



## Original Article

# Association of the Polymorphism of GSTP1 with the Susceptibility to the Development of Schizophrenia

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## ABSTRACT

Schizophrenia is a complex mental illness characterized by the presence of symptoms such as hallucinations, delusions, catatonic behavior, cognitive impairment among others. Although the studies exceed 100 years, it is one of the mental illnesses less understood. Oxidative stress has been investigated as one of the potential stimulant factors in the development of schizophrenia. For the study of these relationships, the research focuses on polymorphisms of antioxidant enzymes, such as glutathione S-transferase (GST), an important phase II detoxification enzyme. In this context, the aim of the study is to associate the GSTP1 gene polymorphism with the susceptibility to the development of schizophrenia through a case-control study. The knowledge of the genetic predisposition comes as a support for the understanding of schizophrenia, allowing later the establishment of markers of susceptibility to the disease, which when identified will allow the taking of preventive measures and better targeting of the treatment. Methods: For the analysis of the polymorphisms using the PCR-RFLP technique, the samples collected at the Brain Institute Clinic were divided into two groups, case and control, for later study of the heterozygous genotypes (Ile/Val), wild homozygote (Ile/Ile) and mutant homozygote (Val/Val). Results: There was no statistically significant correlation between GSTP1 polymorphism and the risk of developing schizophrenia. Conclusions: In this sense, more studies should be carried out in search of more consistent results, thus allowing a more accurate correlation regarding the role of this polymorphism with the susceptibility to schizophrenia.

## 1. Introduction

Mental disorders are among the seven major causes of disability and are indicated as 90% of the causes of suicide among young people, therefore, represent a serious health problem among the world's adult population (Gustavson et al., 2018; Zatti et al., 2015). There are different mental disorders, characterized by divergent presentations with significant impacts on health (World Health Organization-WHO, 2018). In Brazil, available data are often outdated for psychiatric specialties. (SUS), but the Department of Informatics of the Unified Health System (DATASUS) reports that, in 2017, 152,172 psychiatric hospitalizations were performed, of which 12,097 were registered in the Central-West region (Brasil, 2016). Among the most prominent disorders are

depression, alcohol use disorders, bipolar disorder, and schizophrenia (World Health Organization-WHO, 2018).

Schizophrenia is a disabling mental disorder that stands out due to the high prevalence rate, besides the high economic cost generated in the treatment of these patients (Daltio et al., 2007). This severe psychotic disorder affects about 1% of the world population and is characterized by the presence of symptoms called psychotic, or positive (hallucinations, delusions and disturbances of thoughts and movements), negative symptoms (affective insensitivity, speech loss and anhedonia) and cognitive impairment. These symptoms appear gradually and usually the disease is pronounced between the ages of 20 and 30 years. But there are cases where the disease can begin in adolescence, from the age of 16 (Frangou, 2008). Schizophrenia affects both men and

women, however, sexual differences are indicated as an important aspect of the disease. The incidence of schizophrenia in men is approximately 1.5 times higher than in women. In addition, men have worse pre-morbid adjustment and have negative and less depressive symptoms worse than women. The specific endocrine effects of sex on the disease and the response to antipsychotics are potentially complex and the role of estrogen is not yet clear (Kim; Kim; Jeong, 2017).

The pathophysiology of schizophrenia in recent years has been the focus of several studies in search of greater clarification. Although the causes that lead to the appearance of its characteristic symptoms are not completely known, it is believed that chemical imbalances of neurotransmitters, for example, dopamine, serotonin and glutamate, are important factors (Frangou, 2008). The operational diagnostic criteria for the disorder described require the presence of at least two of the central symptoms over a period of six months, and such symptom must remain active for at least one month (Singh et al., 2017). The treatment is basically focused on the symptoms, in order to generate a decrease in their frequency and severity, as well as decrease the mortality rate and improve the quality of life of the patient. Treatments include administration of antipsychotic medications in the long term and psychosocial therapies. They usually start early in the acute phase when positive symptoms are exposed and the diagnosis of the disease can be made more accurately (Frangou, 2008).

However, administration of medications can cause side effects and are responsible for the appearance of a series of risk factors (weight gain, dyslipidemia, hyperglycemia, hypercholesterolemia and hypertriglyceridemia) that may contribute to the development of metabolic syndrome (Nandra; Agius, 2012; Teixeira; Rocha, 2006). These metabolic changes result in a greater chance of cardiovascular events in these patients, giving them a lower life expectancy (Saruwatari et al., 2013). The side effects caused by these drugs and the need for long-term treatment to reach a satisfactory efficacy, generate a low adhesion to the treatment by the patients (Elkis; Meltzer, 2007).

In addition, study reveal that about 20% to 40% of patients do not respond satisfactorily to conventional antipsychotic treatment, even when given in large doses, and, in this case, the patient may present with refractory schizophrenia (Melnik et al., 2010). The clozapine has become the "gold standard" of the treatment, however, the daily and prolonged exposure of the body to this drug, or other xenobiotics, can trigger a series of harmful biological responses, toxicity, mutagenicity, among others (Elkis; Meltzer, 2007).

According to OS and Marcelis (1998), schizophrenia is a multifactorial disease and may be associated with environmental (prenatal and perinatal complications, drug use, life events) and genetic factors (Van OS; Marcelis, 1998). Studies show that the chances of developing the disease are much higher in individuals who have first-degree relatives with schizophrenia, reaching about 10% of these individuals and 50% in cases of identical twins (Cardno; Gottesman, 2000; Castellani et al., 2017). Studies of broad genomic association identified more than 100 loci related to the susceptibility of the individual to the disease, among them the genes CNTN4, GATAD2A, GPM6A, MMP16, PSMA4, TCF4, ZNF804A, DRD4 (Xu, Wu, Zhang, Wang & Yao, 2018; Kuswanto et al., 2012; Ma et al., 2018). Among these, the genes encoding enzymes of the Glutathione S-transferase family (GSTs) (Pavarino et al., 2013). Studies have shown that GST levels of cerebrospinal fluid have been decreased in patients with schizophrenia, suggesting that GSTs may play a significant role in the

development and progression of schizophrenia (Kim et al., 2015).

GST is a Phase II detoxifying enzyme that plays a key role in cell proliferation and death, DNA synthesis and repair, regulation of protein synthesis, prostaglandin synthesis, amino acid transport, regulation of immune functions, and catalyzes the reaction of conjugation between reduced glutathione (GSH) to oxidizing agents and a variety of xenobiotics, hydrophobic and electrophilic, facilitating their excretion and protecting the cell against oxidative stress and other damages (Pavarino et al., 2013). GSTs form a multigenic superfamily where cytosolic and mitochondrial enzymes are divided into classes. The classes of cytosolic GSTs known in mammals currently are: alpha, mu, pi, sigma, zeta, omega and theta, and the known mitochondrial GST is kappa (McIlwain; Townsend; Tew, 2006). Each of these enzymes differs in their amino acid sequence and hence in their functionality (Pavarino et al., 2013).

The GST family presents several polymorphisms known in humans that affect its activity and expression, among which, the most studied polymorphisms are the total deletion polymorphisms of the GSTT1, GSTM1 isoenzyme genes and the Single Nucleotide Polymorphism (SNP) polymorphism in the isoenzyme GSTP1, resulting in the absence or decrease of the enzymatic activity of these isoforms (Gravina et al., 2011; Kim et al., 2014). GSTP1 (glutathione S-transferase pi 1) is an important enzyme involved in the inactivation of carcinogenic substances in the cellular defense system (Kim et al., 2014). GSTP1 is highly expressed in normal human epithelial tissues, being abundant mainly in the lung, esophagus and placenta. In addition, studies indicate that there is overexpression of this enzyme in several tumor lesions (Song; Wang; Hu, 2014). The GSTP1 gene, located on the long arm of chromosome 11 at position 11q13, has 7 exons and a total of 10,059 base pairs and the enzyme encoded by it has a sequence of 210 amino acids (Kim et al., 2014).

SNPs of the GSTP1 gene have been cited as risk factors for the development of various diseases such as squamous cell carcinoma of the larynx, lung diseases associated with cigarette smoking such as lung cancer, type 2 Diabetes mellitus, various types of cancerous diseases among others (Harries et al., 1997; Mastana et al., 2013; Song; Wang; Hu, 2014). Polymorphisms in genes encoding GSTs cause a reduction in the activity of these enzymes. This decreases the ability of cellular detoxification and, consequently, favors the increase of reactive oxygen species (ROS) in the body. Patients with schizophrenia who undergo antipsychotic treatment naturally present high concentrations of ROS, due to the metabolism of the drug. Polymorphism in genes encoding GSTs in patients with schizophrenia may result in potentiation of damage to the patient. In this sense, studies involving polymorphisms in the genes encoding GSTs isoforms become interesting for the correlation with schizophrenia (Kim et al., 2015).

Some studies correlating the GSTP1 polymorphism with have been described to be involved in T2DM development, diabetes-related complications, lymphocytic leukemia, lymphoblastic leukemia and end stage renal disease (Guven et al., 2015; Nomani et al., 2016; Pinheiro et al., 2013; Saadat Mostafa, 2017; Yuille et al., 2002). To date there is no association between the GSTP1 polymorphism and schizophrenia. Therefore, the objective of the present study is to verify if there is an association of the abovementioned polymorphism with the susceptibility to schizophrenia in the population of Central Brazil.

## 2. Material and methods

### 2.1. Obtaining samples

This study was carried out with 87 individuals (convenience sample), aged between 18 and 65 years, divided into two groups: case and control. The case group was formed by patients attended at the Instituto do Cérebro, Brazil, diagnosed with refractory schizophrenia. All selected patients were being treated with clozapine for at least one year to ensure diagnosis. The control group consisted of healthy individuals with no history of drug abuse and psychiatric or psychotic disorder, including schizophrenia, bipolar disorder and major depression. Samples (1mL of peripheral blood in a vacuum tube containing EDTA) were collected at the time of consultation. The samples were centrifuged and the leukocyte ring was stored in cryotubes at -20°C and then subjected to DNA extraction. Participants from both groups signed a commitment and clarification term for participation in the study (Annex I), there was no withdrawal of participation. In order to carry out the present project, the favorable opinion of the Institutional Ethics Committee (n° 039/13, of February 25, 2013) was obtained.

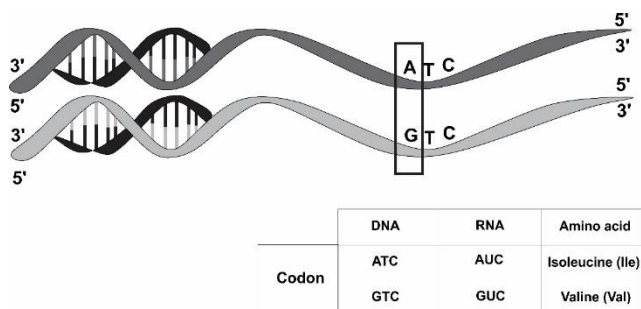
### 2.2. DNA Extraction and Quantification

Extraction and purification of the samples obtained were performed with the commercial extract Kit Illustra Genomic Prep Mini Spin (GE Healthcare®, USA) according to the extraction protocol suggested by the manufacturer. Samples were labeled and stored at -20°C. Samples were quantified in the Epoch spectrophotometer (Biotek®) and after 30 days were submitted to polymerase chain reaction (PCR) amplification.

### 2.3. Analysis of the SNP Ile105Val polymorphism of GSTP1 by PCR-RFLP

The samples were subjected to the conventional Polymerase Chain Reaction (PCR) Polymerase Chain Reaction - Restriction-Fragment-Length-Polymorphism-(PCR-RFLP). The primers used and PCR conditions were based on the model previously suggested by Harries et al. (1997) with adaptations. Initial denaturation was 94°C for 5 minutes, followed by 35 cycles with the following amplification conditions: denaturation at 94°C for 30 seconds; annealing at 55°C for 30 seconds and elongation at 72°C for 30 seconds. The final elongation was performed at 72°C for 5 minutes with final maintenance at 4°C. To confirm the amplification of the initial fragment containing 176 bp the PCR products were analyzed on agarose gel (3.0%) and stained in solution with Ethidium Bromide.

The SNP studied in the present work presents an A-to-G exchange in codon 105 that results in the exchange of the encoded amino acid, passing from isoleucine to valine (Figure 1).



**Figure 1:** Exchange of bases in the genetic sequence of the GSTP1 gene resulting in the amino acid exchange in the final protein (Adapted Kim et al., 2014; Gravina et al., 2011).

Thus, for genotyping of the GSTP1 gene alleles the products obtained in the conventional PCR were submitted to the enzyme restriction with the use of Alw-26I enzyme, following the manufacturer's protocol (ThermoScientific®). The enzymatic restriction followed for 16 hours at 37°C, 20 minutes at 65°C and maintenance of the samples at 4°C (hold). The digested of the fragments were visualized on polyacrylamide gel (12%) using a 25-bp ladder, stained with silver nitrate solution (2g/L). After enzymatic restriction the genotypes were determined according to each polymorphism specified in Table 1.

**Table 1:** Classification of genotypes according to fragment size obtained

Genotypes	Fragments
Heterozygous (Ile / val)	176 bp
Wild Homozygous (Ile / Ile)	176, 91, 85 bp
Homozygous Mutant (Val / Val)	91 e 85 bp

Ile: Isoleucine Amino acid; Val: Valine Amino acid; bp: base pairs

### 2.4 Statistical Analysis

The evaluation of the balance between the genotypic proportions and the genetic frequencies was made from the Hardy-Weinberg Equilibrium Test performed through the Arlequin software (version 3.5.1.2). Statistical analyzes were performed using the BioEstat® software (version 5.3) to compare the genotype frequencies between the case and control groups. The chi-square test ( $\chi^2$ ) was used. Finally, to assess the risk of a particular genotype and the susceptibility to the development of schizophrenia in relation to the control group, the Odds Ratio was calculated, with a 95% confidence interval. The value of  $p < 0.05$  was considered statistically significant.

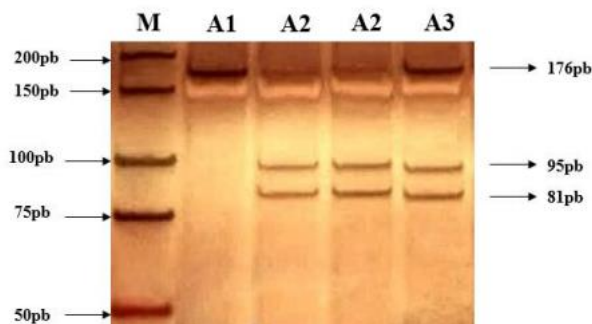
### 3.1. Results

#### 3.1.1. Characteristics demographics

The main characteristics demographics, clinical and laboratory parameters were evaluated in this study in a total of 87 individuals (case=27 and control=60). Regarding the distribution by gender, age, clozapine dosage, alcohol consumption and smoking there was no significant difference, indicating homogeneity between the groups.

#### 3.1.2. PCR-RFLP reading on polyacrylamide gel

The band combinations observed after RFLP show bands of 176 bp, 91 bp and 85 bp (Figure 2).



**Figure 2.** Polyacrylamide gel stained in silver nitrate solution. Representation of the evaluated bands PCR-RFLP, being the molecular marker of 25bp, only 176bp band, A2 individuals presenting bands of 95pb and 81pb and A3 heterozygotes presenting as three bands 176pb, 95pb and 81pb. bp: base pairs.

**Table 2-** Main characteristics demographics of case and control groups

Variables	case (n=27)	control (n=60)	p-value
<b>Gender, n (%)</b>			
Male	17 (62.96)	37 (61.67)	0.91
Female	10 (37.04)	23 (38.33)	
<b>Ager, years</b>			
Average, SD	38.67 (±09.90)	39.03 (±8.06)	0.82
<b>Clozapine dosage (mg/d)</b>	537.04 (± 157.27)	-----	-----
<b>Alcohol Consumption n (%)</b>			
Positive	6 (22.22)	20 (33.33)	0.29
Negative	21 (77.78)	40 (66.67)	
<b>Smoking Habits n (%)</b>			
Positive	7 (25.93)	25 (41.67)	0.16
Negative	20 (74.07)	35 (58.33)	

Data are reported as absolute (n) and relative frequency (%); Statistical Analysis by Student's T-Test or Chi-Square. Level of significance (p <0.05).

### 3.1.3. Genotypic distribution and association of GSTP1 polymorphism with schizophrenia

A total of 87 individuals (27 cases and 60 controls) were genotyped for the SNP polymorphism of the GSTP1 gene. In the patients in the case group the percentage of wild, heterozygous and mutant individuals was 40.7%, 48.1% and 11.1% respectively. For the control group, the percentage of wild, heterozygous and mutant individuals was 31.6%, 61.6% and 6.66%, respectively (Table 2). According to the  $\chi^2$  test there is no statistically significant difference between the genotypic proportions observed in the case and control groups, since, the value of p > 0.05.

**Table 3:** Genotypic proportions of the case and control n (%) - Number (percentage); P: genotype frequency;  $\chi^2$  - chi-square; GL - degree of freedom; p-value 0.05

Genotype	Case n (%)	Control n (%)	P	$\chi^2$	GL	p-value
Wild	11 (40,7)	19 (31,6)	0,344	1,494	2	0,4738
Heterozygous	13 (48,1)	37 (61,6)	0,574			
Mutant	3 (11,1)	4 (6,66)	0,08			
Total	27 (100)	60 (100)	1			

n (%) - Number (percentage); P: genotype frequency;  $\chi^2$  - chi-square; GL - degree of freedom; p-value 0.05.

The values obtained by the Hardy-Weinberg Equilibrium Test suggest that the genotypic distribution of GSTP1 polymorphism in the control group is not in equilibrium (Table 4).

The results of the verification between the presence of the Ile/Val and Val/Val genotypes, considered as risk genotypes, with the risk of developing the disease by the Odds Ratio, being considered the wild genotype (Ile/Ile) as without risk (Table 5).

**Table 4:** Hardy-Weinberg Equilibrium Test, expected (HE) and observed (HO) heterozygosity values and p-value for the case group.

Group	Case		p-value	Control		p-value
	Ho	HE		Ho	HE	
Wild	11 (40,7)	11.34 (42.00)	0.7725	19 (31,6)	23.44 (39.07)	0.0145
Heterozygous	13 (48,1)	12.32 (45.63)		37 (61,6)	28.13 (46.89)	
Mutant	3 (11,1)	3.34 (12.37)		4 (6,66)	8.44 (14.06)	
Total	27 (100)	27 (100)		60 (100)		
allele wild	0.65	$\chi^2$ : 0.0836		allele wild	0.63	$\chi^2$ : 5.97
allele mutant	0.35	DF:1		allele mutant	0.37	DF:1

HE - Expected heterozygosity; HO - Observed heterozygosity;  $\chi^2$ : Chi Square Test; DF: Degree of freedom; p-value <0.05

**Table 5:** Odds Ratio (OR) values and their respective confidence intervals and p-values for each genotype according to the number of individuals with or without risk genotype for the GSTP1 polymorphism in the case and control groups

Genotype	Case		Control		OR	IC 95%	p-value
	GR	GNR	GR	GNR			
Ile/Ile	-----	11	-----	19	Ref	-----	-----
Ile/Val	13	11	37	19	0,60	(0,22-1,60)	0,4497
Val/Val	3	11	4	19	1,29	(0,2436-6,88)	0,8976
Ile/Val + Val/Val	16	11	41	19	0,67	(0,2631-1,72)	0,5619

GR - Risk genotype; GNR - Genotype not considered risk; OR - Odds Ratio; CI - Confidence interval; p-value <0.05.

#### 4. Discussion

The proportion of individuals with wild genotype (40.7%), heterozygous (48.1%) and mutant (11.1%) in the case group differs from the proportion reported by Rossini et al. (2002) for the Brazilian population, 49.7%, 38.1% and 12.2%, respectively. In the control group the proportion found for wild genotype was apparently lower than that found in case control studies conducted in other countries such as Korea and Japan (Matsuzawa et al., 2009; Pae et al., 2003). In the case of the proportion of heterozygotes, the value found (61.6%) is apparently higher than those found in the studies that range from 25% to 30% (Matsuzawa et al., 2009; Pae et al., 2003). This difference in the proportions of individuals for a given genotype may be due to the ethnic difference between the populations compared. But in order to reach a conclusion, other studies with a larger number of participants are needed. The fact is that the profile identified in the Brazilian population was already expected, given the heterogeneity of the population.

The genotypic distribution in the control group is not in Hardy-Weinberg equilibrium, given similar to that of the study performed in the Iranian population (Safarinejad et al., 2011). When a set of samples is in Hardy-Weinberg Equilibrium it means that the expected heterozygosity, i.e. proportion of heterozygous individuals, is the same, or close, of the observed heterozygosity. To statistically validate this difference is given the value of  $p$  that when  $<0.05$  is considered significant. When the Hardy-Weinberg hypotheses are not satisfied and the samples are not in equilibrium, this condition may indicate consanguinity, population stratification, genotyping problems, or may have been due to the small number of samples (Wigginton; Cutler; Abecasis, 2005). By the  $\chi^2$  test the differences observed between the case and control group were not statistically significant ( $p > 0.4738$ ), which is a distribution of corrections of similar age to what was expected, in the case of group and control.

Analysis of the association between the three different genotypes and the risk of developing schizophrenia showed a higher risk in mutant homozygous individuals (OR = 1.29; 95% CI: 0.24-6.88). However, this result was not statistically significant since the value of  $p > 0.05$ . Therefore, similar to the study by Gravina et al. (2011) found no significant association between GSTP1 polymorphism and schizophrenia.

Association of GSTP1 polymorphism with schizophrenia was found when combined with the genes GSTM1 and GSTT1 in a case-control study of the Iranian population (Safarinejad et al., 2011). According to Watson et al. (1998), heterozygous and mutant individuals have a significantly lower activity than wild individuals, which emphasizes the possibility of increased risk of schizophrenia in mutant individuals (Watson et al., 1998).

Val/Val genotype of GSTP1 has already been correlated as a risk factor for several diseases such as lung cancer and diabetes (Harries et al., 1997; Mastana et al., 2013; Song; Wang; Hu, 2014). Mastana et al. (2013) indicated the said mutant genotype as a factor to increase the risk of developing Type 2 Diabetes Mellitus. According to Kim et al. (2014) GSTP1 polymorphism is considered a protective factor in the advancement of pelvic organ prolapses. In the study by Safarinejad et al (2011) the Ile105Val SNP is related as a risk factor for prostate cancer. The results obtained in the study require more analysis, with more samples, in order to obtain more reliable and accurate results. In addition, parameters such as sex, age, exposure to risk factors, and other variables that may act as confounding factors in disease susceptibility should be considered.

Although a known part of the role of GSTs in the metabolism of important antipsychotics used in the treatment of schizophrenia it should be emphasized that the relationship between the GSTP1 polymorphism and schizophrenia is not well known. In this sense, more studies should be carried out in search of more consistent results, thus allowing the exact correlation of the role of this polymorphism with schizophrenia, aiming at better treatment outcomes, reducing side effects, and providing data for later studies, such as development of new medicines.

With regard to the limitations of this study, we can point to the possibility of individuals who develop schizophrenia. Another limitation is the relatively small sample size case group.

#### 5. Conclusion

In the present study there was no statistically significant difference in the risk of developing schizophrenia for individuals with GSTP1 polymorphisms. However, additional studies are required with a larger number of participants (case and control).

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