Four polymorphisms of the pericentriolar material 1 (PCM1) gene are not associated with schizophrenia in a Japanese population

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Schizophrenia is one of the most severe psychiatric disorders. Previous studies implicated centrosomal dysfunction as a source of various neuropsychiatric disorders, including schizophrenia (Ishizuka et al., 2006). Pericentriolar material 1(PCM1) is a component of the centriolar satellite (Dammermann and Merdes, 2002). Suppression of PCM1 in the developing cerebral cortex leads to neuronal migration defects (Kamiya et al., 2008). Several studies suggested that the PCM1 gene on chromosome 8p22 is one of the candidate genes for schizophrenia in a Caucasian population (Gurling et al., 2001). However, recent meta-analyses of the association between the PCM1 gene and schizophrenia are inconsistent (Hashimoto et al., 2011; Moens et al., 2010). In this study, we investigated whether single nucleotide polymorphisms (SNPs) found in exons of the PCM1 gene are associated with schizophrenia in a Japanese population.

The subjects comprised 485 unrelated Japanese patients with schizophrenia fulfilling the ICD-10 diagnostic criteria based on a structured clinical interview (250 males and 235 females, mean age±SD, 50.4±12.8 years). Subsequently, we subcategorized the subjects with schizophrenia by clinical subtype (232 were the hebephrenic subtype and 216 were the paranoid subtype). We chose 497, age-, sex-, and geographical origin-matched control subjects (250 males and 247 females, mean age± SD, 50.9±14.5 years). We selected 173 cSNPs of the PCM1 gene from the dbSNP home

page (http://www.ncbi.nlm.nih.gov/SNP/) first. Among these SNPs, four fulfilled the criteria of a minor allele frequency cut-off >5% and missense mutations. Finally, we selected rs412750 (Ser159Ala), rs208753 (Val597Met), rs17635381 (Ala691Ser), and rs370429 (Thr1543Ile) for genetic association analyses.

The four SNPs did not deviate significantly from Hardy-Weinberg equilibrium. We did not find significant differences in genotypic and allelic distribution between controls and schizophrenia patients, hebephrenic subtypes or paranoid subtypes of schizophrenia (Table1). In the HAPMAP data for the Japanese population, we found one linkage disequilibrium (LD) block containing rs412750 (Ser159Ala), rs208753 (Val597Met), and rs17635381 (Ala691Ser). In this LD block, the estimated frequency of a two-marker haplotype consisting of rs412750 (Ser159Ala)-rs208753 (Val597Met) showed the smallest global p value (global permutation p value=0.0095). Additionally, the haplotype consisting of rs412750 (Ser159Ala)-rs208753 (Val597Met) had a significantly higher Ser159/597Met frequency in patients with the hebephrenic subtype of schizophrenia than in controls (permutation p value=0.0025) (Table 1). To examine the functions of these two SNPs, we used the in silico analysis program Polyphen (http://www.niehs.nih.gov/snpinfo). Rs208753 (Val597Met) had a high predicted sequence conservation score (1.0) and was predicted to be “probably damaging”.

Rs412750 (Ser159Ala) also had a high predicted sequence conservation score (0.997).

Our study has a limitation that should be addressed. The absolute frequencies of this haplotype were quite low in both groups: 2.8% in patients and 0.7% in controls. The rarity of these frequencies would be due to tight LD between these two SNPs.

We failed to find an association between the PCM1 gene and schizophrenia in a Japanese population. One risk haplotype associated with the hebephrenic subtype of schizophrenia was found. Further replication studies are required to confirm the association between the PCM1 gene and schizophrenia.

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5. Table(s)

Table 1.Genetic association analyses and haplotype frequencies in controls and patients

Genetic association analyses in controls and patients

	N	Genotype (%)			p value	Allele (%)		p value
rs412750 (Ser159Ala)		Ser/Ser	Ser/Ala	Ala/Ala		Ser	Ala	
controls	493	226(45.8)	212(43.0)	55(11.2)		664(67.3)	322(32.7)	
schizophrenia	466	199(42.7)	216(46.4)	51(10.9)	0.56	614(65.9)	318(34.1)	0.46
hebephrenic subtype	229	99(43.2)	108(47.2)	22(9.6)	0.55	306(66.8)	152(33.2)	0.84
paranoid subtype	211	90(42.7)	96(45.5)	25(11.8)	0.74	276(65.4)	146(34.6)	0.48
rs208753 (Val597Met)		Val/Val	Val/Met	Met/Met		Val	Met	
controls	492	234(47.6)	212(43.1)	46(9.3)		680(69.1)	304(30.9)	
schizophrenia	467	210(45.0)	211(45.2)	46(9.8)	0.72	631(67.6)	303(32.4)	0.47
hebephrenic subtype	229	104(45.5)	107(46.8)	18(7.7)	0.60	315(68.8)	143(31.2)	0.90
paranoid subtype	213	95(44.6)	93(43.7)	25(11.7)	0.57	283(66.4)	143(33.6)	0.32
rs17635381 (Ala691Ser)		Ala/Ala	Ala/Ser	Ser/Ser		Ala	Ser	
controls	493	142(28.8)	255(51.7)	96(19.5)		539(54.7)	447(45.3)	
schizophrenia	473	162(34.3)	229(48.4)	82(17.3)	0.18	553(58.5)	393(41.5)	0.09
hebephrenic subtype	232	76(32.8)	116(50.0)	40(17.2)	0.51	268(57.8)	196(42.2)	0.27
paranoid subtype	215	72(33.5)	106(49.3)	37(17.2)	0.43	250(58.1)	180(41.9)	0.23
rs370429 (Thr1543Ile)		Thr/Thr	Thr/Ile	Ile/Ile		Thr	Ile	
controls	493	420(85.2)	69(14.0)	4(0.8)		909(92.2)	77(7.8)	
schizophrenia	472	398(84.3)	69(14.6)	5(1.1)	0.88	865(91.6)	79(8.4)	0.65
hebephrenic subtype	230	196(85.2)	32(13.9)	2(0.9)	1.00	424(92.2)	36(7.8)	0.99
paranoid subtype	216	180(83.3)	33(15.3)	3(1.4)	0.69	393(91.0)	39(9.0)	0.65

Haplotype frequencies of 492 controls and 227 hebephrenic patients

rs412750-rs208753 haplotype	Controls Frequency	Patients Frequency	Permutation p value
Ser/Val	0.67	0.65	0.43
Ala/Met	0.30	0.29	0.57
Ala/Val	0.024	0.039	0.10
Ser/Met	0.007	0.028	**0.0025**

The grobal permutation p value was 0.0095.