

Supplementary Material and Methods

Title: Detection of genetic loci associated with plasma fetuin-A: A meta-analysis of genome-wide association studies from the CHARGE Consortium

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Study Samples, genotyping, and imputations

Participants for the current analysis were drawn from six cohort studies, including the following studies from the CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) Consortium: Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Framingham Heart Study (FHS). In addition, data from the Health, Aging, and Body Composition (Health ABC) Study and the Nurses' Health Study (NHS) were also included. Local ethical committees at each institution approved the individual study protocols.

The Atherosclerosis Risk in Communities (ARIC):

The ARIC study is a longitudinal cohort study of atherosclerosis and its clinical sequelae. Investigators recruited a population-based sample of 15,792 men and women aged 45–64 years from four U.S. communities in 1987-89(1). Fetuin-A was measured in a case-cohort sample designed to investigate predictors of incident diabetes. The cohort was stratified by ethnicity (white / black) and sampling frequencies for cases and the cohort sample varied across strata. Genotyping was performed using the Affymetrix 6.0 Gene Chip V6.0. SNPs were excluded for not being autosomal SNPs, not passing laboratory QC, no chromosome location, being monomorphic, SNP call rate <95%, Hardy-Weinberg equilibrium p -value < 10^{-5} . Following genotyping, the subjects with a call rate < 95%, with a mismatch between called and phenotypic gender, with a mismatch on >10 of 47 previously analyzed SNPs in ARIC, all but one in sets of first degree relatives, and genetic outliers. Imputation to approximately 2.5 million HapMap SNPs was performed

using MACH. In total, 485 European American and 366 African American participants with genotypes and fetuin-A measures were available for the genome-wide association study.

Cardiovascular Health Study (CHS):

The CHS is a population-based cohort study of risk factors for CHD and stroke in adults ≥ 65 years conducted across four field centers.(2) The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists and an additional 687 African-Americans were enrolled in 1992-1993 for a total sample of 5,888. The study consisted of baseline and follow-up clinic visits that collected clinical and medical history information. DNA was extracted from blood samples drawn on all participants at their baseline examination. In 2007–2008, genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV BeadChip system on CHS participants who were free of CVD at baseline, consented to genetic testing, and had DNA available for genotyping. Following genotyping, participants were excluded if they had a call rate $\leq 95\%$ or if their genotype was discordant with known sex or prior genotyping (to identify possible sample swaps). Genotyping was attempted in 4,129 participants and was successful in 3,869 persons. Imputation to approximately 2.5 million HapMap SNPs was performed using BIMBAM. SNPs for which testing Hardy–Weinberg equilibrium resulted in $p < 10^{-5}$ (CHS) were excluded from imputation. After excluding subjects with no fetuin-A

measures, the final study population comprised 2742 European Americans and 725 African Americans.

Framingham Heart Study (FHS): The FHS started in 1948 with 5,209 randomly ascertained participants from Framingham, Massachusetts, United States, who had undergone biannual examinations to investigate cardiovascular disease and its risk factors. In 1971, the Offspring cohort (comprised of 5,124 children of the Original cohort, and children's spouses),(3) and in 2002, the Third Generation (consisting of 4,095 children of the Offspring cohort), were recruited. FHS participants are primarily white, of European ancestry. Genotyping was carried out as a part of the SHARe project (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v10.p5) using the Affymetrix 500K mapping array (250K Nsp and 250K Sty arrays) and the Affymetrix 50K supplemental gene focused array. Genotyping resulted in 503,551 SNPs with successful call rate >95% and Hardy-Weinberg equilibrium $>10^{-6}$. Imputation of 2,543,887 autosomal SNPs in HapMap release 22, build 36, CEU sample was conducted using the algorithm implemented in MACH (version 1.0.15). The final sample for the fetuin-A analysis included 3592 individuals. The Framingham Heart Study was approved by the institutional review boards of Boston University and the National Institutes of Health. All participants provided written informed consent.

The Health, Aging, and Body Composition (Health ABC) study:

Health ABC is a longitudinal, prospective cohort of well-functioning older men and women recruited from Memphis, TN and Pittsburgh, PA from Medicare beneficiary

records. Recruitment began in 1997-1998 when participants were between 70 and 79 years of age and entry into study was dependent on participants' ability to walk one-quarter mile and climb 10 steps without difficulty. Genomic DNA was extracted from buffy coat collected using PUREGENE® DNA Purification Kit during the baseline exam. In 2009, genotyping was performed by the Center for Inherited Disease Research (CIDR) using the Illumina Human1M-Duo BeadChip system. Samples were excluded from the dataset for the reasons of sample failure, genotypic sex mismatch, and first degree relative of an included individual based on genotype data. Genotyping was successful in 1663 Caucasians and 1139 African Americans. Before imputation, genotypes were available on 914,263 SNPs that met the criteria of call rate < 97%, HWE $p < 10^{-6}$, and MAF < 1%. Imputation was done with MACH (version 1.0.16) and the (NCBI build) Hapmap CEU release 22 build 36 backbone. Fetuin-A was measured on baseline specimens in 753 of the genotyped individuals.

The Multi-Ethnic Study of Atherosclerosis (MESA) study

MESA is a prospective cohort study of 6,814 men and women aged 45–84 years recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). MESA was designed to determine the characteristics of subclinical cardiovascular disease and its progression, hence adults were considered and individuals with symptoms or history of medical or surgical treatment for cardiovascular disease were excluded. Participants were enrolled between July 2000 and August 2002 and self-reported their race/ethnicity group as Caucasian or white, African American or black, Spanish/Hispanic/Latino, or Chinese

American. Affymetrix 6.0 SNP array genotyping of MESA samples with genotype quality control (QC) steps included the exclusion of individuals with >10% missing data, and the exclusion of SNPs with call rates <95. We used IMPUTE2 to impute untyped SNPs.

The Nurses' Health Study

The NHS is a prospective cohort study of 121,700 female registered nurses who were 30 to 55 years old at study inception in 1976. In 1990-1994, blood samples were collected from participants free of CVD and cancer. Study samples included in GWAS were of European ancestry and nested case control studies were initially designed to address various chronic diseases. Details regarding the study design, genotyping quality control, and assurance of these GWASs have been reported elsewhere.(4, 5) Briefly, genotyping was performed using the Affymetrix 6.0 Gene Chip V6.0 and the Birdseed calling algorithm. Genotypic data for a total of 96% of the samples passed laboratory technical quality control criteria and missing call rate <0.05. The GWAS was restricted to samples without substantial evidence of non-European genetic ancestry (n=24 excluded). SNPs that were monomorphic, had a missing call rate $\geq 2\%$, a HWE p-value $< 1 \times 10^{-4}$, or a MAF < 0.02 were excluded, leaving a total of 721,316 SNPs. Imputation of ~2.5 million SNPs was performed using MACH software (v1.0.16) with HapMap CEU phased II data (Release 22) as the reference panel. The study was approved by the institutional review boards at Brigham and Women's Hospital and Harvard School of Public Health. After excluding participants with these chronic diseases at baseline, a total of 1029 initially healthy women who were part of the case control studies of type 2 diabetes (n=288) and coronary heart disease (n=741), were analyzed separately for the GWAS of fetuin-A

levels.

Laboratory Measurements of Fetuin-A

ARIC: Samples were collected at the baseline (1987-89) study visit and stored at -70° Celsius until 2009 when they were thawed and fetuin-A levels were measured in plasma using an enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA). The measurements were conducted at the ARIC Lipid Laboratory at Baylor College of Medicine. The assay uses a 2-site “sandwich” technique with polyclonal antibodies that bind different epitopes of human fetuin-A. Serum samples were measured twice in each participant, and results were averaged. The reliability coefficient estimated from 38 pairs of blind replicate samples was 0.77, and the overall CV from these replicates was 8%.

CHS: Samples were collected at the 1992-93 study visit and stored at -70° Celsius until 2010 when it was thawed and fetuin-A levels were measured in plasma using an enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA). The measurements were conducted at the CHS Central Blood Analysis Laboratory at the University of Vermont (Burlington, VT). The assay uses a 2-site “sandwich” technique with polyclonal antibodies that bind different epitopes of human fetuin-A. Plasma samples were measured twice in each participant, and results were averaged. The coefficients of variation (CV) ranged between 3 and 9%, with a mean CV of 6%.

FHS: **The study sample was derived from 4095 participants in the Framingham Third Generation cohort, in total 3592 individuals had both genotype and fetuin-A**

measures available for analyses. Serum fetuin-A was measured in mg/L from fasting samples using a commercially available kit from Biovendor (Candler, NC). The mean interassay CV was 2.4%. (6)

HABC: Samples were collected at baseline (April 1997 to June 1998) study visit and stored until 2007 when fetuin-A levels were measured in serum using a human fetuin-A enzyme linked immunosorbent assay (ELISA) kit (Epitope Diagnostics, San Diego, CA). The assay uses a two-site “sandwich” technique with two polyclonal antibodies that bind to different epitopes of human fetuin-A. Measurements were performed at the Laboratory for Clinical Biochemistry Research at the University of Vermont. Fetuin-A was measured twice for each participant and results were averaged in g/L. Intra-assay and interassay coefficients of variation were less than 5%. (7)

MESA: Venous blood samples were collected at the baseline visit 2002-2002 and serum was frozen at -70 °C. In 2009, specimens were thawed and fetuin-A was measured at the Clinical Chemistry Laboratory at the University of Maryland with a human ELISA kit (Epitope Diagnostics). Average CV was 5%.

NHS: Between 1989 and 1990, a blood sample was requested from all active participants in NHS and collected from 32,826 women. Blood samples were collected in tubes treated with liquid sodium heparin, placed on ice packs, stored in Styrofoam containers, returned to our laboratory by overnight courier, centrifuged, and divided into aliquots for storage in liquid-nitrogen freezers (-130°C or colder) until 2010 when it was thawed and fetuin-A levels were measured in plasma using an enzyme linked immunosorbent assay kit

(Epitope Diagnostics, R & D). The measurements were conducted in the blood laboratory of Nader Rifai (Boston, MA). The overall CV for Fetuin A, calculated from masked replicate quality control samples placed in each batch, was 15%. Furthermore, the spearman correlation and intraclass correlation between samples collected 1 year apart from the same participants was $r=0.9$.

Statistical Analyses within Each Cohort

The statistical analyses were performed separately in each cohort using the software programs R (CHS, MESA, FHS,) and ProbABEL (ARIC, NHS, HABC). Additive genetic effects were assumed in all analyses, and each analysis adjusted for age, sex, field center, and population stratification, where appropriate. To measure potential inflation in type-I error, a genomic control lambda was computed for each cohort separately. λ_{gc} values in European Americans were CHS: 1.024, ARIC: 1.004, HABC: 0.996, MESA: 1.001, NHS: 1.004, FHS: 0.999, resulting in an overall of 1.025 and in African Americans they were CHS: 1.027, ARIC: 1.006, HABC: 0.977, MESA: 0.985, resulting in an overall lambda of 1.007.

In ARIC, mutually exclusive sets of cases and controls were selected from the case-cohort sample to simplify the design and analysis; cases and controls were analyzed separately but were not otherwise weighted by selection probabilities.

In NHS, that data on fetuin-A was available on a subset of cases and control of a nested case-control study of CHD. Thus, analyses were conducted in the combined populations with adjustment for case-control status (though all individuals were free of CVD at the time of genotyping and fetuin-A measurements).

In FHS, the `lmekin` function from the R kinship package was used to fit linear mixed effect models to account for familial relationships by using subject-specific random effects that are correlated within family with correlation proportional to kinship coefficients between family members.

Meta-analysis

We performed inverse variance–weighted fixed-effect meta-analyses in European and African Americans separately, as implemented in the software METAL.(38) The p-value threshold of genome-wide significance was chosen as 5×10^{-8} , which corresponds to a Bonferroni correction for an estimated 1 million independent tests in the genome of European descendants.(8) For the conditional analysis, we performed meta-analysis similarly, combining the point estimates and standard errors for each cohort's estimates based on a model that adjusted for rs4917.

References

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Supplemental Tables

Table S1. Description of the study populations. European Americans

	COHORT	CHS	ARIC	HABC	MESA	NHS	FHS
COHORT INFORMATION	Ethnicity	European descent	European descent	European descent	European descent	European descent	European descent
	Country	USA	USA	USA	USA	USA	USA
	Collection type	Population-based	Population-based	Population-based, medicare eligible adults over age 70 in Pittsburgh, PA and Memphis, TN	Population-based	Population-based	Population-based
FETUIN MEASUREMENTS	Sample	fasting plasma	fasting plasma	fasting plasma	fasting serum	70% fasting plasma	fasting serum
	Collection method	venipuncture	Venipuncture	Venipuncture	venipuncture	venipuncture	venipuncture
	Assay	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)	enzyme linked immunosorbent assay kit (Epitope Diagnostics, R&D systems)	enzyme linked immunosorbent assay kit (Biovendor, Candler, NC)
	Reference (PMID)	PMID: 22511752		PMID: 18612115	PMID: 22511752	PMID: 22923470	PMID: 22855337

GENOTYPING	Genotyping platform and SNP panel	Illumina HumanCNV370-Duo BeadChip	Affy 6.0	Illumina 1M	Affy6.0	Affy 6.0	Affymetrix 50K Affymetrix 50K supplemental
	Genotyping centre	General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai	BROAD Institute of MIT and Harvard	CIDR	Broad Institute	Rosetta/Merck Research Laboratories, North Wales, PA	
	Genotyping calling algorithm	Illumina BeadStudio software	Birdseed	Illumina GenomeStudio	Birdseed v1.33	Birdseed	Affymetrix
SAMPLE QC	Call rate [filter detail / N individuals excluded]	< 95%	< 95%	97%	95%	>95%	<97%
	Heterozygosity [filter detail / N individuals excluded]	none	none	N/A	none	none	none

	Ethnic outliers / other exclusions	non-European descent	mismatch on sex / mismatches with > 10 of 47 previously analyzed SNPs / all but one in sets of first degree relatives	genotype was discordant with known sex or prior genotyping, no first degree relatives (IBD exclusion at > 0.125, keeping random proband), Within expected distance from eigenvectors for relevant HapMap3 reference populations	Ethnic outliers	non-European descent	
SNP QC (prior to imputation)	MAF [filter detail / N SNPs excluded]	none	<0.01	> 0.01	0.01	<0.02	<0.01
	HWE [filter detail / N SNPs excluded]	P > 10-5	P < 10-5	1.00E-05	-	P > 10-4	HWE p<1E-6
	Call rate [filter detail / N SNPs excluded]	<97%	< 95%	0.97	<97%	<97%	<97%

	Other	<=2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap.		Non-random missing by Haplotype p-value < !E-5		Y chromosome	mishap p<1e-9; >100 Mendelian errors; not available on Hapmap
	SNP number in QC'd dataset	306655	669,450	899818	881666	721,316	378,163
IMPUTATION STATS	Imputation software	BIMBAM v0.99 with reference to HapMap CEU using release 22, build 36	MACH software (v1.0.16)	MACH software (v1.0.16) with HapMap CEU phased II data (Release 22) as the reference panel	IMPUTE2	MACH software (v1.0.16) with HapMap CEU phased II data (Release 22) as the reference panel	MACH software (v1.0.15) with HapMap CEU phased II data (Release 22) as the reference panel
	Imputation quality metrics	observed/expected variance ratio < 0.01	r ² > 0.3	RSQR	info>0.4	r ²	observed/expected variance ratio
	Other SNP QC filters applied?	dosage variance <0.01	none	N/A		none	None
DATA ANALYSIS	Number of SNPs in analysis	2,396,830	2,536,535	2,481,240	2,545,377	2,472,017	2,535,623
	Trait transformation Fetuin	untransformed	untransformed	Untransformed	untransformed	untransformed	untransformed

	Adjustments	age,age2 sex, clinic site	age, age2, sex, clinic site (stratified on case-control status)	age,age2 sex, clinic site, pcs 1-2	age, age2, gender,2 PCs	age, age2, case control status	age,age2,sex
	Analysis method	linear regression	linear regression	linear regression	linear regression	linear regression	linear mixed effects model
	Software for analysis	R	ProbABEL with robust option	mach2qtl	SNPTEST	ProbABEL	R
	Genomic Control Lambda	1.024	1.004	0.996	1.001	0.985	0.999
Percentage of Variance Explained by rs4917	adjusted r2 for full model: fetuin ~ age + sex + rs4917	0.223	0.315	0.02954	0.1567 (in MESA the SNP in strongest LD with rs4917 was used: rs2248690)	0.1383	0.11132
	adjusted r2 for basic model: fetuin ~ age + sex	0.0288	0.002	0.001249	0.0421	0.0102	0.0203658
		0.1942	0.313	0.028291	0.1146	0.1281	0.1113176
REFEREN CES	Reference cohort (PMID)	PMID: 1669507	PMID: 2646917	PMID: 10865790	PMID:12397006	PMID: 9065374	
	Reference GWAS (PMID)	PMID: 20031568	PMID: 20031568	None	PMID:12397006	PMID: 21880673	

Table S2. Description of the study populations. African Americans

	COHORT	CHS	ARIC	HABC	MESA
COHORT INFORMATION	Ethnicity	African Americans	African Americans	African American	African Americans
	Country	USA	USA	USA	USA
	Collection type	Population-based	Population-based	Population-based, medicare eligible adults over age 70 in Pittsburgh, PA and Memphis, TN	Population-based
FETUIN MEASUREMENTS	Sample	fasting plasma	fasting plasma	fasting plasma	Fasting serum
	Collection method	venipuncture	Venipuncture	venipuncture	Venipuncture
	Assay	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)	enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA)
GENOTYPING	Genotyping platform and SNP panel	Illumina HumanOmni1-Quad_v1 BeadChip system	Affy 6.0	Illumina 1M	Affy6.0

	Genotyping centre	General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai	BROAD Institute of MIT and Harvard	CIDR	Broad Institute
	Genotyping calling algorithm	Illumina GenomeStudio	Birdseed	Illumina GenomeStudio	Birdseed v1.33
	Call rate [filter detail / N individuals excluded]	95%	< 95%	97%	95%
	Heterozygosity [filter detail / N individuals excluded]		None	N/A	N/A
SAMPLE QC	Ethnic outliers / other exclusions	genotype was discordant with known sex or prior genotyping	mismatch on sex / mismatches with > 10 of 47 previously analyzed SNPs / all but one in sets of first degree relatives	genotype was discordant with known sex or prior genotyping, no first degree relatives (IBD exclusion at > 0.125, keeping random proband), Within expected distance from eigenvectors for relevant HapMap3 reference populations	Ethnic outliers

	MAF [filter detail / N SNPs excluded]	NA	<0.01	> 0.01	0.01
SNP QC (prior to imputation)	HWE [filter detail / N SNPs excluded]	1.00E-05	P < 10-5	1.00E-05	-
	Call rate [filter detail / N SNPs excluded]	0.97	< 95%	0.97	<97%
	Other	1 duplicate error or Mendelian inconsistency (for reference CEPH trios), heterozygote frequency = 0		Non-random missing by Haplotype p-value < !E-5	
	SNP number in QC'd dataset	963248	669,450	992212	881666
	Imputation software	BEAGLE version 3.2.1 using the default value of 10 iterations	MACH software (v1.0.16)	MACHv1.16	IMPUTE2
IMPUTATION STATS	Imputation quality metrics	observed/expected variance ratio < 0.01	r2 > 0.3	RSQR	info>0.4

	Other SNP QC filters applied?	Imputation was preformed in a two step process. The data were imputed to HapMap Phase III using reference panels from the ASW, YRI and CEU panels. They were separately imputed using HapMap Phase II using the CEU and YRI reference panels (build 36). For each imputation the observed data was subset to the markers also observed in the given HapMap reference panel. The resulting two sets of imputed data were merged. If a marker was imputed in both the Phase II and Phase III data the Phase III data was used. Directly-genotyped SNPs that were in the HapMap samples were not overwritten, but any missing data for a genotyped SNP was filled-in using imputation. The final number snps in the imputed data set was 2,770,583.	None	Carried out at meta-analysis	
	Number of SNPs in analysis	2,603,662	2,649,157	1,920,922	2,938,825
DATA ANALYSIS	Trait transformation on Fetuin	untransformed	Untransformed	untransformed	untransformed
	Adjustments	age,age2 sex, clinic site,	age, age2, sex, clinic site,	age,age2 sex, clinic site,	age, age2, gender,2 PCs

		10PC	and 1st 3 principal components (stratified on case-control status)	10PC	
	Analysis method	linear regression	linear regression	linear regression	linear regression
	Software for analysis	R	ProbABEL with robust option	mach2qtl	SNPTEST
	Genomic Control Lambda	1.027	1.006	0.977	0.985
	adjusted r2 for full model: fetuin ~ age + sex + rs4917	0.1033	0.452	0.001157	0.0963
Percentage of Variance Explained by rs4917	adjusted r2 for basic model: fetuin ~ age + sex	0.0024	0.001	0.004028	0.0409
	Difference between 2 models	0.1009	0.451	-0.002871	0.0554

Table S3. Association of the top SNPs with fetuin-A levels in European Americans

SNP	Chr	Position	Coded allele	Alle freq	β	SE	P	Direction*	N	Closest Gene	Distance ^y
rs4917	3	187820407	t	0.32	-0.0657	0.0018	1.27E-303	----?--	7963	AHSG	1395
rs4918	3	187821076	c	0.67	0.0659	0.0018	5.18E-303	++++?++	7963	AHSG	726
rs1900618	3	187820829	t	0.67	0.0659	0.0018	6.44E-303	++++?++	7963	AHSG	973
rs7635884	3	187823885	t	0.67	0.0655	0.0018	8.50E-301	++++?++	7963	AHSG	2083
rs13073106	3	187824754	t	0.67	0.0651	0.0018	6.00E-300	++++?++	7963	AHSG	2952
rs2593813	3	187815265	a	0.67	0.0654	0.0018	1.95E-299	++++?++	7963	AHSG	1722
rs4634107	3	187824087	t	0.53	0.0601	0.0016	3.37E-296	+++++++	9056	AHSG	2285
rs2070633	3	187818635	t	0.46	-0.059	0.0016	1.27E-292	-----	9055	AHSG	3167
rs2518136	3	187820521	t	0.49	-0.0595	0.0016	1.73E-291	-----	9055	AHSG	1281
rs4498037	3	187823957	t	0.24	-0.0673	0.0019	1.99E-277	-----	9056	AHSG	2155
rs10937254	3	187807940	c	0.24	-0.0639	0.0018	5.03E-267	-----	9055	AHSG	5603
rs10937255	3	187807955	t	0.76	0.0639	0.0018	5.05E-267	+++++++	9055	AHSG	5588
rs12493525	3	187806598	a	0.24	-0.0639	0.0018	9.67E-267	-----	9056	AHSG	6945
rs12486044	3	187810767	t	0.76	0.0638	0.0018	1.52E-266	+++++++	9055	AHSG	2776
rs2248690	3	187812782	a	0.76	0.0634	0.0018	1.69E-264	+++++++	9056	AHSG	761
rs6788635	3	187810815	a	0.24	-0.0632	0.0018	6.35E-264	-----	9055	AHSG	2728
rs1071592	3	187821119	a	0.25	-0.0675	0.002	1.64E-252	-----	9056	AHSG	683
rs13080283	3	187826181	a	0.46	0.0575	0.0017	8.50E-241	+++++++	9056	AHSG	4379
rs1029353	3	187820927	a	0.46	0.0574	0.0017	1.27E-240	+++++++	9055	AHSG	875
rs13098866	3	187822401	a	0.54	-0.0575	0.0017	1.62E-240	-----	9055	AHSG	599
rs2077119	3	187813156	t	0.54	-0.0572	0.0017	5.24E-238	-----	9056	AHSG	387
rs2070635	3	187818870	a	0.54	-0.0565	0.0017	9.80E-237	-----	9056	AHSG	2932
rs9814347	3	187835554	c	0.51	0.0599	0.0024	1.66E-139	+++++++	9055	FETUB	5288
rs9870756	3	187827308	t	0.12	-0.0669	0.0027	3.52E-137	-----	9056	AHSG	5506

rs4686428	3	187730067	a	0.77	0.0463	0.002	2.26E-122	+++++++	9056	CRYGS	8859
rs9846507	3	187722490	c	0.77	0.0462	0.002	2.65E-122	+++++++	9056	CRYGS	16436
rs9846350	3	187722373	t	0.77	0.0462	0.002	2.81E-122	+++++++	9056	CRYGS	16553
rs7627243	3	187720527	a	0.75	0.0462	0.002	9.29E-120	+++++++	9056	CRYGS	18399
rs11717166	3	187831525	t	0.38	0.0563	0.0024	8.42E-119	+++++++	9056	FETUB	9317
rs13084035	3	187832106	t	0.38	0.0555	0.0024	5.32E-117	+++++++	9055	FETUB	8736
rs4686784	3	187716558	t	0.77	0.0456	0.002	7.09E-117	+++++++	9056	CRYGS	22368
rs2377868	3	187719728	t	0.21	-0.05	0.0022	1.05E-115	-----	9054	CRYGS	19198
rs13096010	3	187833829	a	0.36	0.0594	0.0026	3.16E-115	+++++++	9056	FETUB	7013
rs6776042	3	187772016	a	0.17	-0.0531	0.0024	2.25E-110	-----	9056	DNAJB11	856
rs2889755	3	187770471	t	0.16	-0.0551	0.0025	2.60E-109	-----	9056	DNAJB11	689
rs6444147	3	187799894	t	0.89	0.0522	0.0025	9.67E-96	+++++++	9055	DNAJB11	13612
rs6444150	3	187808522	t	0.89	0.0528	0.0026	7.62E-93	+++++++	9056	AHSG	5021
rs3933692	3	187800057	t	0.89	0.0524	0.0026	7.04E-92	+++++++	9056	AHSG	13486
rs6444151	3	187808610	c	0.89	0.0527	0.0026	1.02E-91	+++++++	9056	AHSG	4933
rs8179931	3	187798664	t	0.12	-0.0523	0.0026	4.16E-91	-----	9056	DNAJB11	12382
rs1447668	3	187827054	t	0.88	0.0509	0.0026	1.02E-86	+++++++	9056	AHSG	5252
rs1530641	3	187718601	t	0.68	0.0294	0.0018	5.20E-57	+++++++	9056	CRYGS	20325
rs13062057	3	187758067	a	0.15	0.0335	0.0024	1.05E-43	+++++++	9056	TBCCD1	9739
rs1868156	3	187719527	t	0.85	-0.032	0.0023	1.85E-42	-----	9056	CRYGS	19399
rs2377869	3	187721660	t	0.85	-0.0319	0.0023	2.28E-42	-----	9056	CRYGS	17266
rs9290835	3	187801480	a	0.74	0.0261	0.002	1.91E-40	+++++++	9056	AHSG	12063
rs11714927	3	187779572	a	0.60	0.0237	0.0019	3.95E-37	+++++++	9055	DNAJB11	6710
rs17297584	3	187832190	a	0.11	-0.0442	0.0035	4.09E-37	-----	9056	FETUB	8652
rs4488820	3	187822311	t	0.92	-0.0595	0.0047	2.20E-36	---+---	9056	AHSG	509
rs2280390	3	187776514	t	0.28	-0.0261	0.0022	2.21E-31	-??----	8559	DNAJB11	5354
rs16860933	3	187822954	c	0.93	-0.0539	0.0048	1.35E-29	---+---	9056	AHSG	1152
rs4686791	3	187831567	t	0.28	-0.0278	0.0025	4.82E-29	-----	9056	FETUB	9275
rs2121752	3	187778998	a	0.35	-0.0196	0.0019	2.62E-25	-----	9055	DNAJB11	7284

rs6763361	3	187793068	a	0.21	-0.0202	0.0021	1.59E-21	-----	9055	DNAJB11	6786
rs13073740	3	187730131	a	0.97	-0.0868	0.0092	6.60E-21	----?--	7963	CRYGS	8795
rs3856928	3	187796265	a	0.79	0.0202	0.0022	1.48E-20	+++++++	9056	DNAJB11	9983
rs4686799	3	187933930	t	0.24	-0.0187	0.002	4.52E-20	---+---	9056	KNG1	8884
rs710449	3	187935514	a	0.23	-0.0188	0.0021	6.27E-20	---+---	9055	KNG1	7300
rs10513803	3	187910755	t	0.57	0.0155	0.0017	8.21E-20	+++++++	9056	KNG1	7058
rs13315296	3	187911695	t	0.57	0.0155	0.0017	1.08E-19	+++++++	9056	KNG1	6118
rs9817038	3	187912118	t	0.57	0.0155	0.0017	1.12E-19	+++++++	9055	KNG1	5695
rs11918665	3	187696478	a	0.13	-0.0234	0.0026	1.79E-19	-----	9056	CRYGS	42448
rs1868149	3	187703499	a	0.12	-0.0243	0.0029	2.07E-17	---+---	9056	CRYGS	35427
rs1868146	3	187704565	a	0.12	-0.025	0.0029	2.39E-17	---+---	9056	CRYGS	34361
rs1868145	3	187705041	t	0.11	-0.0255	0.003	2.95E-17	---+---	9056	CRYGS	33885
rs1868152	3	187702757	a	0.13	-0.0234	0.0028	1.87E-16	-----	9056	CRYGS	36169
rs4686787	3	187746909	t	0.97	0.0623	0.0076	3.19E-16	?++++++	6314	TBCCD1	86
rs9830330	3	187743712	t	0.97	0.0621	0.0076	3.89E-16	?++++++	6314	CRYGS	1149
rs843991	3	187999122	t	0.51	0.0132	0.0017	2.63E-14	+++++++	9056	RFC4	7862
rs710450	3	188005327	a	0.54	0.0135	0.0018	2.80E-14	+++++++	9056	RFC4	1657
rs266754	3	187991660	t	0.47	-0.0133	0.0018	3.33E-14	-----	9055	EIF4A2	1283
rs6787877	3	187792995	c	0.71	0.0141	0.0019	3.98E-14	+++++++	9055	DNAJB11	6713
rs187868	3	187992211	a	0.47	-0.0131	0.0017	4.54E-14	-----	9055	EIF4A2	1834
rs3846211	3	187789235	t	0.30	-0.014	0.0019	4.58E-14	-----	9056	DNAJB11	2953
rs266759	3	187991006	t	0.48	-0.0131	0.0017	4.68E-14	-----	9055	EIF4A2	629
rs11921733	3	187781801	a	0.09	0.0228	0.003	5.21E-14	+++++++	9056	DNAJB11	4481
rs7645347	3	187701643	a	0.39	0.014	0.0019	6.10E-14	+++++++	9055	CRYGS	37283
rs3936433	3	187794438	a	0.29	-0.0139	0.0019	1.40E-13	-----	9055	DNAJB11	8156
rs185554	3	187977116	a	0.46	-0.0134	0.0018	1.53E-13	-----	9056	EIF4A2	6938
rs182051	3	187980192	t	0.23	-0.0167	0.0023	1.63E-13	-----	9056	EIF4A2	3862
rs11918289	3	187914126	a	0.33	-0.0134	0.0018	1.98E-13	-----	9056	KNG1	3687
rs745588	3	187712697	t	0.80	-0.0199	0.0027	3.33E-13	-----	9056	CRYGS	26229

rs4686429	3	187744041	a	0.09	0.0219	0.0031	7.22E-13	+++++++	9056	CRYGS	820
rs3774803	3	187742653	t	0.09	0.0219	0.0031	8.28E-13	+++++++	9056	CRYGS	2208
rs16860878	3	187738205	t	0.09	0.0218	0.0031	8.78E-13	+++++++	9056	CRYGS	721
rs266733	3	187976007	t	0.53	0.0129	0.0018	1.04E-12	+++++++	9051	EIF4A2	8047
rs1656941	3	188001835	a	0.77	0.0149	0.0021	1.72E-12	+++++++	9056	RFC4	5149
rs2889756	3	187735465	a	0.91	-0.0211	0.003	1.76E-12	-----	9056	CRYGS	3461
rs1648703	3	188001830	a	0.77	0.0149	0.0021	1.90E-12	+++++++	9056	RFC4	5154
rs1621816	3	187921867	t	0.72	-0.0136	0.0019	2.23E-12	---+---	9056	KNG1	4054
rs3917113	3	188000310	a	0.78	0.0153	0.0022	2.42E-12	+++++++	9056	RFC4	6674
rs5030072	3	187938240	t	0.56	-0.0123	0.0018	4.35E-12	-----	9056	KNG1	4574
rs9833880	3	187779703	t	0.18	0.0152	0.0022	7.77E-12	+++++++	9055	DNAJB11	6579
rs9870051	3	187692542	t	0.78	0.0165	0.0024	8.33E-12	+++++++	9055	CRYGS	46384
rs10937253	3	187781338	a	0.82	-0.0152	0.0022	8.91E-12	---+---	9055	DNAJB11	4944
rs13326516	3	187784534	t	0.82	-0.0151	0.0022	9.02E-12	---+---	9055	DNAJB11	1748
rs9859857	3	187781036	t	0.82	-0.0152	0.0022	9.95E-12	---+---	9055	DNAJB11	5246
rs11928493	3	187781516	a	0.82	-0.0152	0.0022	1.03E-11	---+---	9055	DNAJB11	4766
rs9840074	3	187781075	a	0.18	0.0152	0.0022	1.04E-11	+++++++	9056	DNAJB11	5207
rs7624836	3	187779264	c	0.18	0.0152	0.0022	1.10E-11	+++++++	9055	DNAJB11	7018
rs2280389	3	187776584	t	0.84	-0.0161	0.0024	1.10E-11	-----	9055	DNAJB11	5424
rs7622195	3	187778948	t	0.18	0.0152	0.0022	1.18E-11	+++++++	9055	DNAJB11	7334
rs8147	3	187784397	a	0.82	-0.0149	0.0022	1.32E-11	---+---	9055	DNAJB11	1885
rs6784026	3	187782599	t	0.82	-0.0149	0.0022	1.46E-11	---+---	9055	DNAJB11	3683
rs9851299	3	187783377	t	0.18	0.0149	0.0022	1.48E-11	+++++++	9055	DNAJB11	2905
rs6770868	3	187782308	a	0.18	0.0149	0.0022	1.54E-11	+++++++	9055	DNAJB11	3974
rs713484	3	187772367	t	0.82	-0.0151	0.0022	1.55E-11	---+---	9055	DNAJB11	1207
rs7609902	3	187774993	t	0.18	0.0151	0.0022	1.56E-11	+++++++	9055	DNAJB11	3833
rs2280388	3	187776642	a	0.82	-0.015	0.0022	1.81E-11	---+---	9056	DNAJB11	5482
rs2280391	3	187776282	a	0.82	-0.015	0.0022	1.86E-11	---+---	9056	DNAJB11	5122
rs12330397	3	187770674	t	0.83	-0.0157	0.0024	2.42E-11	---+---	9056	DNAJB11	486

rs2228243	3	187877807	a	0.80	-0.0145	0.0022	3.56E-11	---+---	9053	HRG	909
rs12330139	3	187770343	t	0.17	0.0155	0.0023	3.89E-11	+++++++	9056	DNAJB11	817
rs7642903	3	187695671	t	0.34	0.0125	0.0019	4.01E-11	+++++++	9055	CRYGS	43255
rs12330875	3	187768680	t	0.17	0.0149	0.0023	4.13E-11	+++++++	9056	TBCCD1	874
rs16860992	3	187876732	c	0.20	0.0145	0.0022	5.74E-11	+++++++	9056	HRG	1984
rs5030023	3	187927338	a	0.23	0.0133	0.002	6.04E-11	+++0+++	9056	KNG1	9525
rs1047148	3	187990451	a	0.14	0.0197	0.003	7.05E-11	+++++++	9055	EIF4A2	74
rs5030062	3	187936874	a	0.62	-0.0114	0.0017	7.14E-11	-----	9056	KNG1	5940
rs5030028	3	187928448	t	0.23	0.0132	0.002	7.41E-11	+++0+++	9056	KNG1	10635
rs16861189	3	188018128	c	0.55	0.0127	0.002	9.13E-11	+++++++	9056	RFC4	11144
rs13094303	3	188016808	t	0.45	-0.0127	0.002	9.23E-11	-----	9056	RFC4	9824
rs6780323	3	187702792	a	0.67	-0.013	0.002	1.22E-10	-----	9055	CRYGS	36134
rs9878039	3	187691172	a	0.90	0.0189	0.0029	1.45E-10	+++++++	9056	CRYGS	47754
rs9836109	3	187679848	a	0.10	-0.0189	0.003	2.18E-10	-----	9056	CRYGS	59078
rs11017848	10	132949189	t	0.99	-0.2091	0.0332	2.88E-10	?????--	4333	TCERG1L	50785
rs4686794	3	187881384	a	0.53	-0.0141	0.0023	4.05E-10	-----	9056	HRG	2668
rs1447670	3	187737526	a	0.85	-0.0146	0.0024	1.34E-09	---+---	9055	CRYGS	1400
rs9898	3	187873321	t	0.34	0.0111	0.0018	1.63E-09	+++++++	9055	HRG	5395
rs1868154	3	187857365	a	0.55	-0.0106	0.0018	3.11E-09	---+---	9055	FETUB	3875
rs1868143	3	187705664	t	0.17	-0.0154	0.0026	6.61E-09	---+---	9044	CRYGS	33262
rs1131364	3	187853027	t	0.46	0.0103	0.0018	7.05E-09	+++0+++	9055	FETUB	463
rs4615068	3	187572403	t	0.17	-0.0144	0.0025	1.04E-08	---+---	9055	DGKG	9686
rs1426810	3	187986129	a	0.62	-0.0099	0.0018	1.59E-08	+-----	9056	EIF4A2	2075
rs11720187	3	187860423	t	0.54	-0.01	0.0018	1.62E-08	---+---	9056	HRG	6068
rs3733159	3	187843103	t	0.68	-0.0105	0.0019	1.76E-08	-----	9056	FETUB	2261
rs6796803	3	187946801	t	0.27	-0.0124	0.0022	2.96E-08	-----	9056	KNG1	2366
rs6809265	3	187664220	a	0.24	-0.0121	0.0022	3.26E-08	---+---	9056	CRYGS	74706
rs1042464	3	187878266	a	0.52	-0.0095	0.0018	6.17E-08	---+---	9056	HRG	450
rs3856930	3	187941016	t	0.35	0.0097	0.0018	8.29E-08	+++++++	9056	KNG1	1798

*Direction: shows the direction of the association for the coded allele in each cohort in the following order: CHS, ARIC set 1, ARIC set 2, HABC, MESA, NHS, FHS.

^YDistance: is the distance in base pairs from the closest known gene

Table S4. Association of the top SNPs with fetuin-A levels in African Americans

SNP	Chr	Position	Coded allele	MAF	β	SE	p	Direction*	N	Closest Gene	Distance ^Y
rs1900618	3	187820829	t	0.67	0.0477	0.003	1.58E-56	+++++	2119	AHSG	973
rs10937254	3	187807940	c	0.31	-0.0467	0.0033	9.31E-47	----	2119	AHSG	5603
rs2593813	3	187815265	a	0.62	0.0436	0.003	9.49E-47	+++++	2119	AHSG	1722
rs12486044	3	187810767	t	0.74	0.047	0.0033	9.31E-46	+++++	2119	AHSG	2776
rs6788635	3	187810815	a	0.26	-0.0469	0.0033	9.36E-46	----	2119	AHSG	2728
rs10937255	3	187807955	t	0.74	0.047	0.0033	1.03E-45	+++++	2119	AHSG	5588
rs4917	3	187820407	t	0.26	-0.0413	0.0034	1.20E-34	---+	2119	AHSG	1395
rs7635884	3	187823885	t	0.76	0.0426	0.0035	4.82E-34	+++++	2118	AHSG	2083
rs4498037	3	187823957	t	0.15	-0.0476	0.0041	1.13E-30	----	2119	AHSG	2155
rs12493525	3	187806598	a	0.23	-0.0391	0.0037	2.46E-26	----	2119	AHSG	6945
rs2518136	3	187820521	t	0.68	-0.0352	0.0034	1.57E-25	---+	2119	AHSG	1281
rs2070633	3	187818635	t	0.66	-0.0341	0.0033	2.05E-24	----	2119	AHSG	3167
rs4634107	3	187824087	t	0.30	0.0355	0.0035	1.07E-23	+++++	2118	AHSG	2285
rs4918	3	187821076	c	0.66	0.0435	0.0045	2.36E-22	?++++	1394	AHSG	726
rs1071592	3	187821119	a	0.16	-0.0493	0.0051	4.18E-22	---??	1091	AHSG	683
rs2248690	3	187812782	a	0.73	0.0318	0.0035	2.93E-20	+++++	2118	AHSG	761
rs8179931	3	187798664	t	0.18	-0.0342	0.004	6.09E-18	---?-	1769	DNAJB11	12382
rs16860933	3	187822954	c	0.84	-0.0391	0.0046	1.09E-17	---?-	1769	AHSG	1152
rs6444147	3	187799894	t	0.82	0.0334	0.0039	1.14E-17	+++?+	1769	DNAJB11	13612
rs1447668	3	187827054	t	0.95	0.0533	0.0064	9.50E-17	+++++	2119	AHSG	5252
rs4488820	3	187822311	t	0.83	-0.0321	0.0043	4.86E-14	----	2119	AHSG	509
rs3933692	3	187800057	t	0.77	0.0269	0.0037	2.30E-13	+++?+	1768	AHSG	13486
rs9870756	3	187827308	t	0.09	-0.0413	0.0057	5.52E-13	-+---	2119	AHSG	5506
rs2377868	3	187719728	t	0.16	-0.028	0.004	3.48E-12	----	2117	CRYGS	19198
rs10962420	9	16413076	a	0.98	-0.1378	0.0203	1.16E-11	?--?-	1044	BNC2	13575
rs9846507	3	187722490	c	0.83	0.0276	0.0041	1.70E-11	+++++	2119	CRYGS	16436

rs17297964	4	120969220	a	0.99	0.0868	0.0135	1.43E-10	+++??	1091	PDE5A	199791
rs6444150	3	187808522	t	0.91	0.0344	0.0054	2.23E-10	+++?+	1769	AHSG	5021
rs1029353	3	187820927	a	0.13	0.0298	0.0048	4.57E-10	+++++	2119	AHSG	875
rs2077119	3	187813156	t	0.88	-0.0303	0.0049	8.42E-10	---+-	2119	AHSG	387
rs9846350	3	187722373	t	0.79	0.0232	0.0038	1.58E-09	+++++	2119	CRYGS	16553
rs9872086	3	187828594	t	0.58	-0.0189	0.0032	4.96E-09	-+---	2119	AHSG	6792
rs17384987	3	154009694	t	0.99	-0.1212	0.0208	5.76E-09	?+?-	1044	P2RY1	25731
rs13098866	3	187822401	a	0.89	-0.0293	0.0051	8.05E-09	---?-	1769	AHSG	599
rs17217936	4	182981555	t	0.99	-0.1071	0.0186	9.08E-09	-???	1403	ODZ3	500575
rs17297584	3	187832190	a	0.05	-0.0404	0.0071	1.06E-08	---?-	1769	FETUB	8652
rs16878361	4	26070983	a	0.01	-0.0558	0.0098	1.16E-08	-+?-	1769	CCKAR	21132
rs13080283	3	187826181	a	0.11	0.0285	0.0051	2.03E-08	+++?+	1769	AHSG	4379
rs2070635	3	187818870	a	0.88	-0.0271	0.0048	2.32E-08	---+-	2119	AHSG	2932
rs6444151	3	187808610	c	0.94	0.0352	0.0064	4.34E-08	+++++	2116	AHSG	4933
rs4686428	3	187730067	a	0.86	0.029	0.0053	4.96E-08	+++??	1091	CRYGS	8859
rs4686432	3	187800551	t	0.33	0.0177	0.0033	6.33E-08	+++++	2119	AHSG	12992

*Direction: shows the direction of the association for the coded allele in each cohort in the following order: : CHS, ARIC set 1, ARIC set 2, HABC, MESA.

^YDistance: is the distance in base pairs from the closest known gene

Figure S1: Meta-analysis of six genome-wide association analyses of fetuin-A levels in a total of 9,055 European Americans. Figure displays p-value for association for each SNP on a $-\log_{10}$ scale.

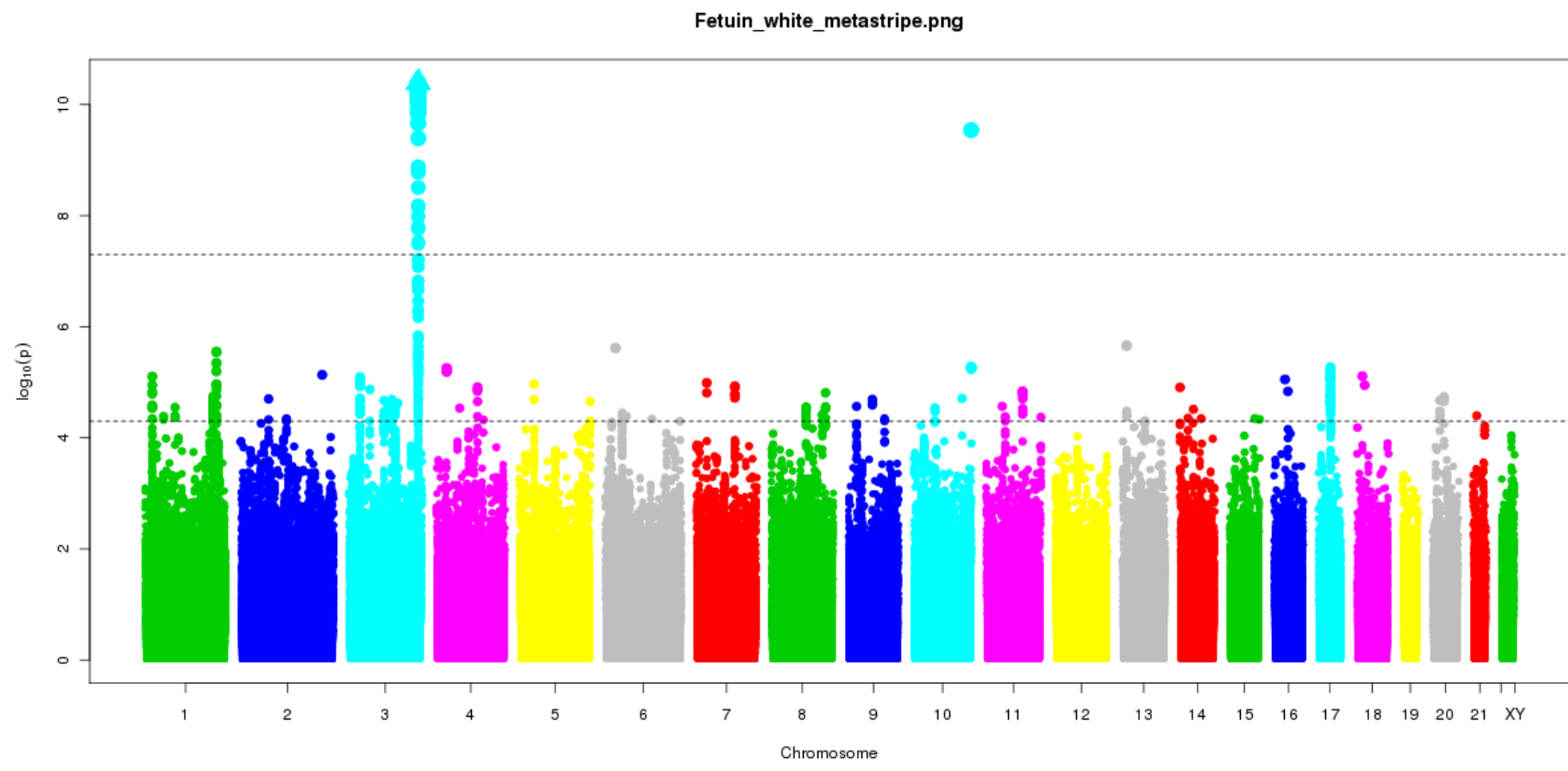


Figure S2B: Display of genetic region and LD of SNPs that were associated with fetuin-A levels ($p < 5 \times 10^{-8}$) among European American participants, zoomed in on region around rs4917. Light blue dots represent variants in low LD ($0.2 < r^2 < 0.4$) with rs4917 (rs2077119; rs2070635; rs1029353; rs13098866; rs13080283).

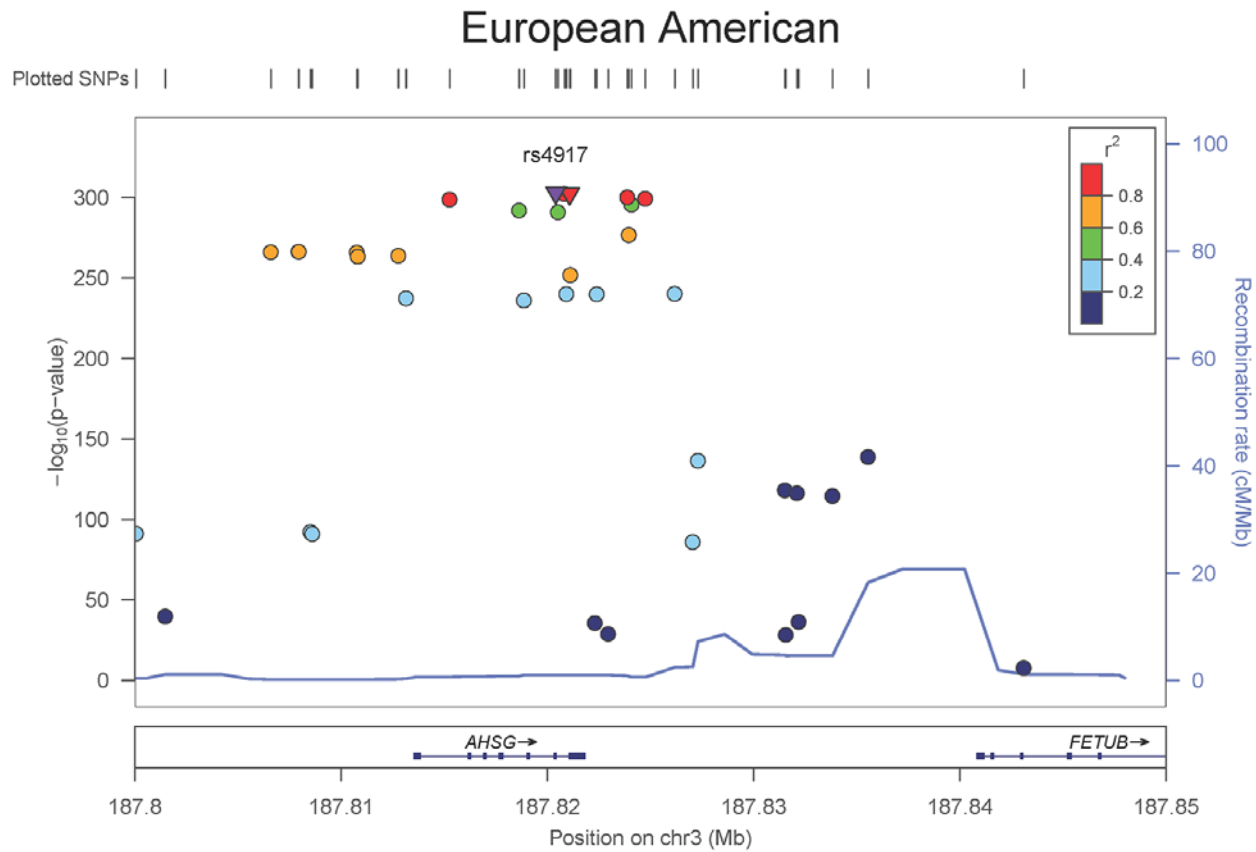


Figure S3: Meta-analysis of six genome-wide association analyses of fetuin-A levels in a total of 2,119 African Americans. Figure displays p-value for association for each SNP on a $-\log_{10}$ scale.

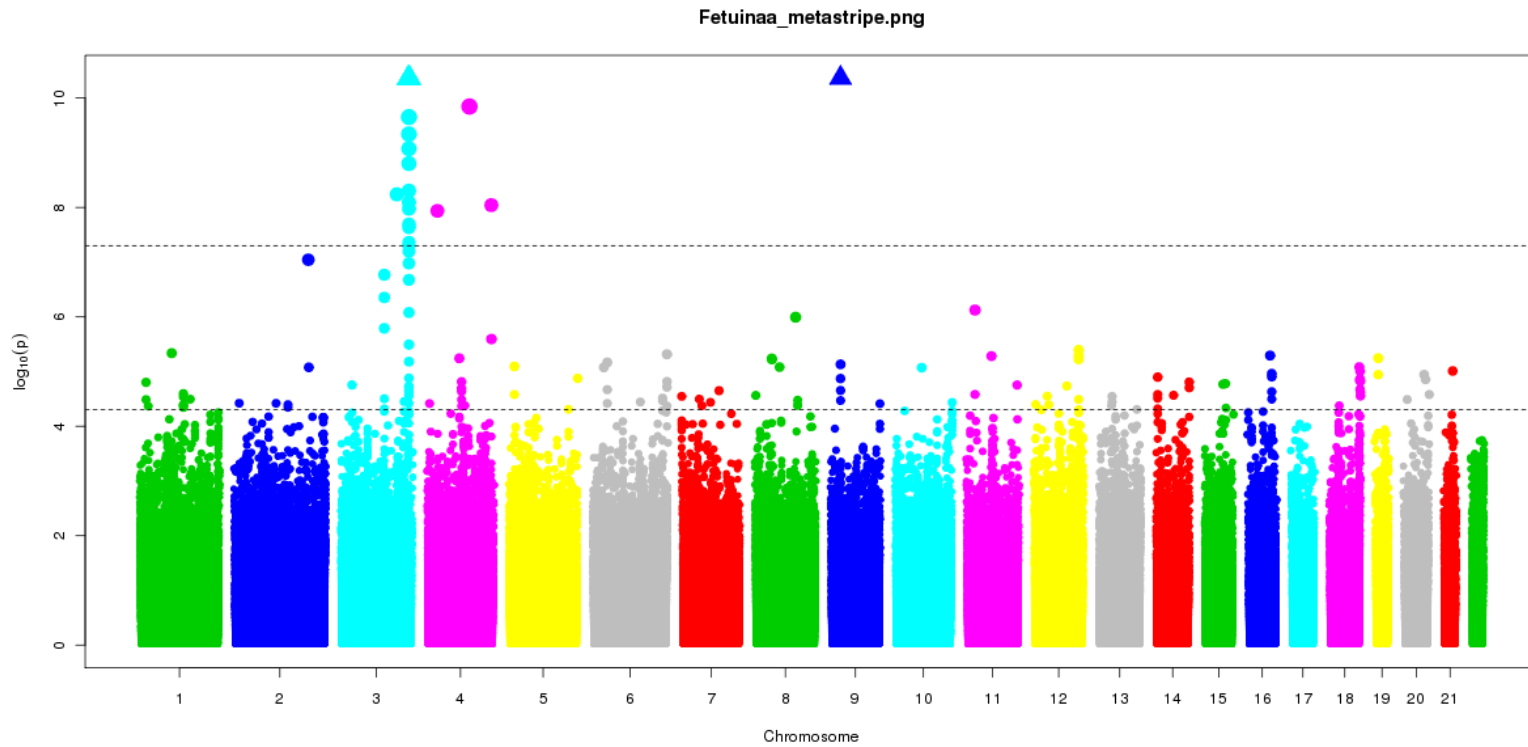


Figure S4. Display of genetic region and LD of SNPs that were associated with fetuin-A levels ($p < 5 \times 10^{-8}$) among African American participants

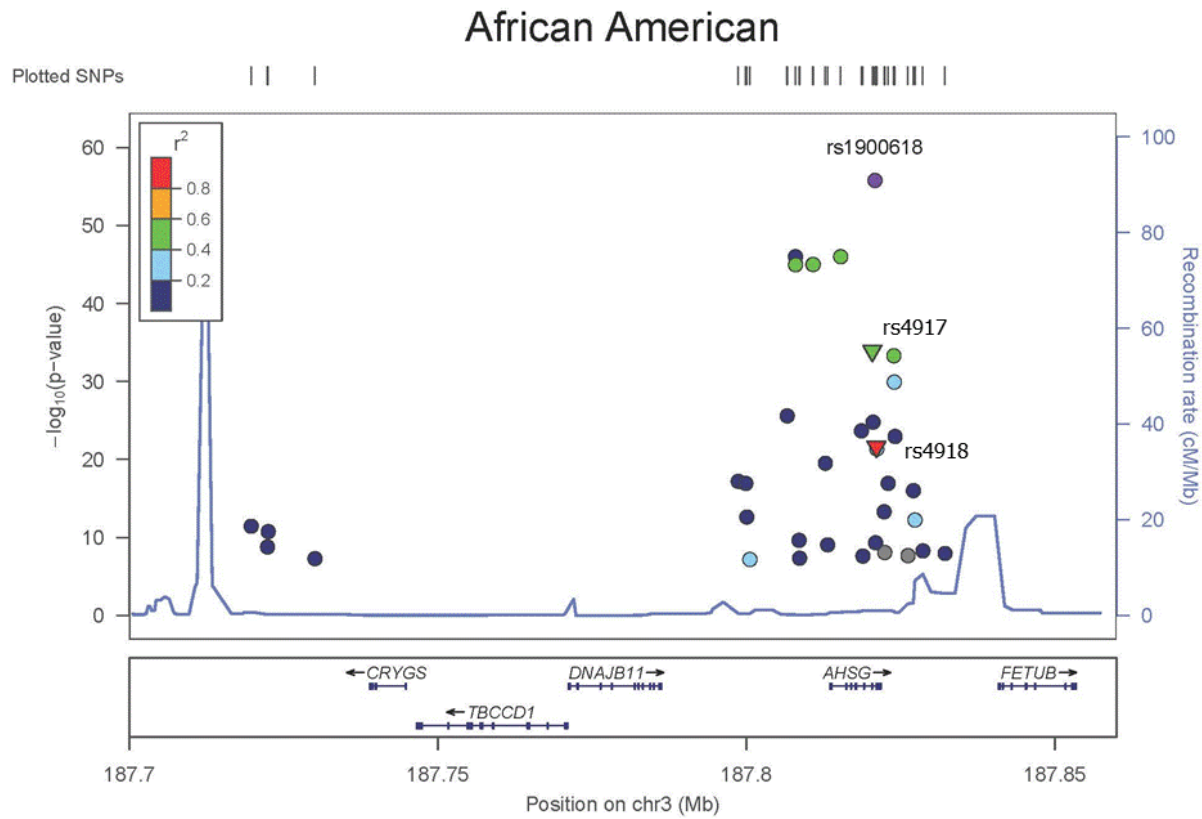


Figure S5. Meta-analysis of six genome-wide association analyses of fetuin-A levels in European American participants, conditional on rs4917. Figure displays p-value for association for each SNP on a $-\log_{10}$ scale.

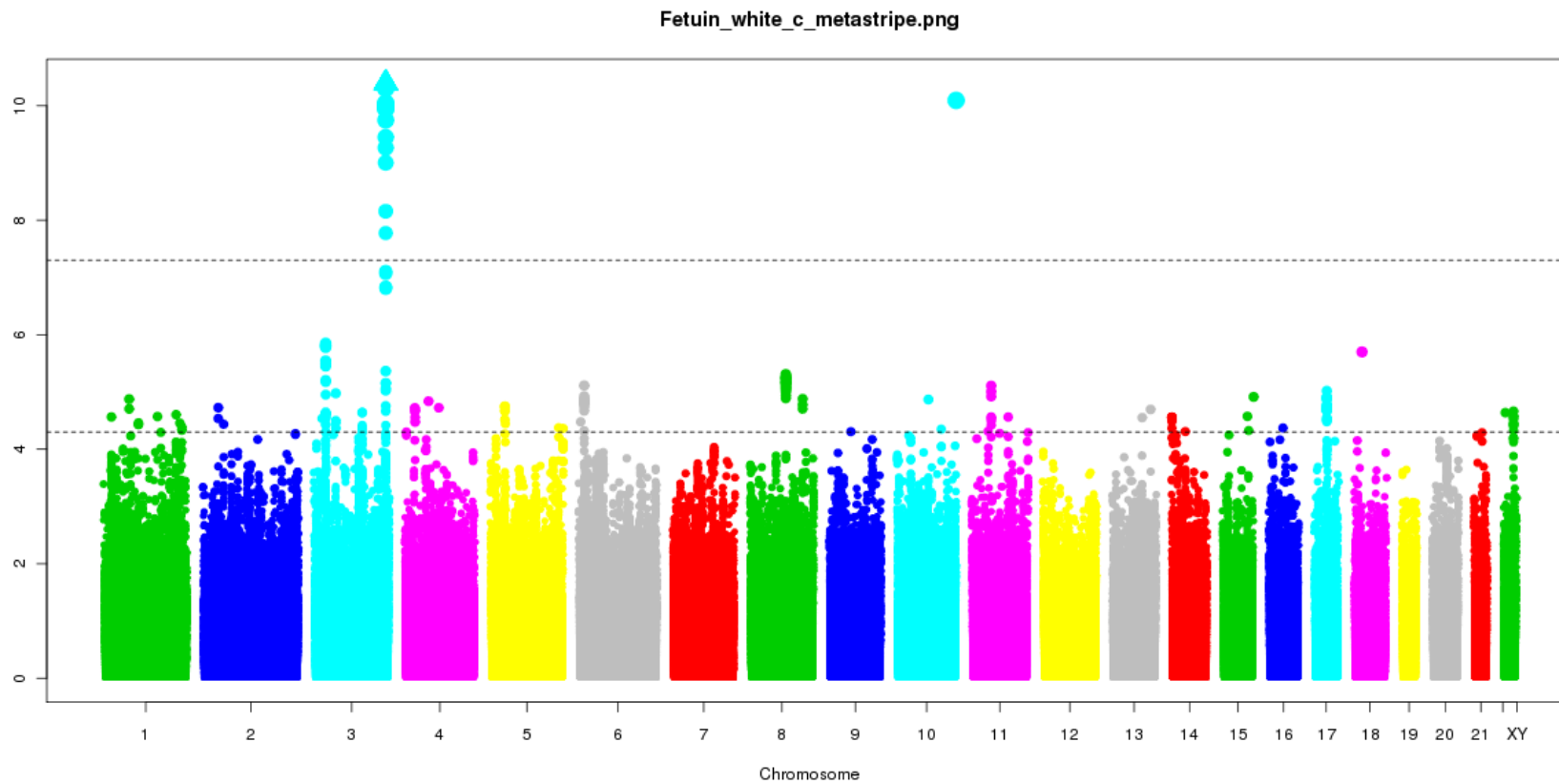


Figure S6. Meta-analysis of four genome-wide association analyses of fetuin-A levels in African Americans, conditional on rs4917.

Figure displays p-value for association for each SNP on a $-\log_{10}$ scale

