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Letter to the Editors

No association between the NDE1 gene and schizophrenia in the Japanese population

Dear Editors,

Series of studies have implicated that Disrupted in Schizophrenia 1 (DISC1) and its pathways are in the pathophysiology of schizophrenia (SZ) (Callicott et al., 2005; Hennah et al., 2003; Yamada et al., 2004). Recently, Hennah et al reported that the schizophrenic samples for the presence of SZ risk allelic haplotype (HEP3) of the DISC1 gene displayed an evidence for linkage of 16p13 (LOD=3.17) that contains the NDE1 gene. In addition, they also showed a significant association between specific haplotypes of the NDE1 gene (rs4781678-rs2242549-rs881803-rs2075512) and affected females with SZ spectrum disorders (Hennah et al., 2007). The NDE1 gene encodes a protein which interacts with the DISC1 protein (Millar et al., 2003; Brandon et al., 2004) and mouse models with NDE1 homozygous mutations displayed disordered cortex (Feng and Walsh, 2004). To confirm the association of the NDE1 gene with SZ, we performed the case-control association study in the Japanese population.

We used genomic DNA samples from 726 SZ patients: 406 male (mean age: 48.6±13.8 years), 320 female (mean age: 49.2±14.5 years) from the Tokushima University Hospital, affiliated psychiatric hospitals of the University of Tokushima, the Ehime University Hospital and the Osaka University Hospital in Japan. The diagnosis of SZ was made by at least two experienced psychiatrists according to DSM-IV criteria. 744 controls: 419 male (mean age: 45.8±11.3 years), 325 female (mean age: 45.2±10.5) were selected from volunteers without the psychiatric problems. All subjects were unrelated Japanese origin and signed written informed consent to participate in the genetic association studies approved by the institutional ethics committees. Genotyping was performed using commercially available TaqMan probes for the NDE1 gene with the Applied Biosystems 7500 Fast Real Time PCR System. We selected seven single nucleotide polymorphic (SNP) markers for genotyping from the public databases (dbSNP Home page) as reference for International Hap Map Project and Hennah's report (Hennah et al., 2007). The SNPs we selected includes six of seven of Hennah's because they are suitable for association study in the Japanese population. Haplotype block structure was determined using the HAPLOVIEW program (Barrett et al., 2005) defined according to the criteria of Gabriel et al. (Gabriel et al., 2002). Allelic and genotypic frequencies of patients and control subjects were compared using Fisher's exact test. The SNPAlyze 3.2Pro software (DYNACOM, Japan) was used to estimate haplotype frequencies, LD, permutation p values (10,000 replications) and deviation from Hardy–Weinberg (HW) distribution of alleles. Pair-wise LD indices (D' and r^2) were calculated for the control subjects. Power calculations for our sample size performed using the G*Power program (Erdfelder et al., 1996). The criterion for significance was set at $p<0.05$ for all tests.

Genotypic and allelic frequencies of the NDE1 gene are shown in Table 1. In power calculations using the G*Power program, our sample size had >0.97 power for detecting a significant association (alpha<0.05) when an effect size index of 0.2 was used. Genotypic distributions of these seven SNPs did not deviate significantly from HW equilibrium in either group ($p>0.05$). There were no significant differences in genotypic and allelic frequencies between cases and controls in all seven SNPs. LD between each pair of all the SNPs is relatively high ($D' \geqq 0.76$, $r^2 \geqq 0.39$). There were two LD blocks in NDE1 with rs2242549 and rs881803 residing in block 1 and rs2075512 and rs2384933 residing in block 2. The two marker haplotypes of block 1 and block 2 were not associated with SZ (permutation $p=0.93$, 0.36, respectively). When the data were subdivided on the basis of gender, no significant association was observed in seven SNPs either in male or female samples. The two marker haplotypes of block 1 and block 2 were not associated with SZ either in male and female (permutation p of block 1=0.73 and 0.26, permutation p of block 2=0.49 and 0.21, respectively). In addition, a tag-haplotype (rs4781678-rs2242549-rs881803-rs2075512) that Hennah et al reported a significant association with SZ

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Table 1
Genotypes and allele frequencies for the seven polymorphism

SNP	Total samples									Female			Male		
	Diagnosis	Allele		*p*-value genotype				*p*-value frequency		Allele		*p*-value	Allele		*p*-value
		C	A		C/C	C/A	A/A			C	A		C	A	
rs4781678	SZ	923	519	0.56	299	325	97	0.75	0.36	408	226	0.91	515	293	0.54
	CT	963	517		321	321	98		0.349	420	228		543	289	
		C	T		C/C	C/T	T/T			C	T		C	T	
rs6498567	SZ	814	632	0.5	226	362	135	0.58	0.437	347	289	0.26	467	343	0.96
	CT	851	627		249	353	137		0.424	372	272		479	355	
		T	G		T/T	T/G	G/G			T	G		T	G	
rs2242549	SZ	762	690	0.61	196	370	160	0.35	0.475	324	316	0.22	438	374	0.69
	CT	793	691		221	351	170		0.466	352	298		441	393	
		C	T		C/C	C/T	T/T			C	T		C	T	
rs881803	SZ	689	761	0.66	159	371	195	0.47	0.475	320	318	0.13	369	443	0.49
	CT	694	794		168	358	218		0.466	298	352		396	442	
		C	T		C/C	C/T	T/T			C	T		C	T	
rs2075512	SZ	714	736	0.51	174	366	185	0.51	0.492	316	324	0.87	398	412	0.49
	CT	751	737		197	357	190		0.505	324	326		427	411	
		C	T		C/C	C/T	T/T			C	T		C	T	
rs2384933	SZ	936	516	0.54	298	340	88	0.71	0.355	414	226	0.68	522	290	0.64
	CT	976	512		321	334	89		0.344	428	222		548	290	
		G	A		G/G	G/A	A/A			G	A		G	A	
rs11130	SZ	699	741	0.55	162	375	183	0.07	0.485	313	323	1	386	418	0.43
	CT	738	748		197	344	202		0.497	320	330		418	418	

spectrum disorders in female was not associated with SZ either in male and female (permutation $p=0.90$, 0.054, respectively) of the Japanese population.

Although an association between specific haplotypes of NDE1 and a broad spectrum of SZ specific females was reported (Hennah et al., 2007), we could not replicate significant associations between seven NDE1 SNPs and SZ in our Japanese samples. Different results between our study and Hennah's study may be that (a) different end-state diagnosis subjects used; Hennah et al used a broad spectrum of SZ including SZ, schizoaffective disorder, schizophrenia spectrum conditions and mood disorder, (b) ethnic difference; different allele frequency and different LD patterns (Supplementary Table), (c) different sample size.

In conclusion, we failed to find the association between the NDE1 gene and SZ in the Japanese population. This gene may not play a major role in the etiology of SZ. However we can not rule out a possibility that DISC1-NDE1 interaction may be involved in the etiology of schizophrenia. Further studies will be needed to conclude whether DISC1-NDE1 interaction is associated with SZ.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2007.10.032.

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