Supplemental Data

Supplemental Figures and Legends

Figure S1. Distributional characteristics of genotyped SNPs. Distributions of successfully genotyped variants (A) by MAF for each race/ethnicity, and (B) by functional effect as determined by SnpEff for all variants genotyped in ≥1 race/ethnicity (includes monomorphic sites).

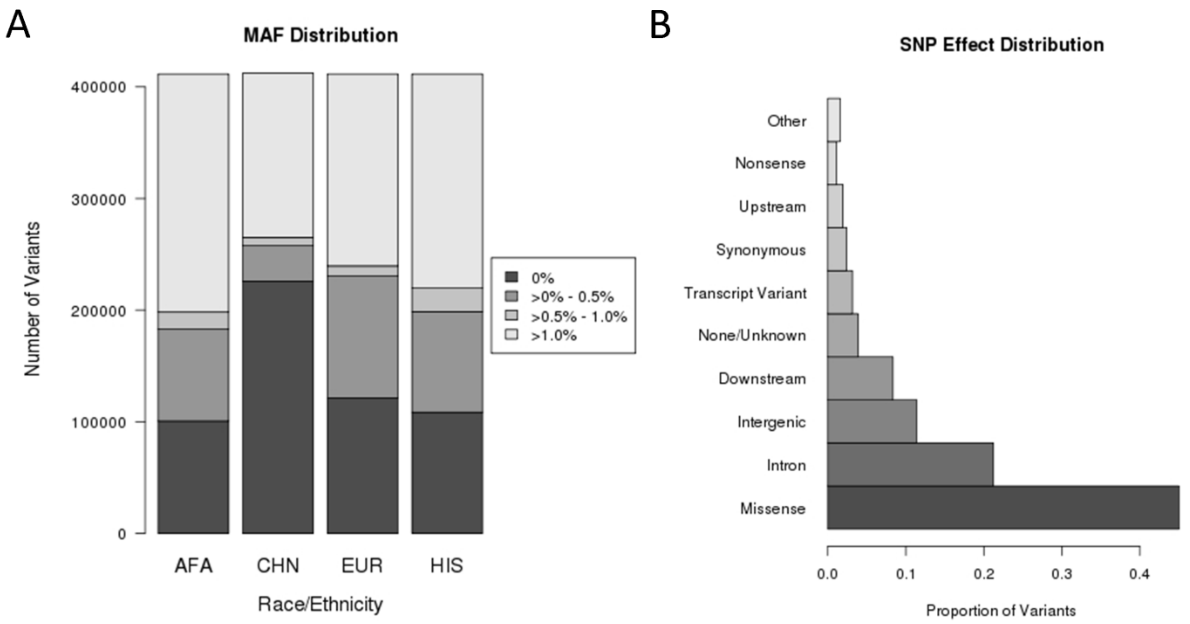


Figure S2. Manhattan plots for the serum HGF single-variant ethnicity stratified association analyses. Results from the single-variant association analyses (-$\log_{10}$(p)) plotted by chromosomal positions (NCBI build 37) for associations with (A) African American, (B) Chinese American, (C) European American, and (D) Hispanic American subjects. Results were adjusted for age, sex, and the first three PCs. Significant results labeled by rsID.

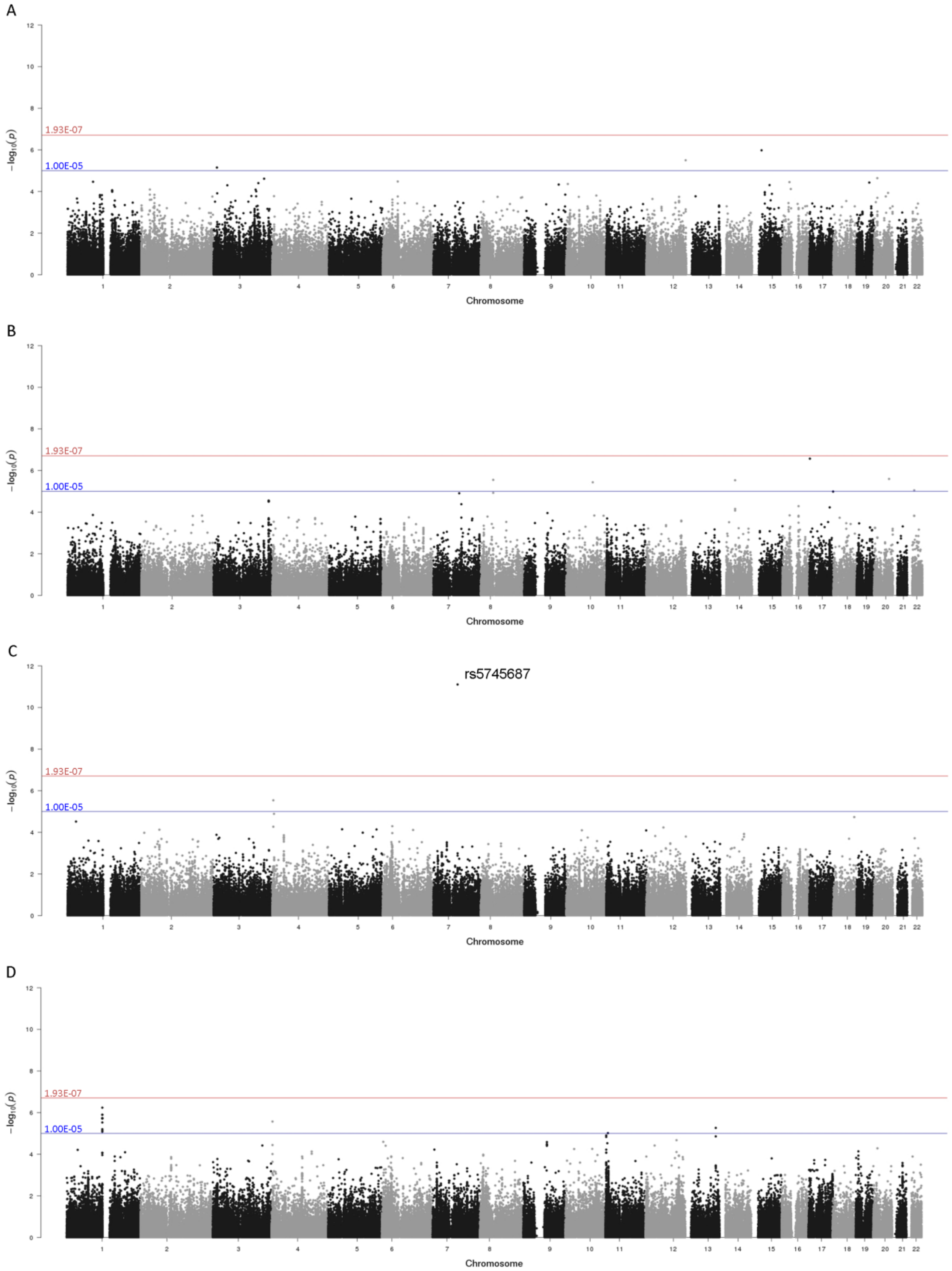


Figure S3. QQ-plot of SNP-level association results. Observed and expected –log10 P-values from the race/ethnicity-stratified single-SNP testing and METASOFT meta-analysis, differentiated by plot symbol. The 90% confidence region is indicated by the greyed area, while the significance threshold (1.95E-07) is demarcated by the dashed line. Significantly associated variants are labeled by rsID.

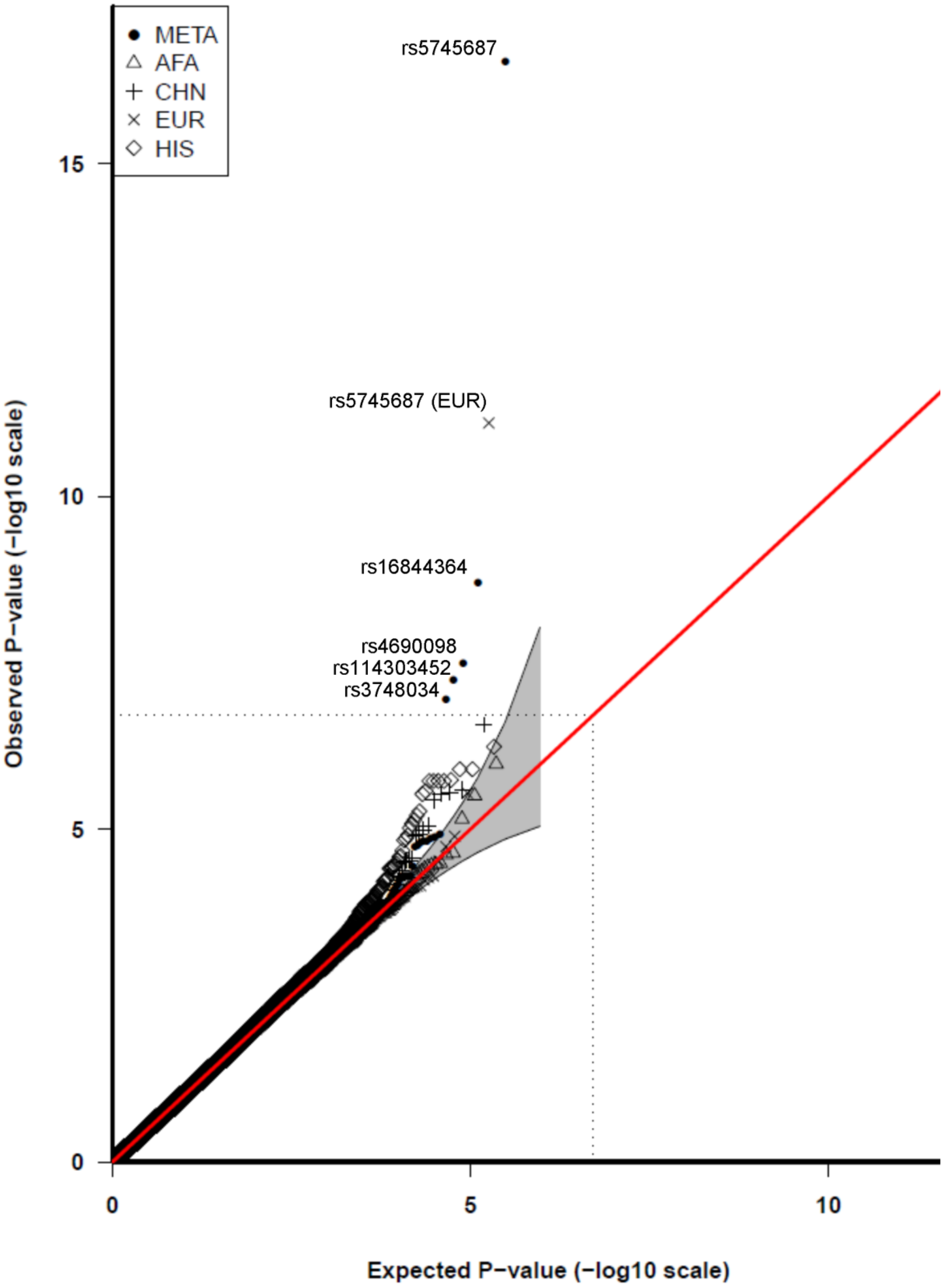
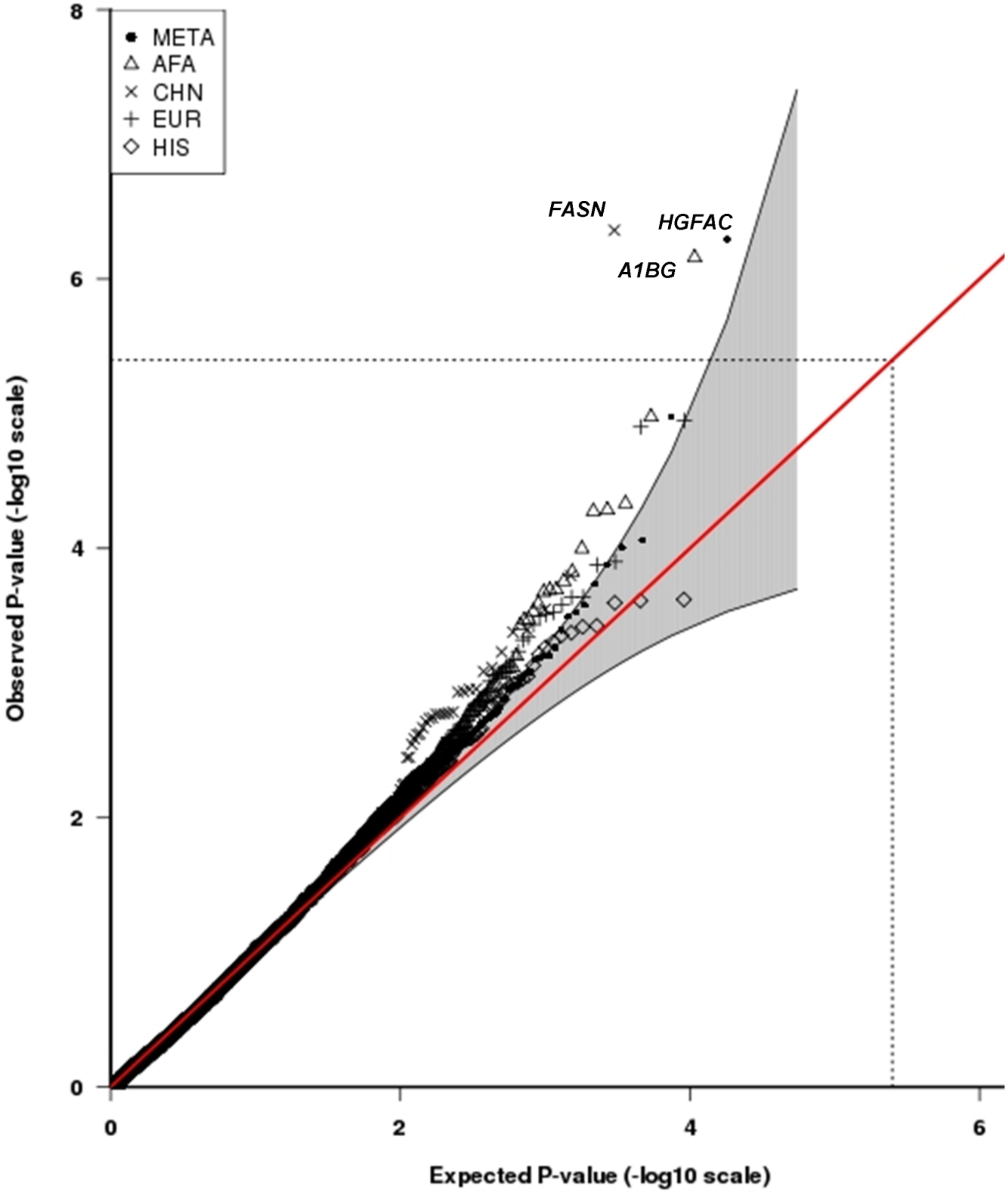


Figure S4. QQ-plot of gene-level association results. Observed and expected –log10 P-values from the race/ethnicity-stratified SKAT-O and MetaSKAT gene-based testing, differentiated by plot symbol. The 90% confidence region is indicated by the greyed area, while the significance threshold (4.00E-06) is demarcated by the dashed line. Significantly associated genes are labeled by gene symbol.



Supplemental Tables

Table S1. Exam 1 characteristics by race/ethnicity for all participants with genotype data, presented as count (%) or Mean (SD).

	Race				
Characteristics	AFA	CHN	EUR	HIS	*P*[*]
n (%)	1634 (26)	764 (12)	2491 (39)	1428 (23)	
Age, years	62 (10)	62 (10)	63 (10)	61 (10)	0.0019
Sex, n (%) female	880 (54)	387 (51)	1297 (52)	736 (52)	0.43
Body mass index, kg/m2	30 (5.9)	24 (3.3)	28 (5.1)	29 (5.1)	<0.0001
Systolic blood pressure, mmHg	132 (22)	125 (22)	123 (20)	127 (22)	<0.0001
Diastolic blood pressure, mmHg	74 (10)	72 (10)	70 (9.9)	72 (10)	<0.0001
Hypertension, n (%) Yes	965 (59)	289 (38)	964 (39)	596 (42)	<0.0001
Diabetes mellitus, n (%) Yes	275 (17)	101 (13)	149 (6)	252 (18)	<0.0001
Total cholesterol, mg/dl	189 (36)	192 (31)	196 (35)	198 (38)	<0.0001
HDL cholesterol, mg/dl	52 (15)	49 (12)	52 (15)	47 (13)	<0.0001
LDL cholesterol, mg/dl	116 (33)	115 (29)	117 (30)	120 (33)	0.02
Triglycerides, mg/dl	105 (70)	143 (84)	133 (90)	159 (102)	<0.0001
Antilipidemic therapy, % Yes	259 (16)	109 (14)	453 (18)	190 (13)	0.0004
Current smoker, n (%) Yes	300 (18)	43 (6)	286 (12)	193 (14)	<0.0001
Current use of alcohol, n (%) yes	803 (50)	234 (31)	1772 (72)	667 (47)	<0.0001
CAC > 0, n (%) yes	719 (44)	388 (51)	1412 (57)	653 (46)	<0.0001
CAC Categories, Agatston score					<0.0001
< 50, n (%)	1226 (75)	538 (70)	1581 (64)	1054 (74)	
50-149, n (%)	160 (10)	105 (14)	275 (11)	153 (11)	
150-399, n (%)	118 (7)	70 (9)	308 (12)	105 (7)	
> 400, n (%)	130 (8)	51 (7)	327 (13)	116 (8)	
CHD events (all), n (%)	100 (6)	34 (5)	188 (8)	91 (6)	

AFA, African American; CAC, coronary artery calcium; CHD, coronary heart disease; CHN, Chinese American; EUR, European American; HDL, high-density lipoprotein; HIS, Hispanic American; LDL, low-density lipoprotein

*Comparison across race/ethnicity using analysis of variance (Krusal-Wallis) for continuous variables and chi-square test (exact) for categorical variables.

Table S2. Marginal associations of Exam 1 Characteristics (Beta per SD of HGF) with circulating serum HGF levels.

	RACE							
Characteristics	AFA		CHN		EUR		HIS	
	BETA	P-VALUE	BETA	P-VALUE	BETA	P-VALUE	BETA	P-VALUE
Age	0.024	<0.0001	0.027	<0.0001	0.026	<0.0001	0.025	<0.0001
Gender (female)	0.032	0.48	<0.0001	0.72	0.163	<0.0001	0.099	0.07
BMI	0.015	<0.0001	0.045	<0.0001	0.046	<0.0001	0.048	<0.0001
LDL	-0.002	0.002	-0.001	0.43	-0.001	0.10	-0.003	0.0001
HDL	-0.006	<0.0001	-0.006	0.016	-0.006	<0.0001	-0.007	0.0006
Triglycerides	0.001	0.0003	0.001	0.0003	0.001	<0.0001	-0.0001	0.71
Hypertension (no)	-0.326	<0.0001	-0.374	<0.0001	-0.391	<0.0001	-0.393	<0.0001
Diabetes (no)	-0.342	<0.0001	-0.524	<0.0001	-0.698	<0.0001	-0.511	<0.0001
Smoking	-	<0.0001	-	0.010	-	<0.0001	-	0.0002
Never	-0.371	<0.0001	-0.336	0.0010	-0.324	<0.0001	-0.328	<0.0001
Former	-0.242	0.0002	-0.434	0.002	-0.327	<0.0001	-0.208	0.017
Current (ref)	-	-	-	-	-	-	-	-
Alcohol (no)	0.082	0.07	0.076	0.23	0.220	<0.0001	0.136	0.012

AFA, African American; BMI, body mass index; BP, blood pressure; CHN, Chinese American; EUR, European American; HDL, high-density lipoprotein; HIS, Hispanic American; LDL, low-density lipoprotein

Table S3. Distribution of SNP and gene counts by race/ethnicity.

	Single SNPs			Genes
Race	MAF >0.5%	Monomorphic	Total	# Testable
AFA	228547	102943	417752	10765
CHN	154497	230385	418460	3005
EUR	181029	123939	417771	9146
HIS	213057	111045	417770	9085

AFA, African American; CHN, Chinese American; EUR, European American; HIS, Hispanic American; MAF, minor allele frequency; SNP, single nucleotide polymorphism

Table S4. Significant (P<4E-06) and suggestive (P<1E-04) gene-based associations with HGF.

	Gene-based P-value				
Gene	META	AFA	CHN	EUR	HIS
FASN	0.153	1.000	4.34E-07	0.645	0.868
HGFAC	5.09E-07	0.706	0.770	1.12E-05	0.013
A1BG	0.003	6.93E-07	-	0.151	0.183
*NHLRC1**	1.06E-05	1.06E-05	-	-	-
*OR10A7**	0.199	0.676	0.126	1.25E-05	1.000
*ACSM5**	0.019	4.65E-05	-	0.561	0.894
*C11orf30**	0.006	5.19E-05	-	-	0.364
*LRRC27**	0.019	5.30E-05	0.879	0.188	1.000
*YTHDF2**	8.68E-05	0.059	-	4.58E-04	0.003
*HGF**	9.84E-05	0.014	-	-	0.001

*Not statistically significant at α=4E-06

AFA, African American; CHN, Chinese American; EUR, European American; HIS, Hispanic American

Table S5. Characteristics of A1BG variants from gene-level significant test result in African Americans.

rsID	Chr	Position	Ref/Alt	MAC	Impact	SIFT Prediction	PolyPhen Prediction
rs145144275	19	58861808	G/A	8	p.C252R	Deleterious	Possibly Damaging
rs140084941	19	58861838	G/A	8	p.I242V	Tolerated	Benign
rs145532647	19	58862937	A/G	2	p.R122W	Tolerated	Benign
rs115704323	19	58863753	A/G	40	p.A170V	Tolerated	Possibly Damaging
rs144305381	19	58864359	A/G	2	p.R92H	Deleterious	Possibly Damaging
rs151098196	19	58864366	A/G	1	p.R90C	Deleterious	Benign
rs145851378	19	58864476	G/A	1	p.L53P	Deleterious	Probably Damaging
rs7256067	19	58864491	A/G	5	p.T48M	Deleterious	Probably Damaging

MAC, Minor allele count

Table S6. Characteristics of FASN variants from gene-level significant test result in Chinese Americans

rsID	Chr	Position	Ref/Alt	MAC	Impact	SIFT Prediction	PolyPhen Prediction
rs2228306	17	80040034	A/G	15	p. V2005A	tolerated	benign
rs17848945	17	80040513	G/A	16	p. V1937I	tolerated	benign
rs148840593	17	80040530	G/A	3	p. R1931Q	tolerated	benign
rs2228305	17	80042792	G/A	7	p. V1483I	tolerated	benign
rs200840955	17	80043274	G/A	2	p. A1376V	tolerated	benign
rs150915750	17	80043506	G/A	1	p. P1325L	tolerated	possibly_damaging

MAC, Minor allele count

Table S7. Characteristics of variants included in the gene-level meta-analysis significant test result HGFAC.

SNP	Chr	Position	MAC				Ref/Alt	Impact	Sift Prediction	PolyPhen Prediction
			AFA	CHN	EUR	HIS				
rs143571255	4	3444460	0	12	0	0	T/A	p.N40I	deleterious	possibly_damaging
rs148006288	4	3444477	5	0	1	5	G/C	p.E46Q	tolerated	benign
rs144680516	4	3444510	5	0	0	2	G/A	p.T57A	tolerated	benign
rs140416920	4	3445858	4	0	9	16	A/G	p.R190W	deleterious	possibly_damaging
rs151270002	4	3446117	38	0	0	3	T/A	p.E226D	tolerated	probably_damaging
rs199942662	4	3446140	0	1	0	2	A/G	p.R234Q	tolerated	benign
rs201082880	4	3446150	0	0	2	0	C/G	p.C237W	deleterious	probably_damaging
rs140008278	4	3446161	0	0	3	1	A/G	p.R241Q	tolerated	benign
rs142652510	4	3447042	0	0	1	1	A/G	p.A356V	tolerated	benign
rs140988254	4	3447063	0	0	3	1	A/G	p.R363H	tolerated	benign
rs201249501	4	3447821	0	1	2	0	A/G	p.E385D	tolerated	benign
rs143981206	4	3449284	0	0	4	0	A/C	p.T474M	deleterious	probably_damaging
rs139240360	4	3449360	0	0	0	1	G/A	Splice Site	-	-
rs146026447	4	3449667	4	0	4	0	A/G	p.S514L	deleterious	probably_damaging
rs139967384	4	3449863	21	0	1	0	A/G	p.G549S	tolerated	benign
rs114303452	4	3449915	8	0	83	15	G/A	p.K566R	tolerated	benign
rs186999542	4	3449941	0	6	0	0	A/G	p.A575T	tolerated	benign
rs148123448	4	3451120	9	0	0	0	A/G	p.P648S	tolerated	benign
rs16844370	4	3446112	128	0	0	22	A/G	p.V225M	deleterious	probably_damaging
rs16844401	4	3449652	106	124	357	204	A/G	p.R509H	tolerated	benign
rs2498323	4	3451109	319	70	478	230	A/G	p.R644Q	tolerated	benign
rs41264743	4	3446079	11	1	54	25	A/C	p.G214C	deleterious	probably_damaging

AFA, African American; CHN, Chinese American; EUR, European American; HIS, Hispanic American; MAC, Minor allele count

Table S8: Association p-values of serum HGF levels with subclinical and clinical disease.

Outcome	**AFA**	**CHN**	**EUR**	**HIS**
CAC	**P**	**P**	**P**	**P**
Model 1	<0.0001	0.07	<0.0001	0.09
Model 2	0.002	0.96	<0.0001	0.92
Time to CHD	**P**	**P**	**P**	**P**
Model 1	0.003	0.20	<0.0001	0.27
Model 2	0.38	0.44	<0.0001	0.67

AFA, African American; CAC, coronary artery calcium; CHD, coronary heart disease; CHN, Chinese American; EUR, European American; HIS, Hispanic American

Model 1 = age and sex

Model 2 = age, sex, BMI, smoking status, LDL, HDL, triglycerides, hypertension, diabetes

Table S9. Associations of serum HGF-associated variants with subclinical and clinical cardiovascular disease in MESA.

	African American		Chinese Americans		European American		Hispanic American	
rs5745687								
CAC	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*
Model 1	-191.6 (120.9)	0.113	-	-	25.2 (36.3)	0.488	132.4 (66.5)	0.046
Model 2	-182.5 (10.1)	0.129	-	-	15.9 (36.2)	0.661	140.4 (65.6)	0.032
CHD	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Model 1	1.35 (0.53,3.49)	0.531	-	-	0.95 (0.65,1.39)	0.796	1.62 (0.93,2.83)	0.090
Model 2	1.33 (0.50,3.49)	0.568	-	-	0.93 (0.64,1.37)	0.726	1.59 (0.89,2.79)	0.111
rs16844364								
CAC	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*
Model 1	36.6 (40.6)	0.368	-7.1 (24.1)	0.768	-32.7 (23.2)	0.158	-78.4 (31.4)	0.013
Model 2	24.7 (40.7)	0.544	-22.0 (23.6)	0.352	-35.2 (23.2)	0.129	-72.8 (31.0)	0.019
CHD	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Model 1	1.34 (0.93,1.94)	0.121	1.19 (0.74,1.18)	0.464	0.93 (0.74,1.18)	0.563	0.99 (0.73,1.35)	0.968
Model 2	1.29 (0.89,1.87)	0.178	1.15 (0.72,1.84)	0.549	0.93 (0.74,1.18)	0.566	1.01 (0.74,1.37)	0.948
rs4690098								
CAC	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*
Model 1	130.2 (55.6)	0.019	9.3 (24.1)	0.700	31.2 (22.6)	0.167	26.3 (33.0)	0.425
Model 2	143.3 (55.5)	0.010	20.9 (23.5)	0.373	34.3 (22.5)	0.128	31.3 (32.5)	0.335
CHD	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Model 1	1.26 (0.75,2.11)	0.380	0.88 (0.57,1.37)	0.575	1.08 (0.86,1.34)	0.524	0.85 (0.61,1.18)	0.331
Model 2	1.27 (0.75,2.13)	0.374	0.89 (0.56,1.41)	0.610	1.12 (0.90,1.40)	0.313	0.81 (0.58,1.14)	0.227
rs114303452								
CAC	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*
Model 1	-	-	-	-	12.5 (72.6)	0.863	-0.24 (176.6)	0.999
Model 2	-	-	-	-	11.4 (72.4)	0.875	52.4 (171.7)	0.716
CHD	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Model 1	-	-	-	-	1.18 (0.60,2.29)	0.635	-	-
Model 2	-	-	-	-	1.12 (0.59,2.15)	0.729	-	-
rs3748034								
CAC	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*	*Beta (S.E.)*	*p value*
Model 1	82.1 (63.6)	0.197	-21.1 (25.9)	0.414	13.8 (27.2)	0.612	-62.2 (41.9)	0.138
Model 2	71.1 (63.6)	0.264	-24.5 (25.4)	0.334	14.3 (27.2)	0.598	-56.7 (41.2)	0.169
CHD	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Model 1	1.23 (0.68,2.23)	0.494	1.08 (0.68,1.74)	0.740	1.16 (0.90,1.51)	0.253	0.77 (0.49,1.21)	0.252
Model 2	1.22 (0.68,2.19)	0.515	1.08 (0.67,1.75)	0.742	1.16 (0.90,1.50)	0.259	0.79 (0.51,1.23)	0.294

CI, confidence interval; CAC, coronary artery calcium; CHD, coronary heart disease; HR, hazard ratio; SE, standard error.

Model 1 = age and sex

Model 2 = age, sex, BMI, smoking status, LDL, HDL, triglycerides, hypertension, diabetes

An additive model was fit modeling 0, 1, or 2 copies of the minor allele; associations with nominal $P<0.05$ are highlighted in gray.