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Influence of *GRIA1*, *GRIA2* and *GRIA4* polymorphisms on diagnosis and response to antipsychotic treatment in patients with schizophrenia

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ABSTRACT

The present study is aimed at exploring whether some single nucleotide polymorphisms (SNPs) within *GRIA1*, *GRIA2* and *GRIA4* could be associated with schizophrenia and whether they could predict clinical outcomes in Korean in-patients treated with antipsychotics. One hundred forty five patients with MD, 221 in-patients with schizophrenia and 170 psychiatrically healthy controls were genotyped for 17 SNPs within *GRIA1*, *GRIA2* and *GRIA4*. Baseline and final clinical measures, including the Positive and Negative Symptoms Scale (PANSS), were recorded. No significant association was found with the diagnosis of schizophrenia. We observed an association between rs3813296 genotype and improvement on PANSS negative scores. Our findings provide no evidence for an association between SNPs within *GRIA1*, *GRIA2* and *GRIA4* under investigation and schizophrenia susceptibility, although rs3813296 (*GRIA2*) could be associated with improvement on PANSS negative scores. 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 severe psychiatric disorder that affects approximately one percent of the population worldwide [13]. Although both genetic and environmental factors are thought to play a significant role into the development of SKZ [27], genetic factors seem to play a major role [32,36]. In particular, evidence from twin, family and adoption studies points to a strong genetic component, with an estimated heritability as high as 70% [32].

In recent years, several post-mortem and in vivo receptor studies provided evidence for a significant disruption of the glutamatergic system in subjects with SKZ [4,18,21,24,44,45,47] leading to the development of the "glutamatergic dysfunction hypothesis of SKZ". Such hypothesis focuses on the abnormalities in genes involved in the glutamatergic system [15], including those coding for glutamate receptors (AMPA, NMDA, kainite and metabotropic receptors) [20] and is supported by a growing amount of empirical research suggesting a link between this neurotransmitter and SKZ [7].

More in detail, several studies showed abnormal levels of AMPA receptor transcripts and/or proteins in brains of SKZ patients [14]. AMPA receptors mediate fast excitatory synaptic transmission in the CNS and play a key role in hippocampal synaptic long-term potentiation (LTP) and depression (LTD) [8]. Of note, abnormalities of AMPA receptors may be well reconciled with recent hypotheses of SKZ as a disorder of the CNS plasticity and/or development [38]. AMPA receptors are composed of four types of subunits, referred to as GluR1 (*GRIA1*), GluR2 (*GRIA2*), GluR3 (*GRIA3*), and GluR4, alternatively called GluRA-D2 (*GRIA4*), which are combined to form tetramers [35]. In particular, in this paper, we focused our attention on *GRIA1*, *GRIA2* and *GRIA4*.

GRIA1 is located on chromosome 5q33 and encodes for the GluR1 subunit. *GRIA1* is primarily found in the forebrain and hippocampus, brain areas that are particularly involved in memory formation and retention of spatial memory tasks [39]. *GRIA1* itself was found to influence cognitive functions, such as working memory and reward learning [39]. Furthermore, increasing evidence points to the involvement of this receptor in psychiatric disorders such as psychotic bipolar disorder (BD) [23]. Also, polymorphisms

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within this gene have been associated with SKZ [28] and regional specific abnormalities in gene expression have been reported in postmortem brains of individuals with SKZ [2].

GRIA2 is located on chromosome 4q32–33 and encodes for GluR2 subunits. This chromosomal region was found to be in strong association with some psychiatric disorders such as BD and SKZ [11,33]. As an example, Hovatta and colleagues reported the 4q31 region to be linked to SKZ [19]. Also, *GRIA2* is one of the genes down-regulated by chronic lithium treatment [40]. Furthermore, chronic lithium or valproate treatment causes decreased synaptic expression of GluR2 in hippocampal neurons [10].

GRIA4 maps on 11q22–23 and encodes for GluR4 subunits. *GRIA4* is localized in a chromosomal region where a higher rate of induced fragile sites has been observed in SKZ patients [46]. In addition, an abnormal expression of *GRIA4* is observed in the brains of SKZ patients [34]. As an example, Makino and colleagues reported that a rs609239, rs641574 and rs659840 haplotype (G-G-A) within *GRIA4* was positively associated with SKZ in the Japanese population [30]. However, the same polymorphisms were not associated with SKZ in a following study in a Chinese sample [17].Taking into account the dearth of studies focusing on such SNPs and the substantial risk for Type I (false positive) errors in genetic association studies [25], the aim of this study is to investigate the existence of possible associations between a set of *GRIA1* (rs707176 and rs6875572), *GRIA2* (rs6536221, rs4260586, rs4302506, rs4441804, rs3813296 and rs4403097) and *GRIA4* (rs11226805, rs2166318, rs11822168, rs1938956, rs10736648, rs528205, rs11226867, rs667174 and rs641574) SNPs and SKZ. In addition, in the present study we investigate, to the best of our knowledge for the first time, the effects of the same SNPs on clinical improvement in a sample of SKZ in-patients treated with antipsychotics.

2. Methods

2.1. Sample

The sample under investigation in the present study included 221 SKZ in-patients who were consecutively recruited at the Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. Patients were eligible for inclusion if they had a documented clinical diagnosis of SKZ according to the DSM-IV criteria, as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) [42]. The same sample has been previously investigated by our group regarding other gene variants [41].

No particular restriction was employed with regard to treatments, duration of illness and first vs. following episodes of disease. However, patients were excluded if they had current severe or unstable medical and neurological conditions, current treatment with a long-acting antipsychotic, concomitant alcohol and substance abuse disorders and if they were not of Korean ethnicity. A further sample of 170 Korean psychiatrically healthy subjects, who underwent the same assessment of psychiatric patients to exclude possible psychiatric disorders, deriving from the same location of the psychiatric patients included in the present study, was also included to compare genotype and allelic frequencies between SKZ patients and psychiatrically healthy controls.

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) [22]. Scorers were trained with the specific instruments with good inter-rater reliability ($k > 0.8$). Additionally, the following clinical and demographic variables were recorded: gender, age, age at onset, familiar history of psychiatric disorders (based on subjects' reports after direct questioning by clinicians), lifetime suicide attempts, duration of admission, drugs at discharge and concomitant anxiolytics. 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.

2.2. Outcome measures

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 17 SNPs within *GRIA1*, *GRIA2* and *GRIA4* under investigation on clinical improvement as measured with the PANSS in SKZ patients. Further outcomes of interests included baseline and endpoint PANSS scores, baseline and endpoint CGI scores and response rates. Both continuous and categorical analyses were performed. In accordance with previous studies, response was *a priori* defined as a $\geq$50% symptoms' reduction from baseline to discharge [26].

2.3. DNA analysis

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 the SNPs mentioned above (Table 1). Genetic SNPs were chosen among those (1) previously investigated in association with schizophrenia (e.g. [28,29]), (2) with a reported prevalence of at least 5% for the variant allele among Asian samples (data from http://hapmap.ncbi.nlm.nih.gov/, $R^2 = 0.08$ and MAF = 0.05) or (3) with availability of a validated assay in our laboratory. 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.

2.4. Statistical analysis

Statistical analyses were performed using 'Statistica' package [43]. 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:

$$\left(\frac{\text{PANSS}_{\text{final}} - \text{PANSS}_{\text{baseline}}}{\text{PANSS}_{\text{baseline}}}\right) \times 100$$

In the 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.

All *p*-values were 2-tailed, and statistical significance was conservatively set at the 0.005 level (corresponding to the Bonferroni correction for the 10 blocks of SNPs under investigation, see below for further information) in order to reduce the likelihood of false positive results. 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 (OR) of 2.1 between the schizophrenic patients and the group of controls and to detect a

Table 1
GRIA1, *GRIA2* and *GRIA4* SNPs considered in this study.

SNP ID	Position[a]	Distance	HWE[b]	Alleles	Location
GRIA1					
rs707176	153029960 (159512)		1.0	C/T	Coding exon
		48,550			
rs6875572	153078510 (208062)		–	A/G	Coding exon
GRIA2					
rs6536221	158143886 1015		–	A/G	Intron
		13,581			
rs4260586	158157467 14596		0.78	A/T	Intron
		81,363			
rs4302506	158238830 95959		0.83	C/T	Coding exon
		28,705			
rs4441804	158267535 124664		0.22	C/T	Intron
		13,988			
rs3813296	158281523 138652		0.87	G/T	Intron
		4074			
rs4403097	158285597 142726		0.86	C/T	3′-UTR
GRIA4					
rs11226805	105482024 300		0.45	C/T	Intron
		1637			
rs2166318	105483661 1937		0.68	A/G	Intron
		147,142			
rs11822168	105630803 149079		0.74	A/G	Intron
		9301			
rs1938956	105640104 158380		0.96	G/T	Intron
		2832			
rs10736648	105642936 161212		0.87	A/G	Intron
		76,586			
rs528205	105719522 237798		0.62	G/T	Intron
		14,805			
rs11226867	105734327 252603		0.86	A/G	Intron
		18,708			
rs667174	105753035 271311		0.84	C/T	Intron
		59,804			
rs641574	105812839 331115		1.0	A/G	Intron

HWE, Hardy–Weinberg equilibrium.
[a] Absolute chromosomal position. The relative position to the start codon is given in parenthesis.
[b] Note that such value is referred to the control sample. All data from www.snpper.chip.org.

medium ($d = 0.5$) effect size for patients with SKZ carrying the TT genotype of rs4260586 as compared with those carrying the TA genotype [6]. Such effects sizes corresponded to the possibility of detecting final differences on PANSS scores of about 5 points. Note, however, that if an OR of 1.5 was employed rather than an OR of 2.1 the power of our study decreased to a sub-optimal level of 0.15.

3. Results

3.1. Socio-demographic features of MD patients and controls

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 characteristic of samples.

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	
Discharge	76.63 ± 9.01	
Age at onset	28.46 ± 10.98	
Fam. hist. of psychiatric disorders		
Yes	38(17%)	
No	183(83%)	
Suicide attempts		
Yes	43(19%)	
No	178(81%)	
Duration of admission (days)	37.64 ± 16.75	
Drug		
Risperidone	78(34%)	
Olanzapine	54(24%)	
Amisulpiride	32(15%)	
Quetiapine	13(6%)	
Others	6(4%)	
Missing value	38(17%)	
Concomitant anxiolytics		
Alprazolam	23(10%)	
Lorazepam	198(90%)	

The groups did not differ with respect to such variables (gender: $\chi^2 = 1.72$, $p = 0.18$; age: $F = 0.79$, $p = 0.37$). There were no associations between any of the SNPs under investigation and baseline clinical variables (all p-values > 0.005).

3.2. Hardy–Weinberg equilibrium (HWE) and linkage disequilibrium for GRIA1, GRIA2 and GRIA4 SNPs

Two out of 19 SNPs under investigation were not polymorphic in the present sample (rs6875572 and rs6536221 in *GRIA1* and *GRIA2*, respectively) and were therefore systematically excluded from the study. In addition, rs3813296 and rs4403097 were in complete linkage disequilibrium. As a consequence we focused only on the first of such two SNPs. The remaining SNPs were all in HWE (Table 1). Strong LD was observable between rs4260586, rs4302506, rs4441804, rs3813296 and rs4403097, between rs11226805, rs2166318 and rs11822168, between rs1938956, rs10736648 and rs528205 and between rs11226867, rs667174 and rs641574 (Supplementary material, Figs. 1 and 2). Patients and healthy volunteers separately analyzed yielded similar results (data not shown).

3.3. Differences between genotype and allelic frequencies in SKZ patients and in healthy controls

There were no significant differences between allelic and genotype frequencies in SKZ patients and healthy controls (Supplementary material, Table 3; all p-values > 0.005).

3.4. Influence of GRIA1, GRIA2 and GRIA4 variants on clinical improvement as measured with PANSS total scores

We did not observe any significant associations between the genetic variants under investigation in the present study and PANSS total scores (Supplementary material, Table 4; all p-values > 0.005). The haplotype analysis focusing on the sliding windows haplotypes mentioned above did not find any significant association as well.

3.5. Influence of GRIA1, GRIA2 and GRIA4 variants on PANSS positive, negative and general scores' improvement, response rates and on further clinical and socio-demographical variables in patients with SKZ

We observed a significant association between rs3813296 and improvement on PANSS negative scores, such that individual carrying the TT genotype were significantly less likely to benefit from treatment as compared with those carrying the TG and the GG genotype ($F = 6.71$, d.f. = 2218, $p = 0.001$, Supplementary material, Table 4). Of note, such association remained significant when baseline PANSS negative scores were introduced as a covariate ($F = 4.95$, d.f. = 2217, $p = 0.005$). Furthermore, a similar association was observed in the allelic analysis as well. Indeed, subjects carrying the T allele were significantly less likely to improve on PANSS negative scores as compared with those carrying the G allele ($F = 9.36$, d.f. = 1440, $p = 0.002$). However, such association was no longer significant when we introduced baseline scores as a covariate ($F = 6.42$, d.f. = 1439, $p = 0.01$). No further association was observed between the SNPs under investigation and any of the remaining clinical and socio-demographic variables. The haplotype analysis focused on the sliding windows haplotypes mentioned above. None of the haplotypes was significantly associated with any of the outcomes of interest.

4. Discussion

In the present study we did not find any association between the SNPs under investigation and SKZ. Of note, the results of the present study differ from those reported by Makino and colleagues [30] suggesting that a rs609239-rs641574-rs659840 haplotype (G-G-A) within *GRIA4* was positively associated with SKZ in the Japanese population. Indeed, we did not find evidence for any association in the haplotype analysis, possibly because we focused on different polymorphisms. Furthermore, on the contrary of Magri and colleagues, we did not find any association between rs707176 within *GRIA1* and SKZ [28]. On the other hand, Magri et al. also found a lack of association between SKZ and a set of SNPs within *GRIA2* and *GRIA4* [29]. Of note, we studied the same variants within *GRIA2* and one common SNP (rs641574) within *GRIA4*, finding similar results. Finally, in line with our findings, Guo and colleagues did not find any association between rs641574 and SKZ in a Chinese sample [17].In the present study we aimed to investigate whether polymorphisms within *GRIA1*, *GRIA2* and *GRIA4* were associated with response to antipsychotics as well. Indeed, in vivo experiments showed that several antipsychotics may impact the functionality of NMDA receptors in the rat brain [3]. Moreover, long-term action of antipsychotic drugs may regulate AMPA receptor responsiveness to agonist stimulation via post-transcriptional factors [31]. Chronically administered antipsychotic drugs have several effects on the levels of specific glutamate receptor subunits. In particular haloperidol was found to increase NMDAR1 subunit immunereactivity (and mRNA levels) in the striatum, and haloperidol and clozapine were found to increase GluR1 levels in the medial prefrontal cortex [12]. Furthermore, clozapine was found to decrease *GRIA1* and increase *GRIA3* mRNA expression in Rhesus monkeys, and both clozapine and haloperidol could increase the expression of *GRIA2* subunit mRNA [37]. Finally, Giegling and colleagues recently showed a marginal significant association between PANSS positive scores and genetic variations within *GRIA1* (rs1461231) [16]. Of note, in line with these findings, our results showed a significant association between rs3813296 (within *GRIA2*) and improvement on PANSS negative scores, indicating that individuals carrying the TT genotype were significantly less likely to benefit from treatment as compared with those carrying the TG and the GG genotype. However, it is worth mentioning that no further association has been observed in the present study, preliminary suggesting that the polymorphisms under investigation do not significantly affect the response to antipsychotics.

Possible explanations for the discrepancy observed between the results of the present study and those of other studies could be imputed to the use of different antipsychotics, the investigation of different SNPs and the different ethnicity of patients. A further limitation of the present study could be related to the incomplete coverage of genes under investigation, due to the tagging approach [9]. Therefore, future studies should be carried out that explore more informative SNPs within these genes. Also, treatment was not standardized, leading to an improvement of generalizability but not allowing to understand which are the effects of specific SNPs on single antipsychotics. Similarly, we did not control for population heterogeneity, though all subjects belonged to Korean ethnicity, which is considered to be genetically homogenous [5].

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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.neulet.2011.10.074.

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