Characteristic	GHS Discovery Cohort (N = 46,544)	GHS Bariatric Surgery Cohort (N = 2,644)	Dallas Heart Study (N = 1,357)	Penn Medicine Biobank (N = 8,526)
Age (years) – median (IQR)	63 (50 - 74)	53 (44 - 61)	46 (38 - 54)	68 (60 - 76)
Female sex – number (%)	26,875 (58)	2,119 (80)	724 (53)	3,242 (38)
Body mass index – median (IQR)	30 (25 - 45)	47 (42 - 54)	28 (25 - 32)	30 (25 - 32)
Transaminase level (U/L) – median (IQR)				
Alanine aminotransferase (ALT)	22.0 (17.0 - 29.0)	23.0 (17.5 - 29.5)	20.0 (15.0 - 27.0)	22.0 (17.0 - 30.0)
Aspartate aminotransferase (AST)	23.0 (20.0 - 27.5)	23.0 (20.0 - 27.0)	21.0 (18.0 - 25.0)	24.0 (20.0 - 30.5)
Presence of liver disease – N (%)				
Alcoholic liver disease	197 (0.4)	7 (0.3)	-	-
Alcoholic cirrhosis	130 (0.3)	3 (0.1)	-	-
Nonalcoholic (non-viral) liver disease	1,938 (4.2)	1,543 (58.4)	-	-
Nonalcoholic cirrhosis	382 (0.8)	24 (0.9)	-	-
Hepatocellular carcinoma	76 (0.2)	1 (0.04)	-	-
No liver disease	30,628 (65.8)	1 (0.04)	-	-

Figure 1

Trait	Chr	BP	Ref	Alt	rsID	Gene	Annotation	AA Substitution	Beta (SE)	P	AAF	N
ALT	1	220970028	A	G	rs2642438	*MARC1*	missense	p.Thr165Ala	0.008 (0.001)	4.67E-08	0.7067	40,834
	4	88231392	T	TA	rs72613567	*HSD17B13*	splice donor		-0.009 (0.001)	4.16E-12	0.2634	40,834
	8	144997604	C	T	rs371119003	*PLEC*	missense	p.Ala2302Thr	-0.160 (0.026)	1.30E-09	0.0005	40,833
	8	145008502	G	A		*PLEC*	missense	p.Arg522Cys	-0.268 (0.032)	3.26E-17	0.0003	40,834
	8	145692918	G	A	rs35968570	*KIFC2*	missense	p.Glu174Lys	-0.033 (0.005)	1.40E-11	0.0139	40,834
	8	145730072	G	A	rs143408057	*GPT*	missense	p.Arg83His	-0.314 (0.036)	3.28E-18	0.0003	40,834
	8	145730161	C	T	rs201815297	*GPT*	missense	p.Ala87Val	-0.224 (0.014)	6.28E-59	0.0018	40,834
	8	145730221	G	A	rs112574791	*GPT*	missense	p.Arg107Lys	-0.033 (0.005)	4.25E-11	0.0136	40,834
	8	145731636	T	G	rs145155876	*GPT*	stop gained	p.Tyr326*	-0.235 (0.031)	1.76E-14	0.0004	40,814
	8	145732114	G	C	rs141505249	*GPT*	missense	p.Glu430Gln	-0.224 (0.013)	8.84E-64	0.0019	40,795
	8	145732151	G	A	rs143462595	*GPT*	missense	p.Arg442His	-0.077 (0.013)	1.18E-09	0.0021	40,826
	8	145732180	G	C	rs147998249	*GPT*	missense	p.Val452Leu	-0.225 (0.013)	8.19E-65	0.0019	40,833
	8	145732305	G	GC		*GPT*	frameshift	p.Glu475fs	-0.271 (0.031)	1.00E-18	0.0004	40,834
	8	145748532	A	G	rs567402720	*LRRC24*	missense	p.Leu290Ser	-0.185 (0.028)	3.42E-11	0.0004	40,813
	9	117122202	C	T	rs3748177	*AKNA*	synonymous	p.Glu755Glu	-0.007 (0.001)	9.51E-09	0.5232	40,834
	9	117124731	G	A	rs3748176	*AKNA*	missense	p.Pro624Leu	-0.007 (0.001)	4.31E-09	0.5230	40,832
	10	101595996	T	A	rs17222723	*ABCC2*	missense	p.Val1188Glu	-0.015 (0.003)	2.97E-08	0.0608	40,834
	10	101606861	G	T	rs1137968	*ABCC2*	synonymous	p.Val1430Val	-0.015 (0.003)	2.71E-08	0.0608	40,834
	10	101610533	C	T	rs8187707	*ABCC2*	synonymous	p.His1496His	-0.015 (0.003)	2.77E-08	0.0608	40,834
	10	101611294	G	A	rs8187710	*ABCC2*	missense	p.Cys1515Tyr	-0.015 (0.003)	2.15E-08	0.0611	40,834
	10	101912064	T	C	rs2862954	*ERUN1*	missense	p.Ile291Val	-0.012 (0.001)	2.43E-21	0.4755	40,834

Gray shading indicates variants having exome-wide-significant associations with both ALT and AST.

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 2

										N			Mean ALT or AST level (U/L)		
Trait	Chr	BP	Ref	Alt	rsID	Gene	Annotation	AA Substitution	Ref/Ref	Ref/Alt	Alt/Alt	Ref/Ref	Ref/Alt	Alt/Alt
ALT	1	2.2E+08	A	G	rs2642438	*MARC1*	missense	p.Thr165Ala	3,515	17,262	20,637	23.88	24.52	24.92
	4	8.8E+07	T	TA	rs72613567	*HSD17B13*	splice donor		22,441	16,130	2,843	25.02	24.26	24.1
	8	1.4E+08	C	T	rs371119003	*PLEC*	missense	p.Ala2302Thr	41,373	40	0	24.67	18.1	NA
	8	1.5E+08	G	A		*PLEC*	missense	p.Arg522Cys	41,387	27	0	24.67	13.8	NA
	8	1.5E+08	G	A	rs35968570	*KIFC2*	missense	p.Glu174Lys	40,271	1,133	10	24.67	12.07	NA
	8	1.5E+08	G	A	rs142408057	*GPT*	missense	p.Arg83His	41,393	21	0	24.67	12.07	NA
	8	1.5E+08	C	T	rs201815297	*GPT*	missense	p.Ala87Val	41,270	144	0	24.7	14.68	NA
	8	1.5E+08	G	A	rs112574791	*GPT*	missense	p.Arg107Lys	40,293	1,111	10	24.71	23.09	18.35
	8	1.5E+08	T	G	rs145155876	*GPT*	stop gained	p.Tyr326*	41,364	30	0	24.67	14.07	NA
	8	1.5E+08	G	C	rs141505249	*GPT*	missense	p.Glu430Gln	41,223	150	2	24.7	14.48	13.75
	8	1.5E+08	G	A	rs143462595	*GPT*	missense	p.Arg442His	41,232	174	0	24.68	20.87	NA
	8	1.5E+08	G	C	rs147998249	*GPT*	missense	p.Val452Leu	41,254	159	0	24.7	14.74	NA
	8	1.5E+08	G	GC		*GPT*	frameshift	p.Glu475fs	41,385	29	0	24.67	14.24	NA
	8	1.5E+08	A	G	rs567402720	*LRRC24*	missense	p.Leu290Ser	41,358	35	0	24.67	17.71	NA
	9	1.2E+08	C	T	rs3748177	*AKNA*	synonymous	p.Glu755Glu	9,414	20,645	11,355	25.12	24.72	24.18
	9	1.2E+08	G	A	rs3748176	*AKNA*	missense	p.Pro624Leu	9,427	20,634	11,351	25.12	24.73	24.17
	10	1E+08	T	A	rs17222723	*ABCC2*	missense	p.Val1188Glu	36,543	4,704	167	24.77	23.97	22.12
	10	1E+08	G	T	rs1137968	*ABCC2*	synonymous	p.Val1430Val	36,543	4,704	167	24.77	23.97	22.04
	10	1E+08	C	T	rs8187707	*ABCC2*	synonymous	p.His1496His	36,542	4,706	166	24.77	23.97	22.03
	10	1E+08	G	A	rs8187710	*ABCC2*	missense	p.Cys1515Tyr	36,519	4,726	169	24.77	23.97	21.99
	10	1E+08	T	C	rs2862954	*FRMT*	missense	p.Ile291Val	11,318	20,819	9,277	25.32	24.71	23.77

Gray shading indicates variants having exome-wide-significant associations with both ALT and AST.

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 2 (cont.)

Trait	Chr	BP	Ref	Alt	rsID	Gene	Annotation	AA Substitution	Beta (SE)	P	AAF	N
	10	101977883	C	T	rs2230804	*CHUK*	missense	p.Val268Ile	-0.009 (0.001)	1.93E-13	0.5072	40,834
	10	113917085	T	A	rs2254537	*GPAM*	synonymous	p.Pro681Pro	-0.008 (0.001)	4.61E-10	0.7073	40,834
	10	113940329	T	C	rs2792751	*GPAM*	missense	p.Ile43Val	-0.008 (0.001)	2.54E-10	0.7097	40,832
	14	94844947	C	T	rs28929474	*SERPINA1*	missense	p.Glu366Lys	0.042 (0.005)	9.28E-21	0.0171	40,834
	19	19379549	C	T	rs58542926	*TM6SF2*	missense	p.Glu167Lys	0.014 (0.002)	4.76E-09	0.0759	40,833
	22	44324727	C	G	rs738409	*PNPLA3*	missense	p.Ile148Met	0.023 (0.002)	1.34E-50	0.2351	40,834
	22	44324730	C	T	rs738408	*PNPLA3*	synonymous	p.Pro149Pro	0.023 (0.002)	1.11E-50	0.2349	40,834
	22	44342116	A	G	rs2294918	*PNPLA3*	missense	p.Lys434Glu	0.007 (0.001)	8.26E-08	0.5986	40,832
	22	44368122	A	G	rs3761472	*SAMM50*	missense	p.Asp110Gly	0.019 (0.002)	8.85E-30	0.1682	40,833
	22	44395451	T	C	rs1007863	*PARVB*	missense	p.Trp37Arg	0.011 (0.001)	7.98E-16	0.3963	40,834
AST	4	88231392	T	TA	rs72613567	*HSD17B13*	splice donor		-0.005 (0.001)	6.24E-10	0.2638	40,193
	10	18242311	A	G	rs10764176	*SLC39A12*	missense	p.Ser36Gly	-0.006 (0.001)	1.09E-10	0.2881	40,193
	10	101157378	CGTT	C		*GOT1*	inframe indel	p.Asn389del	-0.221 (0.024)	1.96E-20	0.0002	40,193
	10	101165533	G	C	rs374966349	*GOT1*	missense	p.Gln208Glu	0.271 (0.027)	2.43E-24	0.0002	40,193
	10	101912064	T	C	rs2862954	*ERLIN1*	missense	p.Ile291Val	-0.005 (0.001)	4.82E-09	0.4754	40,193
	11	22271870	A	T	rs7481951	*ANO5*	missense	p.Leu322Phe	0.004 (0.001)	9.61E-08	0.5833	40,162
	14	94844947	C	T	rs28929474	*SERPINA1*	missense	p.Glu366Lys	0.027 (0.003)	2.44E-20	0.0172	40,193
	19	19379549	C	T	rs58542926	*TM6SF2*	missense	p.Glu167Lys	0.008 (0.002)	6.54E-08	0.0760	40,192
	22	44324727	C	G	rs738409	*PNPLA3*	missense	p.Ile148Met	0.014 (0.001)	8.31E-46	0.2343	40,193
	22	44324730	C	T	rs738408	*PNPLA3*	synonymous	p.Pro149Pro	0.014 (0.001)	8.93E-46	0.2341	40,193
	22	44368122	A	G	rs3761472	*SAMM50*	missense	p.Asp110Gly	0.011 (0.001)	1.22E-22	0.1680	40,192
	22	44395451	T	C	rs1007863	*PARVB*	missense	p.Trp37Arg	0.006 (0.001)	1.31E-13	0.3961	40,193

Gray shading indicates variants having exome-wide-significant associations with both ALT and AST.

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 2 (cont.)

									N			Mean ALT or AST level (U/L)		
Trait	Chr	BP	Ref	Alt	rsID	Gene	Annotation	AA Substitution	Ref/Ref	Ref/Alt	Alt/Alt	Ref/Ref	Ref/Alt	Alt/Alt
	10	101977883	C	T	rs2230804	*CHUK*	missense	p.Val268Ile	10,048	20,733	10,633	25.18	24.75	24.01
	10	113917085	T	A	rs2254537	*GPAM*	synonymous	p.Pro681Pro	3,627	16,984	20,803	25	24.97	24.36
	10	113940329	T	C	rs2792751	*GPAM*	missense	p.Ile43Val	3,567	16,910	20,935	25	24.98	24.35
	14	94844947	C	T	rs28929474	*SERPINA1*	missense	p.Glu366Lys	40,006	1,399	9	24.58	26.91	43.89
	19	19379549	C	T	rs58542926	*TM6SF2*	missense	p.Glu167Lys	35,388	5,780	245	24.52	25.46	26.84
	22	44324727	C	G	rs738409	*PNPLA3*	missense	p.Ile148Met	24,257	14,837	2,320	24.06	24.99	28.91
	22	44324730	C	T	rs738408	*PNPLA3*	synonymous	p.Pro149Pro	24,273	14,824	2,317	24.06	24.98	28.92
	22	44342116	A	G	rs2294918	*PNPLA3*	missense	p.Lys434Glu	6,691	19,833	14,888	24.15	24.47	25.15
	22	44368122	A	G	rs3761472	*SAMM50*	missense	p.Asp110Gly	28,626	11,618	1,169	24.23	25.36	28.45
	22	44395451	T	C	rs1007863	*PARVB*	missense	p.Trp37Arg	15,036	19,920	6,458	24.15	24.6	26.09
AST	4	88231392	T	TA	rs72613567	*HSD17B13*	splice donor		22,068	15,870	2,815	24.47	24.1	23.96
	10	18242311	A	G	rs10764176	*SLC39A12*	missense	p.Ser36Gly	20,645	16,738	3,370	24.47	24.15	23.85
	10	101157378	CGTT	C		*GOT1*	inframe indel	p.Asn389del	40,733	20	0	24.29	14.7	NA
	10	101165533	G	C	rs374966349	*GOT1*	missense	p.Gln208Glu	40,736	17	0	24.28	44.5	NA
	10	101912064	T	C	rs2862954	*ERLIN1*	missense	p.Ile291Val	11,138	20,486	9,129	24.59	24.26	23.99
	11	22271870	A	T	rs7481951	*ANO5*	missense	p.Leu322Phe	7,123	19,686	13,913	24.03	24.22	24.53
	14	94844947	C	T	rs28929474	*SERPINA1*	missense	p.Glu366Lys	39,361	1,384	8	24.24	25.76	34.5
	19	19379549	C	T	rs58542926	*TM6SF2*	missense	p.Glu167Lys	34,811	5,698	243	24.21	24.74	25.43
	22	44324727	C	G	rs738409	*PNPLA3*	missense	p.Ile148Met	23,889	14,622	2,242	23.96	24.48	26.62
	22	44324730	C	T	rs738408	*PNPLA3*	synonymous	p.Pro149Pro	23,905	14,609	2,239	23.96	24.47	26.63
	22	44368122	A	G	rs3761472	*SAMM50*	missense	p.Asp110Gly	28,170	11,450	1,132	24.07	24.64	26.24
	22	44395451	T	C	rs1007863	*PARVB*	missense	p.Trp37Arg	14,761	19,678	6,314	24.02	24.23	25.1

Gray shading indicates variants having exome-wide-significant associations with both ALT and AST.

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 2 (cont.)

Trait	Chr	BP	Ref	Alt	RSID	Gene	Annotation	AA Substitution	GHS Discovery Cohort		
									Beta (SE)	P discovery	N
ALT	1	220970028	A	G	rs2642438	*MARC1*	missense	p.Thr165Ala	0.008 (0.001)	4.67E-08	40834
	4	88231392	T	TA	rs72613567	*HSD17B13*	splice donor		-0.009 (0.001)	4.16E-12	40834
	8	144997604	C	T	rs371119003	*PLEC*	missense	p.Ala2302Thr	-0.160 (0.026)	1.30E-09	40833
	8	145008502	G	A		*PLEC*	missense	p.Arg522Cys	-0.268 (0.032)	3.26E-17	40834
	8	145692918	G	A	rs35968570	*KIFC2*	missense	p.Glu174Lys	-0.033 (0.005)	1.40E-11	40834
	8	145730072	G	A	rs143408057	*GPT*	missense	p.Arg83His	-0.314 (0.036)	3.28E-18	40834
	8	145730161	C	T	rs201815297	*GPT*	missense	p.Ala87Val	-0.224 (0.014)	6.28E-59	40834
	8	145730221	G	A	rs112574791	*GPT*	missense	p.Arg107Lys	-0.033 (0.005)	4.25E-11	40834
	8	145731636	T	G	rs145155876	*GPT*	stop gained	p.Tyr326*	-0.235 (0.031)	1.76E-14	40814
	8	145732114	G	C	rs141505249	*GPT*	missense	p.Glu430Gln	-0.224 (0.013)	8.84E-64	40795
	8	145732151	G	A	rs143462595	*GPT*	missense	p.Arg442His	-0.077 (0.013)	1.18E-09	40826
	8	145732180	G	C	rs147998249	*GPT*	missense	p.Val452Leu	-0.225 (0.013)	8.19E-65	40833
	8	145732305	G	GC		*GPT*	frameshift	p.Glu475fs	-0.271 (0.031)	1.00E-18	40834
	8	145748532	A	G	rs567402720	*LRRC24*	missense	p.Leu290Ser	-0.185 (0.028)	3.42E-11	40813
	9	117122202	C	T	rs3748177	*AKNA*	synonymous	p.Glu755Glu	-0.007 (0.001)	9.51E-09	40834
	9	117124731	G	A	rs3748176	*AKNA*	missense	p.Pro624Leu	-0.007 (0.001)	4.31E-09	40832
	10	101595996	T	A	rs17222723	*ABCC2*	missense	p.Val1188Glu	-0.015 (0.003)	2.97E-08	40834

Gray shading indicates P-values meeting the Bonferroni significance threshold of $P < 1.43 \times 10^{-3}$

* Replication meta-analysis includes the three replication cohorts: GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

* Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3

Trait	Chr	BP	Ref	Alt	RSID	Gene	Annotation	AA Substitution	GHS Discovery Cohort		
									Beta (SE)	P discovery	N
	10	101606861	G	T	rs113796	*ABCC2*	synonymous	p.Val1430Val	-0.015 (0.003)	2.71E-08	40834
	10	101610533	C	T	rs818770	*ABCC2*	synonymous	p.His1496His	-0.015 (0.003)	2.77E-08	40834
	10	101611294	G	A	rs818771	*ABCC2*	missense	p.Cys1515Tyr	-0.015 (0.003)	2.15E-08	40834
	10	101912064	T	C	rs286295	*ERLIN1*	missense	p.Ile291Val	-0.012 (0.001)	2.43E-21	40834
	10	101977883	C	T	rs223080	*CHUK*	missense	p.Val268Ile	-0.009 (0.001)	1.93E-13	40834
	10	113917085	T	A	rs225453	*GPAM*	synonymous	p.Pro681Pro	-0.008 (0.001)	4.61E-10	40834
	10	113940329	T	C	rs279275	*GPAM*	missense	p.Ile43Val	-0.008 (0.001)	2.54E-10	40832
	14	94844947	C	T	rs289294	*SERPINA1*	missense	p.Glu366Lys	0.042 (0.005)	9.28E-21	40834
	19	19379549	C	T	rs585429	*TM6SF2*	missense	p.Glu167Lys	0.014 (0.002)	4.76E-09	40833
	22	44324727	C	G	rs738409	*PNPLA3*	missense	p.Ile148Met	0.023 (0.002)	1.34E-50	40834
	22	44324730	C	T	rs738408	*PNPLA3*	synonymous	p.Pro149Pro	0.023 (0.002)	1.11E-50	40834
	22	44342116	A	G	rs229491	*PNPLA3*	missense	p.Lys434Glu	0.007 (0.001)	8.26E-08	40832
	22	44368122	A	G	rs376147	*SAMM50*	missense	p.Asp110Gly	0.019 (0.002)	8.85E-30	40833
	22	44395451	T	C	rs100786	*PARVB*	missense	p.Trp37Arg	0.011 (0.001)	7.98E-16	40834

Gray shading indicates P-values meeting the Bonferroni significance threshold of $P < 1.43 \times 10^{-3}$

* Replication meta-analysis includes the three replication cohorts: GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

* Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

Trait	Chr	BP	Ref	Alt	RSID	Gene	Annotation	AA Substitution	GHS Discovery Cohort		
									Beta (SE)	P discovery	N
AST	4	88231392	T	TA	rs72613567	*HSD17B13*	splice donor		-0.005 (0.001)	6.24E-10	40193
	10	18242311	A	G	rs10764176	*SLC39A12*	missense	p.Ser36Gly	-0.006 (0.001)	1.09E-10	40193
	10	101157378	CGTT	C		*GOT1*	inframe indel	p.Asn389del	-0.221 (0.024)	1.96E-20	40193
	10	101165533	G	C	rs374966349	*GOT1*	missense	p.Gln208Glu	0.271 (0.027)	2.43E-24	40193
	10	101912064	T	C	rs2862954	*ERLIN1*	missense	p.Ile291Val	-0.005 (0.001)	4.82E-09	40193
	11	22271870	A	T	rs7481951	*AMD5*	missense	p.Leu322Phe	0.004 (0.001)	9.61E-08	40162
	14	94844947	C	T	rs28929474	*SERPINA1*	missense	p.Glu366Lys	0.027 (0.003)	2.44E-20	40193
	19	19379549	C	T	rs58542926	*TM6SF2*	missense	p.Glu167Lys	0.008 (0.002)	6.54E-08	40192
	22	44324727	C	G	rs738409	*PNPLA3*	missense	p.Ile148Met	0.014 (0.001)	8.31E-46	40193
	22	44324730	C	T	rs738408	*PNPLA3*	synonymous	p.Pro149Pro	0.014 (0.001)	8.93E-46	40193
	22	44368122	A	G	rs3761472	*SAMM50*	missense	p.Asp110Gly	0.011 (0.001)	1.22E-22	40192
	22	44395451	T	C	rs1007863	*PARVB*	missense	p.Trp37Arg	0.006 (0.001)	1.31E-13	40193

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.43x10-3

* Replication meta-analysis includes the three replication cohorts: GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

* Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

Trait	Chr	Replication Cohorts									
		GHS Bariatric Surgery Cohort			Dallas Heart Study			Penn Medicine Biobank			
		Beta (SE)	P	N	Beta (SE)	P	N	Beta (SE)	P	N	
ALT	1	0.005 (0.005)	3.10E-01	2475	0.009 (0.008)	2.58E-01	1356	0.006 (0.004)	1.81E-01	6158	
	4	-0.010 (0.005)	5.57E-02	2475	-0.014 (0.008)	9.68E-02	1356	-0.012 (0.004)	4.85E-03	6158	
	8	-0.492 (0.165)	2.84E-03	2475	NA (NA)	NA	NA	-0.054 (0.071)	4.46E-01	6158	
	8	-0.161 (0.165)	3.29E-01	2475	NA (NA)	NA	NA	-0.259 (0.143)	6.90E-02	6158	
	8	-0.009 (0.02)	6.48E-01	2475	0.027 (0.035)	4.48E-01	1355	-0.051 (0.019)	7.52E-03	6158	
	8	-0.189 (0.165)	2.50E-01	2475	NA (NA)	NA	NA	-0.305 (0.101)	2.54E-03	6158	
	8	-0.341 (0.074)	3.64E-06	2475	NA (NA)	NA	NA	-0.144 (0.054)	7.67E-03	6158	
	8	-0.009 (0.02)	6.45E-01	2475	0.024 (0.035)	5.01E-01	1356	-0.059 (0.018)	1.13E-03	6158	
	8	-0.314 (0.165)	5.71E-02	2475	-0.334 (0.137)	1.49E-02	1355	-0.151 (0.143)	2.90E-01	6157	
	8	-0.273 (0.048)	9.83E-09	2474	-0.244 (0.073)	8.91E-04	1356	-0.188 (0.041)	5.52E-06	6157	
	8	-0.115 (0.058)	4.82E-02	2475	-0.092 (0.097)	3.43E-01	1355	-0.042 (0.043)	3.36E-01	6157	
	8	-0.273 (0.050)	4.26E-08	2475	-0.198 (0.068)	3.90E-03	1356	-0.188 (0.041)	5.52E-06	6158	
	8	-0.161 (0.165)	3.29E-01	2475	NA (NA)	NA	NA	-0.506 (0.202)	1.22E-02	NA	
	8	-0.161 (0.165)	3.29E-01	2475	NA (NA)	NA	NA	-0.303 (0.143)	3.37E-02	NA	
	9	-0.004 (0.005)	4.09E-01	2475	0.003 (0.008)	6.46E-01	1356	-0.007 (0.004)	6.38E-02	6158	

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.43x10-3

* Replication meta-anayais includes the three replication cohorts: GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

* Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

Trait	Chr	Replication Cohorts								
		GHS Bariatric Surgery Cohort			Dallas Heart Study			Penn Medicine Biobank		
		Beta (SE)	P	N	Beta (SE)	P	N	Beta (SE)	P	N
	9	-0.004 (0.005)	3.90E-01	2475	0.002 (0.008)	7.69E-01	1355	-0.007 (0.004)	5.29E-02	6158
	10	-0.002 (0.010)	8.01E-01	2475	-0.003 (0.017)	8.37E-01	1356	-0.015 (0.007)	4.49E-02	6158
	10	-0.003 (0.010)	7.74E-01	2475	-0.005 (0.017)	7.49E-01	1356	-0.014 (0.007)	4.86E-02	6158
	10	-0.003 (0.010)	7.93E-01	2475	-0.005 (0.017)	7.49E-01	1356	-0.014 (0.007)	5.02E-02	6158
	10	-0.001 (0.010)	9.11E-01	2475	-0.008 (0.016)	6.41E-01	1356	-0.013 (0.007)	7.46E-02	6158
	10	-0.01 (0.005)	2.91E-02	2475	-0.006 (0.007)	4.02E-01	1356	-0.009 (0.004)	2.06E-02	6158
	10	-0.006 (0.005)	2.05E-01	2475	-0.001 (0.007)	9.07E-01	1356	-0.011 (0.004)	5.26E-03	6158
	10	-0.003 (0.005)	5.80E-01	2475	-0.014 (0.008)	8.25E-02	1356	-0.007 (0.004)	7.45E-02	6158
	10	-0.003 (0.005)	5.61E-01	2475	-0.014 (0.008)	9.08E-02	1356	-0.008 (0.004)	6.34E-02	6158
	14	0.035 (0.020)	7.97E-02	2475	0.044 (0.032)	1.63E-01	1356	0.056 (0.013)	1.38E-05	6158
	19	0.040 (0.010)	2.40E-05	2475	0.025 (0.014)	7.24E-02	1356	0.013 (0.008)	1.07E-01	6158
	22	0.019 (0.006)	5.54E-04	2475	0.005 (0.009)	5.75E-01	1356	0.018 (0.005)	5.51E-05	6158
	22	0.019 (0.006)	5.51E-04	2475	0.005 (0.009)	5.75E-01	1356	0.018 (0.005)	5.78E-05	6158
	22	0.001 (0.005)	7.77E-01	2475	0.004 (0.008)	6.26E-01	1356	0.005 (0.004)	2.00E-01	6158
	22	0.009 (0.006)	1.66E-01	2475	-0.002 (0.01)	8.80E-01	1356	0.021 (0.005)	5.29E-05	6158
	22	0.003 (0.005)	5.22E-01	2475	0.007 (0.008)	3.31E-01	1356	0.008 (0.004)	3.82E-02	6158

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.43x10-3

* Replication meta-analysis includes the three replication cohorts: GHS Bariatric Surgery Cohort, Dallas Heart Study, and Penn Medicine Biobank

* Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Surgery Cohort, Dallas Heart Study, and Penn Medicine Biobank

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

Trait	Chr	Replication Meta-analysis* (N=3)		Joint Meta-analysis** (N=4)	
		Beta (SE)	P replication	Beta (SE)	P joint
ALT	1	0.006 (0.003)	4.77E-02	0.007 (0.001)	6.91E-09
	4	-0.012 (0.003)	1.67E-04	-0.010 (0.001)	3.85E-15
	8	-0.124 (0.066)	5.92E-02	-0.155 (0.024)	2.41E-10
	8	-0.259 (0.143)	6.90E-02	-0.264 (0.03)	4.65E-18
	8	-0.024 (0.013)	6.89E-02	-0.032 (0.005)	3.36E-12
	8	-0.305 (0.101)	2.54E-03	-0.308 (0.033)	2.21E-20
	8	-0.213 (0.044)	1.01E-06	-0.223 (0.013)	4.00E-64
	8	-0.029 (0.013)	2.09E-02	-0.032 (0.005)	2.89E-12
	8	-0.264 (0.085)	1.84E-03	-0.238 (0.029)	1.35E-16
	8	-0.227 (0.029)	2.39E-15	-0.224 (0.012)	1.94E-77
	8	-0.070 (0.033)	3.12E-02	-0.076 (0.012)	1.12E-10
	8	-0.218 (0.029)	3.94E-14	-0.224 (0.012)	2.92E-77
	8	-0.506 (0.202)	1.22E-02	-0.272 (0.030)	6.42E-20
	8	-0.303 (0.143)	3.37E-02	-0.189 (0.027)	2.99E-12
	9	-0.005 (0.003)	9.79E-02	-0.007 (0.001)	3.57E-09

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.43x10-3

** Replication meta-analysis includes the three replication cohorts: GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank*

*** Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank*

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

Trait	Chr	Replication Meta-analysis* (N=3)		Joint Meta-analysis** (N=4)	
		Beta (SE)	P replication	Beta (SE)	P joint
	9	-0.005 (0.003)	7.27E-02	-0.007 (0.001)	1.19E-09
	10	-0.01 (0.006)	8.55E-02	-0.014 (0.002)	9.49E-09
	10	-0.01 (0.006)	7.96E-02	-0.014 (0.002)	8.03E-09
	10	-0.01 (0.006)	8.38E-02	-0.014 (0.002)	8.70E-09
	10	-0.009 (0.006)	1.19E-01	-0.014 (0.002)	1.07E-08
	10	-0.009 (0.003)	1.14E-03	-0.011 (0.001)	1.76E-23
	10	-0.008 (0.003)	5.11E-03	-0.009 (0.001)	4.17E-15
	10	-0.007 (0.003)	2.44E-02	-0.008 (0.001)	3.82E-11
	10	-0.007 (0.003)	2.13E-02	-0.008 (0.001)	1.85E-11
	14	0.049 (0.010)	1.51E-06	0.044 (0.004)	9.55E-26
	19	0.024 (0.006)	1.58E-05	0.016 (0.002)	1.35E-12
	22	0.017 (0.003)	2.60E-07	0.022 (0.001)	7.75E-56
	22	0.017 (0.003)	2.71E-07	0.022 (0.001)	6.77E-56
	22	0.004 (0.003)	2.03E-01	0.006 (0.001)	6.49E-08
	22	0.014 (0.004)	2.57E-04	0.018 (0.002)	2.36E-32
	22	0.006 (0.003)	2.63E-02	0.01 (0.001)	1.83E-16

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.43x10-3

* Replication meta-analysis includes the three replication cohorts: GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

* Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

Trait	Chr	Replication Cohorts								
		GHS Bariatric Surgery Cohort			Dallas Heart Study			Penn Medicine Biobank		
		Beta (SE)	P	N	Beta (SE)	P	N	Beta (SE)	P	N
AST	4	-0.010 (0.003)	3.12E-03	2469	-0.012 (0.006)	5.87E-02	1356	-0.006 (0.004)	1.02E-01	6166
	10	-0.010 (0.003)	2.91E-03	2469	-0.003 (0.006)	6.25E-01	1356	-0.010 (0.004)	6.75E-03	6166
	10	-0.205 (0.062)	8.57E-04	2469	NA (NA)	NA	NA	-0.244 (0.089)	5.90E-03	6165
	10	NA (NA)	NA	2469	NA (NA)	NA	NA	0.339 (0.079)	1.85E-05	6166
	10	-0.004 (0.003)	1.54E-01	2469	-0.007 (0.006)	2.18E-01	1356	-0.003 (0.003)	3.13E-01	6166
	11	-0.001 (0.003)	7.85E-01	2466	0.006 (0.006)	2.80E-01	1356	-0.003 (0.003)	3.54E-01	6165
	14	0.023 (0.013)	7.79E-02	2469	0.046 (0.024)	6.09E-02	1356	0.052 (0.011)	4.75E-06	6166
	19	0.023 (0.006)	1.99E-04	2469	0.010 (0.011)	3.42E-01	1356	0.004 (0.007)	5.94E-01	6166
	22	0.014 (0.004)	1.27E-04	2469	0.004 (0.007)	5.53E-01	1356	0.017 (0.004)	1.16E-05	6166
	22	0.014 (0.004)	1.32E-04	2469	0.004 (0.007)	5.53E-01	1356	0.017 (0.004)	1.17E-05	6166
	22	0.008 (0.004)	6.03E-02	2469	-0.001 (0.008)	9.33E-01	1356	0.018 (0.005)	6.47E-05	6166
	22	0.003 (0.003)	4.12E-01	2469	0.006 (0.006)	3.03E-01	1356	0.009 (0.003)	1.37E-02	6166

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.43x10-3

** Replication meta-analysis includes the three replication cohorts: GHS Bariatric Surgery Cohort, Dallas Heart Study, and Penn Medicine Biobank*

** Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Surgery Cohort, Dallas Heart Study, and Penn Medicine Biobank*

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

Trait	Chr	Replication Meta-analysis* (N=3)		Joint Meta-analysis** (N=4)	
		Beta (SE)	P replication	Beta (SE)	P joint
AST	4	-0.009 (0.002)	1.69E-04	-0.006 (0.001)	1.13E-12
	10	-0.009 (0.002)	8.86E-05	-0.006 (0.001)	9.66E-14
	10	-0.205 (0.062)	8.57E-04	-0.220 (0.022)	1.66E-24
	10	0.339 (0.079)	1.85E-05	0.271 (0.027)	2.43E-24
	10	-0.004 (0.002)	3.92E-02	-0.005 (0.001)	5.52E-10
	11	-0.001 (0.002)	7.03E-01	0.004 (0.001)	1.48E-06
	14	0.040 (0.008)	6.56E-07	0.029 (0.003)	2.78E-25
	19	0.014 (0.004)	1.20E-03	0.009 (0.002)	5.92E-10
	22	0.014 (0.002)	2.00E-08	0.014 (0.001)	1.12E-52
	22	0.014 (0.002)	2.10E-08	0.014 (0.001)	1.26E-52
	22	0.011 (0.003)	1.77E-04	0.011 (0.001)	1.01E-25
	22	0.005 (0.002)	1.34E-02	0.006 (0.001)	6.61E-15

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.43x10-3

** Replication meta-analysis includes the three replication cohorts: GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank*

*** Joint meta-analysis includes the discovery cohort and the three replication cohorts: GHS Discovery Cohort, GHS Bariatric Sugery Cohort, Dallas Heart Study, and Penn Medicine Biobank*

Abbreviations: AAF, alternate allele frequency; Alt, alternate allele; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ref, reference allele; SE, standard error;

Figure 3 (cont.)

CHR:BP:Ref:Alt	Gene	rsID	Alcoholic liver disease		Alcoholic cirrhosis	
			OR (95% CI)	P	OR (95% CI)	P
4:88231392:T:TA	*HSD17B13*	rs72613567	0.62 (0.48-0.81)	1.82E-04	0.56 (0.41-0.78)	3.35E-04
8:145730161:C:T	*GPT*	rs201815297	3.83 (1.05-13.94)	8.88E-02	6.33 (1.71-23.43)	2.88E-02
8:145732114:G:C	*GPT*	rs141505249	0.77 (0.06-10.73)	8.43E-01	1.13 (0.08-15.39)	9.30E-01
8:145732180:G:C	*GPT*	rs147998249	0.73 (0.05-11.76)	8.17E-01	1.07 (0.07-17.16)	9.60E-01
10:18242311:A:G	*SIC39A12*	rs10764176	0.85 (0.68-1.07)	1.64E-01	0.92 (0.70-1.22)	5.80E-01
10:101157378:CGTT:C	*GOT1*		4.60 (0.25-86.41)	3.93E-01	7.11 (0.38-133.19)	3.00E-01
10:101165533:G:C	*GOT1*	rs374966349	2.20 (0.13-37.68)	6.24E-01	3.47 (0.20 - 59.04)	4.70E-01
10:101912064:T:C	*ERLIN1*	rs2862954	0.92 (0.75-1.12)	4.05E-01	1.05 (0.82-1.34)	7.13E-01
14:94844947:C:T	*SERPINA1*	rs28929474	2.49 (1.49-4.17)	2.30E-03	3.35 (1.93-5.83)	3.01E-04
19:19379549:C:T	*TM6SF2*	rs58542926	1.47 (1.06-2.04)	2.76E-02	1.35 (0.89-2.04)	1.80E-01
22:44324727:C:G	*PNPLA3*	rs738409	1.76 (1.43-2.18)	4.98E-07	2.07 (1.60-2.67)	1.08E-07
22:44324730:C:T	*PNPLA3*	rs738408	1.77 (1.43-2.18)	4.70E-07	2.07 (1.61-2.67)	1.03E-07
22:44368122:A:G	*SAMM50*	rs3761472	1.90 (1.52-2.38)	1.36E-07	2.28 (1.75-2.98)	1.83E-08

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.92x10-3

Figure 4

CHR:BP:Ref:Alt	Gene	rsID	Nonalcoholic liver disease		Nonalcoholic cirrhosis		Hepatocellular carcinoma	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
4:88221392:T:TA	*HSD17B13*	rs72613567	0.84 (0.78-0.91)	1.31E-05	0.74 (0.62-0.88)	4.48E-04	0.67 (0.45-1.00)	4.66E-02
8:145730161:C:T	*GPT*	rs201815297	0.23 (0.04-1.14)	1.86E-02	1.25 (0.24-6.38)	7.98E-01	3.66 (0.70-19.01)	2.01E-01
8:145732114:G:C	*GPT*	rs141505249	1.02 (0.49-2.11)	9.70E-01	0.36 (0.02-5.37)	3.82E-01	1.84 (0.15-23.25)	6.88E-01
8:145732180:G:C	*GPT*	rs147998249	1.03 (0.49-2.17)	9.30E-01	0.34 (0.02-5.59)	3.67E-01	1.74 (0.11-27.05)	7.21E-01
10:18242311:A:G	*SLC39A12*	rs10764176	0.92 (0.86 (0.99)	3.43E-02	1.03 (0.88-1.21)	7.15E-01	1.29 (0.93-1.79)	1.37E-01
10:101157378:CGTT:C	*GOT1*		2.37 (0.61-9.27)	2.50E-01	8.27 (1.44-47.49)	5.92E-02	9.81 (0.52-183.54	2.43E-01
10:101165533:G:C	*GOT1*	rs374966349	1.63 (0.53-4.96)	4.20E-01	1.17 (0.07-20.09)	9.13E-01	5.37 (0.32-91.12)	3.55E-01
10:101912064:T:C	*ERLIN1*	rs2862954	0.98 (0.91-1.04)	4.61E-01	1.13 (0.98-1.31)	9.90E-02	0.94 (0.69-1.28)	6.94E-01
14:94844947:C:T	*SERPINA1*	rs28929474	1.50 (1.21-1.87)	5.29E-04	2.99 (2.11-4.24)	9.08E-08	1.86 (0.74-4.67)	2.40E-01
19:19379549:C:T	*TM6SF2*	rs58542926	1.36 (1.21-1.52)	2.42E-07	1.64 (1.31-2.05)	6.04E-05	1.93 (1.22-3.04)	1.08E-02
22:44324727:C:G	*PNPLA3*	rs738409	1.65 (1.54-1.78)	1.31E-41	2.05 (1.76-2.38)	1.70E-19	2.20 (1.60-3.02)	5.59E-06
22:44324730:C:T	*PNPLA3*	rs738408	1.65 (1.54-1.78)	1.42E-41	2.05 (1.77-2.38)	1.45E-19	2.20 (1.60-3.03)	5.41E-06
22:44368122:A:G	*SAMM50*	rs3761472	1.52 (1.41-1.65)	7.33E-24	1.86 (1.58-2.19)	1.81E-12	1.66 (1.16-2.39)	1.05E-02

Gray shading indicates P-values meeting the Bonferroni significance threshold of P < 1.92x10-3

Figure 4 (cont.)

Characteristic	Dallas Liver Study Cases (N = 517)	Dallas Liver Study Controls (N = 4,279)	Dallas Pediatric Liver Study Cases (N = 203)	Dallas Pediatric Liver Study Controls (N = 244)
Age (years) -- median (IQR)	55 (48 - 60)	44 (36 - 53)	12 (10 - 15)	12 (11 - 14)
Female sex -- number (%)	277 (54)	2,494 (58)	65 (32)	126 (52)
Body mass index -- median (IQR)	30 (27 - 35)	30 (26 - 35)	30 (27 - 34)	31 (28 - 35)
Self-reported ethnicity				
African American	33 (6)	2,291 (54)	-	-
European American	158 (31)	1,266 (30)	-	-
Hispanic American	326 (63)	722 (17)	203 (100)	244 (100)
Presence of liver disease -- N (%)				
Alcoholic liver disease	223 (43)	-	-	-
Alcoholic cirrhosis	215 (42)	-	-	-
Nonalcoholic (non-viral) liver disease	212 (20)	-	-	-
Nonalcoholic cirrhosis	100 (19)	-	-	-
Hepatocellular carcinoma	44 (9)	-	-	-
No liver disease	-	4,279 (100)	-	244 (100)

Figure 5

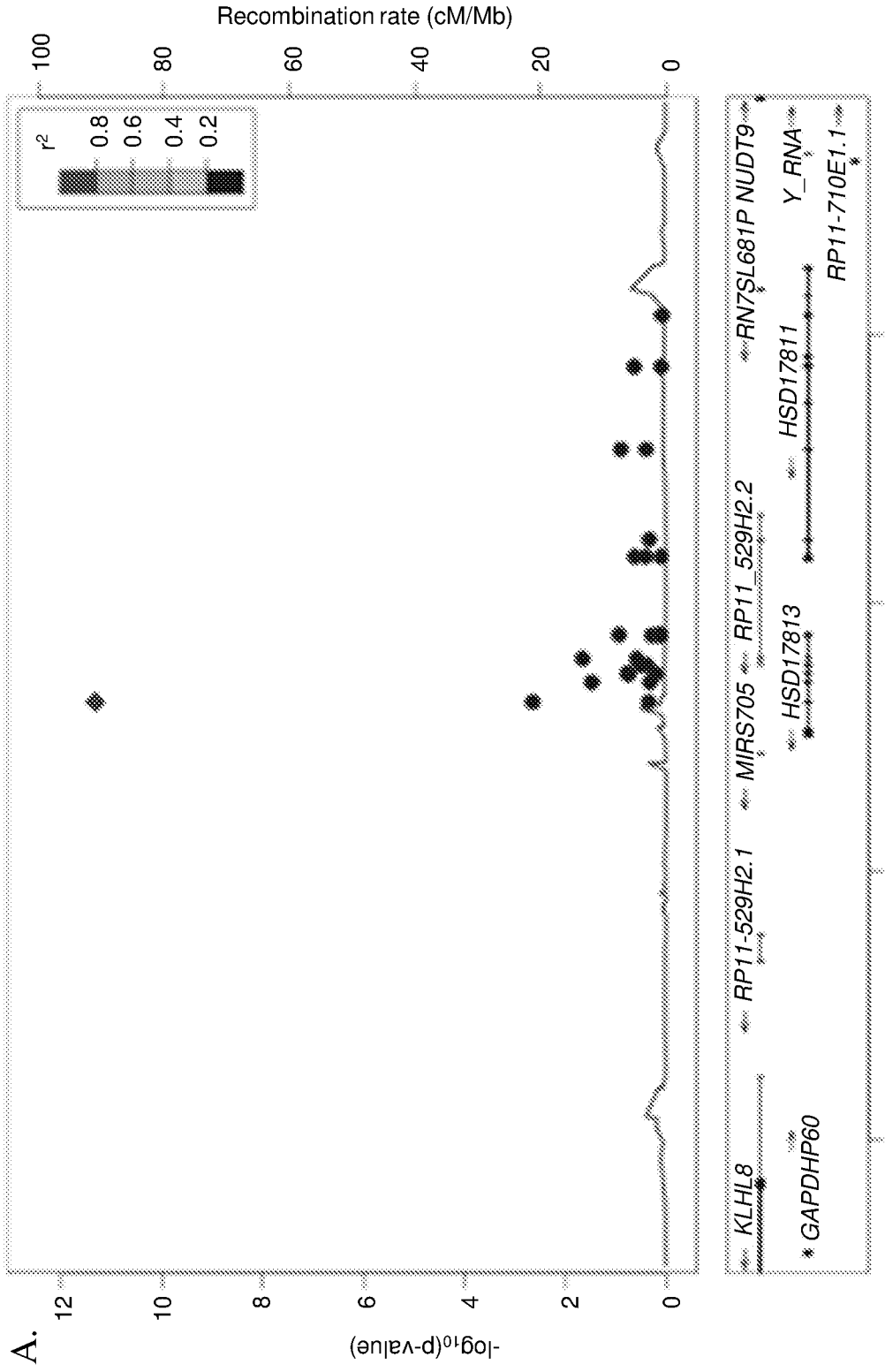

A.
-log10(p-value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
KLHL8
RP11-529H2.1
MIRS705
RP11_529H2.2
RN7SL681P NUDT9
GAPDHP60
HSD17813
HSD17811
Y_RNA
RP11-710E1.1
Position on chr4 (Mb)

Figure 6

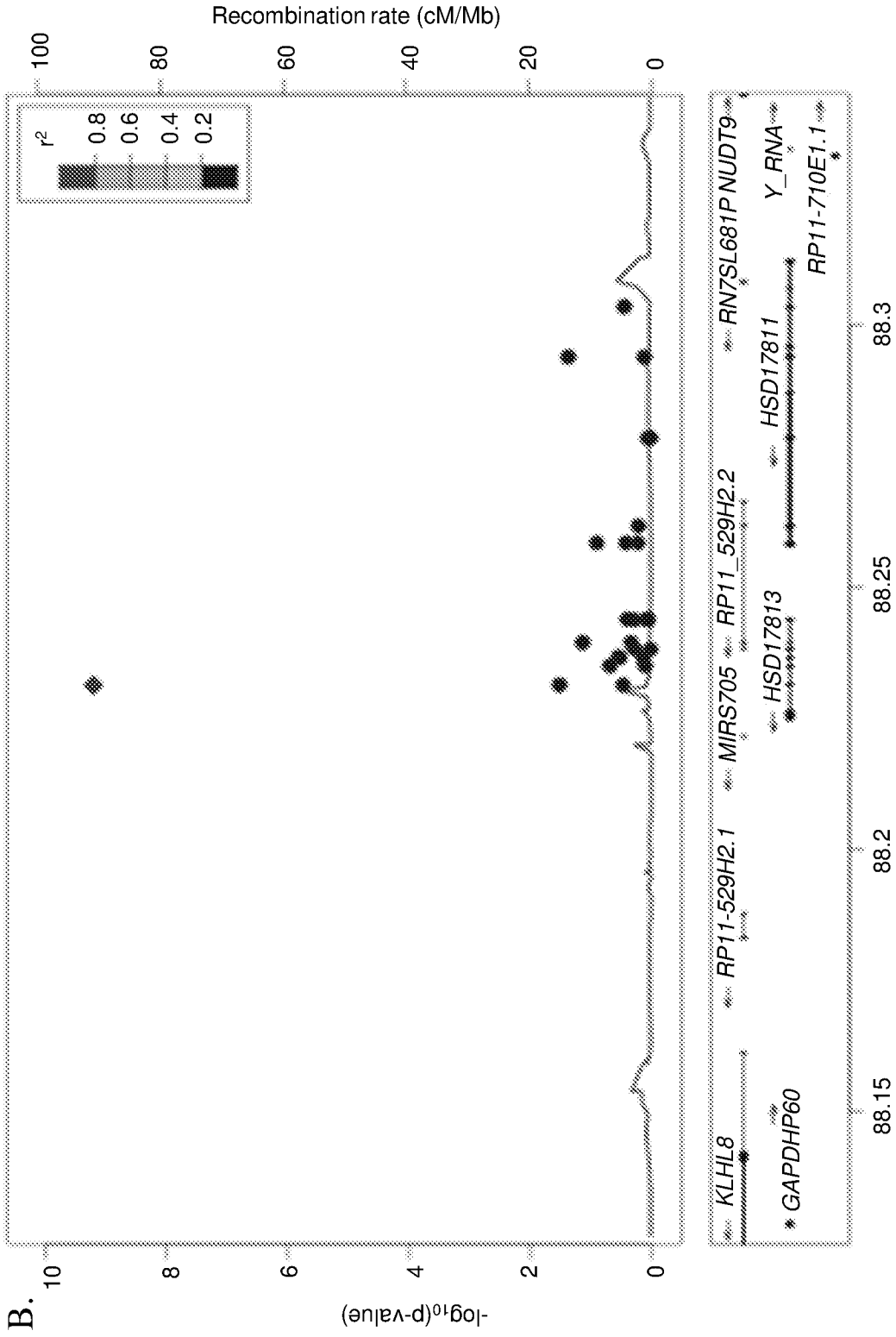


Figure 6 (cont.)

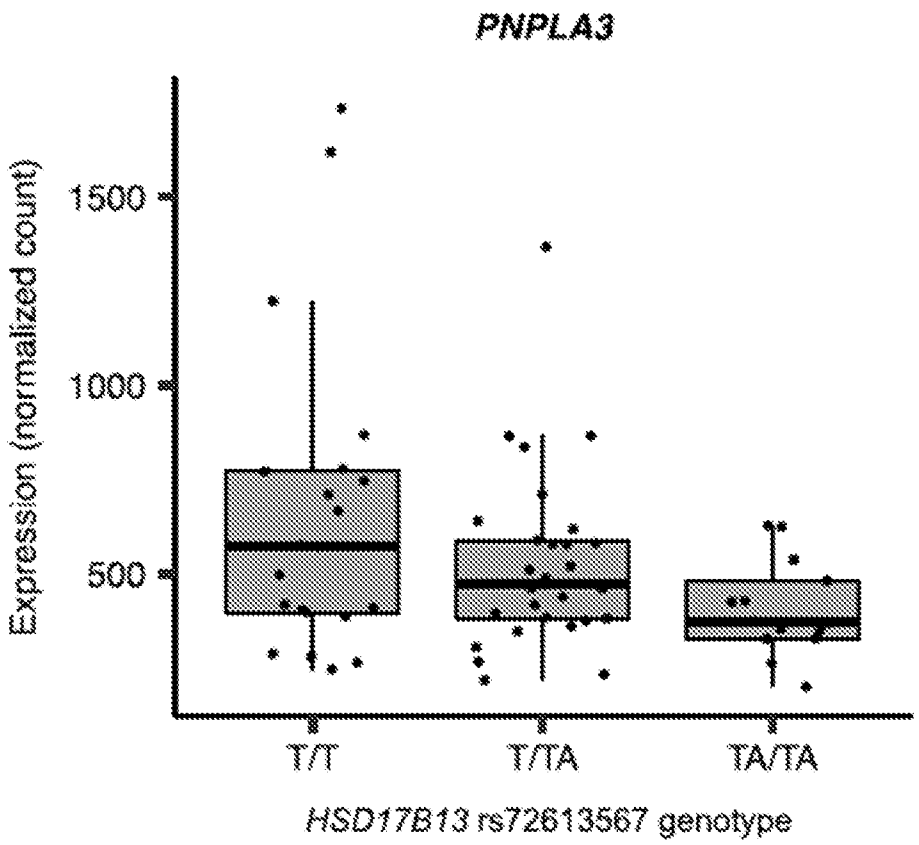

PNPLA3
Expression (normalized count)
1500
1000
500
T/T
T/TA
TA/TA
HSD17B13 rs72613567 genotype

Figure 7

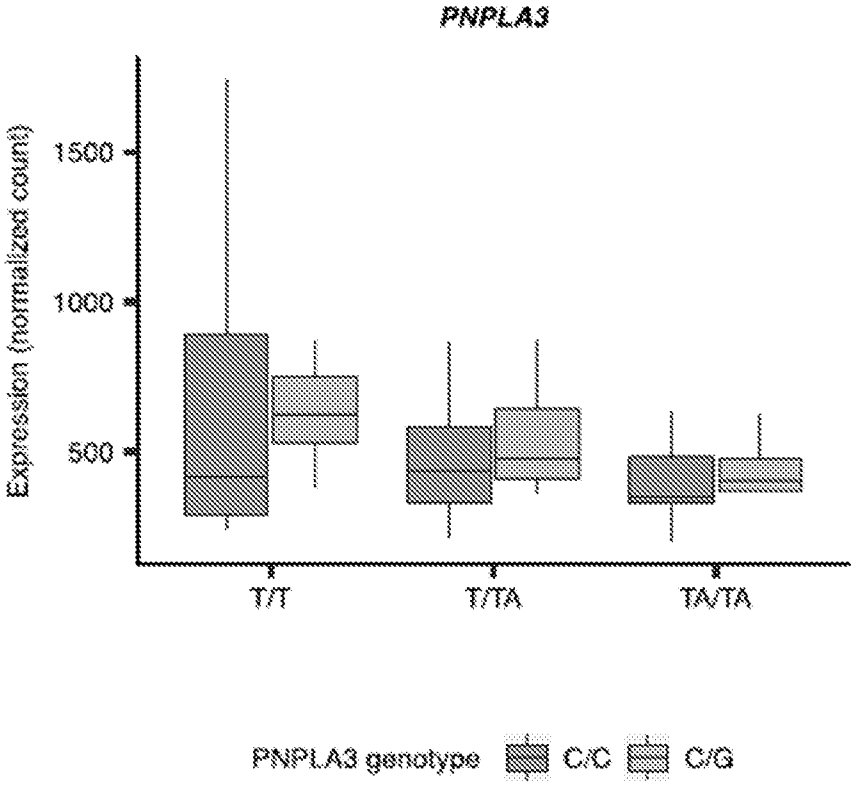

PNPLA3
Expression (normalized count)
1500
1000
500
T/T
T/TA
TA/TA
PNPLA3 genotype
C/C
C/G

Figure 8

Phenotype/Subset	N	*HSD17B13 rs72613567 :* [Interaction effect]			*HSD17B13 rs72613567* [Main effect]			*PNPLA3 rs738409* [Main effect]		
log_{10} (ALT)										
Subset	N	Effect (95% CI)	P	AAF	Effect (95% CI)	P	AAF	Effect (95% CI)	P
All	43,309	-0.007 (-0.011,-0.002)	**1.80E-03**	26.36%	-0.006 (-0.009,-0.003)	**1.88E-04**	23.54%	0.026 (0.022,0.029)	**1.97E-50**
Obese	23,051	-0.01 (-0.015,-0.004)	**1.01E-03**	26.48%	-0.009 (-0.013,-0.005)	**6.53E-05**	23.57%	0.037 (0.032,0.042)	**3.13E-53**
Non-obese	20,258	-0.004 (-0.01,0.002)	1.49E-01	26.22%	-0.002 (-0.007,0.002)	3.53E-01	23.51%	0.013 (0.008,0.018)	**1.56E-07**
log_{10} (AST)										
Subset	N	Effect (95% CI)	P	AAF	Effect (95% CI)	P	AAF	Effect (95% CI)	P
All	42,662	-0.004 (-0.007,-0.001)	**4.53E-03**	26.40%	-0.004 (-0.006,-0.002)	**4.78E-04**	23.47%	0.016 (0.014,0.018)	**9.69E-46**
Obese	22,719	-0.006 (-0.01,-0.003)	**1.04E-03**	26.51%	-0.006 (-0.009,-0.003)	**1.42E-04**	23.53%	0.023 (0.02,0.027)	**7.65E-49**
Non-obese	19,943	-0.001 (-0.005,0.003)	4.97E-01	26.26%	-0.001 (-0.004,0.002)	3.42E-01	23.41%	0.008 (0.005,0.011)	**1.56E-06**
Nonalcoholic liver disease										
Subset	N Controls	N Cases	OR (95% CI)	P	AAF	OR (95% CI)	P	AAF	OR (95% CI)	P
All	29,928	1,857	0.919 (0.812,1.039)	1.78E-01	26.43%	0.88 (0.787,0.983)	**2.40E-02**	23.51%	1.764 (1.606,1.938)	**1.76E-32**
Obese	14,243	1,445	0.906 (0.786,1.044)	1.74E-01	26.36%	0.894 (0.788,1.012)	**7.81E-02**	23.65%	1.714 (1.537,1.91)	**2.06E-22**
Non-obese	15,685	412	0.964 (0.75,1.235)	7.71E-01	26.50%	0.845 (0.662,1.069)	1.67E-01	23.38%	1.887 (1.566,2.269)	**1.96E-11**
Alcoholic liver disease										
Subset	N Controls	N Cases	OR (95% CI)	P	AAF	OR (95% CI)	P	AAF	OR (95% CI)	P
All	29,928	190	1.112 (0.749,1.637)	5.94E-01	26.57%	0.578 (0.391,0.834)	**4.56E-03**	22.99%	1.689 (1.298,2.185)	**7.80E-05**
Obese	14,243	97	1.295 (0.741,2.224)	3.56E-01	26.59%	0.501 (0.283,0.839)	**1.22E-02**	22.83%	1.533 (1.052,2.201)	**2.30E-02**
Non-obese	15,685	93	0.956 (0.544,1.65)	8.72E-01	26.55%	0.666 (0.382,1.105)	1.33E-01	23.13%	1.853 (1.275,2.664)	**1.00E-03**

Figure 9

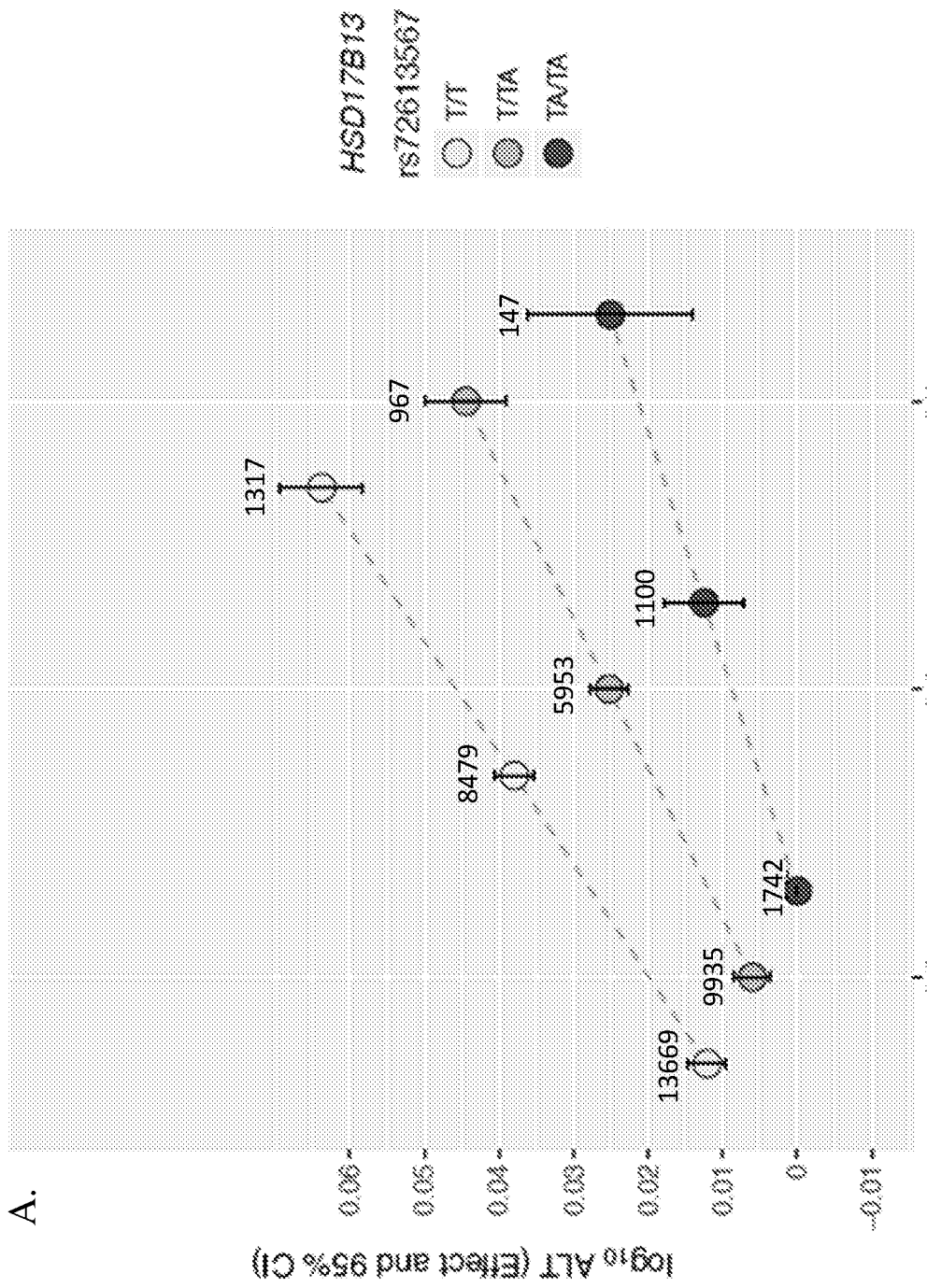

A.
log10 ALT (Effect and 95% CI)
0.06
0.05
0.04
0.03
0.02
0.01
0
-0.01
1317
967
147
8479
5953
1100
13669
9935
1742
C/C
C/G
G/G
PNPLA3 rs738409
HSD17B13
rs72613567
T/T
T/TA
TA/TA

Figure 10

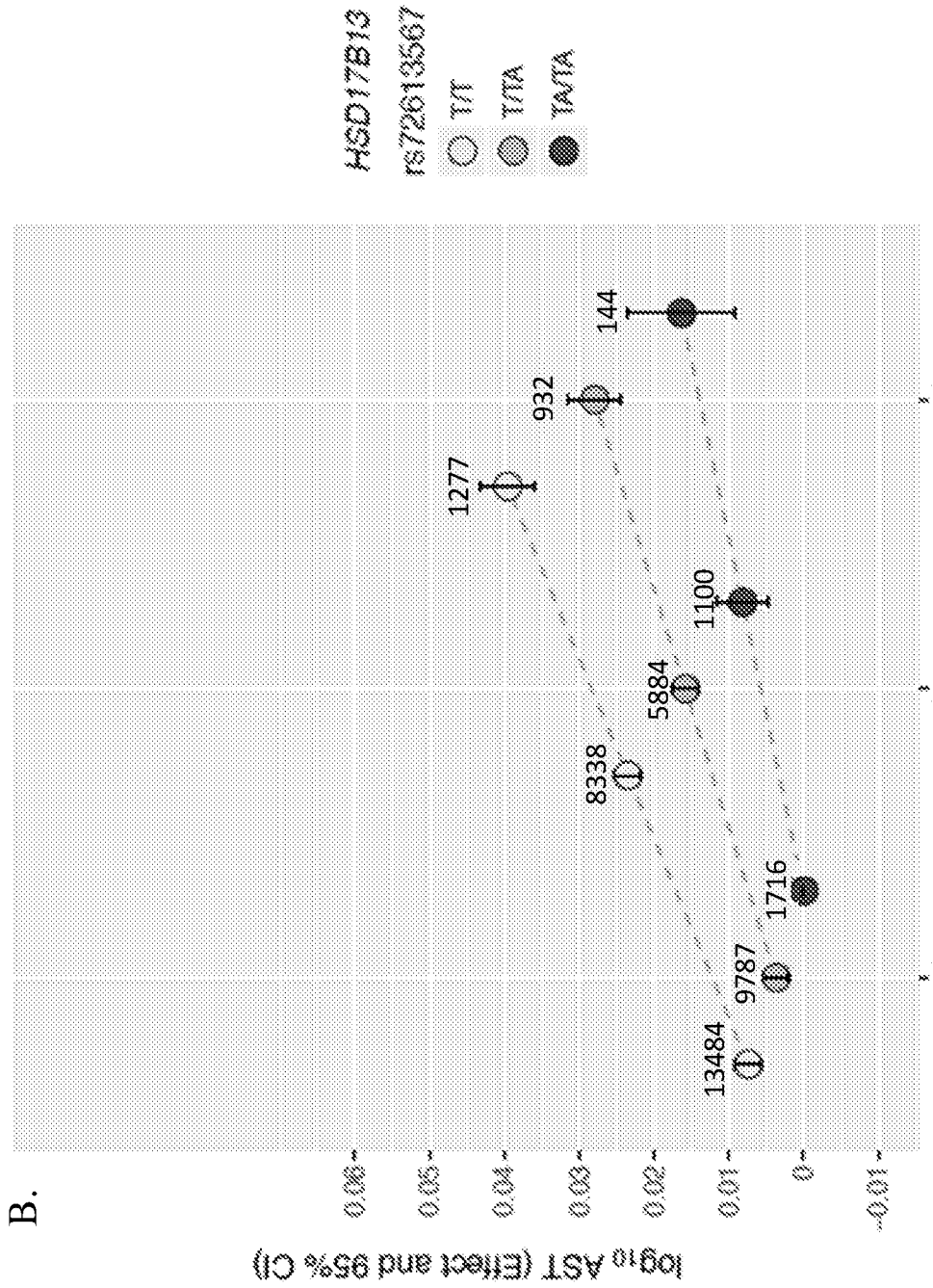


Figure 10 (cont.)

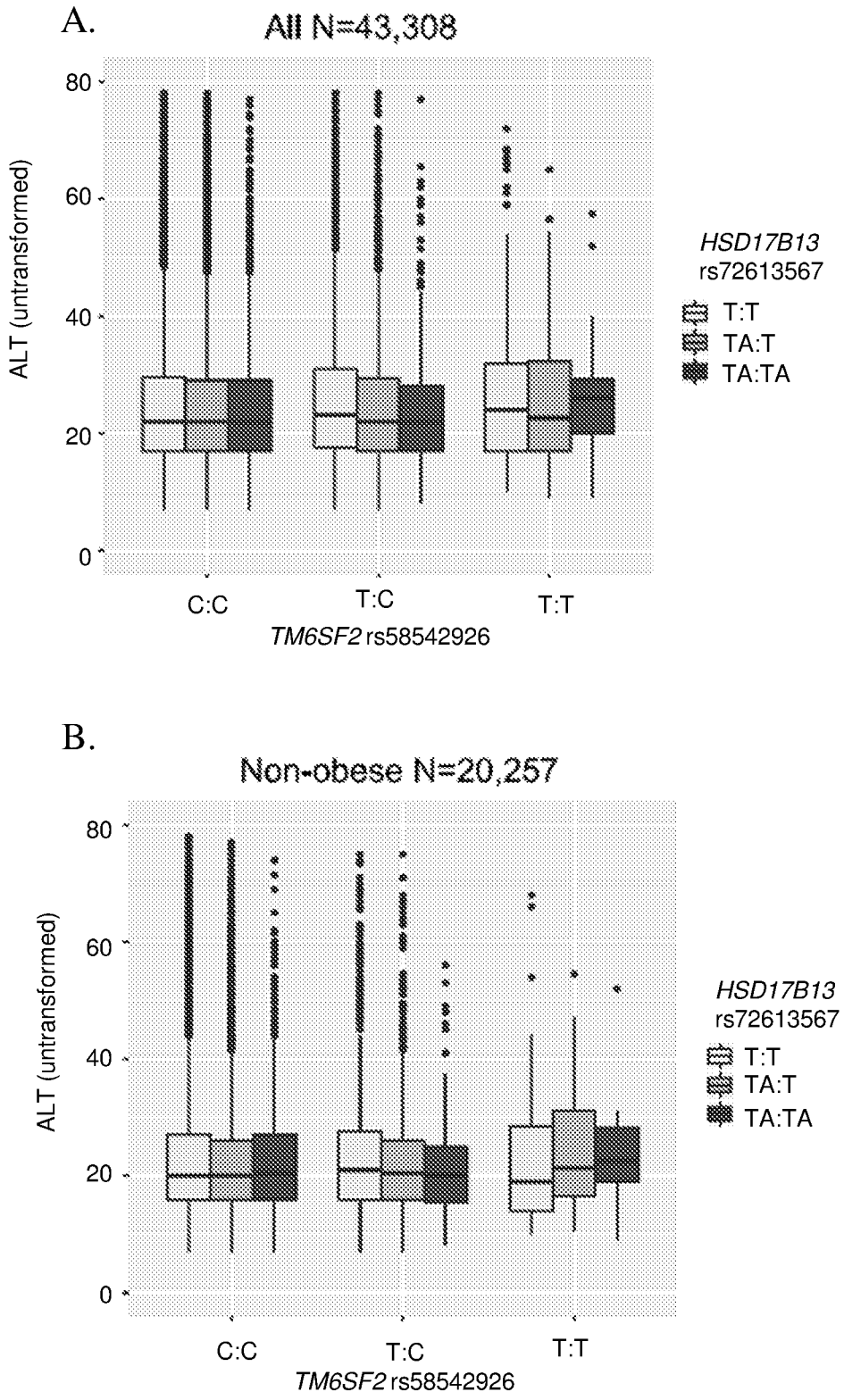
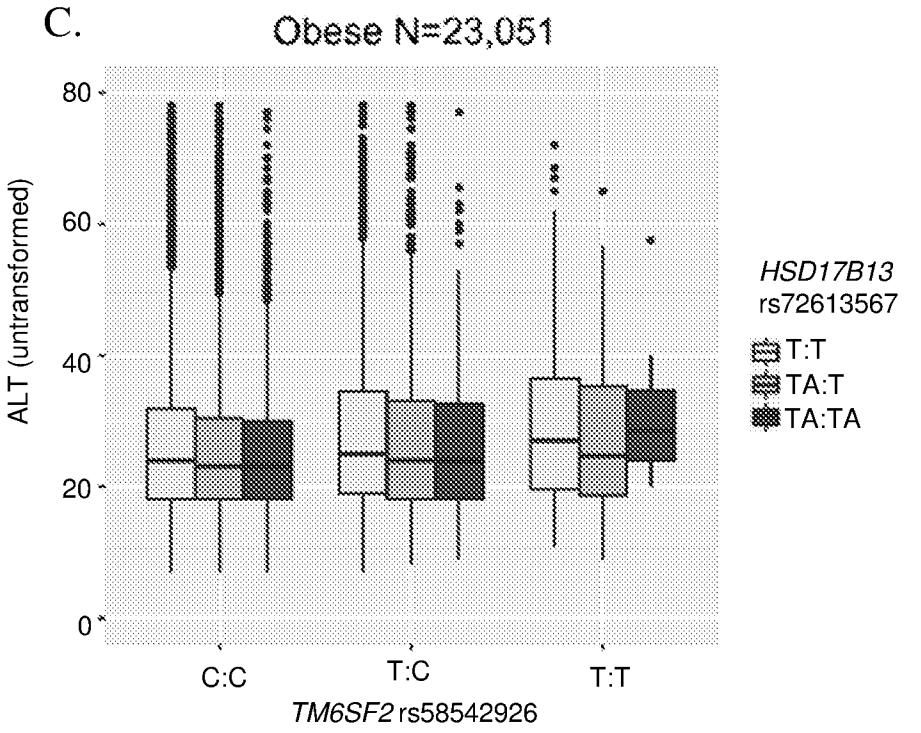

A.
All N=43,308
ALT (untransformed)
80
60
40
20
0
C:C
T:C
T:T
TM6SF2 rs58542926
HSD17B13
rs72613567
T:T
TA:T
TA:TA
B.
Non-obese N=20,257
ALT (untransformed)
80
60
40
20
0
C:C
T:C
T:T
TM6SF2 rs58542926
HSD17B13
rs72613567
T:T
TA:T
TA:TA

Figure 11



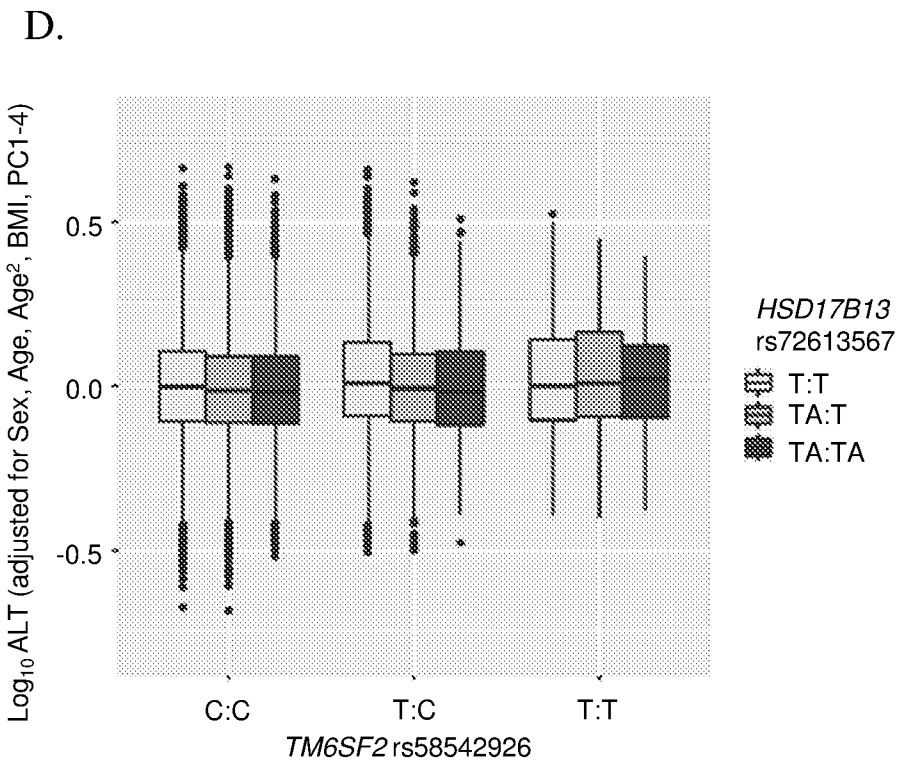
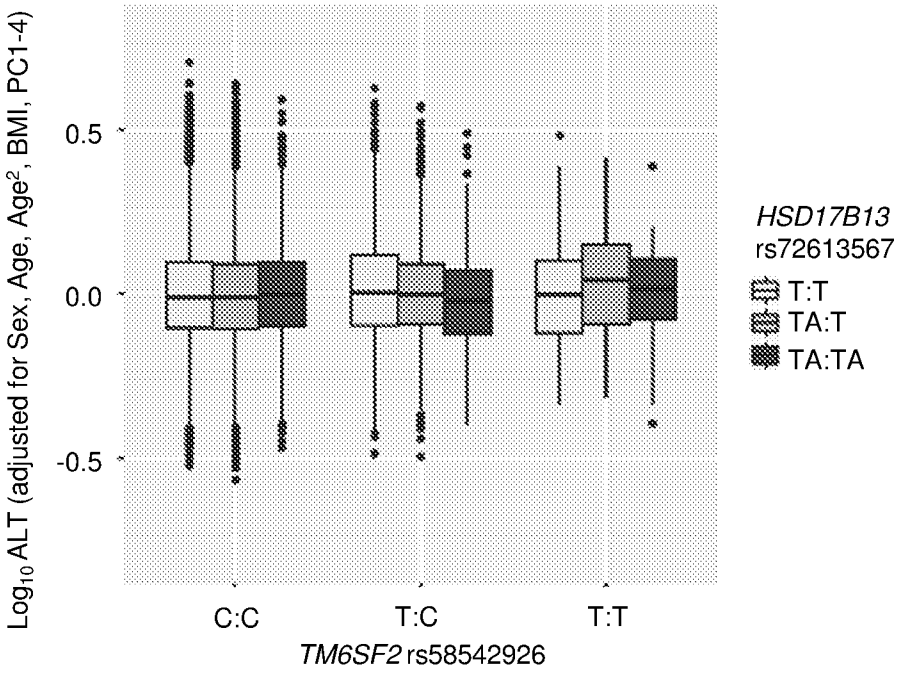


Figure 11 (cont.)

E.



F.

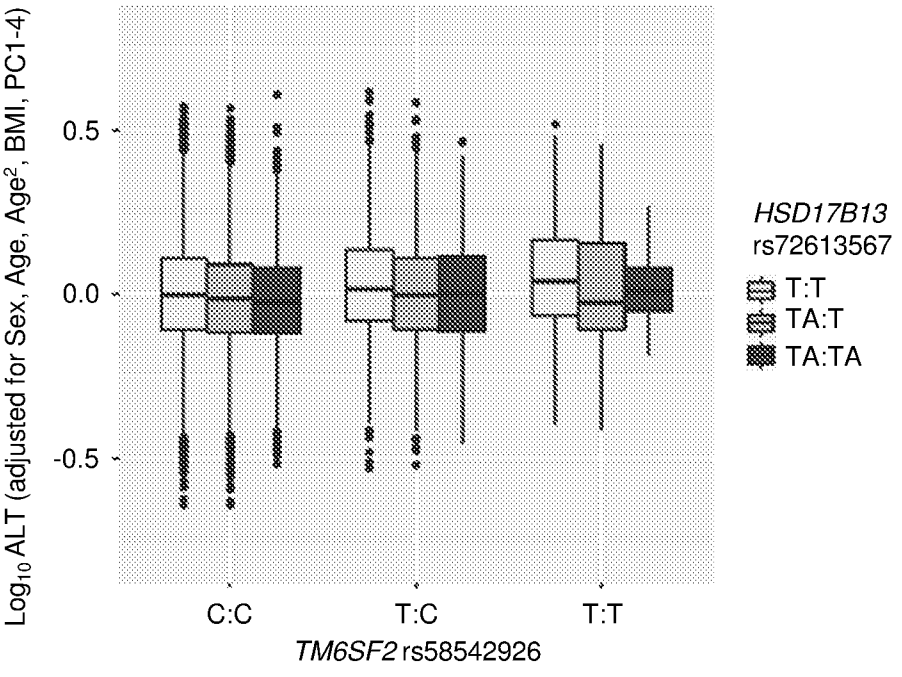


Figure 11 (cont.)

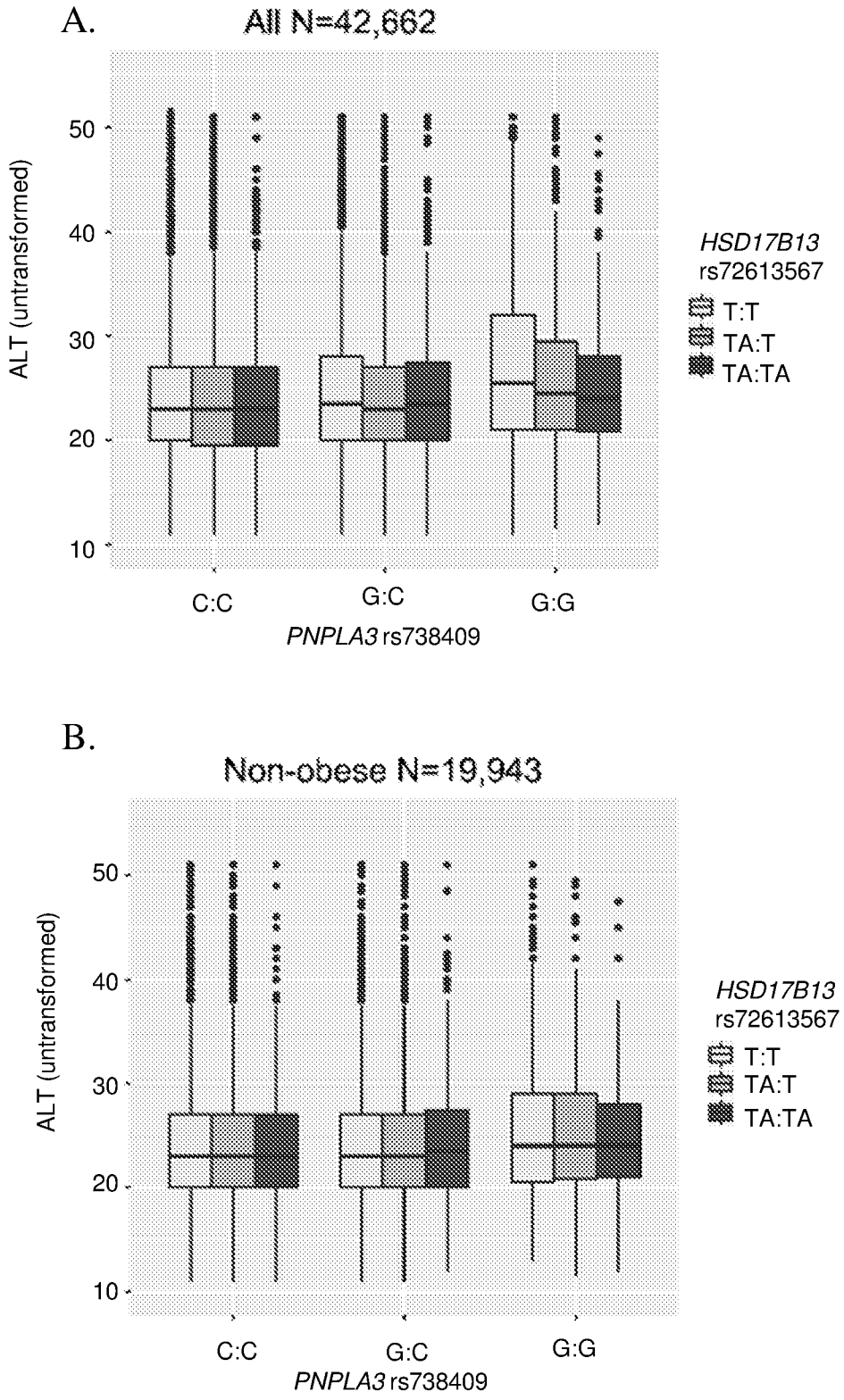
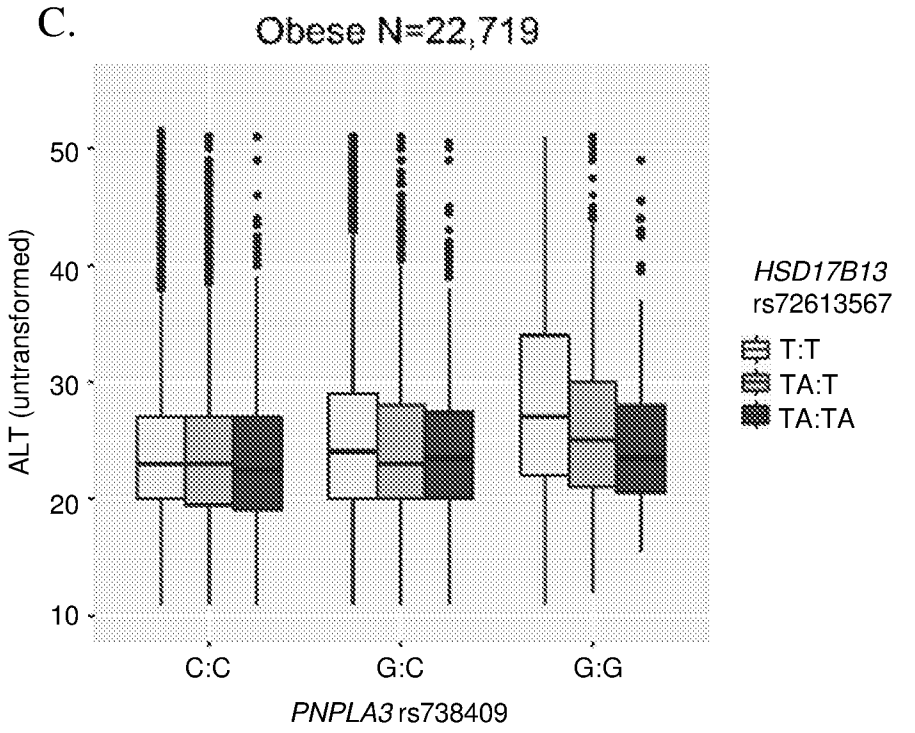

A.
All N=42,662
ALT (untransformed)
50
40
30
20
10
C:C
G:C
G:G
PNPLA3 rs738409
HSD17B13
rs72613567
T:T
TA:T
TA:TA
B.
Non-obese N=19,943
ALT (untransformed)
50
40
30
20
10
C:C
G:C
G:G
PNPLA3 rs738409
HSD17B13
rs72613567
T:T
TA:T
TA:TA

Figure 12



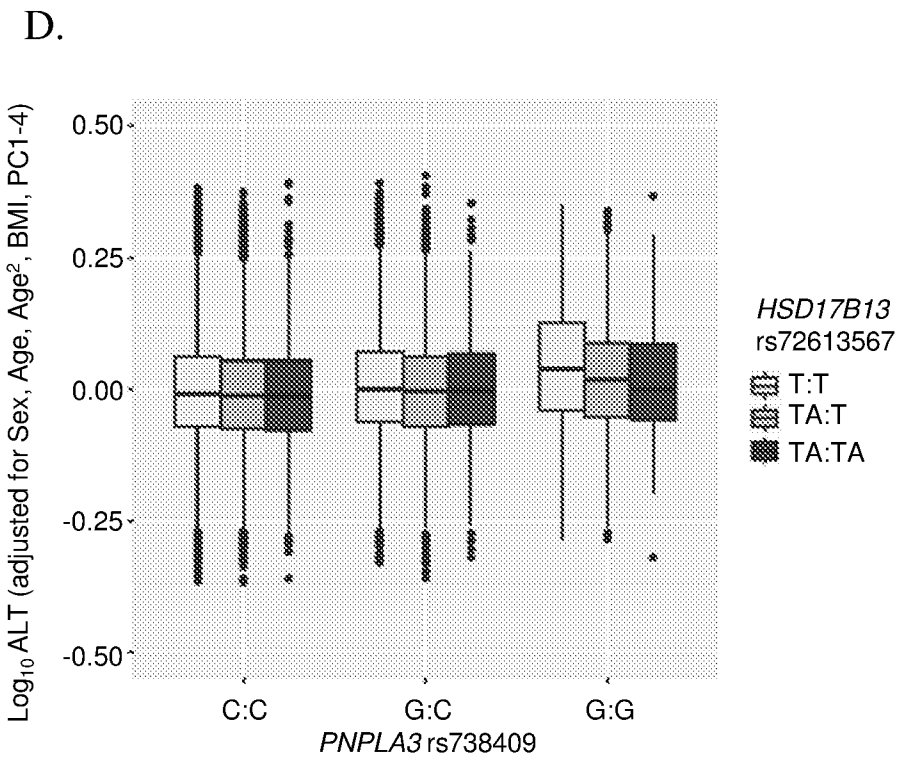
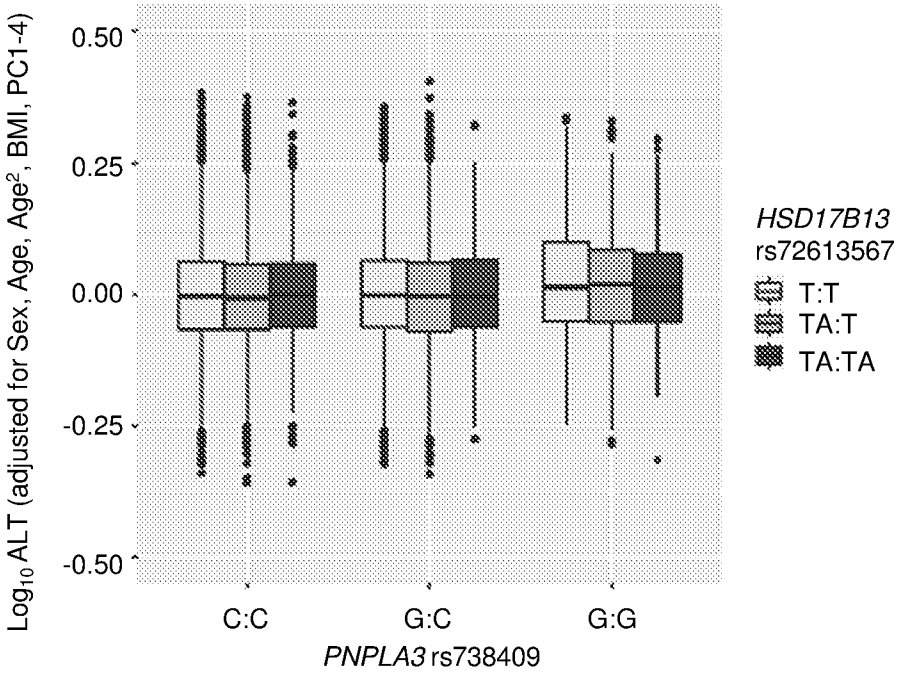


Figure 12 (cont.)

E.



F.

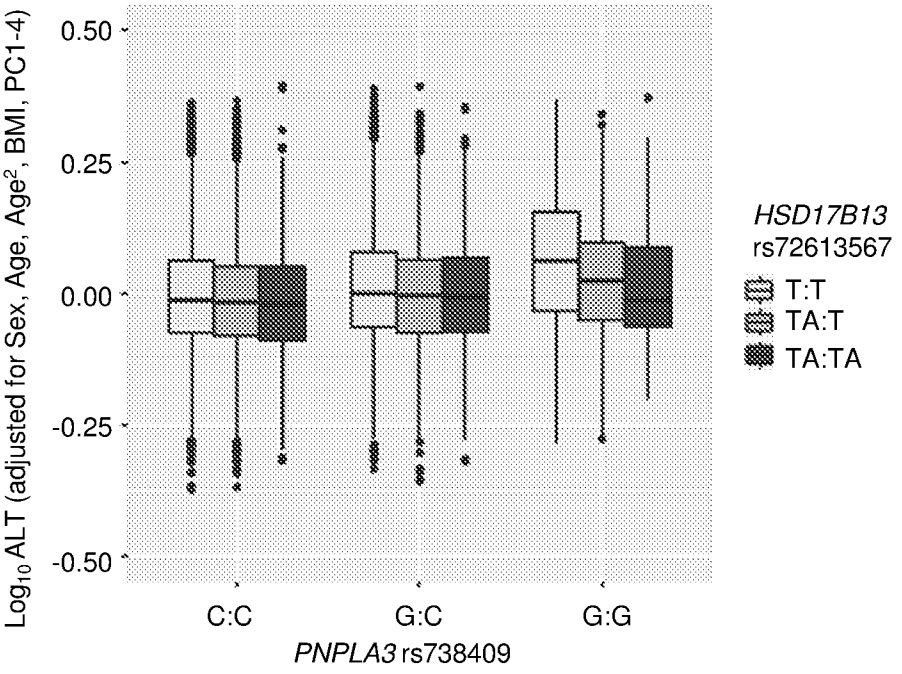


Figure 12 (cont.)

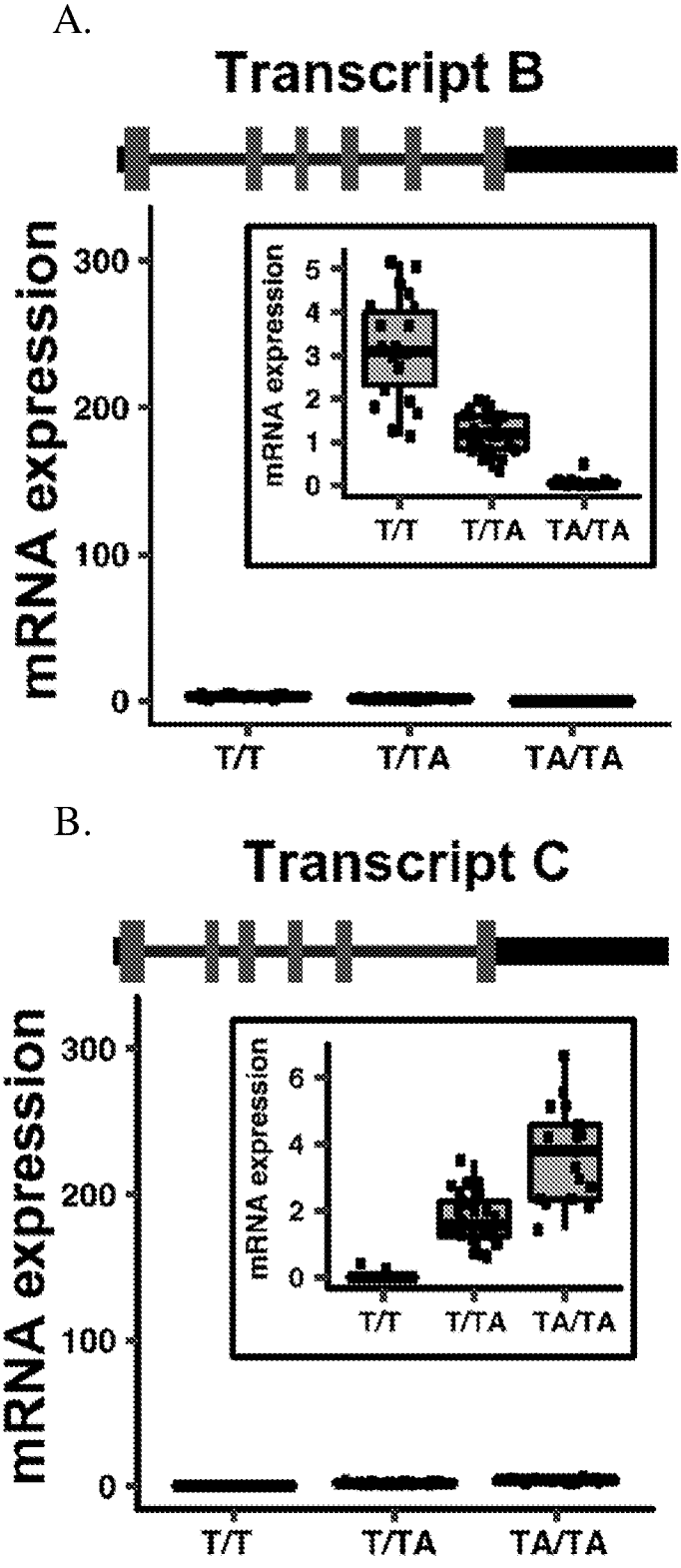
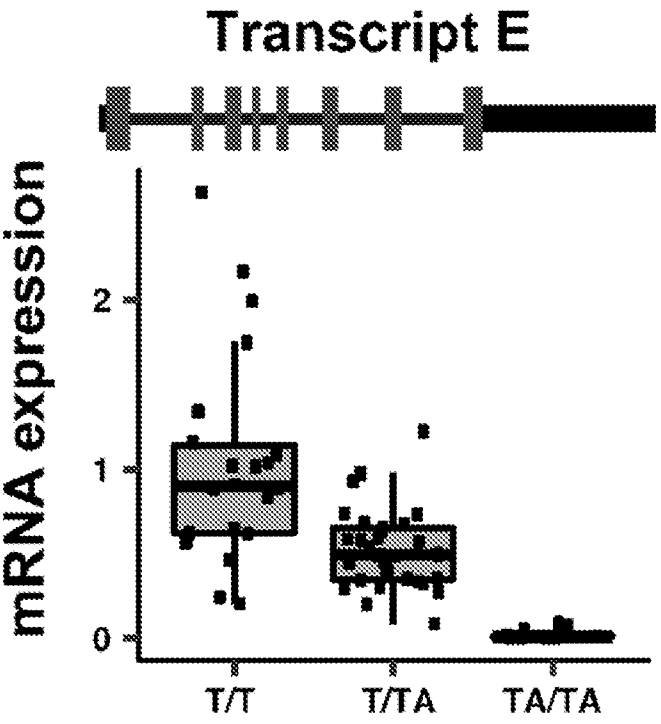

A.
Transcript B
mRNA expression
300
200
100
0
T/T
T/TA
TA/TA
mRNA expression
5
4
3
2
1
0
T/T
T/TA
TA/TA
B.
Transcript C
mRNA expression
300
200
100
0
T/T
T/TA
TA/TA
mRNA expression
6
4
2
0
T/T
T/TA
TA/TA

Figure 13

C.



D.

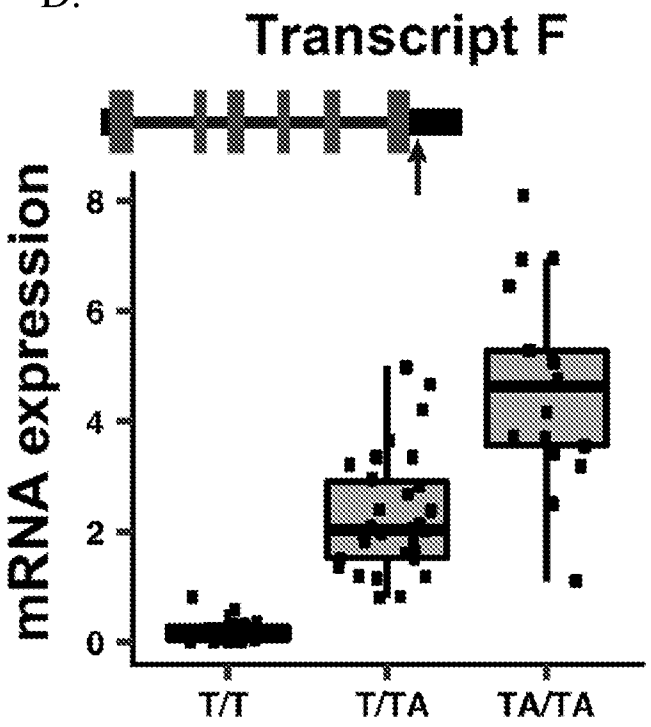
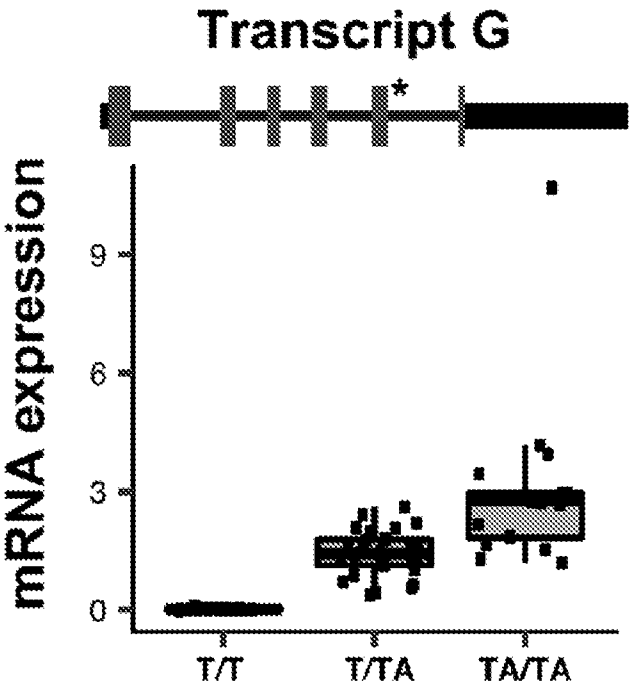


Figure 13 (cont.)

E.



F.

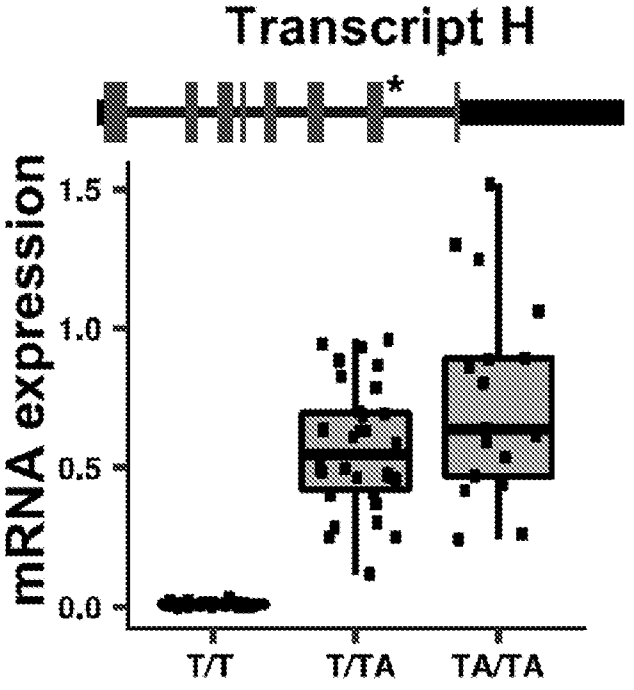


Figure 13 (cont.)

A.

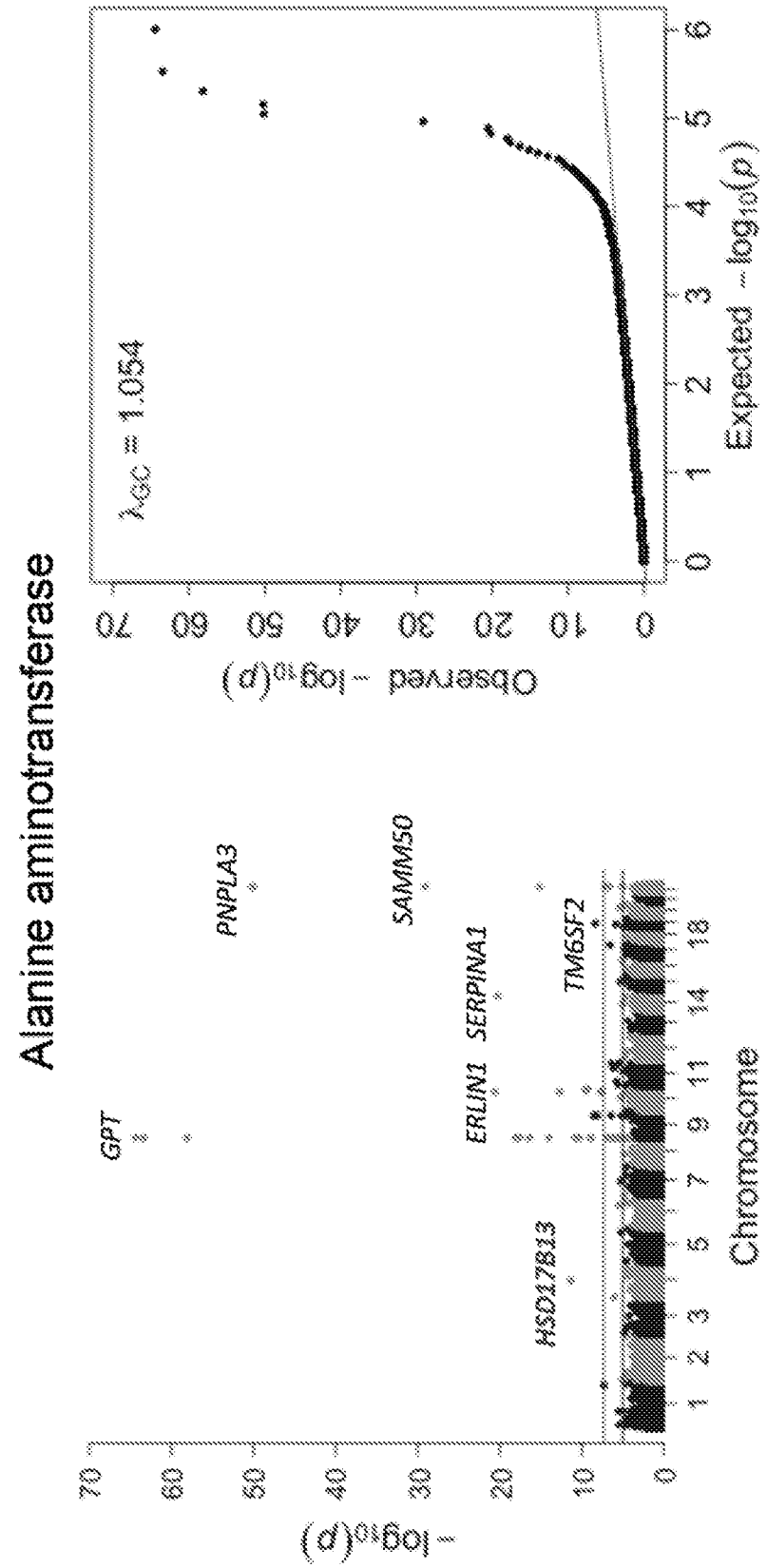

Alanine aminotransferase
GPT
PNPLA3
SAMM50
ERLIN1
SERPINA1
TM6SF2
HSD17B13
−log10(p)
Chromosome
Observed −log10(p)
Expected −log10(p)
λGC = 1.054

Figure 14

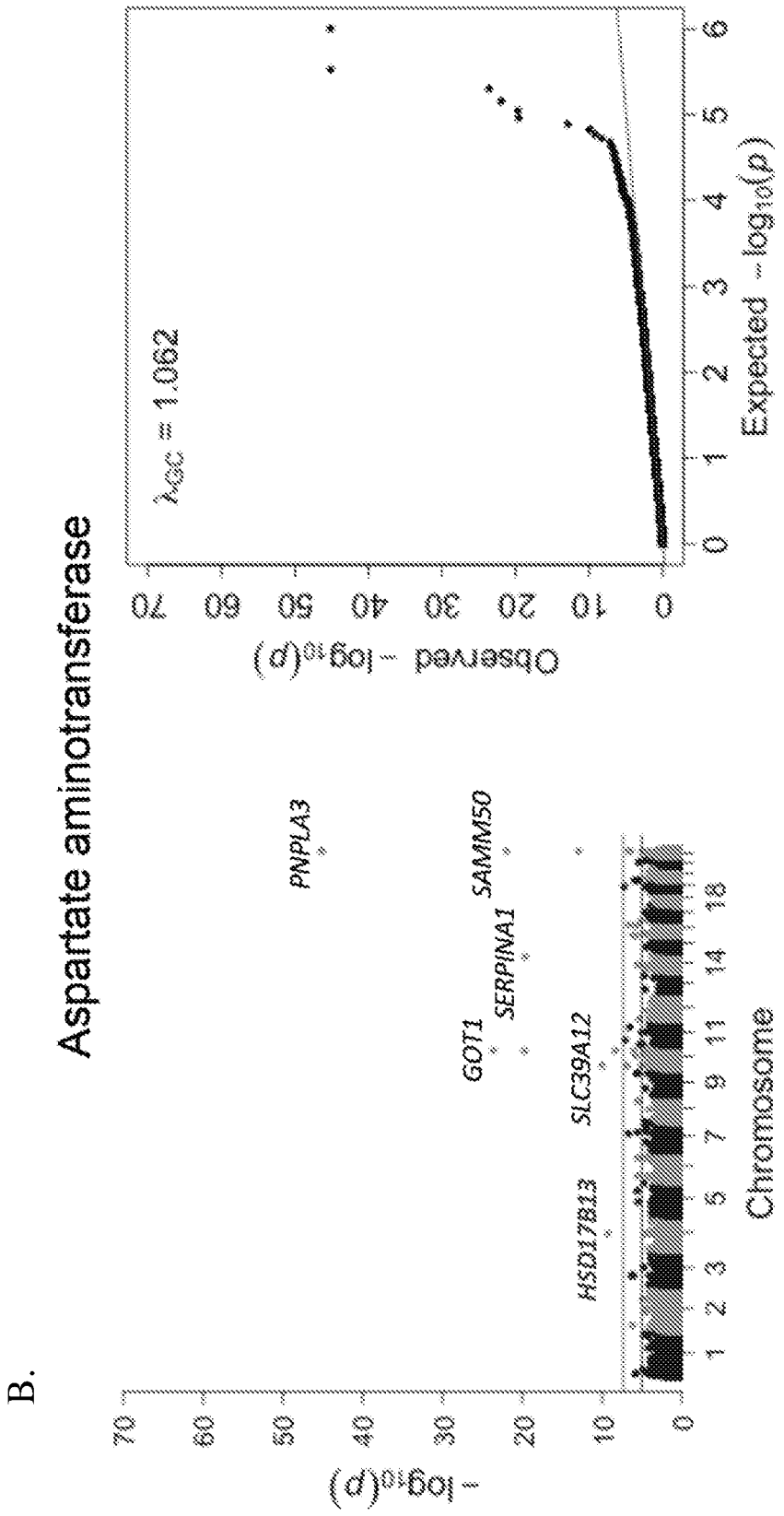


Figure 14 (cont.)

A.

Description	Genotype	Case	Control	Genotypic OR (95% CI)	Allelic OR (95% CI)	P-value
Alcoholic liver disease (n=190) vs. Normal (n=29928)	T/T	128	16084	1(--)		
	T/TA	54	11754	0.58 (0.42-0.80)	-0.62 (0.48-0.81)	1.82e-04
	TA/TA	8	2090	0.47 (0.23-0.97)		
Alcoholic cirrhosis (n=124) vs. Normal (n=29928)	T/T	85	16084	1(--)		
	T/TA	36	11754	0.58 (0.39-0.86)	0.56 (0.41-0.78)	3.35e-04
	TA/TA	3	2090	0.27 (0.09-0.85)		
Nonalcoholic liver disease (n=1857) vs. Normal (n=29928)	T/T	1090	16084	1(--)		
	T/TA	665	11754	0.83 (0.75-0.92)	0.84 (0.78-0.91)	1.31e-05
	TA/TA	102	2090	0.70 (0.57-0.87)		
Nonalcoholic cirrhosis (n=374) vs. Normal (n=29928)	T/T	231	16084	1(--)		
	T/TA	127	11754	0.74 (0.60-0.93)	0.74 (0.62-0.88)	4.48e-04
	TA/TA	16	2090	0.51 (0.31-0.85)		
Hepatocellular carcinoma (n=75) vs. Normal (n=29928)	T/T	49	16084	1(--)		
	T/TA	23	11754	0.65 (0.39-1.06)	0.67 (0.45-1.00)	4.66e-02
	TA/TA	3	2090	0.48 (0.15-1.56)		

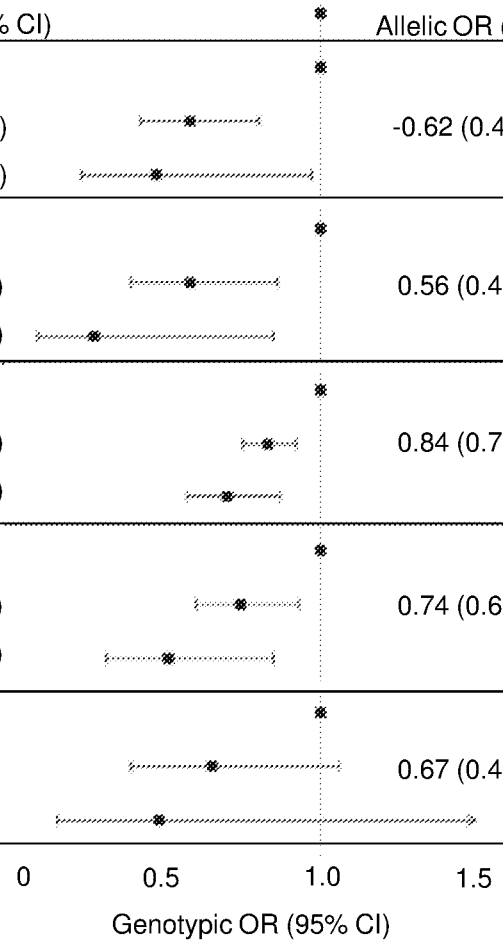


Figure 15

B.

Description	Genotype	Case	Control	Genotypic OR (95% CI)	Allelic OR (95% CI)	P-value
Any liver disease (n=517) vs. Normal (n=4279)	T/T	399	3238	1(--)		
	T/TA	108	910	0.74 (0.57-0.97)	0.70 (0.57-0.88)	1.77e-03
	TA/TA	10	131	0.41 (0.21-0.83)		
Alcoholic liver disease (n=223) vs. Normal (n=4279)	T/T	167	3238	1(--)		
	T/TA	52	910	0.85 (0.59-1.23)	0.77 (0.57-1.04)	7.65e-02
	TA/TA	4	131	0.37 (0.13-1.08)		
Alcoholic cirrhosis (n=215) vs. Normal (n=4279)	T/T	163	3238	1(--)		
	T/TA	49	910	0.83 (0.57-1.20)	0.72 (0.53-0.99)	4.37e-02
	TA/TA	3	131	0.29 (0.09-0.97)		

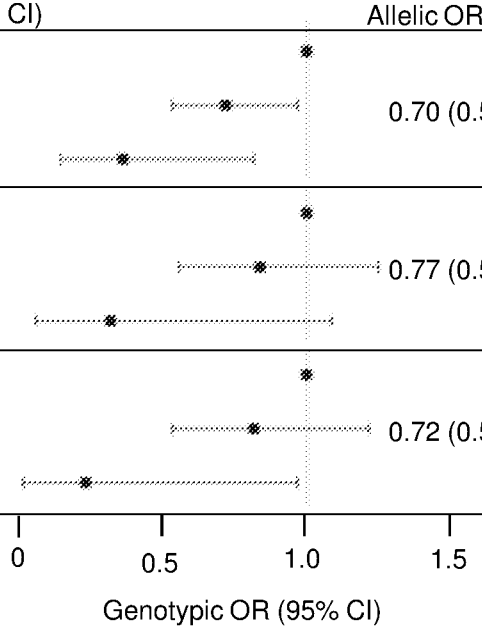


Figure 15 (cont.)

Description	Genotype	Case	Control	Genotypic OR (95% CI)	Allelic OR (95% CI)	P-value
Nonalcoholic liver disease (n=212) vs. Normal (n=4279)	T/T	170	3238	1(--)	0.63 (0.45-0.88)	7.84e-03
	T/TA	38	910	0.61 (0.41-0.91)		
	TA/TA	4	131	0.45 (0.16-1.29)		
Nonalcoholic cirrhosis (n=100) vs. Normal (n=4279)	T/T	81	3238	1(--)	0.65 (0.40-1.07)	8.96e-02
	T/TA	16	910	0.53 (0.29-0.97)		
	TA/TA	3	131	0.79 (0.23-2.74)		
Hepatocellular carcinoma (n=44) vs. Normal (n=4279)	T/T	34	3238	1(--)	0.79 (0.42-1.52)	4.85e-01
	T/TA	8	910	0.65 (0.28-1.54)		
	TA/TA	2	131	0.93 (0.20-4.39)		

Figure 15 (cont.)

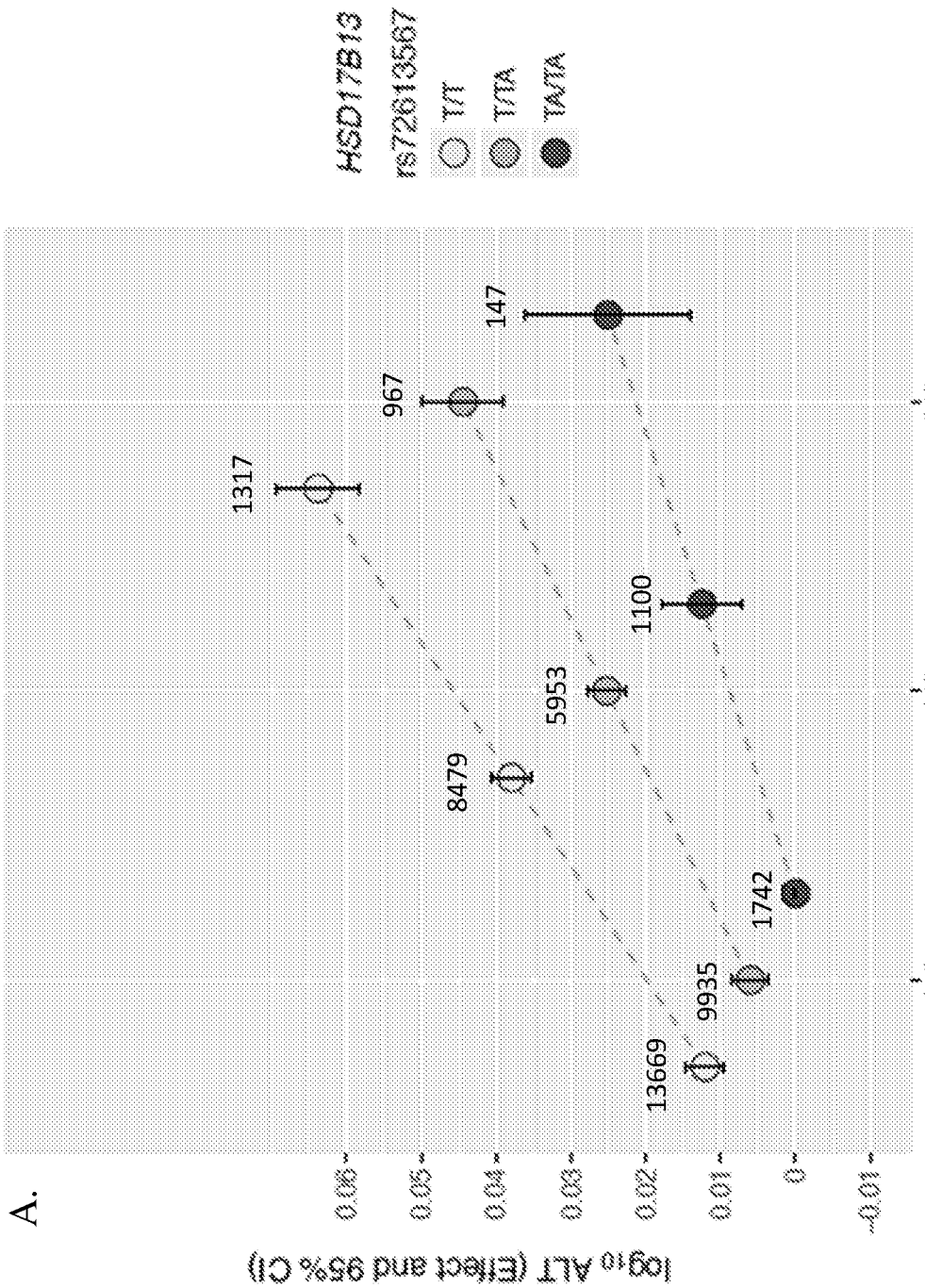

A.
log10 ALT (Effect and 95% CI)
0.06
0.05
0.04
0.03
0.02
0.01
0
-0.01
1317
967
147
8479
5953
1100
13669
9935
1742
C/C
C/G
G/G
PNPLA3 rs738409
HSD17B13
rs72613567
T/T
T/TA
TA/TA

Figure 16

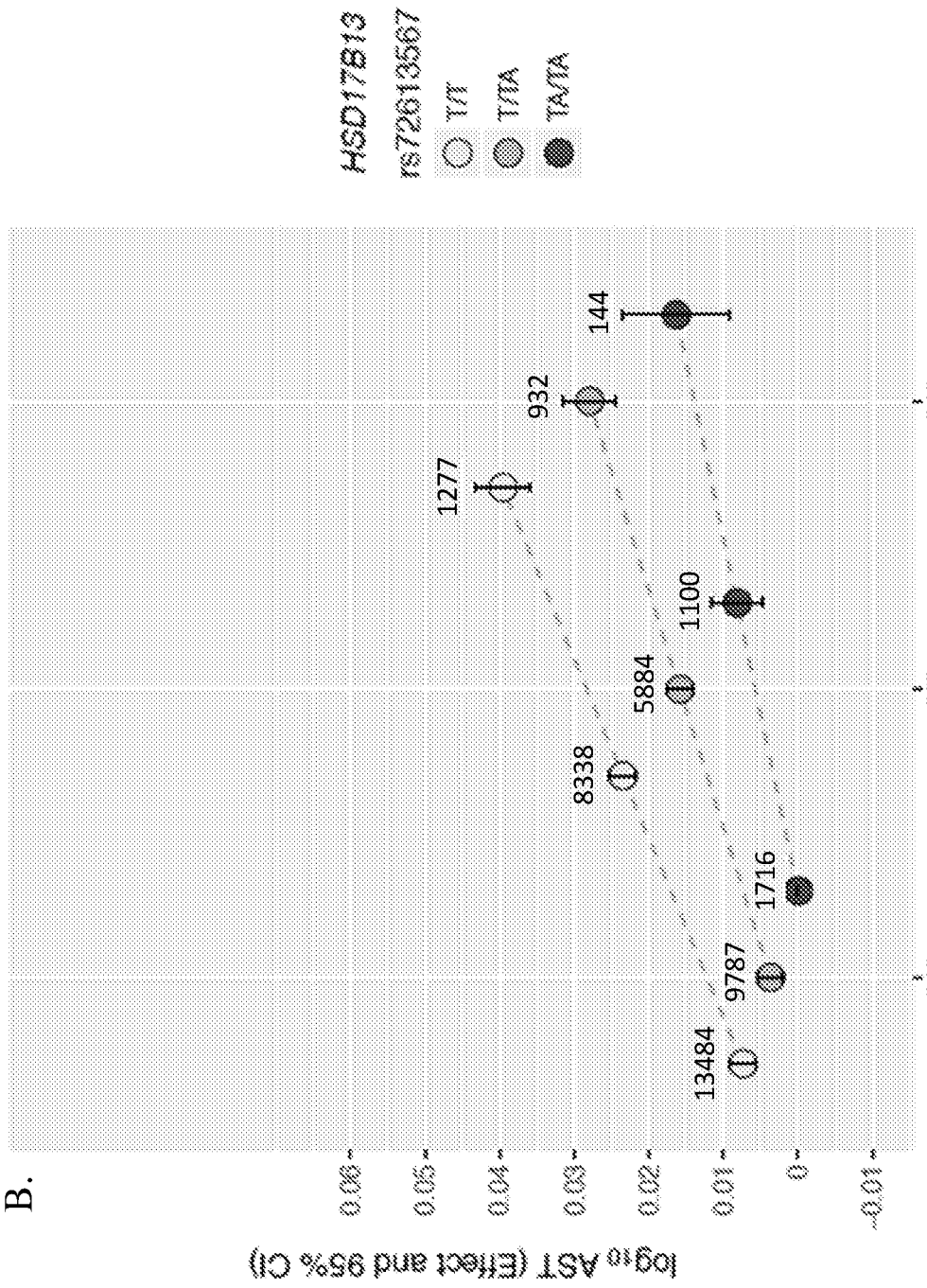


Figure 16 (cont.)

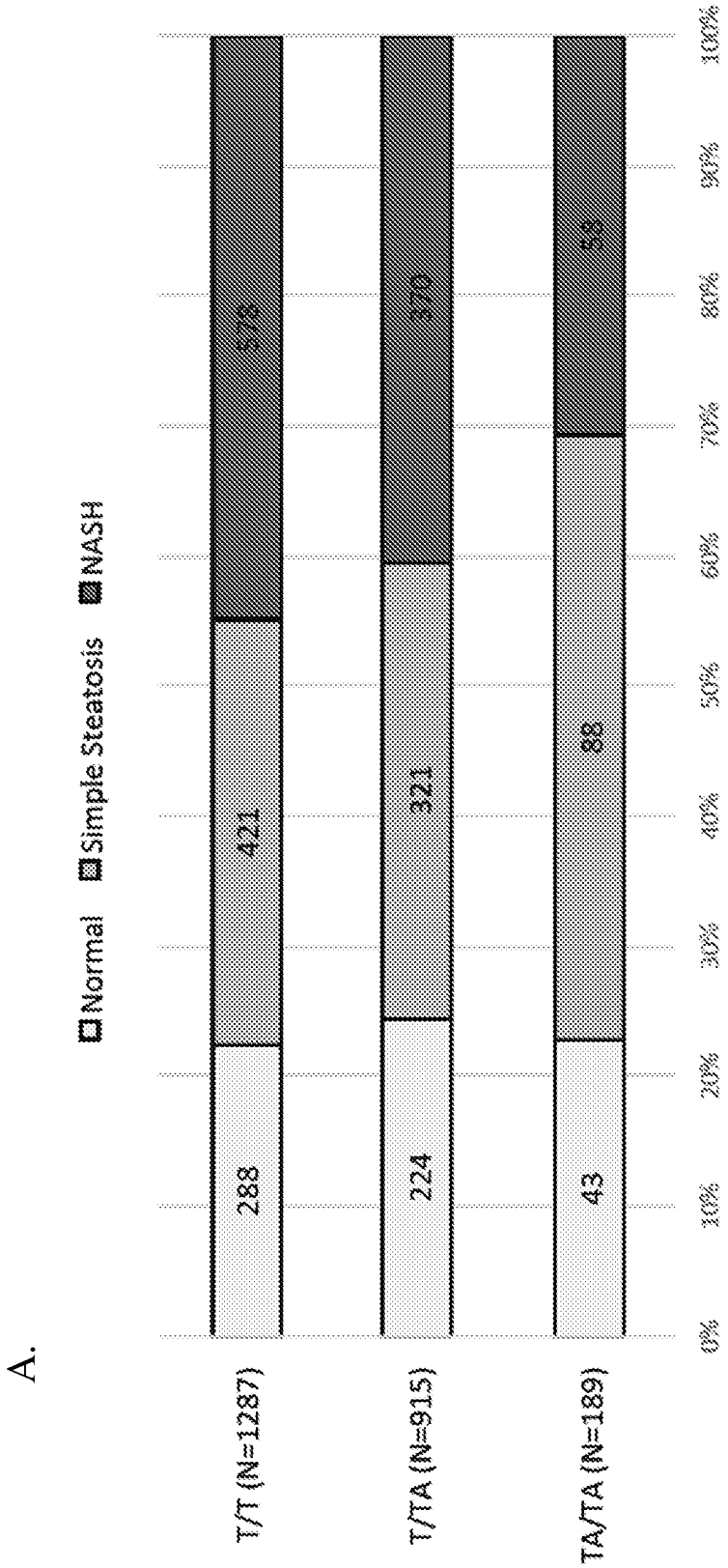

A.
Normal
Simple Steatosis
NASH
T/T (N=1287)
T/TA (N=915)
TA/TA (N=189)
288
421
578
224
321
370
43
88
59
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Figure 17

B.

Description	Genotype	Case	Control	Genotypic OR (95% CI)	Allelic OR (95% CI)	P-value
Simple steatosis (n=830) vs. Normal (n=555)	T/T	421	288	1(--)		
	T/TA	321	224	1.00 (0.80-1.27)	1.11 (0.94-1.32)	2.11e-01
	TA/TA	88	43	1.43 (0.95-2.16)		
NASH (n=1006) vs. Normal (n=555)	T/T	578	288	1(--)		
	T/TA	370	224	0.87 (0.69-1.09)	0.86 (0.72-1.02)	8.53e-02
	TA/TA	58	43	0.71 (0.45-1.11)		
NASH (n=1006) vs. Simple steatosis (n=830)	T/T	578	421	1(--)		
	T/TA	370	321	0.87 (0.71-1.06)	0.77 (0.66-0.90)	6.47e-04
	TA/TA	58	88	0.48 (0.33-0.70)		

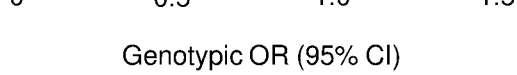


Figure 17 (cont.)

A.

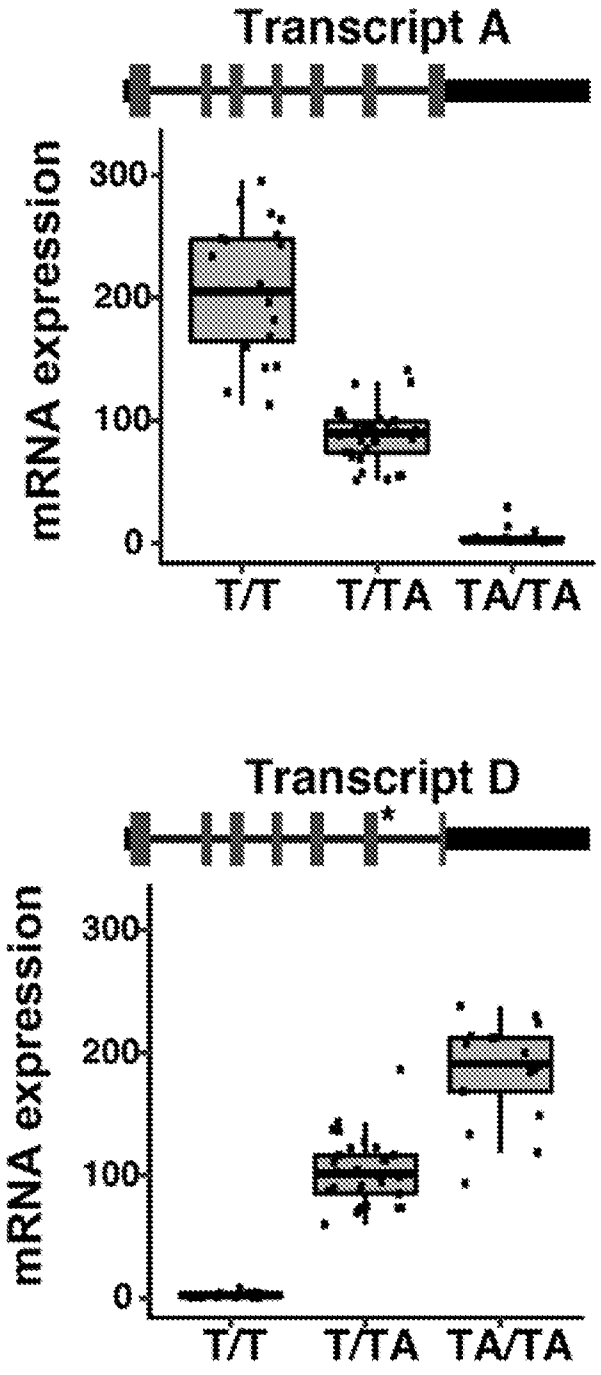

Transcript A
mRNA expression
300
200
100
0
T/T
T/TA
TA/TA
Transcript D
mRNA expression
300
200
100
0
T/T
T/TA
TA/TA

Figure 18

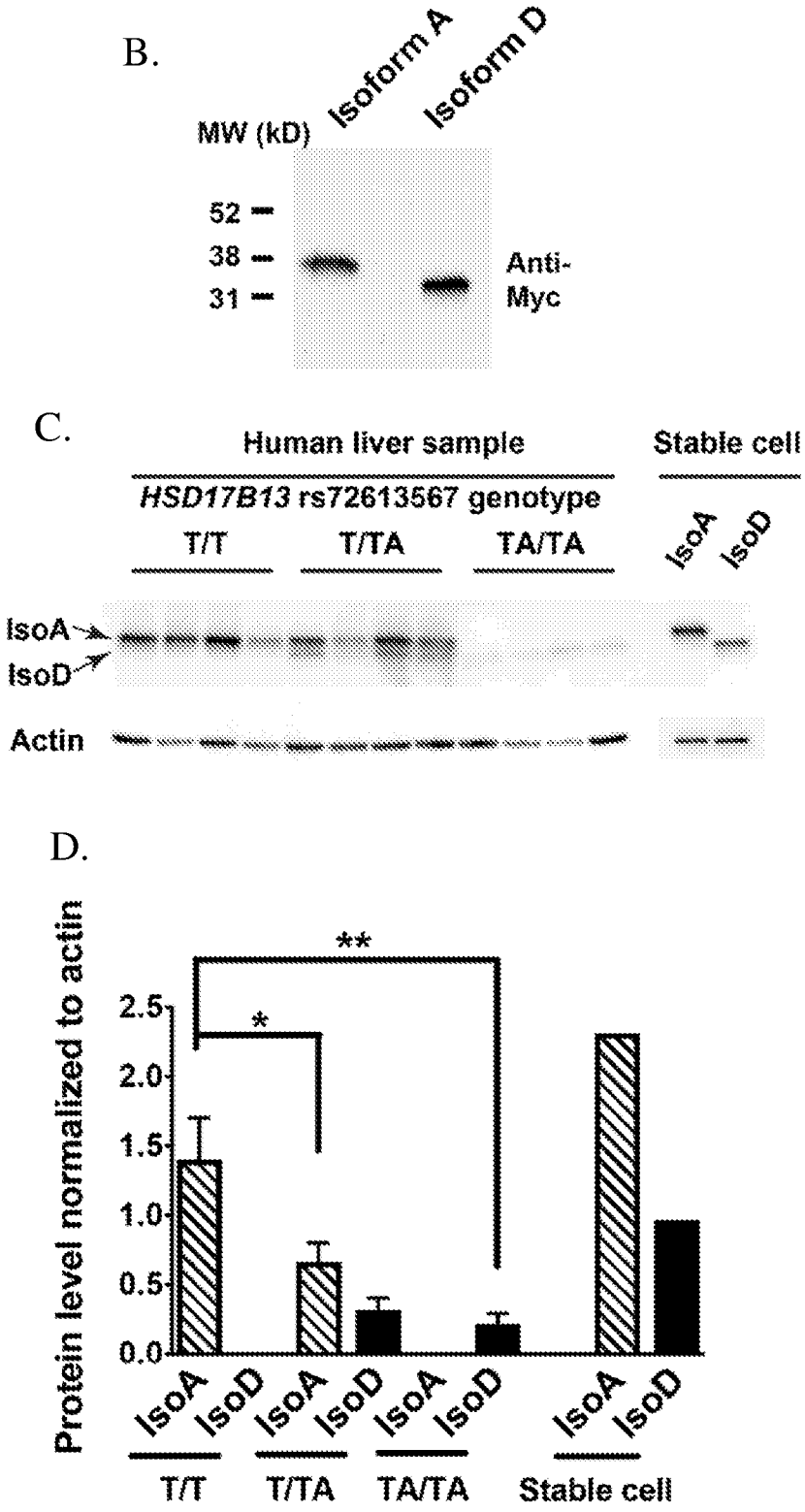


Figure 18 (cont.)

E.

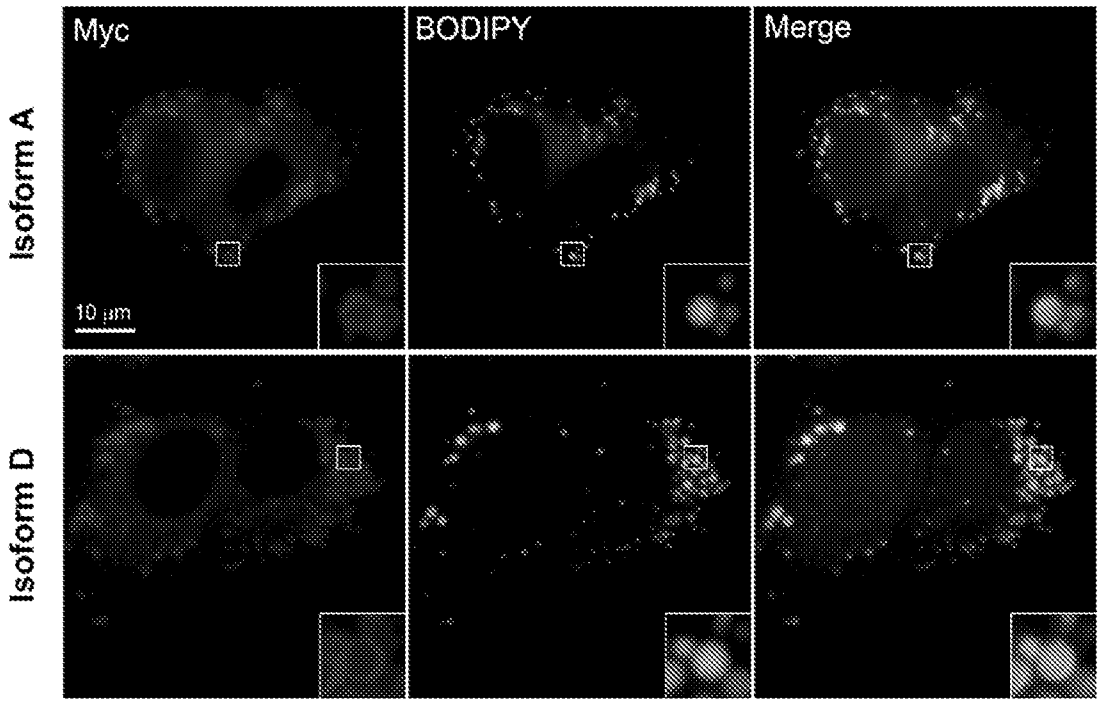
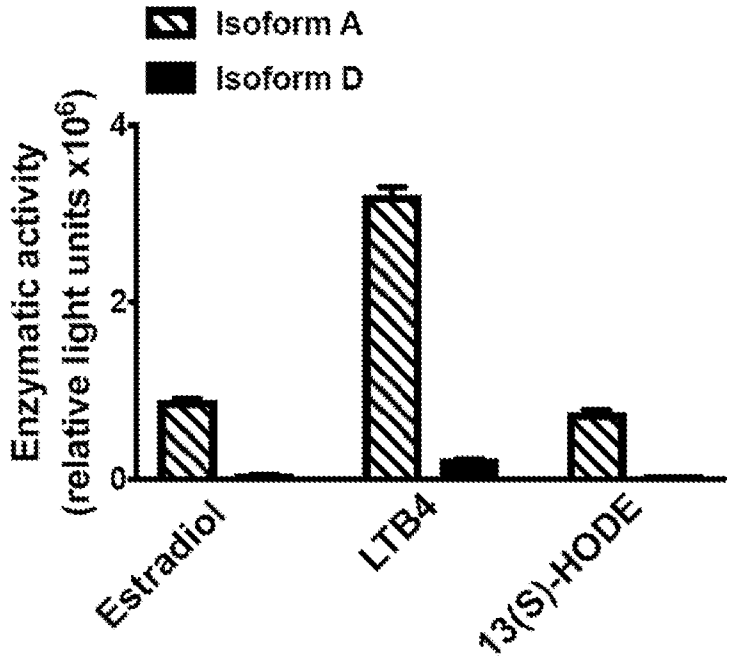


Figure 18 (cont.)

F.



G.

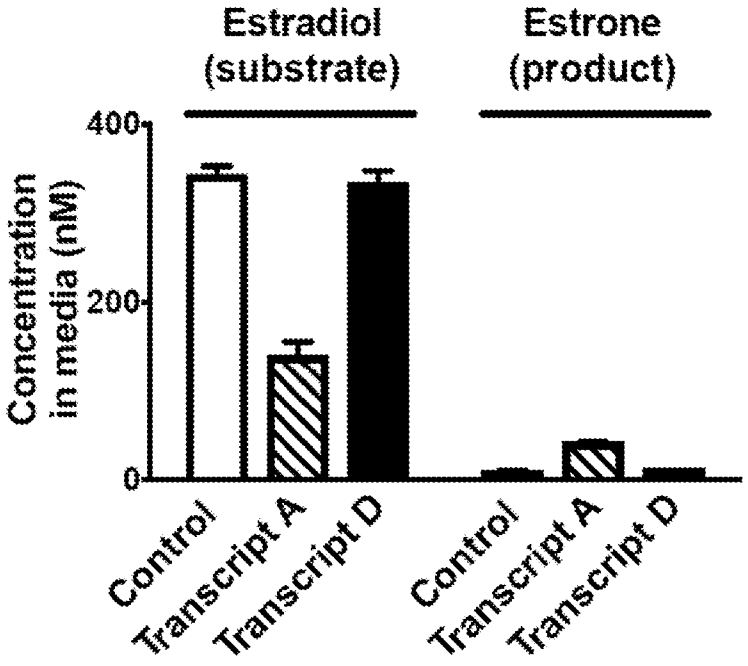


Figure 18 (cont.)

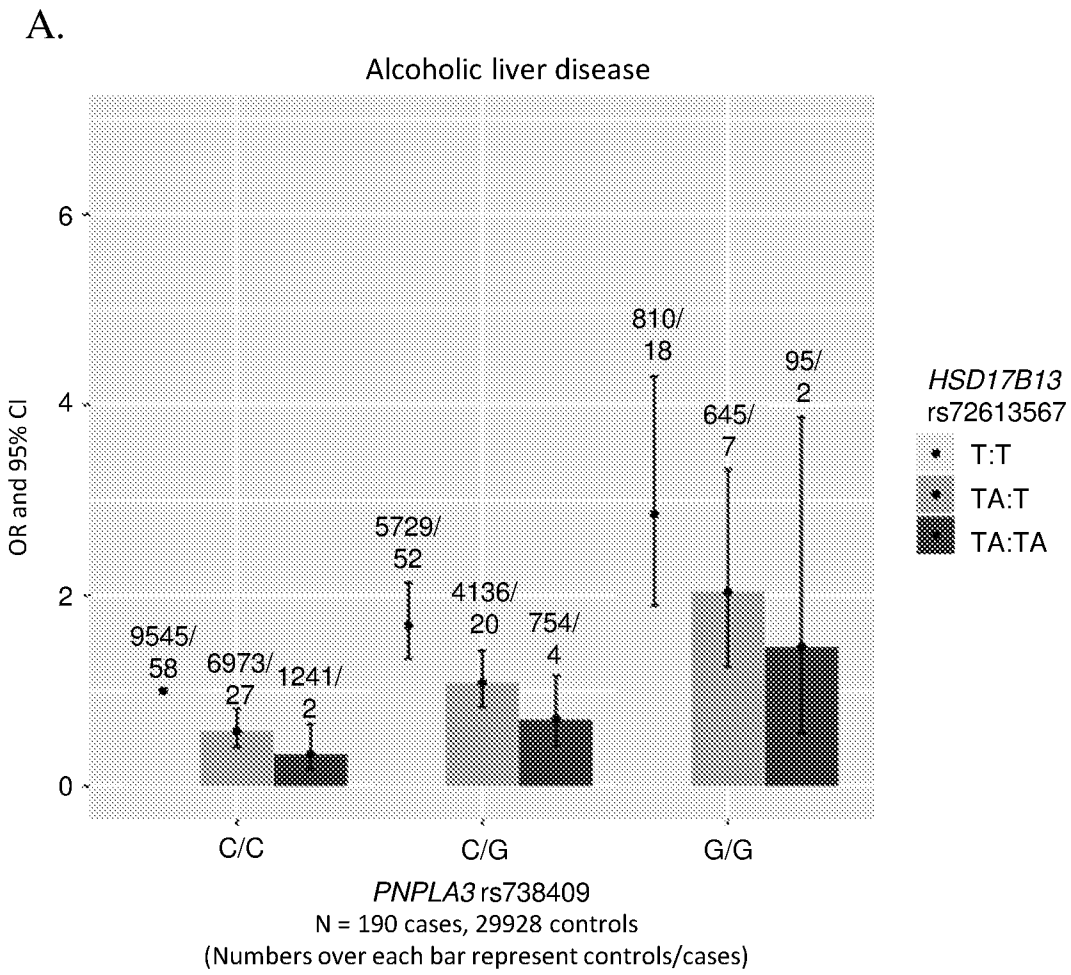

A.
Alcoholic liver disease
OR and 95% CI
0
2
4
6
9545/
58
6973/
27
1241/
2
5729/
52
4136/
20
754/
4
810/
18
645/
7
95/
2
C/C
C/G
G/G
PNPLA3 rs738409
N = 190 cases, 29928 controls
(Numbers over each bar represent controls/cases)
HSD17B13
rs72613567
T:T
TA:T
TA:TA

Figure 19

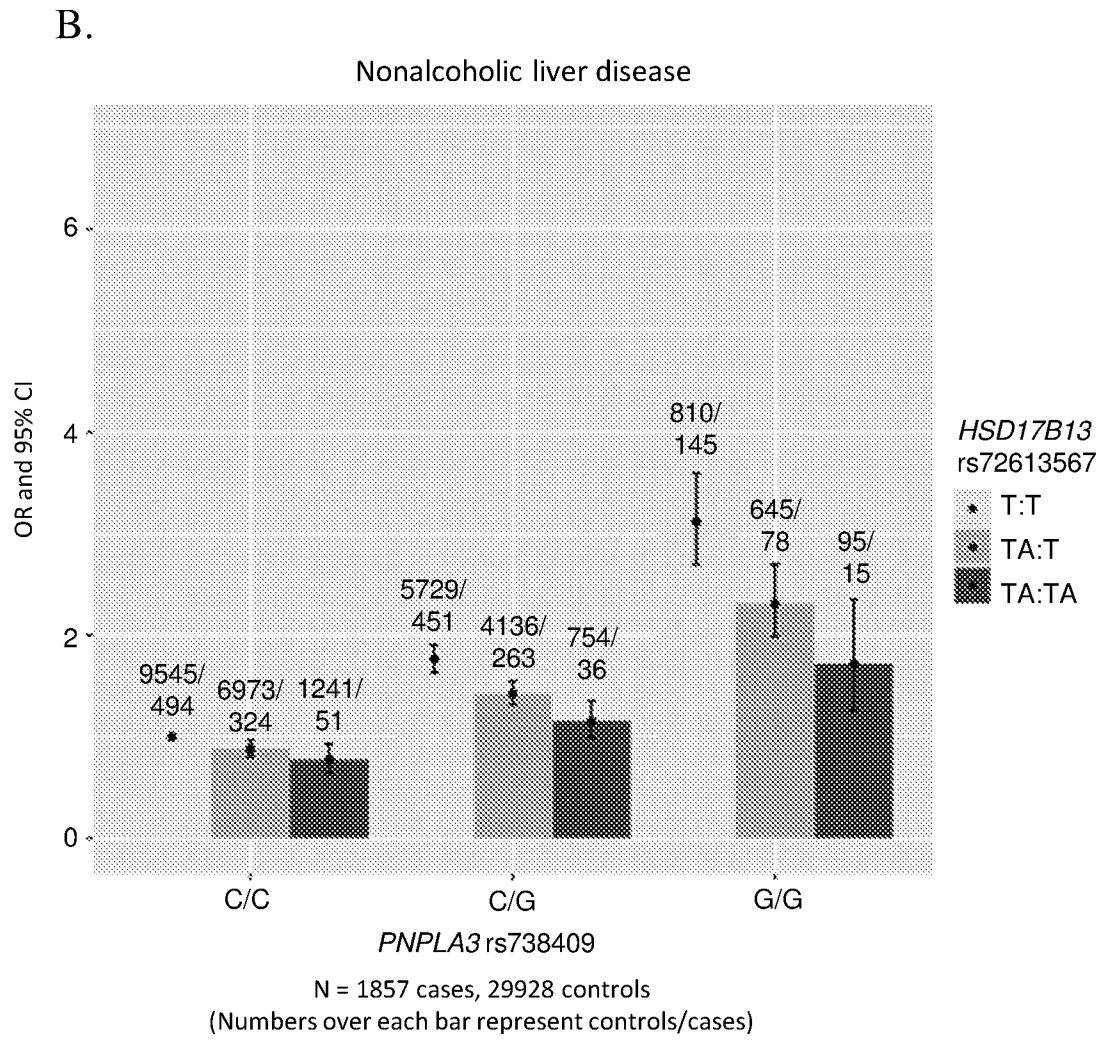


Figure 19 (cont.)