

The CYP2C19*2 and CYP2C19*17 Polymorphisms Influence Responses to Clozapine for the Treatment of Schizophrenia

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Introduction: Clozapine (CLZ) is the gold standard drug for treatment-refractory schizophrenia (TRS). However, approximately 30% of patients partially respond to CLZ, defining this subset with super refractory schizophrenia (SRS). Alterations in enzyme activity may affect CLZ responses; the CYP3A4, CYP1A2 and CYP2C19 genes are primarily responsible for CLZ metabolism.

Objective: The aim of this study was to assess if CYP2C19 variants were associated with TRS or SRS.

Methods: CYP2C19*2 loss-of-function and CYP2C19*17 gain-of-function polymorphism genotype testing were performed in 108 individuals undergoing pharmacological treatment for TRS or SRS. DNA was extracted and polymorphisms were analyzed by polymerase chain reaction (PCR) and sequencing.

Results: CYP2C19*17 had positive correlations with SRS and lower Brief Psychiatric Rating Scale (BPRS) scores for TRS. In addition, CYP2C19*2 was associated with lower CLZ dosages for TRS.

Conclusion: These results show that CYP2C19*2 and CYP2C19*17 polymorphisms influence CLZ responses during schizophrenia treatment.

Keywords: schizophrenia, CYP2C19*2, CYP2C19*17, treatment response, clozapine

Introduction

Schizophrenia is a chronic and severe psychiatric disorder that exhibits variability in response to many antipsychotic drugs. Although pharmacotherapy can be used to treat this disorder, approximately one-third to one half of patients are unresponsive to current treatments, and are therefore deemed to exhibit treatment-refractory-schizophrenia (TRS).^{1,2}

Refractoriness is defined as the lack of satisfactory clinical response to treatments with at least two antipsychotic drugs, of the first or second generation, given at therapeutic doses and for at least six weeks during treatment.³ When refractoriness occurs, CLZ is the drug of choice for treatment.⁴⁻⁶ Nevertheless, approximately 30% of TRS patients do not fully respond to CLZ as a monotherapy, meaning these patients are as known as CLZ non-responders or super-refractory schizophrenics (SRS).⁷⁻⁹ For this condition, treatments are combined with CLZ and other antipsychotics, antidepressants or mood stabilizers.^{10,11}

Factors such as ethnicity, co-medication, age, gender, diet, as well as genetic variability to cellular receptors and drug metabolism, have been shown to affect CLZ

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responses.^{12–14} With regards to TRS and SRS genetic components, variability in cytochrome P450 (CYP) enzyme activities have been described as significant in influencing CLZ bioavailability.^{15–17} CYP3A4 and CYP1A2 are primarily responsible for the formation of N-desmethylclozapine,^{18,19} with CYP2C19 playing a role and CYP2C9 and 2D6 playing more modest roles.²⁰ In light of these functions, our group previously observed *CYP1A2*1F* polymorphism associations with SRS,⁹ thereby shedding some light on the relevance of CYP-genetic polymorphisms in CLZ responses. Although involvement of the *CYP1A2*1F* polymorphism in response to CLZ treatment has been shown, there are little data evaluating associations between CYP2C19 polymorphisms and TRS or SRS.

Thirty-five polymorphic variants have been identified in the CYP2C19 gene (<https://www.pharmgkb.org/page/cyp2c19>), of which three are clinically relevant (CYP2C19*2, *3 and *17); CYP2C19*3 is significantly frequent in Asian populations.¹⁶ CYP2C19*2 (c.681G>A, rs4244285) is an allelic variant that encodes for a non-functional protein^{21–23} and CYP2C19*17 (–806C>T, rs12248560) affects promoter responsiveness, increasing CYP2C19 expression.^{13,23–25} Phenotypically, CYP2C19*2 and CYP2C19*17 variants are associated with poor metabolizers (PM) and ultra-rapid metabolizers (UM), respectively, while extensive metabolizers (EM) are homozygous for the wild-type allele, *1.²⁵ Subjects with *2/*2 genotype are PM, those heterozygous for *1/*2 or *2/*17 are intermediate metabolizers (IM), and *1/*17 and *17/*17 are UM.^{21,23,25}

We recently identified a relationship between the *CYP1A2*1F* polymorphism and CLZ therapeutic outcomes;⁹ however, there is a dearth of research investigating associations of CYP2C19 polymorphisms with refractoriness to CLZ responses. Therefore, this study sought to evaluate pharmacogenetic associations of CYP2C19*2 and CYP2C19*17 polymorphisms with TRS and SRS.

Materials and Methods

Subjects

One hundred and eight schizophrenia patients (108) from Goiás state, Brazil, were included. Inpatients and outpatients were recruited from the Brain Institute – Bueno Medical Centre or the Distribution Centre of High-Cost Drugs of the Secretary of Health. For allele and genotype frequency comparisons, 137 healthy individuals (control group; both sexes, 28 ± 11 years old) were also included in the study. All selected individuals were classified as

pardos, according to classifications used by the Brazilian Institute of Geography and Statistics (IBGE).²⁶ Pardos consider themselves as a mixture of native Brazilian, European, West African and/or South Asian.

Schizophrenia diagnosis was defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Psychopathological and clinical data were acquired by interviews with patients or accessing their medical records. All participants provided informed written consent, and all study protocol were approved by the research ethics committee from the Federal University of Goiás and Goiás State Secretary of Health (protocols 1,483734 and 1,537538, respectively), in accordance with the World Medical Association Declaration of Helsinki.

Only individuals receiving CLZ for at least six months were included in the study. Patients were classified as TRS (n = 63) or SRS (n = 45) following criteria described by Kane et al (1988)⁴ and de Brito et al (2015).⁹ Characteristics of the study population are shown (Table 1).

For the 45 SRS patients for whom another drug was added, 52% received a second-generation antipsychotic, with risperidone being the most frequent (30%), followed by quetiapine (11%), olanzapine (3.7%), aripiprazole (3.7%), and ziprasidone (3.7%). 48% received a first-generation agent. Five patients received lamotrigine in combination with CLZ and other antipsychotics. None of the CLZ-associated drugs were metabolized primarily by 2C19 enzyme.

Genotyping

Genomic DNA was obtained from whole-blood using the PureLink™ Genomic DNA Mini Kit (Invitrogen™, Carlsbad, CA, USA). We then used PCR to amplify the regions of interest. Reactions consisted of 50 µL final volume, containing PCR buffer 10X, 2 mM MgCl₂, 0.1 mM dNTPs, 100 ng genomic DNA, 1 U Taq DNA polymerase (Invitrogen™) and 0.5 µM of each oligonucleotide. *CYP2C19*2* was amplified using the following primers; Forward; 5'-CAACCAGAGC TTGGCATATTGTATC-3' and Reverse; 5'-GCCCTTAGCA CCAAATTCTC-3'; and *CYP2C19*17* was amplified using the following primers; Forward; 5'-TAAAGTCCCGAGG GTTGTTG-3' and Reverse 5'-ATTTAACCCCTAAAA AAACG-3'. Cycling conditions for the *2 allele were 40 cycles at 95°C/45 s; 56°C/30 s; and 72°C/30 s. Cycling conditions for the *17 polymorphism were 35 cycles at 94°C/30 s; 52°C/30 s; and 72°C/30 s. PCR products were electrophoresed in a 1% agarose gel and excised fragments were purified using the GFX™ PCR DNA and Gel Band Purification Kit

Table 1 Characteristics of Patients

Characteristics	TRS (n=63)		SRS (n=45)		Significance Level P
	n	%	n	%	
Age (mean ± SD, years)	40 ± 11		39 ± 9		0.16
BMI (mean ± SD)	28.4 ± 5.3		27.7 ± 5.5		0.77
Clozapine Dosage (mg/day) (mean ± SD)	425.8 ± 159.4		593.3 ± 119.5		<0.0001
BPRS (mean ± SD)	35 ± 18		49 ± 13		<0.0001
Gender					
Male	43	68.2	25	55.5	0.22
Female	20	31.8	20	44.5	
Smoking Status					
Smoking	19	30.1	16	35.5	0.67
Non-smoking	44	69.9	29	64.5	
Coffee Status					
Coffee drinkers	51	89.9	31	68.9	0.17
Non-coffee drinkers	12	19.1	14	31.1	

Notes: Age, BMI, clozapine dosage and BPRS: unpaired test “t”. Sex, Smoking and coffee drinkers status: Fisher’s exact test. P<0.05 significance level.

(GE Healthcare, Chicago, Illinois, USA), followed by sequencing on an ABI3500 Genetic Analyzer (Applied Biosystems, Foster City, California, USA) using BigDye Terminator Mix v. 3.1 chemistry (Applied Biosystems).

Statistical Analyses

Statistical analyses were performed using GraphPad Prism (version 6.0, GraphPad Prism Software Inc., San Diego, CA, USA), and $P < 0.05$ was the threshold for statistical significance. Allelic and genotypic frequencies, sex, smoking and coffee status were assessed using the chi-square or Fisher’s exact tests. Age, BMI (body mass index), CLZ dosage and BPRS scores were analyzed using “t” tests or ANOVA for two or more groups, respectively. Genotype frequencies were obtained by direct count, and Hardy–Weinberg Equilibrium (HWE) was calculated using the χ^2 goodness-of-fit statistic. Differences in allele and genotype frequencies were evaluated using the χ^2 test (and Fisher’s exact). Haplotype frequency estimations (analysis of multiple genotype associations of A (CYP2C19*2) and T (CYP2C19*17) polymorphisms) and associations between polymorphisms and TRS, SRS or schizophrenia risk were evaluated using multivariate logistic regression analyses, using three models (co-dominant, dominant and recessive) on SNPStats software.²⁷ Additionally, we assessed if BPRS or different oral CLZ dosages were independently associated with each single nucleotide polymorphism (SNP) (*2 or *17) in TRS or SRS, adjusting for potential confounding effects and dichotomising patients

using observed global median of BPRS scores (<38 or ≥ 38) and CLZ doses (<400 or ≥ 400 mg/kg) as reference. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated.

Results

Demographic data showed significantly higher BPRS scores and CLZ dosages in the SRS group when compared with the TRS group. Factors such as age, gender, smoking, and coffee drinking were not significantly different between SRS and TRS groups (Table 1). The genotype distribution in the study sample did not deviate from HWE ($P = 0.54$ for TRS, and $P = 0.06$ for SRS). The distributions of alleles and genotypes showed a significantly increased frequency of CYP2C19*17 in the SRS group when compared with the control ($P = 0.007$ and $P = 0.0002$, respectively) and TRS ($P = 0.028$ and $P = 0.003$, respectively) groups (Table 2). The CYP2C19*2 allele showed a similar frequency between SRS, TRS and control groups (Table 3). Genotype frequencies showed that the heterozygous genotype, CYP2C19*1/*17 was significantly associated with SRS, when compared with the control (OR = 4.24, 95% CI, 2.08–8.65; $P < 0.0001$) and the TRS group (OR = 4.20, 95% CI, 1.86–9.47; $P < 0.00001$). Haplotype estimations revealed a significant association of GT with SRS (OR = 2.85, 95% CI, 1.32–6.18; $P < 0.0091$). The presence of *2 and *17 polymorphisms in the same individual (CYP2C19*2/*17) meant these individuals were classified as intermediate metabolizers.^{21,23,25} Frequencies of

Table 2 Allelic and Genotype Frequencies of CYP2C19*17 in Control (Healthy Individuals), TRS and SRS Individuals. Statistical Analysis Values (χ^2 , P-value), Found for Frequencies Comparisons Between Three Groups, are Presented Too

		Control n (%)	TRS n (%)	SRS n (%)	Control X TRS (χ^2 ; P-value)	Control X SRS (χ^2 , P-value)	TRS X SRS (χ^2 , P-value)
Allele frequencies	C	228 (83)	105 (83)	61 (68)	(0.0009; 0.975)	(9.865; 0.007)	(7.141; 0.028)
	T	46 (17)	21 (17)	29 (32)			
Genotype frequencies	C/C	96 (70)	44 (70)	16 (36)	(0.036; 0.982)	(22.02; 0.0002)	(15.63; 0.003)
	C/T	36 (26)	17 (27)	29 (64)			
	T/T	5 (4)	2 (3)	NA			

Notes: Allele and genotypes frequencies analyzed by chi-square test. P<0.05 significance level.

Abbreviations: NA, not available; C, Cytosine Nucleotide; T, Thymine Nucleotide.

Table 3 Allelic and Genotype Frequencies of CYP2C19*2 in Control (Healthy Individuals), TRS and SRS Individuals. Statistical Analysis Values (χ^2 , P-value), Found for Frequencies Comparisons Between Three Groups, are Presented Too

		Control n (%)	TRS n (%)	SRS n (%)	Control X TRS (χ^2 , P-value)	Control X SRS (χ^2 , P-value)	TRS X SRS (χ^2 , P-value)
Allele frequencies	G	242 (88)	108 (86)	85 (94)	(0.5363; 0.464)	(2.782; 0.2489)	(4.206; 0.1221)
	A	32 (12)	18 (14)	5 (6)			
Genotype frequencies	G/G	109 (80)	45 (71)	40 (89)	(4.721; 0.094)	(2.546; 0.636)	NA
	G/A	24 (18)	18 (29)	5 (11)			
	A/A	4 (3)	NA	NA			

Notes: Allele and genotypes frequencies analyzed by chi-square test. P<0.05 significance level.

Abbreviations: NA, not available; G, Guanine Nucleotide; A, Adenine Nucleotide.

CYP2C19*2/*17 were similar for the TRS (5%), SRS (9%) and control group (6%) ($P > 0.05$).

We asked if each SNP was associated with BPRS scores and oral CLZ doses in TRS or SRS independently of each other, and found that the lowest oral CLZ dose (<400 mg/day) in the TRS group was associated with the CYP2C19*2 allele (OR = 0.29, 95% CI, 0.09–0.90; $P < 0.031$). However, the CYP2C19*17 allele showed a significant association with lower BPRS scores (<38) in the TRS group (OR = 0.13, 95% CI, 0.03–0.61; $P < 0.0025$). In the SRS group, oral CLZ doses did not show associations with SNPs; however, the lowest BPRS scores (<38) revealed a significant association with the CYP2C19*2 allele (OR = 0.12, 95% CI, 0.02–0.86; $P < 0.034$).

Discussion

Pharmacogenetic studies investigate genetic sources of inter-individual variation that can impact on clinical outcomes.^{1,25,27} Previous reports have highlighted the clinic influence of CYP2C19 polymorphisms in therapeutic responses to proton pump inhibitors, anti-platelet and anti-depressant drugs, as well as associations with breast cancer risk.^{28–32} In terms of antipsychotic responses, specifically

for CLZ treatments, a previous study found no differences in the distribution of the CYP2C19*17 polymorphism between TRS and SRS patients and healthy controls.³³ Interestingly, a more recent study suggested that CYP2C19*17 is protective against the development of diabetes during CLZ treatment, and increases the likelihood of improving schizophrenia.³⁴ Our findings revealed an association between CYP2C19*17 and SRS, suggesting this allele is related to therapeutic response impairments for CLZ treatment.

A previous study found that 74% of SRS patients possessed a gain-of-function polymorphism from CYP1A2 (CYP1A2*1F).⁹ Similar to CYP2C19*17, CYP1A2*1F is a variant that encodes increased enzymatic activity.^{21,35} In this work, we detected the CYP2C19*17 polymorphism in 64% of patients from our SRS subgroup, of which 55.5% had the UM genotype (*1/*17). These two enzymes contribute more than 50% to in vitro CLZ biotransformation²⁰ which may explain the findings of major frequencies of the two polymorphic variants in patients with incomplete response to CLZ – SRS.

As expected, CLZ doses were higher in SRS patients, when compared with TRS patients. Interestingly, those

TRS patients carrying the CYP2C19*2 allele had lower average CLZ doses, suggesting that these doses, in carriers of this polymorphism, are adequate to maintain tissue levels for an effective therapeutic response. In contrast to our data, Piatkov et al (2017)³⁴ observed that carriers of CYP2C19*17 required lower average CLZ doses, which was associated with better clinical responses. However, these authors did not evaluate the CYP2C19*2 allele, nor the association of CYP2C19*17 with SRS. On the other hand, we observed that TRS patients carrying the CYP2C19*17 variant generated lower BPRS scores which may be associated with better clinical responses, corroborating elements from Piatkov et al (2017).³⁴

Van de Bilt et al (2015)³³ evaluated if refractory patients would have ended up in this condition because they would be UM and the hypothesis was not confirmed, because the CYP2C19*17 was equally distributed between refractory and non-refractory patients. Our study showed that this polymorphism was more frequent in SRS patients; however, this observation is not related to disease risk, since CYP2C19*17 is equally distributed between refractory patients and healthy controls. Finally, we observed a CYP2C19*2 allele association with lower BPRS scores in the SRS group, suggesting protective effects in these patients. This interesting finding will require more studies to delineate this association.

Our study had some limitations; we did not have access to CLZ and norclozapine metabolite plasma levels measures, and we did not determine CYP2C19 expression or levels in patient samples.

Conclusions

Our results indicate that the CYP2C19*17 allele is associated with SRS, whereas the CYP2C19*2 allele is associated with better clinical responses to CLZ in TRS patients. These findings should be validated and replicated in larger scale studies assessing CLZ plasma levels measurements, before any clinical implications should be considered.

Disclosure

The authors report no conflicts of interest in this work.

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