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Screening of ERBB4 SNP rs1026882 in a group of Schizophrenia patients and controls

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Abstract

Schizophrenia is a multifactorial psychiatric disorder which is affected by genetic, environmental, and several other factors. ERBB4 is a gene with polymorphic sites which reported to be associated with schizophrenia. In this prospective study, we have tested the association of schizophrenia with one of the single nucleotide polymorphisms (SNP) called rs1026882 in the ERBB4 gene. We have screened the genotypes of rs1026882 in a case group consisted of 96 schizophrenia patients and 100 healthy controls. All samples were collected from the population living in Malatya-Turkey. First, we compared the distributions of SNP genotypes and alleles between the case and control groups, then between the subgroups of patients defined according to SAPS and SANS parameters and phenotypical outcomes of the disease. Even though there was no significant difference between the case and control groups, comparing the subgroups of patients revealed that, the CC genotype was more common than the CT through the patients showing avolition-apathy symptom (one of the parameters in SANS). In addition, TT genotype was significantly more frequent in the subgroup of patients exhibiting the phenotype of suicidal thoughts.Our study was limited with a relatively small sample size and a population living in a small geographical region. Therefore, screening of rs1026882 genotypes in larger case-control groups from different populations is thought to help to reveal stronger evidence for presence of the association between this SNP and schizophrenia phenotypes. As conclusion, we did not find a direct association between rs1026882 genotype and schizophrenia in general, but the TT genotype was associated with the phenotype of suicidal thoughts, and the CC genotype seems related to avolition-apathy symptom in our sample.

Keywords: Schizophrenia, genetic, association, SNP, ERBB4, rs1026882

Introduction

Schizophrenia is a chronic psychiatric disease (MIM181500). In the general population, its prevalence is around 0.5% to 1%. Cognitive deficits as well as positive and negative symptoms are major clinical characteristics of schizophrenia [1]. The estimated heritability of schizophrenia based on twin studies is around 80% [2]. Because it is a multifactorial complex disorder, environmental, epigenetic, or stochastic factors contribute to development of schizophrenia in addition to genetic factors [3]. In accordance with its multifactorial nature, multiple susceptibility genes have been reported to be associated with schizophrenia [4]. The previously published genome wide association studies (GWAS), case-control studies, and meta-analyses indicated several candidate genes and interactions. Nonetheless the molecular pathology of schizophrenia is still unclear [5]. One of the reasons for this obscureness is the presence of discrepancies between association studies performed in distinct populations. Therefore, the positive or negative associations of SNPs in other populations contribute to understand the genetic and molecular basis of the disease [6,7].

Several genes were shown to be associated with schizophrenia [8]. NRG1 is the first gene reported to have risk alleles associated with development of schizophrenia [9-11]. The protein product of NRG1 gene, neuregulin-1 is one of the ligands for the membrane receptor ErbB4 (HER4/p180erbB4) [12,13]. This receptor is encoded by the ERBB4 gene which is also suggested to be associated with schizophrenia in some populations [14,15]. In the previous studies carried out by our research team, we have screened three SNPs (rs83952, rs7598440 and rs707284) located in the ERBB4 gene in a Turkish population. Even though those SNPs were reported to be associated with schizophrenia in some other populations [16,17], our case-control study did not reveal sufficient evidence to support that association [7]. In the present study, we have screened another SNP (rs1026882) located in the ERBB4 gene in the same case-control group from Malatya-Turkey to figure out if there is an association of schizophrenia in our population with this SNP. Our reason to select this SNP was its epistatic interaction which has been previously reported to effect development of schizophrenia in another population [18].

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Materials and Methods

All procedures and applications in this study have been ethically approved according to Declaration of Helsinki by the local ethics committee (Protocol # 2019-114). The volunteers included in case and control groups provided written informed consents forms.

The patients and controls were clinical diagnosed and evaluated by the first author and the third author who is a senior psychiatrist at Inonu University, School of Medicine, Department of Psychiatry. For diagnosis, The Structured Clinical Interview for the DSM-V (SCID-I) was used [19].

All patients in the cases group have been evaluated using Scale for the Assessment of Positive Symptoms

Diagnostic and clinical assessments of patients recruited for the Psychosis study included Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) [20] in addition to Global Assessment of Functioning (GAF) criteria *The positive symptoms (SAPS) were hallucinations, delusions, bizarre behavior, positive formal thought disorder and the negative symptoms (SANS) were affective flattening, or blunting, alogia, avolition – apathy, anhedonia – asociality, attention. The Cronbach alpha values for these two tests were reported as 0.844 and 0.914 respectively [21]. The designation of deficit syndrome schizophrenia was based on the Schedule for the Deficit Syndrome, a semi-structured interview with known reliability [22] by a study psychiatrist (by the first author or the third author) trained for reliability at Inonu University, School of Medicine, Department of Psychiatry. Collateral information was obtained whenever possible.*

In the group of cases, we had 96 unrelated schizophrenia patients consisting of 46 males and 54 females from a city located in Eastern Anatolian Region of Turkey, Malatya. The age average in the patient's group was 36.67±11.03 (34.15±10.85 for females, and 38±10.98 for males). Considering the family histories for psychotic disorders, 59.4 % of patients had no family history whereas the first-degree relatives of 27.1% and the second or third-degree relatives of 13.5% of the patients exhibited a disease phenotype.

SAPS, SANS and GAF grade averages in the case group were 51±13.3; 49±19.4 and 50±8.3 respectively. All patients in this study were followed for 15 years in average (min. 3 years, SD: 10 years). The average age of diagnosis was 24.4 with a standard deviation of 8.6. All the patients declared having Turkish ethnic origin. The excluded samples in this study were the patients with schizoid disorder, schizophrenia form disorder, paranoid personality disorder, mood disorder showing psychotic features, schizoaffective disorder, psychotic disorder which was substance-induced, psychotic disorder due to a general medical condition and schizotypal disorder.

In the control group, we included 100 healthy people (63 males and 33 females) who identified themselves to be in Turkish ethnic origin. *The samples in control group were selected from the healthy volunteers.* All controls were evaluated by the first or third author and confirmed not to have symptoms of Axis I psychotic disorders. Also, none of their first-degree relatives had any psychotic disorders either.

Isolation of DNA

The blood samples were collected from the patients who were already being followed in the Psychiatry Department of our hospital during their routine visits. The total DNA samples were isolated using Purelink DNA mini kit (Invitrogen, California, USA) from peripheral blood collected in the tubes coated with EDTA *as soon as they were obtained. These procedures were carried out in the genetics laboratory of Molecular Biology and Genetics Department at Inonu University by the first and second authors.* For protecting the confidentiality of the volunteers coding systems were applied to all DNA and blood samples. *All DNA samples were arranged in standard 96 well plate format. The excess of samples and repeat samples were collected in additional plates. All real-time PCR tests were done in 96 well plates.*

Determination of SNP genotypes

We determined SNP genotypes of each sample on a real-time PCR system (Applied Biosystems-Step One Plus-California, USA) using TaqMan®PCR Master Mix (Catalog number: 4304437) and specific assays designed by Applied Biosystems for genotyping the SNP rs1026882 (TaqMan®Catalog number: 4351379, C___1863176_20).

The PCR conditions were adjusted to the suggestions of manufacturer (40ng of genomic DNA, 5µL of Universal PCR Master Mix produced for TaqMan ®genotyping, 0.5µL of TaqMan ® genotyping assay and water to complete the volume to 10µL). Before thermal cycles, we applied a 95°C hot start for 10 minutes. The following 40 cycles of PCR were 15 seconds at 95°C and 1 minute at 60°C. For SNP detection, endpoint plate reads were done by the end of PCR. The data collected from real-time PCR genotyping used for association analyses. *These procedures were carried out by the third author in the genetics laboratory of Molecular Biology and Genetics Department at Inonu University by the first and second authors.*

Statistical analysis

The real-time PCR data were used to determine genotype and allele counts and frequencies of SNP rs1026882 in the case and control groups. The accordance of the groups with Hardy–Weinberg equilibrium was tested with Pearson's Chi-Square method. For deviation from Hardy-Weinberg Equilibrium, we set the p- value to less than 0.01 [24]. The statistical significances of differences in genotype and allele counts between the case and control groups were also tested by Chi-Squared test.

In the event of finding an association between a phenotype and the SNP, we tested the recessive models of each allele to determine the dominant or recessive behavior of candidate allele. For the recessive models, we compared the number of homozygotes of the suspected allele with the sum of numbers of homozygotes of the alternative allele and the number of heterozygotes. We tested the statistical significance by chi-square method. Microsoft Excel software was used for all chi-squared tests. We calculated the statistical power of this study with G*Power software [23]. At a significance level of 0.05, the statistical power has been calculated to be greater than 80% for detecting a locus with an effect size of 0.3. The accordance of numeric data with normal distribution

was tested using Shapiro-Wilk method using the software IBM SPSS Statistics for Windows version 22.0 (Armonk, NY). Since Normal distribution was not approved, data were given as median, minimum, and maximum values. We used Kruskal-Wallis test and Conover method for comparisons (software: IBM SPSS Statistics for Windows version 22.0-Armonk, NY). The significance levels for all statistical tests were accepted as $p \leq 0.05$ except for Hardy-Weinberg tests for which we accepted the significance level $p \geq 0.01$.

We used the genotyping data for three main steps of analyses. At the first step, we compared the distributions of genotypes and alleles of rs1026882 between case and control groups. For the second step, we included the SANS and SAPS data of the patients to see if these parameters are affected by the SNP genotypes. At last, we categorized the patients according to five phenotypic outcomes of the disease *(age of onset, schizophrenia subtype as deficit or nondeficit, the presence of suicidal thoughts, the presence of aggressive behaviors, the presence of lack of insight)* and compared distributions of genotypes between these *phenotypic* subgroups. *These procedures were carried out in the Bioinformatics Section of Molecular Biology and Genetics Department at Inonu University by the first and second authors.*

Results

We have performed a case-control study to understand whether if there is a genotypic or allelic association between the rs1026882 SNP of ERBB4 gene and development of schizophrenia. In Table-1, we have presented the distributions of genotypes and alleles of rs1026882 in our case and control groups and their comparisons. The distributions were shown as counts (n) and frequencies. The p-values of Pearson's Chi-squared test comparing those distributions are given in the (P) line of the same table. Since none of those p-values were below 0.05, we can suggest that none of the differences appeared between the case and control groups in the distributions of genotypes and alleles of rs1026882 were statistically significant. The Hardy-Weinberg equilibriums were approved in case and control groups (Table-1, column: HWE-p).

Table 1. Distributions of genotypes and alleles of SNP rs1026882 in the case and control group as counts and frequencies

	Genotypes Counts (Frequencies)				Alleles Counts (Frequencies)	
	CC	CT	TT	HW-p*	C	T
Case	32 (0.33)	37 (0.38)	27 (0.28)	0.026	101 (0.52)	91 (0.47)
Control	27 (0.27)	45 (0.45)	28 (0.28)	0.265	99 (0.48)	101 (0.51)
P-Value		0.581			0.475	

In the second step of analyses, we have separated patients into subgroups according to their rs1026882 genotypes and compared the medians and IRQs of SANS and SAPS grades between three subgroups (CC, CT and TT) (Table 2). Based on the post-hoc analyzes, in our samples, the avolition symptom was more common in the subgroup of patients carrying CC genotype.

Table 2. Comparison of SANS and SAPS grades as medians and IRQs in genotype groups of patients

	Genotype						p
	C C		C T		T T		
	Medyan	IQR	Medyan	IQR	Medyan	IQR	
SAPS	51	18	50	19	53	15	0.401
Hallucinations	10.5	10	11	8	14	10	0.395
Delusions	21	9	22	8	21	7	0.733
Bizarre Behavior	6	5.5	5	3	5	6	0.677
Positive Formal Thought Disorder	9	3	9	5	10	7	0.094
SANS	55.5	12	42	24	46	35	0.144
Affective Flattening or Blunting	18.5	8	15	13	15	16	0.166
Alogia	11	8	11	9	11	9	0.894
Avolition – Apathy	10	4	7	7	8	5	0.035
Anhedonia – Asociality	8	7	5	2	8	7	0.059
Attention	6	3	6	3	6	4	0.955

Table 3. Distributions of rs1026882 genotypes and alleles in the patient subgroups

	Type	Total	Genotype n (frequency)			Allelen (frequency)	
			C C	C T	T T	C	T
Age of Onset	≤18	27	9 (0.33)	9 (0.33)	9 (0.33)	27 (0.50)	**27 (0.50)**
	>18	69	23 (0.33)	28 (0.41)	18 (0.26)	74 (0.54)	64 (0.46)
P-Value:				0.730		0.65	
Schizophrenia Subtype	Nondeficit	61	22 (0.36)	23 (0.38)	16 (0.26)	67 (0.55)	55 (0.45)
	Deficit	35	10 (0.29)	14 (0.4)	11 (0.31)	34 (0.49)	36 (0.51)
P-Value:				0.733		0.39	
Suicidal Thoughts	Absent	76	28 (0.37)	31 (0.41)	17 (0.22)	87 (0.57)	65 (0.43)
	Present	20	4 (0.20)	6 (0.30)	10 (0.50)	14 (0.35)	26 (0.65)
P-Value:				0.046		0.01	
Agressive Behaviours	Absent	72	24 (0.33)	31 (0.43)	17 (0.24)	79 (0.55)	65 (0.45)
	Present	24	8 (0.33)	6 (0.25)	10 (0.42)	22 (0.46)	26 (0.54)
P-Value:				0.164		0.28	
Lack of Insight	Absent	66	20 (0.30)	26 (0.39)	20 (0.30)	66 (0.50)	66 (0.50)
	Present	30	12 (0.4)	11 (0.37)	7 (0.23)	35 (0.58)	25 (0.42)
P-Value:				0.613		0.28	

At last, we have investigated the differences between distributions of genotypes after categorizing them according to their age of onset and deficit or nondeficit subtype of schizophrenia as well as the presence of suicidal thoughts, aggressive behaviors, and lack of insight. When we compared the patients who had suicidal thought with the rest of case group, we observed an elevated frequency in the T allele and TT genotype in this subgroup. The statistical tests indicated that the difference between two subgroups was significant (p=0.046 for the distributions of genotypes and P=0.01 for the distributions of alleles).

To clarify the situation better *and to determine if the associated allele acts in dominant or recessive fashion, we have tested the association in recessive models of C and T alleles (Table 4). In the T recessive model, the association of TT genotype with the phenotype of suicidal thought was more obvious. The frequency of TT genotype was higher in the subgroup of patients exhibiting suicidal thoughts compared to the rest of patients and this difference was statistically significant* (P=0.014).

Table 4. Recessive models for association of rs1026882 alleles with presence of suicidal thoughts in the patients

Suicidal Thoughts	**C-Recessive Model**	
	T-Absent (C C)	**T-Present (C T + T T)**
Absent	28 (0.37)	48 (0.63)
Present	4 (0.20)	16 (0.80)
P:	**0.155**	
	T-Recessive Model	
	C-Absent (T T)	C-Present (C T + C C)
Absent	17 (0.22)	59 (0.78)
Present	10 (0.50)	10 (0.50)
P:	**0.014**	

Discussion

Schizophrenia is a chronic psychiatric disorder affected by heterogeneous genetic and neurobiological background which affects the early brain development [25]. Genetic screening studies done in different populations indicated association between development of schizophrenia and several SNPs in a lot of genes including ERBB4 [14,16]. In the present study, we have investigated the association of rs1026882 SNP of ERBB4 gene in a Turkish case-control group. We determined the genotypes of case and control samples by a real-time PCR based genotyping method and analyzed the results in three main steps.

At the first step, we have looked for potential single-SNP associations by comparing the distributions of genotypes and alleles between the case and control groups without separating the patients into subgroups. We observed quite slight differences after comparing the counts of individuals carrying each genotype in the case and control groups, but they were not statistically significant according to chi-squared test results. Apart from the genotypes, we have also compared those two groups of samples for counts of the alleles. This comparison revealed that there was no allelic association between development of schizophrenia and the ERBB4 SNP rs1026882 either.

Following the single-SNP association tests carried out in case-control format, we have split the patients into three subgroups according to their SNP genotypes and compared the medians and IRQs of SANS and SAPS values between these subgroups to see if the rs1026882 genotypes have effects on the positive and negative symptoms seen with schizophrenia. The negative symptoms (SANS) which we evaluated here were, affective flattening or blunting, alogia, avolition–apathy, anhedonia–asociality, attention; and the positive symptoms (SAPS) were hallucinations, delusions, bizarre behavior, positive formal thought disorder. We have tested the potential associations between the extents of these symptoms and rs1026882 genotypes. There were no significant differences between the patients carrying different genotypes for SAPS and SANS total scores. When the sub-parameters were evaluated, only avolition symptom from the SANS parameters was found to be significant (p=0.035). The post-hoc analyzes showed that the avolition symptom can be seen more common in the group of patients carrying CC genotype when compared to heterozygotes.

At the third step of our analyses, we have separated the patients into five subgroups according to five other clinical outcomes of the disease including age of onset, deficit or nondeficit type of schizophrenia, the presence of suicidal thoughts, aggressive behaviors, and lack of insight. Afterwards, we compared the distributions of genotypes and alleles in each of these five subgroups with rest of the case group separately. Even though we were not able to observe statistically significant differences with four phenotypical subgroups, only the one consisting of patients who had suicidal thoughts appeared to have an elevated frequency of T allele and TT genotype of rs1026882. The statistical test done by Pearson's goodness of fit chi squared method indicated that the difference between this subgroup and rest of the patients was significant (p=0.046 for the distributions of genotypes and P=0.01 for the distributions of alleles). To clarify the association, we tested the C and T recessive models as well. In the T recessive model, the difference was more obvious since the frequency of TT genotype (absence of C allele) was much higher in the subgroup of patients exhibiting suicidal thoughts compared to rest of the patients who did not show this this phenotype (p=0.014).

To date, several SNPs in the ERBB4 gene were found to be associated with schizophrenia. The haplotypes constructed by several SNPs in this gene were found to be associated with the disease as well [14 and 15]. In Turkish population, rs83952, rs7598440 and rs707284 SNPs were screened to uncover their association with schizophrenia, but the result was negative, even though there were positive associations in some other populations [7]. Our database search indicated that the SNP rs1026882 was screened only in a single study which was done in a German sample [18]. In that study, an epistatic interaction of rs1026882 was found to be related with schizophrenia. But the single SNP association of this polymorphism with the phenotypes and symptoms of schizophrenia we have investigated in this study were not evaluated. According to this, the association of TT genotype of rs1026882 with the phenotype of suicidal thoughts in schizophrenia was probably revealed in our study. Also, no previous studies in the literature were encountered noticing the SANS parameter avolition-apathy could be related with the CC genotype of the same SNP which we have found in our sample. The absence of a disease association in the general patients' group in our study is still in accordance with the other previously published studies which report the other non-associated SNPs in the ERBB4 gene [7].

Conclusion

To our knowledge, this is the first study to investigate association of ERBB4 SNP rs1026882 with schizophrenia and some of its phenotypes in a population from Turkey. Since our sample is limited to a population living in a single city (Malatya), our results may not reflect the whole population of Turkey. As conclusion, in this sample we have not been able to find sufficient evidence to support the presence of a single SNP association of the SNP rs1026882 in the ERBB4 gene with schizophrenia phenotype. However, when the SAPS and SANS parameters are considered, avolition symptom seems more common in the patients with CC genotype than the ones with CT. In the other hand, separation of the patients into subgroups according to clinical outcomes of disease revealed, the TT genotype may have an association with the phenotype of suicidal thoughts. Since our sample was limited to a small population from a narrow geographical region, investigation of the genetic association between rs1026882 and schizophrenia in larger case-control groups from different populations, and separation of patients into more homogenous phenotypic subgroups should reveal more confidential results.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical approval
The ethical approval for the study was obtained from the Social Sciences and Humanities Eth-ics Committee of a university (Date: 8 March 2021, No: 2021-3).

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