

Supporting Information for Genome-Wide Interaction Analysis of Quantitative Traits in Outbred Mice

WEIJUN MA¹, CHAOFENG YUAN¹, HAIDONG LIU¹, WEI ZHENG², YING ZHOU^{1,*}

¹*School of Mathematical Sciences, Heilongjiang University, Harbin 150080, China*

²*School of Mathematical Sciences and LPMC, Nankai University, Tianjin 300071, China*

*Corresponding Author

E-mail address: yzhou@aliyun.com

Running Title: Genome-Wide Interaction Analysis of QTL

File 1

Table S1. *Shared GO terms for SNP pairs selected based on model (1) for trait GLU*

Locus 1		Locus 2		P-value	^a Shared GO terms
Chr	Position	Chr	Position		
17	87128520	18	78042984	1.47E-6	c(1) c(1)
12	31034312	19	41373867	1.12E-5	c(1,2,3) c(1,2,3)
12	31425125	19	41373867	1.67E-5	c(1,2) c(1,2)
19	41373867	12	30900056	1.95E-5	c(1,2,3) c(1,2,3)
12	31425125	19	41373867	1.67E-5	c(1,2) c(1,2)
19	41373867	12	30900056	1.95E-5	c(1,2,3) c(1,2,3)
12	31641402	19	41373867	4.21E-5	m(1) m(1)
5	121142226	12	30998502	4.52E-5	c(1) c(1)
6	147670244	11	103860253	3.77E-5	b(1,2) b(1,2)
12	31034312	15	77655021	6.65E-5	c(1,2,4) m(2) c(1,2,4) m(2)
2	145354828	6	148651203	6.75E-5	b(1,2) b(1,2)
1	82999924	6	148651203	9.95E-5	c(5,6) b(2) c(5,6) b(2)
12	31034312	15	77655021	6.65E-5	c(1,2,5) c(1,2,5)
10	120184726	12	31034312	1.13E-4	c(2,3) c(2,3)
11	59386096	12	31034312	1.20E-4	c(2,3) c(2,3)
6	147701407	15	11931111	1.16E-4	c(1,5) c(1,5)
6	148651203	14	74751288	1.28E-4	c(1,6) c(1,6)
4	95689182	18	78042984	1.52E-4	c(1,4) m(1,2) c(1,4) m(1,2)
3	75843721	12	31425125	1.56E-4	c(2,5,7) c(2,5,7)
12	113645375	16	66284359	1.57E-4	c(1)m(1) c(1)m(1)
2	113601947	6	148651203	1.60E-4	b(1,4) b(1,4)
11	59386096	12	31425125	1.60E-4	c(7,2) c(7,2)

Note: ^a Shared GO terms, e.g, c(1,2,3) denotes the first, the second and the third GO term in cellular component in Table S5; m(1) denotes the first GO term in molecular function; and b(1,2) denotes the first and the second GO term in biological process.

Table S2. Shared GO terms for SNP pairs selected based on model (1) for trait HDL

Locus 1		Locus 2		P-value	Shared GO terms
Chr	Position	Chr	Position		
4	150470889	17	32007869	2.06E-7	c(1,5) b(5)
1	164206594	17	72311236	3.01E-6	m(3)
1	187715529	4	150470889	4.95E-6	c(1)
1	187546188	4	150470889	5.54E-6	c(1)
4	150470889	14	74796750	6.08E-6	c(1)
5	66555742	13	63998360	6.32E-6	m(3,5) c(5)
4	150470889	13	72937018	7.99E-6	c(5) b(6)
4	150470889	14	74643795	8.51E-6	c(1)
4	150470889	5	7551869	8.68E-6	m(4) b(5)
1	93041586	4	150470889	1.08E-5	c(1,5) b(5,6,7)
2	169373228	4	150470889	1.12E-5	m(4) b(5)
4	150470889	14	75077934	1.15E-5	c(1)
4	150470889	14	75281562	1.3E-5	m(4) b(5)
4	150470889	11	60676347	1.34E-5	m(4) b(5)
4	150470889	14	75322223	1.54E-5	m(4) b(5)
4	119245276	4	150470889	1.62E-5	c(5) b(6,7)
4	150470889	14	65649908	1.65E-5	c(1,5) m(4)
4	150470889	14	75211499	1.83E-5	m(4) b(5)
2	169666723	4	150470889	1.9E-5	c(5) b(6,7)
4	150470889	13	72244167	1.96E-5	c(5) b(6)
4	150470889	17	31684235	2.39E-5	m(4) b(5)
4	150470889	17	31834912	2.45E-5	c(1,5)
4	150470889	14	65598744	2.74E-5	c(1,5) m(4)
14	38267243	4	124862424	2.74E-5	m(1)
4	150470889	13	71785689	2.78E-5	c(5) b(6)
1	108404737	4	150470889	3.04E-5	c(1,5)
4	150470889	17	4500798	3.14E-5	c(1)
1	144157359	4	150470889	3.25E-5	c(5) b(7)
4	150470889	13	69430669	3.27E-5	c(1,5) m(4)
1	193226184	13	63998360	3.4344E-5	c(1,4,5) b(8)
2	121396755	4	150470889	3.51E-5	c(1) m(4) b(5)
4	150470889	18	65250593	3.52E-5	c(1,5)
4	150470889	7	78961795	3.7E-5	m(4) b(5)
4	150470889	13	67528097	3.73E-5	m(4) b(5)
4	150470889	14	74751288	3.74E-5	c(1)
1	95122536	4	150470889	3.79E-5	m(4) b(5)
4	150470889	13	76055027	4.04E-5	c(1)
1	163821472	17	72311236	4.04E-5	c(2,7)
5	35784080	8	66607493	4.19E-5	c(8) m(6,7,8,9,10) b(9)
1	108404737	2	169666723	4.25E-5	c(5) m(1,7) b(10)
1	163821472	19	27626251	4.32E-5	c(9) b(5)
1	164192774	12	15610886	4.41E-5	c(1,4)
4	150470889	13	58967683	4.32E-5	c(1)
1	95122536	2	169373228	4.59E-5	m(4) b(5)
4	150470889	8	91016460	4.61E-5	c(1,5) b(6,7)
4	150470889	12	70501102	4.77E-5	c(1)
4	150470889	13	59096902	5.05E-5	c(1)
4	150470889	13	63741934	5.05E-5	c(1,5) b(5)
4	150470889	18	71036938	5.05E-5	c(1,5) b(6,7)
4	150470889	16	90997009	5.4E-5	c(1)
1	94378666	14	38267243	5.47E-5	c(2,3,7)
4	150470889	6	108178333	5.68E-5	c(1)
18	65192764	4	119612776	5.73E-5	c(1,5)
13	63998360	1	192409810	5.8264E-5	c(1) m(3) b(5)
4	150470889	13	59025053	5.83E-5	c(1)
8	66607493	17	10402573	6.03E-5	b(11,12)
4	147955504	4	150470889	6.05E-5	c(1,5)
2	169427598	12	10494602	6.19E-5	c(5) m(4)
1	164192774	13	69200543	6.34E-5	c(1) m(3)
1	164192774	13	69437541	6.34E-5	c(1) m(3)

Locus 1		Locus 2		P-value	Shared GO terms
Chr	Position	Chr	Position		
5	66918383	13	63998360	6.42E-5	c(1,5)
1	167019835	4	150470889	6.49E-5	c(5) b(6,7)
2	169666723	18	65250593	6.49E-5	c(5) m(1)
4	150470889	2	91168054	6.69E-5	c(5) m(4) b(5)
4	150470889	5	88641059	6.75E-5	m(4) b(5)
15	22997680	17	32007869	6.87E-5	b(5)
15	25252330	17	32007869	6.87E-5	c(1,5) m(1) b(5)
4	89252643	4	150470889	6.95E-5	c(5) m(4) b(5,6,7)
4	150470889	8	91009674	7.1E-5	c(1,5) b(6,7)
4	150470889	13	69202456	7.2651E-5	c(1,5) m(4)
4	150470889	9	83521562	7.34E-5	c(5) m(4) b(5)
1	94276205	7	79580474	7.43E-5	b(5)
1	163821472	13	69200543	7.47E-5	c(2,7) m(4)
1	163821472	13	69437541	7.5052E-5	c(2,7) m(4)
4	150470889	5	106928986	8.2101E-5	m(4) b(5)
4	150470889	12	25843393	8.69E-5	c(1,5)
4	150470889	11	28283252	8.71E-5	m(4) b(5)
1	133925518	4	150470889	8.72E-5	c(1,5) m(4) b(5,6,7)
5	36105885	8	66607493	8.79E-5	m(7,10)
5	36112348	8	66607493	8.87E-5	m(7,10)
13	90419142	1	192409810	8.92E-5	c(2) m(4) b(5)
1	93041586	2	169666723	9.06E-5	c(5) m(1) b(6,7)
2	121279712	4	150470889	9.15E-5	c(1,5) m(4) b(5)
4	150470889	13	71266220	9.2319E-5	c(5) b(6)
1	94276205	4	136530818	9.24E-5	c(5) m(1,4,7)
1	94731259	4	136530818	9.24E-5	c(2,3,10)
1	93041586	2	169373228	9.35E-5	b(5)
4	83992833	4	150470889	9.4E-5	c(1,5) b(6,7)
4	150470889	5	48513012	9.49E-5	c(1)
4	150470889	5	66441724	9.78E-5	c(5)
4	150470889	9	33324402	9.76E-5	c(1,5) b(6,7)
4	119937270	1	94201252	1.39E-4	c(1,5,11) m(11) b(6,7,13,14)
13	63998360	14	73964257	1.89E-4	c(12) m(3)
1	94276205	15	100946027	1.91E-4	c(5,11) m(1,4) b(2,15)
1	194906168	2	169427598	1.93E-4	c(5) b(5,12)
6	118580661	18	65192764	2.06E-4	c(1) m(1,12) b(16)
2	169666723	9	119306965	1.32E-4	m(1,7) b(6)
1	94276205	4	119937270	2.43E-4	c(1,5,11) m(11) b(6,7,13,14)
4	150470889	10	5381998	2.45E-4	c(1,5) b(6,7)
2	169666723	13	72244167	2.47E-4	c(5) b(6)
1	94378666	14	37867554	2.49E-4	c(2,7) m(13,14) b(17,18,19)
4	150470889	18	70867711	2.76E-4	c(1,5) b(6,7)
1	94276205	4	119613207	2.82E-4	c(1,5) m(7) b(6,7,20)
1	176467522	5	130322237	2.91E-4	c(1,9)
2	123490697	2	169666723	2.94E-4	m(1) b(12)
2	169427598	7	134800915	3.20E-4	c(5) m(4,7) b(6,7)
2	169666723	18	72528831	3.22E-4	m(1) b(12)
2	169666723	2	123667469	3.23E-4	m(1) b(12)
1	72835776	6	116903972	3.23E-4	c(8,13,14)
2	169666723	17	53799440	3.26E-4	c(5),m(1),b(6,7)
3	36311946	17	53135963	3.27E-4	c(2,7) m(14) b(19)
16	87953395	14	111139686	3.27E-4	c(2,3,7)
17	31834912	19	45610512	3.27E-4	c(1,5) m(1,7,15)
8	66607493	2	123667469	3.29E-4	b(11,12)
1	94731259	14	37955766	3.31E-4	c(2,13)
1	133925518	2	169427598	3.39E-4	c(5) m(4) b(6,7)
8	66607493	14	64728569	3.55E-4	m(6,9) b(9)
5	121547740	13	63741934	3.98E-4	c(1,2,5,12,15)m(1,6,10,16) b(21,22)
7	73110830	8	66607493	4.02E-4	m(6,9) b(9)
8	66607493	18	58914240	4.82E-4	c(8) m(6,7,8,9,10,17) b(9)
1	94201252	4	119612776	4.89E-4	c(1,5) m(7) b(6,7,20)

Table S3. *Shared GO terms for SNP pairs selected based on model (1) for trait DBP*

Locus 1		Locus 2		P-value	Shared GO terms
Chr	Position	Chr	Position		
3	109582676	109582676	41310194	9.57E-6	c(2,3,16)
3	107095513	107095513	81252760	3.18E-5	c(2,3) b(2,23)
5	146079102	146079102	65601942	3.53E-5	c(5)
7	81252760	81252760	43252605	4.34E-5	c(2)
1	32566218	32566218	99110211	4.38E-5	c(5) b(6,7)
9	114756592	114756592	65601942	4.91E-5	c(1)
3	106925166	106925166	81252760	5.12E-5	c(2,3,6) b(2,23)
1	34117244	34117244	49190728	5.59E-5	c(1,2,3,7,17)
7	81252760	81252760	42971949	8.61E-5	c(2,7)
6	15080147	15080147	31519509	8.69E-5	m(1)
3	105333107	105333107	81252760	9.11E-5	c(2,3,6,7) b(2)
5	145629309	145629309	65601942	9.24E-5	c(1,5) m(1,17) b(24)
8	127354528	127354528	31519509	1.04E-4	c(1,4) m(1)
3	118438780	118438780	53233250	1.05E-4	m(18)
3	104409801	104409801	81252760	1.24E-4	c(2,3,6,7) b(2,25)
7	81252760	81252760	42983346	1.36E-4	c(2,7)
3	103840660	103840660	81252760	1.37E-4	c(2,3) m(15)
1	34117244	34117244	41310194	1.39E-4	c(2,3) b(26)
4	155390467	155390467	98884204	1.46E-4	m(1) b(14)
2	85845117	85845117	142031773	1.48E-4	c(2)
13	99383540	99383540	52605913	1.52E-4	c(2,7)
11	31519509	31519509	120045644	1.62E-4	c(8,14) m(1)
5	129416004	129416004	81252760	1.85E-4	c(2,3)
2	85845117	85845117	96895446	1.89E-4	c(2,3,7)
18	65601942	65601942	99110211	1.91E-4	c(5)
1	108240310	108240310	81252760	2.02E-4	c(2)
6	98884204	98884204	49190728	2.06E-4	m(1)
7	81216075	81216075	19802913	2.17E-4	c(2,3,7)
16	52605913	52605913	68357062	2.20E-4	c(2,7)
7	81252760	81252760	143625565	2.23E-4	c(2)
3	36275199	36275199	81252760	2.32E-4	c(2,3,7)
7	81252760	81252760	49850128	2.86E-4	c(2,3,6,7)
7	81252760	81252760	110658192	2.99E-4	c(2,3,6,7,17)
1	133741570	133741570	81252760	3.21E-4	c(2,7) b(2,27)

Table S4. *Shared GO terms for SNP pairs selected based on model (1) for trait TG*

Locus 1		Locus 2		P-value	Shared GO terms
Chr	Position	Chr	Position		
9	116453569	13	104033960	6.72E-7	c(1) m(7,15,19,20,21,22) b(27,28)
2	151987662	10	4558359	5.06E-6	c(5)
1	195979059	12	17139883	1.11E-5	c(2,7)
1	136058019	3	99000613	1.3E-5	c(1)
1	181407446	5	123349051	1.58E-5	c(5) m(7,1) b(29)
11	98860813	14	17179014	1.88E-5	c(5,24,25) m(5,7,18,23,24,25,26,27,28,29) b(30,31,32,33,34,35,36,37)
4	10784867	9	120440907	1.95E-5	c(3)
3	99000613	5	73725499	1.99E-5	c(26)
1	136058019	14	70811432	1.99E-5	c(1)
4	10784867	9	116453569	1.99E-5	c(1,3)
3	99000613	9	102048873	2.15E-5	c(1) m(3)
3	99000613	5	73732287	2.27E-5	c(26)
1	181436563	5	123349051	2.4E-5	c(1) m(1,7) b(38)
3	99000613	17	32035365	2.74E-5	c(1) m(3)
11	98860813	17	32035365	3E-5	c(5) m(3,7,26,30)
14	17179014	15	51609210	3E-5	c(1,5) m(1,7)
3	129089662	9	116453569	3.01E-5	c(2,3,7,27) m(7,15)
5	73732287	7	75956192	3.24E-5	c(10)
3	129089662	12	39337185	3.59E-5	
3	99000613	12	82932844	3.88E-5	m(3)
3	99000613	15	81491304	4E-5	c(1)
1	99300264	14	17179014	4.15E-5	c(1)
9	102048873	11	98860813	4.91E-5	m(3)
3	129089662	4	5.15E-5	m(6,7,8,9,10) b(9)	
11	99310169	13	104008591	5.26E-5	c(1)
11	98860813	15	81491304	5.38E-5	c(5) m(3,27) b(14)
3	138625427	5	73732287	5.74E-5	c(26)
11	36072713	14	17179014	5.8E-5	c(5) m(18)
7	143625565	12	17139883	6.07E-5	c(2)
1	136058019	18	61241371	6.25E-5	c(1,13,28) b(39)
3	99000613	11	98860813	6.68E-5	m(5)
3	19148216	13	103607804	6.7E-5	m(7)
14	17179014	17	32035365	6.83E-5	c(1,5,11) m(1,5,7,26)
7	143871643	12	17139883	7.32E-5	c(2)
9	111673603	15	81491304	7.7E-5	c(1) m(7)
3	129089662	6	65836389	7.72E-5	m(7,15)
9	96703289	13	64335402	8.08E-5	c(5) m(6)
3	140961472	5	73732287	8.38E-5	c(26)
1	195979059	5	73732287	8.43E-5	c(2,7)
3	99000613	17	31895362	8.59E-5	c(1) m(3)
3	99000613	17	32034176	8.59E-5	c(1) m(3)
3	99000613	17	31865542	8.59E-5	c(1) m(3)
1	107141806	8	11915011	8.79E-5	c(2,7)
1	195979059	17	32035365	8.85E-5	b(12)
9	89545898	11	120587173	8.9E-5	c(2)
14	17179014	17	31761309	10.2E-5	c(1,511) m(7,31)
11	98860813	17	32034176	10E-5	c(5) m(3,7,26,30)
11	98860813	17	31895362	11.2E-5	c(5) m(3,7,26,30)
11	98860813	17	31865542	11.2E-5	c(5) m(3,7,26,30)
1	170167462	6	65836389	11.6E-5	c(5) m(32) b(6,7)
11	98860813	15	51609210	12.9E-5	c(5) m(7,32)
11	120587173	17	3865865	13.7E-5	c(2,13) m(1,33) b(40)
14	17179014	17	32034176	14.8E-5	c(1,5,11) m(1,3,7,26)
11	98860813	17	31761309	15E-5	c(5) m(7,18,31)
1	127541285	9	102232841	15.1E-5	c(2,37) b(19)
5	129825667	6	65836389	15.6E-5	c(5) b(6,7)
14	17179014	17	31865542	16.5E-5	c(1,5,11,26) m(1,3,7)
3	19148216	11	86813002	18.4E-5	m(6,7,34)

Table S5. *Shared GO terms*

ID	Biological process	Cellular component	Molecular function
1	protein transport	cytoplasm	protein binding
2	transport	membrane	actin binding
3	transmembrane transport	plasma membrane	nucleotide binding;
4	intracellular protein transport	cytoskeleton	molecular function
5	biological process	nucleus	nucleic acid binding
6	regulation of transcription, -templated;	integral component of plasma membrane	hydrolase activity
7	transcription, -templated	integral component of membrane	metal ion binding
8	cellular response to damage stimulus	extracellular region	metallopeptidase activity
9	proteolysis	endoplasmic reticulum	peptidase activity
10	regulation of gene expression	endosome	zinc ion binding
11	cell differentiation	cytosol	protein kinase binding
12	multicellular organismal development	mitochondrion	ion channel binding
13	positive regulation of cell proliferation	extracellular vesicular exosome	protein coupled receptor activity
14	positive regulation of transcription from polymerase promote	extracellular space	signal transducer activity
15	negative regulation of transcription from polymerase promoter	colocalizes with golgi apparatus	transferase activity
16	regulation of ion transmembrane transport	anchored component of membrane	protein complex binding
17	protein coupled receptor signaling pathway	apical plasma membrane	ubiquitin-protein transferase activity
18	response to stimulus	axon	protein homodimerization activity
19	signal transduction	basolateral plasma membrane	kinase activity
20	positive regulation of transcription, -templated	dendrite	nucleotide binding
21	brain development	neuron projection	protein kinase activity
22	glucose homeostasis	synapse	transferring phosphorus-containing groups
23	ion transmembrane transport	synaptic vesicle	chromatin binding
24	protein ubiquitination	topoisomerase complex (-hydrolyzing)	topoisomerase activity
25	organic anion transport	nucleoplasm	topoisomerase type (-hydrolyzing) activity
26	cell adhesion	mitochondrion	histone deacetylase binding
27	phosphorylation	external side of plasma membrane	isomerase activity
28	protein phosphorylation	lysosome	protein -terminus binding
29	chromatin modification		protein kinase binding;
30	catabolic process		magnesium ion binding
31	metabolic process		enzyme binding
32	topological change		sequence-specific binding
33	unwinding involved in replication;		oxidoreductase activity
34	mitotic integrity checkpoint		phosphoric diester hydrolase activity
35	mitotic recombination		
36	resolution of meiotic recombination intermediates;		
37	sister chromatid segregation		
38	chromatin modification		
39	positive regulation of 1 and 2 cascade;		
40	oxidation-reduction process		

File 2

Genotypes of loci 3 and 4 are generated from the following joint distribution:

Locus 3	Locus 4		
	1	0	-1
1	$(1 - \theta)^2 * p^2$	$2(1 - \theta) * \theta * p * q$	$\theta^2 * q^2$
0	$2 * (1 - \theta) * \theta * p^2$	$2((1 - \theta)^2 + \theta^2) * p * q$	$2 * \theta * (1 - \theta) * q^2$
-1	$\theta^2 * p^2$	$2(1 - \theta) * \theta * p * q$	$(1 - \theta)^2 * q^2$

Where q is minor allele frequency of locus 4 and θ is linkage disequilibrium coefficient or $p(a|B) = \theta$. It is clear that $Var(Y) = 2pq * \beta_1^2 + 2pq * \beta_2^2 + Var(X_3X_4)\beta_5^2 + \sigma^2$, where $Var(X_3X_4) = (p^2 + q^2)((1 - \theta)^2 + \theta^2) - (1 - 2\theta)^2(p^2 + q^2)^2$. So

$$H_i = \frac{2pq * \beta_i^2}{Var(Y)}, i = 1, 2, \text{ and } H = \frac{Var(X_3X_4)\beta_5^2}{Var(Y)}.$$