

Supporting Information

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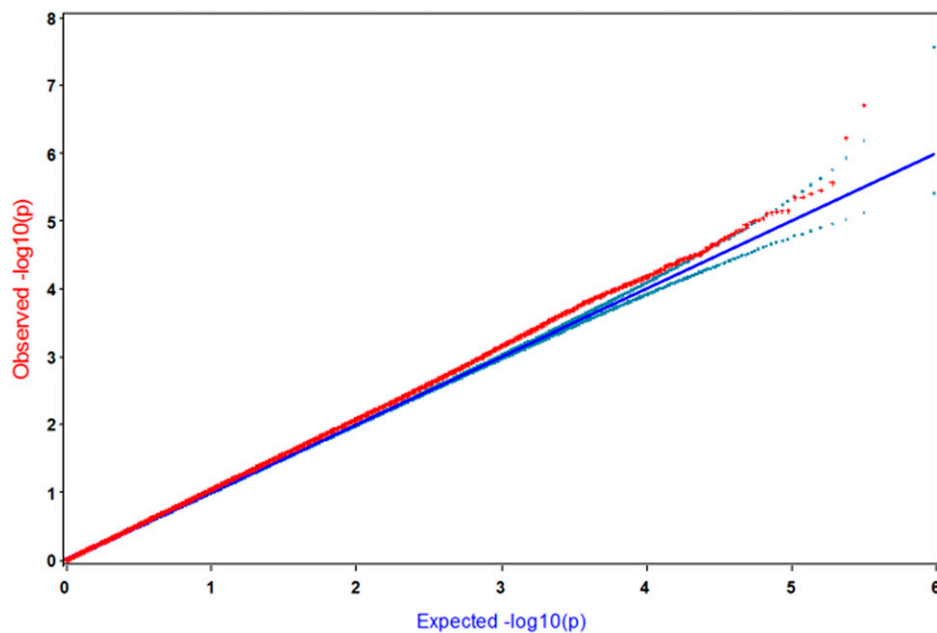


Fig. S1. Q-Q plot of the observed (in red) and expected (in blue) P values obtained from multivariate logistic models testing for association with alcohol dependence.

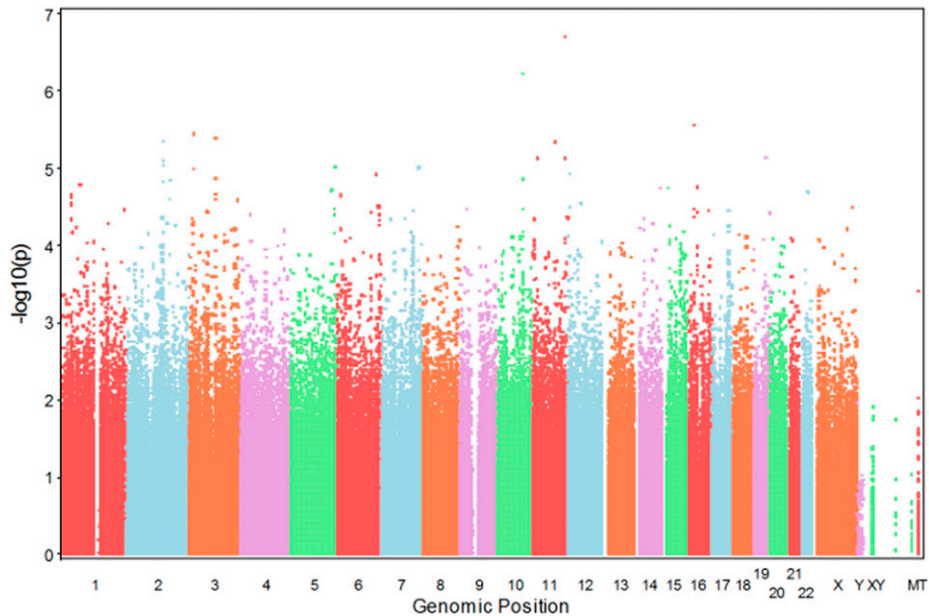


Fig. S2. Manhattan plot of P values from multivariate logistic regression models testing for association with alcohol dependence.

Table S1. Characteristics of alcohol-dependent cases and nondependent controls by source study

Characteristic	COGA		COGEND		FSCD	
	Cases <i>n</i> = 899	Controls <i>n</i> = 509	Cases <i>n</i> = 450	Controls <i>n</i> = 927	Cases <i>n</i> = 548	Controls <i>n</i> = 496
Sex, <i>n</i> (%)						
Males	610 (67.9)	148 (29.1)*	233 (51.8)	247 (26.6)*	312 (56.9)	211 (42.5)*
Females	289 (32.1)	361 (70.9)	217 (48.2)	680 (73.4)	236 (43.1)	285 (57.5)
Age, years						
Mean ± SD.	41.5 ± 10.2	45.3 ± 10.2	37.1 ± 5.9	37.1 ± 6.8	36.5 ± 9.0	37.1 ± 8.9
Range	18.0–77.0	24.0–65.0	25.0–61.0	25.0–65.0	18.0–60.0	18.0–60.0
Self-reported race, <i>n</i> (%)						
European-American	612 (68.1)	412 (80.9)*	343 (76.2)	774 (83.5)	280 (51.1)	247 (49.8)
African-American	287 (31.9)	97 (19.1)	107 (23.8)	153 (16.2)	268 (48.9)	249 (50.2)
Self-reported ethnicity, <i>n</i> (%)						
Hispanic	65 (7.2)	38 (7.5)	11 (2.4)	18 (1.9)	11 (2.4)	18 (1.9)
Alcohol dependence						
Diagnosis, <i>n</i> (%)	899 (100.0)	0 (0.0)*	450 (100.0)	0 (0.0)*	548 (100.0)	0 (0.0)*
Number of symptoms, $\bar{x} \pm s$	5.5 ± 1.3	0.1 ± 0.3*	4.4 ± 1.4	0.1 ± 0.9*	5.3 ± 1.5	0.6 ± 0.8*
Comorbid diagnoses, <i>n</i> (%)						
Marijuana dependence	297 (33.0)	0 (0.0)*	104 (23.1)	0 (0.0)*	262 (47.8)	0 (0.0)*
Cocaine dependence	396 (44.0)	0 (0.0)*	80 (17.8)	0 (0.0)*	440 (80.3)	0 (0.0)*
Opioid dependence	119 (13.2)	0 (0.0)*	27 (6.0)	0 (0.0)*	117 (21.4)	0 (0.0)*
Other dependence	230 (25.6)	0 (0.0)*	42 (9.3)	0 (0.0)*	197 (35.9)	0 (0.0)*
Smoked 100+ cigarettes	792 (88.1)	172 (33.8)*	443 (98.4)	883 (95.3)	472 (86.1)	84 (16.9)*
Nicotine dependence**	543 (60.4)	66 (13.0)*	261 (58.0)	14 (1.5)*	355 (64.8)	15 (3.0)*

COGA, Collaborative Study on the Genetics of Alcoholism; COGEND, Collaborative Genetic Study of Nicotine Dependence; FSCD, Family Study of Cocaine Dependence.

*Difference between cases and controls, $P < 0.0001$.

**Nicotine dependence defined by a score of 4 or greater on the Fagerström Test for Nicotine Dependence.

Table S3. Replication studies: Adjusted odds ratios and confidence limits for the top 15 SNPs identified in the SAGE sample for the COGA family-based genetic sample and the German case-control sample

SNP	SAGE risk allele	COGA <i>P</i> *	Frequency of risk allele		OR (95% CI)	<i>P</i>
			Cases	Controls		
rs10893366	T	0.44	0.15	0.17	0.84 (0.69–1.04)	0.103
rs2039617	T	0.17				
rs9302534	C	0.36	0.37	0.36	1.03 (0.88–1.20)	0.689
rs1318937	G	0.75	0.12	0.12	0.97 (0.77–1.22)	0.821
rs2700648	A	0.57				
rs10803574	A	0.61	0.42	0.43	0.96 (0.82–1.11)	0.554
rs6483362	A	0.15				
rs2722650	A	0.35				
rs10893365	C	0.51				
rs1386449	T	0.09				
rs750338	C	0.50	0.21	0.23	0.87 (0.73–1.05)	0.143
rs1505846	A	0.62	0.42	0.43	0.95 (0.82–1.10)	0.501
rs9636231	A	0.33	0.29	0.32	0.87 (0.74–1.03)	0.106
rs1363605	A	0.91				
rs10224675	G	0.08				

SAGE, Study of Addiction: Genetics and Environment.

*COGA tested using Family-Based Association Test (FBAT); 258 families, 2249 individuals.

Table S5. SAGE association results for all GABRA2 SNPs

SNP	Chr	Position	COGA <i>P</i> *	Risk allele	SAGE			
					Frequency of risk allele		Adjusted OR (95% CI)	<i>P</i>
					Cases	Controls		
rs16859193	4	45,890,861		G	0.128	0.099	0.87 (0.72–1.04)	1.17E-01
rs1440133	4	45,896,677		A	0.367	0.361	1.13 (1.02–1.25)	1.95E-02
rs495752	4	45,900,293		A	0.360	0.355	1.13 (1.02–1.26)	1.85E-02
rs522636	4	45,922,604		T	0.463	0.511	0.91 (0.82–1.01)	6.95E-02
rs534787	4	45,927,453		T	0.462	0.510	0.91 (0.82–1.01)	8.34E-02
rs16859210	4	45,931,211		T	0.063	0.047	0.90 (0.71–1.13)	3.58E-01
rs478179	4	45,933,494		T	0.237	0.249	0.97 (0.86–1.09)	6.18E-01
rs511310	4	45,934,761		A	0.082	0.083	1.11 (0.93–1.33)	2.51E-01
rs16859227	4	45,945,362		T	0.220	0.206	1.16 (1.03–1.31)	1.43E-02
rs572227	4	45,946,150	3.80E-02	A	0.376	0.366	1.15 (1.04–1.27)	8.89E-03
rs534459	4	45,951,562		C	0.473	0.521	0.90 (0.82–1.00)	4.84E-02
rs505474	4	45,955,344		A	0.524	0.476	1.10 (1.00–1.22)	5.73E-02
rs554112	4	45,957,533		T	0.383	0.368	1.16 (1.05–1.29)	4.46E-02
rs548583	4	45,958,101	1.20E-02	T	0.404	0.385	1.14 (1.03–1.26)	1.05E-02
rs526805	4	45,958,148		G	0.421	0.396	1.15 (1.04–1.27)	5.51E-03
rs2119183	4	45,967,563		A	0.080	0.087	1.00 (0.84–1.20)	9.82E-01
rs502038	4	45,975,075		G	0.401	0.385	1.13 (1.02–1.25)	1.61E-02
rs279873	4	45,999,124		T	0.472	0.520	0.90 (0.81–1.00)	4.19E-02
rs279864	4	46,005,792		C	0.473	0.520	0.90 (0.82–1.00)	5.18E-02
rs1808851	4	46,006,204		G	0.396	0.380	1.15 (1.04–1.28)	5.29E-03
rs279858	4	46,009,350	8.70E-03	G	0.375	0.366	1.16 (1.05–1.28)	5.04E-03
rs16859306	4	46,010,737		C	0.101	0.077	0.88 (0.72–1.07)	1.97E-01
rs279856	4	46,012,680		T	0.497	0.457	1.11 (1.00–1.23)	4.28E-02
rs3775282	4	46,016,620		C	0.139	0.142	1.06 (0.92–1.22)	4.09E-01
rs279843	4	46,019,961	4.90E-02	T	0.444	0.421	1.11 (1.00–1.22)	4.24E-02
rs279841	4	46,035,520	3.80E-02	A	0.368	0.364	1.13 (1.02–1.25)	2.29E-02
rs189957	4	46,041,436		G	0.469	0.448	1.09 (0.98–1.20)	1.06E-01
rs16859325	4	46,047,625		A	0.026	0.017	1.04 (0.74–1.47)	8.22E-01
rs10805145	4	46,053,088		C	0.459	0.439	1.09 (0.99–1.20)	8.53E-02
rs1442060	4	46,060,824		G	0.446	0.487	0.88 (0.80–0.98)	1.47E-02
rs3849591	4	46,063,398		T	0.149	0.149	1.12 (0.98–1.29)	9.63E-02
rs9291283	4	46,066,590		A	0.282	0.252	1.12 (1.00–1.25)	4.44E-02
rs13152740	4	46,075,978		A	0.269	0.243	1.12 (1.00–1.26)	4.88E-02
rs10013922	4	46,084,118		G	0.272	0.248	1.10 (0.98–1.23)	9.26E-02
rs3756007	4	46,085,821		C	0.039	0.039	1.15 (0.89–1.48)	2.84E-01
rs894269	4	46,088,369		T	0.164	0.175	1.01 (0.88–1.15)	8.79E-01
rs1025852	4	46,095,088		A	0.366	0.389	0.88 (0.79–0.97)	1.35E-02
rs6847731	4	46,096,909		G	0.415	0.437	0.91 (0.83–1.01)	7.62E-02
rs1545234	4	46,099,170		G	0.301	0.300	1.01 (0.91–1.13)	8.55E-01

*COGA family-based association from ref. 1.

- Edenberg HJ, et al. (2004) Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. *Am J Hum Genet* 74:705–714.

Table S6. SAGE association results by self-reported race for all GABRA2 SNPs

African-American (n = 1161)

European-American (n = 2668)

SNP	Position	Risk allele	Frequency of risk allele			European-American (n = 2668)			African-American (n = 1161)					
			Cases		Controls	OR (95% CI)		P	Cases		Controls	OR (95% CI)		P
			Cases	Controls	OR (95% CI)	P	Cases	Controls	OR (95% CI)	P				
rs16859193	45,890,861	G	0.002	0.003	0.36 (0.10–1.32)	1.22E-01	0.362	0.376	0.90 (0.75–1.07)	2.34E-01				
rs1440133	45,896,677	A	0.422	0.397	1.15 (1.02–1.29)	2.65E-02	0.265	0.255	1.10 (0.90–1.34)	3.61E-01				
rs522636	45,922,604	T	0.575	0.599	0.88 (0.78–0.99)	3.56E-02	0.252	0.258	0.99 (0.81–1.21)	8.90E-01				
rs534787	45,927,453	T	0.575	0.598	0.88 (0.78–0.99)	3.40E-02	0.251	0.254	1.00 (0.82–1.23)	9.67E-01				
rs16859210	45,931,211	T	0.002	0.002	0.65 (0.14–2.93)	5.74E-01	0.178	0.178	0.92 (0.73–1.16)	4.92E-01				
rs478179	45,933,494	T	0.272	0.277	0.94 (0.82–1.08)	3.82E-01	0.170	0.169	1.07 (0.85–1.36)	5.53E-01				
rs511310	45,934,761	A	0.113	0.103	1.13 (0.93–1.37)	2.15E-01	0.023	0.024	1.03 (0.58–1.83)	9.17E-01				
rs16859227	45,945,362	T	0.253	0.230	1.15 (1.00–1.32)	5.01E-02	0.155	0.131	1.20 (0.93–1.55)	1.64E-01				
rs572227	45,946,150	A	0.424	0.398	1.15 (1.02–1.30)	2.04E-02	0.288	0.271	1.13 (0.93–1.38)	2.22E-01				
rs534459	45,951,562	C	0.566	0.592	0.87 (0.77–0.98)	2.23E-02	0.299	0.317	0.97 (0.80–1.18)	7.67E-01				
rs505474	45,955,344	A	0.429	0.403	1.14 (1.01–1.29)	2.91E-02	0.699	0.682	1.03 (0.85–1.25)	7.50E-01				
rs554112	45,957,533	T	0.430	0.400	1.17 (1.03–1.32)	1.18E-02	0.291	0.273	1.15 (0.94–1.39)	1.72E-01				
rs48583	45,958,101	T	0.430	0.401	1.16 (1.03–1.31)	1.54E-02	0.356	0.341	1.11 (0.92–1.33)	2.93E-01				
rs526805	45,958,148	G	0.430	0.401	1.16 (1.03–1.31)	1.54E-02	0.404	0.380	1.14 (0.95–1.37)	1.60E-01				
rs2119183	45,967,563	A	0.111	0.111	0.97 (0.80–1.17)	7.50E-01	0.022	0.018	1.31 (0.69–2.46)	4.08E-01				
rs502038	45,975,075	G	0.427	0.400	1.15 (1.02–1.30)	1.93E-02	0.349	0.338	1.09 (0.90–1.32)	3.74E-01				
rs279873	45,999,124	T	0.562	0.590	0.86 (0.76–0.97)	1.49E-02	0.303	0.318	0.98 (0.81–1.19)	8.50E-01				
rs279864	46,005,792	C	0.562	0.590	0.86 (0.77–0.97)	1.67E-02	0.305	0.318	0.99 (0.82–1.20)	9.35E-01				
rs1808851	46,006,204	G	0.435	0.407	1.17 (1.04–1.32)	1.05E-02	0.323	0.300	1.13 (0.93–1.36)	2.10E-01				
rs279858	46,009,350	G	0.434	0.406	1.17 (1.03–1.31)	1.20E-02	0.265	0.246	1.15 (0.94–1.41)	1.73E-01				
rs16859306	46,010,737	C	0.002	0.003	0.37 (0.10–1.40)	1.43E-01	0.286	0.290	0.91 (0.74–1.11)	3.37E-01				
rs279856	46,012,680	T	0.434	0.406	1.16 (1.03–1.31)	1.50E-02	0.611	0.600	1.01 (0.84–1.21)	9.48E-01				
rs3775282	46,016,620	C	0.174	0.166	1.07 (0.91–1.25)	4.09E-01	0.073	0.071	1.02 (0.72–1.45)	9.03E-01				
rs279843	46,019,961	T	0.437	0.411	1.15 (1.02–1.30)	2.23E-02	0.459	0.448	1.03 (0.86–1.23)	7.47E-01				
rs279841	46,035,520	A	0.432	0.408	1.14 (1.02–1.29)	2.70E-02	0.248	0.237	1.10 (0.89–1.35)	3.74E-01				
rs189957	46,041,436	G	0.457	0.430	1.15 (1.02–1.29)	2.40E-02	0.490	0.497	0.98 (0.82–1.17)	8.12E-01				
rs16859325	46,047,625	A	0.000	0.000	1.14 (1.01–1.28)	9.99E-01	0.076	0.064	1.08 (0.77–1.53)	6.47E-01				
rs10805145	46,053,088	C	0.456	0.431	0.87 (0.77–0.98)	3.15E-02	0.464	0.462	1.01 (0.85–1.21)	8.96E-01				
rs1442060	46,060,824	G	0.491	0.521	0.87 (0.77–0.98)	2.51E-02	0.361	0.391	0.91 (0.75–1.09)	3.01E-01				
rs3849591	46,063,398	T	0.182	0.171	1.15 (0.98–1.34)	7.74E-02	0.088	0.086	1.02 (0.74–1.40)	9.03E-01				
rs9291283	46,066,590	A	0.266	0.241	1.13 (0.98–1.29)	9.08E-02	0.313	0.281	1.13 (0.93–1.38)	2.15E-01				
rs13152740	46,075,978	A	0.265	0.240	1.12 (0.98–1.29)	9.96E-02	0.275	0.249	1.13 (0.92–1.38)	2.45E-01				
rs10013922	46,084,118	G	0.266	0.242	1.10 (0.96–1.27)	1.60E-01	0.281	0.255	1.11 (0.91–1.35)	3.24E-01				
rs3756007	46,085,821	C	0.053	0.049	1.12 (0.86–1.47)	4.06E-01	0.014	0.011	1.36 (0.60–3.08)	4.55E-01				
rs894269	46,088,369	T	0.209	0.211	0.97 (0.84–1.13)	7.21E-01	0.078	0.069	1.24 (0.88–1.73)	2.18E-01				
rs1025852	46,095,088	A	0.354	0.377	0.88 (0.77–1.00)	4.78E-02	0.387	0.425	0.88 (0.73–1.05)	1.48E-01				
rs6847731	46,096,909	G	0.423	0.439	0.92 (0.81–1.04)	1.74E-01	0.397	0.431	0.90 (0.75–1.08)	2.42E-01				
rs1545234	46,099,170	G	0.306	0.307	1.01 (0.89–1.15)	8.61E-01	0.293	0.283	1.01 (0.83–1.22)	9.57E-01				

Table S7. Adjusted odds ratios and confidence intervals for SNPs with $P \leq 1 \times 10^{-6}$ identified in SAGE European-Americans and corresponding results in SAGE African-Americans

SNP	Chr	Position	Gene	Risk Allele	European-Americans (n = 2668)				African-Americans (n = 1161)					
					Frequency of risk allele		AdjustedOR (95% CI)	P	FDR	Frequency of risk allele		Adjusted OR (95% CI)	P	FDR
					Cases	Controls				Cases	Controls			
rs10913569	1	176,784,631	<i>Ctorf220</i>	A	0.11	0.15	0.64 (0.54–0.76)	9.22E-07	0.251	0.61	0.61	0.95 (0.79–1.13)	5.45E-01	0.999
rs433303	3	11,219,906	<i>HRH1</i>	T	0.43	0.37	1.34 (1.19–1.51)	1.72E-06	0.251	0.09	0.10	0.86 (0.64–1.16)	3.29E-01	0.996
rs6701037	1	173,386,702		C	0.47	0.40	1.34 (1.19–1.51)	1.75E-06	0.251	0.33	0.34	0.91 (0.76–1.10)	3.40E-01	0.999
rs12776254	10	2,144,862		G	0.18	0.14	1.48 (1.26–1.74)	1.82E-06	0.251	0.08	0.10	0.76 (0.56–1.03)	7.94E-02	0.994
rs1057302	1	173,393,046		C	0.46	0.40	1.34 (1.19–1.51)	1.94E-06	0.251	0.27	0.30	0.89 (0.73–1.08)	2.27E-01	0.995
rs1057239	1	173,396,827	<i>LOC100129443</i>	T	0.46	0.40	1.34 (1.19–1.51)	2.01E-06	0.251	0.38	0.40	0.91 (0.76–1.09)	3.01E-01	0.995
rs7445832	5	62,622,057		A	0.28	0.21	1.40 (1.22–1.61)	2.26E-06	0.251	0.35	0.40	0.91 (0.76–1.10)	3.39E-01	0.996
rs6425323	1	173,391,659		T	0.46	0.40	1.34 (1.19–1.51)	2.27E-06	0.251	0.33	0.35	0.93 (0.77–1.11)	4.06E-01	0.996
rs750338	11	124,677,803	<i>PKNOX2</i>	C	0.26	0.20	1.40 (1.22–1.61)	2.39E-06	0.251	0.47	0.45	1.14 (0.96–1.36)	1.39E-01	0.994
rs1894709	1	173,398,994	<i>LOC100129443</i>	A	0.46	0.40	1.33 (1.18–1.50)	2.78E-06	0.262	0.38	0.41	0.90 (0.75–1.07)	2.25E-01	0.999
rs9540953	13	66,421,259	<i>PCDH9</i>	C	0.19	0.15	1.47 (1.25–1.72)	3.42E-06	0.293	0.16	0.16	1.01 (0.79–1.29)	9.62E-01	0.999
rs4233175	1	176,784,214	<i>Ctorf220</i>	A	0.11	0.14	0.65 (0.55–0.78)	3.78E-06	0.297	0.50	0.50	1.01 (0.85–1.20)	9.06E-01	0.999
rs2011946	2	136,534,066		G	0.32	0.37	0.75 (0.66–0.85)	4.15E-06	0.301	0.79	0.78	1.09 (0.88–1.36)	4.19E-01	0.996
rs17791001	13	66,419,015	<i>PCDH9</i>	C	0.19	0.15	1.45 (1.24–1.71)	5.40E-06	0.358	0.16	0.16	1.03 (0.81–1.32)	8.12E-01	0.999
rs4907956	1	102,085,291	<i>OLFM3</i>	T	0.40	0.34	1.33 (1.18–1.51)	5.83E-06	0.358	0.07	0.09	0.71 (0.52–0.98)	3.62E-02	0.994
rs2842576	1	52,096,816	<i>NRD1</i>	C	0.07	0.09	0.59 (0.47–0.74)	6.07E-06	0.358	0.09	0.10	0.92 (0.67–1.25)	5.86E-01	0.999
rs17427389	6	151,204,808	<i>PLEKHG1</i>	A	0.20	0.15	1.44 (1.23–1.69)	6.45E-06	0.358	0.06	0.05	1.07 (0.73–1.58)	7.15E-01	0.999
rs11870068	17	63,374,977	<i>BTF</i>	C	0.24	0.19	1.39 (1.20–1.61)	7.67E-06	0.383	0.16	0.15	1.08 (0.84–1.37)	5.50E-01	0.999
rs6585783	10	85,779,290		T	0.62	0.55	1.32 (1.17–1.49)	8.02E-06	0.383	0.13	0.15	0.82 (0.64–1.06)	1.30E-01	0.994
rs12284594	11	124,685,063	<i>PKNOX2</i>	G	0.19	0.15	1.44 (1.22–1.68)	8.12E-06	0.383	0.33	0.33	1.04 (0.86–1.25)	6.79E-01	0.999

Table S8. Adjusted odds ratios and confidence intervals for SNPs with $P \leq 1 \times 10^{-6}$ identified in SAGE African Americans and corresponding results in SAGE European Americans

SNP	Chr	Position	Risk Allele	African-Americans (n = 1161)				European-Americans (n = 2668)					
				Frequency of risk allele		Adjusted OR (95% CI)	P	FDR	Frequency of risk allele		Adjusted OR (95% CI)	P	FDR
				Cases	Controls				Cases	Controls			
rs7777391	7	117,409,113	A	0.42	0.32	1.59 (1.31–1.92)	2.70E-06	0.994	0.38	0.38	1.00 (0.88–1.13)	9.85E-01	0.999
rs1530485	13	63,130,342	A	0.56	0.48	1.50 (1.27–1.79)	3.52E-06	0.994	0.03	0.03	0.82 (0.59–1.12)	2.12E-01	0.966
rs4610908	X	35,094,456	A	0.33	0.23	1.69 (1.35–2.12)	5.49E-06	0.994	0.25	0.25	1.00 (0.86–1.17)	9.92E-01	0.999
rs1386449	11	19,444,659	T	0.14	0.07	2.01 (1.49–2.72)	5.68E-06	0.994	0.00	0.00	0.00 (0.00–0.00)	9.99E-01	0.999
rs699771	1	119,673,500	A	0.17	0.11	1.84 (1.41–2.40)	8.87E-06	0.994	0.01	0.01	0.81 (0.43–1.54)	5.26E-01	0.999
rs2810864	13	63,140,115	A	0.55	0.47	1.48 (1.25–1.76)	9.00E-06	0.994	0.03	0.03	0.78 (0.54–1.11)	1.69E-01	0.958
rs11727470	4	30,153,112	A	0.50	0.58	0.67 (0.56–0.80)	9.68E-06	0.994	0.27	0.29	0.97 (0.86–1.11)	6.98E-01	0.999