

Association analysis of *PDE4B* polymorphisms with schizophrenia and smooth pursuit eye movement abnormality in a Korean population

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Abstract. Schizophrenia is a debilitating mental disorder with a high heritability rate. Located on chromosome 1p31.3, the human *cAMP-specific 3',5'-cyclic phosphodiesterase 4B (PDE4B)* gene has been considered as an important candidate gene for the risk of schizophrenia. Several genetic association studies reported the association between *PDE4B* polymorphisms and the risk of schizophrenia in Caucasian, African American, Indian, and Japanese populations. The aim of this study is to examine the association of *PDE4B* variations with schizophrenia and smooth pursuit eye movement (SPEM) abnormality in a Korean population. A case-control association analysis was carried out by comparing the genotype distribution of eight *PDE4B* polymorphisms between 457 schizophrenia patients and 386 normal healthy subjects. Differences in the frequency distribution of *PDE4B* single-nucleotide polymorphisms (SNPs) and haplotypes were analyzed by logistic regression analyses controlling for age as a covariate. Statistical analyses revealed nominal significant associations of *rs1040716*, *rs472952*, *rs1321177*, and *rs2144719* with the risk of schizophrenia ($p = 0.02\sim 0.05$). The *rs11208756* polymorphism showed a nominal significant association with SPEM abnormality ($p = 0.05$). In a meta-analysis with Japanese and Korean populations, three SNPs (*rs472952*, *rs1040716*, and *rs2180335*) revealed significant associations with schizophrenia (meta- p value = 0.0038~0.019). Our results support previously reported association of *PDE4B* variations with schizophrenia in other populations. The findings in this study add a new evidence for the involvement of *PDE4B* gene in schizophrenia etiology.

Key words: *PDE4B* — Schizophrenia — Single-nucleotide polymorphism — SPEM abnormality — Genetic factor

Abbreviations: LD, linkage disequilibrium; PDE, phosphodiesterase; SNP, single-nucleotide polymorphism; SPEM, smooth pursuit eye movement.

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Introduction

Schizophrenia is a debilitating mental disease affecting 1% of the general population in the world. The development of schizophrenia has been known to be highly heritable as shown by twin studies (Cardno and Gottesman 2000). Through previous studies about genetic variations associated with schizophrenia (Kirov et al. 2004; Li et al. 2006; Silberberg et al. 2006; Numata et al. 2008; Chen et al. 2009; Lepagnol-Bestel et al. 2010), disrupted in schizophrenia 1 (DISC1), neuregulin 1 (NRG1) and dystrobrevin binding protein 1 (DTNBP1) have emerged as considerable causal genes. Among them *DISC1* was reported originally as a risk factor for major mental illness by a study of a large Scottish family in which a balanced translocation between chromosomes 1 and 11 cosegregates with schizophrenia, bipolar disorder, and recurrent major depression (Millar et al. 2000). The outcome of the translocation was direct simultaneous disruption of *DISC1*, a conventional protein coding gene, and *DISC2*, an antisense noncoding RNA gene on chromosome 1 (Millar et al. 2000).

Disruption of the *phosphodiesterase 4B (PDE4B)* gene in two cousins, one with schizophrenia and the other psychosis, by different chromosomal translocation at 1p31.2 locus was reported later and PDE4B interacted dynamically with DISC1, possibly modulating cAMP levels in a protein kinase A phosphorylation-dependent manner (Davis et al. 1995; Millar et al. 2005). Thereafter evidences of genetic association between *PDE4B* polymorphisms and schizophrenia from different ethnicity such as Caucasian, African American, Indian, and Japanese populations were reported (Fatemi et al. 2008; Numata et al. 2008).

The class I PDE super-family in mammals is consisted of 11 members, each of them with distinct kinetic and regulatory properties. Among them, PDE4, 7 and 8 specifically hydrolyze cAMP. PDE1, 2, 3, 10 and 11 hydrolyze both cAMP and GMP. PDE5, 6 and 9 hydrolyze just cGMP. PDE4s are highly conserved over evolution, being found in *Drosophila melanogaster* and *Caenorhabditis elegans*; isoforms in man and mouse exhibit near identical sequences (Houslay 2010). And the mutation of *dunce* gene encoding PDE in *Drosophila melanogaster* can attribute to increase of cAMP level, and it was related with deficits in olfactory learning and behavioral defects (Davis et al. 1995).

Four genes (*PDE4A/B/C/D*) encode over 20 distinct PDE4 isoforms as a result of mRNA splicing and the use of distinct promoters (Houslay 2010). The human *PDE4B* gene on the 1p31.3 region is comprised of 17 exons spanning 580kb (Houslay and Adams 2003). *PDE4B* gene was suggested as a risk factor for schizophrenia because PDE is a key molecule to inactivate cAMP which is involved in learning, memory, and mood (Davis et al. 1995; Millar et al. 2005) and mediates cAMP signaling by interaction with

DISC1 (Millar et al. 2005). Taken together, *PDE4B* gene can be a considerable causal gene involved in schizophrenia pathogenesis with genetic, biochemical and pharmacological evidences as described above. In this study, we performed association analysis of *PDE4B* variations with schizophrenia and smooth pursuit eye movement (SPEM) abnormality in a Korean population.

Materials and Methods

Subjects

A total of 843 subjects were included in the study. Schizophrenia patients ($n = 457$) were recruited from Jinju Mental Hospital, Soonyoung Hospital, Hadong Wooridde Hospital (Gyeongsang Nam Do, Korea), Seoul National Hospital (Seoul, Korea) and Keyo Hospital (Kyunggi-Do, Korea) and unrelated healthy controls ($n = 386$) were recruited from Hangang Sacred Heart Hospital and the Center for Health Promotion in Seoul National University Hospital (Seoul, Korea). The protocols were approved by Institutional Review Board of the each hospital, and the experiments were undertaken with the understanding and written informed consent of each subject. Trained psychiatrists diagnosed schizophrenia based on the criteria set forth by the Diagnostic Statistical Manual of Mental Disorders IV (DSM-IV) (Association 2000). Patients with complicating diagnoses of mental retardation, organic brain damage, drug or alcohol abuse, neurological disorders, autoimmune disorders, and low comprehension skills were excluded from the study.

Measurement of smooth pursuit eye movement (SPEM)

A total of 113 schizophrenia patients who were able to understand the procedure of the experiment underwent an eye tracking task as described previously (Bae et al. 2012). The setting for the SPEM task was a darkened quiet room, wherein the schizophrenia patients were instructed to sit in front of a 19-in. computer monitor at a distance of 40 cm and asked to closely observe a moving target spot (0.8×1 cm) which appeared at the center of the computer monitor screen for 0.5 s and then moved horizontally back and forth in an 18.2° of visual arc to each side of the screen at a constant speed of 28.2° per second. Electrophysiological analog signals of SPEM were amplified and sampled at 400 Hz and converted into digitized files using BiopacMP150 (BIOPAC Systems, Goleta, CA, USA). During the challenge, 15 s of measurement period was sampled at 4 Hz and passed through a 2-Hz low-pass filter. The electro-oculogram (EOG) data underwent fast Fourier transformation, and the natural logarithmic value

of signal/noise (Ln S/N ratio) was calculated from analysis of the power spectrum curves. With an Ln S/N ratio of 3.97, subjects were categorized into 'good' and 'poor' performers according to their SPEM function.

Selection and genotyping of *PDE4B* polymorphisms

The peripheral blood leukocyte samples from 843 samples were collected in tubes containing sodium ethylenediaminetetraacetic acid, and then genomic DNA was obtained by the QIAamp blood extraction kit (QIAGEN, Valencia, USA). Eight single-nucleotide polymorphisms (SNPs; *rs11208756*, *rs6700403*, *rs599381*, *rs1040716*, *rs2180335*, *rs472952*, *rs1321177*, and *rs2144719*) in *PDE4B* were selected from polymorphisms in the literature and genotyped for the present study (Fatemi et al. 2008; Numata et al. 2008; Holliday et al. 2009). Commercially available pre-designed TaqMan probes and primers (Applied Biosystems, Foster City, CA, USA) were used in genotyping (see Table S1 in Supplementary Material). Haplotypes were inferred from the genotyped SNPs using the PHASE algorithm ver. 2.0 (Stephens et al. 2001), and those with frequency of over 0.05 were included in the association analysis.

Statistical analysis

We examined Lewontin's D' ($|D'|$) and linkage disequilibrium (LD) coefficient r^2 between all pairs of biallelic loci using Haploview algorithm (Barrett et al. 2005). Odds ratio (95% confidence interval) and corresponding p -values were calculated using logistic model controlling for age as a covariate. Ln S/N ratio was calculated from analysis of the power spectrum curves, and results were used in logistic analysis of SPEM abnormality. Statistical power of single associations was determined using the Power for Genetic Association Analyses (PGA) software (Menashe et al. 2008). The average statistical power was 74.6%. The meta-analysis was conducted by using PLINK (<http://pngu.mgh.harvard.edu/~purcell/plink/metaanal.shtml>). After p -values and odd ratios were obtained from literatures, meta- p values were

calculated according to PLINK's protocol. If odds ratios were not included in literatures, we used a tool in MedCalc (http://www.medcalc.org/calc/odds_ratio.php) to calculate odds ratios from each number of genotypes in cases and controls.

Results

Characteristics of study subjects

In this study, we explored a genetic association between *PDE4B* polymorphisms and the risk of schizophrenia with 843 subjects divided into 457 schizophrenia patients and 386 healthy controls. The summary of clinical profiles in this study was listed in Table 1. In some of schizophrenia patients ($n = 113$), we measured Ln S/N ratios of SPEM abnormality by an eye tracking task. A significant difference of Ln S/N between good and poor groups ($p < 0.001$) was observed (Table 1).

Genotyping of *PDE4B* polymorphisms

Total eight polymorphisms (*rs11208756*, *rs6700403*, *rs599381*, *rs1040716*, *rs2180335*, *rs472952*, *rs1321177*, and *rs2144719*) in intronic region of *PDE4B* gene were selected from International HapMap database and successfully genotyped in a total of 843 subjects (Figure 1, Table S2 in Supplementary Material). With an average call rate of over 95%, all eight *PDE4B* SNPs were successfully genotyped in a total 843 subjects. None of variants revealed significant deviations from Hardy-Weinberg equilibrium (Table S2). Pair-wise comparison of the genotyped SNPs revealed 3 tight LD blocks (Figure 1B). Seven major haplotypes with frequency over 0.05 were inferred from these LD blocks (Figure 1C). Among these constructed haplotypes, only two haplotypes (*BL1_ht2* and *BL3_ht3*) were used further association analysis because other five haplotypes (*BL1_ht1*, *BL_ht3*, *BL2_ht1*, *BL2_ht2*, and *BL3_ht1*) were equivalent to some SNPs.

Table 1. Summary of clinical profiles

Parameters	Schizophrenia patients		Healthy control
Number of subjects	457		386
Age (Range)	44.78 (23–76)		54.72 (28–79)
Sex (n , male/female)	255/202		217/169
SPEM measurement in patients	Subjects (N)	Age (year)	Ln S/N ratio of SPEM*
Poor (<3.97)	64	46.2 ± 9.3	3.26 ± 0.59
Good (≥3.97)	49	44.3 ± 9.9	4.30 ± 0.28

Values are mean ± SEM. Ln S/N, natural logarithmic values of the signal/noise; * significant difference between poor and good SPEM (smooth pursuit eye movement) groups ($p < 0.001$).

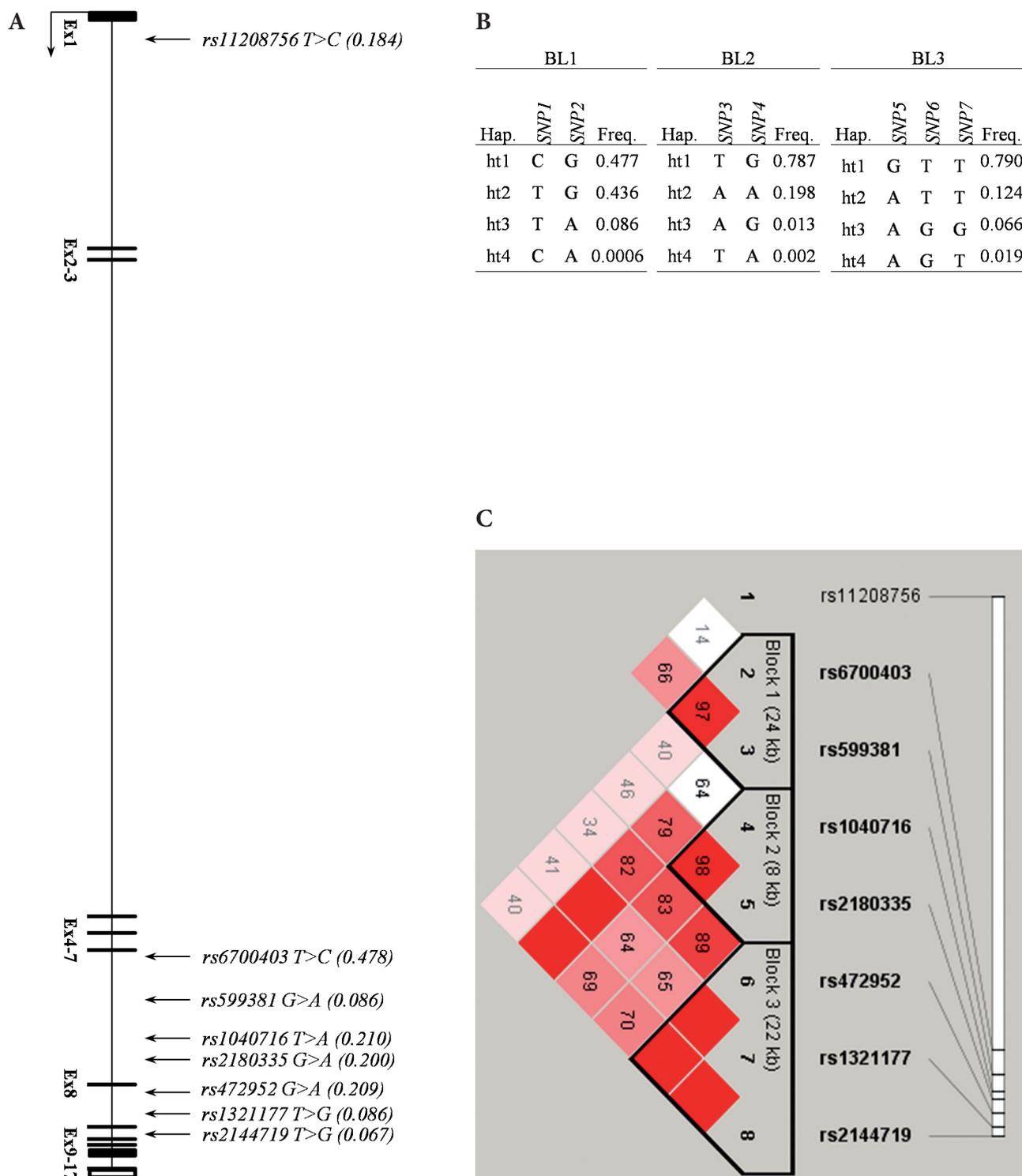


Figure 1. Physical map, Linkage disequilibrium (LD), and haplotypes of the *PDE4B* gene. **A.** Schematic gene map and single-nucleotide polymorphisms (SNPs) of *PDE4B* on chromosome 1p31.3. Black blocks represent coding exons. The first base of translation site was denoted as nucleotide +1. **B.** Haplotypes of *PDE4B*. List of SNP1~7: *rs6700403*, *rs599381*, *rs1040716*, *rs2180335*, *rs472952*, *rs1321177*, *rs2144719*, respectively. **C.** LD coefficient ($|D'|$) among *PDE4B* SNPs in a Korean population. Numbers in blocks represent values of multi-allelic D' . Shades of red/pink indicate Log of the Odds (LOD) ≥ 2 , whereas white blocks indicate LOD < 2 ($D' < 1$).

Association analysis of *PDE4B* variations with schizophrenia and SPEM abnormality

Allele frequencies of 8 SNPs and 2 haplotypes were compared between schizophrenia patients and healthy controls using logistic analysis controlling age as covariate. The results revealed that 4 SNPs (*rs1040716*, *rs472952*, *rs1321177*, and *rs2144719*) were nominally associated with a risk of schizophrenia ($p = 0.02\sim 0.05$, odds ratio = 0.62~0.72) (Table 2). Since SPEM has been reported to be one of the most consistency neurophysiologic abnormalities associated with schizophrenia, we also conducted case-control association analysis among schizophrenia patients who were classified into poor and good SPEM performers at an Ln S/N ratio

value of 3.97. In the analysis, *rs11208756* showed a nominal association with SPEM abnormality ($p = 0.05$, odds ratio = 0.48) (Table 3).

Meta-analysis of *PDE4B* polymorphisms with schizophrenia

We conducted meta-analysis and summarized the outcome in Table 4 comparing our current results with other studies. The combined analysis suggested that three polymorphisms (*rs1040716*, *rs2180335*, and *rs472952*) in *PDE4B* gene are risk factors for schizophrenia in Japanese and Korean populations (meta- p value = 0.0038~0.019). The *rs472952* showed the strongest association for schizophrenia in the two populations (meta- p value = 0.0038, odds ratio = 0.71) (Table 4).

Table 2. Association analysis of *PDE4B* polymorphisms with the risk of schizophrenia

SNP name	MAF		Co-dominant		Dominant		Recessive		Statistical power [†]
	Schizophrenia	Control	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	
<i>rs11208756</i>	0.180	0.188	0.93 (0.71–1.24)	0.64	0.89 (0.64–1.24)	0.48	1.18 (0.51–2.72)	0.71	80.593
<i>rs6700403</i>	0.499	0.453	1.24 (0.99–1.55)	0.06	1.34 (0.95–1.91)	0.10	1.32 (0.90–1.92)	0.15	93.114
<i>rs599381</i>	0.080	0.094	0.98 (0.67–1.44)	0.93	0.99 (0.65–1.50)	0.95	0.91 (0.18–4.70)	0.91	57.277
<i>rs1040716</i>	0.198	0.223	0.77 (0.59–1.01)	0.06	0.72 (0.52–0.99)	0.05	0.81 (0.37–1.74)	0.58	84.843
<i>rs2180335</i>	0.193	0.208	0.82 (0.62–1.09)	0.17	0.78 (0.56–1.07)	0.12	0.96 (0.42–2.19)	0.91	83.212
<i>rs472952</i>	0.198	0.223	0.72 (0.55–0.96)	0.02	0.73 (0.53–1.00)	0.05	0.47 (0.20–1.13)	0.09	84.843
<i>rs1321177</i>	0.072	0.102	0.64 (0.43–0.95)	0.03	0.64 (0.42–0.97)	0.04	0.24 (0.03–2.32)	0.22	60.246
<i>rs2144719</i>	0.054	0.083	0.62 (0.40–0.96)	0.03	0.62 (0.39–0.99)	0.04	0.24 (0.03–2.30)	0.22	52.802
<i>BL1_ht2</i>	0.423	0.451	0.83 (0.67–1.04)	0.10	0.84 (0.60–1.18)	0.31	0.70 (0.47–1.04)	0.08	–
<i>BL3_ht2</i>	0.125	0.122	0.86 (0.61–1.20)	0.37	0.85 (0.59–1.23)	0.40	0.73 (0.17–3.07)	0.67	–

Logistic regression analyses was used to calculate odds ratios (95% confidential interval) controlling for age (continuous value) as a covariate. SNP, single-nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; [†] statistical power was calculated by the Power for Genetic Association Analyses (PGA) software. Bold values indicate significant differences ($p < 0.05$).

Table 3. Association analysis of *PDE4B* polymorphisms with SPEM abnormality in schizophrenia patients

SNP name	MAF		Co-dominant		Dominant		Recessive	
	Good SPEM	Poor SPEM	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
<i>rs11208756</i>	0.104	0.219	0.48 (0.23–0.98)	0.05	0.44 (0.19–1.02)	0.06	0.25 (0.03–2.53)	0.24
<i>rs6700403</i>	0.537	0.447	1.42 (0.84–2.39)	0.19	2.56 (1.08–6.04)	0.03	1.00 (0.43–2.31)	1.00
<i>rs599381</i>	0.060	0.070	0.84 (0.31–2.28)	0.73	0.93 (0.31–2.81)	0.90	—	–
<i>rs1040716</i>	0.197	0.143	1.63 (0.78–3.41)	0.19	1.79 (0.81–3.95)	0.15	0.92 (0.06–15.40)	0.96
<i>rs2180335</i>	0.194	0.143	1.65 (0.79–3.45)	0.18	1.81 (0.82–4.01)	0.14	0.93 (0.06–15.30)	0.96
<i>rs472952</i>	0.187	0.158	1.39 (0.69–2.81)	0.36	1.62 (0.74–3.58)	0.23	0.54 (0.05–6.33)	0.62
<i>rs1321177</i>	0.074	0.063	1.48 (0.50–4.36)	0.48	1.48 (0.50–4.36)	0.48	—	—
<i>rs2144719</i>	0.059	0.053	1.40 (0.44–4.45)	0.57	1.40 (0.44–4.45)	0.57	—	—
<i>BL1_ht2</i>	0.403	0.482	0.73 (0.43–1.24)	0.24	0.92 (0.42–2.01)	0.83	0.41 (0.16–1.08)	0.07
<i>BL3_ht2</i>	0.112	0.096	1.23 (0.53–2.89)	0.63	1.16 (0.47–2.84)	0.75	—	—

SPEM, smooth pursuit eye movement; SNP, single-nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval. Bold values indicate significant differences ($p < 0.05$).

Table 4. Comparison and meta-analysis of genetic effect of *PDE4B* polymorphisms with schizophrenia in previous studies

Population	Sample (case/control)	<i>p</i> -value [Odds ratio]								Reference
		<i>rs11208756</i>	<i>rs6700403</i>	<i>rs599381</i>	<i>rs1040716</i>	<i>rs2180335</i>	<i>rs472952</i>	<i>rs1321177</i>	<i>rs2144719</i>	
Caucasian	644/604	-	-	0.30	0.0031	-	-	0.0004	0.0006	Fatemi et al. (2008)
African American	234/604	-	-	0.005	0.0087	-	-	0.51	0.47	Fatemi et al. (2008)
India	124 families	0.003	0.008	-	-	-	-	0.046	-	Holliday et al. (2009)
Japanese	444/452	-	-	0.92 [1.06]	0.012 [0.75]	0.0014 [0.70] ^a	0.0037 [0.72]	-	-	Numata et al. (2009)
Korean	457/386	0.64 [0.93]	0.06 [1.24]	0.93 [0.98]	0.05 [0.72] ^b	0.17 [0.82]	0.02 [0.72]	0.03 [0.64]	0.03 [0.62]	This study
Meta-analysis ^c										
<i>p</i> -value		-	-	0.90 [1.02]	0.0088 [0.74]	0.019 [0.75]	0.0038 [0.71]	-	-	
(Case/control)		-	-	(901/838)	(901/838)	(901/838)	(901/838)	-	-	

^a Odds ratio was calculated by each genotypes of cases and controls using a tool in MedCalc (http://www.medcalc.org/calc/odds_ratio.php). ^b *p*-value in a dominant model; other *p*-values in a co-dominant model in Korean; ^c The meta-analysis performed with Japanese and Korean because other studies were not include enough data to conduct the meta-analysis. The meta-analysis was conducted by PLINK (<http://pngu.mgh.harvard.edu/~purcell/plink/metaanal.shtml>). Bold values indicate significant differences ($p < 0.05$).

Discussion

PDE4B was evidenced as a considerable causal gene for schizophrenia from the previous observations. Firstly, 1p31.2 translocation directly disrupted *PDE4B* gene, resulting in schizophrenia occurrence (Millar et al. 2005). Secondly, high cAMP level was revealed to be related with behavioral defects (Davis et al. 1995) and human *PDE4B* plays an important role in cAMP hydrolysis (Uzunov and Weiss 1972). Thirdly, schizophrenia patients had a low expression of *PDE4B* level compared with healthy control subjects in postmortem brain tissue, which implicates that the dysregulation of *PDE4B* is associated with schizophrenia (Fatemi et al. 2005, 2008). Fourthly, genetic associations between *PDE4B* polymorphisms and schizophrenia (Fatemi et al. 2008; Numata et al. 2008; Holliday et al. 2009) from different ethnic populations such as Caucasians, African Americans, Indians, and Japanese were reported (Table 4).

The first association study between *PDE4B* polymorphisms and schizophrenia was conducted in Caucasian and African American populations (Fatemi et al. 2008). Among twenty seven variations investigated, they found that two SNPs, *rs1321177* and *rs2144719*, were most significantly associated with schizophrenia in Caucasian ($p = 0.0004$ and 0.0006 , respectively). However, in contrast, this association was not detected in African American. It was also observed that three SNPs (*rs1040716*, *rs2180335*, and *rs472952*) and two SNPs (*rs11208756* and *rs6700403*) were significantly related with schizophrenia in Japanese and Indian populations,

respectively (Numata et al. 2008; Holliday et al. 2009). All positive findings indicated that *PDE4B* polymorphisms were significantly associated with the risk of schizophrenia.

In the current study, we conducted a replication study for these positive findings in a Korean population. As a result, we also identified that four SNPs (*rs1040716*, *rs472952*, *rs1321177*, and *rs2144719*) showed nominal associations for schizophrenia in a Korean population ($p = 0.02\sim 0.05$). The *rs1040716* polymorphism showed positive associations for schizophrenia among Caucasian, African American, Japanese, and Korean population ($p = 0.0031\sim 0.05$). In the case of *rs472952*, Japanese and Korean populations showed significant associations for schizophrenia ($p = 0.0037\sim 0.02$) (Table 4). In order to assess genetic effect of *PDE4B* SNPs in all populations, a meta-analysis was conducted. Three SNPs (*rs1040716*, *rs2180335*, and *rs472952*) revealed significant associations in Japanese and Korean populations (meta-*p* value = $0.0038\sim 0.019$, odds ratio = $0.71\sim 0.75$) (Table 4). Among them, *rs472952* showed the strongest association with the risk of schizophrenia (meta *p*-value = 0.0038 , odds ratio = 0.71).

Since SPEM abnormality is proposed as one of the most consistent neurophysiological endophenotype in schizophrenia, it would be valuable to investigate the genetic effect of the polymorphisms for schizophrenia. In this study, schizophrenia patients were divided into two categories based on SPEM abnormality into good and poor performers. Among eight variations, the *rs11208756* polymorphism was revealed to have a nominal association for SPEM abnormality ($p =$

0.05, odds ratio = 0.48) (Table 3). Patients with rare allele (C) of the *rs11208756* SNP showed a lower frequency in poor group (Ln S/N ratio < 3.97) than good group (Ln S/N ratio ≥ 3.97). It implicates that the rare allele may be a genetic factor for SPEM abnormality. However, since the current study examined the relationship between *PDE4B* SNPs and SPEM abnormality with small samples, further replication study would be required to further assess the genetic effect of the polymorphisms with a larger cohort. In case of normal healthy subjects, we did not perform association analysis of SPEM function abnormality because there are low incidence of SPEM impairment in healthy subjects (<10%).

In summary, we scrutinized the association of *PDE4B* polymorphisms with schizophrenia and SPEM abnormality in a Korean population. Our results in this study replicated the positive associations of *PDE4B* polymorphisms with schizophrenia in other previous studies. We found that three SNPs (*rs1040716*, *rs2180335*, and *rs472952*) revealed significant associations in meta-analysis in Japanese and Korean populations (meta-*p* value = 0.0038~0.019). The finding indicates that *PDE4B* SNPs might be the genetic factor for schizophrenia. Furthermore, we identified a nominal association between SPEM abnormality and schizophrenia in this study. Thus, we provide new evidence from the Korean population for the involvement of *PDE4B* gene in the development of schizophrenia and SPEM abnormality in the disease.

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Conflict of interest: The authors declare no conflict of interest.

Supplementary Material

Table S1. Assay IDs of *PDE4B* polymorphisms

SNP name	Assay-on-demand ID
<i>rs11208756</i>	C_31224243_10
<i>rs6700403</i>	C__1270990_10
<i>rs599381</i>	C___599289_10
<i>rs1040716</i>	C__1270948_20
<i>rs2180335</i>	C__1270935_10
<i>rs472952</i>	C__8362833_10
<i>rs1321177</i>	C__8363076_10
<i>rs2144719</i>	C__16074734_10

TaqMan assay IDs from Applied Biosystems, CA, USA. SNP, single-nucleotide polymorphism.

Table S2. Genotype and allele frequency distribution of *PDE4B* polymorphisms

SNP name	Allele	Location	Genotype	Sample number	MAF	HWE * <i>p</i> -value
<i>rs11208756</i>	T>C	Intron 1	TC(247)	824	0.184	0.973
<i>rs6700403</i>	T>C	Intron 7	TC(416)	827	0.478	0.817
<i>rs599381</i>	G>A	Intron 7	GA(130)	835	0.086	0.728
<i>rs1040716</i>	T>A	Intron 7	TA(274)	816	0.210	0.698
<i>rs2180335</i>	G>A	Intron 7	GA(270)	825	0.200	0.514
<i>rs472952</i>	G>A	Intron 8	GA(293)	834	0.209	0.075
<i>rs1321177</i>	T>G	Intron 8	TG(131)	835	0.086	0.957
<i>rs2144719</i>	T>G	Intron 9	TG(100)	837	0.067	0.212

SNP, single-nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium. * *p*-values of deviation from HWE in Korean population.

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