**PRODH Polymorphisms, Cortical Volumes and Thickness in Schizophrenia**

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**Abstract**

Schizophrenia is a neurodevelopmental disorder with high heritability. Several lines of evidence indicate that the PRODH gene may be related to the disorder. Therefore, our study investigates the effects of 12 polymorphisms of PRODH on schizophrenia and its phenotypes. To further evaluate the roles of the associated variants in the disorder, we have conducted magnetic resonance imaging (MRI) scans to assess cortical volumes and thicknesses. A total of 192 patients were evaluated using the Structured Clinical Interview for DSM-IV (SCID), Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale, Global Assessment of Functioning (GAF) and Clinical Global Impression (CGI) instruments. The study included 179 controls paired by age and gender. The samples were genotyped using the real-time polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP)-PCR and Sanger sequencing methods. A sample of 138 patients and 34 healthy controls underwent MRI scans. One polymorphism was associated with schizophrenia (rs2904552), with the G-allele more frequent in patients than in controls. This polymorphism is likely functional, as predicted by PolyPhen and SIFT, but it was not associated with brain morphology in our study. In summary, we report a functional PRODH variant associated with schizophrenia that may have a neurochemical impact, altering brain function, but is not responsible for the cortical reductions found in the disorder.

**Introduction**

Schizophrenia is currently considered to be a neurodevelopmental disease that arises from a complex phase-specific interaction of genetic and environmental factors [1–3]. The prevalence of schizophrenia in the general population is estimated to be 0.3%–1.6% [4,5]. The high heritability (~64%–83%) of schizophrenia [6,7] may be due to a combination of multiple common alleles, each one with a small to moderate effect, and some rare alleles with much larger effect sizes [8].

One of the strongest known genetic risk factors for schizophrenia is the 22q11 deletion [9]. Up to one-third of patients with 22q11 deletion syndrome (22q11DS), also known as DiGeorge or velocardiofacial syndrome, develop schizophrenia or schizoaffective disorder [10]. Moreover, while the prevalence of the chromosome 22q11 deletion in the general population is one in 4000 individuals, its frequency is estimated to be approximately 1% in adult patients with schizophrenia [11–14]. Therefore, the 22q11DS deletion has been suggested as a genetic subtype of schizophrenia, and the genes located in this region might therefore contribute to susceptibility to the disease. One of the genes commonly deleted in 22q11DS is the proline dehydrogenase (PRODH) gene, which encodes the proline dehydrogenase enzyme that catalyzes the first step in proline catabolism [15]. The PRODH gene, consisting of 14 coding exons and located in a low copy repeat sequence, is widely expressed in the brain and in other tissues [16,17]. The resulting enzyme, also known as proline oxidase (POX), is a mitochondrial tumor suppressor [18] that inhibits proliferation and induces apoptosis [19]. High proline concentrations appear to activate NMDA and...
AMP-A receptors and may therefore act as a neuromodulator [20–22]. Proline is also a precursor of the neurotransmitter glutamate [23], which seems to be involved in schizophrenia pathophysiology. Moreover, whereas high levels of plasma proline are found on a relatively common basis in patients with 22q11DS [24,25], some evidence suggests that hyperprolinemia may lead to neurocognitive dysfunction in animal models [26,27] and may be involved in the cognitive and psychiatric features of 22q11DS [25].

Patients with 22q11.2 deletion syndrome present abnormalities in brain structure, such as a global brain volumetric reduction that includes several cortical regions, the cerebellum and the hippocampus [28]. Similarly, patients with schizophrenia consistently present brain volumetric reductions compared to healthy controls, specifically due to grey matter reductions of the anterior cingulate, frontal (particularly medial and inferior) and temporal lobes, hippocampus/amygda, thalamus, andinsula that may be magnified over time [29]. A widespread cortical thickness reduction has also been found in the frontal, parietal, temporal and occipital regions of patients with schizophrenia [30].

Only two previous studies have investigated the role of PRODH in brain volume. The first, employing a sample of 92 healthy controls, observed a decrease in the striatal grey matter volumes of carriers of the functional risk haplotype, which contains the PRODH polymorphisms in both normal and pathological conditions. In the second study, employing a sample of 51 patients with schizophrenia (Negative, Positive, Disorganization, Excited and Anxiety/Depression) were classified according to the PANSS ratings [35]. Treatment-resistant (TR) status was defined, in accordance with the International Psychopathological Criteria (IPAP) [www.ipap.org], as a failure to respond to 4- to 6-week trials of monotherapy with two different antipsychotics at adequate doses (equivalent to 5 mg of risperidone or 400 mg of chlorpromazine). A 1.5 Mb microdeletion in 22q11.2 was detected in one patient with schizophrenia using multiplex ligation-dependent probe amplification [11]. Therefore, this subject was excluded from the analyses, as this deletion could be a confounding genotype factor. A total of 179 healthy subjects with no family history of severe psychiatric illness were recruited by UNIFESP. These subjects were also investigated using a modified version of SCID screening to exclude any with a previous illness episode with psychotic features or a family history of similar diseases. Considering that the Brazilian population is admixed, the population structure was verified for a sample of our study population (Table 1).

DNA Isolation and Population Structure Analysis

Whole blood was collected into EDTA tubes and genomic DNA isolation was performed using the Gentra Puregene Kit (Qiagen, Maryland, USA) according to the manufacturer’s protocol. The population genetic ancestry structure was assessed by a panel of 48 ancestry-informative insertion-deletion polymorphisms, previously described and validated in the Brazilian population [36], analyzed in three multiplex PCR assays followed by capillary electrophoresis.

PRODH Genotyping

A total of 12 PRODH SNPs were interrogated (Figure 1) by real-time polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP)-PCR and sequencing techniques, as this deletion could be a confounding genotype factor. For real-time PCR, three SNPs (rs4819756 in exon 5, rs450046 in exon 14 and rs372055 in exon 15) were genotyped using commercially available predesigned TaqMan® probes and primers (Applied Biosystems, Foster City, USA), as described by the manufacturer. One polymorphism (L289M in exon 8) was investigated by the RFLP-PCR technique using the BsaI enzyme and the following PCR primers: 5'-TGGTGGGGAGGAGGAGGTCA-3' (forward) and 5'-CAGCCAGGACTGGGAGACGCT-3' (reverse). The other eight SNPs in exon 12 (rs1693466, rs2238731, rs2904552, rs2904551, rs3970539, rs2238730, rs2870984 and rs2870983) were investigated using Sanger sequencing. The PCR primers were as follows: 5'-TCCCCACTGCATTTGGTCCTC-3' (forward) and 5'-CCTGGCCCTGAGACAGAG-3' (reverse). The PCR conditions are available upon request.

Genetic Analysis

The characteristics of the study population are described in Table 1. First, the Hardy-Weinberg equilibrium was verified for all
SNPs using the chi-square test. Logistic regression was then performed to associate each genotype with the diagnosis of schizophrenia, using age as a covariate. The Bonferroni correction for multiple comparisons was performed. The linkage disequilibrium and haplotypes were assessed using Haploview [37]. The associations between the haplotypes and the disease were investigated using the chi-square test.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 15.0), and the level of significance was set at 0.05.

In silico Analysis

For the SNPs associated with schizophrenia, we tested the predictive values using SIFT (http://sift.jcvi.org/) and PolyPhen (http://genetics.bwh.harvard.edu/pph/) and analyzed the amino acid conservation using the UCSC genome browser (http://genome.ucsc.edu). Both SIFT and PolyPhen predict whether an amino acid substitution affects protein function. SIFT prediction is based on the degree of conservation of amino acid residues in sequence alignments [38], while PolyPhen uses straightforward physical and comparative considerations [39].

| Variables | SCZ patients | Controls | p-values |
|-----------|--------------|----------|----------|
| Gender | N | Frequency/values | N | Frequency/values | 0.375 |
| Male | 131 | 68.2% | 114 | 63.7% |
| Female | 61 | 31.8% | 65 | 36.3% |
| Age (years) | 192 | 35.68±10.38 | 178 | 38.29±12.88 | 0.033 |
| Ancestry | | | | | |
| European | 164 | 0.67±0.22 | 137 | 0.69±0.19 | 0.278 |
| African | 164 | 0.18±0.17 | 137 | 0.17±0.16 | 0.454 |
| Native-American | 164 | 0.15±0.14 | 137 | 0.14±0.11 | 0.426 |
| Age at onset | 176 | 23.32±7.24 |
| Treatment response | 145 | | | |
| TR | 71 | 50.3% |
| NTR | 70 | 49.7% |
| GAF | 144 | 50.00±13.29 |
| CGI | 144 | 3.84±1.07 |
| PANSS - Negative symptoms | 144 | 25.24±8.04 |
| PANSS – Positive symptoms | 143 | 16.88±5.98 |
| PANSS - Excited | 143 | 7.31±2.51 |
| PANSS – Anxiety/depression | 144 | 9.21±3.23 |
| Calgary | 144 | 2.79±3.87 |

TR: Treatment resistant; NTR: Non-treatment resistant; GAF: Global Assessment of Functioning; CGI: Clinical Global Impression; PANSS: Positive and Negative Syndrome Scale; N: sample size; SCZ: schizophrenia.

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Figure 1. Diagram of the PRODH gene, representing the variants investigated in this study and their locations.

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Weinberg equilibrium and with a minor allele frequency.

was found (adjusted p-values = 0.024; OR = 2.77; 95%CI
(grouping GA and AA genotype carriers), a stronger association
5.03). Comparing the GG homozygotes to the A-allele carriers
 carriers (adjusted p-value = 0.048, OR = 2.61, 95%CI = 1.36–
found that the GG-genotype carriers were at greater risk for a

Comparing the genotypes of rs2904552, we
were included (rs16983466, rs2238731, rs2904552, rs2870983 and

determined using G*Power 3.1.6.

Association between PRODH Variants and Schizophrenia

The genotype and allele frequencies for each variant are
represented in Table S1. The genotype distributions did not
deviate from those predicted by the Hardy-Weinberg equilibrium
in both the case and control groups (p = 0.965). Controls carrying the GA genotype had an increased
pars opercularis volume (p = 0.00020; effect size = 0.081; power
= 0.965). Controls carrying the GA genotype had an increased
volume (6261.50 ± 2733.26 mm³) in this region compared to
carriers of the GG genotype (4193.37 ± 733.26 mm³).
However, in schizophrenia patients, GA genotype carriers had a smaller
volume (3796.68 ± 527.12 mm³) than did GG carriers
(3993.41 ± 733.26 mm³).

Discussion

In this study, one PRODH variant (rs2904552 or R431H) and its
haplotypes were associated with schizophrenia, with the GG
genotype present at a higher frequency among patients than
among healthy controls. To further understand the role of this
SNP, we investigated its role in brain volumes and cortical
thicknesses.

PRODH Polymorphisms and Schizophrenia

Among the 12 investigated SNPs, 10 had been previously
associated with schizophrenia (rs372055, rs450046), hyperprolinemia
(1,289M, rs2870983, rs4819756, rs2904552, rs2870984) and
both (rs2904551, rs2238731, rs3970559); two SNPs had not been
previously investigated (rs16983466, rs2238731).

Different lines of evidence suggest an important role for PRODH
in schizophrenia: 1) it is located at 22q11.2, the deletion of which
is one of the strongest genetic risk factors for schizophrenia; 2) PRODH
deletion/misense mutations have been described in
patients with schizophrenia [41,42]; 3) an association between
schizoaffective disorders and moderate hyperprolinemia was
previously been detected [43]; 4) it is widely expressed in the

Imaging Acquisition

Brain MRIs were obtained from 138 subjects with schizophrenia
(93 men, age = 35.21 ± 10.21; 45 women, age = 39.27 ± 11.24) and
34 healthy controls (23 men, age = 32.43 ± 7.33; 11 women,
age = 38.72 ± 15.78) using a 1.5T scanner (Magnetom Sonata
(Maestro Class) Siemens AG, Medical Solutions, Erlangen,
Germany) with an eight-channel head coil. A series of exploratory
sagittal images (nine to eleven slices of 5 mm with 1 mm spacing)
was performed to evaluate the image quality and the positioning of
the head of each subject. T1 images were acquired sequentially
using a pulse sequence (SPGR) with the following parameters: TR
= 2000 ms, TE = 3.42 ms, matrix size = 256 x 256, FOV
= 245 mm, flip angle = 15 degrees, NEX = 1, 1.0 mm slice
thickness with no gaps, yielding 192 slices.

Imaging Preprocessing – FreeSurfer

The MRI scans were analyzed using the FreeSurfer software
package (version 5.0 http://surfer.nmr.mgh.harvard.edu) based
on established processing steps (recon-all pipeline). The cortical
volumes and thickness of information of the brain regions were
estimated using the automated parcellation of the Desikan-
Killiany Atlas [40] and exported to SPSS for further analysis.

Imaging Group Analysis

First, a general linear model (GLM) was used to assess the
association of each cortical and subcortical volume and thickness
with schizophrenia. Then, all measures were inserted as dependent
variables, and each SNP, schizophrenia diagnosis and the interaction between them were included as
fixed factors. The total intracranial volume (TIV), gender and age were included as covariates. Statistical significance was set a priori at a two-tailed alpha of 0.05.

Results

Association between PRODH Variants and Schizophrenia

The genotype and allele frequencies for each variant are
represented in Table S1. The genotype distributions did not
deviate from those predicted by the Hardy-Weinberg equilibrium
in both the case and control groups (p = 0.05) for all variants,
except for rs4819756 (controls: χ² = 4.38, df = 1, p = 0.036; cases:
χ² = 9.70, df = 1, p = 0.002) and rs450046 (cases: χ² = 4.20, df
= 1, p = 0.040).

Regarding allele comparisons, one polymorphism was associated
with schizophrenia [rs2904552 (G-allele): p = 0.002, OR
= 2.65, 95%CI = 1.45–4.86] after Bonferroni correction (adjusted
p-value = 0.024). Comparing the genotypes of rs2904552, we
found that the GG-genotype carriers were at greater risk for a
schizophrenia diagnosis in comparison to the AG-genotype
carriers (adjusted p-value = 0.048, OR = 2.61, 95%CI = 1.36–
5.03). Comparing the GG homozygotes to the A-allele carriers
grouping GA and AA genotype carriers), a stronger association
was found (adjusted p-values = 0.024; OR = 2.77; 95%CI
= 1.45–5.30). In all these analyses, the power was >80% as
determined using G*Power 3.1.6.

For the haplotype analyses, only polymorphisms in Hardy-
Weinberg equilibrium with a minor allele frequency >5% were included (rs16983466, rs2238731, rs2904552, rs2870983 and
rs372055). The results of the linkage disequilibrium test are described in Figure S1. One haplotype block composed of three
variants, and five composed of two variants, were analyzed (Table S2).
Concerning the haplotype composed by three variants, a significant association was detected between the A/G/C haplotype (rs2904552/rs2238731/rs16983466) and schizophrenia (p
= 0.001). Analyzing the combinations of two variants, only those
haplotypes constructed with rs2904552 SNP remained significant
(p < 0.05 – Table S2).

Association between PRODH Variants and Schizophrenia Phenotypes

We analyzed the association of age at onset, TR, GAF, CGI,
Calgary, Negative, Positive, Disorganized, Excited and Anxiety/
Depression clusters with each PRODH polymorphism, but no
significant associations were detected.

In silico Analysis

To predict the likely pathogenicity of rs2904552, we conducted an
in silico analysis. This SNP seems to have a functional role, as it
was classified as “probably damaging,” with a score of 0.996, using
PolyPhen and as “damaging,” with a score of 0.04, using SIFT.
Data were also available for five orthologous species (three
mammals, one frog and one fish), and the residues showed
functional origin and evolutionary conservation in all these organisms. Furthermore, this
method was reported in a previous study to decrease the enzyme
activity [41].

Association between MRI and Schizophrenia

For the cortical and subcortical volumes, 21 regions were
associated with schizophrenia after Bonferroni correction and are
described in Table S3. In terms of cortical thickness, seven regions
differed between the cases and controls (Table S4).

Association between PRODH Variants and MRI

In the comparison of all PRODH genotypes with all brain
volumes and cortical thicknesses, only one association remained
significant after Bonferroni correction: the interaction between
rs2238731 (V427M) and schizophrenia was associated with right
pars opercularis volume (p = 0.00020; effect size = 0.081; power
= 0.965). Controls carrying the GA genotype had an increased
volume (6261.50 ± 144.95 mm³) in this region compared to
carriers of the GG genotype (4193.37 ± 628.09 mm³).
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previously been detected [43]; 4) it is widely expressed in the
brain; 5) mice with PRODH deficiency show elevated plasma and brain proline levels, locally decreased glutamate and γ-aminobutyric acid (GABA) levels and a deficit in sensorimotor gating [17,44]; 6) the PRODH enzyme is rate limiting in the conversion of proline to glutamate [41], which is important for signal transduction between neurons and for synaptic plasticity [45] and seems to be deregulated in schizophrenia [46].

Indeed, a recent metabolomics study reported abnormalities related to proline metabolism in schizophrenia [47]. Furthermore, Savio et al. [2012] reported that long-term exposure to proline induced behavioral changes in adult zebrafish that were reversed by the acute administration of atypical antipsychotics [48]. In this vein, several studies have investigated peripheral proline levels as a risk factor for schizophrenia (reporting no association) [49,50] or the positive associations between hyperprolinemia and schizophrenia [43] and schizophrenia in women [51]. Despite these mixed findings, the data still support a functional role for PRODH variants and hyperprolinemia in the pathophysiology of schizophrenia [31].

Along with its role in proline catabolism, PRODH is also known as a key enzyme in controlling homeostasis, providing energy and shuttling redox potential between cellular compartments and the production of reactive oxygen species [52].

PRODH rs2904552 is a nonsynonymous mutation that causes the substitution of an arginine for a histidine in codon 431. This change seems to promote a functional effect, according to our in silico findings, and also results in a moderate decrease (30–70%) of PRODH enzyme activity [41]. Also, another study has detected this polymorphism in combination with L441P in a subject with a vein, several studies have investigated peripheral proline levels as a risk factor for schizophrenia (reporting no association) [49,50] or the positive associations between hyperprolinemia and schizophrenia [43] and schizophrenia in women [51]. Despite these mixed findings, the data still support a functional role for PRODH variants and hyperprolinemia in the pathophysiology of schizophrenia [31].

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**Conclusions**

This study represents the first report of the effects of PRODH polymorphisms on brain morphology in both patients and healthy controls, testing for the interaction between this SNP and a diagnosis of schizophrenia. Only one SNP (rs2238731) seemed to be significantly associated with right pars opercularis volume, but this finding should be confirmed in larger samples. Therefore, considering the functional effect of rs2904552 and the importance of proline levels in schizophrenia, this SNP may act by altering neurochemistry and is not responsible for the deficits in brain structure found in schizophrenia.

In summary, this study indicates that the PRODH rs2904552 polymorphism may be a genetic risk factor for developing schizophrenia, and further studies should address how disturbance of the proline pathway could affect brain function.

**Supporting Information**

Figure S1 Linkage disequilibrium plot across the proline dehydrogenase (PRODH) gene. Numbers within the diamonds are D’ values for the respective SNP pairs. (TIF)

Table S1 Genotype and allele frequencies of PRODH variants. (DOCX)

Table S2 Haplotype frequencies of PRODH variants in patient and control group. (DOCX)

Table S3 Association between cortical and subcortical volumes and schizophrenia. (DOCX)

Table S4 Association between cortical thickness and schizophrenia. (DOCX)

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**Author Contributions**

Conceived and designed the experiments: SIB AG RAB APJ FTB DMC MIM JJM MAS. Performed the experiments: AG CN VKO FTB MLS. Analyzed the data: JRS IBA APJ SIB AG VKO. Contributed reagents/materials/analysis tools: AKR SS MIM MAS. Wrote the paper: VKO FTB AG DMC JJM MIM MAS RAB APJ JRS SIB.
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