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Original Article

Glutamate ionotropic receptor AMPA type subunit 1 gene polymorphism (gly>ser) and its association with schizophrenia in Pakistani population: A pilot study.

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Abstract

Background: Neurobiology of schizophrenia involves impairment of glutamatergic neurotransmission. In this context, polymorphism in glutamate Ionotropic receptor a-amino-3-hydroxy-5-methyl-4-propionic acid (AMPA) type subunit 1 encoded by Glutamate Ionotropic Receptor AMPA Type Subunit 1 Gene (*GRIA)*, (rs1127386, G/A) can be considered as a substantial contributor in pathogenesis of schizophrenia. Therefore, a pilot study was planned to find out if the single nucleotide polymorphism of *GRIA* (rs1127386, G/A) is a risk factor for schizophrenia in the population of Pakistan. It maps at 5q33, a schizophrenia susceptible locus as per genome-wide association studies.

Methodology: Following Diagnostic and Statistical Manual 5 (DSM 5) criteria guidelines, 50 schizophrenia cases were incorporated in this case-control study and 51 controls, individuals without any psychiatric illness. The sternness of illness was figured out using positive and negative syndrome scale score (PANSS) score. Genomic DNA was extracted from blood, and further analysis was done on gel electrophoresis after conducting ARMS (amplification refractory mutation system) PCR. Frequencies of reported genotype and allele within both groups were determined using the chi-square test.

Results: Statistically significant difference was not found in genotype and allele frequencies of (rs1127386, G/A) ($p>0.05$) between cases and controls in the study population. The severity status of the disease was also independent of the polymorphism ($p>0.05$).

Conclusion: This pilot study specifies that polymorphism rs1127386 is not a risk factor for schizophrenia, at least in the Pakistani population.

Keywords

Schizophrenia, Glutamate, Single Nucleotide Polymorphism.

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Introduction

Schizophrenia is a chronic and serious neurological disorder, mostly observed in the later stage of adolescence or primary adulthood [1]. Schizophrenia affects how a person thinks, feels, reacts, and behaves. It is characterized by positive symptoms, including hallucinations and delusions. In contrast, negative symptoms include flat affect, social deficits, and anhedonia while, impairments of cognition include attention deficit, insufficient working memory, and impaired executive functions[1]. Approximately 1.1% of the world's population is suffering from schizophrenia. The exact prevalence of schizophrenia in Pakistan is unknown, but it is estimated that 1–2% of the population is affected by this neurological disorder[2].

The pathogenesis of schizophrenia is a big question. There are two major hypotheses, the dopamine hypothesis and the glutamate hypothesis, which explain the connection between distorted brain function and schizophrenia. The dopamine hypothesis has been considered a dominant theory since the 1970s[3,4], but the glutamate hypothesis is one of the major hypotheses and now gaining much attention[4]. Glutamate is an "excitatory" neurotransmitter in the brain; it activates neurons and other brain cells and plays an important role in learning and memory. Glutamate receptors are of two types: metabotropic and ionotropic receptors. Ionotropic receptors are further classified into N-methyl-D aspartate (NMDA), a-amino-3-hydroxy-5-methyl-4-propionic acid (AMPA), and kainite (KA) receptors. AMPA receptors are mainly responsible for mediating synaptic plasticity[5]. The GRIA gene encodes the GluA1 subunit of the AMPA receptor. *GRIA* spans 320 kb of DNA consisting of 16 exons transcribing an mRNA of 3242bp. It has two isoforms resulting from alternative splicing. According to three genome-wide scans for schizophrenia, cytogenetic region 5q33 is a susceptible locus. *GRIA* lies in that region[6].

Data from postmortem studies and in vivo studies show glutamate's involvement in the pathogenesis of schizophrenia. It is reported that increased *GRIA* expression was found in the pyramidal brain cells of schizophrenia patients[7]. Moreover, *GRIA* knock-out (KO) mice have shown schizophrenia-related behavior such as hyper locomotor activity under stress conditions and abnormality in social behaviors[8]. Further, studies have indicated that mutation in the phosphorylation site of GluA1 subunits leads to abnormal synaptic plasticity. Single nucleotide polymorphism (SNP) rs1127386, G>A is a non-synonymous exonic variant of *GRIA* gene[9]. It is present at chromosome 5 and results in glycine>serine substitution. Glycine is a nonpolar hydrophobic amino acid that provides flexibility to protein and helps in protein folding, whereas serine is a polar hydrophilic amino acid. Due to these reasons, the mutation rs1127386, G>A (glycine> serine) can affect the protein folding and other functions of receptor[10]. Therefore, it was hypothesized that mutation in *GRIA1*, rs1127386, G>Amight be associated with schizophrenia. Hence, a pilot study was planned to explore whether single nucleotide polymorphism in *GRIA* (rs1127386, G/A) is a risk factor for schizophrenia in the population of Pakistan.

Methodology

Study population selection

The pilot study included 100 individuals with 50 schizophrenia patients and 51 controls. Psychiatric patients (14-50 years of age) fulfilling the Diagnostic and Statistical Manual for classification of Psychiatric disorder 5 (DSM 5) standards for schizophrenia were involved in the study. Exclusion criteria for the case group included the presence of any neurological and psychiatric disorder other than schizophrenia. Healthy individuals with matched age and gender along with no psychiatric illness were recruited as controls.

The ethical approval was taken from the Institutional Review Board of Dow University of Health Sciences (Ref no. IRB-928/DUHS/Approval/2017/157). Written informed consent was obtained from participating individuals or their caregivers (as few of the schizophrenia patients were unable to give consent). Basic demographics of study participants were obtained via questionnaire (designed in

English and explained in the local language- Urdu where required). Schizophrenia patients were recruited from the inpatients and outpatients department of Dr. Abdul Qadeer Khan Institute of Behavioral Sciences, Dow University of Health Sciences, Karachi, Pakistan, from June 2019 to November 2019.

Evaluation of Clinical and Psychopathological Symptoms

Experienced psychiatrists administered positive and negative syndrome scale scores (PANSS) to examine the severity of illness, categorizing the symptoms into positive, negative, and general psychopathological sub-scales. These subscales were added to compute the total score. Beck Depression Inventory-II (BDI-II) was used to rule out depression in controls.

Genomic DNA extraction

Around 3 ml of peripheral blood was drawn to extract genomic DNA using Gene JET Genomic DNA Purification Kit (Thermo Scientific- K0721). Briefly, in the first step, white blood cells (WBCs) were separated as a pellet settled at the bottom of a sterile centrifuge tube. WBCs present in the pellet was then used to extract genomic DNA. The purity and concentration of DNA were checked through a Nanodrop spectrophotometer.

Amplification-Refractory Mutation System Polymerase Chain Reaction (ARMS PCR)

To amplify the genomic region of interest-specific primers were designed using primer 3 software while Allele-specific primers were modified manually. ARMS PCR was performed to detect single base mutation in the region using two outer and two inner or allele-specific primers having the following sequences, forward outer primer 5'TTCCATGGAACACTCTTGGGTTCTGAATTT3', reverse outer 5'TGGCAGAGCCAAGTCTAGAATCTGTGTTG3', forward inner 5' CCACGTGATTGAAATGAAACATGCCA3' and reverse inner primer sequence was 5' TAAAGGGGGACCTTACCTTTCGGATTCC3'.

Before PCR was run, the quantity and purity of all un-diluted extracted DNA samples were evaluated using a DNA putiTM spectrophotometer (Thermofisher Scientific). The instrument was first blanked by loading 1.5 µl of autoclaved nano-pure water onto the top of the NanodropTM sensor. Next, 1.5 µl of DNA sample was loaded onto the top of the NanodropTM sensor to measure optical density at 260/280 nm while concentration was taken in ng/dl. Further, gel electrophoresis was also used to check the quality of DNA. Agarose gel 1(%) was prepared, and 2 µl of extracted DNA was run on the gel. After the quality check, DNA samples were stored at -80 ^{o}C until further use for PCR. ARMS PCR was performed on all DNA samples using a master mix from Thermo fisher scientific with a final volume of 20 µl. PCR was run according to the following conditions: Hot start at 95°C for 5 minutes followed by 30 cycles consisting of denaturation at 94°C for 30 seconds, annealing at 57 ^{0}C for 45 seconds, extension at 72°C for 45 seconds, and then final extension at 72°C for 10 minutes.

Gel Electrophoresis and DNA Visualization

Polymerase chain reaction (PCR) results were visualized using agarose gel electrophoresis. The gel was set by melting 2 g agarose in 100 ml of TEA buffer, 2 µl of ethidium bromide was used to stain nucleic acid. 5 µl sample and 8 µl ladder (100 bp) were loaded on the gel. The gel was run on 70V for 90 min. The gel was visualized using a UV Trans-illuminator followed by genotyping each sample as per the band size of specific alleles.

Statistical analysis

SPSS version. 20.0 was used to analyze the data collected for the study. Results were displayed as mean ± SD, percentage & frequency of quantitative & qualitative variables, respectively. An independent sample t-test was performed to compare two groups' mean and one-way ANOVA for comparing more than two groups' mean. A Chi-square test was also used to find an association between genotype and allele frequency and the onset of schizophrenia. A $p<0.05$ was considered statistically significant. Hardy Weinberg Equilibrium (HWE) was calculated for both cases and controls.

Results

Basic characteristics of study participants

Altogether 101 participants (50 cases, 51 controls) were engaged in the study. The case group consisted of 76% males and 24% females, while in the control group, 55% were males and 45% were females. In relation to gender distribution among case groups, a significant difference was observed between males and females schizophrenia patients (p= 0.026), with more males (76%) affected with schizophrenia than females (24%). The mean age of the case group was 34.44 ± 9.2 years ranging from 15-65 years, while that of the control group was 29.47 ± 10.7 years. There was no biasness regarding age and gender between the groups (p>0.05). Similarly, no difference was observed for BMI among cases and controls (23.5 ± 4.6 & 23.1 ± 4.9) m/kg^2 respectively (p>0.05).

Various ethnic backgrounds were viewed with no noteworthy variation among cases and controls (p=0.127). As ethnicities other than Urdu, Sindhi, and Punjabi speaking were observed in very small numbers, therefore were merged in one single group as others. Regarding abuse of psychoactive substances, no significant difference was reported between the two groups (p=0.128) (Table 1).

Table 1: Comparison between cases and controls regarding literacy rate, ethnicity, and addiction status.

Variables		Cases	Controls	p-value
		n(%)		
Education	Illiterate	15(30)	8(15.6)	0.106
	School	7(14)	8(15.6)	
	College And Above	28(56)	35(68.6)	
Ethnicity	Sindhi	19(37. 2)	18(35.2)	0.127
	Punjabi	2(4.0)	8(15.6)	
	Urdu Speaking	2(4.0)	-	
	Others	27(54)	25(49.0)	
Addiction	Yes	15(30.0)	9(18.0)	0.148
	No	35(70)	42(84)	

*p<0.05 is considered statistically significant.

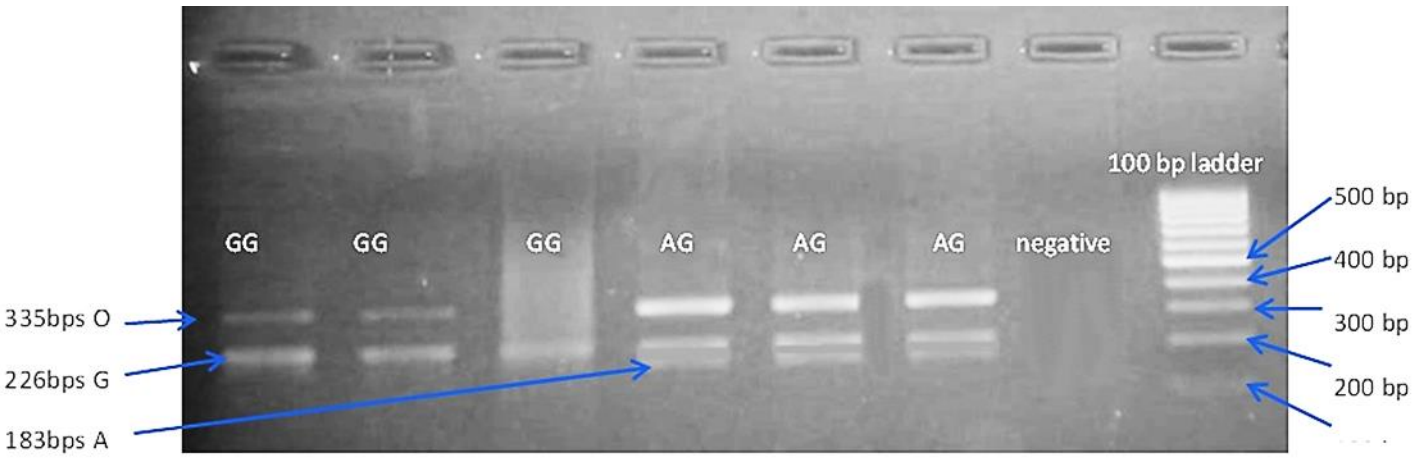

Figure 1: Agarose gel electrophoresis representing bands resulted from ARMS PCR rs112386, GRIA1 gene.

Band O represents the entire length of the amplicon; Band G represents the amplicon containing ancestral allele (GGC); Band A represents the amplicon containing mutated allele (AGC)

Genotyping

The amplicons generated by ARMS PCR produced three bands; band O represents the entire length of amplicon (335 base pairs), band G represents amplicon containing ancestral allele G (226 base pairs), and band A represent amplicon containing mutated allele A (183 base pairs) (Figure 1).

Genotypic frequency of GRIA gene polymorphism, rs1127386

Genotype distributions of rs1127386 were in Hardy Weinberg Equilibrium (HWE) (P>0.05) and were similar between cases and controls (p>0.05). In the control group, 3.9% of individuals were detected as wild-type homozygous (GG), whereas 96.1% of individuals were heterozygous (AG). Whereas in cases, 4% were detected as wild-type homozygous and 96% as heterozygous. No homozygous mutant (AA) was observed in either cases or the control group (Table 2).

Table 2: Percentage of genotypic and Allele in cases and control

SNP rs1127368	Genotype			p-value	Allele		p-value	p-value (HWE)
	GG	AG	AA		G	A		
Cases	4.0%	96.0%	0%	0.984	52%	48%	0.995	0.52
Controls	3.9%	96.1%	0%		53%	49%		0.519

SNP: Single Nucleotide Polymorphism, HWE: Hardy- Weinberg Equilibrium, * Odds Ratio (Genotype) = 1.02, OR (allele) = 1.00, Confidence Interval= 95%, P<0.05 considered as statistically significant, G = Guanine, A = Adenine

Allele frequency of *GRIA* gene polymorphism, rs1127386

We observed a similar frequency of alleles G and A in both cases and controls. In cases, the frequency of the A allele was 48%, while that of the G allele was 52%. Whereas in controls, the frequency of the A allele was 49%, while of the G allele was 53% (Table 2).

Association of rs1127386 with PANSS score

Statistical analysis revealed SNP rs1127386 has no effect on the severity status of schizophrenia as shown by PANSS sub-scale scores (p>0.05) (Table 3).

Table 3: Association of rs1127386, GRIA gene with severity status of schizophrenia as evaluated via PANSS score.

Genotypes of rs1127368	PANSS Score							
	Positive		Negative		Gen. Psychopathological		Total	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value	Mean SD	p-value
G/G	67.0±1.41	0.178	57.0±25.4	0.522	68.5±9.19	0.178	192.5±36.1	0.158
A/G	69.9±17.7		68.5±18.3		70.9±16.7		209.3±11.5	

SNP: Single Nucleotide Polymorphism, PANSS: Positive and Negative Syndrome Scale, P<0.05 considered as statistically significant.

Discussion

Schizophrenia has affected 1% of the population globally; although the exact frequency of schizophrenia in Pakistan is not known, it is estimated that 1–2% of the population is predisposed to this mental problem[11]. Population-based genetic studies are required to explore the genetic basis of the disease. Due to genetic diversity among different populations, this pilot study was designed to report genetic data from Pakistan for *GRIA1* gene polymorphism and schizophrenia.

Analysis of demographic data revealed no difference between cases and controls for age, gender, and BMI. However, men are more affected than females (Table 1) in our study group. This finding is similar to other studies reporting more males being affected with schizophrenia[12]. The presence of estrogen may be the underline cause for this small number of female schizophrenic patients than males[13]. Moreover, estrogen therapy has shown improvement in PANSS scores in women suffering from schizophrenia. This provides support to the protective mechanism of estrogen in women[14]. As far as ethnicity is concerned, Urdu and Sindhi speaking individuals were recruited in larger numbers; probably because, being a cosmopolitan city, Karachi houses all ethnic groups of Pakistan, with Urdu speaking population as the predominant group followed by Punjabi, Sindhi, and other ethnic groups[15]. Patients belonging to other ethnicities were also recruited in the study, but they were a comparatively small number (Table 1). Statistical analysis revealed no significant difference in literacy rate among cases and controls. This finding is contrary to what is reported by Escott and colleagues, who described the decline in educational achievements in schizophrenia patients[16]. This non-significant difference might be due to the small sample size of our study sample. As far as drug abuse is concerned, 50% of individuals with schizophrenia are reported to be found addicted to psychoactive substance[17]. However, the present study's findings are contrary to these studies, which might be due to lesser sample size.

Due to the high percentage of treatment-resistant patients in schizophrenia, researchers are trying to find newer targets involved in the pathology of schizophrenia to find alternative better treatment approaches. In this aspect glutamate postulate of schizophrenia is gaining much consideration[18]. Studies have highlighted *GRIA1* gene polymorphism as a risk factor for developing schizophrenia[5,9,19], although discrepancies exist[20,21]. Polymorphism rs1127386 G/A of *GRIA1* is an exonic missense variant present in chromosome 5 at position 153686318[9]. The missense SNP results in glycine (nonpolar hydrophobic) to serine (polar hydrophilic) substitution and might inhibit the receptor's normal function or can affect the passage of neurotransmitters. Moreover, SNP rs1127386 lies in a potential locus (5q33) susceptible for schizophrenia[22]. Due to the above-stated facts and lack of sufficient data regarding the association of *GRIA1* polymorphism rs1127386 with schizophrenia.

Statistical analysis of the present pilot study revealed no significant difference in allele and genotype frequency for the rs1127386 G/A among schizophrenic patients and healthy controls belonging to Pakistan. The study results are contrary to the study of Kang et al., which have reported a positive association of schizophrenia with different polymorphisms of *GRIA1* gene[5]. However, our results are similar to what is reported by Leon and colleagues, who have reported no association of *GRIA1* gene polymorphisms with schizophrenia in the German population[20]. The results are also in line with the results reported by Magri et al. However; they conducted the study in a sub-group of 20 individuals only to select the SNP with minor allele frequency higher than 0.1 for further study. It was also not mentioned either the selected individuals were cases or controls[9]. In addition, the present results are in harmony with the findings of Niu and co-workers, who have reported no association of *GRIA1* gene polymorphism with schizophrenia in the Chinese population[23].

Moreover, our findings did not support Bygrave et al., who described a systematic link between *the*

GRIA1 gene and schizophrenia[19]. On the other hand, present study findings are analog with the results of Crisafulli et al., where no association of schizophrenia was found with *GRIA1* gene variations[21]. Regarding the effect of rs1127386 G/A, *GRIA1* on the severity status of schizophrenia, our results are in line with those reported by Crisafulli et al., who also found no association *GRIA1* polymorphism with the PANSS scale. This is contrary to the findings of Drago and co-workers who reported a positive link of *GRIA1* variation in modulating antipsychotic response as evaluated through PANSS score[24].

The case-control study design is the strength of the study; however, the study's sample size is limited and focused on just one polymorphism of *GRIA 1.* It is therefore recommended that studies targeting other polymorphisms at 5q33 should be done.

Conclusion

In conclusion, our study does not support the hypothesis regarding the role of *GRIA1* gene polymorphism (rs1127386) in the pathophysiology of schizophrenia or with the severity status of schizophrenia in the Pakistani population. Further research with a large sample size should be conducted to confirm our findings. Furthermore, studies on other SNPs of *the GRIA 1* gene and their haplotypes should also be conducted to explore their role in the etiology of schizophrenia.

Conflicts of Interest

The authors have declared that no competing interests exist.

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