CACNA1C gene and schizophrenia: a case–control and pharmacogenetic study

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Aim **The present study aimed to explore whether 24 single nucleotide polymorphisms (SNPs) within the *CACNA1C* gene were associated with schizophrenia (SCZ) and antipsychotic response.**

Methods **A sample of 176 SCZ inpatients and 326 healthy controls of Korean ethnicity was collected for this purpose. Psychopathological status was evaluated at baseline and at discharge using the Positive and Negative Syndrome Scale (PANSS).**

Results **In the case–control study, rs1006737 ($P = 0.05$) and rs2239104 ($P = 0.03$) were associated with SCZ. Further, the rs10848635–rs1016388–rs1006737 haplotype was also associated with SCZ ($P = 0.03$, simulate $P = 0.02$). In the pharmacogenetic analyses, we did not find any association among the investigated SNPs and improvement in the PANSS total score. However, rs723672 and rs1034936 were associated with improvement in the PANSS positive subscale (respectively, $P = 0.02$ and 0.05), rs2283271 in the negative subscale ($P = 0.01$), rs10848635 and rs1016388 in the general subscale (respectively, $P = 0.03$ and 0.04), and the rs3819536–rs2238062 haplotype (global statistics, $P = 0.1$; simulate $P = 0.04$).**

Conclusions **Our findings further support a role for the *CACNA1C* gene, particularly for the rs1006737, in SCZ. Further, five SNPs were associated with improvement in PANSS subscales, suggesting a role for this gene in antipsychotic response as well. However, taking into account the limitations of the present study, further research is needed to confirm our findings.** ***Psychiatr Genet*** **25:163–167**

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Introduction

Schizophrenia (SCZ) affects about 1% of the population and it ranks among the top 10 causes of disability worldwide (Tandon *et al.*, 2008). In the Korean population, the lifetime prevalence was between 3.1 and 5.4 cases/1000 (Lee *et al.*, 1990a, 1990b). Although environmental factors play a relevant role in the development of SCZ, a growing body of evidence suggests a strong genetic component in the etiology of the disease (Schlossberg *et al.*, 2010). Similarly, a genetic contribution for antipsychotic response has been suggested (Tandon *et al.*, 2008; Crisafulli *et al.*, 2011).

Recent genome-wide association studies on psychiatric disorders detected several new risk genes, but their neurobiological function is widely unknown. Thus, the ones with known functions are now considered to be among the most promising genes in the field of psychiatric genetics. Among these is the gene encoding the α-1C subunit of the L-type voltage-gated calcium channel (*CACNA1C*), which has been associated both with SCZ and with bipolar disorder (Hamshere *et al.*, 2013; Zheng *et al.*, 2014).

For these reasons, in the present paper, we investigated the impact of 24 single nucleotide polymorphisms (SNPs) within the *CACNA1C*, including the most replicated variant rs1006737 (Zheng *et al.*, 2014), along with tag SNPs with a prevalence of at least 5% among the Korean population (*http://hapmap.ncbi.nlm.nih.gov/*), on both the risk of SCZ and the antipsychotic response.

Patients and methods

Characteristics of the samples

We recruited 176 SCZ Korean inpatients and 326 Korean psychiatrically healthy individuals. Inclusion criteria were as follows: a diagnosis of SCZ according to the *Diagnostic and Statistical Manual of Mental Disorders* IV ed. – Text Revised (American Psychiatric Association, 2000) criteria, as assessed by the Mini-International Neuropsychiatric Interview (Sheehan *et al.*, 1998). Exclusion criteria were as follows: current severe or unstable medical and neurological conditions, current treatment with a long-acting

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antipsychotic, concomitant alcohol and substance abuse disorders, and ethnicities other than Korean. Healthy participants were voluntary controls who underwent the same assessment as psychiatric patients to exclude possible psychiatric disorders.

All patients admitted to the hospital were assessed for the severity of illness at baseline and at discharge through the administration of the Positive and Negative Symptom Scale (PANSS) (Kay *et al.*, 1987). Scorers were trained with good inter-rater reliability ($k = 0.8$). In addition, several clinical and demographic variables were recorded. The study protocol was approved by the institutional review board (approval number HC10TISI0031). All participants provided written informed consent before participating in the study.

Genotyping

Genomic DNA was extracted from blood using standard methods and quantified. The genotyping method using pyrosequencer (Biotage AB, Uppsala, Sweden) was used for genotyping 24 SNPs within the *CACNA1C* gene under investigation. PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer) used for the pyrosequencing assay were designed using the Pyrosequencing Assay Design Software v1 (Biotage AB), and one primer of each primer set was biotinylated. All procedures were performed according to the manufacturer's protocol (Bioneer).

The following SNPs were investigated: rs723672, rs2283271, rs758723, rs10848635, rs1016388, rs1006737, rs11615998, rs2370419, rs3819536, rs2238062, rs11062196, rs880342, rs17223841, rs7135609, rs2239085, rs10848664, rs2239104, rs1034934, rs1034936, rs215976, rs2283326, rs12422549, rs758559, and rs11062296.

Statistical analyses

Traditional statistical analyses were carried out using 'Statistica' package (StatSoft I. STATISTICA 7.0 per Windows, 1984–2004; Tulsa, Oklahoma, USA), whereas tests for association using multimarker haplotypes were performed using the statistic environment 'R cran', package 'haplo.score' (*http://cran.r-project.org/*). The main outcome measures were as follows: (a) differences among genotypic and allelic frequencies between the two samples and (b) influence of the 24 SNPs within the *CACNA1C* gene on clinical improvement, as measured by the PANSS total scale. Further outcomes of interests included improvement in PANSS subscales.

Differences in the allelic and genotype frequencies were calculated using the χ^2-statistics. Repeated-measure analysis of variance was used to investigate the antipsychotic response. All *P*-values were two-tailed. We did not apply any statistical correction because the gene investigated is considered among the most promising candidate genes and present analyses are considered confirmatory. With these parameters ($P = 0.05$), we had a sufficient power (0.80) to detect a small-medium effect size ($w = 0.14$). Haploview 3.2 (Broad Institute, Cambridge, Massachusetts, USA) was used to generate a linkage disequilibrium (LD) map and to test for Hardy–Weinberg equilibrium (Barrett, 2009). Haplotype 3.2 software automatically generates the haplotypes to be investigated on the basis of the algorithm developed by Gabriel *et al.* (2002). Further, other haplotypes were selected by authors on the basis of strong LD ($D' > 85$), proximity of SNPs, and prevalence more than 1%. Permutations ($n = 100\,000$) were performed to estimate the global significance of the positive results obtained. In case of positive findings, the following clinical variables were added as covariates: sex, age, age at onset, psychiatric diseases in family, previous suicide attempts, duration of the illness, duration of hospitalization, and antipsychotic treatment.

Results

Sociodemographic characteristics of the samples such as sex, age, and other clinical and sociodemographical variables are reported in Table 1. Patient and control samples differed with respect to sex, with a high percentage of women in the healthy sample ($\chi^2 = 7.56$, $d.f. = 1$, $P = 0.006$), and age ($F = 45.5$, $P < 0.01$).

All the considered SNPs were in Hardy–Weinberg equilibrium in the entire sample, except rs1016388 and rs12422549. Further, for two SNPs (rs11615998 and rs2370419), a very small variation was observed in our samples (see Table 2). Therefore, these SNPs were excluded from further analyses. Several SNPs investigated were in reciprocal LD (see Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/PG/A139*).

Table 1 Clinical and demographic characteristics of the sample

Variables	Schizophrenia ($n = 176$)	Controls ($n = 326$)
Sex		
Males	102 (57.9)	147 (45.1)
Females	74 (42.0)	179 (54.9)
Age (years)	37.19 ± 12.67	45.36 ± 13.09
PANSS total score		
Baseline	94.46 ± 14.26	
Discharge	75.84 ± 8.85	
Age at onset (years)[a]	28.76 ± 11.47	
Family history of psychiatric disorders		
Yes	29 (16.48)	
No	147 (83.52)	
Suicide attempts		
Yes	33 (18.7)	
No	143 (81.2)	
Antipsychotic drug		
Risperidone	23 (13.1)	
Olanzapine	108 (61.4)	
Quetiapine	45 (25.6)	

Data represent mean ± SD or *n* (%).
PANSS, Positive and Negative Syndrome Scale.

Table 2 Genotype and allele frequency of the single nucleotide polymorphisms under investigation in the present study

							Genotype		Allele	
SNPs	Position[a]	HWE's *P* value	Location	Genotype	Schizophrenia ($n=176$) [*n* (%)]	Control ($n=326$) [*n* (%)]	χ^2	*P* value	χ^2	*P* value
rs723672	2161561	0.97	Promoter	CC	3 (1.7)	15 (4.6)	2.78	0.25	0.90	0.34
				CT	54 (30.9)	97 (29.9)				
				TT	118 (67.4)	212 (65.4)				
rs2283271	2182298	0.46	Intron	AA	45 (25.8)	88 (27.0)	0.90	0.64	0.04	0.83
				AT	96 (54.5)	164 (50.3)				
				TT	35 (19.9)	74 (22.7)				
rs758723	2220405	0.87	Intron	AA	25 (14.3)	49 (15.0)	0.12	0.93	< 0.01	0.99
				AT	86 (49.1)	155 (47.5)				
				TT	64 (36.6)	122 (37.4)				
rs10848635	2316195	0.58	Intron	AA	21 (12.0)	43 (13.3)	2.39	0.30	0.53	0.47
				AT	92 (52.6)	147 (45.4)				
				TT	62 (35.4)	134 (41.4)				
rs1016388	2321868	< 0.01	Intron	AA	59 (33.5)	126 (38.6)	2.09	0.35	1.74	0.19
				AT	95 (54.0)	170 (52.1)				
				TT	22 (12.5)	30 (9.2)				
rs1006737	**2345295**	**0.70**	**Intron**	**AA**	**0**	**2 (0.6)**	**5.96**	**0.05**	**2.77**	**0.10**
				AG	**23 (13.1)**	**23 (7.1)**				
				GG	**153 (86.9)**	**301 (92.3)**				
rs11615998	2360166	1.0	Intron	CC	175 (99.4)	326 (100)	NA	NA	NA	NA
				CG	1 (0.6)	0				
				GG	0	0				
rs2370419	2423857	1.0	Intron	AA	0	0	NA	NA	NA	NA
				AG	0	1 (0.3)				
				GG	176 (100)	325 (99.7)				
rs3819536	2436998	0.15	Intron	AA	55 (31.2)	87 (26.7)	1.19	0.55	0.91	0.34
				AG	90 (51.1)	176 (54.0)				
				GG	31 (17.6)	63 (19.3)				
rs2238062	2438265	0.86	Intron	AA	134 (76.1)	255 (78.2)	0.74	0.69	0.45	0.50
				AC	39 (22.2)	68 (63.5)				
				CC	3 (1.7)	3 (0.9)				
rs11062196	2460107	0.52	Intron	AA	3 (1.7)	2 (0.6)	1.49	0.47	0.72	0.40
				AG	27 (15.3)	47 (14.4)				
				GG	146 (82.9)	277 (85.0)				
rs880342	2481607	0.19	Intron	CC	104 (59.1)	191 (58.6)	0.28	0.87	< 0.01	0.95
				CT	64 (36.4)	123 (37.7)				
				TT	8 (4.5)	12 (3.7)				
rs17223841	2521812	0.95	Intron	AA	79 (44.9)	154 (47.2)	0.42	0.81	0.40	0.53
				AG	77 (43.7)	140 (42.9)				
				GG	20 (11.4)	32 (9.8)				
rs7135609	2561951	0.36	Intron	CC	17 (9.7)	25 (7.7)	3.74	0.15	0.65	0.42
				CT	68 (38.6)	146 (44.8)				
				TT	91 (51.7)	155 (47.5)				
rs2239085	2585216	1.0	Intron	CC	131 (74.4)	250 (76.7)	0.88	0.64	0.12	0.73
				CT	43 (24.4)	70 (21.5)				
				TT	2 (1.1)	6 (1.8)				
rs10848664	2590769	1.0	Intron	AA	126 (71.6)	253 (77.6)	3.16	0.21	1.42	0.23
				AC	48 (27.3)	67 (20.5)				
				CC	2 (1.1)	6 (1.8)				
rs2239104	**2623543**	**0.31**	**Intron**	**GG**	**5 (2.8)**	**30 (9.2)**	**7.14**	**0.03**	**2.89**	**0.09**
				GT	**78 (44.3)**	**136 (41.7)**				
				TT	**93 (52.8)**	**160 (49.1)**				
rs1034934	2660096	0.89	Intron	CC	0	0	< 0.01	0.98	< 0.01	0.99
				CG	14 (7.9)	26 (8.0)				
				GG	162 (92.1)	299 (92.0)				
rs1034936	2661160	0.28	Intron	CC	6 (3.4)	22 (6.7)	3.54	0.17	3.00	0.08
				CT	67 (38.1)	135 (41.4)				
				TT	103 (58.5)	169 (51.8)				
rs215976	2694638	0.58	Coding exon	CC	92 (52.3)	150 (46.1)	2.04	0.36	1.98	0.16
				CT	72 (40.9)	145 (44.6)				
				TT	12 (6.8)	30 (9.2)				
rs2283326	2699492	0.89	Intron	AA	43 (24.4)	61 (18.7)	2.96	0.23	2.85	0.09
				AG	88 (50.0)	164 (50.3)				
				GG	45 (25.6)	101 (31.0)				
rs12422549	2752745	< 0.01	Intron	CC	121 (70.8)	208 (64.2)	2.88	0.24	1.42	0.23
				CT	48 (28.1)	114 (35.2)				
				TT	2 (1.2)	2 (0.6)				
rs758559	2761891	0.61	Intron	CC	17 (9.7)	23 (7.1)	1.18	0.55	0.19	0.66
				CT	65 (36.9)	129 (39.6)				
				TT	94 (53.4)	174 (53.4)				
rs11062296	2766253	0.65	Intron	AA	136 (77.3)	240 (73.6)	1.21	0.54	0.50	0.48
				AG	37 (21.0)	82 (25.1)				
				GG	3 (1.7)	4 (1.2)				

Bold indicates SNP with nominal associations.
HWE, Hardy–Weinberg equilibrium; SNPs, single nucleotide polymorphisms.
[a]Data from *http://snpper.chip.org*.

Table 3 Pharmacogenetics study results

		PANSS total			PANSS positive			PANSS negative			PANSS general		
SNPs	Analysis	*d.f.*	*F*	*P*	*d.f.*	*F*	*P*	*d.f.*	*F*	*P*	*d.f.*	*F*	*P*
rs723672	Genotypic	2, 172	1.83	0.16	**2, 172**	4.05	0.02	2, 172	1.45	0.24	2, 172	1.21	0.30
	Allelic	1, 348	1.47	0.23	**1, 348**	7.27	0.01	1, 348	1.04	0.31	1, 348	0.34	0.56
rs2283271	Genotypic	2, 173	2.67	0.07	2, 173	0.16	0.85	**2, 173**	**4.46**	**0.01**	2, 173	1.24	0.29
	Allelic	1, 350	2.64	0.10	1, 350	0.16	0.69	**1, 350**	**3.49**	**0.06**	1, 350	1.52	0.22
rs758723	Genotypic	2, 172	0.91	0.40	2, 172	0.69	0.50	2, 172	0.19	0.82	2, 172	1.61	0.20
	Allelic	1, 348	1.15	0.28	1, 348	0.08	0.77	1, 348	0.28	0.59	1, 348	2.70	0.10
rs10848635	Genotypic	2, 172	1.14	0.32	2, 172	0.91	0.40	2, 172	0.98	0.38	**2, 172**	**3.54**	**0.03**
	Allelic	1, 348	0.92	0.34	1, 348	0.83	0.36	1, 348	0.69	0.41	**1, 348**	**3.06**	**0.08**
rs1016388	Genotypic	2, 173	0.76	0.47	2, 173	1.20	0.30	2, 173	0.51	0.60	**2, 173**	**3.23**	**0.04**
	Allelic	1, 350	0.35	0.56	1, 350	1.15	0.28	1, 350	0.28	0.60	**1, 350**	**2.05**	**0.15**
rs1006737	Genotypic	1, 174	0.53	0.46	1, 174	0.08	0.78	1, 174	0.34	0.56	1, 174	0.40	0.52
	Allelic	1, 350	0.50	0.48	1, 350	0.07	0.79	1, 350	0.32	0.57	1, 350	0.38	0.54
rs11615998	Genotypic	1, 174	0.87	0.35	**1, 174**	**3.93**	**0.05**	1, 174	2.15	0.14	1, 174	0.64	0.42
	Allelic	1, 350	0.87	0.35	**1, 350**	**3.89**	**0.05**	1, 350	2.14	0.14	1, 350	0.64	0.42
rs2370419	Genotypic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Allelic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs3819536	Genotypic	2, 173	0.45	0.64	2, 174	0.95	0.39	2, 173	0.29	0.75	2, 173	0.14	0.87
	Allelic	1, 350	0.79	0.37	1, 350	1.81	0.18	1, 350	0.55	0.46	1, 350	0.01	0.99
rs2238062	Genotypic	2, 173	0.43	0.65	2, 173	0.14	0.87	2, 173	0.76	0.47	2, 173	1.70	0.18
	Allelic	1, 350	0.01	0.96	1, 350	0.03	0.86	1, 350	1.5	0.22	1, 350	0.28	0.60
rs11062196	Genotypic	2, 173	1.01	0.37	2, 173	0.32	0.72	2, 173	0.85	0.43	2, 173	0.56	0.57
	Allelic	1, 350	1.73	0.19	1, 350	0.72	0.40	1, 350	1.61	0.20	1, 350	0.57	0.45
rs880342	Genotypic	2, 173	1.52	0.22	2, 173	1.47	0.23	2, 173	1.62	0.20	2, 173	0.69	0.50
	Allelic	1, 350	2.13	0.14	1, 350	2.83	0.09	1, 350	3.01	0.08	1, 350	0.01	0.92
rs17223841	Genotypic	2, 173	0.02	0.98	2, 173	0.70	0.50	2, 173	0.70	0.50	2, 173	0.06	0.94
	Allelic	1, 350	0.03	0.85	1, 350	0.37	0.54	1, 350	1.07	0.30	1, 350	0.02	0.90
rs7135609	Genotypic	2, 173	0.18	0.83	2, 173	0.25	0.78	2, 173	1.45	0.24	2, 173	0.08	0.92
	Allelic	1, 350	0.04	0.85	1, 350	0.42	0.52	1, 350	0.83	0.36	1, 350	0.06	0.81
rs2239085	Genotypic	2, 173	0.14	0.87	2, 173	0.32	0.72	2, 173	1.48	0.23	2, 173	0.32	0.72
	Allelic	1, 350	0.08	0.77	1, 350	0.01	0.95	1, 350	2.02	0.16	1, 350	0.18	0.67
rs10848664	Genotypic	2, 173	0.28	0.76	2, 173	0.29	0.75	2, 173	2.34	0.10	2, 173	0.20	0.82
	Allelic	1, 350	0.44	0.51	1, 350	0.10	0.75	1, 350	3.27	0.07	1, 350	0.05	0.82
rs2239104	Genotypic	2, 173	1.63	0.20	2, 173	2.01	0.14	2, 173	1.70	0.19	2, 173	0.43	0.65
	Allelic	1, 350	2.14	0.14	1, 350	3.03	0.08	1, 350	2.78	0.10	1, 350	0.01	0.92
rs1034934	Genotypic	1, 174	0.08	0.78	1, 174	0.01	0.96	1, 174	2.85	0.09	1, 174	0.26	0.61
	Allelic	1, 350	0.08	0.78	1, 350	0.01	0.96	1, 350	2.72	0.10	1, 350	0.25	0.61
rs1034936	Genotypic	2, 173	1.57	0.21	**2, 173**	**3.05**	**0.05**	2, 173	1.26	0.29	2, 173	0.01	0.99
	Allelic	1, 350	2.71	0.10	**1, 350**	**5.37**	**0.02**	1, 350	2.08	0.15	1, 350	0.01	0.90
rs215976	Genotypic	2, 173	0.03	0.97	2, 173	0.87	0.42	2, 173	0.01	0.99	2, 173	0.18	0.84
	Allelic	1, 350	0.05	0.83	1, 350	1.54	0.22	1, 350	0.01	0.99	1, 350	0.32	0.57
rs2283326	Genotypic	2, 173	0.27	0.76	2, 173	0.12	0.89	2, 173	0.50	0.60	2, 173	1.24	0.29
	Allelic	1, 350	0.55	0.46	1, 350	0.24	0.62	1, 350	0.05	0.82	1, 350	2.09	0.15
rs12422549	Genotypic	2, 168	0.69	0.50	2, 168	0.31	0.73	2, 168	2.27	0.11	2, 168	0.19	0.83
	Allelic	1, 340	0.05	0.82	1, 340	0.43	0.51	1, 340	1.66	0.20	1, 340	0.01	0.93
rs758559	Genotypic	2, 173	0.25	0.78	2, 173	0.05	0.95	2, 173	0.44	0.65	2, 173	0.39	0.67
	Allelic	1, 350	0.55	0.46	1, 350	0.05	0.82	1, 350	0.66	0.42	1, 350	0.80	0.37
rs11062296	Genotypic	2, 173	0.38	0.68	2, 173	1.18	0.31	2, 173	0.47	0.62	2, 173	0.41	0.66
	Allelic	1, 350	0.01	0.93	1, 350	0.08	0.77	1, 350	0.22	0.64	1, 350	0.13	0.72

Bold indicates nominal associations.
PANSS, Positive and Negative Syndrome Scale; SNPs, single nucleotide polymorphisms.

In the case–control analysis, we found two SNPs (rs1006737 and rs2239104) to be associated marginally with SCZ (respectively, $\chi^2 = 5.96$, $P = 0.051$ and $\chi^2 = 7.14$, $P = 0.03$) as well as the rs10848635–rs1016388–1006737 haplotype (global statistics, $P = 0.03$; simulate, $P = 0.02$). Taking into account that for rs1006737, only two participants carried the AA genotype (consistently with the Asian population frequencies as reported in *http://hapmap.ncbi.nlm.nih.gov/*), we repeated the χ^2 analysis excluding these participants, finding a stronger association ($\chi^2 = 4.86$, $P = 0.03$). In the pharmacogenetic analyses (see Table 3), we failed to find any association with improvement in the PANSS total scale. Also taking into account only patients treated with olanzapine ($n = 108$), no association with improvement in the PANSS total scale was found. Nonetheless, rs723672 and rs1034936 were associated with improvement in the PANSS positive subscale (respectively, genotype analysis, $P = 0.02$ and 0.05; allelic analysis, $P = 0.007$ and 0.02), rs2283271 with improvement in the negative subscale (genotype analysis, $P = 0.01$; allelic analysis, $P = 0.06$), rs10848635 and rs1016388 with improvement in the general subscale (respectively, genotype analysis, $P = 0.03$ and 0.04) as well as the rs3819536–rs2238062 haplotype (global statistics, $P = 0.1$; simulate, $P = 0.04$). The results did not change after the inclusion of the covariates and type of antipsychotic drug included. Although our results did not withstand the application of strictly statistical corrections

as in Bonferroni's test (corrected $P=0.002$), we decided not to apply any correction because the gene investigated was selected on the basis of previous literature data and our main finding is a replication of previous results. Furthermore, taking into account the relatively small sample size, the lack of strong associations may represent false-negative results.

Discussion

The present study aimed to investigate whether 24 SNPs within the *CACNA1C* gene were associated with SCZ as well as with antipsychotic response.

Several studies repeatedly showed that the rs1006737 A allele was associated with a high risk of SCZ (Zheng *et al.*, 2014). Therefore, our result replicated previous findings confirming that the A allele may increase the risk of SCZ also in the Korean population, likely in interaction with other SNPs in LD, as suggested by the haplotype analysis. Interestingly, it has been shown that this allele is associated both with the relative amygdala volume (Wolf *et al.*, 2014) and with its activity during emotional processing in patients with SCZ (Tesli *et al.*, 2013). Furthermore, Krug *et al.* (2010) reported that the rs1006737 was associated with episodic memory encoding and retrieval in the right hippocampus, with the risk variant A associated with lower activation of this area. These data suggest that the rs10067370 may be implicated in the genesis of disturbances in neuronal circuits such as the cortico-striato-thalamo-cortical loop, which have been linked to SCZ and its etiopathology. However, to the best of our knowledge, rs2239104 has never been associated with SCZ as well as with some specific neurobiological function. Thus, further studies are required to confirm our preliminary results and to provide some biological explanations for this association. In the pharmacogenetic study, we failed to find any association with the global improvement, suggesting that the *CACNA1C* may not play a major role in antipsychotic response. However, the associations observed with improvement in the PANSS subscales may suggest a role for this gene in the response of some specific symptom clusters to antipsychotic treatment. Consistently, it has been hypothesized that a disturbed calcium metabolism could represent the neurobiological background of affective symptoms in SCZ, as partially supported by our results of negative and general symptomatology. Our pharmacogenetics results should be considered carefully because of the effects of some confounding factors such as previous antipsychotic treatments, the different antipsychotics used, and the different dosages used, which cannot be ruled out completely by the statistical analysis carried out. Nonetheless, the antipsychotics used shared several pharmacodynamic mechanisms of action (Miyamoto *et al.*, 2005) and the exploratory analysis in the subsample of patients treated with olanzapine confirmed our results. Therefore, further studies are required to replicate our preliminary findings and to better explore the effect of the investigated SNPs on the different symptom clusters of SCZ, particularly taking into account the relatively small sample size and the lack of statistical correction in the present study.

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Conflicts of interest

There are no conflicts of interest.

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