Appendix A: Quality control of genetic data

Quality control (QC) was performed separately for each of the 4 ethnic groups: African American Phase 1 & 2 (AA12), European Americans Phase 1 (EA1), Japanese Americans Phase 1 (JA1), and Mexican Americans Phase 1 & 2 (MA12). The "Phase" denotes the ascertainment of particular pedigree structures. Phase 1 consists mostly of larger, multi-generational pedigrees whereas in Phase 2, the ascertainment focused mostly on sibships (Raffel, Robbins, Norris, Boerwinkle, & et al., 1996).

Genotyping at NorthWest Genomics Center (NWGC)

The Northwest Genomics Center (NWGC) at the University of Washington, Seattle centralizes all receipt, tracking and quality control/assurance of DNA samples. Samples are assigned unique barcode tracking numbers and have a detailed sample manifest (i.e., identification number/code, sex, DNA concentration, barcode, extraction method) linked to each sample within our laboratory information management system (LIMS - GENEus; Genologics). Initial QC entails DNA quantification and gender validation. Samples are failed if: (1) the total amount, concentration or integrity of DNA is too low (genotyping requires a minimum of 250ng of genomic DNA); or (2) sex-typing is inconsistent with the sample manifest.

DNA samples were derived from Epstein-Barr virus (EBV) transformed blood lymphocyte cell lines from the Coriell repository and used the Gentra Autopure extraction method on the Qiagen Autopure LS instrument according to the manufacturer's methods. The samples were genotyped in 2 batches corresponding to 96-well plates. Each plate and batch was noted by the Nickerson lab at the University of Washington, Seattle.

Samples are normalized to 50 ng/µL (200 ng in 4 µL) in preparation for the Illumina Infininium LCG genotyping assay, using the Multi-EthnicGlobal beadchip (v1.0, genome build 37). The genotyping calling was performed and using the Genotyping Module v 1.9.4 in GenomeStudio version 2011.1. The array consisted of a total of 1,779,819 variants, including 824,388 (46.32%) "rs" SNPs, 4,642 (0.26%) "kgp" (1000 Genomes) SNPs, 215,267 (12.09%) "exm" (exome) SNPs, 711,064 (39.95%) other SNPs, and 24,458 indels (1.37%). There were also 11,468 markers that were not assigned a chromosome because of either non-valid probe mappings or multiple mappings due to multiple best scoring alignments that were identified for the probe sequence (Illumina, 2018).

Samples submitted for genotyping: A total of 1,568 GENNID subjects (1,559 unique subjects and 3 trios (each trio from the African American (AA), Japanese Americans (JA), and Mexican Americans (MA) ethnic groups) were replicates) were submitted for genotyping. There were no replicates in the European American (EA) ethnic group. Specifically, there were 288 subjects in 73 AA Phase 1 & 2 families, 526 subjects from 79 EA families, 131 subjects from 36 JA families and 614 MA Phase 1 & 2 subjects from 113 MA families.

Samples failed Nickerson lab pre-genotyping quality control (QC): A total of 24 samples were flagged as not passing pre-genotyping QC. There were 13 samples that were removed due to unresolved QC issues which included 4 samples (3 EA1 & 1 MA1) that did not have enough DNA, and 9 samples had sex-typing that was inconsistent to the sample manifest obtained from the American Diabetes Association (ADA). Issues with the remaining 11 samples were resolved and were genotyped. We corrected the sex discrepancies of 2 samples based on pedigree checking, and 9 samples were correctly indicated as replicates and thus had enough DNA to be genotyped.

Samples failed post-genotyping QC: There were 5 samples that failed post-genotyping QC; The five samples (2 AA1, 1 CA1, 1 JA1 and 1 MA2 subjects) were excluded because of low call rates less than 97% (based on Genome Studio software).

Final data released by NWGC: Overall, a total of 1550 samples (including 3 trio replicates) passed pre- and post-genotying QC at NWGC and were genotyped on the Illumina Infinium Multi-Ethnic Global array. The median call rate is 100% (99.7% mean call rate). Supplemental Table A.1 summarizes the final released data for each ethnic group.

Supplemental Table A.1: Summary of NWGC data release by ethnic group (before post-genotyping QC)

Ethnic group	Number of Subjects (Males / Females)	Number of families (including singletons)	Number of singletons	Number of replicates	Fraction of Autosomal markers with missing call rate < 2%	Fraction of X chromosome markers with missing call rate < 2%	Fraction of Y chromosome markers with missing call rate < 2%
EA1	521 (229 / 292)	78	11	0	97.4	96.4	98.4
JA1	132 (68/64)*	17	1	3	96.2	94.6	97.8
AA12	288 (91/197)	73	5	3	93.9	92.4	19.4**
MA12	610 (220/390)	111	18	3	99.3	99.0	97.9

* includes one female founder of Korean descent from EA1 family

** 96.5% of Y chromosome markers with missing call rate < 5%

Quality control process

Genotypic data that passed initial quality control at the NWGC at the University of Washington were released to the investigator's analysis team at the Epidemiology Department of the University of California, Irvine. The QC software used included R packages GWASTools (Gogarten et al., 2012), PEDCHECK (O'Connell & Weeks, 1998), GCTA's PCA method (Yang, Lee, Goddard, & Visscher, 2011), and PLINK version 1.9 (Chang et al., 2015). The QC methods generally follow the guidelines in Laurie et al. (2010).

Annotated Sex and Genetic Sex Discrepancies: Subjects with Klinefelter Syndrome (XXY) and with Turner Syndrome (X) were found when these subjects did not cluster by annotated sex in X chromosome heterozygosity and intensity plots of the X and Y chromosomes. These subjects were removed from the dataset because these sex chromosomal conditions influence metabolic traits and might confound the results of analyses. Sex chromosome data (X and XY; Y and XY; only X) was also removed if there was evidence of mosaicism and/or deletions.

Chromosomal Abnormalities: Anomalies per subject were detected using BAF and LOH methods in the GWASTools R package. The BAF method detected anomalies from low quality samples by identifying high segmentation based on high B allele variance. The LOH method identified anomalies from low quality samples with high segmentation due to high Log R ratio (LRR) variance. The genotypes within the anomalies detected in given subjects were blanked.

Estimated Identical-by-Descent (IBD) and Expected IBD discrepancies: Estimated IBD sharing in PLINK's program was compared to expected IBD based on pedigree relationships. First, all autosomal markers were pruned to approximate linkage equilibrium, resulting in a set of independent markers. Within a window of 10000kb, all pairwise r2 was calculated for all autosomal markers. A marker in each pair was pruned out if r2>0.5. The window then slides 1000kb down the genome, and the pruning repeats. PLINK then estimates the IBD sharing between each pair of subjects. Pedigree relationships (originally verified by PedCheck using microsatellites) were corrected based on estimated IBD sharing between subjects. The following expected relationships based on pedigree structure were checked with estimated IBD sharing: (1) parent-offspring (PO) (2) full sibling (FS) (3) half sibling (HS) (4) other (OT) such as 2nd/3rd degree relatives (5) unrelated (UN) from different families. Monozygotic twins were identified, and discordant marker genotypes within each twin pair were flagged.

Removal of Contaminated Samples with High Heterozygosity: Samples with an autosomal heterozygosity that is greater than 4 standard deviation units from the mean was labeled as contaminated and removed from the dataset.

High Missing Rate: Markers (except for Y chromosome) with >=2% missing were removed. Chromosome Y markers with >=2.5% missing were removed. After ignoring regions with blanked chromosomal abnormalities, samples with >=2% missing across

the genome were removed. Samples with missing rate per chromosome that was > 2% were flagged and were verified that the high missing rate for the given chromosome was due to chromosomal abnormalities being removed in Step 2.

Batch Effects: The samples were processed together in 2 batches using 96-well plates. The missing call rate by batch was reviewed to identify any batch with an increased missing call rate while also considering the number of samples per batch using an ANOVA test. There could also be genotyping plate effects present if there were differences in allelic frequencies of the given plate compared to the pooled frequencies of the other plates. The odds ratio (OR) from Fisher's exact test for each SNP and each plate were calculated and then averaged over SNPs across samples. The mean odds ratio was calculated as 1/min(OR, 1/OR). A high value of this statistic across plates indicates some evidence of plate effects.

*Duplicate sample discordance (GWASTools)***:** The pairs of duplicate samples and/or monozygotic twin pairs were used to determine markers that were discordant in at least two pairs of duplicates/MZ twins. These markers were blanked in the entire dataset.

*Mendelian Errors (GWASTools & PLINK)***:** Markers with more than 2 Mendelian errors were blanked using GWASTools. All subjects in families with more than 2% Mendelian Errors were removed. Duplicate/replicate samples were removed. Subject genotype errors were blanked using PLINK (with a first pass evaluating Mendelian errors using 3-generational pedigrees and a second filtering based on nuclear families.

Filtering markers (PLINK): The following removal of markers was implemented in filtering: (1) Monomorphic markers (2) markers with unassigned chromosomes (due to bad probes) (3) HWE testing in founders with $p - value < \alpha = 10^{-6}$ or with $p - value \leq 10^{-4}$ and did not cluster by genotype in intensity plots (4) minor allele frequency, $MAF < 0.01$ (5) duplicated SNP positions based on alignment with the HRC panel. The perl script (HRC-1000G-check-bim.pl) checks plink .bim files against HRC/1000G for strand, id names, positions, alleles, ref/alt assignment (Rayner, 2015) and automatically removes the duplicate positional SNPs that are not on the HRC panel.

Alignment to 1000G/HRC: In the first pass of the QC pipeline, the EA1 samples were aligned to 1000G EUR, the AA12 samples were aligned to 1000G AFR, the JA1 samples to 1000G EAS, and MA12 samples to 1000G AMR. In the second pass of the QC pipeline, all ethnic groups were aligned to the Haplotype Reference Consortium (HRC) reference panel (McCarthy et al., 2016). The HRC-1000G-check-bim.pl perl script was used to make the alignment to these reference panels. The following markers were removed: (1) located in indels (2) located on skipped chromosomes on X, XY, Y, and MT, (3) No match to reference panel (4) Allele frequency difference of more than 20% with reference (5) Palindromic SNPs with MAF>0.4 (6) Non-matching alleles (7) Positional duplicates. Variants were then checked based on chromosome and position and were flipped accordingly.

Post-QC analysis of 1000G aligned data: Two analyses using both PLINK and GCTA programs further examined whether samples should be removed due to their difference in ethnic backgrounds.

Samples with F inbreeding coefficient > 0.125 were removed. First the variants were pruned to approximate linkage equilibrium using a window of 10000kb, where all pairwise LD r2 was calculated, then a SNP was removed for each pair with r2>0.5, and the window slides down 1000kb and the pruning continues. Then using PLINK's --het function and small sample size option, the method of moment's inbreeding F coefficient was calculated, and subjects with F > 0.125 were identified and removed.

In the 1000G dataset, including ethnic groups EUR, EAS, AFR, and AMR from the PLINK's resource website, there were 1092 subjects (525 males, 567 females) consisting of 1083 founders and 9 non-founders. Based on the markers common to GENNID and the 1000G set described above, the two datasets were merged. The merged dataset was then LD-pruned using the same approach as above for F inbreeding coefficient calculations. PCA was performed in three different ways: (1) naively with all subjects together in the GENNID + 1000G merged dataset (2) projected the relateds onto the unrelated in the GENNID + 1000G merged dataset (3) projecting the GENNID dataset onto the 1000G dataset. Subjects that did not cluster with their annotated family's ethnic group were identified and removed.

Summary of First Pass of QC Pipeline: Supplemental Table A.2 summarizes the first pass of the QC pipeline separately for each ethnic group. The first pass of the QC pipeline identified subjects for removal prior to the second pass of the QC pipeline, which then focused on marker and subject removal. Each step is consecutive, and subjects and markers are removed before moving to the next step. The subjects in Step 1ab and 11 are removed before implementing the second pass of QC. Please note that not all checks were performed for the 1st QC pass of the EA1 samples due to initial processing of the QC pipeline.

Supplemental Table A.2: Sample Quality Control: Summary of 1st pass of QC pipeline (N=1,779,819 loci)

	EA1	MA12	AA12	JA1
1. Annotated and Genetic Sex check				
a. No. of X Subjects removed	0	1	1	0
b. No. of XXY subjects removed	1	3	0	0
No. of subjects with mosaicism	0	0	1	2
(remove X & XY)	0	1	1	0
No. of subjects with deletion (remove	0	0	0	1
of Y & XY)				
No. of subjects with deletion (remove				
of X)				
2. Chromosomal Anomalies				
No. of anomalous segments deleted	10[f]	8,510	668	1,042
No. Subjects with anomalous	9	595	221	118
segments				
3. IBD sharing & Updated pedigree				
relationships	10	34	12	5
No. of pedigrees updated	3	0	2	0
No. of MZ Twin pairs	0	3	3	3
No. of duplicate/replicate pairs				
4. Contaminated samples with high	2	1	0	0
heterozygosity				
No. of samples with high				
heterozygosity				
5. High missing rate				
No. of samples with > 2% missing	0	1	0	0
No. of markers with > 2% missing[a]	46,634	13,000	111,264	76,757
6. Batch Effects				
ANOVA test variation of missing rate	-	0.4	0.001[g]	0.9
p-value	No	no	no	no
Presence of plate effects				
7. Duplicate sample discordance[b]				
No. of markers discordant in at least 2	-	0	1	0
pairs				
8. Mendelian Errors (ME)				
No. of samples in families with > 2 ME	0	0	0	0
No. of markers with > 2 ME	1141	980	653	326
No. of ME in 3-generational checks	161,115	74,063	32,076	21,764
No. of ME in nuclear family checks	1,677	2,565	4,556	301
9. Filtering Markers				
No. of monomorphic markers	786,847	800,635	547,911	1,005,330
No. of markers with unassigned probe	1,964	2,958	3,321	1,176
No. of markers with HWE $p<10^{-6}$	1	0	27	0
No. of markers HWE $10^{-6}<p<10^{-4}$ & no	0	1	47	1
clustering[c]	149,247	256,576	133,491	38,531

No. of markers with MAF<0.01				
10. Alignment to 1000G[d]				
No. of markers in indels	1,525	1,664	1,877	1,234
No. of markers in skipped chrom X,	3,893	4,064	5,277	2,333
XY, Y, MT	16,181	19,705	23,605	13,188
No. of markers not matched to	35,022	38,656	50,306	32,844
reference panel	6,822	6,983	6,245	6,452
No. of markers with allele freq	7,375	8,474	10,315	6,017
difference >20%[e]	17,880	19,180	19,114	11,490
No. of palindromic SNPs with MAF>0.4				
No. of markers with non-matching alleles				
No. of markers removed in positional duplicates				
11. Post-QC analysis of QC'ed data				
No. of samples: F inbreeding	-	0	2	3
coefficient > 0.125	3	3	1[h]	0
No. of samples not clustering with 1000G reference				
No. of Subjects Removed (Steps 1ab	4	7	3	3
& 11)	517	603	285	128
No. of Subjects Remaining				

[a]After accounting for the removal of chromosomal anomalies
[b]Duplicate pairs of samples includes replicates and MZ Twins
[c]No clustering by genotype in intensity plots
[d]EA1 (European American) GENNID subjects were aligned to 1000G EUR; MA12 (African American) GENNID subjects were aligned to 1000G AMR; AA12 (African American) GENNID subjects were aligned to 1000G AFR; JA1 (Japanese American) GENNID subjects were aligned to 1000G EAS.
[e]Allele frequency difference between GENNID sample and reference panel
[f] Only 5 Mb anomalous segments were removed in EA1.
[g]Although significant, all missing call rates were small < 0.001
[h]This subject also had F inbreeding coefficient > 0.125

Final Quality Control: Summary of Second Pass of QC Pipeline The second pass of the QC pipeline removed subjects previously identified in the first QC pass (Steps 1ab and 11) summarized in Table A.3. Further removal of variants and subjects were made to obtain a final set of high quality samples and variants for analysis. Supplemental Table A.4 describes the final dataset used for analysis.

Supplemental Table A.3: Sample Quality Control: Summary of 2nd pass of QC pipeline

	EA1	MA12	AA12	JA1
Initial Dataset size (N=1,779,819 markers)	517	603	285	128
No. of subjects				
1. Annotated and Genetic Sex check				
No. of subjects with mosaicism	0	0	1	2
(remove X & XY)	0	1	2	0
No. of subjects with deletion (remove	0	0	0	1
of Y & XY)				
No. of subjects with deletion (remove				
of X)				
2. Chromosomal Anomalies				
No. of anomalous segments deleted	2389	8469	665	1,022
No. Subjects with anomalous	461	593	221	115
segments				
3. IBD sharing & Updated pedigree				
relationships	12	32	14	4
a. No. of pedigrees updated	3	0	2	0
b. No. of MZ Twin pairs	0	3	3	3
c. No. of duplicate/replicate pairs				
4. Contaminated samples with high	1	1	1	0
heterozygosity				
No. of samples with high				
heterozygosity				
5. High missing rate				
a. No. of samples with > 2% missing[a]	0	1	0	0
b. No. of markers with > 2% missing[b]	45,993	12,981	110,221	73,958
6. Batch Effects				
ANOVA test variation of missing rate	0.55	0.43	0.04	0.87
p-value	No	No	No	No
Presence of plate effects				
7. Duplicate sample discordance[c]				
No. of markers discordant in at least 2	0	0	9	0
pairs				
8. Mendelian Errors (ME)				
a. No. of samples in families with > 2 ME	0	0	0	0
b. No. of markers with > 2 ME	1,157	981	647	327
c. No. of ME in 3-generational checks	130,591	74,070	26,369	18,624

d. No. of ME in nuclear family checks	1,761	2,564	4,577	289
9. Filtering Markers				
No. of monomorphic markers	800,635	653,816	549,717	1,007,183
No. of markers with unassigned probe	1,909	2,955	3,316	1,175
No. of markers with HWE $p<10^{-6}$	0	0	1	0
No. of markers HWE $10^{-6}<p<10^{-4}$; no clustering[d]	3	0	2	1
No. of markers with MAF<0.01	137,150	248,092	134,297	39,581
10. Alignment to HRC[e]				
No. of markers in indels	1,525	1,694	1,876	1,238
No. of markers in skipped chrom X, XY, Y, MT	3,899	4,099	5,519	2,345
No. of markers not matched to reference panel	43,405	51,424	58,683	37,300
No. of markers with allele freq difference >20%[f]	33,760	46,993	179,620	161,363
No. of palindromic SNPs with MAF>0.4	5,819	5,946	5,570	5,563
No. of markers with non-matching alleles	1,124	1,240	1,725	1,016
No. of markers removed in positional duplicates	17,240	18,582	18,390	11,039
No. of subjects (Removal Step3c, 4, 5a, 8a)	516	598	281	125
No. of markers (Removal Step 5b, 7,8b-d, 9,10)	686,200	731,016	710,226	437,730

[a]The missing rate for subjects was calculated by ignoring regions with chromosomal anomalies in Step 2.
[b]After accounting for the removal of chromosomal anomalies [c]Duplicate pairs of samples includes replicates and MZ Twins [d]No clustering by genotype in intensity plots [e] AA12 (African American), EA1 (European American), JA1 (Japanese American), and MA12 (African American), GENNID subjects were all aligned to HRC.
[f]Allele frequency difference between GENNID sample and reference panel

Supplemental Table A.4: Summary of dataset after 1st and 2nd pass of the QC pipeline

Ethnic group	Number of Subjects (Males / Females)	Number of families (including singletons)	Number of singletons	Number of markers overlapping with EA1	Number of markers overlapping with JA1	Number of markers overlapping with AA12	Number of markers overlapping with MA12
AA12	281 (88/193)	73	5	458,825	276,111	710,226	478,713
EA1	516 (226/290)	75	8	686,200	344,941	458,825	642,318
JA1	125 (65/60)*	15	0	344,941	437,730	276,111	366,925
MA12	598 (215/383)	96	7	642,318	366,925	478,713	731,016

*Includes one female founder of Korean descent from EA1 family

Appendix B: Gene Dropping for Association Analyses in the JA study

Since Linear Mixed Effects (LMM) models depend on asymptotics requiring large sample size, unconditional Gene Dropping (GD) was used in the Japanese American (JA) study (# families = 17, # individuals = 125 after QC). Producing one unconditional Gene Drop (GD) simulation in Merlin (Abecasis, Cherny, Cookson, & Cardon, 2001) begins by randomly assigning genotypes at the founder level (20 founders in the JA study) according to the MAF estimated in sample. Alleles then flow through the pedigree, where each allele from an assigned genotype has 50% chance of being passed to offspring. An effect size estimate for the GD sample was obtained by performing an additive association test using the genotypes produced by the GD simulation (coded as 0, 1, or 2) and the adjusted phenotype values for each individual. Adjusted phenotype values were found for each individual by using the residuals of a linear model with the original phenotype as the response variable and age, sex, and diabetes status (Yes/No) as covariates. This process was repeated many times to obtain the desired number of GD simulations. The effect size estimates from each GD simulation were collected to build an empirical distribution of the possible effect sizes for a given MAF and pedigree structure. This empirical distribution of effect size estimates was used to estimate a two-tailed p-value for the SNP of interest as the proportion of effect size estimates in the empirical distribution that are larger in magnitude than the observed effect size estimate at the SNP of interest.

We chose to use unconditional GD to most closely align the JA association hypothesis test with the association hypotheses used by the other ethnic groups. Unconditional GD was implemented using the Merlin software (Abecasis et al., 2001), and its hypotheses correspond to H_0: No linkage and no association vs. H_1: Linkage and/or association. Due to the small sample size, we were able to improve the computational efficiency of the GD process by creating empirical effect size distributions for each MAF, instead of individually for each SNP. Since there were 125 individuals, there were 125 possible MAFs described by the set $\left\{{}^{1}/_{250}, {}^{2}/_{250}, \ldots, {}^{125}/_{250}\right\}$. Gene drop simulations for each MAF were generated by creating an initial dummy data set with the corresponding number of minor alleles needed for the given MAF. The desired number of replications were then generated to build empirical distributions for each MAF. When testing for association at a particular SNP, the observed MAF at the SNP was matched to the empirical distribution that was created using the same MAF. The observed effect size estimate at the SNP was then compared to the empirical distribution with the correct MAF to generate the association p-value for the SNP. The standard deviation of the empirical distribution was used as the standard error of the effect size estimate observed at the SNP. Due to missingness, some SNPs had slightly different MAFs than those described in the set above (e.g., ${}^{4}/_{248}$ and ${}^{3}/_{249}$). In this

case, the empirical distribution generated from the MAF with the closest absolute distance was used to produce empirical p-values and standard error estimates ($^4/_{250}$ and $^3/_{250}$, respectively, for the example above).

To begin, 100,000 GD replications were generated for each MAF, creating empirical distributions of 100,000 effect sizes estimates. This initial distribution was able to estimate empirical p-values on the order of 1e-5. Next, additional replications were generated for any MAFs that had SNPs showing stronger significance than 1e-5 from these initial simulations. One million GD replications were generated for the MAFs with suggestive significance on the order of 1e-5, and this allowed empirical p-value estimates on the order of 1e-6. Finally, 20,000,000 GD replications were generated for the MAFs with SNPs showing stronger significance than 1e-6, which allowed estimation of p-values on the order of 5e-8. This tiered approach saved computation time, while still allowing p-value estimation on the order of 5e-8. The effect size estimates and standard errors for each SNP were carried forward to the meta-analyses described in Methods.

Appendix C: Inflation factors of the four meta-analysis methods

Figure 1 shows the inflation factor, λ, for each meta-analysis method for all eight phenotypes (Stram, 2014). The inflation factor, λ, is calculated using the function `infla()` below. It converts the observed p-values to chi-squared statistics, and then compares the median of these chi-squared statistics to the median of a χ_1^2 distribution (expected under the null distribution). In addition to comparing the median of the observed and expected distributions of p-values, we compared the 10th percentile, 1st percentile, and 0.1th percentile using similar functions for each meta-analysis methods' results, to better assess behavior in the tail of the distributions. The results of these comparisons are displayed in Supplemental Tables C.1, C.2, C.3, and C.4. Supplemental Table C.1 shows that while we see more variability in the 1st and 0.1th percentile results than the median results, FE appears to be a well-controlled test using all four metrics. Supplemental Table C.2 shows that the deflation observed for RE2 improves for the 1st and 0.1th percentile results, where we only observe slight deflation in the tail. The TransMeta results in Supplemental Table C.3 show that while the method is slightly deflated at the median, we observe slight inflation in the tail (1st and 0.1th percentile results). With Supplemental Table C.4, we observe slight deflation across all four metrics for MR-MEGA, illustrating this test to be slightly conservative.

```
###function comparing medians
infla=function(pval){
  x=qchisq(1-pval,1)
  lambda=round(median(x)/qchisq(0.5,1),3)
  print(lambda)
}
```

Supplemental Table C.1: Fixed Effects Inflation Factors				
	Median	10^{th} Percentile	1^{st} Percentile	0.1^{th} Percentile
Weight	0.984	0.986	0.974	1.017
Waist	0.990	0.996	0.980	1.013
Triglycerides	0.982	0.990	0.990	0.969
Systolic Average	0.999	0.987	0.997	0.981
Insulin Average	0.990	0.982	0.998	1.014
HDL	0.990	0.988	0.984	0.979
Glucose Average	0.998	0.974	0.953	0.962
Diastolic Average	0.980	1.004	0.993	1.027

Supplemental Table C.2: RE2 Inflation Factors				
	Median	10^{th} Percentile	1^{st} Percentile	0.1^{th} Percentile
Weight	0.921	0.962	0.966	1.003
Waist	0.944	0.969	0.962	0.982
Triglycerides	0.921	0.956	0.966	0.947
Systolic Average	0.938	0.962	0.977	0.972
Insulin Average	0.922	0.966	0.993	1.001
HDL	0.917	0.953	0.974	0.980
Glucose Average	0.939	0.952	0.945	0.950
Diastolic Average	0.933	0.968	0.974	0.994

Supplemental Table C.3: TransMeta Inflation Factors				
	Median	10^{th} Percentile	1^{st} Percentile	0.1^{th} Percentile
Weight	0.863	1.000	1.035	1.045
Waist	0.869	1.016	1.043	1.073
Triglycerides	0.874	1.002	1.028	1.018
Systolic Average	0.881	1.001	1.032	1.015
Insulin Average	0.86	1.006	1.048	1.070
HDL	0.887	1.003	1.027	1.043
Glucose Average	0.873	0.993	1.000	1.016
Diastolic Average	0.878	1.014	1.033	1.066

Supplemental Table C.4: MR-MEGA Inflation Factors				
	Median	10^{th} Percentile	1^{st} Percentile	0.1^{th} Percentile
Weight	0.988	0.976	0.992	0.982
Waist	0.982	0.984	0.981	0.986
Triglycerides	0.988	0.983	0.974	0.977
Systolic Average	0.997	0.976	0.987	0.970
Insulin Average	0.965	0.984	0.994	0.993
HDL	0.995	0.997	0.978	0.980
Glucose Average	0.977	0.969	0.990	0.977
Diastolic Average	0.987	0.987	0.973	0.969

Appendix D: Summary of suggestive and genome-wide significant SNPs

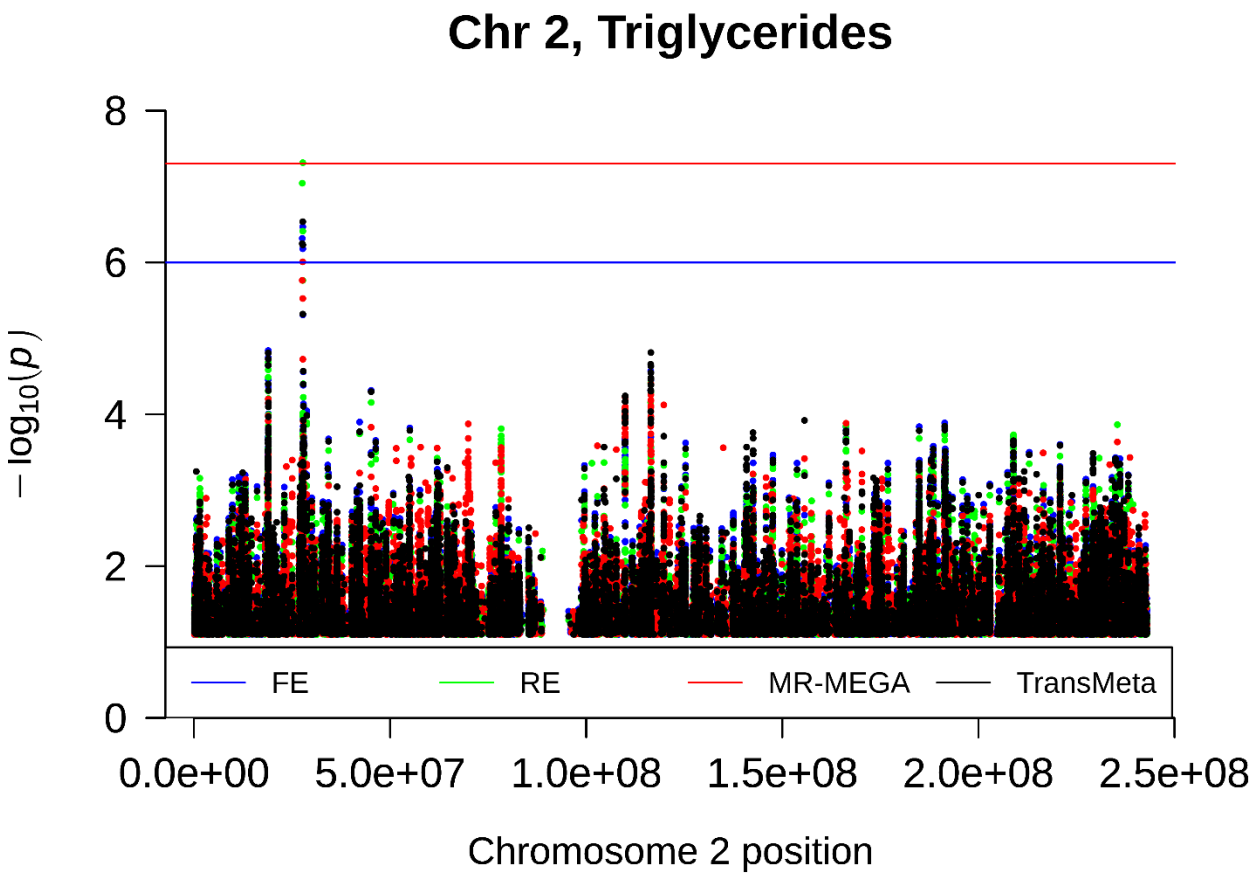
Supplemental Table D.1 summarizes the 78 SNPs found to be suggestive (p-value $< 1e-6$) or genome-wide significant (p-value $< 5e-8$) by at least one of the four meta-analysis methods. The base pair coordinates of the SNPs in this table are in Build 37. For the phenotype column, Systolic BP and Diastolic BP stand for systolic blood pressure and diastolic blood pressure, respectively. Columns 5, 6, 7, and 8 give the p-value for each SNP from the four meta-analysis methods. The p-value testing the significance of Cochran's Q using a χ^2 test is found in the 9th column of Supplemental Table C.1. Low p-values for a test of Cochran's Q suggest evidence of heterogeneity across the effect sizes from each ethnic group. Functional information (10th column) and the nearest gene (11th column) were found for each SNP using ANNOVAR (Wang, Li, & Hakonarson, 2010). The 78 total SNPs comprise 17 total loci (separated by dashed horizontal lines within Supplemental Table C.1).

Supplemental Table D.1: Summary of suggestive and genome-wide significant SNPs										
Chr	Base Pair	rsID	Phenotype	FE P-value	RE2 P-value	TransMeta P-value	MR-MEGA P-value	Cochran's Q P-value	Functional Info	Nearest gene
2	27598097	rs4665972	Triglycerides	4.82E-07	9.04E-08	5.66E-07	1.72E-06	0.0106	intronic	SNX17
2	27730940	rs1260326	Triglycerides	3.39E-07	4.86E-08	2.91E-07	9.83E-07	0.0070	exonic	GCKR
2	27741237	rs780094	Triglycerides	6.60E-07	3.87E-07	5.87E-07	2.98E-06	0.0498	intronic	GCKR
2	65819883	rs1115848	Systolic BP	6.03E-07	8.84E-07	5.78E-07	1.45E-06	0.4796	intergenic	SPRED2;MIR4778
2	65820608	rs11687213	Systolic BP	6.03E-07	8.84E-07	5.78E-07	1.45E-06	0.4796	intergenic	SPRED2;MIR4778
2	65824325	rs12614551	Systolic BP	7.88E-07	1.16E-06	6.33E-07	2.31E-06	0.5475	intergenic	SPRED2;MIR4778
2	65824380	rs12614575	Systolic BP	7.88E-07	1.16E-06	6.33E-07	2.31E-06	0.5475	intergenic	SPRED2;MIR4778
2	161536779	rs4504007	Weight	2.76E-06	3.16E-06	3.01E-07	1.49E-05	0.0223	intergenic	RBMS1;TANK
2	161580892	rs113055309	Weight	1.01E-06	1.43E-06	2.93E-07	4.60E-06	0.0439	intergenic	RBMS1;TANK
2	161650240	rs35013036	Weight	9.79E-07	1.44E-06	3.08E-07	5.71E-06	0.1876	intergenic	RBMS1;TANK
2	161743385	rs1615586	Weight	3.04E-06	4.44E-06	5.72E-07	1.18E-05	0.0807	intergenic	RBMS1;TANK
2	161746908	rs1404359	Weight	3.77E-06	4.35E-06	5.68E-07	9.82E-06	0.0509	intergenic	RBMS1;TANK
2	161755027	rs1710654	Weight	2.95E-06	3.66E-06	2.95E-07	7.05E-06	0.0717	intergenic	RBMS1;TANK
3	2001175	rs12631510	HDL	6.40E-06	7.26E-07	2.80E-07	3.06E-07	0.0021	intergenic	CNTN6;CNTN4
3	2004251	rs17005939	HDL	6.98E-06	5.23E-07	2.80E-07	1.86E-07	0.0011	intergenic	CNTN6;CNTN4
3	105643849	rs6765145	Waist	5.46E-07	7.98E-07	5.75E-07	2.41E-06	0.7921	intergenic	CBLB;LINC00882
4	2707032	rs4690015	Diastolic BP	0.00227145	9.34E-07	0.00245669	0.0013334	1.10E-05	intronic	FAM193A
5	157023304	rs1895338	Triglycerides	0.0204752	5.82E-07	0.014237215	0.00017668	5.22E-07	intergenic	ADAM19;SOX30
8	126485294	rs2954027	Triglycerides	1.63E-06	2.38E-06	2.97E-07	1.64E-06	0.2682	intergenic	TRIB1;LINC00861
8	126486409	rs17321515	Triglycerides	3.18E-06	4.64E-06	6.30E-07	3.53E-06	0.2725	intergenic	TRIB1;LINC00861
8	126488235	rs2980868	Triglycerides	1.54E-06	2.26E-06	5.91E-07	2.83E-06	0.4005	intergenic	TRIB1;LINC00861
8	126488250	rs2980869	Triglycerides	1.54E-06	2.26E-06	5.91E-07	2.83E-06	0.4005	intergenic	TRIB1;LINC00861
8	126491733	rs2954031	Triglycerides	1.13E-06	1.56E-06	1.36E-07	7.09E-07	0.1824	intergenic	TRIB1;LINC00861
8	126495818	rs10808546	Triglycerides	2.06E-06	2.97E-06	2.94E-07	2.47E-06	0.2286	intergenic	TRIB1;LINC00861
9	114376753	rs2418173	Diastolic BP	3.12E-07	4.54E-07	2.92E-07	1.87E-06	0.8098	upstream	LRRC37A5P
9	114377336	rs10817195	Diastolic BP	9.38E-07	1.38E-06	1.10E-06	5.33E-06	0.8902	intergenic	LRRC37A5P; DNAJC25-GNG10
11	89224718	rs2289123	Triglycerides	0.0127646	1.67E-05	0.006225193	7.62E-07	1.50E-05	UTR5	NOX4
13	66731477	rs9599076	Waist	4.80E-08	7.10E-08	6.47E-08	3.29E-07	0.8503	intergenic	MIR548X2; MIR4704

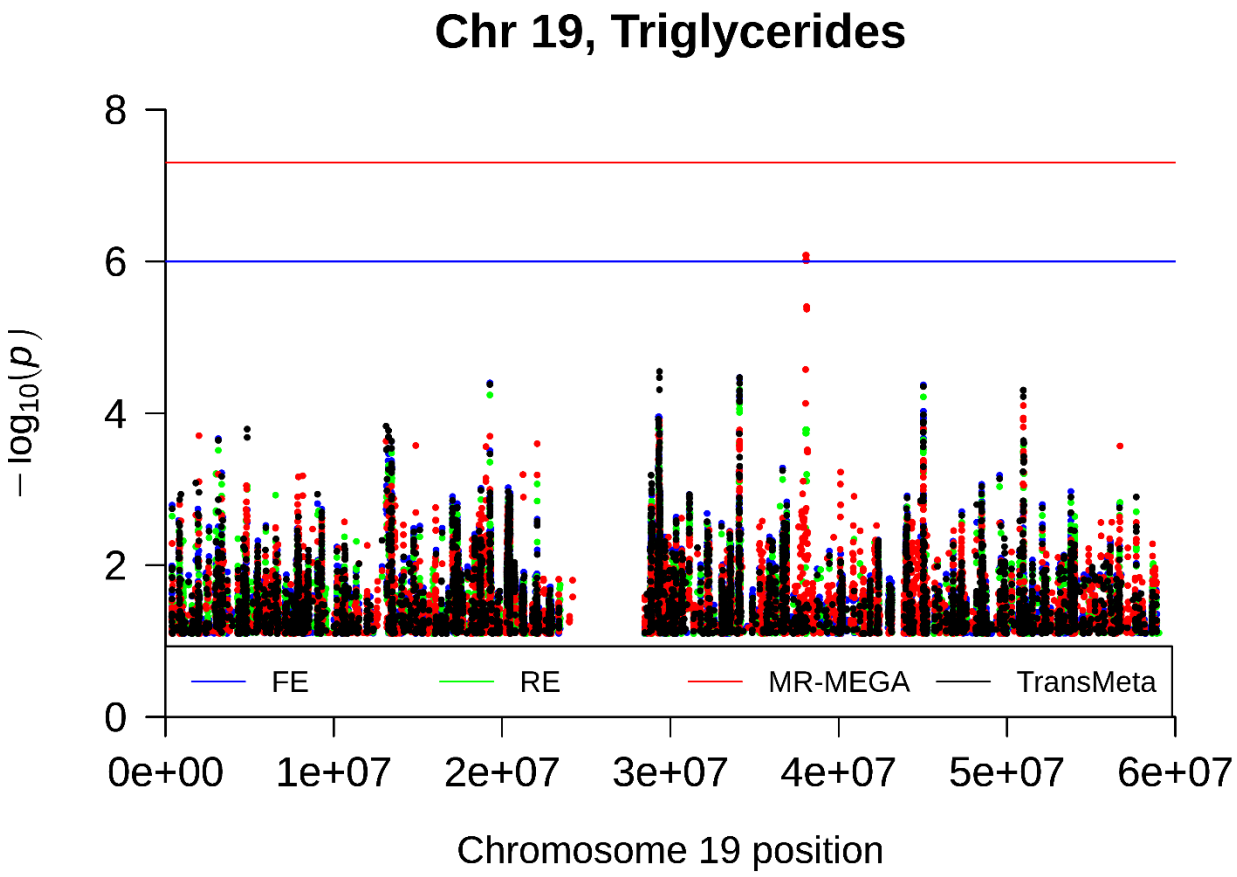
Chr	Base Pair	rsID	Phenotype	FE P-value	RE2 P-value	TransMeta P-value	MR-MEGA P-value	Cochran's Q P-value	Functional Info	Nearest gene
13	66732565	rs9592449	Waist	9.95E-07	1.46E-06	1.11E-06	6.29E-06	0.8952	intergenic	MIR548X2; MIR4704
13	90409398	rs317962	Triglycerides	6.99E-07	1.02E-06	6.03E-07	1.10E-06	0.3117	intergenic	LINC00353; LINC00559
15	29964742	rs4522365	Triglycerides	2.58E-06	7.13E-08	1.65E-07	1.20E-06	0.0013	intergenic	FAM189A1; LOC100130111
15	64276143	rs8038345	Triglycerides	4.46E-07	6.51E-07	2.89E-07	2.71E-06	0.4122	intronic	DAPK2
15	64284719	rs28478668	Triglycerides	4.83E-07	7.08E-07	5.68E-07	2.96E-06	0.5707	intronic	DAPK2
15	64285189	rs11633956	Triglycerides	3.64E-07	5.30E-07	2.87E-07	2.21E-06	0.6302	intronic	DAPK2
15	64285659	rs34867794	Triglycerides	3.61E-07	5.26E-07	2.87E-07	2.19E-06	0.6361	intronic	DAPK2
15	64286221	rs28544905	Triglycerides	3.61E-07	5.26E-07	2.87E-07	2.19E-06	0.6361	intronic	DAPK2
15	64286236	rs28459332	Triglycerides	3.61E-07	5.26E-07	2.87E-07	2.19E-06	0.6361	intronic	DAPK2
15	64286836	rs11631973	Triglycerides	3.61E-07	5.26E-07	2.87E-07	2.19E-06	0.6361	intronic	DAPK2
15	64287495	rs28444644	Triglycerides	5.22E-07	7.64E-07	5.71E-07	3.11E-06	0.6526	intronic	DAPK2
15	64290136	rs7167478	Triglycerides	1.23E-06	1.70E-06	3.16E-07	2.79E-06	0.2719	intronic	DAPK2
15	64290385	rs55963180	Triglycerides	3.53E-07	5.15E-07	1.47E-07	1.48E-06	0.4344	intronic	DAPK2
15	64291219	rs8024045	Triglycerides	3.61E-07	5.26E-07	2.87E-07	2.19E-06	0.6361	intronic	DAPK2
15	64297369	rs11633496	Triglycerides	6.19E-07	9.08E-07	5.75E-07	3.44E-06	0.6399	intronic	DAPK2
15	64297435	rs11633611	Triglycerides	6.19E-07	9.08E-07	5.75E-07	3.44E-06	0.6399	intronic	DAPK2
15	64313764	rs11635284	Triglycerides	1.00E-06	1.47E-06	5.92E-07	5.35E-06	0.4791	intronic	DAPK2
15	64333606	rs7173139	Triglycerides	6.69E-07	9.80E-07	3.07E-07	3.10E-06	0.4899	intronic	DAPK2
15	64334978	rs881232	Triglycerides	5.67E-07	8.27E-07	5.68E-07	3.09E-06	0.5751	intronic	DAPK2
15	64334992	rs968654	Triglycerides	3.84E-07	5.58E-07	2.83E-07	2.08E-06	0.5306	intronic	DAPK2
15	64335225	rs1868444	Triglycerides	5.31E-07	7.76E-07	3.03E-07	2.90E-06	0.5876	intronic	DAPK2
15	64335240	rs1868443	Triglycerides	3.84E-07	5.58E-07	2.83E-07	2.08E-06	0.5306	intronic	DAPK2
16	56987015	rs12446515	HDL	2.44E-07	3.56E-07	1.43E-07	9.03E-07	0.6364	intergenic	HERPUD1;CETP
16	56987369	rs56156922	HDL	1.73E-07	2.51E-07	1.37E-07	6.35E-07	0.6118	intergenic	HERPUD1;CETP
16	56987765	rs56228609	HDL	3.04E-07	4.42E-07	2.80E-07	1.00E-06	0.6451	intergenic	HERPUD1;CETP
16	56988044	rs173539	HDL	7.04E-06	5.39E-06	5.71E-07	8.32E-07	0.0357	intergenic	HERPUD1;CETP
16	56989590	rs247616	HDL	5.54E-08	8.17E-08	6.27E-08	3.82E-07	0.7879	intergenic	HERPUD1;CETP
16	56990716	rs247617	HDL	5.54E-08	8.17E-08	6.27E-08	3.82E-07	0.7879	intergenic	HERPUD1;CETP
16	56991363	rs183130	HDL	5.54E-08	8.17E-08	6.27E-08	3.82E-07	0.7879	intergenic	HERPUD1;CETP

Chr	Base Pair	rsID	Phenotype	FE P-value	RE2 P-value	TransMeta P-value	MR-MEGA P-value	Cochran's Q P-value	Functional Info	Nearest gene
16	56993161	rs12149545	HDL	5.51E-07	8.05E-07	5.65E-07	1.62E-06	0.5903	intergenic	HERPUD1;CETP
16	56993324	rs3764261	HDL	5.73E-06	6.84E-06	6.21E-07	1.57E-06	0.0738	intergenic	HERPUD1;CETP
16	56994528	rs17231506	HDL	3.13E-07	4.55E-07	2.81E-07	1.18E-06	0.5802	intergenic	HERPUD1;CETP
16	56998918	rs12720926	HDL	1.66E-08	2.33E-08	1.37E-08	1.07E-07	0.7494	intronic	CETP
16	56999328	rs11508026	HDL	1.79E-08	2.56E-08	1.39E-08	1.14E-07	0.7455	intronic	CETP
16	57001216	rs4784741	HDL	9.74E-08	1.44E-07	6.62E-08	2.46E-07	0.4294	intronic	CETP
16	57001438	rs12444012	HDL	9.74E-08	1.44E-07	6.62E-08	2.46E-07	0.4294	intronic	CETP
16	57004889	rs7205804	HDL	4.85E-08	7.16E-08	2.90E-08	7.41E-08	0.2832	intronic	CETP
16	57005301	rs1532625	HDL	8.22E-08	1.21E-07	6.23E-08	8.58E-08	0.2118	intronic	CETP
16	57005479	rs1532624	HDL	8.22E-08	1.21E-07	6.23E-08	8.58E-08	0.2118	intronic	CETP
18	74352797	rs9951751	Systolic BP	0.00143975	2.39E-06	3.21E-06	1.17E-07	2.65E-05	intergenic	LINC01927; LINC01879
19	38039675	rs11665759	Triglycerides	0.0640212	0.00018267	0.071594838	8.29E-07	1.71E-05	upstream	ZNF571-AS1
19	38040879	rs73031322	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	ncRNA intronic	ZNF571-AS1
19	38043022	rs73031326	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	ncRNA intronic	ZNF571-AS1
19	38046331	rs111694872	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	ncRNA intronic	ZNF571-AS1
19	38062195	rs2045911	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	ncRNA intronic	ZNF571-AS1
19	38073146	rs73033117	Triglycerides	0.0640212	0.00018267	0.071594838	8.29E-07	1.71E-05	ncRNA intronic	ZNF571-AS1
19	38074152	rs11083427	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	ncRNA intronic	ZNF571-AS1
19	38080535	rs73033129	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	intronic	ZNF540;ZNF571
19	38082385	rs12162238	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	intronic	ZNF540;ZNF571
19	38083967	rs11083428	Triglycerides	0.0478103	0.00016422	0.053617891	9.76E-07	2.60E-05	intronic	ZNF540;ZNF571

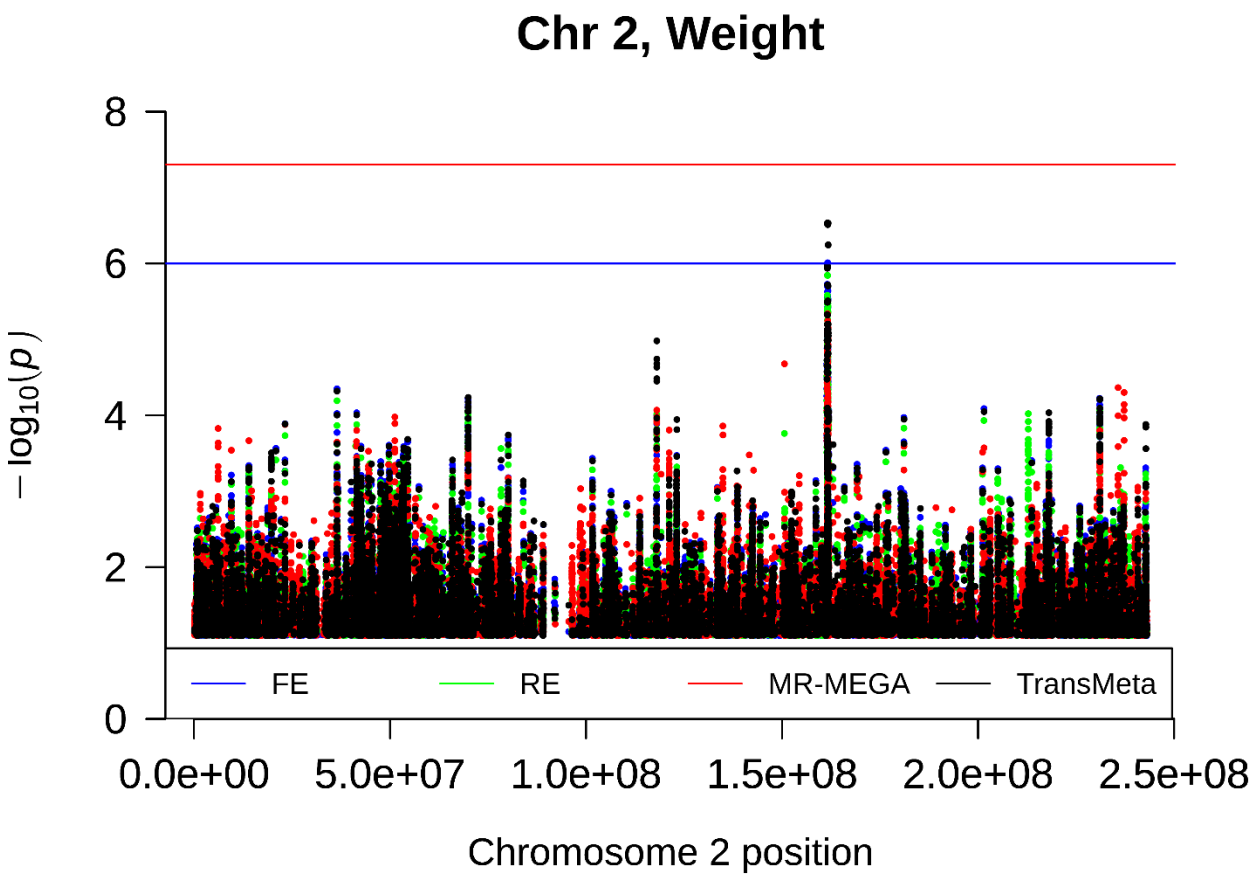
Supplemental Figures



Supplemental Figure S1: Manhattan plot of the locus only detected by RE2 at the genome-wide significant threshold of $5e-8$. The locus at 27.7 Mb on chromosome 2 is found to be associated with Triglycerides.



Supplemental Figure S2: Manhattan plot of the locus only detected by MR-MEGA at the suggestive threshold of $1e-6$. The locus at 38 Mb on chromosome 19 is found to be associated with Triglycerides.



Supplemental Figure S3: Manhattan plot of the locus only detected by TransMeta at the suggestive threshold of $1e-6$. The locus at 161 Mb on chromosome 2 is found to be associated with Weight.

References

Abecasis, G. R., Cherny, S. S., Cookson, W. O., & Cardon, L. R. (2001). Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. *Nature Genetics*, *30*(1), 97–101. https://doi.org/10.1038/ng786

Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience*, *4*(1), 7. https://doi.org/10.1186/s13742-015-0047-8

Gogarten, S. M., Bhangale, T., Conomos, M. P., Laurie, C. A., McHugh, C. P., Painter, I., … Laurie, C. C. (2012). GWASTools: an R/Bioconductor package for quality control and analysis of genome-wide association studies. *Bioinformatics*, *28*(24), 3329–3331. https://doi.org/10.1093/bioinformatics/bts610

Illumina. (2018). No Title. Retrieved from https://support.illumina.com/bulletins/2016/06/-infinium-genotyping-array-manifest-files-what-does-chr-or-mapinfo---mean.html

Laurie, C. C., Doheny, K. F., Mirel, D. B., Pugh, E. W., Bierut, L. J., Bhangale, T., … GENEVA Investigators. (2010). Quality control and quality assurance in genotypic data for genome-wide association studies. *Genetic Epidemiology*, *34*(6), 591–602. https://doi.org/10.1002/gepi.20516

McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A., & Al., E. (2016). A reference panel of 64,976 haplotypes for genotype imputation. *Nature Genetics*, *48*(10), 1279–1283. https://doi.org/10.1038/ng.3643

O'Connell, J. R., & Weeks, D. E. (1998). PedCheck: a program for identification of genotype incompatibilities in linkage analysis. *American Journal of Human Genetics*, *63*(1), 259–266. https://doi.org/10.1086/301904

Raffel, L. J., Robbins, D. C., Norris, J. N., Boerwinkle, E., & et al. (1996). The GENNID Study. A resource for mapping the genes that cause NIDDM. *Diabetes Care*, *19*(8), 864–872. Retrieved from https://tb4cz3en3e.search.serialssolutions.com/?sid=google&auinit=LJ&aulast=Raffel&atitle=The+GENNID+Study:+a+resource+for+mapping+the+genes+that+cause+NIDDM&id=pmid:8842605

Rayner, W. (2015). HRC/1000G Alignment, Version 4.2.7. Retrieved February 12, 2019, from https://www.well.ox.ac.uk/~wrayner/strand/

Stram, D. O. (2014). *Design, Analysis, and Interpretation of Genome-Wide Association Scans*. New York: Springer. Retrieved from http://www.springer.com/series/2848

Wang, K., Li, M., & Hakonarson, H. (2010). ANNOVAR: Functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Research*, *38*(16). https://doi.org/10.1093/nar/gkq603

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). GCTA: A tool for genome-wide complex trait analysis. *American Journal of Human Genetics*, *88*(1), 76–82. https://doi.org/10.1016/j.ajhg.2010.11.011