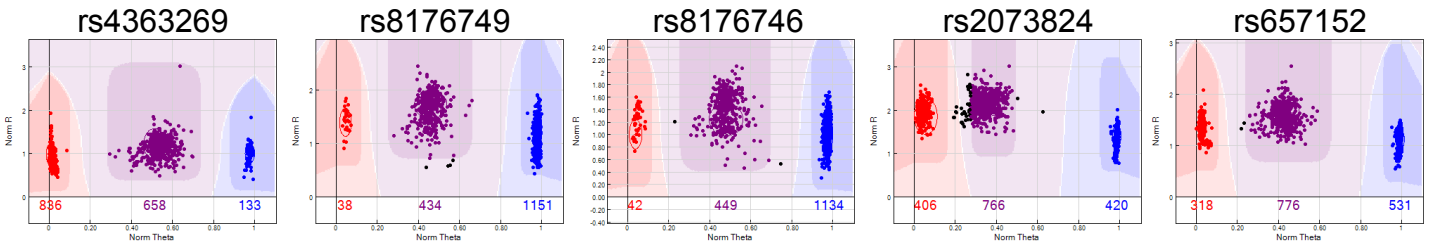


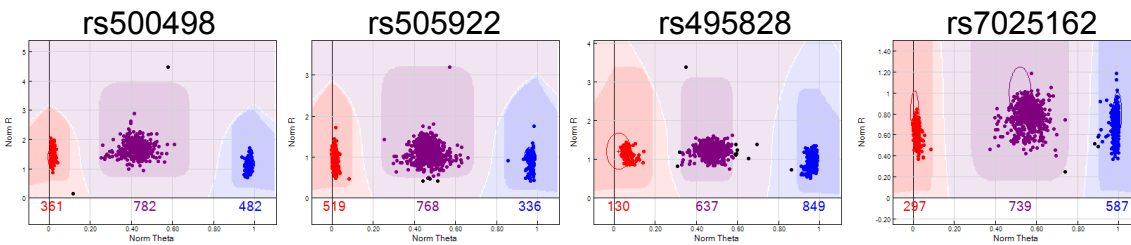
Figure S1

ABO in 9q32

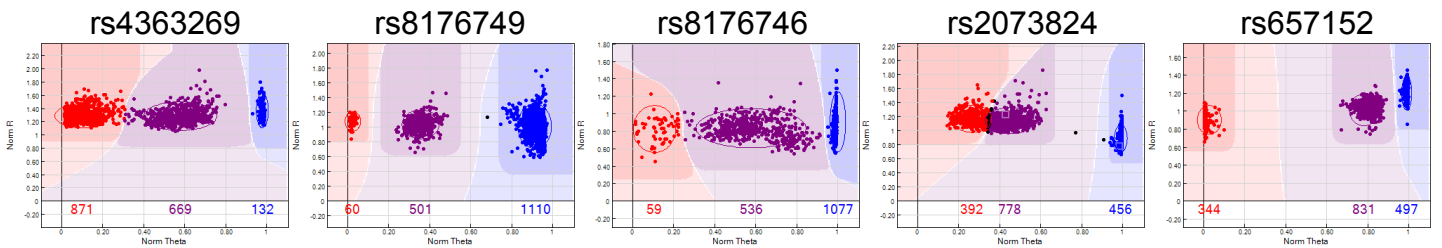
Infinium assay



Infinium assay



Golden Gate assay



Golden Gate assay

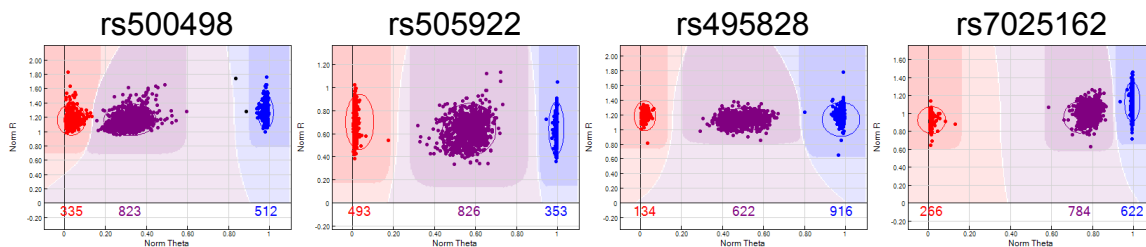
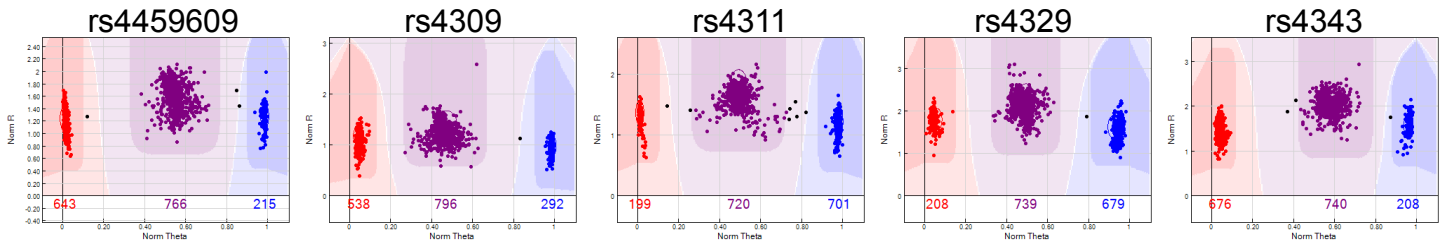


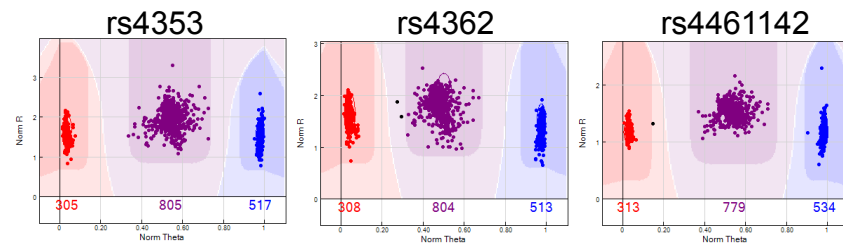
Figure S2

ACE1 in 17q23.2

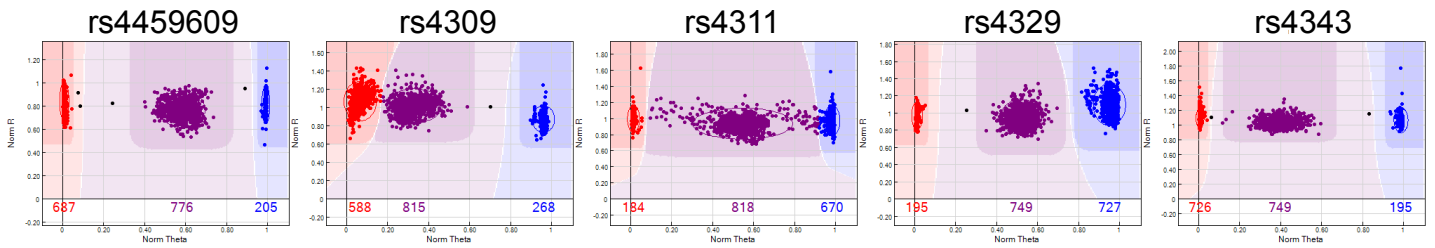
Infinium assay



Infinium assay



Golden Gate assay



Golden Gate assay

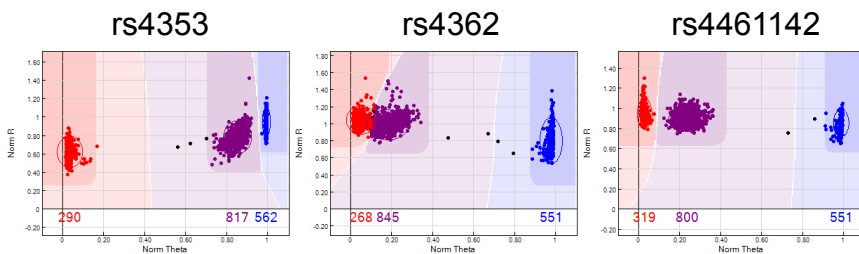


Figure S3

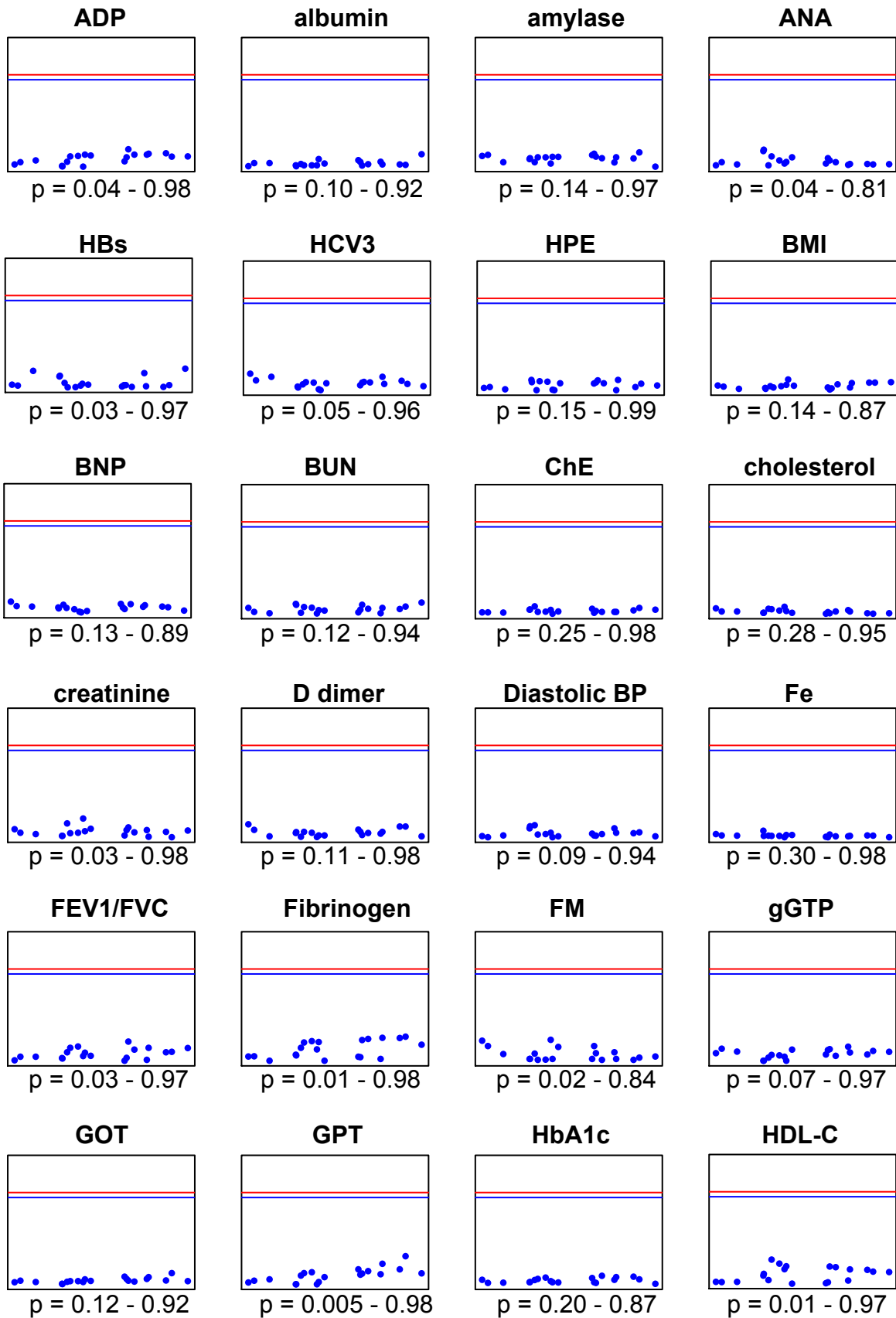


Figure S3 (continued)

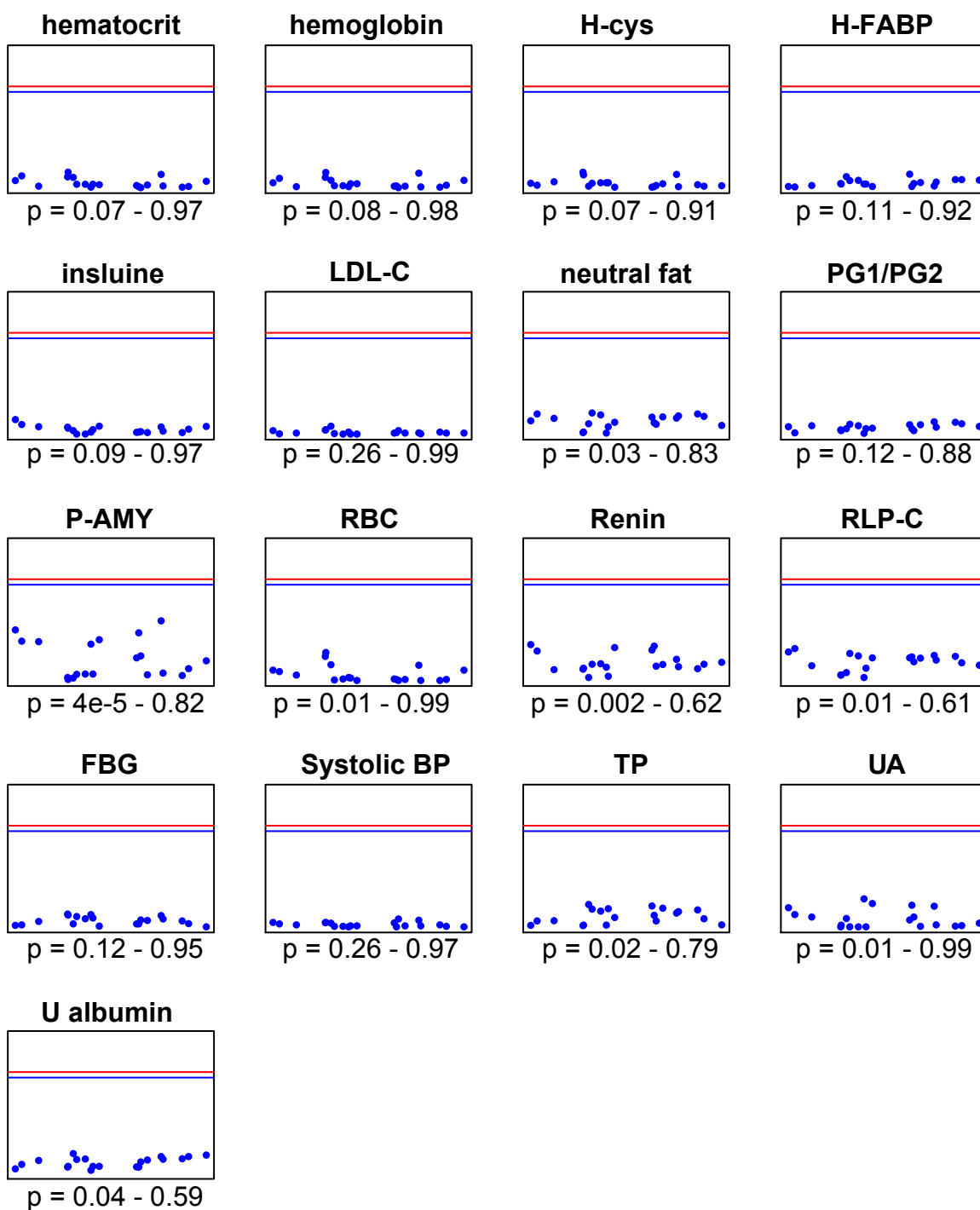
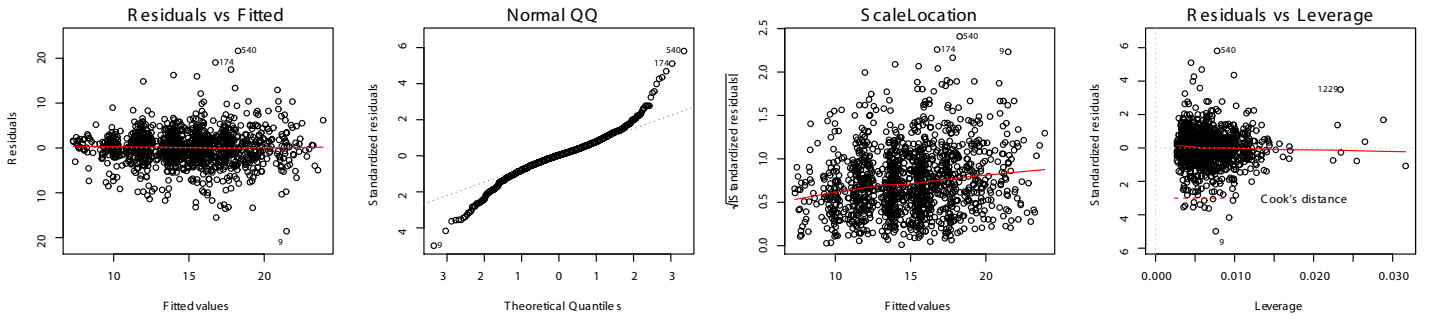
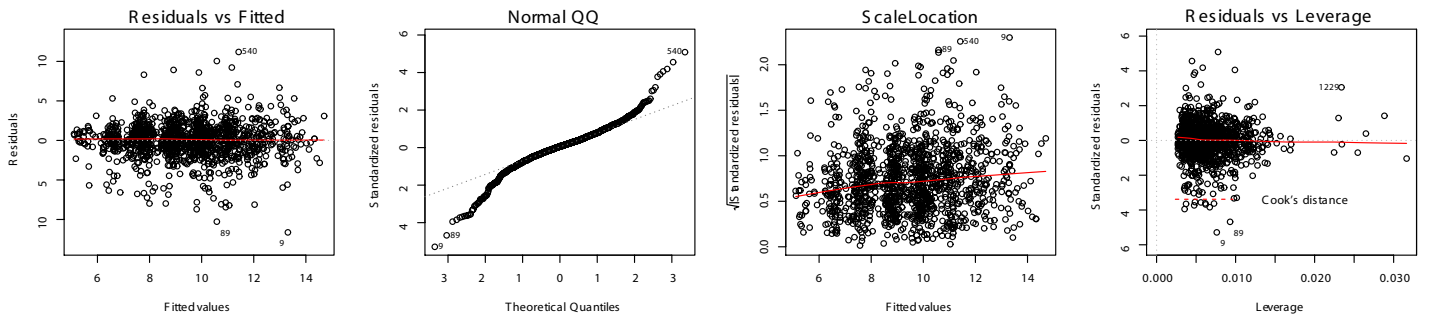


Figure S4

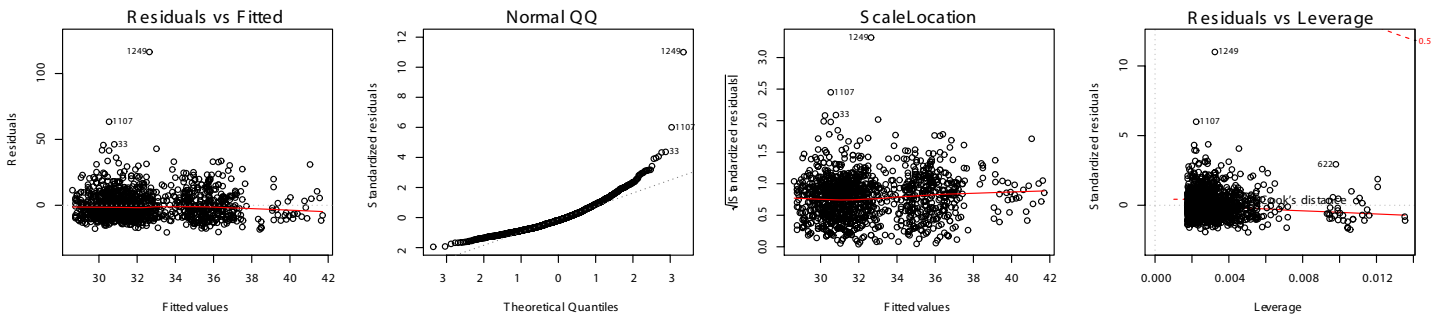
Untransformed ACE



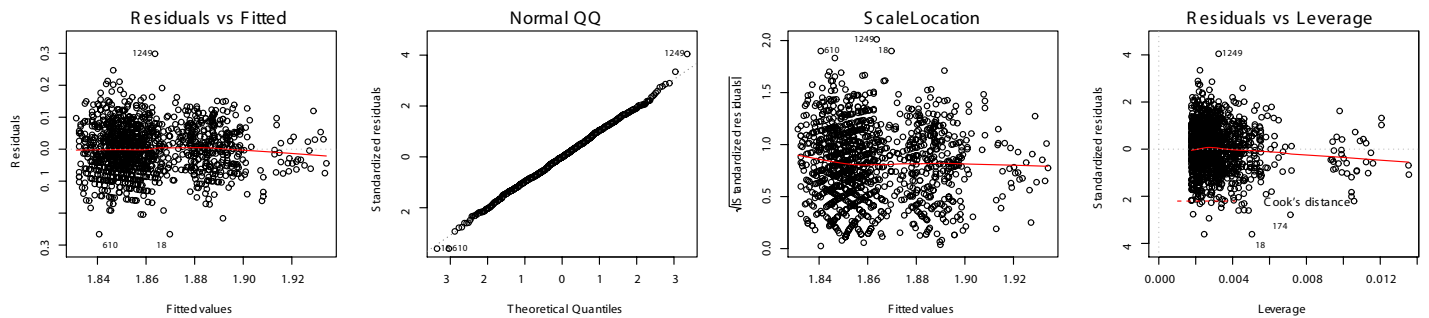
Box-Cox transformed ACE



Untransformed P-LIP



Box-Cox transformed P-LIP



Methods S1

Imputation and test: We first carried out pre-phasing [1] using SHAPEIT [2] based on 1000 Genome Project for chromosome 9, then applied IMPUTE2 [3] to ABO locus to complete imputation for ABO locus. Subsequently we used SNPTEST [4] to examine quantitative traits association with loci after imputation, in which adjustment by age and sex was incorporated. The above procedures were conducted separately for the first and second stage datasets.

[1] Howie B, Fuchsberger C, Stephens M, Marchini J & Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet* 44(8): 955-959 (2012).

[2] Delaneau O, Marchini J & Zagury JF A linear complexity phasing method for thousands of genomes. *Nat. Methods* 9, 179-181 (2011).

[3] Howie BN, Donnelly P & Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* 5(6): e1000529 (2009).

[4] Marchini J, Howie B, Myers S, McVean G & Donnelly P. A new multipoint method for genome-wide association studies via imputation of genotypes. *Nat*

Genet 39: 906-913 (2007).

Regression diagnosis: We carried out regression diagnosis for each marker being significant in GWAS on both ACE and P-LIP for 1st and 2nd stage samples, utilizing four diagnosis plots implemented in R (fitted values vs residuals, normal QQ plot for standardized residuals, fitted values vs $\sqrt{\text{standardized residuals}}$, and leverage vs standardized residuals). We performed the diagnosis plots both for untransformed and for optimally Box-Cox transformed traits ($\lambda = 0.8$ for ACE and $\lambda = -0.4$ for P-LIP).

Table S3. Associations of ABO gene in 9q32 with P-LIP or ACE levels after adjustment by smoking or Box-Cox transformation of trait values

SNPs (position)	minor stage*	minor allele	MAF	P-LIP						ACE					
				adjusted by alcohol intake			Box-Cox transformation***			adjusted by smoking			Box-Cox transformation***		
				beta**	SE	p value	beta**	SE	p value	beta**	SE	p value	beta**	SE	p value
rs4363269 (136123840)	1st	G	0.287	0.0849	0.500	> 1e-7	0.00272	0.003	> 1e-7	-2.01	0.218	9.85e-20	-1.12	0.125	1.20e-18
	2nd	G	0.269	-0.220	0.511	> 1e-7	0.000446	0.003	> 1e-7	-1.99	0.192	1.91e-24	-1.14	0.106	3.56e-26
rs8176749 (136131188)	1st	A	0.161	4.18	0.601	5.55e-12	0.0336	0.004	1.85e-16	2.57	0.266	2.67e-21	1.46	0.153	5.77e-21
	2nd	A	0.188	5.12	0.576	1.61e-18	0.0396	0.004	6.45e-27	2.13	0.219	7.15e-22	1.28	0.123	1.03e-24
rs8176746 (136131322)	1st	A	0.167	4.16	0.593	3.75e-12	0.0476	0.004	4.35e-17	2.58	0.261	3.22e-22	1.47	0.15	7.39e-22
	2nd	A	0.198	5.42	0.562	2.04e-21	0.0580	0.004	3.10e-30	2.11	0.214	2.74e-22	1.26	0.12	8.67e-25
rs2073824 (136132633)	1st	G	0.496	1.29	0.447	> 1e-7	0.00990	0.004	> 1e-7	1.17	0.199	6.25e-9	0.660	0.114	8.21e-9
	2nd	A	0.475	-1.82	0.462	> 1e-7	-0.0127	0.003	> 1e-7	-1.17	0.176	4.00e-11	-0.622	0.099	3.68e-10
rs657152 (136139265)	1st	A	0.440	2.75	0.440	5.63e-10	0.0225	0.003	4.97e-14	-0.593	0.201	> 1e-7	-0.324	0.115	> 1e-7
	2nd	A	0.454	3.38	0.455	1.81e-13	0.0276	0.003	2.47e-21	-0.685	0.178	> 1e-7	-0.417	0.099	> 1e-7
rs500498 (136148647)	1st	A	0.455	-2.71	0.438	8.70e-10	-0.0215	0.003	3.56e-13	0.371	0.2	> 1e-7	0.228	0.114	> 1e-7
	2nd	A	0.445	-3.01	0.456	5.77e-11	-0.0247	0.003	2.28e-17	0.428	0.179	> 1e-7	0.260	0.099	> 1e-7
rs505922 (136149229)	1st	G	0.450	2.62	0.433	1.92e-9	0.0220	0.003	8.64e-14	-0.503	0.199	> 1e-7	-0.274	0.114	> 1e-7
	2nd	G	0.458	3.57	0.452	4.97e-15	0.0294	0.003	3.02e-24	-0.630	0.178	> 1e-7	-0.389	0.099	> 1e-7
rs495828 (136154867)	1st	A	0.281	0.536	0.499	> 1e-7	0.00473	0.003	> 1e-7	-2.34	0.215	2.14e-26	-1.31	0.123	2.30e-25
	2nd	A	0.264	-0.0315	0.509	> 1e-7	0.00214	0.003	> 1e-7	-2.37	0.188	9.84e-35	-1.39	0.104	1.80e-38
rs7025162 (136166346)	1st	A	0.415	-0.834	0.445	> 1e-7	-0.00565	0.003	> 1e-7	-1.50	0.197	5.83e-14	-0.810	0.113	1.11e-12
	2nd	A	0.398	-0.667	0.467	> 1e-7	-0.00632	0.003	> 1e-7	-1.27	0.178	1.52e-12	-0.738	0.099	1.29e-13

* 1st population from the Takahata cohort, 2nd from the Yamagata cohort

** Regression coefficient

*** Optimal lambda value in Box-Cox transformation for P-LIP is -0.4 for all except rs8176746 that has -0.3, whereas that for ACE is 0.8 for all SNPs.

Table S4. Associations of ACE1 in 17q23.3 with ACE level after adjustment by smoking or Box-Cox transformation of trait values

SNPs (position)	stage*	minor allele	MAF	ACE					
				adjusted by smoking			Box-Cox transformation****		
				beta**	SE	p value	beta**	SE	p value
rs4459609 (61548948)	1st	C	0.371	3.06	0.192	3.91e-52	1.82	0.110	3.87e-56
	2nd	C	0.356	2.48	0.177	8.81e-42	1.46	0.098	1.28e-47
rs4309 (61559923)	1st	G	0.426	3.31	0.181	1.03e-65	1.95	0.104	3.83e-69
	2nd	G	0.409	3.27	0.163	1.52e-76	1.87	0.091	7.51e-85
rs4311 (61560763)	1st	A	0.349	3.25	0.189	5.08e-59	1.91	0.109	4.21e-62
	2nd	A	0.346	2.54	0.180	2.99e-42	1.53	0.099	2.80e-50
rs4329 (61563458)	1st	A	0.358	3.25	0.189	2.10e-59	1.92	0.108	2.45e-63
	2nd	A	0.342	2.64	0.176	1.00e-47	1.58	0.097	3.11e-55
rs4343 (61566031)	1st	G	0.360	3.23	0.189	9.54e-59	1.91	0.108	1.09e-62
	2nd	G	0.342	2.65	0.176	6.93e-48	1.58	0.097	2.03e-55
rs4353 (61570422)	1st	A	0.440	3.91	0.173	4.09e-94	2.32	0.098	6.72e-102
	2nd	A	0.422	3.51	0.158	1.07e-94	2.04	0.088	4.47e-104
rs4362 (61573761)	1st	A	0.442	3.94	0.173	1.55e-95	2.33	0.098	3.43e-103
	2nd	A	0.426	3.54	0.157	8.97e-97	2.05	0.087	5.77e-106
rs4461142 (61578048)	1st	A	0.434	2.00	0.194	6.56e-24	1.16	0.111	7.77e-25
	2nd	A	0.433	1.87	0.170	6.41e-27	1.09	0.095	5.04e-29

* 1st population from the Takahata cohort, 2nd from the Yamagata cohort

** Regression coefficient

*** Coefficient t-statistic

**** Optimal lambda value for Box-Cox transformation is 0.8 for all SNPs.

Table S5. Associations of ABO gene in 9q32 with P-LIP or ACE levels after adjustment or subgroup by treatment

SNPs (position)	P-LIP								ACE							
	adjusted by treatment history*				subgroup of notreatment				adjusted by treatment history*				subgroup of notreatment			
	stage**	beta***	SE	p value	stage**	beta***	SE	p value	stage**	beta***	SE	p value	stage**	beta***	SE	p value
rs4363269 (136123840)	1st	-0.0325	0.481	> 1e-7	comb	0.525	0.443	> 1e-7	1st	-1.96	0.212	9.62e-20	comb	-1.89	0.160	3.07e-31
	2nd	-0.343	0.564	> 1e-7					2nd	-1.94	0.194	6.18e-23				
rs8176749 (136131188)	1st	4.40	0.575	3.92e-14	comb	4.04	0.524	2.15e-14	1st	2.52	0.258	1.24e-21	comb	2.30	0.192	9.06e-32
	2nd	5.40	0.635	4.53e-17					2nd	2.35	0.223	4.14e-25				
rs8176746 (136131322)	1st	4.37	0.568	2.79e-14	comb	4.17	0.516	1.32e-15	1st	2.53	0.254	1.83e-22	comb	2.32	0.189	3.00e-33
	2nd	5.69	0.620	1.41e-19					2nd	2.30	0.218	3.23e-25				
rs657152 (136139265)	1st	2.65	0.424	5.38e-10	comb	3.01	0.401	7.37e-14	1st	-0.550	0.195	> 1e-7	comb	-0.680	0.151	> 1e-7
	2nd	3.49	0.506	7.98e-12					2nd	-0.651	0.182	> 1e-7				
rs500498 (136148647)	1st	-2.44	0.421	8.35e-9	comb	-2.56	0.399	1.71e-10	1st	0.362	0.194	> 1e-7	comb	0.386	0.151	> 1e-7
	2nd	-3.02	0.507	3.16e-9					2nd	0.376	0.182	> 1e-7				
rs505922 (136149229)	1st	2.53	0.419	2.22e-9	comb	3.02	0.394	3.25e-14	1st	-0.454	0.193	> 1e-7	comb	-0.598	0.149	> 1e-7
	2nd	3.64	0.501	5.85e-13					2nd	-0.597	0.180	> 1e-7				
rs495828 (136154867)	1st	0.250	0.481	> 1e-7	comb	0.640	0.446	> 1e-7	1st	-2.25	0.209	7.13e-26	comb	-2.32	0.157	2.23e-46
	2nd	-0.182	0.562	> 1e-7					2nd	-2.38	0.190	2.07e-34				
rs7025162 (136166346)	1st	-0.806	0.428	> 1e-7	comb	-0.230	0.402	> 1e-7	1st	-1.41	0.191	2.85e-13	comb	-1.22	0.148	2.12e-16
	2nd	-0.678	0.510	> 1e-7					2nd	-1.29	0.178	7.02e-13				

* Treatment history is coded by 0 for untreated, 1 for treated or NA for not available.

** 1st population from the Takahata cohort and 2nd from the Yamagata cohort, whereas comb is combined populations of certainly untreated individuals in both cohorts.

*** Regression coefficient

Table S6. Associations of ACE1 gene in 17q23.2 with ACE level after adjustment or subgroup by treatment

SNPs (position)	ACE							
	adjusted by treatment history*				subgroup of notreatment			
	stage**	beta***	SE	p value	stage**	beta***	SE	p value
rs4459609 (61548948)	1st	3.11	0.210	5.22e-57	comb	2.86	0.148	7.45e-76
	2nd	2.52	0.179	2.08e-42				
rs4309 (61559923)	1st	3.33	0.195	1.91e-70	comb	3.30	0.135	8.57e-114
	2nd	3.30	0.163	2.25e-80				
rs4311 (61560763)	1st	3.29	0.205	5.39e-64	comb	2.94	0.149	1.50e-78
	2nd	2.62	0.181	1.78e-44				
rs4329 (61563458)	1st	3.30	0.204	7.35e-65	comb	3.02	0.146	1.00e-85
	2nd	2.70	0.177	7.42e-49				
rs4343 (61566031)	1st	3.28	0.204	3.13e-64	comb	3.02	0.146	1.27e-85
	2nd	2.71	0.177	2.88e-49				
rs4353 (61570422)	1st	3.99	0.180	2.32e-105	comb	3.78	0.128	1.49e-155
	2nd	3.60	0.159	1.54e-97				
rs4362 (61573761)	1st	4.01	0.179	1.48e-106	comb	3.77	0.128	6.96e-156
	2nd	3.62	0.158	1.51e-99				
rs4461142 (61578048)	1st	2.03	0.209	4.40e-26	comb	1.89	0.145	7.80e-37
	2nd	1.97	0.172	4.27e-29				

* Treatment history is coded by 0 for untreated, 1 for treated or NA for not available.

** 1st population from the Takahata cohort and 2nd from the Yamagata cohort, whereas comb is combined populations of certainly untreated individuals in both cohorts.

*** Regression coefficient

**** Coefficient t-statistic

Table S7. SNPs associated with P-LIP and/or ACE levels at a genome-wide significance level

locus (chr)	SNPs (build135)	position (GRCh37/hg19)	strand	major allele	minor allele	class		residue change	note
						genome	functional		
ABO (9q32)	rs4363269	136123840	+	A	G	genomic	3' downstream ~6.7kb		
	rs8176749	136131188	-	G	A	coding	synonymous	Leu310Leu	
	rs8176746	136131322	-	C	A	coding	nonsynonymous	Leu266Met	Allele A is associated with B group
	rs2073824	136132633	+	A	G	intron			
	rs657152	136139265	+	C	A	intron			
	rs500498	136148647	-	G	A	intron			
	rs505922	136149229	-	A	G	intron			Allele A is associated with O group
	rs495828	136154867	-	C	A	genomic	5' upstream ~4.2kb		
	rs7025162	136166346	-	G	A	genomic	5' upstream ~15.7kb		
	rs4459609	61548948	+	A	C	genomic	5' upstream ~5.5kb		
ACE1 (17q23.3)	rs4309	61559923	-	A	G	coding	synonymous	Pro405Pro	
	rs4311	61560763	-	G	A	intron			
	rs4329	61563458	+	G	A	intron			
	rs4343	61566031	+	A	G	intron			
	rs4353	61570422	+	G	A	intron			
	rs4362	61573761	-	G	A	coding	synonymous	Phe555Phe	
	rs4461142	61578048	-	G	A	genomic	3' downstream ~2.3kb		

Table S8. Associations of ABO gene in 9q32 with P-LIP and ACE in combined population

SNPs (position)	minor allele	MAF	P-LIP			ACE		
			beta*	T**	p value	beta*	T**	p value
rs4363269	G	0.276	-0.115	-0.321	> 1e-7	-1.94	-14.1	1.87e-43
rs8176749	A	0.177	4.78	11.6	3.02e-30	2.29	14.0	4.08e-43
rs8176746	A	0.186	4.94	12.2	2.01e-33	-1.07	-8.40	7.06e-17
rs657152	A	0.448	3.05	9.61	1.50e-21	0.417	3.26	> 1e-7
rs500498	A	0.449	-2.76	-8.71	5.16e-18	-0.581	-4.57	> 1e-7
rs505922	G	0.455	3.11	9.88	1.18e-22	-2.31	-17.0	> 1e-7
rs495828	A	0.271	0.101	0.282	> 1e-7	-2.27	-10.8	8.24e-62
rs7025162	A	0.404	-0.715	-2.21	> 1e-7	-1.31	-10.3	1.65e-24

* Regression coefficient

** Coefficient t-statistic

Table S9. Associations of ACE gene in 17q23.2 with ACE in combined population

SNPs (position)	minor allele	MAF	ACE		
			beta*	SE	p value
rs4459609	G	0.276	2.765	0.125	9.462e-101
rs4309	A	0.177	3.27	0.116	5.659e-154
rs4311	A	0.186	2.891	0.126	4.389e-108
rs4329	A	0.448	2.945	0.123	3.04e-115
rs4343	A	0.449	2.939	0.123	6.647e-115
rs4353	G	0.455	3.702	0.112	4.446e-205
rs4362	A	0.271	3.726	0.111	1.527e-208
rs4461142	A	0.404	1.923	0.123	8.542e-053

* Regression coefficient

** Coefficient t-statistic

Table S10. Sample numbers removed by each quality control filter

Initial sample size	1639
Individual missing data rate (imiss) > 0.05	16
Individual heterozygosity > 0.35	6
Cryptic relatedness: likely 1st - 3rd relatives*	314
Population outliers (PCA by EIGENSTRAT)	51
Final sample size	1252

*eliminating sample with higher imiss from each pair.

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