

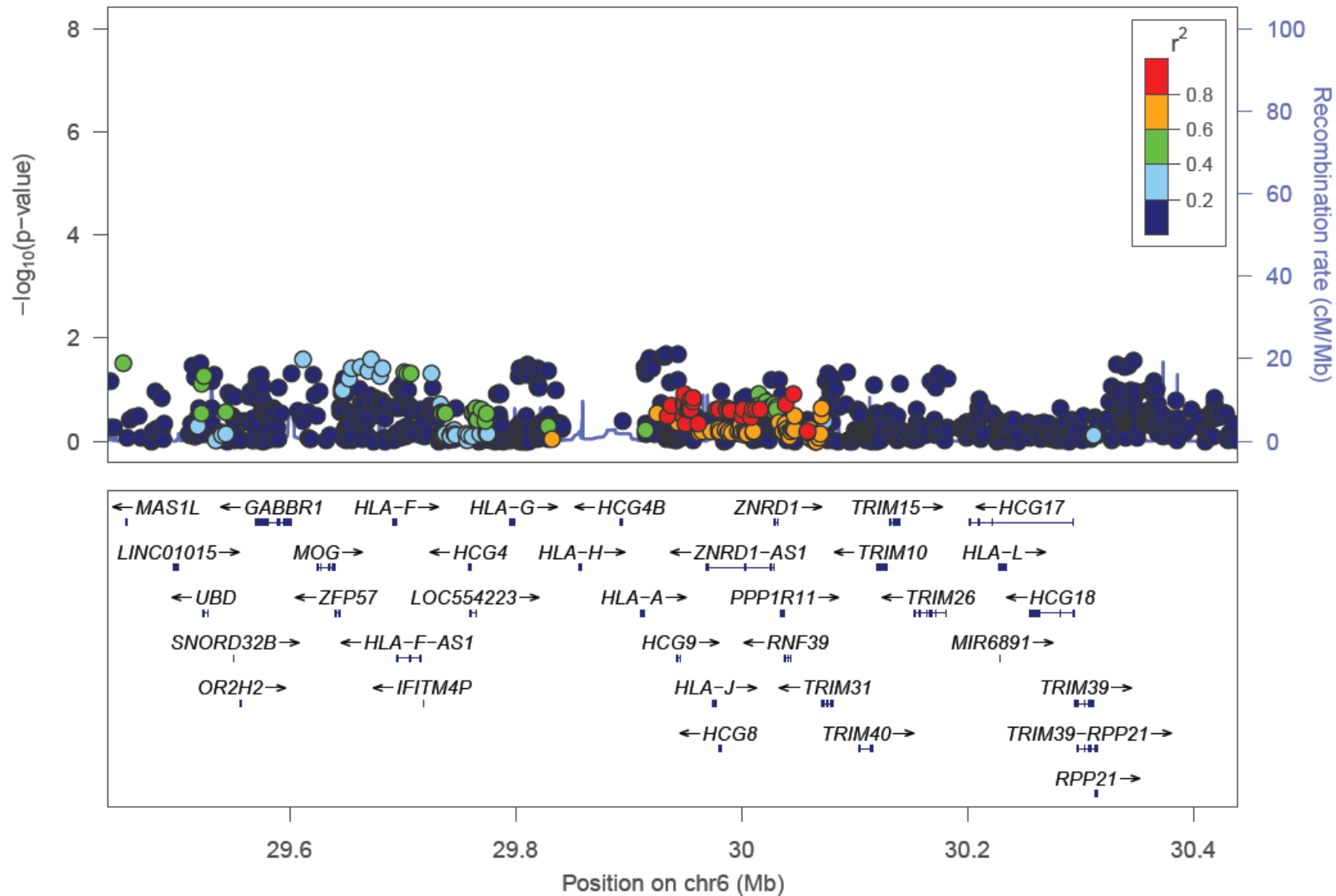
SUPPLEMENTARY INFORMATION

Title: Genome-wide association study identified new susceptible genetic variants in HLA class I region for hepatitis B virus-related hepatocellular carcinoma

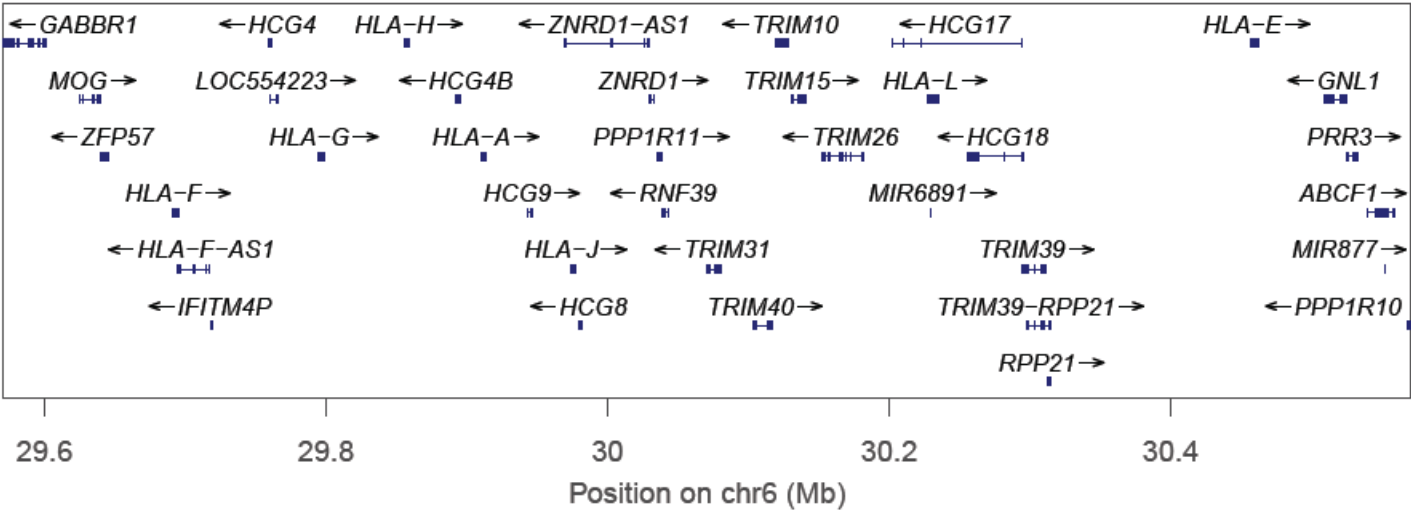
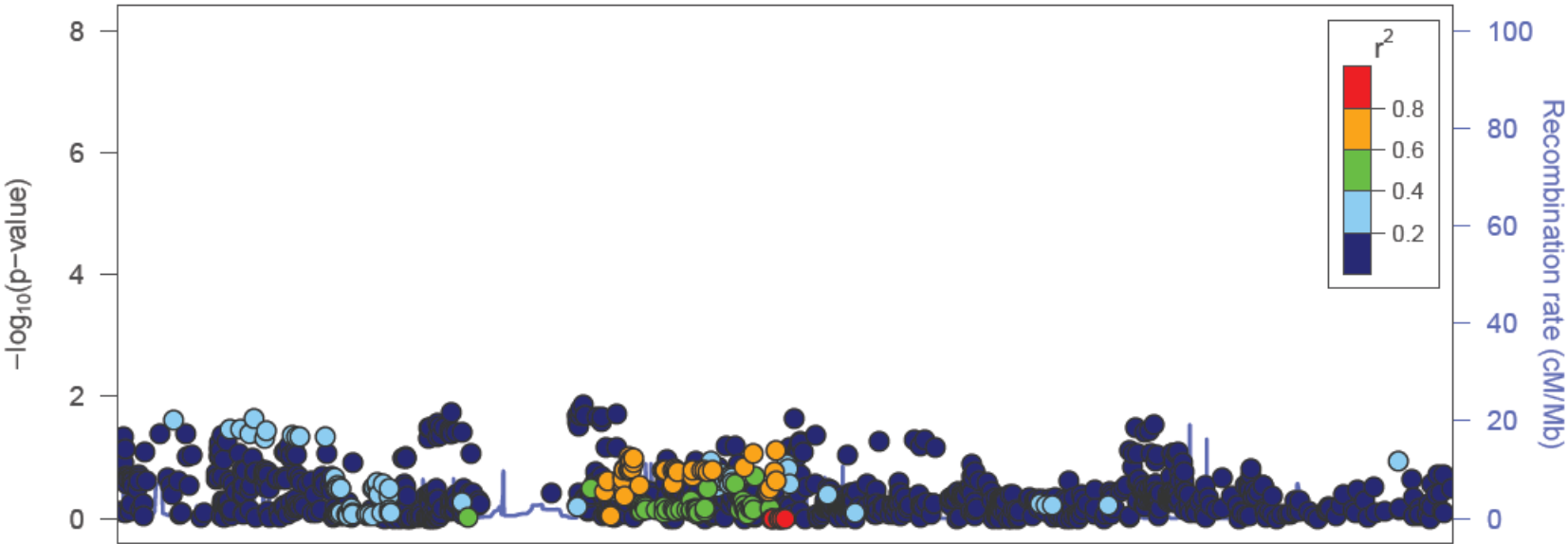
Authors: Hiromi Sawai*, Nao Nishida, Seik-Soon Khor, Masao Honda, Masaya Sugiyama, Natsumi Baba, Kayoko Yamada, Norie Sawada, Shoichiro Tsugane, Kazuhiko Koike, Yuji Kondo, Hiroshi Yatsushashi, Shinya Nagaoka, Akinobu Taketomi, Moto Fukai, Masayuki Kurosaki, Namiki Izumi, Jong-Hon Kang, Kazumoto Murata, Keisuke Hino, Sohji Nishina, Akihiro Matsumoto, Eiji Tanaka, Naoya Sakamoto, Koji Ogawa, Kazuhide Yamamoto, Akihiro Tamori, Osamu Yokosuka, Tatsuo Kanda, Isao Sakaida, Yoshito Itoh, Yuichiro Eguchi, Satoshi Oeda, Satoshi Mochida, Man-Fung Yuen, Wai-Kay Seto, Yong Poovorawan, Nawarat Posuwan, Masashi Mizokami and Katsushi Tokunaga

a) rs2523961

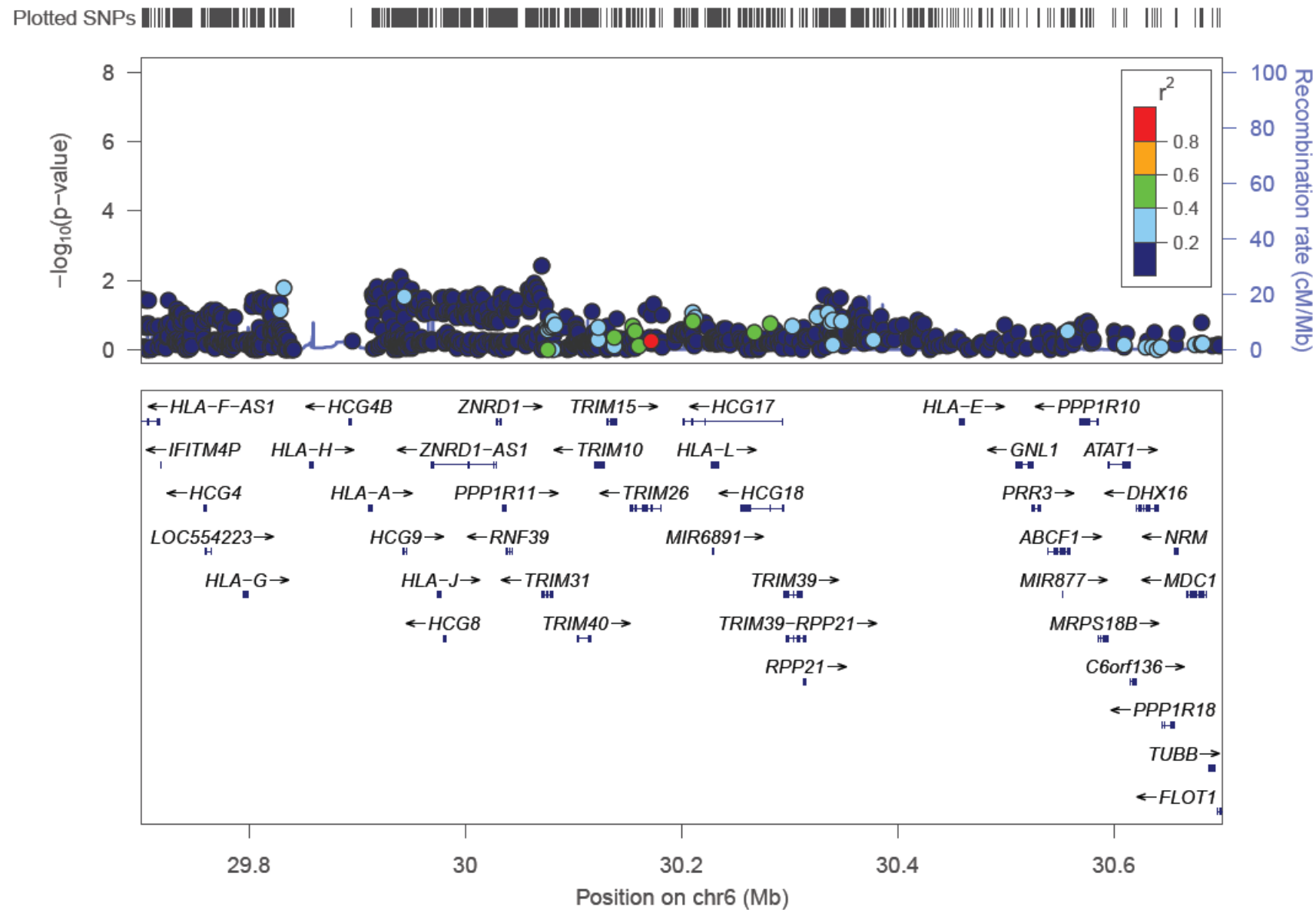
Plotted SNPs



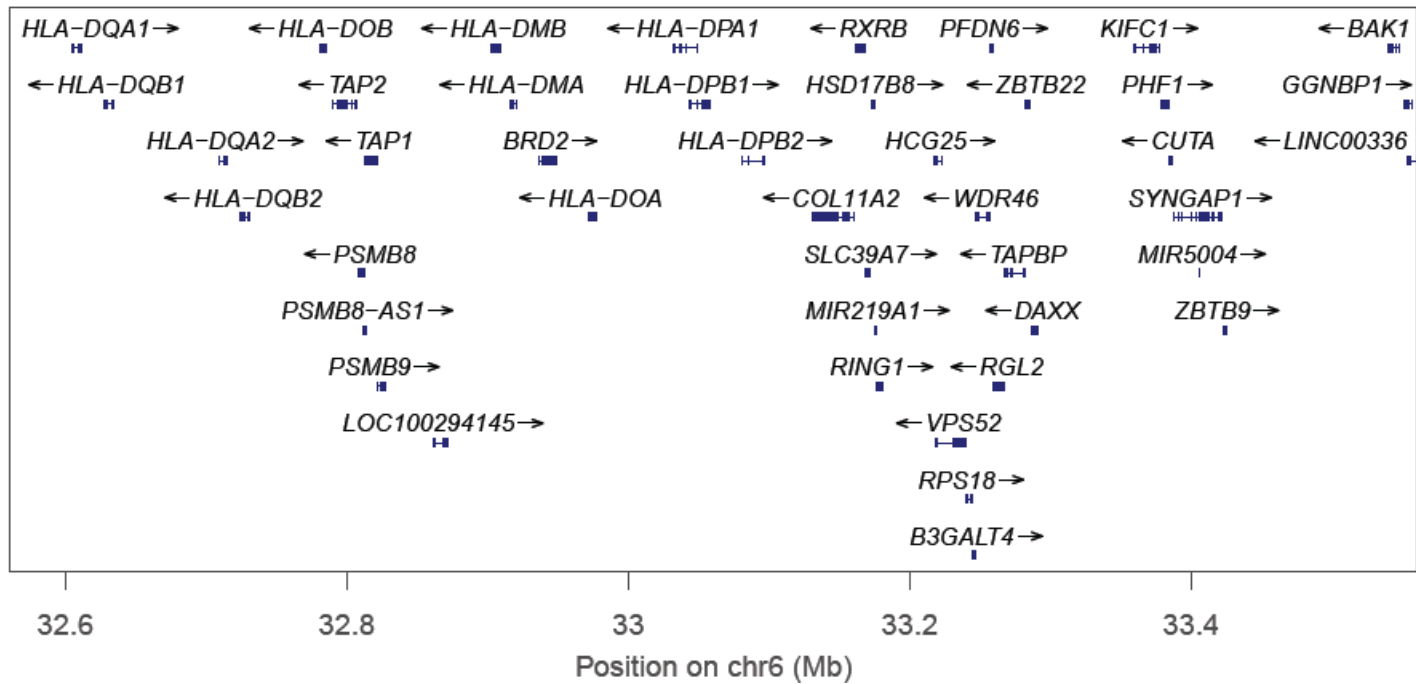
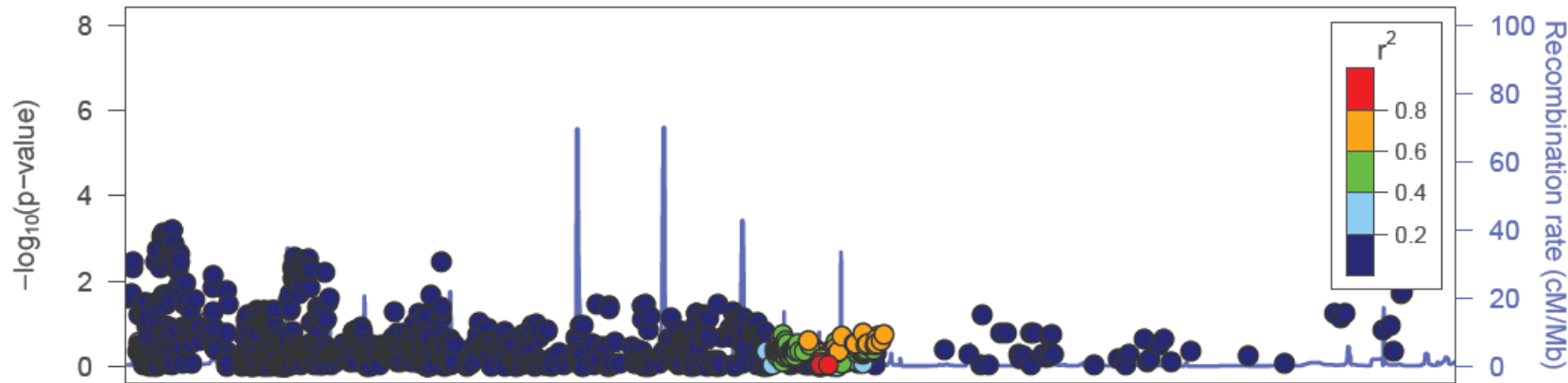
b) rs1110446



c) rs3094137

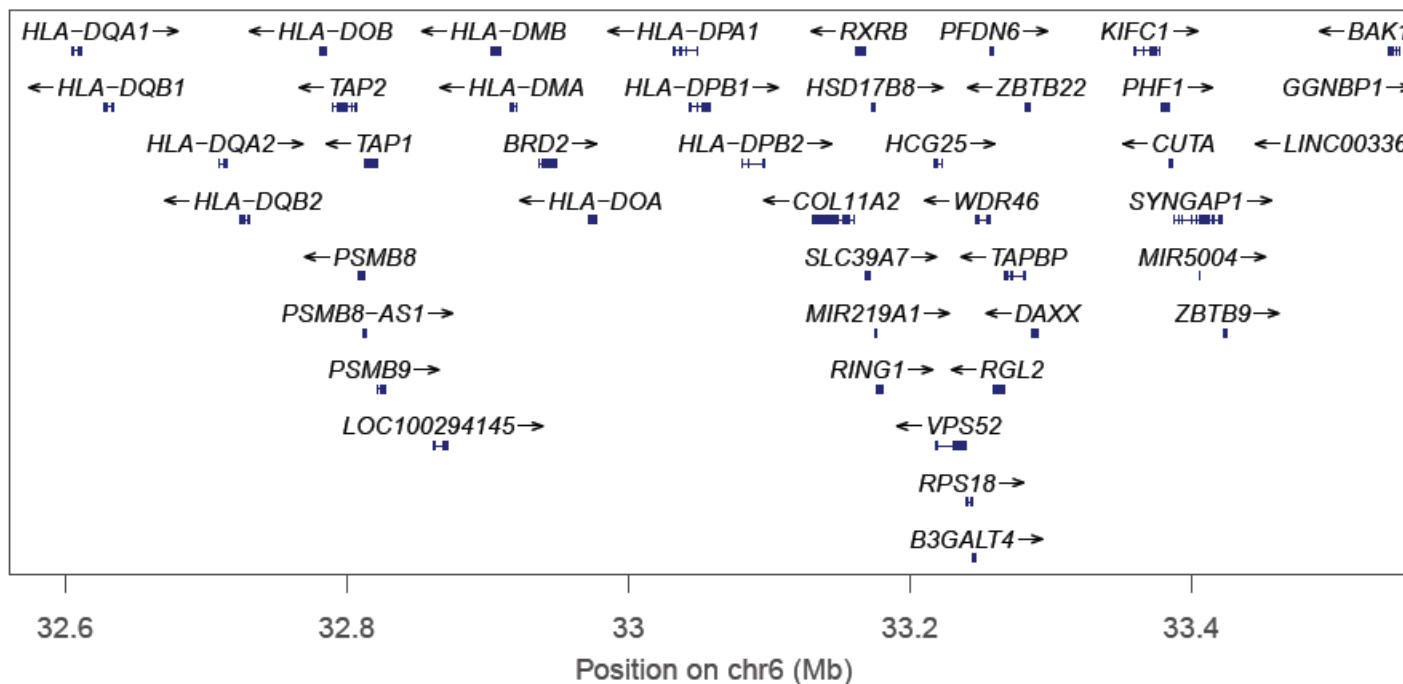
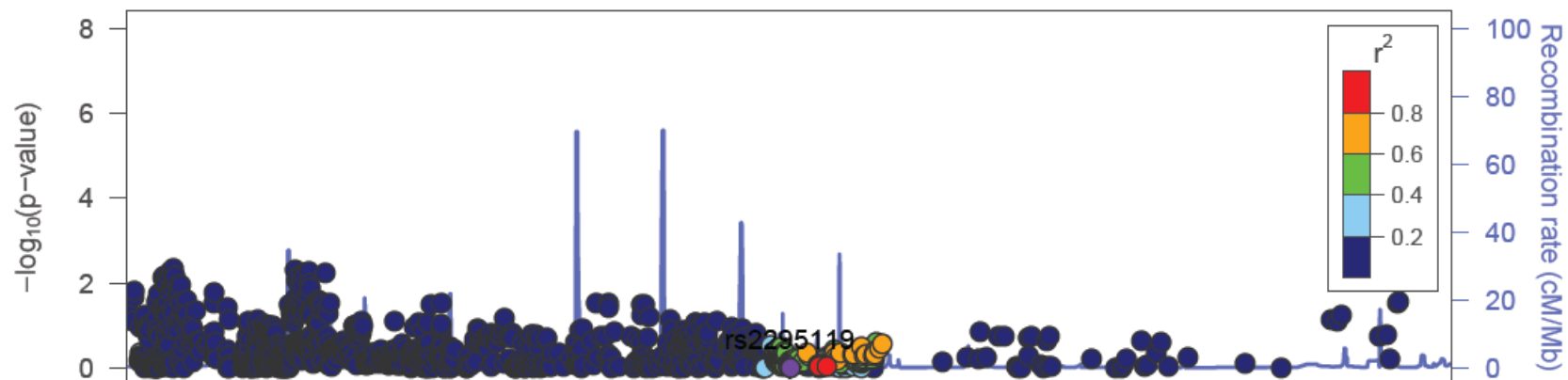


d) rs2295119



e) HLA-DPB1*02:01

Plotted SNPs



2 genes omitted

f) *HLA-A*33:03* and *DPB1*02:01*

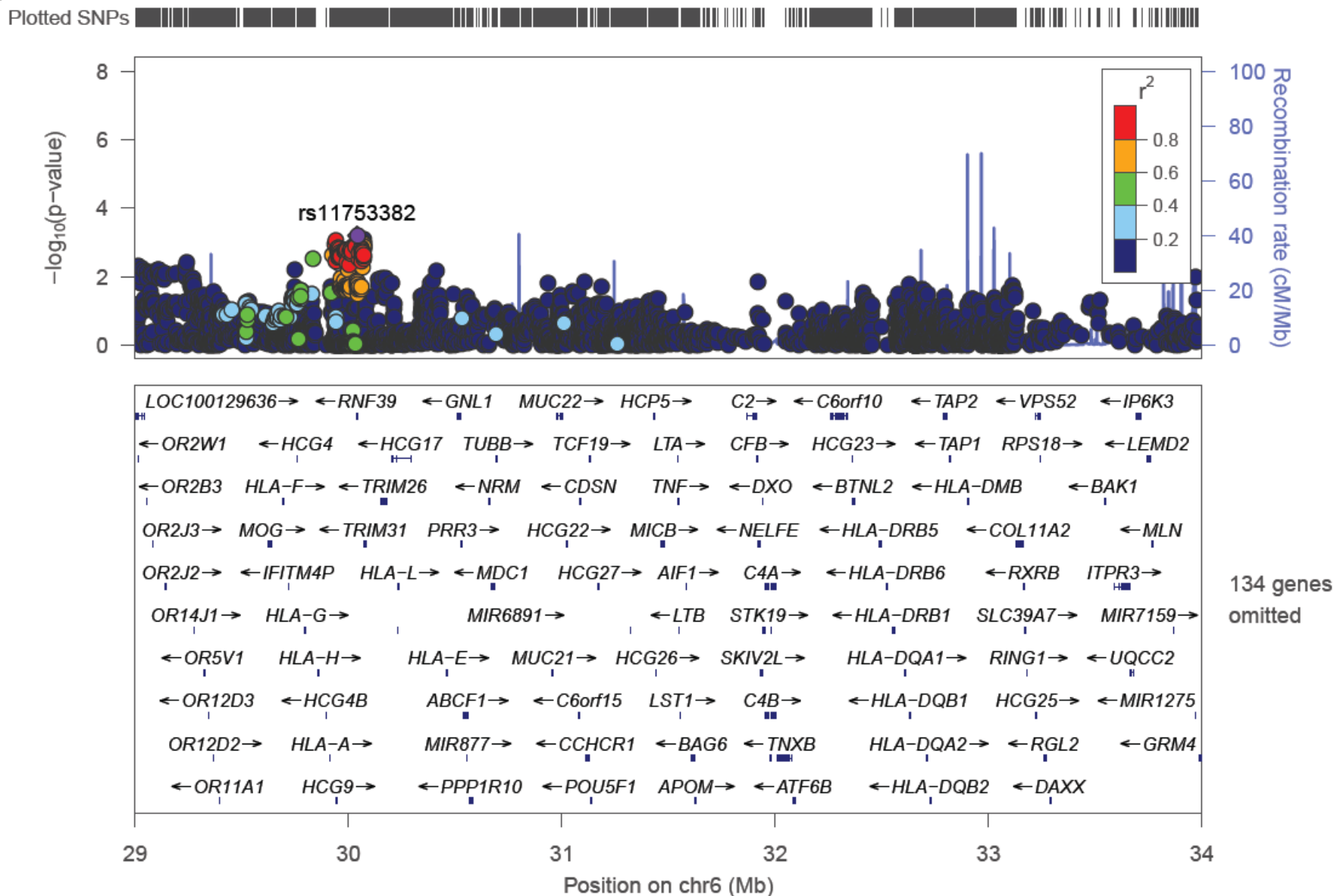
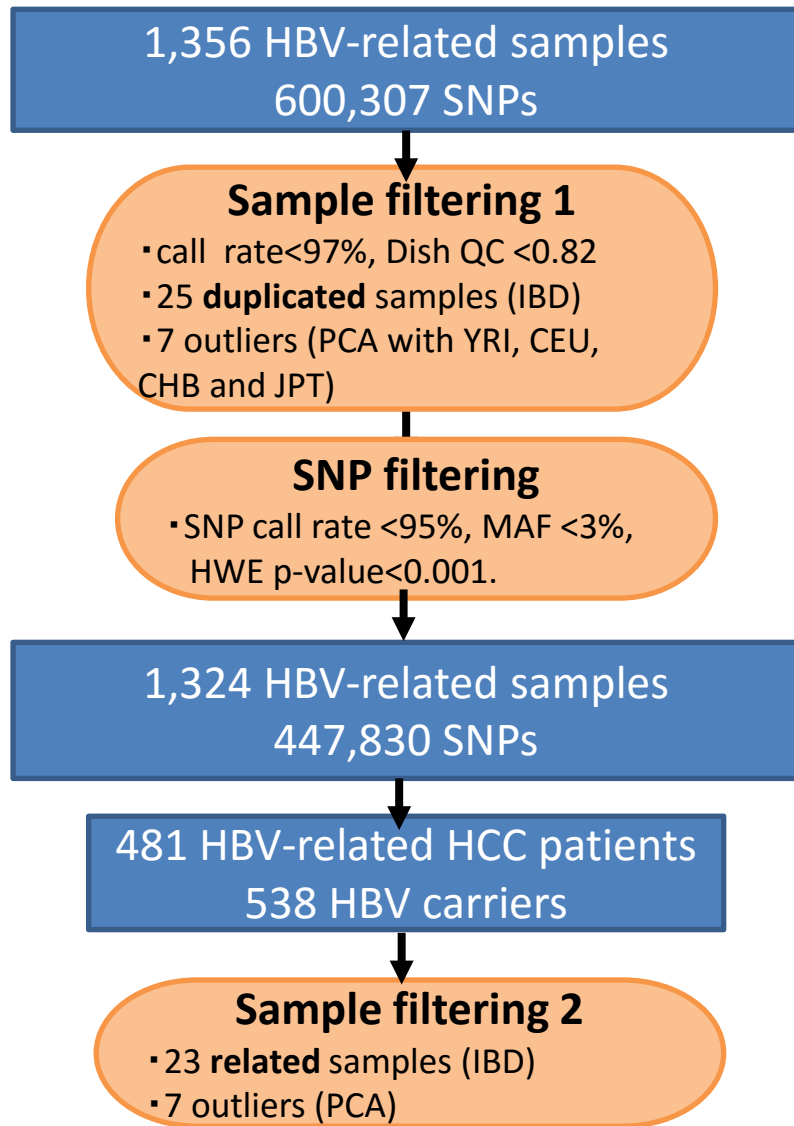


Figure S1. Association plots of chromosome 6 HLA regions

Conditional analysis controlling for the effect of a) rs2523961, b) rs1110446, c) rs3094137, d) rs2295119, e) *HLA-DPB1*02:01*, and f) *HLA-A*33:03* and *DPB1*02:01*.

a) Genome-wide SNP genotyping



b) Genome-wide association study (GWAS)

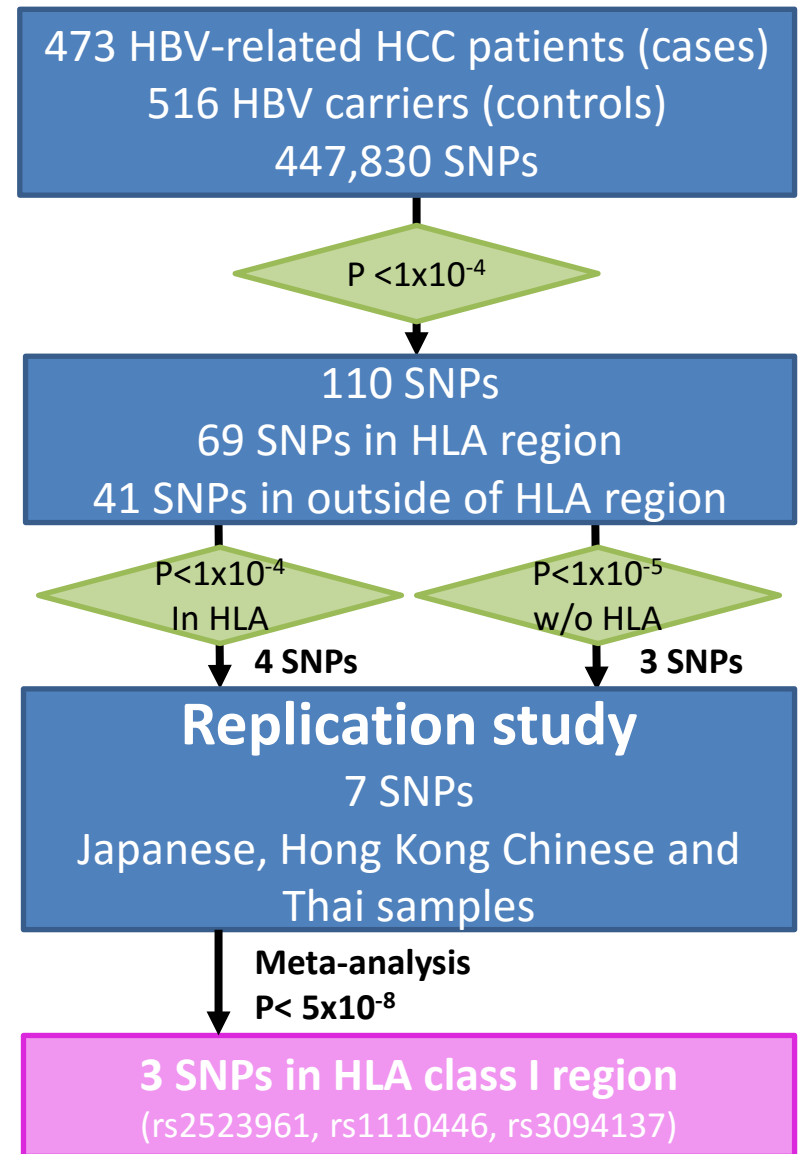


Figure S2. Flowchart describing the analysis strategy for the study

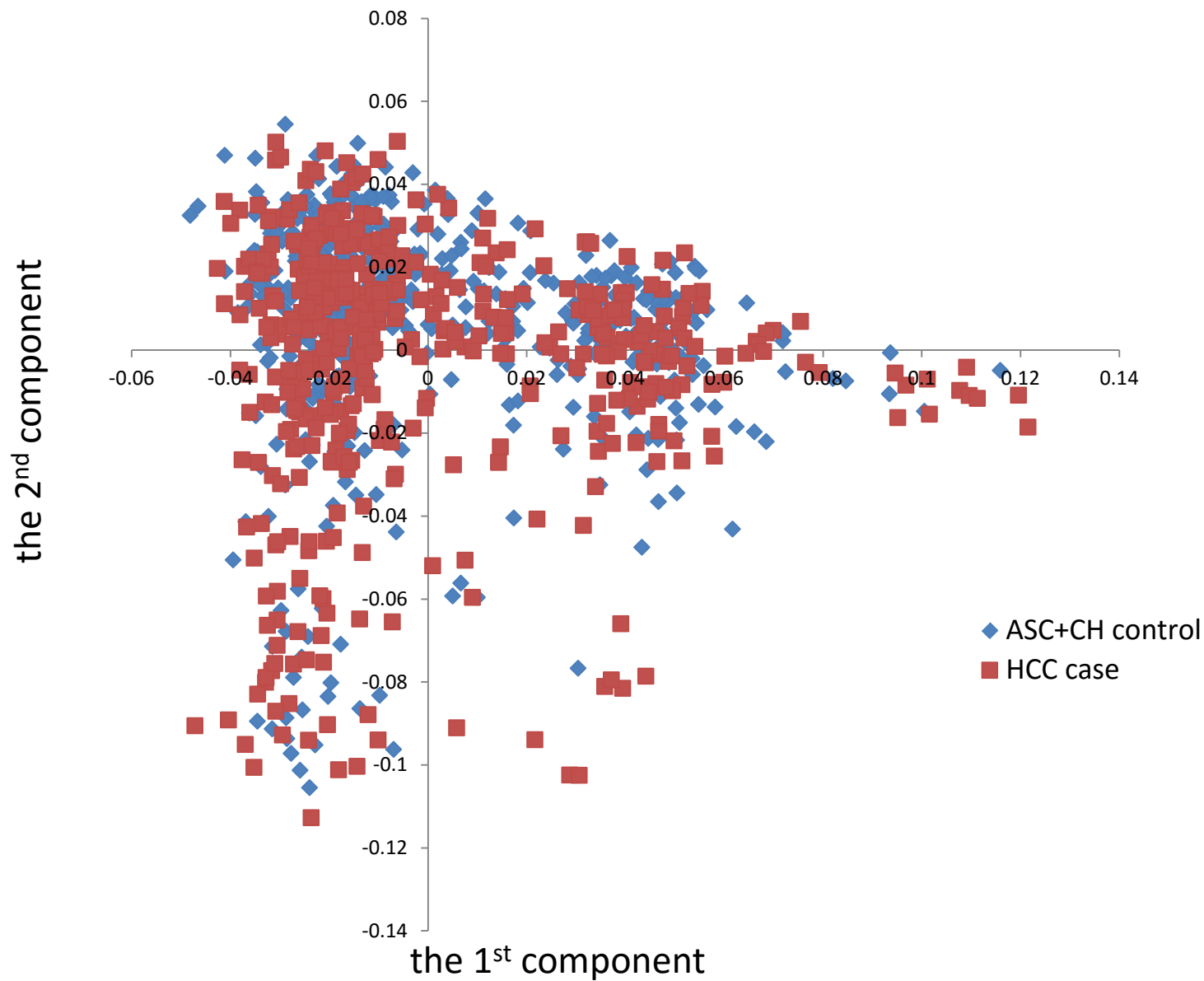
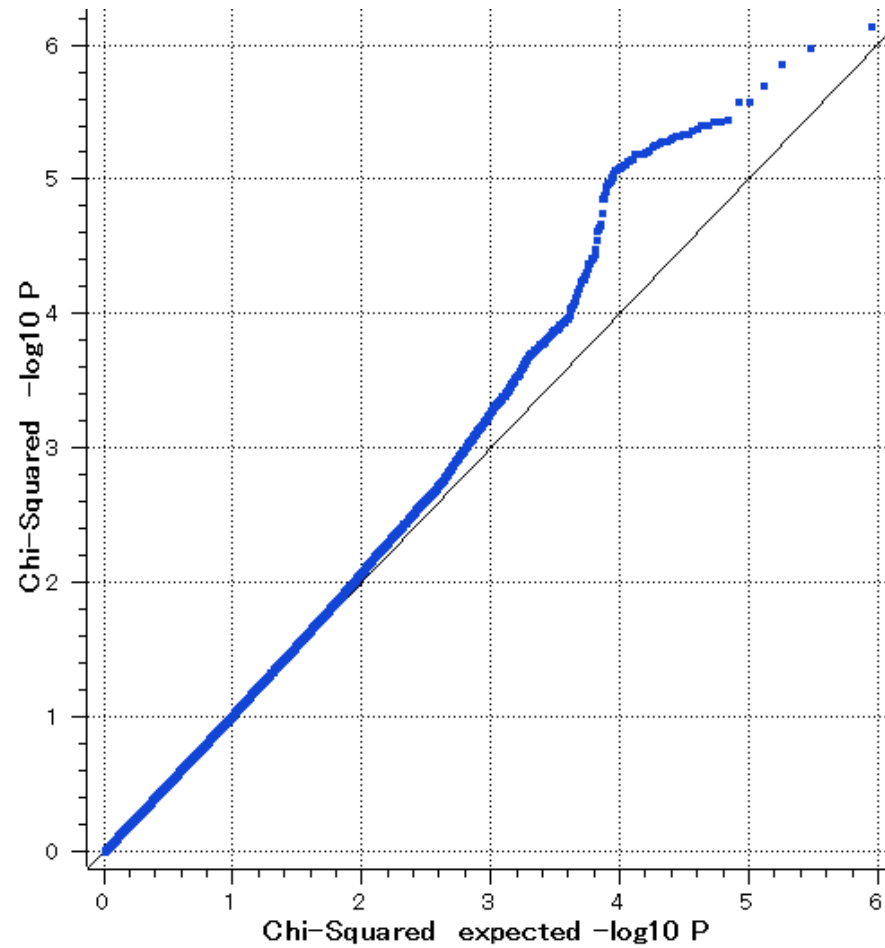


Figure S3. Principal component analysis of 989 samples from the GWAS stage

a) All the tested SNPs



b) SNPs in the HLA region were excluded

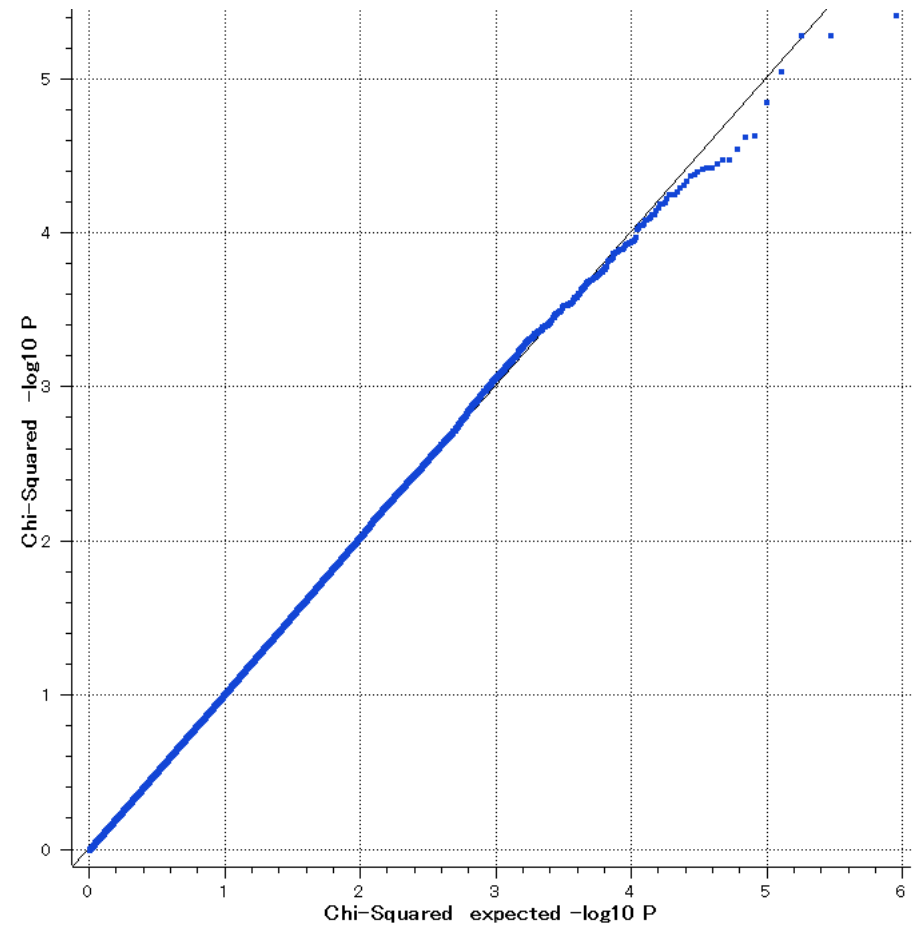


Figure S4. Quantile-quantile plot of the allele-based chi-square test statistics for the GWAS

Table S1. List of 110 SNPs with $P < 10^{-4}$ in the GWAS

Table S1. List of 110 SNPs with P < 10 ⁻⁴ in the GWAS										95% CI		Allele Freq		cases		controls					
Marker	Chro moso	Position	dbSNP RS ID	Associated Gene	Reference Alleles	Chi- Square	P	OR ^a	Low	High	Minor Allele	MAF	Cases	Controls	HWE P (Controls)	DD	Dd	dd	DD	Dd	dd
AX-11378164	1	216681000	rs2244598	ESRRG	[T/C]	8.90E-05	1.50	1.22	1.84	A	0.256	0.296	0.219	0.897		44	188	234	25	174	313
AX-11478368	2	45640334	rs3755072	SRBD1	[T/C]	3.78E-05	1.50	1.24	1.82	B	0.302	0.346	0.261	0.977		57	213	202	35	199	281
AX-12632107	2	45694417	rs7561623	SRBD1	[A/G]	8.91E-06	1.55	1.28	1.88	A	0.297	0.344	0.253	0.999		58	209	205	33	195	288
AX-12558986	3	41081808	rs369775	CTNBN1	[T/G]	7.52E-05	0.61	0.47	0.78	A	0.156	0.123	0.187	0.754		7	102	364	17	159	339
AX-12559031	3	41096041	rs371341	CTNBN1	[T/C]	7.05E-05	0.60	0.46	0.77	A	0.147	0.114	0.177	0.748		6	95	369	15	151	344
AX-12401403	3	105966369	rs10933840	LOC100302640	[T/G]	3.97E-05	1.47	1.22	1.78	A	0.349	0.395	0.307	0.786		71	232	170	50	217	249
AX-12533870	5	4256547	rs263733	LOC340094	[T/C]	7.88E-05	1.50	1.23	1.84	A	0.257	0.298	0.220	0.301		36	209	227	29	169	318
AX-11402615	5	4256610	rs263734	LOC340094	[A/G]	6.35E-05	1.51	1.23	1.85	B	0.258	0.299	0.220	0.301		36	210	226	29	169	318
AX-11427859	5	173760242	rs2936978	MSX2	[C/G]	5.61E-05	0.64	0.51	0.79	A	0.216	0.177	0.251	0.692		12	142	316	34	189	288
AX-11396793	6	29832332	rs2524035	HLA-H	[A/G]	3.68E-06	1.75	1.38	2.21	A	0.172	0.213	0.135	0.514		14	173	284	11	116	386
AX-11221788	6	29924779	rs12665039	HLA-J	[T/C]	1.04E-05	1.70	1.34	2.16	B	0.170	0.209	0.135	0.319		13	172	288	12	115	389
AX-11396327	6	29934543	rs2517677	HLA-J	[A/G]	2.59E-06	1.77	1.39	2.24	A	0.169	0.211	0.131	0.661		13	173	286	10	115	389
AX-11396326	6	29937242	rs2517673	HLA-J	[A/G]	1.39E-05	1.69	1.33	2.14	A	0.172	0.210	0.136	0.196		13	173	287	13	114	386
AX-11396780	6	29939580	rs2523961	HLA-J	[A/G]	2.02E-06	1.78	1.40	2.27	A	0.168	0.210	0.130	0.352		12	174	286	11	111	391
AX-11408202	6	29943490	rs2735076	HLA-J	[A/G]	4.70E-06	1.74	1.37	2.21	A	0.169	0.209	0.132	0.437		14	170	289	11	114	390
AX-11367732	6	29948365	rs1208691	HLA-J	[T/G]	6.16E-06	1.73	1.36	2.19	A	0.169	0.209	0.133	0.466		12	173	286	11	115	390
AX-11408201	6	29948482	rs2735069	HLA-J	[T/G]	8.50E-06	1.72	1.35	2.18	A	0.168	0.207	0.132	0.441		11	173	286	11	114	389
AX-11497582	6	29949123	rs42308	HLA-J	[T/G]	5.56E-06	1.73	1.36	2.20	A	0.169	0.209	0.132	0.437		12	173	287	11	114	390
AX-11490714	6	29949168	rs410909	HLA-J	[T/G]	7.29E-06	1.72	1.36	2.19	A	0.168	0.208	0.132	0.437		11	174	287	11	114	390
AX-11396345	6	29949293	rs2517809	HLA-J	[A/G]	9.50E-06	1.71	1.35	2.17	A	0.170	0.209	0.134	0.510		12	172	284	11	116	387
AX-11312714	6	29949456	rs17180542	HLA-J	[T/C]	5.21E-06	1.74	1.37	2.21	A	0.168	0.208	0.131	0.405		12	171	286	11	113	391
AX-11480967	6	29950140	rs379221	HLA-J	[A/G]	4.28E-06	1.74	1.37	2.22	B	0.169	0.209	0.132	0.433		12	174	287	11	114	391
AX-11313017	6	29952704	rs17186930	HLA-J	[T/C]	2.26E-05	1.68	1.32	2.13	A	0.167	0.204	0.133	0.446		11	170	290	11	114	388
AX-11313018	6	29952814	rs17186937	HLA-J	[T/C]	7.19E-06	1.73	1.36	2.19	B	0.167	0.206	0.131	0.401		12	171	290	11	113	392
AX-11313019	6	29952920	rs17186944	HLA-J	[T/C]	8.50E-06	1.72	1.35	2.19	A	0.166	0.206	0.131	0.401		12	170	290	11	113	392
AX-11173079	6	29953099	rs11755961	HLA-J	[T/C]	8.26E-06	1.72	1.35	2.19	A	0.166	0.206	0.131	0.382		12	170	290	11	112	390
AX-11221640	6	29954111	rs12662947	HLA-J	[T/C]	7.10E-06	1.73	1.36	2.19	B	0.167	0.207	0.131	0.405		12	171	289	11	113	391
AX-11221552	6	29954185	rs12661402	HLA-J	[T/C]	1.75E-05	1.69	1.33	2.16	A	0.164	0.201	0.129	0.585		9	171	290	10	113	391
AX-11221554	6	29954199	rs12661411	HLA-J	[T/C]	7.01E-06	1.73	1.36	2.20	A	0.168	0.207	0.131	0.409		12	171	288	11	113	390
AX-11454807	6	29954617	rs34894339	HLA-J	[A/G]	1.08E-05	1.70	1.34	2.16	B	0.169	0.207	0.133	0.137		13	170	290	13	111	391
AX-11462575	6	29954642	rs35356382	HLA-J	[T/C]	8.40E-06	1.72	1.35	2.19	A	0.167	0.206	0.131	0.405		12	170	289	11	113	391
AX-11313031	6	29955222	rs17187077	HLA-J	[A/C]	1.21E-05	1.70	1.34	2.17	B	0.166	0.204	0.131	0.405		11	171	290	11	113	391
AX-11221795	6	29956842	rs12665186	HLA-J	[A/G]	8.26E-06	1.72	1.35	2.19	B	0.166	0.206	0.131	0.382		12	170	290	11	112	390
AX-11221620	6	29957077	rs12662611	HLA-J	[T/C]	1.04E-05	1.71	1.34	2.17	A	0.168	0.207	0.132	0.248		12	171	289	12	112	390
AX-11313039	6	29961579	rs17187224	HLA-J	[T/C]	7.87E-06	1.73	1.36	2.20	A	0.163	0.202	0.128	0.826		12	167	293	9	114	393
AX-11221524	6	29978027	rs12661053	ZNRD1	[T/C]	6.49E-06	1.73	1.36	2.20	A	0.167	0.207	0.131	0.401		12	171	289	11	113	392
AX-11172899	6	29979643	rs11753431	ZNRD1	[A/G]	7.10E-06	1.73	1.36	2.19	A	0.167	0.207	0.131	0.405		12	171	289	11	113	391
AX-11172945	6	29980240	rs11753960	ZNRD1	[T/C]	6.41E-06	1.73	1.36	2.20	A	0.167	0.207	0.131	0.405		12	171	288	11	113	391
AX-11595286	6	29986142	rs6931672	ZNRD1	[A/G]	7.76E-06	1.72	1.35	2.19	A	0.167	0.207	0.131	0.409		12	171	289	11	113	390
AX-11280252	6	29986684	rs165256	ZNRD1	[T/C]	7.78E-06	1.72	1.35	2.19	B	0.168	0.207	0.132	0.437		11	173	286	11	114	390
AX-11313055	6	29987191	rs17187488	ZNRD1	[A/G]	1.11E-05	1.71	1.34	2.17	A	0.166	0.204	0.131	0.401		11	171	290	11	113	392
AX-11595078	6	29988964	rs6928966	ZNRD1	[T/C]	6.49E-06	1.73	1.36	2.20	B	0.167	0.207	0.131	0.401		12	171	289	11	113	392
AX-11313546	6	29989689	rs10947045	ZNRD1	[T/C]	2.13E-05	1.68	1.32	2.14	A	0.168	0.206	0.134	0.267		12	168	286	12	112	384
AX-11506046	6	29995534	rs4448133	ZNRD1	[A/G]	4.20E-05	1.53	1.25	1.87	B	0.269	0.312	0.229	0.171		37	213	210	25	181	298
AX-11313547	6	30000973	rs10947046	ZNRD1	[T/G]	7.86E-06	1.72	1.35	2.19	A	0.167	0.206	0.131	0.405		12	171	290	11	113	391
AX-11313548	6	30007711	rs10947047	ZNRD1	[A/G]	5.28E-06	1.74	1.37	2.21	A	0.167	0.207	0.131	0.401		12	171	287	11	113	392
AX-11221776	6	30009664	rs12664794	ZNRD1	[A/G]	6.49E-06	1.73	1.36	2.20	B	0.167	0.207	0.131	0.401		12	171	289	11	113	392
AX-11595922	6	30012340	rs6940552	ZNRD1	[A/G]	4.57E-06	1.75	1.38	2.23	A	0.166	0.206	0.129	0.562		12	171	290	10	112	389
AX-11565315	6	30016297	rs6457138	ZNRD1	[A/C]	6.49E-06	1.73	1.36	2.20	B	0.167	0.207	0.131	0.401		12	171				

Table S2. Association analyses of *HLA-B*, *HLA-C*, *-DRB1*, *-DQB1*, and *-DPB1* alleles

HLA-B	case (2n=832)	%	control (2n=922)	%	Fisher's P- value	OR	95% CI	
07:02	23	2.8	26	2.8	1	0.98	0.53	1.80
13:01	14	1.7	16	1.7	1	0.97	0.44	2.13
15:01	51	6.1	78	8.5	0.06704	0.71	0.48	1.03
15:18	12	1.4	15	1.6	0.847	0.88	0.38	2.04
35:01	65	7.8	75	8.1	0.86	0.96	0.67	1.37
39:01	25	3.0	33	3.6	0.5931	0.83	0.47	1.46
40:01	59	7.1	57	6.2	0.5008	1.16	0.78	1.72
40:02	71	8.5	85	9.2	0.6746	0.92	0.65	1.29
40:06	25	3.0	32	3.5	0.5931	0.86	0.49	1.52
44:03	49	5.9	24	2.6	0.0007086	2.34	1.39	4.03
46:01	62	7.5	56	6.1	0.2538	1.25	0.84	1.85
48:01	17	2.0	23	2.5	0.6315	0.82	0.41	1.61
51:01	81	9.7	83	9.0	0.6227	1.09	0.78	1.52
52:01	149	17.9	165	17.9	1	1.00	0.78	1.29
54:01	62	7.5	74	8.0	0.7208	0.92	0.64	1.33
56:01	18	2.2	7	0.8	0.01507	2.89	1.14	8.23
59:01	14	1.7	18	2.0	0.7235	0.86	0.39	1.84
67:01	10	1.2	17	1.8	0.3333	0.65	0.26	1.51
HLA-C	case (2n=896)	%	control (2n=1004)	%	Fisher's P- value	OR	95% CI	
01:02	175	19.5	184	18.3	0.5187	1.08	0.85	1.37
03:03	128	14.3	154	15.3	0.5608	0.92	0.71	1.20
03:04	121	13.5	142	14.1	0.6904	0.95	0.72	1.24
04:01	23	2.6	38	3.8	0.1519	0.67	0.38	1.16
06:02	6	0.7	6	0.6	1	1.12	0.30	4.21
07:02	82	9.2	102	10.2	0.4848	0.89	0.65	1.22
07:04	11	1.2	10	1.0	0.6655	1.24	0.47	3.26
08:01	40	4.5	64	6.4	0.06971	0.69	0.45	1.05
12:02	157	17.5	167	16.6	0.6252	1.06	0.83	1.36
14:02	66	7.4	59	5.9	0.1957	1.27	0.87	1.87
14:03	52	5.8	28	2.8	0.001255	2.15	1.32	3.56
15:02	27	3.0	34	3.4	0.6967	0.89	0.51	1.53
HLA-DRB1	case (2n=914)	%	control (2n=952)	%	Fisher's P- value	OR	95% CI	
01:01	24	2.6	26	2.7	1	0.96	0.52	1.75
04:01	13	1.4	12	1.3	0.8416	1.13	0.47	2.73
04:03	22	2.4	8	0.8	0.009016	2.91	1.24	7.60
04:05	113	12.4	134	14.1	0.3054	0.86	0.65	1.14
04:06	9	1.0	25	2.6	0.008899	0.37	0.15	0.82
04:10	11	1.2	19	2.0	0.1997	0.60	0.26	1.33
08:02	29	3.2	34	3.6	0.701	0.88	0.52	1.51
08:03	106	11.6	89	9.3	0.1299	1.27	0.93	1.73
09:01	173	18.9	205	21.5	0.1671	0.85	0.67	1.07
11:01	21	2.3	15	1.6	0.313	1.47	0.72	3.08
12:01	44	4.8	33	3.5	0.1626	1.41	0.87	2.31
12:02	23	2.5	26	2.7	0.885	0.92	0.50	1.69
13:02	25	2.7	13	1.4	0.04794	2.03	0.99	4.35
14:03	6	0.7	5	0.5	0.7697	1.25	0.32	5.20
14:05	24	2.6	14	1.5	0.1002	1.81	0.89	3.80
14:54	34	3.7	34	3.6	0.902	1.04	0.62	1.75
15:01	64	7.0	82	8.6	0.1974	0.80	0.56	1.14
15:02	163	17.8	163	17.1	0.7146	1.05	0.82	1.34
HLA-DQB1	case (2n=930)	%	control (2n=1012)	%	Fisher's P- value	OR	95% CI	
03:01	105	11.3	94	9.3	0.155	1.24	0.92	1.69
03:02	48	5.2	65	6.4	0.2456	0.79	0.53	1.18
03:03	190	20.4	224	22.1	0.3751	0.90	0.72	1.13

04:01	114	12.3	141	13.9	0.2826	0.86	0.66	1.13
04:02	24	2.6	33	3.3	0.4205	0.79	0.44	1.38
05:01	29	3.1	33	3.3	0.8977	0.95	0.55	1.64
05:02	18	1.9	28	2.8	0.2367	0.69	0.36	1.31
05:03	47	5.1	44	4.3	0.5193	1.17	0.75	1.83
06:01	270	29.0	254	25.1	0.05202	1.22	0.99	1.50
06:02	57	6.1	80	7.9	0.1323	0.76	0.53	1.10
06:04	24	2.6	12	1.2	0.0278	2.21	1.05	4.87

HLA-DPB1	case (2n=926)	%	control (2n=1022)	%	Fisher's P- value	OR	95% CI	
02:01	144	15.6	243	23.8	5.23E-06	0.59	0.47	0.75
02:02	26	2.8	27	2.6	0.8894	1.06	0.59	1.91
03:01	52	5.6	51	5.0	0.5448	1.13	0.75	1.72
04:01	22	2.4	14	1.4	0.1287	1.75	0.85	3.73
04:02	47	5.1	46	4.5	0.5953	1.13	0.73	1.76
05:01	461	49.8	467	45.7	0.07649	1.18	0.98	1.41
09:01	146	15.8	143	14.0	0.2785	1.15	0.89	1.49
13:01	13	1.4	16	1.6	0.8524	0.90	0.39	2.00
14:01	11	1.2	9	0.9	0.5106	1.35	0.51	3.71

Table S3. Demographic details and number of samples analyzed in GWAS and replication study

		GWAS	Replication 1	Replication 2	Replication 3
population		Japanese	Japanese	Hong Kong Chinese	Thai
number of samples	total	989	767	281	383
	HCC	473	153	94	185
	CH, ASC	516	614	187	198
age (sd)	HCC	61.0 (10.34)	61.3 (8.36)	58.0 (10.53)	58.4 (12.02)
	CH, ASC	56.0 (12.63)	55.1 (10.15)	56.9 (8.31)	46.4 (11.07)
gender (male %)	HCC	390 (82.8%)	117 (76.5%)	80 (85.1%)	151 (82.1%)
	CH, ASC	265 (54.6%)	298 (48.5)	159 (85.0%)	131 (66.2%)

Abbreviation: HCC, Hepatocellular Carcinoma; CH, Chronic Hepatitis; ASC, Asymptomatic carrier.