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Evaluating risk loci for schizophrenia distilled from genome-wide association studies in Han Chinese from central China

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Schizophrenia is a complex psychiatric disorder with a high heritability. The exact mechanism and risk factors for this disease have not been sufficiently resolved despite decades of extensive study.[1] Recently, two genome-wide association studies (GWAS) in Han Chinese identified a total of nine single-nucleotide polymorphisms (SNPs) that reached genome-wide significance level,[2,3] but none of these risk loci was overlapped in the two studies. We genotyped these SNPs in Han Chinese from Hunan Province, China, and identified no association of any claimed SNP with schizophrenia.

A total of 976 unrelated schizophrenia patients and 1,043 matched healthy controls, all of Han Chinese, were recruited from Hunan Province in Central China. Patients with schizophrenia were diagnosed independently by two psychiatrists according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria. The controls were clinically diagnosed as having no psychiatric disorders or other diseases. All participants or supervisors of patients signed informed consent and this study was approved by the institutional review boards of the Kunming Institute of Zoology and the Second Xiangya Hospital.

The nine SNPs were genotyped by using SNaPshot (Supplementary Table S1 and Supplementary Figure S1). No deviation from Hardy–Weinberg equilibrium was observed for each SNP in either cases or controls (Table 1). The SNaPshot results were fully validated in 1% of genotyped individuals who were randomly selected for sequencing. There was no significant difference for allele frequency of the nine SNPs in case–control samples (Table 1).

Genotype and haplotype associations were conducted by using PLINK.[4] None of the nine SNPs showed a positive association with schizophrenia ($P > 0.05$; Table 1 and Supplementary Table S2). Note that rs835784 was marginally significant in the dominant model test ($P = 0.047$; Supplementary Table S2), but the significance did not exist after correcting for multiple tests. Haplotype comparison revealed no significant difference between schizophrenia patients and controls (Supplementary Table S3). Linkage disequilibrium (LD) analysis showed similar LD pattern in three blocks for the case and control populations, but the overall LD pattern or SNP allele frequency of Chinese populations differed from those of the HapMap data of Africans and Europeans (Supplementary Figure S2 and Supplementary Table S4), suggesting remarkable ethnic differences.

The lack of validation for any risk SNPs identified in the two GWAS of Han Chinese with schizophrenia[2,3] in our samples was not unexpected, considering the fact that none of the susceptible loci was overlapped in both studies. There are several explanations that would account for the failure to validate the GWAS results.[2,3] First, our sample was not as large as the ones used in both GWAS studies.[2,3] However, the G* power analysis showed that our sample had sufficient power to detect the potential association between SNPs and schizophrenia (Supplementary Materials and methods). Second, confounding factors such as population stratification might have caused an undetected bias and led to a false result. Moreover, single studies (even if based on large sample size) might have limited power to detect small gene effects in complex diseases such as schizophrenia.[5] We found no apparent population stratification between our case and control populations based on the principal component analysis of the matrilineal genetic component of our sample and reported Han Chinese populations across China (authors' unpublished data). Comparison of minor allele frequencies of the nine SNPs between our sample and the GWAS cohorts[2,3] further demonstrated regional difference: significant differences were observed for rs1233710 between our controls and the controls in Yue *et al.*'s study[3] and for rs2142731 between our case or control samples and the controls in Yue *et al.*'s study[3] (Supplementary Table S5). It can be tentatively said that regional differences accounted for the failure of independent validation. Our results supported the notion of high genetic heterogeneity of schizophrenia.[1] Excessive number of variants with smaller effect, structural variations, somatic mutations, gene–gene interactions and the effect of environmental factors may also have a crucial role in schizophrenia and account for the missing heritability.[6]

There are several limitations in the present study. First, we lacked detailed clinical information for each participant among our patients and reported GWAS cohorts, which prevented us from performing further association analysis between specific psychiatric phenotypes and SNP. Aggregating all patients with different subtypes together as a schizophrenia population may camouflage a real association of SNP with subtype. Second, we did not perform a fine-grained analysis for those regions that contained reported susceptible SNPs with a higher density of

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Table 1. Replication study of nine risk SNPs distilled from genome-wide association studies for schizophrenia in 976 Han Chinese with schizophrenia and 1043 matched healthy controls

Chr.	SNP ID	Gene	Alleles[a]	MAF		P-value[b]	OR (95% CI)	Genotype	Number of sample		P-value[c]	HWE P-value[d]
				Case	Control				Case	Control		
1	rs10489202	*BRP44*	G/T	0.155	0.142	0.288	1.102 (0.927–1.311)	GG/GT/TT	706/238/32	768/253/22	0.260	0.156/0.920
6	rs1233710	*ZKSCAN4*	C/T	0.340	0.354	0.372	0.942 (0.827–1.072)	CC/CT/TT	428/432/116	435/478/130	0.620	0.742/0.960
6	rs2142731	*PGBD1*	T/C	0.297	0.289	0.557	1.042 (0.855–1.109)	TT/TC/CC	477/418/81	523/438/82	0.833	0.511/0.605
6	rs1635	*NKAPL*	G/T	0.339	0.345	0.691	0.974 (0.910–1.193)	GG/GT/TT	431/429/116	440/487/116	0.462	0.642/0.417
8	rs1488935	*WHSC1L1*	G/A	0.300	0.299	0.918	1.007 (0.894–1.170)	GG/GA/AA	478/410/88	503/457/83	0.574	1.000/0.230
8	rs16887244	*LSM1*	A/G	0.304	0.299	0.758	1.022 (0.880–1.153)	AA/AG/GG	472/415/89	500/462/81	0.477	0.905/0.157
11	rs11038172	*TSPAN18*	G/A	0.412	0.427	0.355	0.941 (0.825–1.062)	GG/GA/AA	346/456/174	334/528/181	0.183	0.403/0.390
11	rs11038167	*TSPAN18*	C/A	0.382	0.397	0.317	0.936 (0.831–1.067)	CC/CA/AA	383/441/152	368/521/154	0.093	0.279/0.259
11	rs835784	*TSPAN18*	G/A	0.257	0.283	0.065	0.876 (0.762–1.006)	GG/GA/AA	540/371/65	531/434/78	0.138	0.947/0.534

Abbreviations: Chr., chromosome; CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.
SNPs rs10489202, rs1488935 and rs16887244 were initially reported to be susceptible to schizophrenia by Shi *et al*.[2] SNPs rs1233710, rs2142731, rs1635, rs11038172, rs11038167 and rs835784 were reported in Yue *et al*.[3]
[a]Major allele/minor allele.
[b]*P*-value was calculated by PLINK.[5]
[c]*P*-value for genotypes was calculated by χ^2 test.
[d]*P*-value of Hardy–Weinberg equilibrium (HWE) for cases/controls was computed by Monte Carlo permutation test (10 000 simulations).

SNP coverage. Other SNPs, than the reported risk SNPs, in the candidate region/gene may account for the association with schizophrenia in different populations. In spite of these limitations, our current study provided useful data for future meta-analysis of these psychosis markers. Do we have the courage to perform a validation study of risk SNPs distilled from GWAS? Apparently, this will be and will continue to be a challenging question for any validation study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Online Supplementary Data

Supplementary Materials and Methods

Subjects

A total of 976 unrelated patients with schizophrenia and 1043 matched healthy controls, all of Han Chinese descent, were recruited from Hunan Province in Central China. Patients were diagnosed independently by two psychiatrists as schizophrenia according to DSM-IV criteria. The controls were clinically diagnosed as no psychiatric disorders or other diseases and were well matched in geographic origin and ethnicity with schizophrenia patients. All participants or supervisors of patients signed informed consent. This study was approved by the institutional review boards of the Kunming Institute of Zoology and the Second Xiangya Hospital of the Central South University.

Genotyping for SNPs

Genomic DNA was extracted from whole blood by using the AxyPrep™ Blood Genomic DNA Miniprep Kit (Axygen, USA). The 9 SNPs were detected by multiplex PCR and single-base extension method based on SNaPshot assay (Table S1). Briefly, all PCR reactions were carried out in a volume of 8 μL reaction solution with 10-20 ng template DNA, 0.4 mM dNTPs, 0.2-0.5 μM of each primer (Table S1), 2.0 mM $MgCl_2$ and 1.0 U of Fast Star DNA polymerase (Roche Ltd, Basel, Switzerland). The amplification program is consisted of a first denaturation at 94°C for 2 min, followed by 40 cycles at 94°C for 30 s, 55°C for 30 s, 72°C for 1 min, and then ended with an incubation at 4°C. PCR products were cleaned up with 1.0 U of shrimp alkaline phosphatase (SAP) and 0.5 U of Exonuclease I (TaKaRa Biotechnology Co. Ltd. [Dalian, China]) at 37°C for 40 min, followed by a final incubation at 90°C for 10 min. The single-base extension was performed according to the protocol of the ABI PRISM® SNaPshot® Multiplex Kit (Applied Biosystems) in a total of 10 μL reaction solution containing 4 μL of the above treated-PCR products, 5 μL SNaPshot Multiplex Ready Reaction Mix and 0.4-0.8 μM pooled SNP-specific oligonucleotide primers (Table S1; nine SNP-specific oligonucleotide primers contained a special complementary sequence at 5' end with poly [GACT]). The thermal cycling program included 25 cycles of 96 °C for 10 s, 50 °C for 5 s, and 60 °C for 30 s. The final products were purified by treatment with 1.0 U of SAP at 37°C for 40 min and a deactivation at 75°C for 20 min. We loaded 0.5 μL purified product, 9 μL of Hi-Di™ formamide and 0.5 μL of GeneScan™ 120 LIZ™ size standard (Applied Biosystems) for capillary electrophoresis on ABI PRISM ™ 3730xl DNA analyzer (Applied Biosystems). The GeneMarker software (Holland and Parson 2011) was used to read the genotyping result.

Data analysis

Deviation from the Hardy-Weinberg equilibrium was estimated by using the HWsim program (http://krunch.med.yale.edu/hwsim/). Genotype and haplotype associations were performed using PLINK (Purcell et al. 2007). Linkage disequilibrium (LD) patterns of three blocks for the 8 SNPs in our sample and HapMap data sets were calculated according to the r^2 algorithm by using Haploview program (Barrett et al. 2005). We allocated the SNPs according to the

chromosome that they were located and reconstructed the haplotypes, in which block 1 contained rs1233710, rs2142731 and rs1635 in chromosome 6, block 2 contained rs1488935 and rs16887244 in chromosome 8, and block 3 contained rs11038172, rs11038167 and rs835784 in chromosome 11.

Power analysis

We performed a power calculation using the G* power program (Faul et al. 2007). With an effect size index of 0.1 supposing weak gene effect (Cohen 1998), the current sample size had 99% power to detect a significant association ($\alpha<0.05$).

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Table S1. Primers for genotyping 9 SNPs by using SNapShot assay

Chr.	SNP ID	Primer	
1	rs10489202	Forward	TCCAACTTGTCGATCATAAATAAT
		Reverse	TTGCACTTAGACTCTCAATAACTGTC
		Extention	TGCTGTAATAGATATCCTTACTCT
6	rs1233710	Forward	ATGCCTTATCTGACCTTTCA
		Reverse	AAGATACAATAAGCTGTGCTGTTG
		Extention	$(gact)_1$TTCAAGTATAAGTTCTTTGAGGGCAAGGGC
6	rs2142731	Forward	TGCTGCTGTAGCTCTTGGCTCAC
		Reverse	AGCTGCATTCAGGTGGTGAATTA
		Extention	cgt$(gact)_2$AGGAAGCCCAAGCTAGCTATACAGAGGTCA
6	rs1635	Forward	TATGTTCTTCCGAGTTGGAATC
		Reverse	GGGCCGTCTCCAAAGTTC
		Extention	t$(gact)_6$TGCGTTACCTCTTCTTCATCCTCAACTGGG
8	rs1488935	Forward	AACATTTCCTATCCCATGGC
		Reverse	TTAACCTGACTCAGCCACCA
		Extention	$(gact)_4$ATAGTTGGCAAAGACACAAATTAGGGAAAG
8	rs16887244	Forward	TTAATAGAAACACACGCAGATAGTTG
		Reverse	TTTAAATCTTTAGTAGATCTCCTGTACTTTAGT
		Extention	act$(gact)_9$ATTAGAGAAAGCAATTTTGGATAAATCTAC
11	rs11038172	Forward	CAGGTAAATAACACTTGGGTGTG
		Reverse	CTGGGTTTAAGCCTTGGAA
		Extention	t$(gact)_5$TTAATTACTGCTGCTCACTGCCCAGCTACA
11	rs11038167	Forward	AAGTACATCATCTTCATTATTTTTCTCA
		Reverse	AGGCTCAGAGAAACTAAGTGTCTAAA
		Extention	t$(gact)_7$TTTCTCTGTGGGGTCAGTGGGTGAGATGAC
11	rs835784	Forward	CAACCGTGGCTGCCCCTT
		Reverse	TTACTACAGTGAGCGTGTGGC
		Extention	ct$(gact)_8$CTTGCCCATGACTTTTGCTTCATGGCCACT

Chr., chromosome; $(gact)_n$, n repeats of “gact”

Table S2. Association analysis of genotypes under different models

Chr [a]	SNP ID	Test	*P*-value [c]
1	rs10489202	Trend [b]	0.279
1	rs10489202	Dominant model	0.512
1	rs10489202	Recessive model	0.104
6	rs1233710	Trend [b]	0.365
6	rs1233710	Dominant model	0.330
6	rs1233710	Recessive model	0.691
6	rs1635	Trend [b]	0.684
6	rs1635	Dominant model	0.371
6	rs1635	Recessive model	0.591
6	rs2142731	Trend [b]	0.546
6	rs2142731	Dominant model	0.568
6	rs2142731	Recessive model	0.719
8	rs16887244	Trend [b]	0.744
8	rs16887244	Dominant model	0.850
8	rs16887244	Recessive model	0.274
8	rs1488935	Trend [b]	0.914
8	rs1488935	Dominant model	0.736
8	rs1488935	Recessive model	0.393
11	rs11038167	Trend [b]	0.305
11	rs11038167	Dominant model	0.066
11	rs11038167	Recessive model	0.613
11	rs11038172	Trend [b]	0.342
11	rs11038172	Dominant model	0.103
11	rs11038172	Recessive model	0.780
11	rs835784	Trend [b]	0.060
11	rs835784	Dominant model	**0.047**
11	rs835784	Recessive model	0.474

[a] Chr., chromosome

[b] Trend, Cochran-Armitage trend test.

[c] *P*-value < 0.05 was marked in bold.

Table S3. Haplotype distributions in 976 Han Chinese with schizophrenia and 1043 matched controls

Block	Haplotype	Frequency in Cases	Frequency in Controls	*P*-value
B1	TCT	0.248	0.238	0.493
	TTT	0.091	0.109	0.067
	CCG	0.050	0.050	0.965
	CTG	0.611	0.603	0.613
B2	AG	0.300	0.297	0.804
	GA	0.700	0.704	0.804
B3	AAA	0.232	0.257	0.067
	ACA	0.020	0.021	0.948
	AAG	0.130	0.126	0.697
	GAG	0.020	0.017	0.486
	ACG	0.032	0.026	0.300
	GCG	0.565	0.553	0.423

We divided all SNPs (excluding rs10489202 which is located in chromosome 1) into three blocks according to the chromosome in which each SNP belonged to. Block B1 contained rs1233710, rs2142731 and rs1635 in chromosome 6; B2 contained rs1488935 and rs16887244 in chromosome 8; B3 contained rs11038172, rs11038167 and rs835784 in chromosome 11.

Table S4. Allele frequency of 9 SNPs in different populations

Chr.	SNP ID	Major allele / Minor allele	Minor allele frequency [c]													
			GWAS control	Hunan case	Hunan control	CHB	CHD	JPT	CEU	TSI	ASW	LWK	MKK	YRI	GIH	MEX
1	rs10489202	G/T	0.141 [a]	0.155	0.142	0.167	0.129	0.151	0.243	0.182	0.066	0.039	0.122	0.013	0.159	0.380
6	rs1233710	C/T	0.326 [b]	0.340	0.354	0.351	0.339	0.349	0.040	0.091	0.255	0.417	0.329	0.217	0.108	0.130
6	rs1635	G/T	0.241 [b]	0.297	0.289	0.354	0.345	0.360	0.050	0.099	0.302	0.478	0.383	0.298	0.109	0.143
6	rs2142731	T/C	0.330 [b]	0.339	0.345	0.214	0.306	0.227	0.009	0.023	0.075	0.094	0.049	0.027	0.017	0.090
8	rs16887244	A/G	0.316 [a]	0.300	0.299	0.381	0.353	0.349	0.288	0.290	0.151	0.133	0.154	0.124	0.097	0.190
8	rs1488935	G/A	0.317 [a]	0.304	0.299	0.375	0.347	0.349	0.265	0.261	0.208	0.239	0.315	0.164	0.091	0.290
11	rs11038167	C/A	0.424 [b]	0.412	0.427	0.440	0.367	0.365	0.009	NA	0.009	0.022	0.106	0.009	0.006	0.240
11	rs11038172	G/A	0.399 [b]	0.382	0.397	0.464	0.382	0.395	0.009	NA	0.028	0.033	0.087	0.022	0.011	0.280
11	rs835784	G/A	0.277 [b]	0.257	0.283	0.351	0.235	0.203	0.416	0.472	0.441	0.378	0.404	0.496	0.335	0.400

Chr., chromosome. Data of CHB, CHD, JPT, CEU, TSI, ASW, LWK, MKK, YRI, GIH, and MEK are retrieved from HapMap III (Release 2); the GWAS data are adopted from [a] Shi et al. (2011) and [b] Yue et al. (2011).

[c] The minor alleles of SNPs rs11038167 and rs11038172 in CEU, ASW, LWK, MKK, YRI, GIH, and MEX are C and G, respectively. Minor allele of SNP rs835784 is G in CEU, TSI, ASW and YRI. NA, not available.

CHB: Han Chinese in Beijing, China

CHD: Chinese in Metropolitan Denver, Colorado

JPT: Japanese in Tokyo, Japan

CEU: Utah residents with Northern and Western European ancestry from the CEPH collection

TSI: Tuscan in Italy

ASW: African ancestry in Southwest USA

LWK: Luhya in Webuye, Kenya

MKK: Maasai in Kinyawa, Kenya

YRI: Yoruban in Ibadan, Nigeria

GIH: Gujarati Indians in Houston, Texas

MEX: Mexican ancestry in Los Angeles, California

Table S5. Comparison of allele frequencies of 9 SNPs between our sample and reported GWAS samples

SNP ID	Sample [a]	Allele	Allele count		*P*-value [b]
			Hunan	GWAS	
rs10489202	Hunan-ct vs. GWAS-ct	G	1789	7798	0.871
		T	297	1280	
	Hunan-sz vs. GWAS-ct	G	1650	7798	0.117
		T	302	1280	
rs1233710	Hunan-ct vs. GWAS-ct1	C	1348	2155	0.038
		T	738	1043	
	Hunan-ct vs. GWAS-ct2	C	1348	7609	0.003
		T	738	3597	
	Hunan-sz vs. GWAS-ct1	C	1288	2155	0.300
		T	664	1043	
	Hunan-sz vs. GWAS-ct2	C	1288	7609	0.095
		T	664	3597	
	Hunan-ct vs. GWAS-sz1	C	1348	1106	1.53×10^{-9}
		T	738	386	
	Hunan-ct vs. GWAS-sz2	C	1348	5839	1.70×10^{-12}
		T	738	2215	
	Hunan-sz vs. GWAS-sz1	C	1288	1106	2.67×10^{-7}
		T	664	386	
	Hunan-sz vs. GWAS-sz2	C	1288	5839	1.17×10^{-8}
		T	664	2215	
rs2142731	Hunan-ct vs. GWAS-ct1	T	1484	2427	1.19×10^{-4}
		C	602	771	
	Hunan-ct vs. GWAS-ct2	T	1484	8741	8.48×10^{-12}
		C	602	2465	
	Hunan-sz vs. GWAS-ct1	T	1372	2427	9.19×10^{-6}
		C	580	771	
	Hunan-sz vs. GWAS-ct2	T	1372	8741	8.68×10^{-14}
		C	580	2465	
	Hunan-ct vs. GWAS-sz1	T	1484	1214	2.50×10^{-12}
		C	602	278	
	Hunan-ct vs. GWAS-sz2	T	1484	6572	5.96×10^{-26}
		C	602	1482	
	Hunan-sz vs. GWAS-sz1	T	1372	1214	9.34×10^{-14}
		C	580	278	
	Hunan-sz vs. GWAS-sz2	T	1372	6572	1.47×10^{-28}
		C	580	1482	
rs1488935	Hunan-ct vs. GWAS-ct	G	1463	6209	0.123
		A	623	2869	

	Hunan-sz vs. GWAS-ct	G	1366	6209	0.171
		A	586	2869	
rs11038172	Hunan-ct vs. GWAS-ct1	G	1196	1842	0.85
		A	890	1356	
	Hunan-ct vs. GWAS-ct2	G	1196	6511	0.514
		A	890	4695	
	Hunan-sz vs. GWAS-ct1	G	1148	1842	0.392
		A	804	1356	
	Hunan-sz vs. GWAS-ct2	G	1148	6511	0.558
		A	804	4695	
	Hunan-ct vs. GWAS-sz1	G	1196	750	2.85×10^{-5}
		A	890	742	
	Hunan-ct vs. GWAS-sz2	G	1196	4269	7.00×10^{-4}
		A	890	3758	
	Hunan-sz vs. GWAS-sz1	G	1148	750	5.88×10^{-7}
		A	804	742	
	Hunan-sz vs. GWAS-sz2	G	1148	4269	7.57×10^{-6}
		A	804	3758	
rs1635	Hunan-ct vs. GWAS-ct1	G	1367	2143	0.266
		T	719	1055	
	Hunan-ct vs. GWAS-ct2	G	1367	7564	0.079
		T	719	3642	
	Hunan-sz vs. GWAS-ct1	G	1291	2143	0.519
		T	661	1055	
	Hunan-sz vs. GWAS-ct2	G	1291	7564	0.236
		T	661	3642	
	Hunan-ct vs. GWAS-sz1	G	1367	1100	1.76×10^{-7}
		T	719	392	
	Hunan-ct vs. GWAS-sz2	G	1367	5839	4.03×10^{-10}
		T	719	2215	
	Hunan-sz vs. GWAS-sz1	G	1291	1100	1.67×10^{-6}
		T	661	392	
	Hunan-sz vs. GWAS-sz2	G	1291	5839	2.53×10^{-8}
		T	661	2215	
rs11038167	Hunan-ct vs. GWAS-ct1	C	1257	1922	0.908
		A	829	1276	
	Hunan-ct vs. GWAS-ct2	C	1257	6712	0.756
		A	829	4494	
	Hunan-sz vs. GWAS-ct1	C	1207	1922	0.216
		A	745	1276	
	Hunan-sz vs. GWAS-ct2	C	1207	6712	0.107
		A	745	4494	
	Hunan-ct vs. GWAS-sz1	C	1257	774	6.03×10^{-7}

		A	829	718	
	Hunan-ct vs. GWAS-sz2	C	1257	4406	5.31×10^{-6}
		A	829	3648	
	Hunan-sz vs. GWAS-sz1	C	1207	774	4.69×10^{-9}
		A	745	718	
	Hunan-sz vs. GWAS-sz2	C	1207	4406	1.24×10^{-8}
		A	745	3648	
rs835784	Hunan-ct vs. GWAS-ct1	G	1496	2312	0.647
		A	590	886	
	Hunan-ct vs. GWAS-ct2	G	1496	8203	0.161
		A	590	3003	
	Hunan-sz vs. GWAS-ct1	G	1451	2312	0.11
		A	501	886	
	Hunan-sz vs. GWAS-ct2	G	1451	8203	0.296
		A	501	3003	
	Hunan-ct vs. GWAS-sz1	G	1496	980	1.16×10^{-4}
		A	590	512	
	Hunan-ct vs. GWAS-sz2	G	1496	5525	5.98×10^{-3}
		A	590	2529	
	Hunan-sz vs. GWAS-sz1	G	1451	980	3.38×10^{-8}
		A	501	512	
	Hunan-sz vs. GWAS-sz2	G	1451	5525	7.53×10^{-7}
		A	501	2529	
rs16887244	Hunan-ct vs. GWAS-ct	A	1462	6200	0.112
		G	624	2878	
	Hunan-sz vs. GWAS-ct	A	1359	6200	0.253
		G	593	2878	

[a] Data of GWAS-ct1 and GWAS-sz1 (stage I), GWAS-ct2 and GWAS-sz2 (stage II) are from Yue et al. (2011). In Shi et al.'s study (2011), these authors only presented the average minor allelic frequency of controls (GWAS-ct) used in the two stage analyses.
[b] Pearson's Chi-square test.

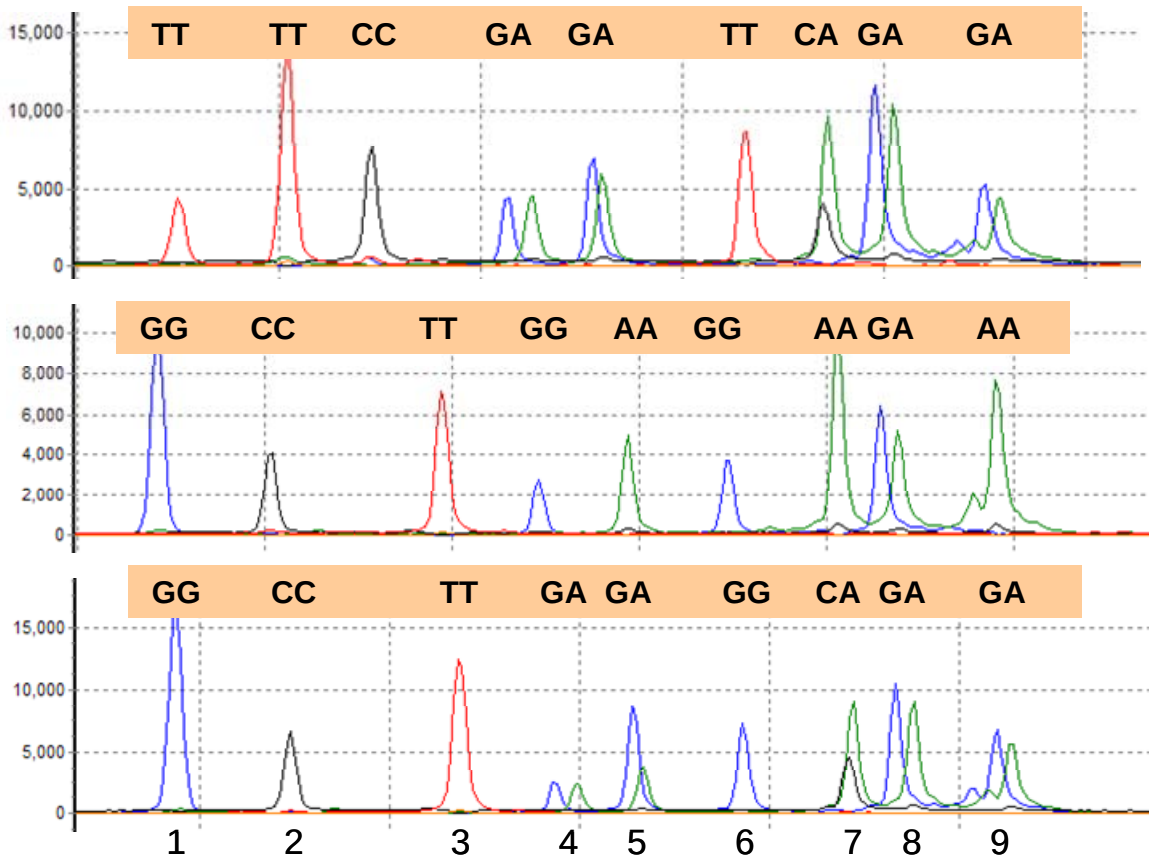

Figure S1. SNaPshot profile of 9 SNPs analyzed in this study. 1. rs10489202; 2. rs1233710; 3. rs2142731; 4. rs1488935; 5. rs11038172; 6. rs1635; 7. rs11038167; 8. rs835784; 9. rs16887244.

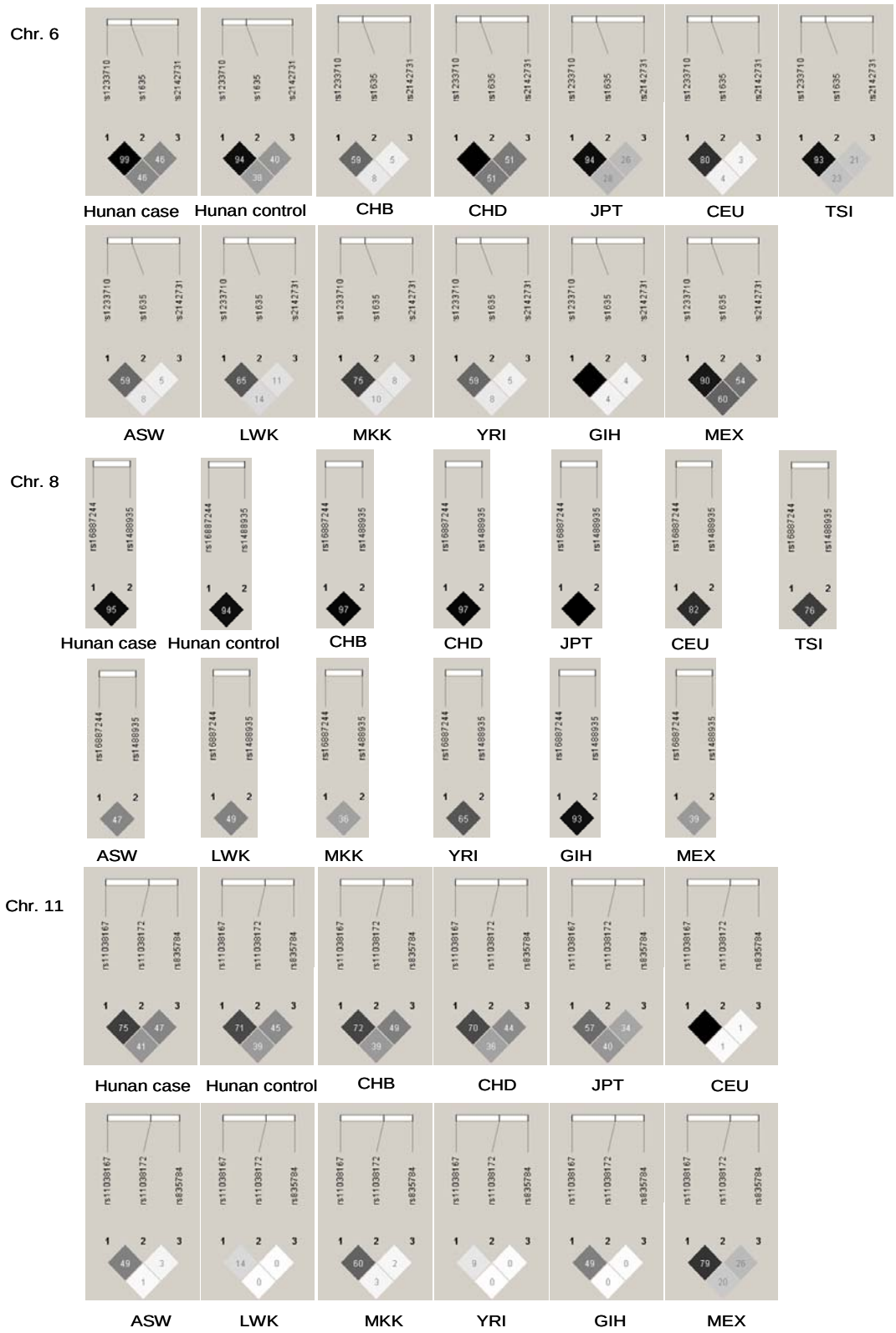

Figure S2. Linkage disequilibrium (LD) pattern of three blocks for 8 SNPs in the case and control samples and the HapMap data sets (HapMap III release 2: http://hapmap.ncbi.nlm.nih.gov/). The value in each square refers to r^2 x 100. We did not construct LD pattern for population TSI for chromosome 11 because only one SNP had polymorphism. For population symbols, refer to note for Table S4.

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