419	535	2,884	0.734	0.591	0.751	1.06	0.46	+-	AC022431.2	1	rs459193	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.081	$5.99 \cdot 10^{-9}$
19	19407718	rs10401969	T	C	3,419	535	2,884	$7.78 \cdot 10^{-2}$	$6.58 \cdot 10^{-2}$	0.176	1.036	0.782	+-	SUGP1	1	rs10401969	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.881	$7.04 \cdot 10^{-9}$
2	165528876	**rs13389219**	C	T	3,419	535	2,884	0.416	0.381	0.7	1.066	0.361	++	COBLL1	1	rs13389219	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.073	$1 \cdot 10^{-8}$
19	19658472	rs16996148	G	T	3,419	535	2,884	$8.12 \cdot 10^{-2}$	$6.96 \cdot 10^{-2}$	0.176	1.041	0.749	-+	CILP2	1	rs16996148	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.889	$1.12 \cdot 10^{-8}$
18	57884750	**rs12970134**	A	G	3,418	535	2,883	0.242	0.18	0.25	1.02	0.796	++	MC4R	1	rs12970134	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.078	$1.19 \cdot 10^{-8}$
13	80717156	rs1359790	A	G	3,419	535	2,884	0.253	0.123	0.268	1.082	0.316	++	SPRY2	1	rs1359790	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.929	$1.39 \cdot 10^{-8}$
10	94257976	**rs11187025**	T	C	3,418	535	2,883	0.193	0.182	0.195	1.092	0.299	++	IDE	1	rs11187025	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.083	$1.68 \cdot 10^{-8}$
11	72669777	rs11605166	C	T	3,413	534	2,879	0.141	0.105	0.146	1.092	0.372	++	FCHSD2	1	rs11605166	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.919	$1.86 \cdot 10^{-8}$
2	60573870	**rs243083**	G	A	3,417	535	2,882	0.498	0.482	0.623	1.038	0.592	++	BCL11A	1	rs243083	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.069	$2.17 \cdot 10^{-8}$
2	165501849	**rs3923113**	A	C	3,419	535	2,884	0.383	0.351	0.645	1.042	0.56	+-	GRB14	1	rs3923113	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.073	$3.28 \cdot 10^{-8}$
16	75247245	rs7202877	G	T	3,419	535	2,884	0.113	0.104	0.185	1.026	0.809	+-	CTRB1	1	rs7202877	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.895	$3.5 \cdot 10^{-8}$
4	153520475	**rs6813195**	C	T	3,418	535	2,883	0.318	0.303	0.437	1.09	0.246	+-	TMEM154	1	rs6813195	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.073	$5.26 \cdot 10^{-8}$
2	43822006	rs6717791	A	G	3,419	535	2,884	0.127	0.116	0.217	1.054	0.615	+-	PLEKHH2	0.958	rs17031133	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.904	$2.69 \cdot 10^{-8}$
12	71425164	**rs7959965**	C	T	3,417	535	2,882	0.531	0.527	0.568	1.071	0.314	++	CTD-2021H9.3	0.909	rs7955901	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.072	$6.51 \cdot 10^{-9}$
19	19379549	rs58542926	C	T	3,419	535	2,884	$6.17 \cdot 10^{-2}$	$3.62 \cdot 10^{-2}$	$6.48 \cdot 10^{-2}$	1.145	0.358	++	HAPLN4	0.879	rs72999033	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.853	$2.6 \cdot 10^{-8}$
11	72669777	rs11605166	C	T	3,413	534	2,879	0.141	0.105	0.146	1.092	0.372	++	STARD10	0.851	rs613937	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.91	$8.64 \cdot 10^{-10}$

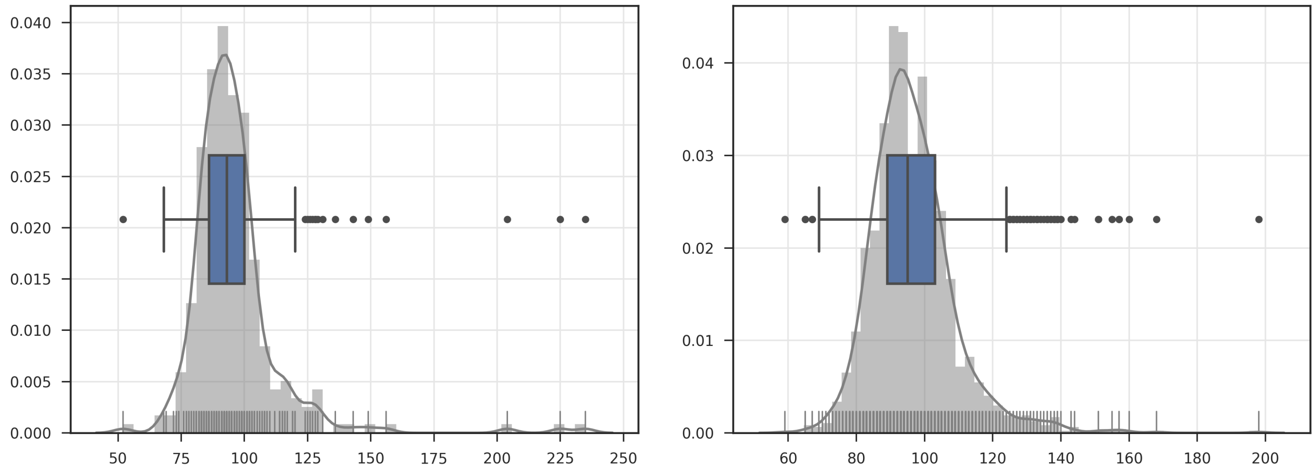
Table 8 shows statistics from the META cohort for 47 loci that were shown to be significantly associated with Type 2 Diabetes in the 2012 Nature Genetics paper by Morris et al [7]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R}^2 < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R}^2 >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 8 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 43 variants in both studies, 36 exhibit the same direction of effect with the known result (binomial test $p = 4.48e - 06$).

Table 8: Top known loci in META model Adjusted AGE_T2D_HEALTH_PROVIDER+SEX+BMI (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	CASE	CTRL	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	OR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$CASE_{KNOWN}$	$CTRL_{KNOWN}$	OR_{KNOWN}	P_{KNOWN}
10	114758349	**rs7903146**	T	C	3,412	533	2,879	0.303	0.287	0.305	1.437	$1.72 \cdot 10^{-6}$	++	TCF7L2	1	rs7903146	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.389	$1.2 \cdot 10^{-139}$
6	20679709	**rs7756992**	G	A	3,411	532	2,879	0.3	0.272	0.526	1.084	0.304	+-	CDKAL1	1	rs7756992	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.167	$6.95 \cdot 10^{-35}$
9	22134094	**rs10811661**	T	C	3,396	533	2,863	0.164	$8.47 \cdot 10^{-2}$	0.173	1.204	$6.04 \cdot 10^{-2}$	++	CDKN2B	1	rs10811661	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.185	$3.72 \cdot 10^{-27}$
3	185511687	**rs4402960**	T	G	3,412	533	2,879	0.359	0.337	0.542	1.22	$7.3 \cdot 10^{-3}$	++	IGF2BP2	1	rs4402960	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.131	$2.39 \cdot 10^{-23}$
16	53819169	**rs9936385**	C	T	3,412	533	2,879	0.424	0.419	0.462	1.016	0.829	+-	FTO	1	rs9936385	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.129	$2.61 \cdot 10^{-23}$
8	118185025	**rs3802177**	G	A	3,412	533	2,879	0.28	0.119	0.3	1.212	$1.97 \cdot 10^{-2}$	+-	SLC30A8	1	rs3802177	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.136	$1.26 \cdot 10^{-21}$
10	94481917	**rs7923837**	G	A	3,410	533	2,877	0.361	0.101	0.393	1.133	$9.87 \cdot 10^{-2}$	++	HHEX	1	rs7923837	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.113	$2.37 \cdot 10^{-18}$
7	28180556	**rs864745**	T	C	3,407	532	2,875	0.471	0.26	0.497	1.084	0.262	+-	JAZF1	1	rs864745	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.099	$2.28 \cdot 10^{-16}$
4	6303022	**rs1801214**	T	C	3,412	533	2,879	0.629	0.624	0.67	1.069	0.371	+-	WFS1	1	rs1801214	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.102	$3.3 \cdot 10^{-15}$
2	227093585	**rs2943640**	C	A	3,411	533	2,878	0.681	0.656	0.887	1.234	$6.72 \cdot 10^{-3}$	++	IRS1	1	rs2943640	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.096	$2.69 \cdot 10^{-14}$
3	123065778	**rs11708067**	A	G	3,406	532	2,874	0.204	0.173	0.207	1.174	$6.62 \cdot 10^{-2}$	+-	ADCY5	1	rs11708067	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.113	$7.19 \cdot 10^{-14}$
10	94374377	**rs10882091**	C	T	3,412	533	2,879	0.64	0.614	0.853	1.14	$7.63 \cdot 10^{-2}$	++	KIF11	1	rs10882091	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.092	$8.31 \cdot 10^{-13}$
11	92673828	rs1387153	C	T	3,412	533	2,879	0.302	0.294	0.369	1.052	0.511	++	MTNR1B	1	rs1387153	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.915	$1.59 \cdot 10^{-11}$
4	6315954	**rs10804976**	T	G	3,410	533	2,877	0.558	0.516	0.564	1.07	0.355	+-	PPP2R2C	1	rs10804976	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.085	$3.77 \cdot 10^{-11}$
3	12391583	**rs2197423**	G	A	3,412	533	2,879	0.122	0.116	0.173	1.248	$4.73 \cdot 10^{-2}$	++	PPARG	1	rs2197423	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.123	$5.25 \cdot 10^{-11}$
3	64705365	**rs6795735**	C	T	3,412	533	2,879	0.502	0.463	0.823	1.049	0.513	++	ADAMTS9	1	rs6795735	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.08	$7.39 \cdot 10^{-11}$
10	80942631	rs12571751	G	A	3,412	533	2,879	0.448	0.446	0.464	1.056	0.449	++	ZMIZ1	1	rs12571751	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.928	$1.02 \cdot 10^{-10}$
11	72433098	rs1552224	C	A	3,411	532	2,879	0.117	$3.63 \cdot 10^{-2}$	0.127	1.034	0.768	+-	ARAP1	1	rs1552224	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.903	$1.79 \cdot 10^{-10}$
17	36099840	**rs11651755**	C	T	3,401	530	2,871	0.48	0.365	0.494	1.018	0.796	+-	HNF1B	1	rs11651755	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.098	$1.84 \cdot 10^{-10}$
7	14922007	rs10276674	T	C	3,412	533	2,879	0.17	0.164	0.217	1.025	0.799	++	DGKB	1	rs10276674	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.908	$2.07 \cdot 10^{-10}$
11	2858546	**rs2237897**	C	T	3,410	533	2,877	$4.69 \cdot 10^{-2}$	$3.95 \cdot 10^{-2}$	0.107	1.212	0.265	+-	KCNQ1	1	rs2237897	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.215	$2.1 \cdot 10^{-10}$
8	41519248	**rs516946**	C	T	3,412	533	2,879	0.749	0.745	0.784	1.137	0.123	+-	ANK1	1	rs516946	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.091	$2.49 \cdot 10^{-10}$
2	43687879	**rs17030845**	C	T	3,412	533	2,879	$9.79 \cdot 10^{-2}$	$9.33 \cdot 10^{-2}$	0.135	1.138	0.288	++	THADA	1	rs17030845	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.14	$3.28 \cdot 10^{-10}$
2	227020653	**rs7578326**	A	G	3,412	533	2,879	0.357	0.347	0.444	1.21	$1.04 \cdot 10^{-2}$	++	NYAP2	1	rs7578326	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.083	$3.81 \cdot 10^{-10}$
12	27965150	**rs10842994**	C	T	3,412	533	2,879	0.18	$5.5 \cdot 10^{-2}$	0.195	1.083	0.399	++	KLHL42	1	rs10842994	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.096	$6.08 \cdot 10^{-10}$
11	17408630	**rs5215**	C	T	3,412	533	2,879	0.675	0.647	0.906	1.242	$4.26 \cdot 10^{-3}$	++	KCNJ11	1	rs5215	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.075	$8.5 \cdot 10^{-10}$
12	66192667	rs2612035	A	G	3,407	531	2,876	0.166	0.123	0.511	1.159	0.152	+-	HMGA2	1	rs2612035	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.889	$2.95 \cdot 10^{-9}$
3	23454790	**rs1496653**	A	G	3,412	533	2,879	0.209	0.191	0.354	1	0.998	+-	UBE2E2	1	rs1496653	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.085	$3.56 \cdot 10^{-9}$
15	77832762	**rs7177055**	A	G	3,412	533	2,879	0.668	0.367	0.705	1.093	0.26	++	HMG20A	1	rs7177055	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.077	$4.6 \cdot 10^{-9}$
11	17418477	**rs757110**	C	A	3,412	533	2,879	0.675	0.645	0.924	1.275	$1.37 \cdot 10^{-3}$	++	ABCC8	1	rs757110	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.074	$5 \cdot 10^{-9}$
9	84308948	**rs2796441**	G	A	3,412	533	2,879	0.361	0.168	0.385	1.039	0.617	++	TLE1	1	rs2796441	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.074	$5.39 \cdot 10^{-9}$
5	55806751	**rs459193**	G	A	3,412	533	2,879	0.734	0.591	0.751	1.074	0.386	+-	AC022431.2	1	rs459193	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.081	$5.99 \cdot 10^{-9}$
19	19407718	**rs10401969**	C	T	3,412	533	2,879	$7.8 \cdot 10^{-2}$	$6.6 \cdot 10^{-2}$	0.176	1.001	0.996	-+	SUGP1	1	rs10401969	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.135	$7.04 \cdot 10^{-9}$
2	165528876	**rs13389219**	C	T	3,412	533	2,879	0.415	0.381	0.7	1.094	0.217	++	COBLL1	1	rs13389219	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.073	$1 \cdot 10^{-8}$
19	19658472	**rs16996148**	T	G	3,412	533	2,879	$8.13 \cdot 10^{-2}$	$6.98 \cdot 10^{-2}$	0.176	1.032	0.81	+-	CILP2	1	rs16996148	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.124	$1.12 \cdot 10^{-8}$
18	57884750	**rs12970134**	A	G	3,411	533	2,878	0.242	0.18	0.25	1.056	0.504	++	MC4R	1	rs12970134	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.078	$1.19 \cdot 10^{-8}$
13	80717156	rs1359790	A	G	3,412	533	2,879	0.252	0.123	0.268	1.044	0.599	++	SPRY2	1	rs1359790	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.929	$1.39 \cdot 10^{-8}$
10	94257976	**rs11187025**	T	C	3,411	533	2,878	0.193	0.182	0.195	1.105	0.259	++	IDE	1	rs11187025	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.083	$1.68 \cdot 10^{-8}$
11	72669777	rs11605166	C	T	3,406	532	2,874	0.14	0.105	0.145	1.114	0.297	++	FCHSD2	1	rs11605166	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.919	$1.86 \cdot 10^{-8}$
2	60573870	**rs243083**	G	A	3,410	533	2,877	0.497	0.482	0.623	1.081	0.28	++	BCL11A	1	rs243083	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.069	$2.17 \cdot 10^{-8}$
2	165501849	**rs3923113**	A	C	3,412	533	2,879	0.383	0.351	0.645	1.08	0.304	++	GRB14	1	rs3923113	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.073	$3.28 \cdot 10^{-8}$
16	75247245	**rs7202877**	T	G	3,412	533	2,879	0.113	0.104	0.185	1.01	0.933	-+	CTRB1	1	rs7202877	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.117	$3.5 \cdot 10^{-8}$
4	153520475	**rs6813195**	C	T	3,411	533	2,878	0.317	0.303	0.437	1.141	$8.99 \cdot 10^{-2}$	+-	TMEM154	1	rs6813195	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.073	$5.26 \cdot 10^{-8}$
2	43822006	rs6717791	A	G	3,412	533	2,879	0.126	0.115	0.217	1.075	0.505	+-	PLEKHH2	0.958	rs17031133	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.904	$2.69 \cdot 10^{-8}$
12	71425164	**rs7959965**	C	T	3,410	533	2,877	0.531	0.527	0.568	1.07	0.339	++	CTD-2021H9.3	0.909	rs7955901	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	1.072	$6.51 \cdot 10^{-9}$
19	19379549	rs58542926	C	T	3,412	533	2,879	$6.18 \cdot 10^{-2}$	$3.62 \cdot 10^{-2}$	$6.5 \cdot 10^{-2}$	1.093	0.557	++	HAPLN4	0.879	rs72999033	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.853	$2.6 \cdot 10^{-8}$
11	72669777	rs11605166	C	T	3,406	532	2,874	0.14	0.105	0.145	1.114	0.297	++	STARD10	0.851	rs613937	$1.5 \cdot 10^5$	34,840	$1.15 \cdot 10^5$	0.91	$8.64 \cdot 10^{-10}$

5 Fasting Glucose (GLU_FAST)

5.1 Summary



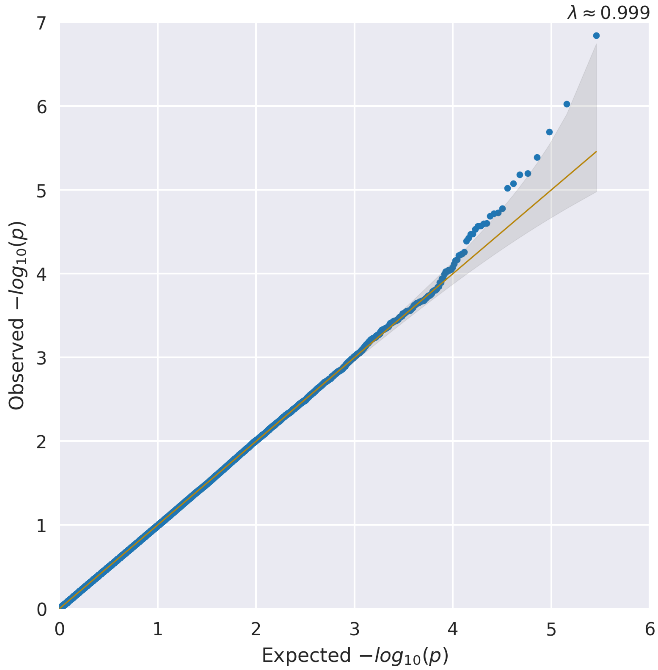
(a) AFR (b) EUR

Figure 5: Distribution of GLU_FAST in META by cohort

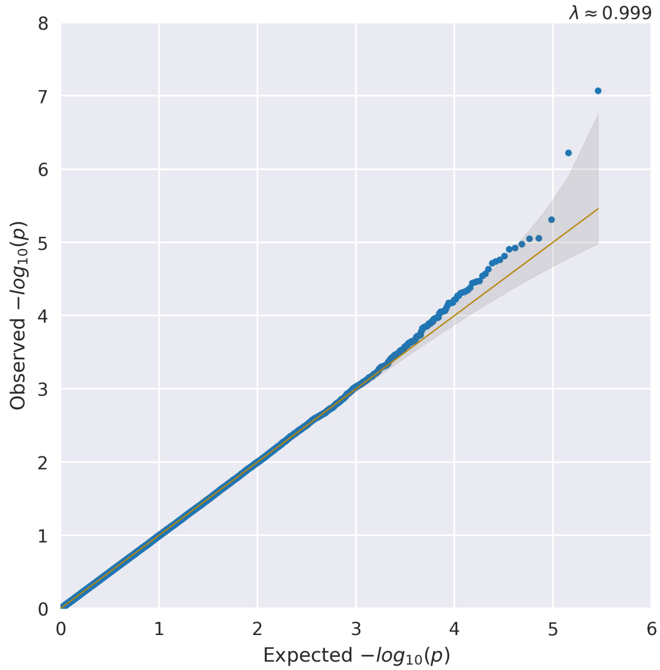
Table 9: Samples with Fasting Glucose data summarized by cohort, transformation, and run-time adjustments

Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Max	Min	μ	$\tilde{x}$	σ
META AFR	EX	AFR	invn	AGE_GLU_INS_FAST+SEX	0	278	141	137	235.0	52.0	96.14	93.0	18.57
			invn	AGE_GLU_INS_FAST+SEX+BMI	0	278	141	137	235.0	52.0	96.14	93.0	18.57
META EUR	EX	EUR	invn	AGE_GLU_INS_FAST+SEX+BMI	0	1678	978	700	198.0	59.0	96.545	95.0	12.372
			invn	AGE_GLU_INS_FAST+SEX	0	1663	968	695	198.0	59.0	96.635	95.0	12.368

5.2 Calibration

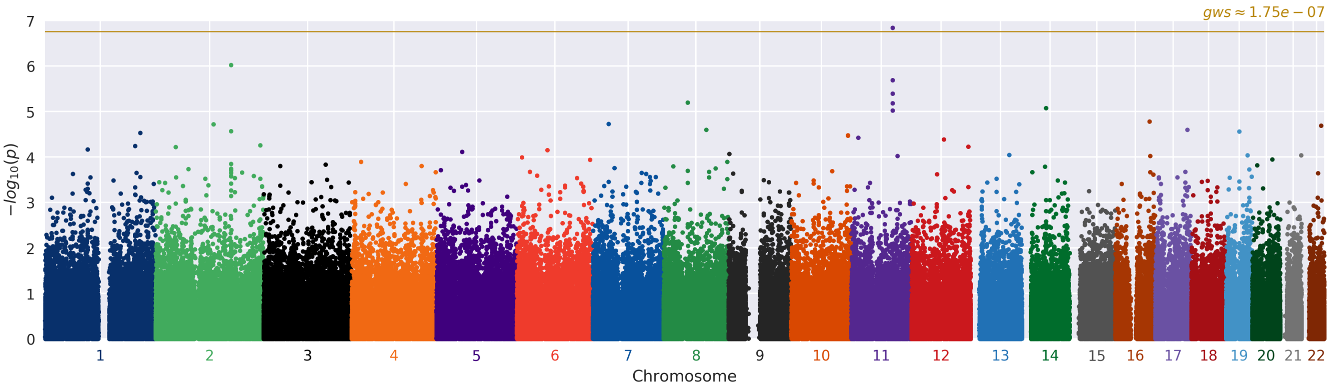


(a) invn Adjusted AGE_GLU_INS_FAST+SEX

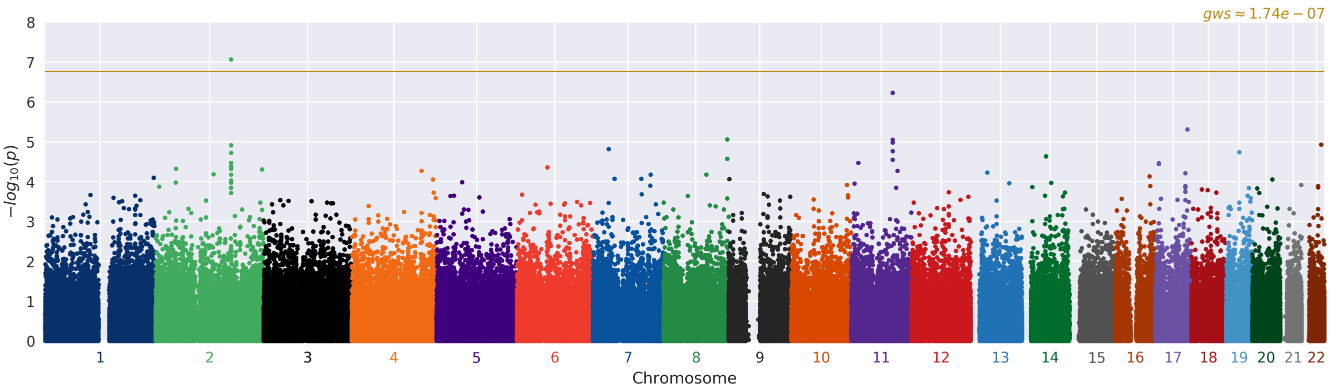


(b) invn Adjusted AGE_GLU_INS_FAST+SEX+BMI

Figure 6: QQ plots for GLU_FAST in the META analysis



(a) invn Adjusted AGE_GLU_INS_FAST+SEX



(b) invn Adjusted AGE_GLU_INS_FAST+SEX+BMI

Figure 7: Manhattan plots for GLU_FAST in the META analysis

5.3 Top associations

Table 10: Top variants in the META invn Adjusted AGE_GLU_INS_FAST+SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	$GENE_{CLOSEST}$	DIR	N	MALE	FEMALE	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	EFFECT	STDERR	OR	ZSCORE	P
11	92698427	**rs10830962**	G	C	**MTNR1B**	++	1,939	1,107	832	0.457	0.4	0.793	0.178	$3.38 \cdot 10^{-2}$	1.195	5.262	$1.43 \cdot 10^{-7}$
2	169763148	**rs560887**	C	T	**G6PC2**	++	1,941	1,109	832	0.748	0.715	0.948	0.182	$3.71 \cdot 10^{-2}$	1.2	4.904	$9.4 \cdot 10^{-7}$
8	54130075	rs2114105	A	G	OPRK1	++	1,941	1,109	832	0.591	0.246	0.648	0.152	$3.36 \cdot 10^{-2}$	1.164	−4.514	$6.36 \cdot 10^{-6}$
14	53885693	rs7152211	A	C	DDHD1	++	1,941	1,109	832	0.664	0.599	0.675	0.152	$3.41 \cdot 10^{-2}$	1.164	4.455	$8.4 \cdot 10^{-6}$
16	77317954	rs61749042	C	T	ADAMTS18	++	1,941	1,109	832	$5.15 \cdot 10^{-3}$	$1.8 \cdot 10^{-3}$	$5.71 \cdot 10^{-3}$	0.964	0.224	2.623	−4.306	$1.66 \cdot 10^{-5}$
7	35626264	rs12113684	C	T	HERPUD2	++	1,937	1,107	830	$6.94 \cdot 10^{-2}$	$5.21 \cdot 10^{-2}$	0.174	0.273	$6.37 \cdot 10^{-2}$	1.313	4.28	$1.87 \cdot 10^{-5}$
2	129912509	rs1113307	A	G	RAB6C	++	1,940	1,108	832	0.158	0.156	0.169	0.187	$4.37 \cdot 10^{-2}$	1.205	4.275	$1.91 \cdot 10^{-5}$
22	43529061	rs77547475	C	A	MCAT	++	1,941	1,109	832	$1.11 \cdot 10^{-2}$	$6.01 \cdot 10^{-4}$	$7.37 \cdot 10^{-2}$	0.665	0.156	1.944	−4.26	$2.04 \cdot 10^{-5}$
17	72056478	rs1457826	T	C	RPL38	++	1,941	1,109	832	0.691	0.399	0.74	0.152	$3.6 \cdot 10^{-2}$	1.164	4.214	$2.5 \cdot 10^{-5}$
8	96592937	rs4532570	G	A	C8orf37	++	1,926	1,100	826	0.13	$9.45 \cdot 10^{-2}$	0.339	0.211	$5 \cdot 10^{-2}$	1.235	4.212	$2.53 \cdot 10^{-5}$
2	169774071	**rs563694**	A	C	**ABCB11**	++	1,940	1,109	831	0.703	0.672	0.885	0.147	$3.5 \cdot 10^{-2}$	1.158	4.198	$2.7 \cdot 10^{-5}$
19	29685293	rs13382050	A	G	UQCRFS1	++	1,941	1,109	832	0.457	0.218	0.497	0.14	$3.33 \cdot 10^{-2}$	1.15	4.196	$2.72 \cdot 10^{-5}$
1	214392240	rs9787247	T	C	SMYD2	++	1,941	1,109	832	$9.17 \cdot 10^{-2}$	$8.18 \cdot 10^{-2}$	0.151	0.237	$5.66 \cdot 10^{-2}$	1.267	4.179	$2.93 \cdot 10^{-5}$
10	127280109	rs2365818	T	C	TEX36	++	1,941	1,109	832	0.447	0.4	0.734	0.137	$3.3 \cdot 10^{-2}$	1.147	4.149	$3.34 \cdot 10^{-5}$
11	15401144	rs4500467	A	G	INSC	++	1,929	1,102	827	0.735	0.715	0.854	0.153	$3.71 \cdot 10^{-2}$	1.165	−4.121	$3.77 \cdot 10^{-5}$
12	72924295	rs997590	T	C	TRHDE	++	1,941	1,109	832	0.14	$9.89 \cdot 10^{-2}$	0.147	0.189	$4.61 \cdot 10^{-2}$	1.208	4.102	$4.09 \cdot 10^{-5}$
2	235570734	rs884062	T	G	ARL4C	+-	1,941	1,109	832	0.447	0.138	0.499	0.136	$3.37 \cdot 10^{-2}$	1.145	−4.034	$5.49 \cdot 10^{-5}$
1	203025428	rs12097602	G	A	PPFIA4	++	1,941	1,109	832	0.164	0.161	0.183	0.175	$4.35 \cdot 10^{-2}$	1.191	−4.023	$5.76 \cdot 10^{-5}$
12	127878414	rs7313873	G	A	TMEM132C	++	1,941	1,109	832	0.404	0.4	0.428	0.128	$3.18 \cdot 10^{-2}$	1.136	−4.017	$5.89 \cdot 10^{-5}$
2	45170515	rs2673270	G	A	SIX3	++	1,928	1,099	829	0.277	0.261	0.371	0.144	$3.59 \cdot 10^{-2}$	1.155	4.011	$6.04 \cdot 10^{-5}$

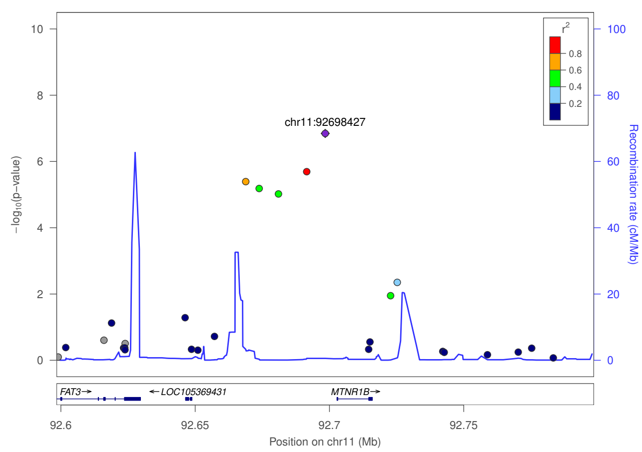


Figure 8: Regional plot for cohort META model invn Adjusted AGE_GLU_INS_FAST+SEX: rs10830962 $\pm 100kb$

Table 11: Top variants in the META invn Adjusted AGE_GLU_INS_FAST+SEX+BMI model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE$_{CLOSEST}$	DIR	N	MALE	FEMALE	FREQ$_{AVG}$	FREQ$_{MIN}$	FREQ$_{MAX}$	EFFECT	STDERR	OR	ZSCORE	P
2	169763148	**rs560887**	C	T	**G6PC2**	++	1,956	1,119	837	0.749	0.716	0.948	0.198	$3.69 \cdot 10^{-2}$	1.219	5.356	$8.53 \cdot 10^{-8}$
11	92698427	**rs10830962**	G	C	**MTNR1B**	++	1,954	1,117	837	0.456	0.4	0.793	0.168	$3.37 \cdot 10^{-2}$	1.183	4.992	$5.97 \cdot 10^{-7}$
17	72056478	rs1457826	T	C	RPL38	++	1,956	1,119	837	0.691	0.399	0.739	0.163	$3.58 \cdot 10^{-2}$	1.178	4.569	$4.91 \cdot 10^{-6}$
8	143761931	rs2294008	T	C	PSCA	++	1,956	1,119	837	0.425	0.38	0.433	0.144	$3.24 \cdot 10^{-2}$	1.155	4.446	$8.75 \cdot 10^{-6}$
22	43529061	rs77547475	C	A	MCAT	++	1,956	1,119	837	$1.1 \cdot 10^{-2}$	$5.96 \cdot 10^{-4}$	$7.37 \cdot 10^{-2}$	0.684	0.156	1.981	-4.38	$1.19 \cdot 10^{-5}$
2	169774071	**rs563694**	A	C	**ABCB11**	++	1,955	1,119	836	0.704	0.674	0.885	0.152	$3.48 \cdot 10^{-2}$	1.164	4.371	$1.24 \cdot 10^{-5}$
7	35626264	rs12113684	C	T	HERPUD2	++	1,952	1,117	835	$6.92 \cdot 10^{-2}$	$5.19 \cdot 10^{-2}$	0.174	0.275	$6.36 \cdot 10^{-2}$	1.316	4.323	$1.54 \cdot 10^{-5}$
19	29685293	rs13382050	A	G	UQCRFS1	++	1,956	1,119	837	0.457	0.218	0.497	0.142	$3.31 \cdot 10^{-2}$	1.152	4.286	$1.82 \cdot 10^{-5}$
14	53885693	rs7152211	A	C	DDHD1	++	1,956	1,119	837	0.664	0.599	0.674	0.144	$3.39 \cdot 10^{-2}$	1.155	4.233	$2.31 \cdot 10^{-5}$
11	15401144	rs4500467	A	G	INSC	++	1,944	1,112	832	0.735	0.715	0.854	0.153	$3.7 \cdot 10^{-2}$	1.166	-4.147	$3.37 \cdot 10^{-5}$
17	7760704	rs8522	A	G	NAA38	++	1,956	1,119	837	0.236	0.223	0.318	0.153	$3.7 \cdot 10^{-2}$	1.166	-4.14	$3.48 \cdot 10^{-5}$
6	68722543	rs13193425	T	C	ADGRB3	++	1,956	1,119	837	0.311	0.131	0.34	0.143	$3.51 \cdot 10^{-2}$	1.154	4.084	$4.43 \cdot 10^{-5}$
2	45834076	rs7591446	C	T	SRBD1	++	1,956	1,119	837	0.763	0.471	0.811	0.158	$3.89 \cdot 10^{-2}$	1.172	4.068	$4.74 \cdot 10^{-5}$
2	239646391	rs12692242	G	A	TWIST2	++	1,956	1,119	837	0.294	0.207	0.308	0.142	$3.49 \cdot 10^{-2}$	1.152	4.059	$4.93 \cdot 10^{-5}$
11	103545761	rs4754977	C	T	DYNC2H1	++	1,956	1,119	837	0.675	0.547	0.696	0.138	$3.42 \cdot 10^{-2}$	1.148	4.04	$5.34 \cdot 10^{-5}$
4	157380782	rs1352701	T	C	PDGFC	++	1,956	1,119	837	0.554	0.527	0.719	0.128	$3.18 \cdot 10^{-2}$	1.137	-4.04	$5.35 \cdot 10^{-5}$
13	36447910	rs4943345	A	G	DCLK1	++	1,955	1,118	837	0.335	0.22	0.353	0.139	$3.45 \cdot 10^{-2}$	1.149	-4.014	$5.96 \cdot 10^{-5}$
17	67086724	rs1860120	C	T	ABCA6	++	1,956	1,119	837	0.878	0.513	0.938	0.214	$5.33 \cdot 10^{-2}$	1.238	4.008	$6.13 \cdot 10^{-5}$
2	129912509	rs1113307	A	G	RAB6C	++	1,955	1,118	837	0.157	0.155	0.169	0.174	$4.37 \cdot 10^{-2}$	1.19	3.991	$6.58 \cdot 10^{-5}$
7	129672975	rs12706910	C	T	ZC3HC1	++	1,955	1,118	837	0.708	0.588	0.728	0.143	$3.58 \cdot 10^{-2}$	1.153	-3.988	$6.66 \cdot 10^{-5}$

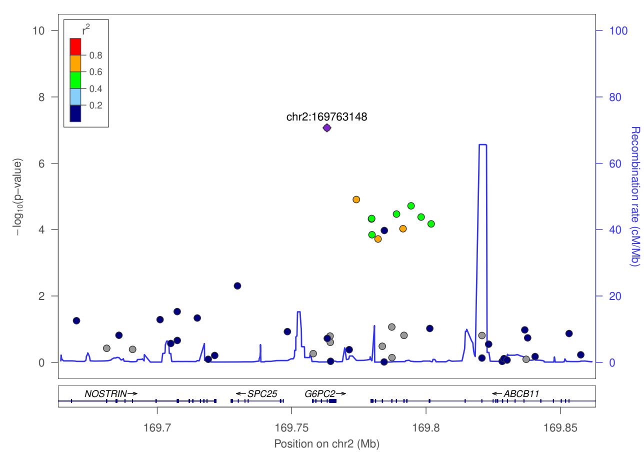


Figure 9: Regional plot for cohort META model invn Adjusted AGE_GLU_INS_FAST+SEX+BMI: rs560887 $\pm 100kb$

5.4 Previously identified risk loci

Table 12 shows statistics from the META cohort for 50 loci that were shown to be significantly associated with Fasting Glucose in the 2012 Nature Genetics paper by Scott et al [8]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R^2} < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R^2} >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 12 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 50 variants in both studies, 39 exhibit the same direction of effect with the known result (binomial test $p = 4.51e - 05$).

Table 12: Top known loci in META model invn Adjusted AGE_GLU_INS_FAST+SEX (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	EFFECT	STDERR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$EFFECT_{KNOWN}$	$STDERR_{KNOWN}$	P_{KNOWN}
2	169763148	**rs560887**	C	T	1,941	0.748	0.715	0.948	0.182	$3.71 \cdot 10^{-2}$	$9.4 \cdot 10^{-7}$	++	G6PC2	1	rs560887	$1.33 \cdot 10^{5}$	$7.1 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$1.4 \cdot 10^{-178}$
2	169791438	**rs552976**	G	A	1,941	0.659	0.61	0.667	0.127	$3.34 \cdot 10^{-2}$	$1.41 \cdot 10^{-4}$	++	ABCB11	1	rs552976	$1.33 \cdot 10^{5}$	$5.7 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$9.03 \cdot 10^{-149}$
11	92673828	**rs1387153**	T	C	1,941	0.305	0.291	0.385	0.155	$3.43 \cdot 10^{-2}$	$6.54 \cdot 10^{-6}$	++	MTNR1B	1	rs1387153	$1.33 \cdot 10^{5}$	$6.1 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$3.91 \cdot 10^{-143}$
7	44231886	**rs6975024**	C	T	1,941	0.154	$8.09 \cdot 10^{-2}$	0.166	0.136	$4.38 \cdot 10^{-2}$	$1.91 \cdot 10^{-3}$	++	GCK	1	rs6975024	$1.33 \cdot 10^{5}$	$6.1 \cdot 10^{-2}$	$2.9 \cdot 10^{-3}$	$2.88 \cdot 10^{-99}$
7	15064309	**rs2191349**	T	G	1,941	0.546	0.544	0.556	$4.59 \cdot 10^{-2}$	$3.21 \cdot 10^{-2}$	0.152	+-	DGKB	1	rs2191349	$1.33 \cdot 10^{5}$	$2.9 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$1.28 \cdot 10^{-42}$
2	27730940	**rs1260326**	C	T	1,941	0.589	0.545	0.849	$6.44 \cdot 10^{-2}$	$3.36 \cdot 10^{-2}$	$5.57 \cdot 10^{-2}$	++	GCKR	1	rs1260326	$1.33 \cdot 10^{5}$	$2.9 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$2.17 \cdot 10^{-41}$
8	118185733	**rs11558471**	A	G	1,941	0.282	0.108	0.311	$6.12 \cdot 10^{-2}$	$3.65 \cdot 10^{-2}$	$9.4 \cdot 10^{-2}$	++	SLC30A8	1	rs11558471	$1.33 \cdot 10^{5}$	$2.9 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$7.8 \cdot 10^{-37}$
15	62383155	**rs4502156**	T	C	1,941	0.462	0.419	0.716	$3.67 \cdot 10^{-2}$	$3.33 \cdot 10^{-2}$	0.27	+-	C2CD4A	1	rs4502156	$1.33 \cdot 10^{5}$	$2.2 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$1.38 \cdot 10^{-25}$
10	114758349	**rs7903146**	T	C	1,941	0.29	0.275	0.292	$1.43 \cdot 10^{-2}$	$3.61 \cdot 10^{-2}$	0.691	+-	TCF7L2	1	rs7903146	$1.33 \cdot 10^{5}$	$2.2 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$2.71 \cdot 10^{-20}$
11	45873091	**rs11605924**	A	C	1,916	0.468	0.141	0.523	$9.19 \cdot 10^{-2}$	$3.38 \cdot 10^{-2}$	$6.6 \cdot 10^{-3}$	++	CRY2	1	rs11605924	$1.33 \cdot 10^{5}$	$2 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$3.93 \cdot 10^{-19}$
3	123065778	**rs11708067**	A	G	1,938	0.206	0.171	0.212	$1.86 \cdot 10^{-2}$	$3.9 \cdot 10^{-2}$	0.633	+-	ADCY5	1	rs11708067	$1.33 \cdot 10^{5}$	$2.3 \cdot 10^{-2}$	$2.6 \cdot 10^{-3}$	$1.3 \cdot 10^{-18}$
11	61604814	**rs174577**	C	A	1,941	0.352	0.335	0.354	$6.2 \cdot 10^{-2}$	$3.29 \cdot 10^{-2}$	$5.96 \cdot 10^{-2}$	++	FADS2	1	rs174577	$1.33 \cdot 10^{5}$	$2 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.34 \cdot 10^{-18}$
9	22134094	**rs10811661**	T	C	1,930	0.166	$9.39 \cdot 10^{-2}$	0.178	$7.41 \cdot 10^{-2}$	$4.35 \cdot 10^{-2}$	$8.85 \cdot 10^{-2}$	++	CDKN2B	1	rs10811661	$1.33 \cdot 10^{5}$	$2.4 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$5.65 \cdot 10^{-18}$
11	61571348	rs174548	C	G	1,941	0.299	0.212	0.314	$5.29 \cdot 10^{-2}$	$3.42 \cdot 10^{-2}$	0.123	+-	FADS1	1	rs174548	$1.33 \cdot 10^{5}$	$-1.9 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.02 \cdot 10^{-17}$
11	61551356	**rs174535**	T	C	1,941	0.326	0.196	0.348	$5.99 \cdot 10^{-2}$	$3.39 \cdot 10^{-2}$	$7.71 \cdot 10^{-2}$	++	MYRF	1	rs174535	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$2.38 \cdot 10^{-17}$
11	61557803	**rs102275**	T	C	1,941	0.395	0.356	0.628	$5.84 \cdot 10^{-2}$	$3.31 \cdot 10^{-2}$	$7.8 \cdot 10^{-2}$	++	TMEM258	1	rs102275	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.97 \cdot 10^{-17}$
10	113042093	**rs10885122**	G	T	1,941	0.801	0.34	0.878	$9.35 \cdot 10^{-2}$	$4.54 \cdot 10^{-2}$	$3.97 \cdot 10^{-2}$	+-	ADRA2A	1	rs10885122	$1.33 \cdot 10^{5}$	$2.7 \cdot 10^{-2}$	$3.3 \cdot 10^{-3}$	$6.32 \cdot 10^{-17}$
5	95539448	rs4869272	C	T	1,941	0.695	0.68	0.788	$5.29 \cdot 10^{-2}$	$3.53 \cdot 10^{-2}$	0.133	++	PCSK1	1	rs4869272	$1.33 \cdot 10^{5}$	$-1.8 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.02 \cdot 10^{-15}$
13	28487599	rs11619319	A	G	1,941	0.235	0.192	0.242	$5.22 \cdot 10^{-3}$	$3.81 \cdot 10^{-2}$	0.891	-+	PDX1	1	rs11619319	$1.33 \cdot 10^{5}$	$-2 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$1.33 \cdot 10^{-15}$
11	47600438	rs2280231	T	C	1,941	0.261	$4.68 \cdot 10^{-2}$	0.297	$5.09 \cdot 10^{-3}$	$3.76 \cdot 10^{-2}$	0.893	+-	KBTBD4	1	rs2280231	$1.33 \cdot 10^{5}$	$-1.8 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$1.67 \cdot 10^{-13}$
2	27995781	**rs3736594**	A	C	1,940	0.685	0.439	0.726	$3.87 \cdot 10^{-2}$	$3.58 \cdot 10^{-2}$	0.28	+-	MRPL33	1	rs3736594	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$3.02 \cdot 10^{-13}$
8	9183358	**rs9987289**	A	G	1,941	0.909	0.827	0.923	0.108	$5.69 \cdot 10^{-2}$	$5.75 \cdot 10^{-2}$	++	RP11-10A14.4	1	rs9987289	$1.33 \cdot 10^{5}$	$2.7 \cdot 10^{-2}$	$3.8 \cdot 10^{-3}$	$6.11 \cdot 10^{-13}$
2	169605967	**rs2390732**	A	G	1,941	0.608	0.581	0.772	$8.58 \cdot 10^{-2}$	$3.33 \cdot 10^{-2}$	$1.01 \cdot 10^{-2}$	++	CERS6	1	rs2390732	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$7.1 \cdot 10^{-13}$
9	4292083	**rs10758593**	A	G	1,941	0.417	0.405	0.489	$9.69 \cdot 10^{-2}$	$3.24 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	++	GLIS3	1	rs10758593	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.17 \cdot 10^{-12}$
7	50791579	rs6943153	C	T	1,941	0.649	0.306	0.707	$1.72 \cdot 10^{-2}$	$3.47 \cdot 10^{-2}$	0.621	++	GRB10	1	rs6943153	$1.33 \cdot 10^{5}$	$-1.5 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.63 \cdot 10^{-12}$
2	169721377	**rs479661**	G	A	1,923	0.848	0.831	0.95	$1.85 \cdot 10^{-2}$	$4.44 \cdot 10^{-2}$	0.677	++	NOSTRIN	1	rs479661	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$8.56 \cdot 10^{-12}$
11	72432985	**rs11603334**	G	A	1,941	0.11	$4.68 \cdot 10^{-2}$	0.121	$2.4 \cdot 10^{-2}$	$5.15 \cdot 10^{-2}$	0.641	+-	ARAP1	1	rs11603334	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$1.12 \cdot 10^{-11}$
2	27951658	**rs867282**	T	C	1,941	0.738	0.561	0.768	$5.56 \cdot 10^{-2}$	$3.73 \cdot 10^{-2}$	0.136	++	AC074091.13	1	rs867282	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$1.76 \cdot 10^{-11}$
20	22557099	**rs6113722**	G	A	1,941	$6.47 \cdot 10^{-2}$	$4.75 \cdot 10^{-2}$	0.167	$2.22 \cdot 10^{-3}$	$6.63 \cdot 10^{-2}$	0.973	-+	FOXA2	1	rs6113722	$1.33 \cdot 10^{5}$	$3.5 \cdot 10^{-2}$	$5.3 \cdot 10^{-3}$	$2.49 \cdot 10^{-11}$
9	111680359	rs16913693	G	T	1,941	$5.46 \cdot 10^{-2}$	$2.29 \cdot 10^{-2}$	0.245	$8.88 \cdot 10^{-2}$	$7.67 \cdot 10^{-2}$	0.247	-+	IKBKAP	1	rs16913693	$1.33 \cdot 10^{5}$	$-4.3 \cdot 10^{-2}$	$6.6 \cdot 10^{-3}$	$3.51 \cdot 10^{-11}$
2	27152874	**rs1371614**	T	C	1,940	0.252	0.234	0.36	$5.17 \cdot 10^{-2}$	$3.71 \cdot 10^{-2}$	0.163	++	DPYSL5	1	rs1371614	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$7.09 \cdot 10^{-11}$
11	47275064	rs10838681	G	A	1,941	0.262	0.23	0.457	$5.14 \cdot 10^{-2}$	$3.74 \cdot 10^{-2}$	0.17	+-	NR1H3	1	rs10838681	$1.33 \cdot 10^{5}$	$-1.5 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$8.84 \cdot 10^{-11}$
11	48009074	rs11039482	T	C	1,941	0.122	$2.16 \cdot 10^{-2}$	0.138	$2.31 \cdot 10^{-2}$	$5.09 \cdot 10^{-2}$	0.65	+-	PTPRJ	1	rs11039482	$1.33 \cdot 10^{5}$	$-2 \cdot 10^{-2}$	$3 \cdot 10^{-3}$	$9.36 \cdot 10^{-11}$
15	62424649	**rs4775471**	C	T	1,941	0.233	0.126	0.251	$7.98 \cdot 10^{-2}$	$3.82 \cdot 10^{-2}$	$3.68 \cdot 10^{-2}$	++	C2CD4B	1	rs4775471	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$9.73 \cdot 10^{-11}$
9	139256766	**rs3829109**	G	A	1,941	0.254	0.192	0.264	$3.96 \cdot 10^{-2}$	$3.73 \cdot 10^{-2}$	0.289	++	DNLZ	1	rs3829109	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.7 \cdot 10^{-3}$	$1.13 \cdot 10^{-10}$
14	100839261	rs3783347	T	G	1,941	0.193	$6.12 \cdot 10^{-2}$	0.215	$1.66 \cdot 10^{-2}$	$4.23 \cdot 10^{-2}$	0.694	+-	WARS	1	rs3783347	$1.33 \cdot 10^{5}$	$-1.7 \cdot 10^{-2}$	$2.6 \cdot 10^{-3}$	$1.32 \cdot 10^{-10}$
11	47929846	rs6485795	A	G	1,941	0.273	$6.83 \cdot 10^{-2}$	0.307	$5.07 \cdot 10^{-2}$	$3.72 \cdot 10^{-2}$	0.173	++	NUP160	1	rs6485795	$1.33 \cdot 10^{5}$	$-1.5 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.81 \cdot 10^{-10}$
1	214159256	**rs340874**	C	T	1,941	0.482	0.182	0.533	$4.46 \cdot 10^{-2}$	$3.33 \cdot 10^{-2}$	0.18	++	PROX1	1	rs340874	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.08 \cdot 10^{-10}$
2	169729849	**rs3821116**	G	T	1,939	0.436	0.338	0.452	$8.65 \cdot 10^{-2}$	$3.29 \cdot 10^{-2}$	$8.52 \cdot 10^{-3}$	++	SPC25	1	rs3821116	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$6.14 \cdot 10^{-10}$
6	20686996	**rs9368222**	A	C	1,939	0.247	0.194	0.256	$6.08 \cdot 10^{-2}$	$3.74 \cdot 10^{-2}$	0.104	++	CDKAL1	1	rs9368222	$1.33 \cdot 10^{5}$	$1.4 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1 \cdot 10^{-9}$
11	92818649	**rs9804472**	T	C	1,941	0.796	0.701	0.811	$5.03 \cdot 10^{-2}$	$3.97 \cdot 10^{-2}$	0.205	++	SLC36A4	1	rs9804472	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$1.18 \cdot 10^{-9}$
11	48333360	rs1483121	A	G	1,941	0.123	$2.34 \cdot 10^{-2}$	0.14	$4.39 \cdot 10^{-2}$	$5.04 \cdot 10^{-2}$	0.384	+-	OR4S1	1	rs1483121	$1.33 \cdot 10^{5}$	$-1.8 \cdot 10^{-2}$	$3.1 \cdot 10^{-3}$	$1.7 \cdot 10^{-9}$
9	139253839	**rs1128905**	T	C	1,932	0.479	0.403	0.492	$1.98 \cdot 10^{-2}$	$3.27 \cdot 10^{-2}$	0.546	++	GPSM1	1	rs1128905	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$5.81 \cdot 10^{-9}$
11	72669777	**rs11605166**	T	C	1,939	0.132	0.101	0.137	$3.73 \cdot 10^{-2}$	$4.72 \cdot 10^{-2}$	0.429	++	FCHSD2	1	rs11605166	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.7 \cdot 10^{-3}$	$6.82 \cdot 10^{-9}$
12	133041618	**rs10747083**	A	G	1,941	0.693	0.661	0.881	$8.45 \cdot 10^{-2}$	$3.53 \cdot 10^{-2}$	$1.68 \cdot 10^{-2}$	++	FBRSL1	1	rs10747083	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$7.57 \cdot 10^{-9}$
20	39743905	**rs6072275**	A	G	1,941	0.133	$8.45 \cdot 10^{-2}$	0.141	$2.01 \cdot 10^{-2}$	$4.76 \cdot 10^{-2}$	0.673	++	TOP1	1	rs6072275	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$1.66 \cdot 10^{-8}$
3	185513392	**rs7651090**	G	A	1,941	0.358	0.323	0.572	$1.58 \cdot 10^{-2}$	$3.41 \cdot 10^{-2}$	0.643	+-	IGF2BP2	1	rs7651090	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.75 \cdot 10^{-8}$
13	33554302	**rs576674**	G	A	1,941	0.754	0.38	0.817	$1.43 \cdot 10^{-2}$	$3.87 \cdot 10^{-2}$	0.711	-+	KL	1	rs576674	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$3 \cdot 10^{-3}$	$2.26 \cdot 10^{-8}$
3	49455330	**rs11715915**	C	T	1,941	0.32	0.218	0.337	$2.08 \cdot 10^{-2}$	$3.44 \cdot 10^{-2}$	0.546	-+	AMT	1	rs11715915	$1.33 \cdot 10^{5}$	$1.2 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.9 \cdot 10^{-8}$
7	44229068	**rs1799884**	T	C	1,941	0.162	0.138	0.166	0.147	$4.25 \cdot 10^{-2}$	$5.72 \cdot 10^{-4}$	++	YKT6	1	rs2908282	$1.33 \cdot 10^{5}$	$5.7 \cdot 10^{-2}$	$2.9 \cdot 10^{-3}$	$1.04 \cdot 10^{-88}$

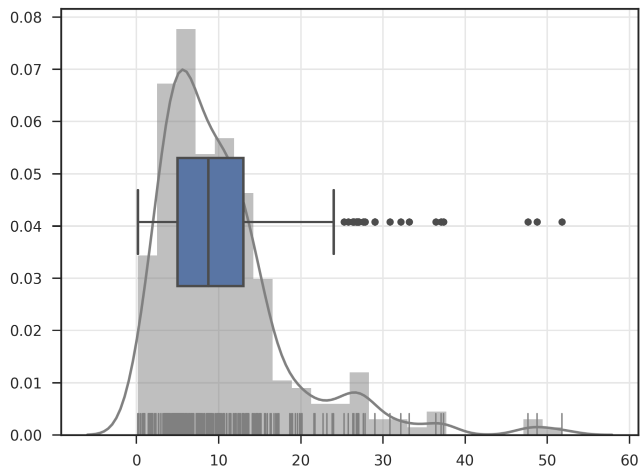
Table 13 shows statistics from the META cohort for 50 loci that were shown to be significantly associated with Fasting Glucose in the 2012 Nature Genetics paper by Scott et al [8]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R^2} < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R^2} >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 15 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 50 variants in both studies, 40 exhibit the same direction of effect with the known result (binomial test $p = 1.19e-05$).

Table 13: Top known loci in META model invn Adjusted AGE_GLU_INS_FAST+SEX+BMI (**bold** variants indicate matching direction of effect)

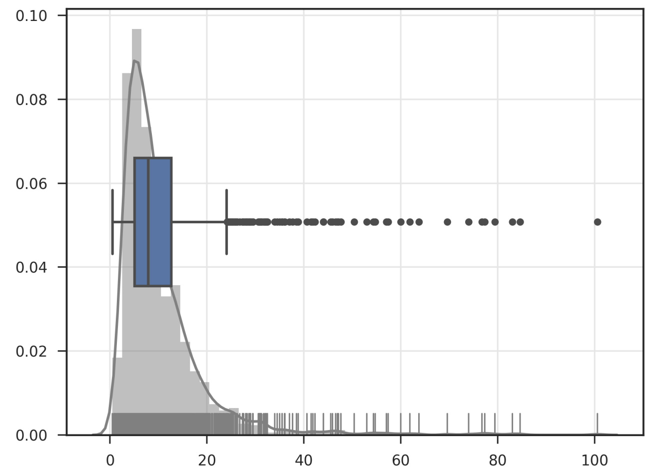
CHR	POS	ID	EA	OA	N	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	EFFECT	STDERR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$EFFECT_{KNOWN}$	$STDERR_{KNOWN}$	P_{KNOWN}
2	169763148	**rs560887**	C	T	1,956	0.749	0.716	0.948	0.198	$3.69 \cdot 10^{-2}$	$8.53 \cdot 10^{-8}$	++	G6PC2	1	rs560887	$1.33 \cdot 10^{5}$	$7.1 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$1.4 \cdot 10^{-178}$
2	169791438	**rs552976**	G	A	1,956	0.66	0.61	0.668	0.13	$3.33 \cdot 10^{-2}$	$9.38 \cdot 10^{-5}$	++	ABCB11	1	rs552976	$1.33 \cdot 10^{5}$	$5.7 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$9.03 \cdot 10^{-149}$
11	92673828	**rs1387153**	T	C	1,956	0.304	0.29	0.385	0.151	$3.43 \cdot 10^{-2}$	$1.06 \cdot 10^{-5}$	++	MTNR1B	1	rs1387153	$1.33 \cdot 10^{5}$	$6.1 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$3.91 \cdot 10^{-143}$
7	44231886	**rs6975024**	C	T	1,956	0.154	$8.09 \cdot 10^{-2}$	0.166	0.133	$4.37 \cdot 10^{-2}$	$2.33 \cdot 10^{-3}$	++	GCK	1	rs6975024	$1.33 \cdot 10^{5}$	$6.1 \cdot 10^{-2}$	$2.9 \cdot 10^{-3}$	$2.88 \cdot 10^{-99}$
7	15064309	**rs2191349**	T	G	1,956	0.546	0.545	0.556	$4.8 \cdot 10^{-2}$	$3.2 \cdot 10^{-2}$	0.133	+-	DGKB	1	rs2191349	$1.33 \cdot 10^{5}$	$2.9 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$1.28 \cdot 10^{-42}$
2	27730940	**rs1260326**	C	T	1,956	0.588	0.545	0.849	$5.85 \cdot 10^{-2}$	$3.35 \cdot 10^{-2}$	$8.07 \cdot 10^{-2}$	++	GCKR	1	rs1260326	$1.33 \cdot 10^{5}$	$2.9 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$2.17 \cdot 10^{-41}$
8	118185733	**rs11558471**	A	G	1,956	0.281	0.108	0.31	$7.18 \cdot 10^{-2}$	$3.64 \cdot 10^{-2}$	$4.86 \cdot 10^{-2}$	++	SLC30A8	1	rs11558471	$1.33 \cdot 10^{5}$	$2.9 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$7.8 \cdot 10^{-37}$
15	62383155	**rs4502156**	T	C	1,956	0.46	0.417	0.716	$3.03 \cdot 10^{-2}$	$3.32 \cdot 10^{-2}$	0.361	++	C2CD4A	1	rs4502156	$1.33 \cdot 10^{5}$	$2.2 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$1.38 \cdot 10^{-25}$
10	114758349	**rs7903146**	T	C	1,956	0.289	0.275	0.292	$2.49 \cdot 10^{-2}$	$3.6 \cdot 10^{-2}$	0.489	++	TCF7L2	1	rs7903146	$1.33 \cdot 10^{5}$	$2.2 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$2.71 \cdot 10^{-20}$
11	45873091	**rs11605924**	A	C	1,931	0.469	0.141	0.523	$8.63 \cdot 10^{-2}$	$3.37 \cdot 10^{-2}$	$1.05 \cdot 10^{-2}$	++	CRY2	1	rs11605924	$1.33 \cdot 10^{5}$	$2 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$3.93 \cdot 10^{-19}$
3	123065778	**rs11708067**	A	G	1,953	0.206	0.171	0.212	$4.99 \cdot 10^{-2}$	$3.9 \cdot 10^{-2}$	0.2	+-	ADCY5	1	rs11708067	$1.33 \cdot 10^{5}$	$2.3 \cdot 10^{-2}$	$2.6 \cdot 10^{-3}$	$1.3 \cdot 10^{-18}$
11	61604814	**rs174577**	C	A	1,956	0.353	0.335	0.355	$6.11 \cdot 10^{-2}$	$3.28 \cdot 10^{-2}$	$6.21 \cdot 10^{-2}$	+-	FADS2	1	rs174577	$1.33 \cdot 10^{5}$	$2 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.34 \cdot 10^{-18}$
9	22134094	**rs10811661**	T	C	1,945	0.167	$9.39 \cdot 10^{-2}$	0.18	$6.76 \cdot 10^{-2}$	$4.33 \cdot 10^{-2}$	0.119	++	CDKN2B	1	rs10811661	$1.33 \cdot 10^{5}$	$2.4 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$5.65 \cdot 10^{-18}$
11	61571348	rs174548	C	G	1,956	0.301	0.212	0.315	$5.8 \cdot 10^{-2}$	$3.41 \cdot 10^{-2}$	$8.86 \cdot 10^{-2}$	+-	FADS1	1	rs174548	$1.33 \cdot 10^{5}$	$-1.9 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.02 \cdot 10^{-17}$
11	61551356	**rs174535**	T	C	1,956	0.327	0.196	0.348	$6.16 \cdot 10^{-2}$	$3.37 \cdot 10^{-2}$	$6.76 \cdot 10^{-2}$	++	MYRF	1	rs174535	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$2.38 \cdot 10^{-17}$
11	61557803	**rs102275**	T	C	1,956	0.396	0.358	0.628	$6.71 \cdot 10^{-2}$	$3.29 \cdot 10^{-2}$	$4.17 \cdot 10^{-2}$	++	TMEM258	1	rs102275	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.97 \cdot 10^{-17}$
10	113042093	**rs10885122**	G	T	1,956	0.799	0.34	0.875	$9.21 \cdot 10^{-2}$	$4.48 \cdot 10^{-2}$	$3.99 \cdot 10^{-2}$	+-	ADRA2A	1	rs10885122	$1.33 \cdot 10^{5}$	$2.7 \cdot 10^{-2}$	$3.3 \cdot 10^{-3}$	$6.32 \cdot 10^{-17}$
5	95539448	rs4869272	C	T	1,956	0.694	0.679	0.788	$4.56 \cdot 10^{-2}$	$3.52 \cdot 10^{-2}$	0.196	++	PCSK1	1	rs4869272	$1.33 \cdot 10^{5}$	$-1.8 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.02 \cdot 10^{-15}$
13	28487599	rs11619319	A	G	1,956	0.236	0.192	0.243	$9.59 \cdot 10^{-3}$	$3.8 \cdot 10^{-2}$	0.8	-+	PDX1	1	rs11619319	$1.33 \cdot 10^{5}$	$-2 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$1.33 \cdot 10^{-15}$
11	47600438	**rs2280231**	C	T	1,956	0.261	$4.68 \cdot 10^{-2}$	0.296	$8.68 \cdot 10^{-4}$	$3.74 \cdot 10^{-2}$	0.982	-+	KBTBD4	1	rs2280231	$1.33 \cdot 10^{5}$	$1.8 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$1.67 \cdot 10^{-13}$
2	27995781	**rs3736594**	A	C	1,955	0.684	0.439	0.725	$3.14 \cdot 10^{-2}$	$3.57 \cdot 10^{-2}$	0.379	+-	MRPL33	1	rs3736594	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$3.02 \cdot 10^{-13}$
8	9183358	**rs9987289**	A	G	1,956	0.907	0.827	0.921	$8.95 \cdot 10^{-2}$	$5.61 \cdot 10^{-2}$	0.11	++	RP11-10A14.4	1	rs9987289	$1.33 \cdot 10^{5}$	$2.7 \cdot 10^{-2}$	$3.8 \cdot 10^{-3}$	$6.11 \cdot 10^{-13}$
2	169605967	**rs2390732**	A	G	1,956	0.608	0.581	0.772	$8.82 \cdot 10^{-2}$	$3.32 \cdot 10^{-2}$	$7.94 \cdot 10^{-3}$	++	CERS6	1	rs2390732	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$7.1 \cdot 10^{-13}$
9	4292083	**rs10758593**	A	G	1,956	0.417	0.405	0.489	$9.38 \cdot 10^{-2}$	$3.22 \cdot 10^{-2}$	$3.64 \cdot 10^{-3}$	++	GLIS3	1	rs10758593	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.17 \cdot 10^{-12}$
7	50791579	**rs6943153**	T	C	1,956	0.651	0.306	0.708	$2.14 \cdot 10^{-3}$	$3.46 \cdot 10^{-2}$	0.951	+-	GRB10	1	rs6943153	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.63 \cdot 10^{-12}$
2	169721377	**rs479661**	G	A	1,938	0.848	0.83	0.95	$2.18 \cdot 10^{-2}$	$4.42 \cdot 10^{-2}$	0.621	++	NOSTRIN	1	rs479661	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$8.56 \cdot 10^{-12}$
11	72432985	**rs11603334**	G	A	1,956	0.11	$4.68 \cdot 10^{-2}$	0.121	$3.54 \cdot 10^{-2}$	$5.12 \cdot 10^{-2}$	0.489	+-	ARAP1	1	rs11603334	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$1.12 \cdot 10^{-11}$
2	27951658	**rs867282**	T	C	1,956	0.737	0.561	0.767	$3.1 \cdot 10^{-2}$	$3.72 \cdot 10^{-2}$	0.405	+-	AC074091.13	1	rs867282	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$1.76 \cdot 10^{-11}$
20	22557099	**rs6113722**	G	A	1,956	$6.47 \cdot 10^{-2}$	$4.77 \cdot 10^{-2}$	0.167	$7.14 \cdot 10^{-3}$	$6.6 \cdot 10^{-2}$	0.914	-+	FOXA2	1	rs6113722	$1.33 \cdot 10^{5}$	$3.5 \cdot 10^{-2}$	$5.3 \cdot 10^{-3}$	$2.49 \cdot 10^{-11}$
9	111680359	rs16913693	G	T	1,956	$5.44 \cdot 10^{-2}$	$2.29 \cdot 10^{-2}$	0.245	$7.11 \cdot 10^{-2}$	$7.65 \cdot 10^{-2}$	0.353	-+	IKBKAP	1	rs16913693	$1.33 \cdot 10^{5}$	$-4.3 \cdot 10^{-2}$	$6.6 \cdot 10^{-3}$	$3.51 \cdot 10^{-11}$
2	27152874	**rs1371614**	T	C	1,955	0.252	0.235	0.36	$4.57 \cdot 10^{-2}$	$3.69 \cdot 10^{-2}$	0.216	++	DPYSL5	1	rs1371614	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$7.09 \cdot 10^{-11}$
11	47275064	rs10838681	G	A	1,956	0.263	0.23	0.457	$4.59 \cdot 10^{-2}$	$3.72 \cdot 10^{-2}$	0.217	+-	NR1H3	1	rs10838681	$1.33 \cdot 10^{5}$	$-1.5 \cdot 10^{-2}$	$2.4 \cdot 10^{-3}$	$8.84 \cdot 10^{-11}$
11	48009074	rs11039482	T	C	1,956	0.122	$2.16 \cdot 10^{-2}$	0.139	$3.81 \cdot 10^{-2}$	$5.06 \cdot 10^{-2}$	0.451	+-	PTPRJ	1	rs11039482	$1.33 \cdot 10^{5}$	$-2 \cdot 10^{-2}$	$3 \cdot 10^{-3}$	$9.36 \cdot 10^{-11}$
15	62424649	**rs4775471**	C	T	1,956	0.232	0.126	0.249	$8.11 \cdot 10^{-2}$	$3.81 \cdot 10^{-2}$	$3.33 \cdot 10^{-2}$	++	C2CD4B	1	rs4775471	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$9.73 \cdot 10^{-11}$
9	139256766	**rs3829109**	G	A	1,956	0.254	0.192	0.264	$6.42 \cdot 10^{-2}$	$3.73 \cdot 10^{-2}$	$8.5 \cdot 10^{-2}$	++	DNLZ	1	rs3829109	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.7 \cdot 10^{-3}$	$1.13 \cdot 10^{-10}$
14	100839261	rs3783347	T	G	1,956	0.193	$6.12 \cdot 10^{-2}$	0.215	$2.85 \cdot 10^{-3}$	$4.22 \cdot 10^{-2}$	0.946	+-	WARS	1	rs3783347	$1.33 \cdot 10^{5}$	$-1.7 \cdot 10^{-2}$	$2.6 \cdot 10^{-3}$	$1.32 \cdot 10^{-10}$
11	47929846	rs6485795	A	G	1,956	0.273	$6.83 \cdot 10^{-2}$	0.307	$4.67 \cdot 10^{-2}$	$3.7 \cdot 10^{-2}$	0.207	++	NUP160	1	rs6485795	$1.33 \cdot 10^{5}$	$-1.5 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.81 \cdot 10^{-10}$
1	214159256	**rs340874**	C	T	1,956	0.483	0.182	0.532	$5.68 \cdot 10^{-2}$	$3.32 \cdot 10^{-2}$	$8.69 \cdot 10^{-2}$	++	PROX1	1	rs340874	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.08 \cdot 10^{-10}$
2	169729849	**rs3821116**	G	T	1,954	0.435	0.338	0.451	$9.21 \cdot 10^{-2}$	$3.28 \cdot 10^{-2}$	$4.95 \cdot 10^{-3}$	++	SPC25	1	rs3821116	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$6.14 \cdot 10^{-10}$
6	20686996	**rs9368222**	A	C	1,954	0.246	0.194	0.255	$8.08 \cdot 10^{-2}$	$3.72 \cdot 10^{-2}$	$3.01 \cdot 10^{-2}$	++	CDKAL1	1	rs9368222	$1.33 \cdot 10^{5}$	$1.4 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1 \cdot 10^{-9}$
11	92818649	**rs9804472**	T	C	1,956	0.796	0.701	0.812	$2.71 \cdot 10^{-2}$	$3.96 \cdot 10^{-2}$	0.494	++	SLC36A4	1	rs9804472	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$1.18 \cdot 10^{-9}$
11	48333360	rs1483121	A	G	1,956	0.123	$2.34 \cdot 10^{-2}$	0.14	$6.31 \cdot 10^{-2}$	$5 \cdot 10^{-2}$	0.207	+-	OR4S1	1	rs1483121	$1.33 \cdot 10^{5}$	$-1.8 \cdot 10^{-2}$	$3.1 \cdot 10^{-3}$	$1.7 \cdot 10^{-9}$
9	139253839	**rs1128905**	T	C	1,947	0.479	0.403	0.492	$2.65 \cdot 10^{-2}$	$3.26 \cdot 10^{-2}$	0.415	++	GPSM1	1	rs1128905	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.5 \cdot 10^{-3}$	$5.81 \cdot 10^{-9}$
11	72669777	**rs11605166**	T	C	1,954	0.132	0.101	0.137	$3.49 \cdot 10^{-2}$	$4.71 \cdot 10^{-2}$	0.459	+-	FCHSD2	1	rs11605166	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.7 \cdot 10^{-3}$	$6.82 \cdot 10^{-9}$
12	133041618	**rs10747083**	A	G	1,956	0.692	0.66	0.881	$8.04 \cdot 10^{-2}$	$3.53 \cdot 10^{-2}$	$2.26 \cdot 10^{-2}$	++	FBRSL1	1	rs10747083	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$7.57 \cdot 10^{-9}$
20	39743905	**rs6072275**	A	G	1,956	0.133	$8.45 \cdot 10^{-2}$	0.141	$1.57 \cdot 10^{-2}$	$4.75 \cdot 10^{-2}$	0.742	++	TOP1	1	rs6072275	$1.33 \cdot 10^{5}$	$1.6 \cdot 10^{-2}$	$2.8 \cdot 10^{-3}$	$1.66 \cdot 10^{-8}$
3	185513392	**rs7651090**	G	A	1,956	0.357	0.322	0.572	$1.38 \cdot 10^{-2}$	$3.4 \cdot 10^{-2}$	0.684	+-	IGF2BP2	1	rs7651090	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.75 \cdot 10^{-8}$
13	33554302	rs576674	A	G	1,956	0.754	0.38	0.816	$3.51 \cdot 10^{-3}$	$3.85 \cdot 10^{-2}$	0.927	+-	KL	1	rs576674	$1.33 \cdot 10^{5}$	$-1.7 \cdot 10^{-2}$	$3 \cdot 10^{-3}$	$2.26 \cdot 10^{-8}$
3	49455330	**rs11715915**	C	T	1,956	0.32	0.218	0.337	$3.72 \cdot 10^{-2}$	$3.43 \cdot 10^{-2}$	0.279	++	AMT	1	rs11715915	$1.33 \cdot 10^{5}$	$1.2 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.9 \cdot 10^{-8}$
7	44229068	**rs1799884**	T	C	1,956	0.162	0.138	0.166	0.143	$4.24 \cdot 10^{-2}$	$7.75 \cdot 10^{-4}$	++	YKT6	1	rs2908282	$1.33 \cdot 10^{5}$	$5.7 \cdot 10^{-2}$	$2.9 \cdot 10^{-3}$	$1.04 \cdot 10^{-88}$

6 Fasting Insulin (INS_FAST)

6.1 Summary



(a) AFR



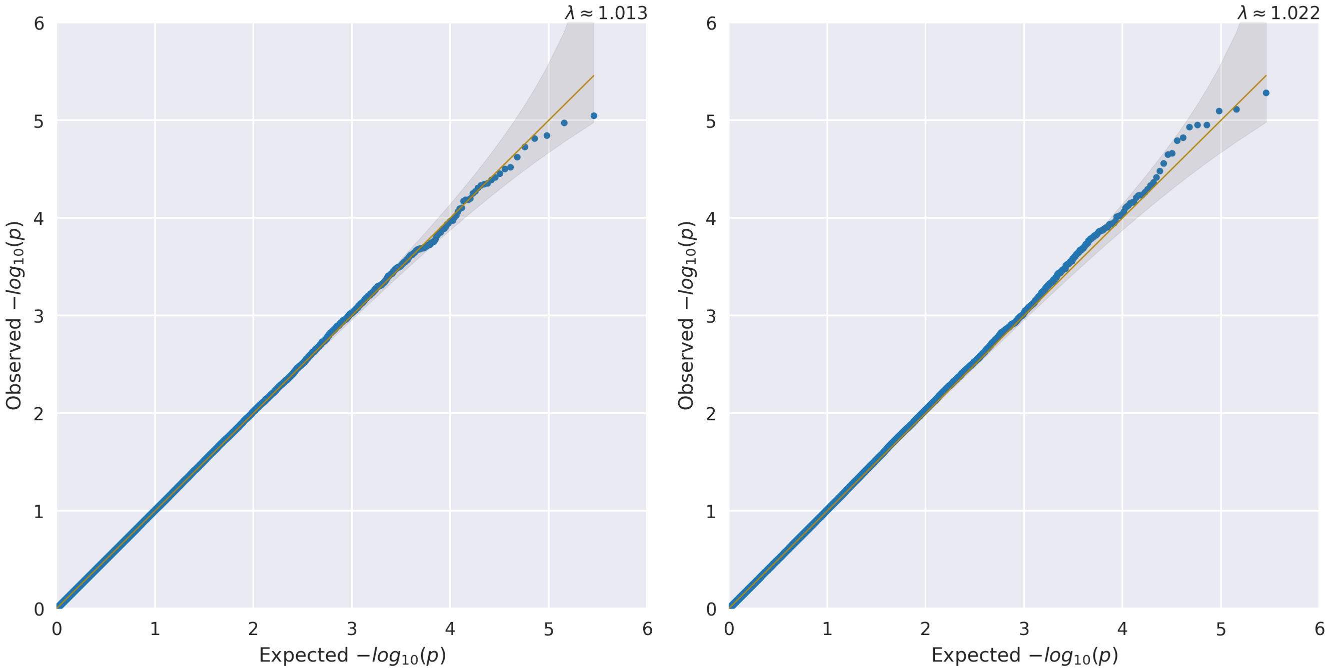
(b) EUR

Figure 10: Distribution of INS_FAST in META by cohort

Table 14: Samples with Fasting Insulin data summarized by cohort, transformation, and run-time adjustments

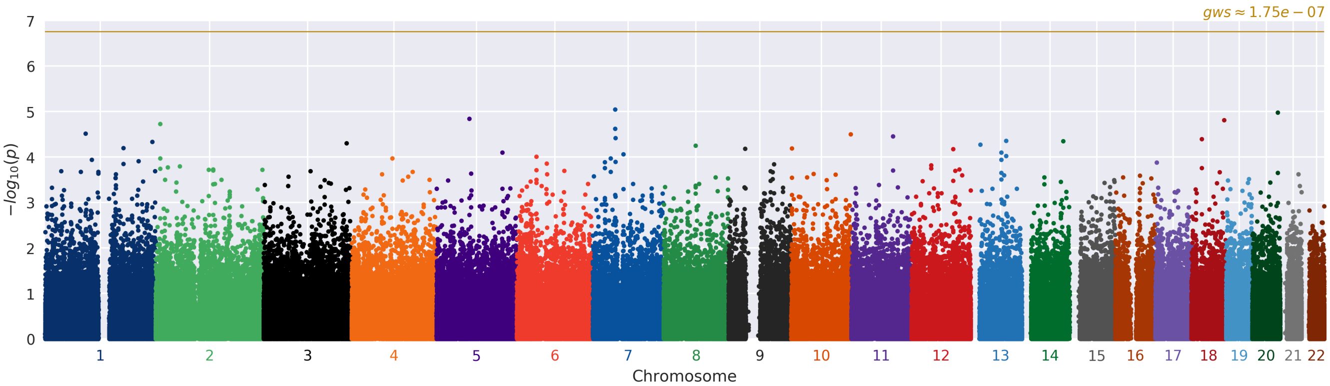
Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Max	Min	μ	$\tilde{x}$	σ
META AFR	EX	AFR	invn	AGE_GLU_INS_FAST+SEX	0	278	141	137	51.78	0.13	10.408	8.67	8.125
			invn	AGE_GLU_INS_FAST+SEX+BMI	6	267	139	128	51.78	0.13	10.304	8.59	8.131
META EUR	EX	EUR	invn	AGE_GLU_INS_FAST+SEX	2	1658	966	692	84.62	0.5	10.265	7.865	8.982
			invn	AGE_GLU_INS_FAST+SEX+BMI	0	1678	978	700	84.62	0.5	10.213	7.8	8.945

6.2 Calibration

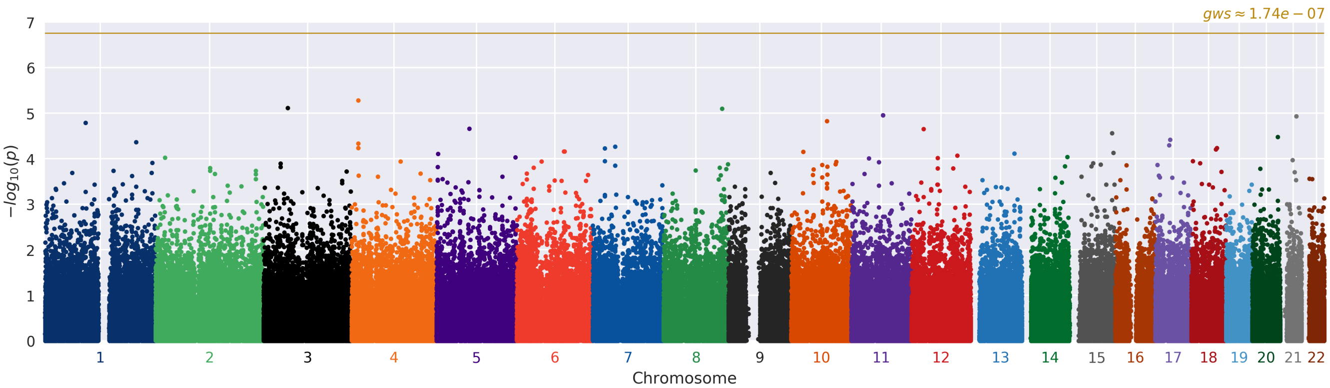


(a) invn Adjusted AGE_GLU_INS_FAST+SEX (b) invn Adjusted AGE_GLU_INS_FAST+SEX+BMI

Figure 11: QQ plots for INS_FAST in the META analysis



(a) invn Adjusted AGE_GLU_INS_FAST+SEX



(b) invn Adjusted AGE_GLU_INS_FAST+SEX+BMI

Figure 12: Manhattan plots for INS_FAST in the META analysis

6.3 Top associations

Table 15: Top variants in the META invn Adjusted AGE_GLU_INS_FAST+SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	$\text{GENE}_{\text{CLOSEST}}$	DIR	N	MALE	FEMALE	FREQ_{AVG}	FREQ_{MIN}	FREQ_{MAX}	EFFECT	STDERR	OR	ZSCORE	P
7	50627101	rs1966839	T	C	DDC	++	1,935	1,107	828	0.325	0.232	0.341	0.152	$3.43 \cdot 10^{-2}$	1.165	−4.441	$8.94 \cdot 10^{-6}$
20	57618794	rs2162593	C	T	PRELID3B	++	1,931	1,103	828	0.423	0.327	0.439	0.143	$3.26 \cdot 10^{-2}$	1.154	4.405	$1.06 \cdot 10^{-5}$
5	74184144	rs10942722	G	T	FAM169A	++	1,933	1,107	826	0.406	0.391	0.495	0.142	$3.27 \cdot 10^{-2}$	1.152	4.34	$1.43 \cdot 10^{-5}$
18	74069122	rs17059264	C	T	ZNF516	+-	1,936	1,107	829	0.513	0.133	0.576	0.146	$3.37 \cdot 10^{-2}$	1.157	−4.324	$1.53 \cdot 10^{-5}$
2	10142302	rs11246	A	G	GRHL1	++	1,935	1,106	829	0.352	0.329	0.489	0.144	$3.35 \cdot 10^{-2}$	1.154	4.281	$1.86 \cdot 10^{-5}$
1	91605491	rs347004	A	G	ZNF644	++	1,935	1,107	828	0.594	0.567	0.599	0.138	$3.31 \cdot 10^{-2}$	1.148	4.172	$3.02 \cdot 10^{-5}$
10	133555393	rs9419646	G	A	PPP2R2D	++	1,936	1,107	829	$8.39 \cdot 10^{-2}$	$6.18 \cdot 10^{-2}$	0.216	0.247	$5.94 \cdot 10^{-2}$	1.28	−4.163	$3.15 \cdot 10^{-5}$
11	93259965	rs2248020	C	A	SMCO4	++	1,936	1,107	829	0.77	0.727	0.777	0.156	$3.76 \cdot 10^{-2}$	1.169	4.137	$3.52 \cdot 10^{-5}$
7	50791579	rs6943153	C	T	GRB10	++	1,936	1,107	829	0.649	0.306	0.707	0.142	$3.45 \cdot 10^{-2}$	1.153	4.117	$3.84 \cdot 10^{-5}$
18	23413944	rs11873555	A	G	SS18	++	1,936	1,107	829	0.507	0.441	0.519	0.132	$3.21 \cdot 10^{-2}$	1.141	4.105	$4.05 \cdot 10^{-5}$
13	79220899	rs12585725	C	A	RNF219	++	1,935	1,106	829	0.178	$3.78 \cdot 10^{-2}$	0.202	0.175	$4.27 \cdot 10^{-2}$	1.191	−4.085	$4.4 \cdot 10^{-5}$
14	93014989	rs943665	T	G	RIN3	++	1,936	1,107	829	0.846	0.835	0.848	0.18	$4.41 \cdot 10^{-2}$	1.197	−4.081	$4.48 \cdot 10^{-5}$
1	241586834	rs1544190	T	C	RGS7	++	1,935	1,107	828	0.154	$9.17 \cdot 10^{-2}$	0.164	0.182	$4.48 \cdot 10^{-2}$	1.2	4.073	$4.65 \cdot 10^{-5}$
3	186724219	rs6788832	G	A	ST6GAL1	++	1,936	1,107	829	0.385	0.362	0.518	0.134	$3.3 \cdot 10^{-2}$	1.143	4.058	$4.94 \cdot 10^{-5}$
13	21595878	rs9552328	C	A	LATS2	++	1,936	1,107	829	$3.72 \cdot 10^{-2}$	$3.08 \cdot 10^{-2}$	$7.55 \cdot 10^{-2}$	0.342	$8.47 \cdot 10^{-2}$	1.408	−4.042	$5.31 \cdot 10^{-5}$
8	72573676	rs10504513	G	A	MSC	++	1,936	1,107	829	0.136	$5.22 \cdot 10^{-2}$	0.15	0.188	$4.66 \cdot 10^{-2}$	1.206	−4.03	$5.58 \cdot 10^{-5}$
1	176571578	rs10798463	G	A	PAPPA2	++	1,936	1,107	829	0.259	0.255	0.26	0.147	$3.68 \cdot 10^{-2}$	1.159	4	$6.32 \cdot 10^{-5}$
10	1424216	rs11596049	G	A	ADARB2	++	1,936	1,107	829	0.171	$8.45 \cdot 10^{-2}$	0.185	0.165	$4.14 \cdot 10^{-2}$	1.18	3.994	$6.5 \cdot 10^{-5}$
9	37745741	rs62640014	G	T	FRMPD1	++	1,936	1,107	829	$1.81 \cdot 10^{-3}$	$3.02 \cdot 10^{-4}$	$1.08 \cdot 10^{-2}$	1.507	0.377	4.511	−3.993	$6.52 \cdot 10^{-5}$
12	94329676	rs1946663	A	G	CRADD	++	1,936	1,107	829	0.426	0.423	0.426	0.13	$3.26 \cdot 10^{-2}$	1.139	3.988	$6.67 \cdot 10^{-5}$

Table 16: Top variants in the META invn Adjusted AGE_GLU_INS_FAST+SEX+BMI model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	$\text{GENE}_{\text{CLOSEST}}$	DIR	N	MALE	FEMALE	FREQ_{AVG}	FREQ_{MIN}	FREQ_{MAX}	EFFECT	STDERR	OR	ZSCORE	P
4	14919063	rs10022899	C	T	CPEB2	++	1,945	1,117	828	0.547	0.543	0.571	0.144	$3.17 \cdot 10^{-2}$	1.155	−4.556	$5.22 \cdot 10^{-6}$
3	53899276	rs1043261	C	T	IL17RB	++	1,945	1,117	828	$7.38 \cdot 10^{-2}$	$7.03 \cdot 10^{-2}$	$9.55 \cdot 10^{-2}$	0.277	$6.19 \cdot 10^{-2}$	1.319	−4.473	$7.73 \cdot 10^{-6}$
8	131745204	rs2917062	A	G	ADCY8	++	1,943	1,116	827	0.692	0.682	0.76	0.153	$3.42 \cdot 10^{-2}$	1.165	−4.465	$7.99 \cdot 10^{-6}$
11	71155974	rs115595829	A	T	DHCR7	++	1,945	1,117	828	$5.66 \cdot 10^{-3}$	$8.94 \cdot 10^{-4}$	$3.56 \cdot 10^{-2}$	0.938	0.213	2.554	4.394	$1.11 \cdot 10^{-5}$
11	71208537	rs35007971	A	G	NADSYN1	++	1,945	1,117	828	$5.66 \cdot 10^{-3}$	$8.94 \cdot 10^{-4}$	$3.56 \cdot 10^{-2}$	0.938	0.213	2.554	4.394	$1.11 \cdot 10^{-5}$
21	35893737	rs8131131	T	C	RCAN1	++	1,910	1,096	814	0.437	0.409	0.609	0.141	$3.23 \cdot 10^{-2}$	1.152	−4.384	$1.17 \cdot 10^{-5}$
10	80605477	rs10824655	G	A	ZMIZ1	++	1,945	1,117	828	0.213	0.211	0.221	0.165	$3.8 \cdot 10^{-2}$	1.179	4.329	$1.5 \cdot 10^{-5}$
1	91605491	rs347004	A	G	ZNF644	++	1,944	1,117	827	0.595	0.564	0.6	0.142	$3.29 \cdot 10^{-2}$	1.152	4.313	$1.61 \cdot 10^{-5}$
5	74184144	rs10942722	G	T	FAM169A	++	1,942	1,117	825	0.404	0.39	0.493	0.137	$3.23 \cdot 10^{-2}$	1.147	4.245	$2.18 \cdot 10^{-5}$
12	27234184	rs61732116	A	C	C12orf71	++	1,945	1,117	828	$1.03 \cdot 10^{-2}$	$5.96 \cdot 10^{-4}$	$7.12 \cdot 10^{-2}$	0.695	0.164	2.004	4.239	$2.24 \cdot 10^{-5}$
15	94968043	rs1000737	G	A	MCTP2	++	1,945	1,117	828	0.177	$7.3 \cdot 10^{-2}$	0.193	0.175	$4.18 \cdot 10^{-2}$	1.192	−4.193	$2.75 \cdot 10^{-5}$
20	57618794	rs2162593	C	T	PRELID3B	+-	1,940	1,113	827	0.421	0.316	0.437	0.134	$3.23 \cdot 10^{-2}$	1.143	4.152	$3.3 \cdot 10^{-5}$
17	33592621	rs2291189	C	T	SLFN5	++	1,945	1,117	828	$6.86 \cdot 10^{-2}$	$6.17 \cdot 10^{-2}$	0.112	0.25	$6.08 \cdot 10^{-2}$	1.284	−4.117	$3.84 \cdot 10^{-5}$
1	205195831	rs7513642	T	C	TMCC2	+-	1,945	1,117	828	0.159	$5.06 \cdot 10^{-2}$	0.176	0.181	$4.42 \cdot 10^{-2}$	1.198	4.09	$4.31 \cdot 10^{-5}$
17	31350133	rs1076198	T	G	ASIC2	++	1,945	1,117	828	0.144	0.122	0.148	0.184	$4.55 \cdot 10^{-2}$	1.202	4.051	$5.09 \cdot 10^{-5}$
7	50627101	rs1966839	T	C	DDC	++	1,944	1,117	827	0.326	0.232	0.341	0.137	$3.4 \cdot 10^{-2}$	1.147	−4.037	$5.42 \cdot 10^{-5}$
18	57854467	rs8082946	C	A	MC4R	++	1,945	1,117	828	0.221	0.206	0.311	0.155	$3.85 \cdot 10^{-2}$	1.167	4.022	$5.77 \cdot 10^{-5}$
7	27408972	rs11563971	T	C	EVX1	++	1,945	1,117	828	0.204	0.114	0.219	0.156	$3.89 \cdot 10^{-2}$	1.169	−4.018	$5.87 \cdot 10^{-5}$
18	55250264	rs317806	T	C	FECH	++	1,945	1,117	828	0.691	0.678	0.777	0.134	$3.34 \cdot 10^{-2}$	1.143	−4.006	$6.18 \cdot 10^{-5}$
6	107955663	rs146747167	G	A	SOBP	++	1,941	1,114	827	$4.38 \cdot 10^{-3}$	$4.18 \cdot 10^{-3}$	$5.64 \cdot 10^{-3}$	0.957	0.24	2.603	3.98	$6.89 \cdot 10^{-5}$

6.4 Previously identified risk loci

Table 17 shows statistics from the META cohort for 17 loci that were shown to be significantly associated with Fasting Insulin in the 2012 Nature Genetics paper by Scott et al [13]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R}^2 < 1$), if available, a tagging variant in LD with the reported variant

($\bar{R^2} >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 1 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 16 variants in both studies, 13 exhibit the same direction of effect with the known result (binomial test $p = 0.0106$).

Table 17: Top known loci in META model invn Adjusted AGE_GLU_INS_FAST+SEX (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	EFFECT	STDERR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$EFFECT_{KNOWN}$	$STDERR_{KNOWN}$	P_{KNOWN}
2	27730940	**rs1260326**	C	T	1,936	0.589	0.545	0.849	$5.22 \cdot 10^{-2}$	$3.38 \cdot 10^{-2}$	0.122	++	GCKR	1	rs1260326	$1.33 \cdot 10^{5}$	$2.1 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$2.74 \cdot 10^{-22}$
2	227093585	**rs2943640**	C	A	1,936	0.686	0.651	0.896	$8.07 \cdot 10^{-2}$	$3.52 \cdot 10^{-2}$	$2.21 \cdot 10^{-2}$	++	IRS1	1	rs2943640	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$7.32 \cdot 10^{-19}$
2	165513091	**rs10195252**	T	C	1,934	0.441	0.397	0.7	$1.74 \cdot 10^{-2}$	$3.31 \cdot 10^{-2}$	0.599	++	COBLL1	1	rs10195252	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$1.26 \cdot 10^{-16}$
2	227020653	**rs7578326**	A	G	1,936	0.361	0.35	0.432	$4.16 \cdot 10^{-2}$	$3.32 \cdot 10^{-2}$	0.21	+-	NYAP2	1	rs7578326	$1.33 \cdot 10^{5}$	$1.8 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$2.25 \cdot 10^{-16}$
8	9185146	**rs2126259**	T	C	1,936	0.901	0.842	0.911	$8.95 \cdot 10^{-2}$	$5.39 \cdot 10^{-2}$	$9.65 \cdot 10^{-2}$	++	RP11-10A14.4	1	rs2126259	$1.33 \cdot 10^{5}$	$2.4 \cdot 10^{-2}$	$3.3 \cdot 10^{-3}$	$3.3 \cdot 10^{-13}$
5	53271420	**rs702634**	A	G	1,936	0.704	0.696	0.754	$4.72 \cdot 10^{-2}$	$3.45 \cdot 10^{-2}$	0.17	+-	ARL15	1	rs702634	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.95 \cdot 10^{-12}$
19	33899065	**rs731839**	G	A	1,936	0.658	0.646	0.66	$1.2 \cdot 10^{-4}$	$3.34 \cdot 10^{-2}$	0.997	-+	PEPD	1	rs731839	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$5.13 \cdot 10^{-12}$
3	12391583	**rs2197423**	G	A	1,936	0.125	0.114	0.191	$6.57 \cdot 10^{-2}$	$4.88 \cdot 10^{-2}$	0.179	+-	PPARG	1	rs2197423	$1.33 \cdot 10^{5}$	$2.1 \cdot 10^{-2}$	$3.1 \cdot 10^{-3}$	$8.98 \cdot 10^{-12}$
3	12116620	rs308971	A	G	1,936	0.851	0.709	0.875	$1.68 \cdot 10^{-2}$	$4.48 \cdot 10^{-2}$	0.708	++	TIMP4	1	rs308971	$1.33 \cdot 10^{5}$	$-2.1 \cdot 10^{-2}$	$3.1 \cdot 10^{-3}$	$2.97 \cdot 10^{-11}$
4	106071064	**rs974801**	G	A	1,934	0.361	0.282	0.374	$4.07 \cdot 10^{-4}$	$3.32 \cdot 10^{-2}$	0.99	-+	TET2	1	rs974801	$1.33 \cdot 10^{5}$	$1.4 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$3.27 \cdot 10^{-11}$
5	55806751	**rs459193**	G	A	1,936	0.724	0.59	0.747	$5.23 \cdot 10^{-2}$	$3.62 \cdot 10^{-2}$	0.148	++	AC022431.2	1	rs459193	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.15 \cdot 10^{-10}$
4	157670537	**rs6855363**	T	C	1,936	0.405	0.353	0.716	$4.41 \cdot 10^{-3}$	$3.41 \cdot 10^{-2}$	0.897	-+	PDGFC	1	rs6855363	$1.33 \cdot 10^{5}$	$1.4 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.77 \cdot 10^{-10}$
1	219652033	**rs2791552**	C	A	1,936	0.647	0.432	0.683	$7.95 \cdot 10^{-3}$	$3.39 \cdot 10^{-2}$	0.815	+-	LYPLAL1	1	rs2791552	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$2.57 \cdot 10^{-9}$
1	219750717	rs4846567	T	G	1,936	0.252	$8.27 \cdot 10^{-2}$	0.28	$6.33 \cdot 10^{-3}$	$3.66 \cdot 10^{-2}$	0.863	++	SLC30A10	1	rs4846567	$1.33 \cdot 10^{5}$	$-1.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$9.61 \cdot 10^{-9}$
4	89739808	rs3775380	A	G	1,935	0.5	0.49	0.556	$6.14 \cdot 10^{-3}$	$3.17 \cdot 10^{-2}$	0.846	+-	FAM13A	1	rs3775380	$1.33 \cdot 10^{5}$	$-1.1 \cdot 10^{-2}$	$2 \cdot 10^{-3}$	$2.92 \cdot 10^{-8}$
4	157615583	**rs1996770**	C	T	1,936	0.433	0.388	0.698	$3.74 \cdot 10^{-2}$	$3.35 \cdot 10^{-2}$	0.263	++	RP11-171N4.2	1	rs1464454	$1.33 \cdot 10^{5}$	$1.2 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$5.11 \cdot 10^{-8}$
12	102912558	**rs35747**	A	G	1,936	0.772	0.428	0.829	$7.37 \cdot 10^{-2}$	$4.05 \cdot 10^{-2}$	$6.88 \cdot 10^{-2}$	++	IGF1	0.993	rs860598	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.7 \cdot 10^{-3}$	$1.46 \cdot 10^{-8}$

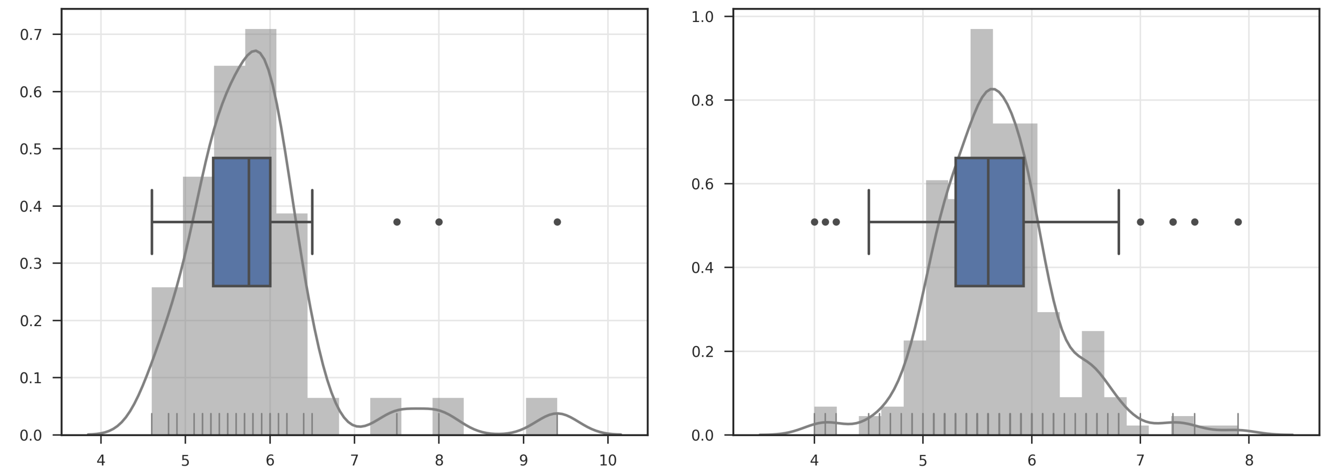
Table 18 shows statistics from the META cohort for 17 loci that were shown to be significantly associated with Fasting Insulin in the 2012 Nature Genetics paper by Scott et al [13]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R^2} < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R^2} >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 3 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 16 variants in both studies, 13 exhibit the same direction of effect with the known result (binomial test $p = 0.0106$).

Table 18: Top known loci in META model invn Adjusted AGE_GLU_INS_FAST+SEX+BMI (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	EFFECT	STDERR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$EFFECT_{KNOWN}$	$STDERR_{KNOWN}$	P_{KNOWN}
2	27730940	**rs1260326**	C	T	1,945	0.586	0.546	0.843	$3.53 \cdot 10^{-2}$	$3.32 \cdot 10^{-2}$	0.287	++	GCKR	1	rs1260326	$1.33 \cdot 10^{5}$	$2.1 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$2.74 \cdot 10^{-22}$
2	227093585	**rs2943640**	C	A	1,945	0.686	0.653	0.895	$9.05 \cdot 10^{-2}$	$3.47 \cdot 10^{-2}$	$9.14 \cdot 10^{-3}$	++	IRS1	1	rs2943640	$1.33 \cdot 10^{5}$	$1.9 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$7.32 \cdot 10^{-19}$
2	165513091	**rs10195252**	T	C	1,943	0.441	0.399	0.702	$4.03 \cdot 10^{-2}$	$3.27 \cdot 10^{-2}$	0.218	++	COBLL1	1	rs10195252	$1.33 \cdot 10^{5}$	$1.7 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$1.26 \cdot 10^{-16}$
2	227020653	**rs7578326**	A	G	1,945	0.36	0.349	0.434	$5.66 \cdot 10^{-2}$	$3.28 \cdot 10^{-2}$	$8.43 \cdot 10^{-2}$	+-	NYAP2	1	rs7578326	$1.33 \cdot 10^{5}$	$1.8 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$2.25 \cdot 10^{-16}$
8	9185146	**rs2126259**	T	C	1,945	0.899	0.837	0.909	$6.27 \cdot 10^{-2}$	$5.27 \cdot 10^{-2}$	0.234	++	RP11-10A14.4	1	rs2126259	$1.33 \cdot 10^{5}$	$2.4 \cdot 10^{-2}$	$3.3 \cdot 10^{-3}$	$3.3 \cdot 10^{-13}$
5	53271420	**rs702634**	A	G	1,945	0.704	0.695	0.762	$9.55 \cdot 10^{-2}$	$3.42 \cdot 10^{-2}$	$5.29 \cdot 10^{-3}$	+-	ARL15	1	rs702634	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.95 \cdot 10^{-12}$
19	33899065	**rs731839**	G	A	1,945	0.656	0.644	0.658	$1.71 \cdot 10^{-2}$	$3.3 \cdot 10^{-2}$	0.605	++	PEPD	1	rs731839	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$5.13 \cdot 10^{-12}$
3	12391583	**rs2197423**	G	A	1,945	0.124	0.114	0.189	$6.49 \cdot 10^{-2}$	$4.83 \cdot 10^{-2}$	0.179	+-	PPARG	1	rs2197423	$1.33 \cdot 10^{5}$	$2.1 \cdot 10^{-2}$	$3.1 \cdot 10^{-3}$	$8.98 \cdot 10^{-12}$
3	12116620	rs308971	A	G	1,945	0.851	0.704	0.875	$1.48 \cdot 10^{-5}$	$4.46 \cdot 10^{-2}$	1	-+	TIMP4	1	rs308971	$1.33 \cdot 10^{5}$	$-2.1 \cdot 10^{-2}$	$3.1 \cdot 10^{-3}$	$2.97 \cdot 10^{-11}$
4	106071064	rs974801	A	G	1,943	0.361	0.27	0.376	$5.15 \cdot 10^{-2}$	$3.3 \cdot 10^{-2}$	0.119	++	TET2	1	rs974801	$1.33 \cdot 10^{5}$	$-1.4 \cdot 10^{-2}$	$2.1 \cdot 10^{-3}$	$3.27 \cdot 10^{-11}$
5	55806751	**rs459193**	G	A	1,945	0.725	0.59	0.746	$2.34 \cdot 10^{-2}$	$3.59 \cdot 10^{-2}$	0.514	+-	AC022431.2	1	rs459193	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$1.15 \cdot 10^{-10}$
4	157670537	**rs6855363**	T	C	1,945	0.405	0.355	0.723	$4.17 \cdot 10^{-2}$	$3.37 \cdot 10^{-2}$	0.216	++	PDGFC	1	rs6855363	$1.33 \cdot 10^{5}$	$1.4 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$4.77 \cdot 10^{-10}$
1	219652033	**rs2791552**	C	A	1,945	0.648	0.427	0.683	$3.95 \cdot 10^{-2}$	$3.35 \cdot 10^{-2}$	0.238	+-	LYPLAL1	1	rs2791552	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$2.57 \cdot 10^{-9}$
1	219750717	**rs4846567**	G	T	1,945	0.255	$8.43 \cdot 10^{-2}$	0.282	$4.22 \cdot 10^{-2}$	$3.6 \cdot 10^{-2}$	0.241	++	SLC30A10	1	rs4846567	$1.33 \cdot 10^{5}$	$1.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-3}$	$9.61 \cdot 10^{-9}$
4	89739808	rs3775380	A	G	1,944	0.498	0.49	0.549	$4.09 \cdot 10^{-2}$	$3.13 \cdot 10^{-2}$	0.191	++	FAM13A	1	rs3775380	$1.33 \cdot 10^{5}$	$-1.1 \cdot 10^{-2}$	$2 \cdot 10^{-3}$	$2.92 \cdot 10^{-8}$
4	157615583	**rs1996770**	C	T	1,945	0.433	0.39	0.708	$3.72 \cdot 10^{-3}$	$3.31 \cdot 10^{-2}$	0.91	+-	RP11-171N4.2	1	rs1464454	$1.33 \cdot 10^{5}$	$1.2 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$5.11 \cdot 10^{-8}$
12	102912558	**rs35747**	A	G	1,945	0.773	0.425	0.828	0.103	$4.02 \cdot 10^{-2}$	$1.03 \cdot 10^{-2}$	++	IGF1	0.993	rs860598	$1.33 \cdot 10^{5}$	$1.5 \cdot 10^{-2}$	$2.7 \cdot 10^{-3}$	$1.46 \cdot 10^{-8}$

7 Hemoglobin A1c (HBA1C)

7.1 Summary



(a) AFR

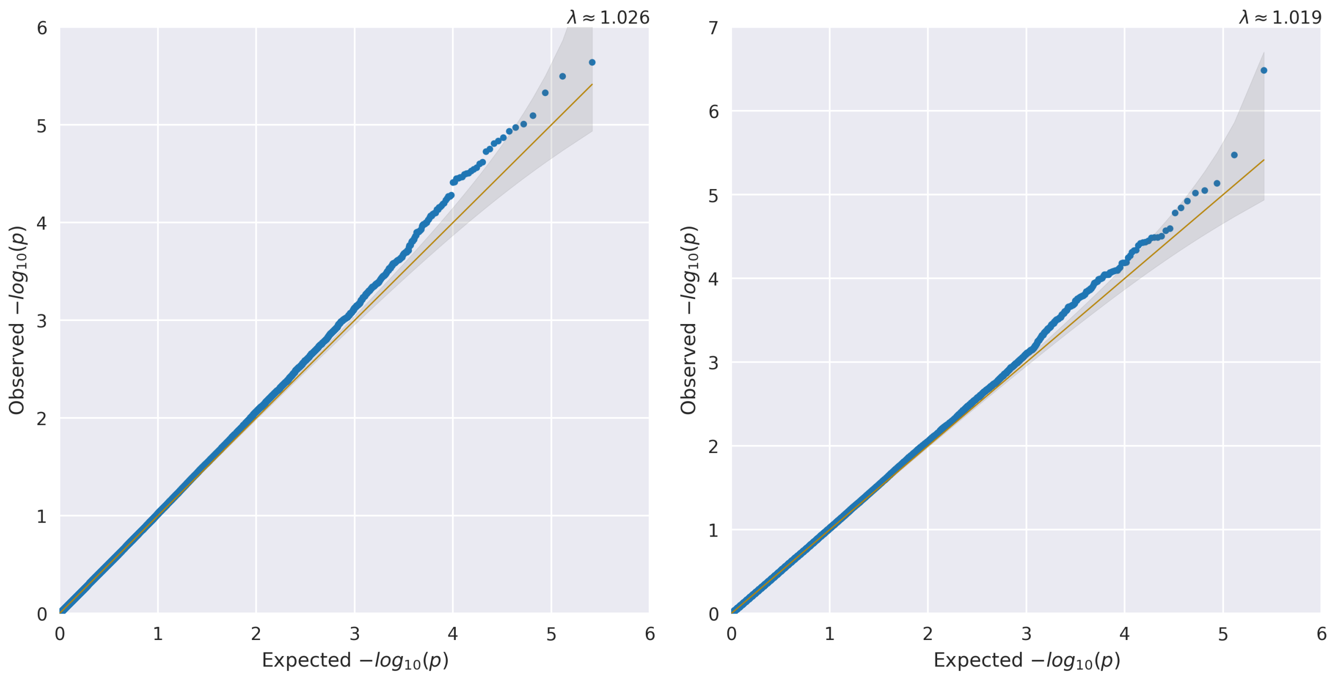
(b) EUR

Figure 13: Distribution of HBA1C in META by cohort

Table 19: Samples with Hemoglobin A1c data summarized by cohort, transformation, and run-time adjustments

Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Max	Min	μ	$\tilde{x}$	σ
META AFR	EX	AFR	invn	AGE_HBA1C+SEX+BMI	0	37	18	19	9.4	4.6	5.816	5.7	0.832
			invn	AGE_HBA1C+SEX	0	37	18	19	9.4	4.6	5.816	5.7	0.832
META EUR	EX	EUR	invn	AGE_HBA1C+SEX	0	215	136	79	7.9	4.0	5.671	5.6	0.549
			invn	AGE_HBA1C+SEX+BMI	0	215	136	79	7.9	4.0	5.671	5.6	0.549

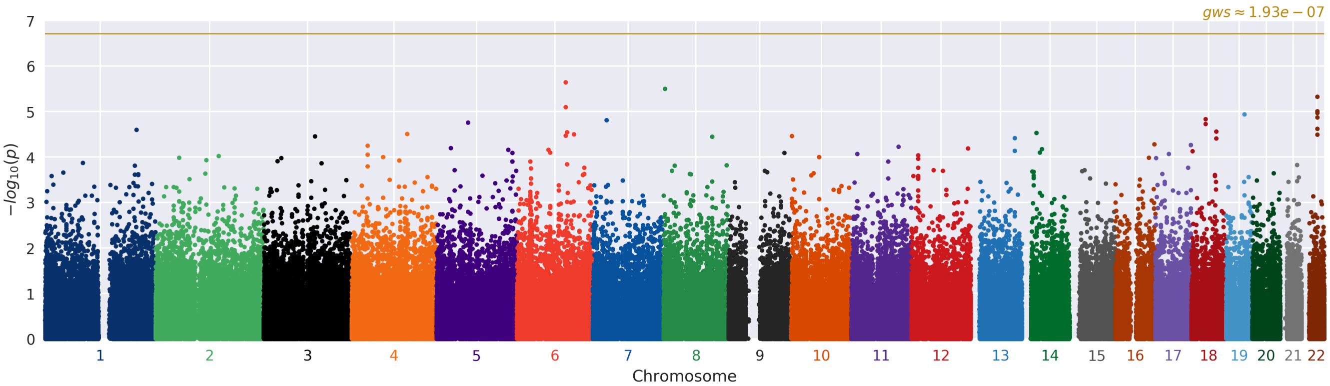
7.2 Calibration



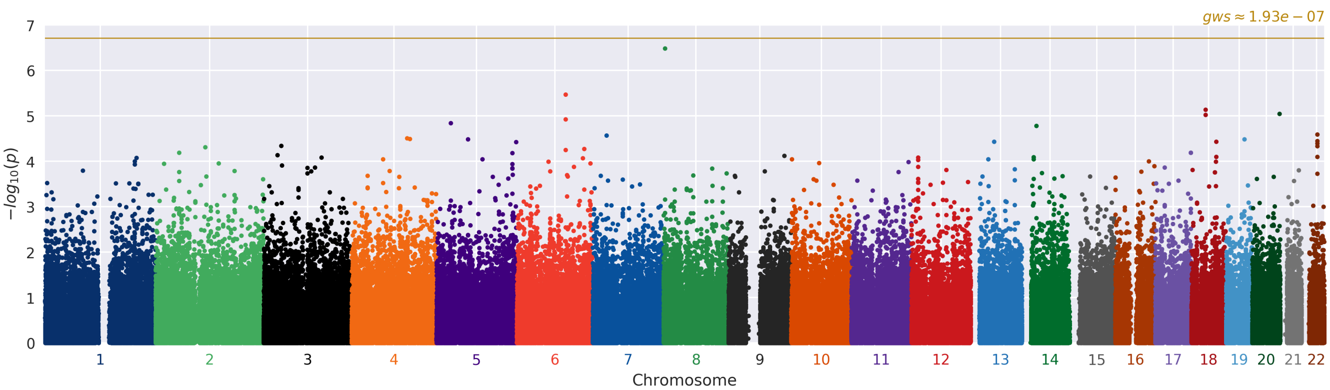
(a) invn Adjusted AGE_HBA1C+SEX

(b) invn Adjusted AGE_HBA1C+SEX+BMI

Figure 14: QQ plots for HBA1C in the META analysis



(a) invn Adjusted AGE_HBA1C+SEX



(b) invn Adjusted AGE_HBA1C+SEX+BMI

Figure 15: Manhattan plots for HBA1C in the META analysis

7.3 Top associations

Table 20: Top variants in the META invn Adjusted AGE_HBA1C+SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE$_{CLOSEST}$	DIR	N	MALE	FEMALE	FREQ$_{AVG}$	FREQ$_{MIN}$	FREQ$_{MAX}$	EFFECT	STDERR	OR	ZSCORE	P
6	109616420	rs9374080	T	C	CD164	++	248	151	97	0.472	0.392	0.486	0.426	$9.02 \cdot 10^{-2}$	1.531	−4.727	$2.28 \cdot 10^{-6}$
8	3520871	rs2624087	T	C	CSMD1	++	252	154	98	0.31	0.295	0.392	0.44	$9.45 \cdot 10^{-2}$	1.553	−4.66	$3.17 \cdot 10^{-6}$
22	35680095	rs2272790	A	G	HMGXB4	++	252	154	98	0.659	0.459	0.693	0.43	$9.39 \cdot 10^{-2}$	1.537	4.579	$4.68 \cdot 10^{-6}$
22	35711098	rs138777	G	A	TOM1	++	252	154	98	0.609	0.203	0.679	0.431	$9.79 \cdot 10^{-2}$	1.539	4.405	$1.06 \cdot 10^{-5}$
19	41723887	rs8101017	G	T	AXL	++	252	154	98	0.264	0.23	0.459	0.432	$9.84 \cdot 10^{-2}$	1.54	−4.386	$1.15 \cdot 10^{-5}$
18	31662506	rs4413039	G	A	NOL4	++	252	154	98	0.847	0.838	0.849	0.513	0.118	1.67	4.335	$1.46 \cdot 10^{-5}$
7	31204503	rs6945601	C	T	ADCYAP1R1	++	252	154	98	0.415	0.365	0.703	0.395	$9.13 \cdot 10^{-2}$	1.484	−4.323	$1.54 \cdot 10^{-5}$
5	70996378	rs4704160	G	T	CARTPT	++	252	154	98	0.502	0.5	0.514	0.371	$8.64 \cdot 10^{-2}$	1.449	−4.294	$1.75 \cdot 10^{-5}$
1	206326498	rs28410805	G	A	CTSE	++	252	154	98	0.25	0.2	0.541	0.442	0.105	1.556	4.215	$2.49 \cdot 10^{-5}$
18	56219590	rs8083368	A	G	ALPK2	++	252	154	98	0.246	0.216	0.251	0.427	0.102	1.532	4.194	$2.74 \cdot 10^{-5}$
6	113140908	rs7739145	G	T	RFPL4B	++	251	154	97	0.857	0.694	0.884	0.53	0.127	1.699	−4.185	$2.85 \cdot 10^{-5}$
14	31989902	rs3945419	G	A	GPR33	++	252	154	98	0.748	0.743	0.749	0.428	0.103	1.534	−4.177	$2.96 \cdot 10^{-5}$
4	124659199	rs17007240	T	C	SPRY1	++	252	154	98	0.546	0.446	0.563	0.374	$8.98 \cdot 10^{-2}$	1.454	−4.166	$3.1 \cdot 10^{-5}$
6	128624360	rs17055587	G	A	PTPRK	-+	252	154	98	$2.98 \cdot 10^{-2}$	$4.65 \cdot 10^{-3}$	0.176	0.988	0.238	2.687	−4.162	$3.16 \cdot 10^{-5}$
10	1430761	rs2387667	T	C	ADARB2	++	252	154	98	0.446	0.297	0.472	0.388	$9.36 \cdot 10^{-2}$	1.474	−4.143	$3.43 \cdot 10^{-5}$
3	115596317	rs9830559	C	T	LSAMP	++	252	154	98	0.417	0.284	0.44	0.366	$8.85 \cdot 10^{-2}$	1.442	4.139	$3.5 \cdot 10^{-5}$
8	109164182	rs672161	A	G	EIF3E	++	252	154	98	0.389	0.176	0.426	0.366	$8.85 \cdot 10^{-2}$	1.442	4.136	$3.54 \cdot 10^{-5}$
13	98354979	rs9556795	C	A	RAP2A	++	252	154	98	0.149	0.112	0.365	0.521	0.126	1.683	4.118	$3.82 \cdot 10^{-5}$
16	87718696	rs1366521	T	C	JPH3	++	252	154	98	0.31	0.297	0.312	0.386	$9.55 \cdot 10^{-2}$	1.472	4.045	$5.23 \cdot 10^{-5}$
17	79668135	rs56058441	G	T	HGS	++	252	154	98	$5.75 \cdot 10^{-2}$	$5.35 \cdot 10^{-2}$	$8.11 \cdot 10^{-2}$	0.786	0.195	2.195	−4.039	$5.37 \cdot 10^{-5}$

Table 21: Top variants in the META invn Adjusted AGE_HBA1C+SEX+BMI model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE$_{CLOSEST}$	DIR	N	MALE	FEMALE	FREQ$_{AVG}$	FREQ$_{MIN}$	FREQ$_{MAX}$	EFFECT	STDERR	OR	ZSCORE	P
8	3520871	rs2624087	T	C	CSMD1	++	252	154	98	0.31	0.295	0.392	0.481	$9.42 \cdot 10^{-2}$	1.618	−5.108	$3.26 \cdot 10^{-7}$
6	109616420	rs9374080	T	C	CD164	++	248	151	97	0.472	0.392	0.486	0.422	$9.08 \cdot 10^{-2}$	1.525	−4.647	$3.36 \cdot 10^{-6}$
18	31662506	rs4413039	G	A	NOL4	++	252	154	98	0.847	0.838	0.849	0.53	0.118	1.699	4.485	$7.3 \cdot 10^{-6}$
20	61292447	rs6011477	A	G	SLCO4A1	++	252	154	98	$7.94 \cdot 10^{-3}$	$2.33 \cdot 10^{-3}$	$4.05 \cdot 10^{-2}$	1.98	0.446	7.244	4.442	$8.92 \cdot 10^{-6}$
5	31957550	rs7702447	C	T	PDZD2	++	250	152	98	0.306	0.278	0.311	0.399	$9.21 \cdot 10^{-2}$	1.491	4.339	$1.43 \cdot 10^{-5}$
14	31989902	rs3945419	G	A	GPR33	++	252	154	98	0.748	0.743	0.749	0.442	0.103	1.556	−4.308	$1.65 \cdot 10^{-5}$
22	35680095	rs2272790	A	G	HMGXB4	++	252	154	98	0.659	0.459	0.693	0.4	$9.51 \cdot 10^{-2}$	1.492	4.211	$2.54 \cdot 10^{-5}$
7	31204503	rs6945601	C	T	ADCYAP1R1	++	252	154	98	0.415	0.365	0.703	0.387	$9.21 \cdot 10^{-2}$	1.472	−4.198	$2.69 \cdot 10^{-5}$
4	124659199	rs17007240	T	C	SPRY1	++	252	154	98	0.546	0.446	0.563	0.374	$8.99 \cdot 10^{-2}$	1.454	−4.166	$3.11 \cdot 10^{-5}$
4	130869806	rs17050760	A	G	C4orf33	++	252	154	98	$2.58 \cdot 10^{-2}$	$2.33 \cdot 10^{-3}$	0.162	1.127	0.271	3.085	4.158	$3.21 \cdot 10^{-5}$
19	41723887	rs8101017	G	T	AXL	++	252	154	98	0.264	0.23	0.459	0.416	0.1	1.516	−4.155	$3.25 \cdot 10^{-5}$
5	70996378	rs4704160	G	T	CARTPT	++	252	154	98	0.502	0.5	0.514	0.361	$8.69 \cdot 10^{-2}$	1.434	−4.153	$3.28 \cdot 10^{-5}$
18	56219590	rs8083368	A	G	ALPK2	++	252	154	98	0.246	0.216	0.251	0.421	0.102	1.523	4.126	$3.69 \cdot 10^{-5}$
13	52313253	rs77486739	A	G	WDFY2	++	252	154	98	$5.95 \cdot 10^{-3}$	$2.33 \cdot 10^{-3}$	$2.7 \cdot 10^{-2}$	2.19	0.531	8.935	4.125	$3.71 \cdot 10^{-5}$
5	178950814	rs1344156	C	A	RUFY1	++	252	154	98	0.778	0.595	0.809	0.42	0.102	1.522	4.12	$3.78 \cdot 10^{-5}$
22	35712553	rs138780	G	A	TOM1	++	252	154	98	0.73	0.351	0.795	0.447	0.109	1.564	4.106	$4.03 \cdot 10^{-5}$
3	39340050	rs7651347	T	C	CX3CR1	++	252	154	98	0.214	0.193	0.338	0.411	0.101	1.509	4.076	$4.59 \cdot 10^{-5}$
2	111712830	rs1877656	G	A	ACOXL	++	252	154	98	$3.57 \cdot 10^{-2}$	$1.86 \cdot 10^{-2}$	0.135	0.989	0.243	2.688	−4.062	$4.87 \cdot 10^{-5}$
6	151439698	rs9478170	G	A	MTHFD1L	++	252	154	98	0.71	0.608	0.728	0.392	$9.7 \cdot 10^{-2}$	1.48	4.04	$5.34 \cdot 10^{-5}$
2	52703590	rs12619788	G	A	ASB3	++	252	154	98	0.474	0.446	0.479	0.35	$8.75 \cdot 10^{-2}$	1.418	−3.997	$6.42 \cdot 10^{-5}$

7.4 Previously identified risk loci

Table 22 shows statistics from the META cohort for 18 loci that were shown to be significantly associated with Hemoglobin A1c in the 2010 Diabetes paper by Soranzo et al [14]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R}^2 < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R}^2 >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 1 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 16 variants in both studies, 7 exhibit the same direction of effect with the known result (binomial test $p = 0.773$).

Table 22: Top known loci in META model invn Adjusted AGE_HBA1C+SEX (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	EFFECT	STDERR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$EFFECT_{KNOWN}$	$STDERR_{KNOWN}$	P_{KNOWN}
17	80685533	rs1046896	C	T	252	0.317	0.189	0.34	$8.14 \cdot 10^{-3}$	$9.42 \cdot 10^{-2}$	0.931	++	FN3KRP	1	rs1046896	46,368	$-3.46 \cdot 10^{-2}$	$3.2 \cdot 10^{-3}$	$1.58 \cdot 10^{-26}$
7	44229068	**rs1799884**	T	C	252	0.167	0.162	0.167	$4.66 \cdot 10^{-2}$	0.118	0.692	++	GCK	1	rs1799884	46,368	$3.8 \cdot 10^{-2}$	$4.1 \cdot 10^{-3}$	$1.45 \cdot 10^{-20}$
6	26093141	rs1800562	A	G	252	$6.35 \cdot 10^{-2}$	$1.35 \cdot 10^{-2}$	$7.21 \cdot 10^{-2}$	$2.79 \cdot 10^{-2}$	0.194	0.885	++	HFE	1	rs1800562	46,368	$-6.36 \cdot 10^{-2}$	$6.9 \cdot 10^{-3}$	$2.59 \cdot 10^{-20}$
17	80791469	**rs9906115**	A	G	252	0.248	$9.46 \cdot 10^{-2}$	0.274	$3.4 \cdot 10^{-2}$	0.101	0.738	+-	ZNF750	1	rs9906115	46,368	$3.54 \cdot 10^{-2}$	$3.8 \cdot 10^{-3}$	$2.65 \cdot 10^{-20}$
7	44235668	**rs4607517**	A	G	252	0.157	$9.46 \cdot 10^{-2}$	0.167	$4.53 \cdot 10^{-2}$	0.125	0.716	++	YKT6	1	rs4607517	46,368	$4.05 \cdot 10^{-2}$	$4.6 \cdot 10^{-3}$	$6.3 \cdot 10^{-19}$
2	169791438	rs552976	A	G	252	0.665	0.662	0.665	$3.27 \cdot 10^{-2}$	$9.53 \cdot 10^{-2}$	0.731	+-	ABCB11	1	rs552976	46,368	$-2.9 \cdot 10^{-2}$	$3.4 \cdot 10^{-3}$	$8.16 \cdot 10^{-18}$
2	169763148	rs560887	T	C	252	0.75	0.714	0.959	$1.92 \cdot 10^{-2}$	0.107	0.857	+-	G6PC2	1	rs560887	46,368	$-3.18 \cdot 10^{-2}$	$3.7 \cdot 10^{-3}$	$1.04 \cdot 10^{-17}$
17	80901020	**rs1044661**	A	G	252	0.254	0.122	0.277	0.201	0.1	$4.55 \cdot 10^{-2}$	+-	TBCD	1	rs1044661	46,368	$3.3 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$1.45 \cdot 10^{-17}$
22	37462936	rs855791	G	A	252	0.613	0.577	0.824	$3.04 \cdot 10^{-2}$	$9.44 \cdot 10^{-2}$	0.747	+-	TMPRSS6	1	rs855791	46,368	$-2.71 \cdot 10^{-2}$	$3.6 \cdot 10^{-3}$	$2.74 \cdot 10^{-14}$
6	25842951	rs1408272	G	T	252	$6.35 \cdot 10^{-2}$	$1.35 \cdot 10^{-2}$	$7.21 \cdot 10^{-2}$	$6.08 \cdot 10^{-2}$	0.193	0.752	++	SLC17A3	1	rs1408272	46,368	$-6.05 \cdot 10^{-2}$	$8.4 \cdot 10^{-3}$	$6.29 \cdot 10^{-13}$
6	25821770	rs17342717	T	C	252	$7.94 \cdot 10^{-2}$	$1.35 \cdot 10^{-2}$	$9.07 \cdot 10^{-2}$	$3.97 \cdot 10^{-2}$	0.171	0.816	++	SLC17A1	1	rs17342717	46,368	$-4.49 \cdot 10^{-2}$	$6.3 \cdot 10^{-3}$	$1.26 \cdot 10^{-12}$
8	41630405	rs4737009	G	A	252	0.278	0.247	0.459	$9.99 \cdot 10^{-2}$	0.106	0.348	+-	ANK1	1	rs4737009	46,368	$-2.69 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$6.12 \cdot 10^{-12}$
10	71091013	**rs10823343**	A	G	252	0.304	0.251	0.608	$3.3 \cdot 10^{-2}$	0.1	0.742	++	HK1	1	rs10823343	46,368	$2.91 \cdot 10^{-2}$	$4.3 \cdot 10^{-3}$	$8.87 \cdot 10^{-12}$
11	92673828	**rs1387153**	T	C	252	0.323	0.321	0.338	$3.37 \cdot 10^{-2}$	$9.26 \cdot 10^{-2}$	0.716	-+	MTNR1B	1	rs1387153	46,368	$2.58 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$3.96 \cdot 10^{-11}$
13	113331868	rs7998202	A	G	252	0.147	0.13	0.243	$2.27 \cdot 10^{-2}$	0.13	0.862	++	ATP11A	1	rs7998202	46,368	$-3.07 \cdot 10^{-2}$	$5.3 \cdot 10^{-3}$	$5.24 \cdot 10^{-9}$
1	158626378	**rs857691**	T	C	251	0.331	0.273	0.662	0.139	$9.96 \cdot 10^{-2}$	0.164	+-	SPTA1	1	rs857691	46,368	$2.25 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$9.43 \cdot 10^{-9}$
2	169748422	rs574981	C	T	252	0.688	0.681	0.73	0.114	$9.19 \cdot 10^{-2}$	0.213	+-	SPC25	0.889	rs853770	46,368	$-2.09 \cdot 10^{-2}$	$3.7 \cdot 10^{-3}$	$2.33 \cdot 10^{-8}$
17	80788492	rs12948179	A	G	250	0.434	0.423	0.5	0.17	$8.7 \cdot 10^{-2}$	$5.02 \cdot 10^{-2}$	+-	B3GNTL1	0.711	rs12949939	46,368	$-2.03 \cdot 10^{-2}$	$3.7 \cdot 10^{-3}$	$3.19 \cdot 10^{-8}$

Table 23 shows statistics from the META cohort for 18 loci that were shown to be significantly associated with Hemoglobin A1c in the 2010 Diabetes paper by Soranzo et al [14]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R}^2 < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R}^2 >= 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 1 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 16 variants in both studies, 8 exhibit the same direction of effect with the known result (binomial test $p = 0.598$).

Table 23: Top known loci in META model invn Adjusted AGE_HBA1C+SEX+BMI (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	$FREQ_{AVG}$	$FREQ_{MIN}$	$FREQ_{MAX}$	EFFECT	STDERR	P	DIR	$GENE_{CLOSEST}$	R^2	ID_{KNOWN}	N_{KNOWN}	$EFFECT_{KNOWN}$	$STDERR_{KNOWN}$	P_{KNOWN}
17	80685533	**rs1046896**	T	C	252	0.317	0.189	0.34	$2.07 \cdot 10^{-3}$	$9.46 \cdot 10^{-2}$	0.983	+-	FN3KRP	1	rs1046896	46,368	$3.46 \cdot 10^{-2}$	$3.2 \cdot 10^{-3}$	$1.58 \cdot 10^{-26}$
7	44229068	**rs1799884**	T	C	252	0.167	0.162	0.167	$1.15 \cdot 10^{-2}$	0.118	0.922	++	GCK	1	rs1799884	46,368	$3.8 \cdot 10^{-2}$	$4.1 \cdot 10^{-3}$	$1.45 \cdot 10^{-20}$
6	26093141	rs1800562	A	G	252	$6.35 \cdot 10^{-2}$	$1.35 \cdot 10^{-2}$	$7.21 \cdot 10^{-2}$	$1.89 \cdot 10^{-2}$	0.194	0.922	++	HFE	1	rs1800562	46,368	$-6.36 \cdot 10^{-2}$	$6.9 \cdot 10^{-3}$	$2.59 \cdot 10^{-20}$
17	80791469	**rs9906115**	A	G	252	0.248	$9.46 \cdot 10^{-2}$	0.274	$5.46 \cdot 10^{-2}$	0.102	0.592	+-	ZNF750	1	rs9906115	46,368	$3.54 \cdot 10^{-2}$	$3.8 \cdot 10^{-3}$	$2.65 \cdot 10^{-20}$
7	44235668	**rs4607517**	A	G	252	0.157	$9.46 \cdot 10^{-2}$	0.167	$8.13 \cdot 10^{-3}$	0.125	0.948	++	YKT6	1	rs4607517	46,368	$4.05 \cdot 10^{-2}$	$4.6 \cdot 10^{-3}$	$6.3 \cdot 10^{-19}$
2	169791438	rs552976	A	G	252	0.665	0.662	0.665	$4.86 \cdot 10^{-2}$	$9.56 \cdot 10^{-2}$	0.612	+-	ABCB11	1	rs552976	46,368	$-2.9 \cdot 10^{-2}$	$3.4 \cdot 10^{-3}$	$8.16 \cdot 10^{-18}$
2	169763148	rs560887	T	C	252	0.75	0.714	0.959	$2.36 \cdot 10^{-2}$	0.107	0.826	+-	G6PC2	1	rs560887	46,368	$-3.18 \cdot 10^{-2}$	$3.7 \cdot 10^{-3}$	$1.04 \cdot 10^{-17}$
17	80901020	**rs1044661**	A	G	252	0.254	0.122	0.277	0.218	0.1	$2.97 \cdot 10^{-2}$	+-	TBCD	1	rs1044661	46,368	$3.3 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$1.45 \cdot 10^{-17}$
22	37462936	rs855791	G	A	252	0.613	0.577	0.824	$2.68 \cdot 10^{-2}$	$9.52 \cdot 10^{-2}$	0.778	+-	TMPRSS6	1	rs855791	46,368	$-2.71 \cdot 10^{-2}$	$3.6 \cdot 10^{-3}$	$2.74 \cdot 10^{-14}$
6	25842951	rs1408272	G	T	252	$6.35 \cdot 10^{-2}$	$1.35 \cdot 10^{-2}$	$7.21 \cdot 10^{-2}$	$6.44 \cdot 10^{-2}$	0.193	0.738	++	SLC17A3	1	rs1408272	46,368	$-6.05 \cdot 10^{-2}$	$8.4 \cdot 10^{-3}$	$6.29 \cdot 10^{-13}$
6	25821770	rs17342717	T	C	252	$7.94 \cdot 10^{-2}$	$1.35 \cdot 10^{-2}$	$9.07 \cdot 10^{-2}$	$4.7 \cdot 10^{-2}$	0.171	0.784	++	SLC17A1	1	rs17342717	46,368	$-4.49 \cdot 10^{-2}$	$6.3 \cdot 10^{-3}$	$1.26 \cdot 10^{-12}$
8	41630405	rs4737009	G	A	252	0.278	0.247	0.459	$9.98 \cdot 10^{-2}$	0.107	0.349	+-	ANK1	1	rs4737009	46,368	$-2.69 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$6.12 \cdot 10^{-12}$
10	71091013	**rs10823343**	A	G	252	0.304	0.251	0.608	$1.98 \cdot 10^{-2}$	0.101	0.844	++	HK1	1	rs10823343	46,368	$2.91 \cdot 10^{-2}$	$4.3 \cdot 10^{-3}$	$8.87 \cdot 10^{-12}$
11	92673828	**rs1387153**	T	C	252	0.323	0.321	0.338	$1.33 \cdot 10^{-2}$	$9.31 \cdot 10^{-2}$	0.887	-+	MTNR1B	1	rs1387153	46,368	$2.58 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$3.96 \cdot 10^{-11}$
13	113331868	rs7998202	A	G	252	0.147	0.13	0.243	$3.34 \cdot 10^{-2}$	0.131	0.8	+-	ATP11A	1	rs7998202	46,368	$-3.07 \cdot 10^{-2}$	$5.3 \cdot 10^{-3}$	$5.24 \cdot 10^{-9}$
1	158626378	**rs857691**	T	C	251	0.331	0.273	0.662	0.141	$9.95 \cdot 10^{-2}$	0.156	+-	SPTA1	1	rs857691	46,368	$2.25 \cdot 10^{-2}$	$3.9 \cdot 10^{-3}$	$9.43 \cdot 10^{-9}$
2	169748422	rs574981	C	T	252	0.688	0.681	0.73	0.124	$9.23 \cdot 10^{-2}$	0.181	+-	SPC25	0.889	rs853770	46,368	$-2.09 \cdot 10^{-2}$	$3.7 \cdot 10^{-3}$	$2.33 \cdot 10^{-8}$
17	80788492	rs12948179	A	G	250	0.434	0.423	0.5	0.17	$8.71 \cdot 10^{-2}$	$5.08 \cdot 10^{-2}$	+-	B3GNTL1	0.711	rs12949939	46,368	$-2.03 \cdot 10^{-2}$	$3.7 \cdot 10^{-3}$	$3.19 \cdot 10^{-8}$

8 Acknowledgements

We would like to acknowledge the following people for their significant contributions to this work.

Ryan Koesterer

Maria Costanzo

Lizz Caulkins

Noel Burtt

Jason Flannick

Miriam Udler

Alisa Manning

Jose Florez

9 References

[1] Plink1.9, https://www.cog-genomics.org/plink2.

[2] Kent WJ, Sugnet CW, Furey TS, Roskin KM, Pringle TH, Zahler AM, Haussler D. The human genome browser at UCSC. Genome Res. 2002 Jun;12(6):996-1006. LiftOver http://hgdownload.soe.ucsc.edu/admin/exe/linux.x86_64/liftOver.

[3] Conomos MP. GENetic EStimation and Inference in Structured samples (GENESIS): Statistical methods for analyzing genetic data from samples with population structure and/or relatedness, https://www.rdocumentation.org/packages/GENESIS/versions/2.2.2.

[4] http://people.virginia.edu/~wc9c/KING/.

[5] 1000 Genomes Phase 3 v5, https://mathgen.stats.ox.ac.uk/impute/1000GP_Phase3.html.

[6] Seed C, Bloemendal A, Bloom JM, Goldstein JI, King D, Poterba T, Neale BM. Hail: An Open-Source Framework for Scalable Genetic Data Analysis. In preparation. https://github.com/hail-is/hail.

[7] Morris A, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet. 2012 Sep; 44(9): 981-990. Published online 2012 Aug 12. doi: 10.1038/ng.2383

[8] Scott RA, et al. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nat Genet. 2012 Sep;44(9):991-1005. doi: 10.1038/ng.2385. Epub 2012 Aug 12

[9] Ehret G, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011 Oct; 478: 103-109. doi:10.1038/nature10405

[10] Willer C, et al. Discovery and Refinement of Loci Associated with Lipid Levels. Nature Genetics. 2013 Nov; 45(11): 1274-1283. doi:10.1038/ng.2797

[11] Locke A, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015 Feb; 518(7538): 197-206. doi:10.1038/nature14177

[12] Willer C, et al. Discovery and Refinement of Loci Associated with Lipid Levels. Nature Genetics. 2013 Nov; 45(11): 1274-1283. doi:10.1038/ng.2797

[13] Scott RA, et al. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nat Genet. 2012 Sep;44(9):991-1005. doi: 10.1038/ng.2385. Epub 2012 Aug 12

[14] Soranzo N, et al. Common variants at 10 genomic loci influence hemoglobin A1(C) levels via glycemic and nonglycemic pathways. Diabetes. 2010 Dec;59(12):3229-39. doi: 10.2337/db10-0502. Epub 2010 Sep 21

[15] Ehret G, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011 Oct; 478: 103-109. doi:10.1038/nature10405

[16] Gilbert C, Ruebenacker O, Koesterer R, Massung J, Flannick J. Loamstream. loamstream 1.4-SNAPSHOT (1.3-202-g7df4815) branch: master commit: 7df4815aa4da7f1845e3e40f931c11fda358c6af built on: 2019-04-10T18:38:22.667Z. https://github.com/broadinstitute/dig-loam-stream.

[17] Koesterer R, Gilbert C, Ruebenacker O, Massung J, Flannick J. AMP-DCC Data Analysis Pipeline. dig-loam-2.5.6. https://github.com/broadinstitute/dig-loam.