



Relationship between polymorphisms in the proline dehydrogenase gene and schizophrenia risk

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Genet. Mol. Res. 14 (4): 11681-11691 (2015)

Received January 21, 2015

Accepted May 11, 2015

Published October 2, 2015

DOI <http://dx.doi.org/10.4238/2015.October.2.1>

ABSTRACT. Previous studies have suggested that an association exists between the proline dehydrogenase gene (*PRODH*) and increased schizophrenia risk. We examined the prevalence of the *PRODH* 757C/T (Arg185Trp), 1766A/G (Gly521Arg), and 1852G/A (intronic mutation) polymorphisms in 175 patients with schizophrenia and 185 control subjects. All subjects were of Iranian ancestry. The *PRODH* 757TT, 1852AA, and 1766GG genotypes were associated with an increased risk of schizophrenia (odds ratio = 1.38, 95% confidence interval: 0.88-2.16, P = 0.001, P = 0.001, respectively). The activity alleles in the *PRODH* genotype combinations were associated with an increased risk of schizophrenia (haplotype analysis, TAG genotype P = 0.007). Our findings support a major role for the *PRODH* 757TT, 1766GG, and 1852AA genotypes alone and in combination for schizophrenia susceptibility.

Key words: Haplotype; Proline dehydrogenase; Schizophrenia

INTRODUCTION

The location of a schizophrenia susceptibility locus at chromosome 22q11 has been suggested by genome-wide linkage studies (Liu et al., 2002a; Gogos and Gerber, 2006). Additional support was provided by the observation of the higher than expected frequency of 22q11 microdeletions in patients with schizophrenia and that 20-30% of individuals with 22q11 microdeletions develop schizophrenia or schizoaffective disorder during adolescence or adulthood (Goldner et al., 2002; Harrison and Weinberger, 2004; Ishiguro et al., 2007; Girard et al., 2011). Analysis of the extent of these microdeletions using polymorphic markers further refined this locus to a region of 1.5 Mb. Recently, a high rate of 22q11 microdeletions was reported in a cohort of 47 patients with childhood-onset schizophrenia, a rare and severe form of schizophrenia with onset by the age of 13 years. Thus, this 1.5-Mb region may contain 1 or more genes that predispose individuals to schizophrenia (Glaser et al., 2006; Ishiguro et al., 2007). Schizophrenia is a common and severe mental illness of thought, emotion, and behavior that affects approximately 1% of the general population (Liu et al., 2002a,b; Lee et al., 2012). Familial, twin, and adoption studies have revealed that genetic factors are involved in the etiology of schizophrenia (Goldner et al., 2002; Liu et al., 2002a; Glaser et al., 2006; Kempf et al., 2008). However, major common risk loci have not been identified. Linkage studies have implicated numerous potential susceptibility loci, including chromosome 22q11 (O'Donovan et al., 2003; Gogos and Gerber, 2006; Ma et al., 2007; Ripke et al., 2013). Patients with velocardiofacial syndrome, who frequently have a 1-2-Mb deletion region in 22q11, show an elevated rate of psychosis. The microdeletion, which has been observed in 2% of adult schizophrenic patients and in 6% of cases with childhood-onset schizophrenia, occurs in the population at a rate of 0.025%, although the results are conflicting (Gogos and Gerber, 2006; O'Tuathaigh et al., 2007; Ishiguro et al., 2007; Ma et al., 2007). Recently, an association between several single-nucleotide polymorphisms (SNPs) within the proline dehydrogenase gene (*PRODH*) and schizophrenia was reported in studies of 3 sets of independent samples. *PRODH*, located in the most centromeric region of the 22q11 microdeletion region, encodes *PRODH*, a mitochondrial enzyme that converts proline to D1-pyrroline-5-carboxylate and is involved in the transfer of the redox potential across the mitochondrial membrane (Jacquet et al., 2002; O'Donovan et al., 2003; Ohtsuki et al., 2004; Gogos and Gerber, 2006; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011). The *PRODH* gene consists of 15 coding exons located in a low-copy repeat sequence and is widely expressed throughout the brain as well as in other tissues (Ohtsuki et al., 2004; Glaser et al., 2006; Ross et al., 2006). Mice homozygous for *PRODH* deficiency showed deficiencies in prepulse inhibition, a measure of sensory motor gating affected in schizophrenics. Hence, the *PRODH* gene is likely to be a promising candidate as a schizophrenia susceptibility gene (Karayiorgou et al., 1995; Goldner et al., 2002; Karayiorgou and Gogos, 2004; Bender et al., 2005). Several studies have demonstrated an association between variations in the *PRODH* gene and psychiatric disorders such as schizophrenia, while others have shown no significant association. Most variations in the *PRODH* gene result in an amino acid substitution in the *PRODH* enzyme (Ohtsuki et al., 2004; Ma et al., 2007; O'Tuathaigh et al., 2007; Roussos et al., 2009; Kim et al., 2011). The amino acid substitution decreases enzyme activity, resulting in less efficient proline breakdown. Previous studies suggested that increased proline levels may affect the action of particular chemicals that relay signals between neurons within the brain (neurotransmitters), resulting in an increased risk of psychiatric disorders (Karayiorgou et al., 1995; Arnold et al., 2005; Glaser et al., 2006).

To further investigate the role of *PRODH* in schizophrenia susceptibility, we used the transmission disequilibrium test and haplotype-based haplotype relative risk method to analyze the transmission of the *PRODH* 757 (C/T), 1766 (A/G), and 1852 (G/A) alleles in the offspring in 175 families with schizophrenia from Iranian populations.

PRODH is a potential susceptibility gene for schizophrenia, although the results of previous studies are controversial. To determine whether the *PRODH* gene is associated with schizophrenia, we genotyped 3 SNPs in this gene, all of which have been previously correlated with schizophrenia, and performed association analyses between alleles, genotypes, and haplotypes. We also examined the effect of different independent elements on this disorder, including gender, season of birth, gender, and level of education. This is the first study to examine the association between the *PRODH* gene and schizophrenia in the Iranian population.

MATERIAL AND METHODS

Literature search

The literature search was conducted in PubMed using the key words “schizophrenia” and “proline dehydrogenase gene”. All references cited in these investigations and published reviews were examined for additional relevant studies.

Inclusion criteria

Studies included met all of the following criteria: 1) they were published in a journal and were independent analyses using original data; 2) they provided sufficient data to calculate the odds ratio (OR) and a P value; 3) they investigated 1 or more of the polymorphisms of interest using either population-based or family-based approaches; 4) they described the relevant genotyping primers, machines, and protocols, or provided references to these items; 5) they diagnosed schizophrenia patients according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, and 6) they included healthy individuals as controls (for case-control studies). Authors were contacted in cases in which there were queries regarding the studies.

Study population

In this study, all cases were of Iranian descent and were recruited from throughout the country. A total of 175 unrelated patients with schizophrenia (including 89 females and 86 males, aged 18-60 years) were obtained from psychiatry hospitals and clinics. These patients were diagnosed according to the DSM, Fourth Edition (DSM-IV), and their disorders were confirmed by psychiatrists. Control cases were collected of a population of volunteers from different regions in Iran. Control subjects were healthy and free from illness. A total of 185 unrelated control individuals were included (including 100 females and 85 males, aged 20-58 years). We obtained a short medical history from all controls and patients by questionnaire. All control subjects were free of psychiatric illness. Patients and controls resided in nearly the same area in Iran. All participants provided written informed consent.

Genotyping

Three SNPs within the *PRODH* gene (1852G/A or rs385440, 757C/T or rs372055,

and 1766 A/G or rs450046) were genotyped in this study. All SNPs were selected based on previous studies suggesting a possible association between the SNP and schizophrenia or related traits. All genotyping was performed using polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) protocols. A total of 360 blood samples were collected (5-10 mL) in tubes containing ethylenediaminetetraacetic acid as an anticoagulant. Genomic DNA was extracted from white blood cells using the salting out method (individual protocol). The DNA from the remaining blood samples was extracted directly from fresh blood samples. DNA was analyzed using a Nanodrop spectrophotometer to determine the absorbance ratio of 260/280 nm. One pair of primers was designed to genotype each SNP using the Oligo 7 software (Molecular Biology Insights, Inc.; Cascade, CO, USA), and PCRs were conducted to amplify exons 1 and 13 and intron 13 of the *PRODH* gene. Genotypes were determined by RFLP with proper restriction enzymes. We genotyped 3 SNP markers, including 757C/T, 1766A/G, and 1852G/A, which are located in exon 1, exon 13, and intron 13 of the *PRODH* gene, respectively. PCR amplicons were digested with *NciI*, *NciI*, and *BsajI* restriction enzymes (Fermentas; Vilnius, Lithuania), respectively, and analyzed by 4% agarose gel electrophoresis. The primers used for PCR included: 5'-GCCCTGTATCCCTGCAC-3' (forward) and 5'-ACCTCCATCACGGGGCCA-3' (reverse) to amplify exon 1 (757C/T); 5'-GCCCTGTATCCCTGCAC-3' (forward) and 5'-ACCTCCATCACGGGGCCA-3' (reverse) to amplify intron 13 (1852G/A); and 5'-CCCATCCTCACCCACACC-3' (forward) and 5'-AGCCGATCTCTGCCGCAC-3' (reverse) to amplify exon 13 (1766A/G). All reactions were performed in a 20- μ L reaction volume containing 0.3 μ L smart tag polymerase (Fermentas), 0.5 μ L DNA template, 1 μ L of each primer pair (1 μ M), and 0.5 μ L dNTPs. The thermal cycling program for 757C/T (exon 1) consisted of activation of *Taq* DNA polymerase at 95°C for 5 min, 30 cycles at 95°C for 1 min and at 61°C for 1 min and at 72°C for 1.15 min, and final extension at 72°C for 7 min. The thermal cycling program for 1852G/A (intron 13) consisted of activation of *Taq* DNA polymerase at 94°C for 3 min, 15 cycles at 95°C for 30 s and 65°C for 45 s (decreasing at 1°C/cycle) and 72°C for 30 s, and 20 cycles at 94°C for 30 s, 50°C for 45 s, and 72°C for 30 s, and final extension at 72°C for 7 min. The thermal cycling program for 1766A/G (exon 13) consisted of activation *Taq* DNA polymerase at 94°C for 3 min and 10 cycles at 95°C for 30 s, 65°C for 1 min (decreasing at 1°C/cycle), 72°C for 30 s, and 20 cycles at 94°C for 30 s, 55°C for 1 min, 72°C for 30 s, and final extension at 72°C for 7 min. PCR amplicons were digested with *NciI*, *BsajI*, and *NciI*, for 757C/T, 1852G/A, and 1766A/G, respectively, for 4 h at 37°C. Next, the samples were run on 4% agarose gels containing ethidium bromide to separate the fragments according to size.

Statistical analysis

Hardy-Weinberg equilibrium was evaluated by the goodness-of-fit chi-squared (χ^2) test for the genotypic distributions of the SNPs studied. Allelic and haplotypic associations and quantitative trait analyses were executed using the SNP analyzer program. The P value was set at 0.05 for significance levels.

RESULTS

Single-marker analysis

Genotypic distributions of the 3 tested SNPs deviated from Hardy-Weinberg equilib-

rium in either the patient group or the control group. In this study, we investigated the relationship between 3 SNP markers in the *PRODH* gene and schizophrenia in an Iranian population.

757C/T SNP marker (rs372055)

The 757C>T polymorphism is located on exon 1, and this codon normally codes for Arg185 in *PRODH*; however, substitution of C>T in this position replaces Arg with Trp. These genotypes were determined using *NciI* restriction digestion. In individuals with the wild-type homozygote genotype (CC), there was 1 cut site that produced 2 bands of approximately 80 and 160 base pairs (bp) on agarose gels. In individuals with the heterozygote genotype (CT), 3 bands were observed on agarose gels at 80, 160, and 240 bp. In addition, in recessive homozygotes with the TT genotype, a strong band at 240 bp was observed (Figure 1a and b). Results of statistical analysis for this SNP marker are shown in Table 1.

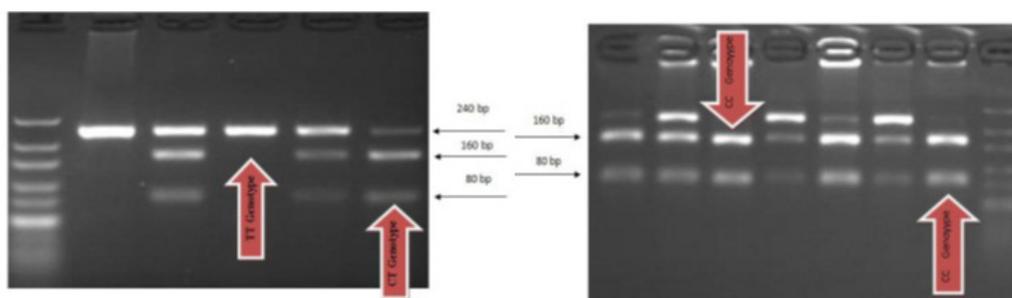


Figure 1. Digestion with *NciI* restriction enzyme. The CC genotype displayed 2 bands, at 80 and 160 bp. The CT genotype displayed 3 bands, at 80, 160, and 240 bp. The TT genotype showed a single 240-bp band.

Table 1. Prevalence of the *PRODH* 757C/T polymorphisms in controls and schizophrenic patients; odds ratios (OR) with 95% confidence intervals (95%CI) were determined to estimate the risk of schizophrenia.

Genotype 757C/T	Controls (N = 185)		Patient (N = 175)		OR	(95%CI)	P value
	Number	%	Number	%			
757CC	95	63.8	54	36.2	1.25	0.97-2.82	
757CT	71	43.6	92	6.4	1	0.90-1.75	0.001
757TT	19	39.6	29	60.4	1.15	0.88-2.16	0.001

Based on these data, there were 29 and 19 individuals with the TT genotype in the patient and control group, respectively, whereas 92 and 71 subjects had the CT genotype in the patient group and control group, respectively.

1852G/A SNP marker (rs385440)

The 1852G/A polymorphism is located on intron 13. These mutations usually have little effect on gene expression and relative protein function, but in some cases, the differences result in variation in mRNA splicing and expression. Genotypes were determined using *BsaI*

restriction digestion. In individuals with the wild-type homozygote genotype (GG), 3 cut sites produced 4 bands at approximately 32, 60, 115, and 165 bp on agarose gels. In individuals with the heterozygote genotype (GA), 5 bands were observed on agarose gels at 32, 60, 115, 165, and 210 bp. In addition, in recessive homozygotes with the AA genotype, 4 bands were observed at 32, 115 (2 bands overlapped), and 210 bp (Figure 2). The results of statistical analysis for this SNP marker are shown in Table 2.

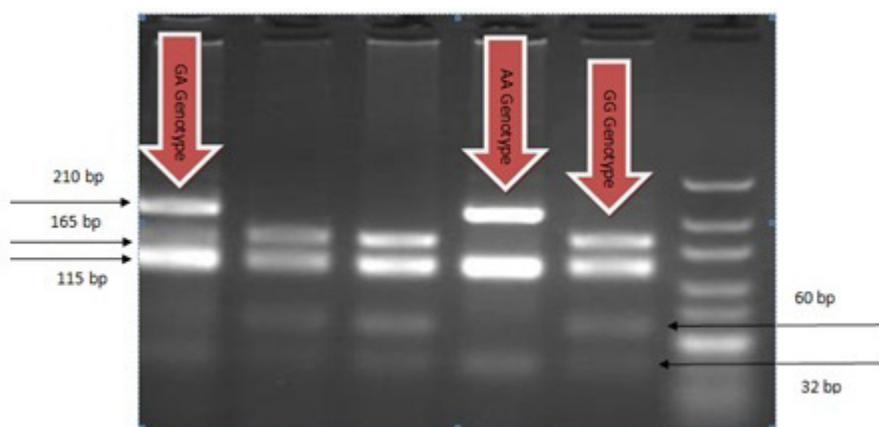


Figure 2. Digestion with *Bsa*I restriction enzyme. The GG genotype displayed 4 bands, at 32, 60, 115, and 165 bp. The GA genotype displayed 5 bands, at 32, 60, 115, 165, and 210 bp. The AA genotype showed 4 bands, at 32, 115 (2 bands overlapped), and 210 bp.

Table 2. Prevalence of the *PRODH* 1852G/A polymorphisms in controls and schizophrenic patients; odds ratios (OR) with 95% confidence intervals (95%CI) were determined to estimate schizophrenia risk.

Genotype 1852G/A	Controls (N = 185)		Patient (N = 175)		OR	(95%CI)	P value
	Number	%	Number	%			
1852GG	157	55.7	124	44.3	1	0.97-2.82	
1852GA	16	22.53	54	77.46	1.35	0.90-1.75	0.001
1852AA	1	13.3	7	85.7	1.65	0.88-2.16	0.000

Based on this data, there were 7 individuals with the AA genotype in the patient group but only 1 individual with this genotype in the control group. A total of 54 subjects had the GA genotype in the patient group while there were 16 subjects with the GA genotype in the control group.

1766A/G SNP marker (*rs450046*)

The 1766A/G polymorphism is located on exon 13 and typically encodes Gly521 in *PRODH*. A substitution of A>G in this position replaces Gly with Arg. Genotypes were determined using *Nci*I restriction digestion. In individuals with the wild-type homozygote genotype (AA), there were no cut sites, resulting only 1 band at approximately 300 bp (290 bp) on agarose gels. In individuals with the heterozygote genotype (AG), 3 bands were observed

on agarose gels at 100, 200, and 300 bp. Furthermore, in recessive homozygotes with the GG genotype, there was 1 cut site with 2 bands at 100 and 200 bp (Figure 3a and b). Statistical analysis results for this SNP marker are shown in Table 3.

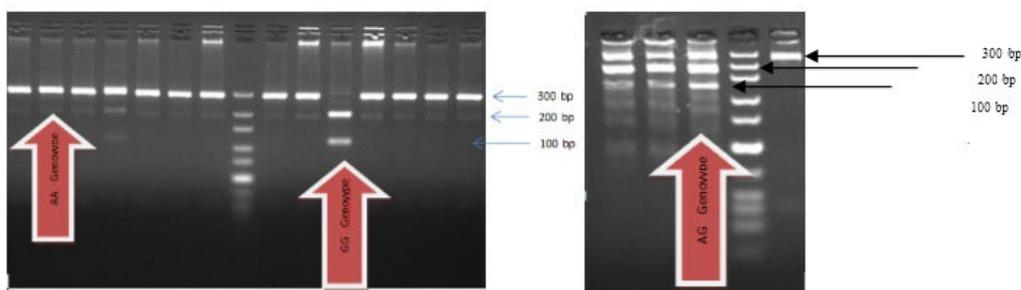


Figure 3. Digestion with *NciI* restriction enzyme. The AA genotype displayed 1 band at 300 bp. The AG genotype displayed 3 bands, at 100, 200, and 300 bp. The GG genotype showed 2 bands, at 100 and 200 bp.

Table 3. Prevalence of the *PRODH* 1766A/G polymorphisms in controls and schizophrenic patients; odds ratios (OR) with 95% confidence intervals (95%CI) were determined to estimate schizophrenia risk.

Genotype 1766A/G	Controls (N = 185)		Patient (N = 175)		OR	(95%CI)	P value
	Number	%	Number	%			
1766AA	174	56.3	135	43.6	1.65	0.97-2.82	
1766AG	10	22.2	35	77.0	1.15	0.90-1.75	0.002
1766GG	1	16.6	5	83.3	1	0.88-2.16	0.001

Based on these data, there were 5 individuals with the GG genotype in the patient group but there was only 1 individual with this genotype in the control group. There were 35 subjects with the AG genotype in the patient group, and 10 with AG in the control group.

Association between risk of schizophrenia and rs372055, rs385440, and rs450046 combinations in *PRODH*

Table 4 shows the frequencies of compound genotypes within the groups of controls and patients. According to the chi-squared test, there was a significant association between *PRODH* 757C/T, 1852G/A, and 1766A/G variants within the group of controls compared to patients. The activity alleles in the *PRODH* genotype combinations were associated with an increased risk of schizophrenia. Based on these data, the TAG and AG combinations were significantly related to schizophrenia in a comparison of the patient and control groups.

Different independent elements in relation to schizophrenia

In this study, we examined the relationships between specific genetic markers and schizophrenia. We also analyzed the effect of independent elements on this disorder and compared the control group and patient group, including season of birth, age, education, and gender.

Table 4. Haplotype distribution of the *PRODH* gene.

Haplotype	Frequency in the controls	Frequency in the patients	P value
TAG	0.159	0.410	0.007
TAA	0.305	0.334	0.125
TGG	0.072	0.099	0.08
CAG	0.105	0.256	0.009

Mutation alleles are marked in bold.

Season of birth

In the northern hemisphere, most schizophrenia patients were born in winter and early spring, whereas the number of schizophrenia patients born during this time of the year in the southern hemisphere was lower than that in the northern hemisphere. These differences likely resulted from the effect of the environment on the mother or growth of the embryos. Based on these data, we found that most patients in our populations were born in the winter and spring seasons and there was a significant difference between the control and patient groups (Table 5).

Table 5. Statistical comparison of seasons of birth between control and patient groups.

Birth group		Patient		Control		df	P value
		Number	(%)	Number	(%)		
Birth group	Winter + Spring	98	57.0	74	43.0	1	0.000
	Summer + Autumn	64	36.6	111	63.4	1	0.000
Total		162	46.7	185	53.3		

Contribution of age, education, and gender to schizotypal personality questionnaire (SPQ) score

To determine the potential contribution of education, age, and gender on the SPQ score, we executed a series of step-by-step linear regression analyses. The results of these analyses are presented in Table 6. Years of education showed significant inverse effects with total SPQ score and 3-factor scores. Gender was significantly related to odd or eccentric behavior and constricted effect subscales. Males showed higher scores on both subscales. Age had a significant inverse effect on the ideas of reference subscale only in that younger subjects had higher scores.

Table 6. Contribution of age, education, and gender to SPQ score.

Variables	Factors	Standardized beta	t	P	r ²	Proportion of attribution
Idea of reference	Age	-0.16	-3.44	0.001	0.025	0.025
Excessive social anxiety	Education	-0.22	-4.94	<0.001	0.05	0.05
Odd beliefs or magical thinking	-	-	-	-	-	-
Unusual perceptual experiences	Education	-0.16	-3.51	<0.001	0.025	0.026
Odd or eccentric behavior	Education	-0.13	-2.92	0.004	0.026	0.017
No close friends	Age	0.23	4.8	<0.001	0.098	0.078
Odd speech	Education	-0.16	-3.22	0.001	0.024	0.024
Constricted affect	Education	-0.16	-3.22	0.001	-	0.024
	Gender	-0.12	-2.78	0.006	-	0.015
Suspiciousness	Education	-0.22	-4.75	<0.001	0.047	0.047
Total score of SPQ	Education	-0.22	-4.75	<0.001	0.047	0.047

DISCUSSION

In the current study, we examined whether the *PRODH* gene is associated with schizophrenia by analyzing SNPs in this gene, including 757C/T (rs372055), 1852G/A (rs385440), and 1766A/G (rs450046). We found that education affected 7 of 9 schizotypal subscales, 3 schizotypal factors, and the total scores of the SPQ, which contributed to 1.3-8.6% of the overall variance in scores (Table 6). In addition, gender had small effects on 2 of the schizotypal subscales (odd or eccentric behavior and constricted affect). Age also had a small effect on the ideas of reference subscale, gender, and years of education, and may not be detected in studies with a small sample size, where they may present as confounding variables. For example, the effect of personal educational attainment on the results of the SPQ may be related to cognitive ability (Liu et al., 2002b; Ma et al., 2007); the latter has shown significant correlations with schizophrenia and SPQ scores (Harrison and Weinberger, 2004). Scores on the schizotypal subscales, factors, and total SPQ scores adjusted by relevant demographic characteristics may provide more stable and accurate quantitative phenotypic traits for molecular genetic studies.

The *PRODH* gene is located on chromosome 22q11.2, in an area highly susceptible to mutations and microdeletions that cause mental diseases, particularly schizophrenia (Liu et al., 2002a; Glaser et al., 2006; O'Tuathaigh et al., 2007). The results of these investigations in some populations indicated that they were related to the disease, while other populations showed no such relationships. We hypothesized that *PRODH* gene is an important gene that contributes to the occurrence of schizophrenia, which has been shown to play a role in susceptibility to schizophrenia in some populations, and may contribute to the occurrence of this disease in the Iranian population.

PRODH, which encodes proline oxidase (POX), has been associated with schizophrenia through linkage, association, and the 22q11 deletion syndrome (Velo-Cardio-Facial syndrome) (Clelland et al., 2011). We showed that functional polymorphisms in *PRODH* are linked to schizophrenia risk. We found a positive association between schizophrenia and previously identified SNPs (Liu et al., 2002a) that increased enzyme activity and a negative association between 3 polymorphisms that decreased POX activity. These 3 SNPs were analyzed because they capture most of the common allelic variation in this gene. Substitution in 757 C/T and 1852G/A reduce enzyme activity, whereas substitution in 1766A/G increases enzyme activity. The 757C/T and 1766A/G polymorphisms are missense mutations, whereas 1852G/A is a nonsense mutation and splicing mutation (Liu et al., 2002b; Gogos and Gerber, 2006; Vrijenhoek et al., 2008; Roussos et al., 2009). Altering mRNA splicing leads to reduced expression and function of the relative protein (POX1). In this study, we found that expression of any of these mutations alone led to disease occurrence in our population. Haplotype analysis showed that the TAG and AG combinations significantly affected schizophrenia occurrence in a comparison of patients and controls. This polymorphism has also been investigated in other populations. For example, a study in 2008 investigated 1766A/G in a European population. A total of 315 Hungarian subjects from 3-member families consisting of parents and a child patient were analyzed. The results showed that the frequency of the mutated allele has no significant association in subjects with the disease (Kempf Let al., 2008). Another polymorphism in this gene was investigated in a different population. The results showed that codon A1766G was located in exon 13 of this gene. In 2009, this codon, together with codons 1945 and 1852, were investigated in 217 subjects in Greece (Roussos et al., 2009). The haploid CGA for these

3 codons, compared to the control group, were related to susceptibility to schizophrenia. In a Chinese population, this codon was reported to be unrelated to schizophrenia. Codon C1482T in exon 11 was also reported to be a high risk factor for the occurrence of different mutations in this gene (Roussos et al., 2009). Our population study showed that the *PRODH* gene is an important candidate gene as related to schizophrenia in the Iranian population. However, additional studies including a larger population should be conducted to determine the effect of this gene on the Iranian population. *PRODH* was shown to be an important genetic factor in schizophrenia occurrence in some of the population, while other subjects showed a smaller effect. Greater understanding of the genetic factors influencing schizophrenia can help to rapidly identify patients and facilitate treatment. However, schizophrenia shows multi-genetic inheritance. Finally, our results may contribute to the construction of rapid molecular diagnostic kits and medications appropriate to the genetic background of individual patient, as is the long-term goal of this research group. We are also studying other mutations in this gene and several other effective genes, including *CLDN5* and *APOa1* (Rahman Zadeh et al., 2012; Heidari Keshel et al., 2013; Ghasemvand et al., 2013).

CONCLUSIONS

Three polymorphic regions were analyzed in the *PRODH* gene in a population of 360 individuals in Iran using an RFLP assay. We found that this gene is significantly related to the incidence of schizophrenia in the Iranian population.

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