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Possible influence of *CREB1*, *CREBBP* and *CREM* variants on diagnosis and treatment outcome in patients with schizophrenia

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ABSTRACT

The present study explores whether some single nucleotide polymorphisms (SNPs) within *CREB1* (rs2709377 and rs6740584), *CREBBP* (rs2239317, rs2239316, rs3025702, rs130021, rs130005, rs129974 and rs9392) and *CREM* (rs1148247, rs4934735, rs12775799, rs6481941 and rs16935888) could be associated with schizophrenia (SKZ) and whether they could predict clinical outcomes in Korean in-patients treated with antipsychotics. Two-hundred twenty one in-patients suffering from SKZ and 170 psychiatrically healthy controls were genotyped for 10 SNPs within *CREB1*, *CREBBP* and *CREM*. All patients were assessed for the severity of illness at baseline and at discharge by means of the Positive and Negative Symptoms Scale (PANSS). Our findings suggest the lack of influence of SNPs under investigation in the present study on the susceptibility to SKZ and on the response to antipsychotics. However, taking into account the several limitations of our study, further research is needed to draw more definitive conclusions.

1. Introduction

Schizophrenia (SKZ) is a complex psychiatric disorder affecting approximately 1% of the population worldwide [8,22]. Both formal and molecular genetics' studies converge on suggesting that such disorder has a strong genetic etiology [12]. However, there is not yet complete consensus about the genetic variants involved [4]. An interesting candidate gene for SKZ is the one coding for the cyclic AMP-responsive element-binding protein-1 (*CREB1*), one of the messenger molecules involved in intracellular signal transduction pathways associated with a large variety of dopamine and serotonin receptor subtypes [6]. In particular, genetic variants within the promoter region of the human *CREB1* could lead to modifications of CREB expression that may influence SKZ liability and pathophysiology [6].

Of note, CREB is a member of a transcription factors' family including also CREM (cAMP response element-modulator) [9]. CREM plays a key physiological and developmental role within the hypothalamic-pituitary-gonadal axis [15]. Furthermore, both CREB and CREM can interact with CREBBP (CREB-binding protein), a protein that has an intrinsic histone acetyltransferase activity and that acts as a scaffold to stabilize additional protein interactions with the transcription complex. Interestingly, CREB–CREBBP signalling regulates long-term potentiation, a cellular mechanism that underpins memory formation [5,19]. Moreover, CATIE trial showed an association between *CREBBP* variants and SKZ [13].

On the basis of these findings, we aimed to investigate whether specific single nucleotide polymorphisms (SNPs) within genes belonging to this biological pathway, including *CREB1* (rs2709377 and rs6740584), *CREBBP* (rs2239317, rs2239316, rs3025702, rs130021, rs130005, rs129974 and rs9392) and *CREM* (rs1148247, rs4934735, rs12775799, rs6481941 and rs16935888) could be associated with the liability and response to treatment of SKZ.

2. Methods

The sample under investigation in the present study included 221 SKZ in-patients who were consecutively recruited at the

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Table 1
CREB1, *CREBBP* and *CREM* SNPs considered in this study. The relative position to the start codon is given in parenthesis. All data from www.snpper.chip.org.

Gene	SNP ID	Position	Distance	Alleles	Location	Amino acid change
CREB1	rs2709377	208393907 (−26453)	−35444	A/T	Promoter	None
CREB1	rs6740584	208429351 (8992)		C/T	Intron	None
CREBBP	rs2239317	3920740 (9178)	6745	C/G	Intron	None
CREBBP	rs2239316	3913995 (15923)	53355	A/G	Intron	None
CREBBP	rs3025702	3860640 (69278)	28169	A/G	Coding exon	313 D/?
CREBBP	rs130021	3832471 (97447)	4123	A/G	Intron	None
CREBBP	rs130005	3828348 (101570)	33056	A/G	Intron	None
CREBBP	rs129974	3795292 (134626)	20123	G/T	Coding exon	1262 I/? 1300 I/?
CREBBP	rs9392	3775169 (154749)		G/A	3′ UTR	None
CREM	rs1148247	35496946 (70183)	216	G/A	Intron	None
CREM	rs4934735	35496730 (69967)	8466	A/G	Intron	None
CREM	rs12775799	35488264 (61501)	48123	C/T	Intron	None
CREM	rs6481941	35440141 (13378)	7736	G/A	Intron	None
CREM	rs16935888	35432405 (5642)		T/C	Intron	None

Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. The sample has been previously investigated by our group with regard to other gene variants (e.g. [14,17]). Briefly, patients were eligible for inclusion if they had a documented clinical diagnosis of SKZ according to the DSM-IV criteria [18]. All patients admitted to the hospital were assessed for the severity of illness at baseline and at discharge by means of the Positive and Negative Symptoms Scale (PANSS) [7]. A further sample of 170 Korean psychiatrically healthy subjects, who underwent the same assessment of psychiatric patients to exclude possible psychiatric disorders as well as a familiarity for 1st and 2nd degree relatives with psychiatric disorders, was also included to compare genotype and allelic frequencies between SKZ patients and psychiatrically healthy controls. The study protocol was approved by the institutional review board (approval number HC10TISI0031). All patients (18–65 years old) provided written informed consent before participating into the study.

The main outcome measures of the present study were (1) differences between genotypic and allelic frequencies in patients with SKZ as compared with healthy control subjects and (2) possible influences of the 14 SNPs mentioned above on clinical improvement as measured with the PANSS total in SKZ patients. Further outcomes of interests included improvements on PANSS subscales, on response rates and on further clinical and socio-demographical variables. Both continuous and categorical analyses were performed. In accordance with previous studies, response was a priori defined as a ≥50% symptoms' reduction from baseline to discharge [10]. Genomic DNA was extracted from blood by standard methods and quantified. The high-throughput genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping 14 SNPs within 3 genes under investigation (Table 1). SNPs were selected balancing criteria of coverage, possible functionality and feasibility. PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v1 (Biotage AB, Sweden) and one primer of each primer set was biotinylated.

Statistical analyses were performed using 'Statistica' package [20]. Differences in the allelic and genetic frequencies between healthy subjects and patients with SKZ as well as effects of such variants on response rates and further categorical outcomes were calculated using the χ^2 statistics. The influence of the SNPs under investigation and continuous outcomes were calculated using the ANOVA. Clinical improvement on PANSS total scores was calculated according to the following formula:

$$\frac{\text{PANSSfinal} - \text{PANSSbaseline}}{\text{PANSSbaseline}} \times 100$$

In case of positive findings, clinical variables correlated with the outcome measures under investigation were added as covariates. Haploview 3.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy–Weinberg equilibrium (HWE) [1]. Tests for associations using multi-marker haplotypes were performed using the statistics environment "R" (http://www.R-project.org), package "haplo.score", to compare clinical and socio-demographic outcomes among different haplotypes. Permutations ($n = 10.000$) were performed to estimate the global significance of the results for all haplotypes analyses. All p-values were 2-tailed. In order to reduce the likelihood of false positive findings, statistical significance was set at the 0.006 level (approximately corresponding to the Bonferroni correction for 8 blocks of SNPs, see below). With these parameters we had a sufficient power (0.80) to detect a small–medium effect size ($\omega = 0.18$) that, as an example, corresponded to an odds ratio of 2.1 between SKZ patients and psychiatrically healthy controls and to detect a medium ($d = 0.25$) effect size for patients with SKZ carrying the GG genotype of rs129974 as compared with those carrying the TG genotype [3]. Such effects size corresponded to the possibility of detecting differences on PANSS total improvement scores of 3.2 points.

3. Results

Socio-demographic features such as gender, age and further clinical and socio-demographical variables are reported in Table 2. For control subjects only data about gender and age were collected.

Table 2
Clinical and socio-demographical variables assessed in the present study.

Clinical and demographic characteristics	Schizophrenia ($n = 221$)	Healthy controls ($n = 170$)
Gender		
Males	126 (57%)	105 (62%)
Females	95 (43%)	65 (38%)
Age	38.01 ± 12.67	38.83 ± 12.80
PANSS total		
Baseline	94.05 ± 13.75	
Disharge	76.63 ± 9.01	
PANSS positive		
Baseline	24.84 ± 4.77	
Disharge	19.86 ± 4.12	
PANSS negative		
Baseline	21.58 ± 5.09	
Disharge	20.30 ± 4.18	
PANSS general		
Baseline	47.62 ± 8.03	
Discharge	36.46 ± 6.28	
Age at onset	28.46 ± 10.98	
Fam. hist. of psychiatric disorders		
Yes	38 (17%)	
No	183 (83%)	
Missing values	0 (0%)	
Suicide attempts		
Yes	43 (19%)	
No	178 (81%)	
Missing value	0 (0%)	
Duration of admission (days)	37.64 ± 16.75	
Drug		
Risperidone	78 (34%)	
Olanzapine	54 (24%)	
Quetiapine	13 (6%)	
Amisulpiride	32 (15%)	
Other	6 (4%)	
Missing value	38 (17%)	
Concomitant anxiolytics		
Alprazolam	22 (10%)	
Lorazepam	198 (90%)	

The groups did not differ with respect to such variables. There were no associations between any of the SNPs under investigation and baseline demographical variables (all p-values > 0.006).

One out of 14 SNPs under investigation was not polymorphic in the present study (rs2709377 in *CREB1*) and was therefore excluded. The large majority of SNPs under investigation was in HWE in the whole sample (rs2239317: $p = 0.77$, rs2239316: $p = 0.25$, rs3025702: $p = 0.65$, rs130021: $p = 0.05$, rs130005: $p = 0.22$, rs129974: $p = 0.59$, rs9392: $p = 0.89$, rs1148247: $p = 0.13$, rs4934735: $p = 0.59$, rs12775799: $p = 0.50$, rs6481941: $p = 0.39$, and rs16935888: $p = 0.58$), being rs6740584 the only exception ($p = 2.8431$ E-25). Strong LD was observable several SNPs (see Figs. 1 and 2). Patients and healthy controls separately analyzed yielded similar results (data not shown).

There were no significant differences between allelic and genotype frequencies in SKZ patients and healthy controls (see Table 3; all p-values > 0.006). Moreover, we did not observe any significant association between the genetic variants under investigation in the present study and PANSS total scores in patients with SKZ (all p-values > 0.006). The haplotype analysis found a significant association between the haplotype block including rs16935888 and rs6481941 and the improvement on PANSS positive score (global-stat = 10.92, df = 2, $p = 0.004$). The inclusion of possible covariates did not significantly influence this result. Furthermore, the allelic analysis showed a significant association between rs2239316 SNP within *CREBBP* and PANSS general baseline score. In particular, subjects carrying the A allele were had a higher score ($F = 7.82$, df = 1.436, $p = 0.005$). Finally, A allele of rs493473 ($F = 8.74$, $p = 0.003$), C allele of rs127757 ($F = 8.05$, $p = 0.004$) and G allele of rs648194 ($F = 8.07$, $p = 0.004$) were associated with a longer duration of admission. No further significant association was observed.

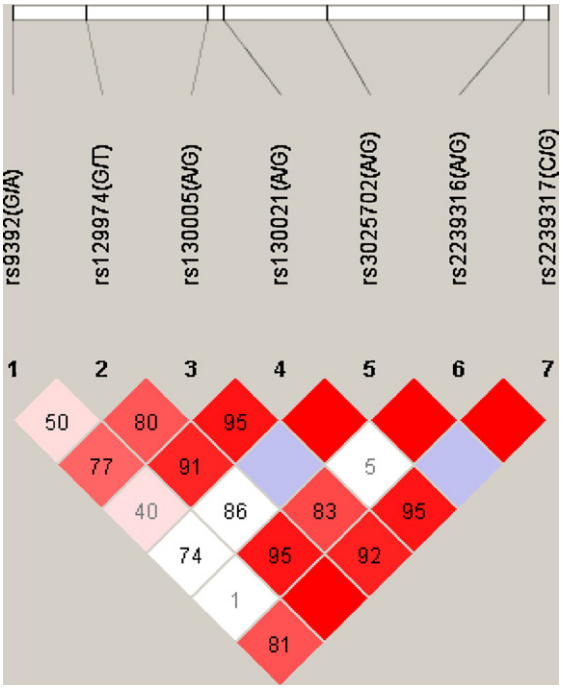

Fig. 1. Linkage disequilibrium of *CREBBP* SNPs under investigation in the present study. D^1 is reported.

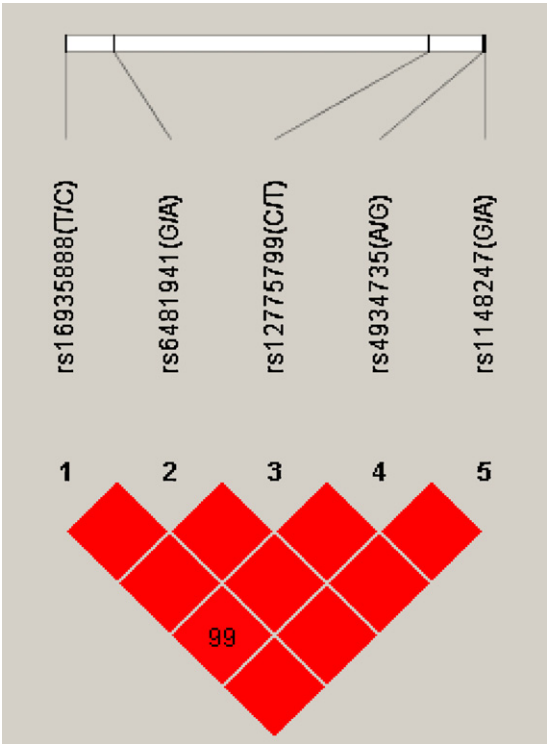

Fig. 2. Linkage disequilibrium of *CREM* SNPs under investigation in the present study.

4. Discussion

Our results do not suggest any significant association between allelic and genotype frequencies under investigation and the

Table 3
Allelic and genotype frequencies of the SNPs under investigation in the present study.

Schizophrenia	Healthy subjects	χ^2	*p*-Value
Genotype frequencies			
CREB1			
rs6740584			
CC: 153 (70%)	CC: 121 (71%)		
TC: 35 (16%)	TC: 23 (14%)	2.04	0.56
TT: 31 (14%)	TT: 26 (15%)		
CREBBP			
rs2239317			
CC: 120 (55%)	CC: 85 (50%)		
CG: 83 (38%)	CG: 69 (41%)	0.99	0.80
GG: 16 (7%)	GG:15 (9%)		
rs2239316			
AG: 110 (50%)	AG: 89 (52%)		
AA: 78 (35%)	AA: 59 (35%)	0.41	0.82
GG: 33 (15%)	GG: 22 (13%)		
rs3025702			
AA: 208 (94%)	AA: 159 (93%)		
AG: 13 (6%)	AG: 10 (6%)	1.30	0.52
GG: 0 (0%)	GG: 1 (1%)		
rs130021			
AG: 98 (45%)	AG: 74 (43%)		
AA: 80 (36%)	AA: 57 (33%)	0.77	0.68
GG: 43 (19%)	GG: 39 (24%)		
rs130005			
AA: 121 (55%)	AA: 87 (51%)		
AG: 81 (37%)	AG: 66 (39%)	0.56	0.76
GG: 19 (9%)	GG: 17 (10%)		
rs129974			
GG: 148 (67%)	GG: 115 (68%)		
TG: 68 (31%)	TG: 50 (29%)	0.24	0.89
TT: 5 (2%)	TT: 5 (3%)		
rs9392			
AG: 110 (50%)	AG: 83 (49%)		
AA: 39 (18%)	AA: 28 (16%)	0.22	0.89
GG: 72 (32%)	GG: 59 (35%)		
CREM			
rs1148247			
AG: 103 (47%)	AG: 84 (49%)		
GG: 98 (44%)	GG: 71 (42%)	0.31	0.85
AA: 20 (9%)	AA: 15 (9%)		
rs4934735			
AA: 121 (55%)	AA: 102 (60%)		
AG: 86 (39%)	AG: 62 (37%)	2.09	0.35
GG: 14 (6%)	GG: 6 (3%)		
rs12775799			
CC: 116 (53%)	CC: 102 (60%)		
TC: 87 (40%)	TC: 62 (37%)	5.73	0.12
TT: 14 (7%)	TT: 6 (3%)		
rs6481941			
GG: 117 (53%)	GG: 98 (58%)		
AG: 90 (41%)	AG: 65 (38%)	1.41	0.49
AA: 14 (6)	AA: 7 (4%)		
rs16935888			
TT: 144 (65%)	TT: 114 (67%)		
TC: 70 (32%)	TC: 52 (31%)	0.31	0.85
CC: 7 (3%)	CC: 4 (2%)		
Allele frequencies			
CREB1			
rs6740584			
C:341 (77%)	C: 265 (78%)	0.00	0.98
T: 97 (23%)	T: 75 (22%)		
CREBBP			
rs2239317			
C: 323 (74%)	C: 239 (70%)	0.88	0.35
G: 115 (26%)	G: 99 (30%)		
rs2239316			
A: 266 (60%)	A: 207 (61%)	0.04	0.84
G: 176 (40%)	G: 133 (39%)		
rs3025702			
A: 429 (97%)	A: 328 (96%)	0.21	0.64
G: 13 (3%)	G: 12 (4%)		
rs130021			
A: 258 (58%)	A: 188 (55%)	0.74	0.39
G: 184 (42%)	G: 152 (45%)		
rs130005			
A: 323 (73%)	A: 240 (71%)	0.59	0.44
G: 119 (27%)	G: 100 (29%)		
rs129974			
G: 364 (82%)	G: 280 (82%)	0.00	1.00
T: 78 (18%)	T: 60 (18%)		
rs9392			
G:254 (57%)	G:201 (59%)	0.21	0.64
A:188 (43%)	A:139 (41%)		
CREM			
rs1148247			
G: 299 (68%)	G: 226 (66%)	0.12	0.73
A: 143 (32%)	A: 114 (34%)		
rs4934735			
G: 328 (74%)	G: 266 (78%)	1.71	0.19
A: 114 (26%)	A: 74 (22%)		
rs12775799			
C: 319 (72%)	C: 115 (34%)	2.31	0.13
T: 123 (28%)	T: 74 (22%)		
rs6481941			
G: 324 (73%)	G: 261 (77%)	1.22	0.27
A: 118 (27%)	A: 79 (23%)		
rs16935888			
T: 358 (81%)	T: 280 (82%)	0.23	0.63
C: 84 (19%)	C: 60 (18%)		

liability and response to treatment of SKZ. These results are in contrast with previous studies focusing on different SNPs within the same genes [6,13]. However, we observed a weak association between rs2239316 within *CREBBP* and PANSS general baseline scores. In particular, subjects carrying the A allele were more likely to show higher PANSS general baseline scores. Moreover we found a significant association between the haplotype block including rs16935888 and rs6481941 within *CREM* and the improvement on PANSS positive score. To the best of our knowledge, this in the first study exploring a possible association between these particular SNPs, SKZ and response to antipsychotic treatment and these findings should therefore be considered with caution. Indeed, previous studies focusing on the SNPs under investigation in this paper were mainly concerned with mood disorders (e.g. [11,16,23]). Further, our results should be considered with caution because candidate gene studies such as the present one are associated with a high likelihood of false positive findings [21]. On the other hand, the lack of association between the SNPs under investigation, SKZ and clinical outcomes could be simply related to the lack of power of our study to detect subtle associations such as those typically observed in genetic studies. Note also that the low percentage of patients reporting a positive familiarity of psychiatric disorders in comparison with previous studies (e.g. [2]) could raise concerns as to whether the sample of patients under investigation in the present study could be representative of patients with SKZ in general. Further concerns are related to the use of different antipsychotics and the limited information about some socio-demographical variables.

In conclusion, our data preliminary suggest that the SNPs under investigation in this paper are not associated with the etiology and response to treatment of SKZ. However, taking into account the limitations stated above and considering the possible involvement of the biological pathway under investigation in our study, independent replications in larger samples focusing on more standardized pharmacological regimens are warranted.

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