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The Association of V427M Missense Mutation of the PRODH Gene with Schizophrenia in the Iranian Patients

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Abstract

Background: PRODH is one of the genes that exists in 22q11.2 location and encodes the prolin oxidase enzyme (POX) in the mitochondrial inner membrane and is expressed in the liver, kidney and brain. The importance of the accompaniment of the PRODH gene's polymorphisms and mutations in increasing the risk of getting afflicted with schizophrenia has been proven in previous Linkage and Association studies. Proline dehydrogenase enzyme (POX) accelerates the converting of prolin into glutamate. Decreased enzyme causes hyperprolinemia resulting in increased proline and decreased glutamate. The activity of NMDA and AMPA receptors decrease and low activation of these receptors cause negative symptoms of schizophrenia disorder. V427M mutation in PRODH has been proven to decrease pox enzyme activity and is associated with schizophrenia disorder.

Objectives: In this project the rs2238731 variant in the PRODH gene was genotyped in 95 schizophrenic patients whose diseases are psychiatrically confirmed and also in 120 healthy people without any history of schizophrenia and bipolarity in their pedigree. For this purpose, their peripheral blood was taken.

Methods: In this study, the PCR-RFLP approach has been adopted in order to identify this variant. The SPSS 24.0 software has been used in order to statistically analyze the association of mutant variants and normal variants among the two groups afflicted with the disease and non-afflicted with the disease. The goal of this study was to shed light over the accompaniment of the rs2238731 variant in the PRODH gene with the risk of getting afflicted with schizophrenia among the Iranian patients.

Results: According to our result, there is no association between V427M missense mutation and schizophrenia disorder in Iranian patients. So the V427M missense mutation could not be regarded as co-related with increasing risk of schizophrenia in Iranian patients.

Keywords: Schizophrenia, Single Nucleotide Polymorphism, Proline Dehydrogenase

1. Background

One of the strongest risk factors for schizophrenia is the deletion in 22q11 (1). More than a third of patients with 22q11 syndrome, known as Digeorge syndrome or Velocardiofacial, are afflicted with schizophrenia or schizoaffective (2). In addition, while the prevalence of 22q11 deletion in the total population is 1 in 4000, its frequency is almost 1% among adult SCZ patients (3). The deletion of 22q11 has been proposed as a genetic cause of schizophrenia, so the genes that are present in this area tends to make people susceptible to the disease. One of the commonly eliminated genes in 22q11 is PRODH which encodes proline dehydrogenase. The PRODH gene contains fourteen exons repeat that are located in a repeat sequence with a low copy and widely expressed in the brain and the rest tissues (4). This gene has a wide range of SNP. This high rate of polymorphisms can be the result of the presence of telomeric unprocessed pseudo gene 4 GB, that is located in chromosome 22 and stores SNPs as a treasury, and can transfer Single Nucleotide Polymorphisms (SNPs) to the PRODH by mechanism of displacement. This mechanism is thought to explain the frequency of polymorphisms in this gene (5). At least sixteen missense mutations have been identified in studies of *hyperprolinemia* (HPI) and 5SZ. Ten mutations were as frequency of polymorphic (5). The gene encodes a mitochondrial enzyme that catalyzes the conversion of proline to glutamate, which catalyzes the first stage in proline catabolism, proline modulates neurotransmitter glutamine and affects the NMDA receptor, as well as known as proline oxidase (POX), a mitochondrial suppressor tumor (6), which inhibits proliferation and induces apoptosis. Knockout mice in PRODH, dopaminergic signaling has been increased and neurotransmitter transfer has been al-

tered, and the learning nerve base of memory is impaired. These changes occur in the frontal cortex during the formation of the synapse (7). There is a lot of evidence suggesting the important role of PRODH in SZ, this evidence includes:

1. This gene is located in the chromosome 22q11.2, and removal in this chromosome is one of the strongest risk factors for schizophrenia.

2. Missense mutations in PRODH have been reported in SZ patients (5).

3. Correlation of schizoaffective disorder and Moderate hyperprolinemia had been previously identified. Hyperprolinemia is an autosomal recessive genetic disorder that occurs due to defective enzyme of Pox (8).

4. The gene is widely expressed in the brain.

5. Mice with defect in PRODH shows increasing proline levels in plasma and in the brain shows local reductions in glutamate and gamma-amino butyric acid (GABA) (9, 10). 6-PRODH enzyme plays a role in the conversion of proline to glutamate, which is important for the signal transduction in neurons and for synaptic plasticity, and it seems that it is not regulated in schizophrenia (11).

PRODH, along with its role in catabolism, is also known as a key enzyme in controlling homeostasis, energy supply and the potential for inter-cellular chemical transfer and reactive oxygen production (12). It is shown that functional polymorphisms in PRODH is associated with SZ risk and correlate with changes in the Prefrontal- striatal circuit of the brain and working memory and the cognitive gating of the brain (13). According to the results of control samples, it has been shown that non-functional SNPs do not have any significant effect on the brain's phenotype. Also, the hypothesis that the alleles should also be present in the healthy siblings of the sick people was investigated. Healthy siblings have SNPs that reduce the activity of POX enzymes (13). Defective Glutamargic neurotransmitter is widely involved in the SZ pathology (13, 14). The glutamargic defect, specifically, the NMDA receptor, plays a role in SZ. The NMDA antagonist injection creates cognitive impairment and SZ symptoms in healthy subjects and changes in the transfer of dopaminergic neurons. The knockout mice in PRODH correlates with the increase of the dopaminergic signaling pathway, also changes the transfer of glutamatergic neurotransmitter transfer and reduces the long-term potential of the learning and memory neural base (10). As a result, SNPs that reduce the activity of POX enzymes produce negative SZ symptoms. Changes in the efficiency of the POX protein can cause significant changes in brain circuits, which results in disruptions in the genotype, such as memory and attention.

2. Methods

2.1. Patients and Controls

In order to genotype the selected SNP, 95 SZ patients were recruited and five mL of blood samples were taken from all participants in EDTA tubes and were immediately processed for DNA extraction. Based on the two approaches of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) symbolism and the Positive and Negative Syndrome Scale (PANSS), patients from Imam Hussein Hospital and Schizophrenic Patient Support institution (AHEBBA) - Both named places located in Tehran- were clinically diagnosed with SZ by an expert psychiatrist. Letter of consent was obtained from all of the participants, and this investigation was carried out in line with the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of, Science and Research Branch, Islamic Azad University, Tehran, Iran. In this study, we also included 120 healthy control people without any psychological history in their families and demographically matched them with SZ patients.

2.2. DNA Extraction and Genotyping

Genomic DNA samples were extracted from whole blood using MagCore HF16 Automatic Nucleic Acid Extractor system (RBC Bioscience Corp, Taiwan) with MagCore blood Genomic DNA Extraction Kit (RBC Bioscience Corp, Taiwan) and were stored in -20°C for future analysis. The quality and quantity of the extracted DNA were respectively determined by nanodrop and 1% agarose gel electrophoresis. Primers for PCR-RFLP and sequencing methods, were designed using gene runner software and www.SNPer.com. In this study, SNP rs2238731, was identified through the PCR-RFLP method. After the proliferation of approximately 100 ng of genomic DNA, the PCR products were digested using Hin1II (NIaIII), restriction enzyme according to the manufacturer's instructions. We ran digested samples on 12% polyacrylamide gel and used silver nitrate to spot the DNAs. In this study and in order to make sure of the results drawn based on the method PCR-RFLP, one third of the samples were sequenced at random using the applied biosystems (AB), (3130 Genetic Analyzer). The genotyping results drawn from the PCR-RFLP method of sequencing and RFLP-PCR were compared for validation. There was complete concordance between sequencing and RFLP-PCR methods for the SNP. The utilized primers and required restriction enzyme were listed in Table 1.

2.3. Statistical Analysis

Chi-Square test was used to evaluate if our data for each SNP is in Hardy-Weinberg equilibrium (HWE) (15). The sta-

Table 1. Primers Used in This Study for PCR-RFLP and Sequencing Methods

Gene	SNP	Primer Sequences	Sequencing Method		
PRODH	rs2238731	F: GGACAGAGGTTGGAGGCCC	315 bp	61	HinIII (NIaIII)
		R: GTTGATGGGGTCCTCATAGCC			

Abbreviation: SNP, single nucleotide polymorphism.

tistical package for the social sciences version 24 (SPSS, version 24; SPSS Inc., Chicago, IL) was used to analyze the results. The Kolmogrov-Smirnov test was used to assess if the data were normally distributed. To assess the association of our selected SNP with SZ, the allelic and genotypic frequencies were compared via non-parametric Pearson $\chi 2$ test for cases and controls with a Bonferroni-corrected statistical significance level. Major allele homozygous, heterozygous and minor allele homozygous groups were determined and OR (odds ratio) and 95% CI (confidence interval) were calculated for each genotype. P value ≤ 0.05 was considered significant.

3. Results

3.1. SZ Patients and Control Subjects

The characteristics of the SZ patients and healthy controls are presented in Table 2.

Table 2. Characteristic of Cases and Control

Diagnosis	Gender, M/F	Age[a]	PANSS[a]
SCZ (n = 95)	65/30	32 ± 12.18	80 ± 10.0039
Control (n = 120)	78/42	35 ± 14.14	-

[a]Values are expressed as mean ±SD.

3.2. Allelic Association

In the Iranian patients group, allele T showed no association in rs2238731 with SZ. The allelic frequency of rs2238731 in the Non-schizophrenic and schizophrenic samples is 0.98/0.01 (C/T). For the allelic frequency of rs2238731, the odds ratio equals 0.81, with confidence interval, 0.05 - 13.02. Pearson $\chi 2$ test for the allelic frequency of rs2238731 equals 0.022 and P value equals 0.881 and is not significant ($P > 0.05$) (Table 3).

3.3. Hardy-Weinberg Equilibrium

The genotypic distribution of the SNP rs2238731 that was addressed in this study in the two groups of case and control was in hardy Weinberg equilibrium (Table 4).

$\chi 2$ was calculated by Hardy-Weinberg equilibrium testing (15) (Table 4).

4. Discussion

In fact, the PRODH gene is the most important gene known in relation with SZ, PRODH codes the proline dehydrogenase protein (POX), which catalyzes proline into glutamate. Any change in the efficiency of the enzyme proline dehydrogenase affects the amount of glutamate and Glutamatergic pathway. The role of the PRODH gene in schizophrenia in different populations has been reported repeatedly (16). SNP; rs2238731 is located in exon 12 of the PRODH gene. SNP, rs2238731 (V427M) is a functional missense mutation. This SNP is located and translated in the exon region and converts amine acid valin into amine acid methionine.

In a study conducted at the Harvard University and John Hopkins in the American population, it has been reported that V427M has reduced the activity of POX enzyme to 30% - 70% in people with schizophrenia. Reducing POX enzyme increases proline and decreases glutamate, followed by it, changes in Glutamatergic efficiency and NMDA receptor efficiency. Decreasing NMDA efficacy is raised in creating negative SZ symptoms (10, 17-19). The hypothesis of glutamargic pathway involvement in SZ disorder was raised many years ago. There have been many reports from 1949 that some patients with SZ have been treated with glutamic acid (20). Studies of expression of NMDA receptor in post mortem samples have reported a decrease in NMDAR1 subunit density in the Superior frontal cortex and superior temporal cortex (21). It seems that abnormality in NMDA receptors in SZ disorder is due to inappropriate density of NMDA receptors (22). This abnormality can be the result of changes in Glutamate receptor trafficking molecules (23). The role of glutamate in SZ physiology is also confirmed with genetic findings. The GRIN2A gene that encodes NMDA receptor subunit is correlated with SZ. Also, SRR, which plays a key role in the activation of NMDA receptors, has also been correlated with SZ (24). The injection of NMDA receptor antagonists, such as phencyclidine (PCP), discipline (MK-801), and ketamine, produce a psychological effects that is very similar to the positive and negative symptoms of SZ (25-27). In another study on the Brazilian population, the relationship between SNP, V427M and cortical cortex thickness was reported, which confirms the role of SNP, rs2238731 in the shape and size of the brain.

Table 3. The Summary Results of Associated SNP of, PRODH

Gene	Chr	SNP	A1/A2	Common Allele	P Value	OR (95% CI)	Pearson $\chi 2$
PRODH	22	rs2238731	T/C	C	0.881	0.81 (0.05 - 13.02)	0.022

Table 4. Genotypic and Allelic Distributions for Controls and Schizophrenia Cases[a]

	N	Genotype Counts (Frequency)			Allele Counts (Frequency)		$\chi 2$ (P Value)
Polymorphism, rs2238731		CC	CT	TT	C	T	
SCZ	95	93 (97.9)	2 (2.1)	0 (0)	0.98	0.01	0.01 (P > 0.05)
Controls	117	114 (97.5)	2 (1.7)	0 (0)	0.98	0.01	0.01 (P > 0.05)

[a] Chi-square's exact P values are shown for allelic distribution between case-controls.

Cortical cortex of brain of patients with GA genotype has a lower thickness than patients with GG genotype (12), which indicates the important role of this variant in modifying proline dehydrogenase function.

In this study, the correlation between V427M (rs2238731) and SZ was evaluated. No association was found between this variant and schizophrenia and the allele frequency of this variant in both healthy and patient groups did not show any significant difference (P = 0.881, OR = 0.81, CI = 0.05 - 13.02). The PRODH gene in relation to SZ has been studied in Iran repeatedly, the association between variants of 1945 T > C, 757 C > T, 1766 A > G and 1852 G > A in the PRODH and SZ gene, has been studied, and significant results have been obtained (28-30). Despite the role of SNP, rs2238731 in the schizophrenia, there was no association between SNP, rs2238731 and schizophrenia in Iranian subjects. The frequency of C and T alleles in SNP rs2238731 did not show a significant difference between two healthy and patient groups (P = 0.881) and SNP rs2238731 in Iranian subjects is in Hardy Weinberg equilibrium (HWE; P > 0.05). In this study, there were 4 GA genotypes in general, 2 of them were SZ and 2 were healthy, and the frequency of alleles A and G did not show significant difference in healthy and patient groups. The frequency of allele-minor A of rs2238731 in the Iranian population is 0.01. And the frequency of allele A, in the American population is 0.20 and has been reported as allele predisposing schizophrenia. A study conducted in 2014 suggested that G allele in SNP rs2238731, possibly by altering brain enzyme activity, should be a protective and preventing factor in schizophrenia (12).

The limitations of this research are small sample size and a small number of the polymorphisms that were addressed in this study. The sample size in this study is too small for us to come to a definite conclusion with regard to the no association between rs2238731 in the gene PRODH and SZ. Therefore, further studies are required in order to confirm the results of this study. Also, in order to confirm the association between the PRODH gene and its polymorphisms and SZ in the Iranian population more SNP's in this gene should be analyzed.

4.1. Conclusion

There was no association between allele A in SNP rs2238731 and SZ in Iranian subjects. Therefore, V427M, in spite of its role in the activity of POX enzyme reported in other populations, is not association with SZ in Iranian subjects and may decrease the activity of POX enzyme in Iranian people due to the involvement of other SNPs in the PRODH gene.

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Footnotes

Conflict of Interests: The authors declare no conflict of interest

Ethical Considerations: Letter of consent was obtained from all of the participants, and this investigation was carried out in line with the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of, Science and Research Branch, Islamic Azad University, Tehran, Iran.

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