J Human Gen Genom. 2021 December; 5(2): A-10-352-1 doi: 10.52547/jhgg.5.2.73
Published online 2023 January 03 Research Article

The Association of PRODH Gene Polymorphism P19Q and the risk of Schizophrenia in the Iranian Patients

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Received 2022 November 26; **Revised** 2022 December 12; **Accepted** 2022 December 15.

Abstract

Background: 22q11.2 deletion is a common microdeletion. About 30% of patients with 22q11.2 deletion develop schizophrenia. PRODH is one of the genes located in 22q11.2 region, which encodes the proline oxidase enzyme (POX) in the inner membrane of mitochondria. PRODG expresses in the skin, kidney, liver, and brain. The polymorphisms of PRODH gene in increasing the risk of getting afflicted with schizophrenia have been demonstrated in previous Association and Linkage studies. The role of proline dehydrogenase enzyme (POX) is to catalyze proline's conversion into glutamate. Reduced enzyme leads to increased proline and decreased glutamate and resulting in hyperprolinemia. It has been proven that P19Q mutation in PRODH reduces pox enzyme activity and is associated with schizophrenia disorder.

Objectives: In the present study, the rs2008720 variant in the PRODH gene was genotyped in 100 schizophrenic patients whose diseases were confirmed by experts and in 100 healthy people without any family history of psychiatric disorder.

Methods: To identify this variant, the PCR-RFLP technique has been adopted. The association of mutant and normal variants between the two groups afflicted with the disease and non-afflicted with the disease has been analyzed by SPSS 16 software.

Results: No association was found between P19Q missense mutation and schizophrenia disorder in Iranian patients. Therefore, the P19Q missense mutation is not considered a risk of schizophrenia in Iranian patients.

Keywords: Schizophrenia, Single Nucleotide Polymorphism, Proline Dehydrogenase

Background

22q11.2 deletion syndrome (DiGeorge/ velocardiofacial syndrome, Cayler syndrome, and conotruncal anomaly face syndromes) is the most common interstitial microdeletion in humans with an incidence of 1 in 4000 live births (1). It is shown that patients with 22q11DS have a reduced cortical surface area (2), congenital heart defects, cleft palate, hypoparathyroidism, and distinct facial features (3,4). Cognitive impairments are associated with autism spectrum disorder (ASD), learning difficulties, and ADHD (5,6). Most 22qDS cases are due to de novo mutation that occurs during gametogenesis. Only 5% to 10% of cases have been inherited from a parent who may have mild manifestations. About 30% of 22q11.2DS patients develop schizophrenia in adulthood, noticeably increasing risk to the

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[DOI: 10.52547/jhgg.73]

general population (7). Cognitive deficits, generalized anxiety disorder (8,9), minor coordination deficits, and early language delays (4) are diagnosed in childhood. It has been shown that microdeletion of 1.5 Mb in the 22q11 region is the susceptible locus for schizophrenia (10). The genes located within this area can induce schizophrenia. Rees et al. showed that (11) the duplications of genes in the 22q11.2 region might decrease the risk of developing schizophrenia. Therefore, this region's duplication could be a protective mechanism for schizophrenia. It is identified that variants of about 35 genes in the 22q11.2 region may have a higher risk of schizophrenia than deletion of them (12). The most susceptible risk genes to schizophrenia are COMT, PRODH, DGCR8, DGCR2, and ZDHHC8 (13).

PRODH, also known as POX, encodes proline oxidase, a mitochondrial enzyme that catalyzes the first step in proline degradation. Mutations in PRODH gene are associated with hyperprolinemia type 1 and susceptibility to schizophrenia (12-14). POX is responsible for the catabolism of proline to glutamate, the main transmitter in the brain (14,15). The genomic rearrangements disrupt the PRODH2 locus, leading to hyperprolinemia, in a small group of Schizophrenia patients that screened for such rearrangements (16). There is a positive association between schizophrenia and the variants that lead to an increase in enzyme activity, and those that reduce POX activity have a negative association between SNPs and schizophrenia (17,18). In the PRODH gene, the most common variations are C757T, G1852A, and A1766G. While C757T and G1852A reduce enzyme activity, A1766G increases proline dehydrogenase activity (17-19).

PRODH-knockout mice show an increased proline level in plasma and glutamatergic signaling in the hippocampus (20). Also, in the frontal cortex, the level of COMT mRNA seems as a compensatory response for abnormal dopamine expression (21). The results show that schizophrenia is a neurodevelopmental multifactor disorder and finding the risk genes in the 22q11.2 region helps better understand the pathogenesis of Schizophrenia disorder. Some studies proved that although PRODH gene has no significant association in Chinese and European populations, in the Iranian patients, it is a risk gene highly associated with schizophrenia (22,23). In this study, we examined the association of the rs2008720 variant (c.56C>A, P19Q) in exon 1 of PRODH with schizophrenia in Iranian patients.

Methods

Sampling

In this study, 100 schizophrenia patients were chosen from the Support Institution (AHEBBA) and Imam Hussein Hospital of Tehran. The patients were clinically diagnosed with SZ by a psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) symbolism and the Positive and Negative Syndrome Scale (PANSS). Also, in this research 100 healthy people without any history of psychiatric disorders were included. The consent letter was taken from all participants and caregivers. This investigation was performed in line with the Declaration of Helsinki. Blood sampling of all participants was performed to genotype the selected variant. Characteristic of Cases and Controls describe in Table 1.

Table 1. Characteristic of Cases and Controls

Diagnosis	Gender,M/F	Age	PANSS
SCZ (n=100)	65/35	32±12.18	80±10.0039
Control (n=100)	68/32	35±14.43	-

DNA Extraction and Genotyping

DNA extraction from whole blood was performed using the MagCore HF16 Automatic Nucleic Acid Extractor system (RBC Bioscience Corp, Taiwan) with MagCore Blood Genomic DNA Extraction Kit (GeneAll). The quality and quantity of the extracted DNA were determined by nanodrop and 1% agarose gel electrophoresis. Primers were designed by the GeneRunner application in order to perform PCR-RFLP and sequencing. Through the PCR-RFLP, SNP rs2008720 was identified. Approximately 100 ng of genomic DNA was proliferated, then due to the manufacturer's instructions, the amplified DNA products were digested using PvuII (GeneAll) restriction enzyme. Digested samples were run on 12% polyacrylamide gel and silver nitrate staining was used to detect the DNAs. The sequences of primers and used restriction enzymes are listed in Table 2.

Table 2. Primers Used in This Study for PCR-RFLP

Gene	SNP	Primer Sequences	Product Length	Enzyme
PRODH	rs2008720	F: GAGGGACCAACAGCGCAC R: ACGACACACCTCCTGGCAC	179	PvuII

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[DOI: 10.52547/jhgg.73]

Statistical Analysis

To check if our data for each SNP is in Hardy-Weinberg equilibrium (HWE), the Chi-Square test was used. The SPSS software (version 16; SPSS Inc., Chicago, IL) was used to analyze the results. To assess the normal distribution of data, the Kolmogorov-Smirnov test was used. To assess the association of the selected SNP with SZ, the allelic and genotypic frequencies were compared via Pearson $\chi 2$ test for patients and controls with a Bonferroni-corrected statistical significance level. Three groups of major allele homozygous, heterozygous, and minor allele homozygous were determined, and OR (odds ratio) and 95% CI (confidence interval) were calculated for each group. P value ≤ 0.05 was considered significant.

Results

SZ Patients and Controls

The features of the SZ patients and healthy controls are described in Table 2.

Genotype Frequency

The frequency of three genotypes, CC, AA, and CA, in patient and control groups are presented in table 3. The genotypic distribution of the SNP rs2008720 in both patients and controls was in hardy Weinberg equilibrium (Table 3). $\chi 2$ was calculated by Hardy-Weinberg equilibrium testing (Table 3).

Table 3. Frequency of three genotypes CC, AA and CA in patient and control groups

p-Value	OR(95%CI)	Control	Cases	Genotype	Model
0.6	1	25(25%)	28(28%)	C/C	Codominant
	1.28(0.66-2.49)	55(55%)	48(48%)	C/A	
	0.93(0.42-2.08)	20(20%)	24(24%)	A/A	
0.63	1	25(25%)	28(28%)	C/C	Dominant
	1.17(0.62-2.19)	75(75%)	72(72%)	C/A-A/A	
0.49	1	80(80%)	76(76%)	C/C-C/A	Recessive
	0.79(0.40-1.55)	20(20%)	24(24%)	A/A	
0.32	1	45(45%)	52(52%)	C/C-A/A	Over dominant
	1.32(0.76-2.31)	55(55%)	48(48%)	C/A	

In this study, the highest percentage of genotype frequency in the patient (48) % and control groups (55) % belongs to the heterozygous genotype of CA, and the lowest percentage of genotype frequency is related to the homozygous genotype of AA in both patients (24%) and control groups (21%). The frequency and proportion of C and A alleles in the patient group are shown in table 4.

Table 4. Frequency and proportion of C and A alleles in patient group.

Allele	All subject		Cases	
	Count	Proportion	Count	Proportion
C	209	0.52	104	0.52
A	191	0.48	96	0.48

Discussion

Many types of research have demonstrated that PRODH can be an essential susceptible gene associated with schizophrenia risk. The association of PRODH variants with Schizophrenia was demonstrated in many pieces of research. The objective of the present study was to investigate the association of rs2008720 (c.56C>A) of the PRODH gene with schizophrenia in Iranian patients. rs2008720 is located in exon 1 and causes the amino acid change from Proline, a nonpolar amino acid to Glutamine that is an uncharged polar amino acid.

Kempf et al showed that some functional variants in PRODH were associated with risk for schizophrenia. They proved rs450046 was associated with increased POX enzyme activity was strongly positively associated with schizophrenia (22). While, the rs4819756 and rs2870983, which were associated with decreased POX activity (14), were significantly negatively associated with schizophrenia. Reduction of bilateral frontal white matter (WM) as an essential endophenotype was reported in relation to rs2008720 in PRODH (24). The relation of the PRODH gene to SZ has been studied in Iran before, the association between PRODH variants of 1945 T > C ,757 C > T, 1766 A > G, and 1852 G > A and SZ have been studied, and significant results have been obtained (23-25).

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[DOI: 10.52547/jhgg.73]

In an association study of PRODH variants and SZ in Iranian patients, it has been shown that G1496A and C1482T polymorphisms in patients were considerably higher than in controls, and correlations between the occurrence of these polymorphisms and schizophrenia in the population were significant. No significant association between G758A in the PRODH gene with schizophrenia was observed (26). Another study has reported no association between rs2238731 (V427M) and schizophrenia in Iranian patients (27).

In the present study, no association was found between rs2008720 variant with schizophrenia. The allele frequency of rs2008720 did not demonstrate any notable difference in control and patient groups.

The limitations of this study were the small sample size and the few polymorphisms which were assessed. Therefore, it is difficult to conclude that there is no association between rs2008720 in the gene PRODH with SZ. Thus, we need further investigations to confirm the results of the current study. Also, some SNPs may be associated with SZ in a haplotype. More SNPs in PRODH are required to assess for finding the association between PRGDH variants with SZ in Iranian patients.

Conclusion

The results show no association between allele A in SNP rs2008720 and SZ in Iranian patients. Thus, despite the role of P19Q in the activity of the POX enzyme reported in other populations, it is not associated with SZ in Iranian patients and the reduction of POX enzyme activity in Iranian patients may be due to the involvement of other variants in the PRODH gene.

Acknowledgement

We thank Imam Hussein Hospital, AHEBBA, and all the schizophrenic participants.

Conflict of Interest

The authors declare no conflict of interest.

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[DOI: 10.52547/jhgg.73]