

REGULAR RESEARCH ARTICLE

Polymorphisms in Schizophrenia-Related Genes Are Potential Predictors of Antipsychotic Treatment Resistance and Refractoriness

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Abstract

Background: Approximately 30% of individuals with schizophrenia (SZ) are resistant to conventional antipsychotic drug therapy (AP). Of these, one-third are also resistant to the second-line treatment, clozapine. Treatment resistance and refractoriness are associated with increased morbidity and disability, making timely detection of these issues critical. Variability in treatment responsiveness is partly genetic, but research has yet to identify variants suitable for personalizing antipsychotic prescriptions.

Methods: We evaluated potential associations between response to AP and candidate gene variants previously linked to SZ or treatment response. Two groups of patients with SZ were evaluated: one receiving clozapine (n = 135) and the other receiving another second-generation AP (n = 61). Single-nucleotide polymorphisms (SNPs) in the genes *OXT*, *OXTR*, *CNR1*, *DDC*, and *DRD2* were analyzed.

Results: Several SNPs were associated with response vs. resistance to AP or clozapine.

Conclusions: This is the first study of its kind, to our knowledge, in our admixed Chilean population to address the complete treatment response spectrum. We identified SNPs predictive of treatment-resistant SZ in the genes *OXT*, *CNR1*, *DDC*, and *DRD2*.

Keywords: Schizophrenia, antipsychotics, clozapine, treatment resistance, treatment refractoriness

Received: August 15, 2021; Revised: March 11, 2022; Accepted: March 30, 2022

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Significance Statement

In this manuscript, we present comparisons between individuals who respond to usual treatment, those who fail to respond to the usual treatment but do respond to clozapine, and those who are also resistant to clozapine. Thus, we encompass the full spectrum of possible treatment outcomes in our analysis. Our study is based on 196 patients with schizophrenia (and 80 healthy controls) and, therefore, contributes to enrich the genetic database for schizophrenia pharmacogenetics with individuals of Hispanic descent, which so far are almost entirely absent in them.

Introduction

Schizophrenia (SZ) is a common chronic disorder that significantly contributes to disability-adjusted life years worldwide. SZ symptoms can be grouped into 3 domains: positive (e.g., delusions and hallucinations), negative (e.g., blunted affect and apathy), and cognitive (e.g., impairments in memory and executive functions) (Kahn et al., 2015). Antipsychotic drug therapy (AP) is the first-line treatment in both acute SZ and maintenance. The main mechanism of action of such drugs is to block postsynaptic D2 dopamine receptors (DRD2) (Zhang & Malhotra, 2011). AP provides significant symptom relief for most patients, but approximately 30% of cases are resistant to treatment. Treatment-resistant SZ (TRS) is defined as persistent, clinically significant psychotic symptoms after 2 courses of AP at an adequate dose and duration (Andreasen et al., 2005).

TRS correlates with lower quality of life; elevated treatment expenses; higher rates of smoking, alcohol, and drug abuse; and greater risk of suicidal ideation. To manage TRS, clinicians may increase dosage, offer a different medication, or use a combination of AP and/or other drugs. In many patients, the most effective alternative is clozapine (Kane et al., 2019). This atypical AP is characterized by its high selectivity for the mesolimbic system, with a preference for DRD2 and DRD4 over DRD1, and a weak partial binding to DRD2 in the nigrostriatal pathway. Clozapine can increase dopamine (DA) metabolism in the prefrontal cortex and decrease DA activity in the nucleus accumbens, thus relieving both negative and positive symptoms. Clozapine is effective in an estimated 30%–60% of patients who failed to respond to other drugs (Schennach et al., 2012). Patients with TRS who show persistent symptoms after using clozapine (i.e., clozapine treatment resistant) can be considered refractory to treatment (Schennach et al., 2012). These patients may be viewed as a separate category within the SZ population, given the specific therapeutic challenges and presumably unique neurobiological underpinnings of this type of resistance. Clinically, it is vital to identify individuals likely to show any degree of resistance to AP as quickly as possible, because early detection allows for timely adjustments to treatment, avoiding complications and side effects from ineffective drugs. Clozapine-dedicated services for managing complex cases have shown long-term benefits. Because a significant proportion of patients are resistant to clozapine as well as typical AP, identifying novel treatments for this subgroup is a priority.

Genetic Factors in Treatment Resistance

Poor compliance, drug abuse, psychosocial stress, early age of onset, and duration of untreated illness are associated with treatment resistance (Nucifora et al., 2019). The role of genetic factors in TRS has been also established by several studies (Buckley and Gaughran, 2014). Strikingly, however, a recent review that gathered data from 92 studies with a total of approximately 9600 patients included only 19 individuals of Hispanic ancestry (Yoshida and Müller, 2019). This gap underscores the

need to adjust internationally developed tools to the local genetic makeup and to update genetic databases with regional information (Yoshida and Müller, 2019). Furthermore, genetic variants that can be used to tailor AP prescriptions have yet to be identified. In this study, therefore, we evaluated potential associations between response to AP and variations in candidate genes previously linked to SZ and/or treatment response. We studied the following single-nucleotide polymorphisms (SNPs): rs1799978 (A-241G) in the DRD2 gene, which codes for the dopamine 2 receptor, the target of AP; rs11238133, rs6951648, rs10499696, and rs921451 in DDC, which codes for l-3,4-dihydroxyphenylalanine (DOPA) decarboxylase, the protein that catalyzes conversion of L-DOPA to DA (Zhang and Malhotra, 2011); rs806368, rs1049353, rs806379, and rs806380 in CNR1, which codes for the CB1 endocannabinoid receptor (Ujike et al., 2002); rs877172, rs2740210, and rs2710204 in OXT, which codes for oxytocin; and rs2254298, rs53576, and rs2228485 in OXTR, which encodes the oxytocin receptor (Haram et al., 2016). We previously studied the rs2228145 polymorphism in a sample of TRS patients with and without improvement after receiving clozapine for at least 3 months. We found no differences in genotype or allele frequency between patients who remitted with clozapine and those with persistent symptoms. Furthermore, we found no difference in the median interleukin-6 plasma level by genotype (Cavieres et al., 2019). For the present study, we compared the full spectrum of treatment responses, from responsive to refractory. We aimed to identify whether these variants could be useful in predicting 2 outcomes: AP responsiveness vs. resistance; and, for AP-resistant individuals, clozapine responsiveness vs. resistance (i.e., “treatment refractoriness”).

METHODS

Study Sample and Clinical Evaluations

For purposes of avoiding genetic stratification, only individuals of Chilean descent were included in the study. Based on their income and occupation, all individuals belonged either to the C2, C3, D, or E socioeconomic stratum. The average Amerindian ancestry estimates for these strata range from 44.81% to 51.61% (Barozet et al., 2021)

Healthy Controls.— Controls were 80 healthy individuals aged 18–55 years with no history of mental disorders according to MINI interview results (Sheehan et al., 1998). Controls were recruited independently from patients. Volunteers were invited from consultants to other clinical departments in the same university hospital where the SZ patients were recruited. Having a personal history of mental disorders or a first-degree relative with a mental disorder was an exclusion criterion.

Patients.— We studied 2 groups of patients; 1 group with established TRS and 1 receiving standard treatment with a second-generation AP (SGAP). All patients were evaluated using either the 18-item Brief Psychiatric Rating Scale (BPRS) or the Positive and

Negative Syndrome Scale (Kay et al., 1987). The BPRS is a widely used, brief, standardized interview validated in Latin American countries. When BPRS scores were not available, we derived them from the Positive and Negative Syndrome Scale score using the conversion rule suggested by Leucht et al. (Brenner et al., 1990).

1. The TRS group consisted of 135 patients from the outpatient unit of Psychiatric Hospital del Salvador in Valparaiso, central region of Chile. Inclusion criteria were age <60 years, diagnosed with SZ according to DSM-IV criteria, having failed at least 2 adequate trials of AP including at least 1 atypical AP drug, and currently receiving at least 300 mg of clozapine for at least 6 months. Exclusion criteria were use of any AP other than clozapine; clozapine dose <300 mg; and any diagnosis of mood disorder, intellectual disability, substance abuse disorder, anxiety disorder, dissociative disorder, somatoform disorder, eating disorder, or personality disorder. Clozapine response status was classified as “remitted” (i.e., responsive to clozapine), defined as a mild or lower score on BPRS items 4, 7, 8, 11, 12, 15, and 16; or “refractory” (i.e., clozapine-treatment resistant), defined as a global score ≥ 45 on the 18-item BPRS or a score ≥ 4 on 2 or more psychotic symptoms, according to the criteria proposed by (Andreasen et al., 2005; Hasan et al., 2012). Those with intermediate scores were excluded from this analysis.
2. The SGAP group consisted of 61 individuals recruited from the main psychiatric centers in the northwestern area of Santiago.

The study was approved by the local institutional review boards, and all individuals included in this study provided written informed consent.

Figure 1 illustrates the study design. Comparisons were performed between the SGAP and TRS groups and between the clozapine-responders and refractory individuals.

Procedures

DNA was extracted from whole blood for genotyping using the NucleoSpin Blood L kit (Macherey-Nagel) and stored at -80°C until analysis. Quantification and purity analyses were performed in a microplate spectrophotometer (Epoch BioTek Instruments, Inc.). Genotyping was carried out using allelic discrimination by quantitative polymerase chain reaction (qPCR), using predesigned TaqMan assays (ThermoFischer). The PCRs were performed following manufacturer’s instructions in an Aria Mix Real-time PCR System (Agilent Technologies).

Statistical Analysis

Descriptive statistics were performed using R software (Ihaka and Gentleman, 1996). Normality was evaluated using a Shapiro-Wilks test. BPRS scores were compared using a Wilcoxon test. Hardy-Weinberg equilibrium for markers with 5 or more observations in each genotype was evaluated using a χ^2 test. For analyses that did not meet the condition (≤ 5), Fisher’s exact test was used.

Comparison of SGAP and TRS Groups.—Allele and genotype frequencies were compared using either a χ^2 or Fisher’s test. Multivariate logistic regression was performed for the subset of 58 AP and 83 TRS patients with extreme BPRS scores. The outcome was response status, and the independent variables were age, gender, and health care system affiliation (which in Chile can be used as a proxy for income). Therefore, this variable could provide information regarding sample stratification. Risk was expressed as an odds ratio (OR). In all statistical analyses, the false discovery rate was applied to correct P values (Benjamini and Hochberg, 1995).

Association Between Variants and Clozapine Response Status

We compared allele and genotype frequencies using a χ^2 or Fisher’s test in the subsets of TRS individuals undergoing clozapine treatment with extreme BPRS scores. Furthermore, we evaluated BPRS score by genotype for the whole TRS group, using an ANOVA or Wilcoxon test.

All analyses were carried out with a significance level of .05. According to statistical power simulations for genetic comparison association studies (Hong and Park, 2012), the estimated power was 80% for alleles with an OR of 1.8.

RESULTS

Clinical Description of Sample

The TRS group was composed of 135 individuals aged 18–69 years (mean = 41.4 years), 68.6% males; the SGAP group was composed of 61 individuals aged 18–58 years (mean = 27.7 years), 72.1% males; controls were 80 individuals aged 18–59 years (mean = 26.2 years), 33.7% male.

Figures 2a and 2b and Table 2 show the BPRS scores for the TRS and SGAP groups. Negative symptom scores did not differ

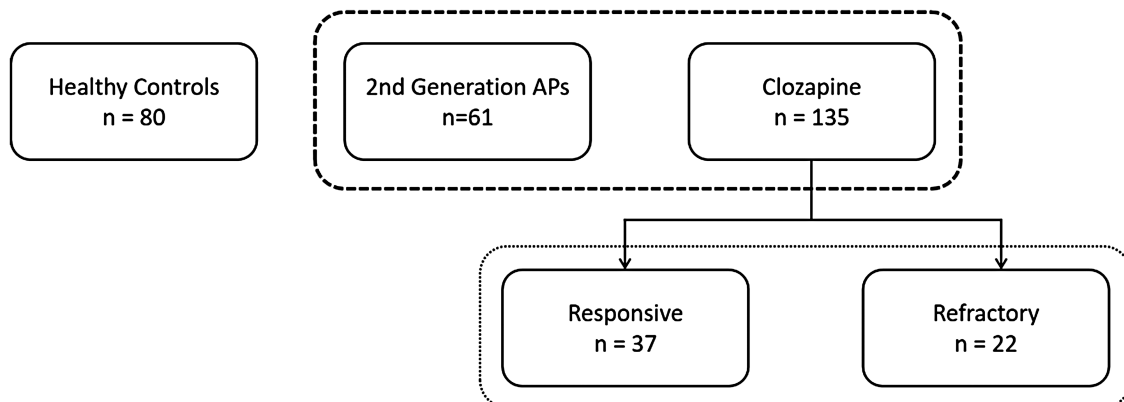


Figure 1. Schematic representation of study design.

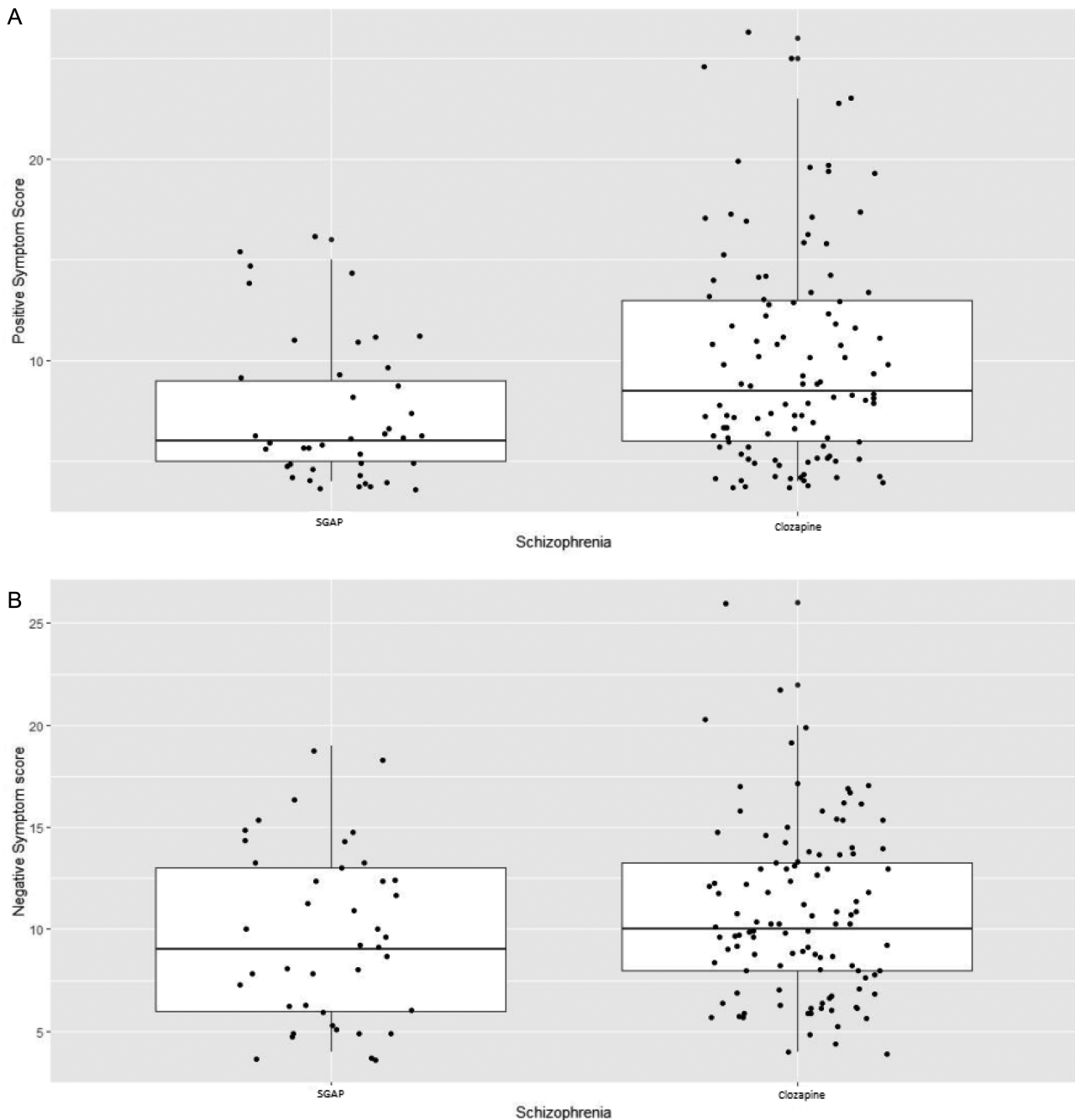


Figure 2. (A) Distribution of positive symptoms in clozapine and second-generation antipsychotics (SGAP) groups. (B) Distribution of negative symptoms in clozapine and SGAP groups.

significantly between groups, whereas positive symptom scores were significantly lower in the SGAP group ($P = .005$).

Associations Between Variants and Treatment Responsiveness

Multiple logistic regression analysis identified 4 SNPs where minor allele homozygosity had a protective role: *OXTR* rs2228485 (OR = 0.07), *CNR1* rs806368 (OR = 0.01), rs1049353 (OR = 0.02), and *DDC* rs10499696 (OR = 0.002). Heterozygosity for the *OXTR*, *CNR1* rs1049353, and *DDC* SNPs was also associated with lower risk (Table 1).

Analysis of deviance with the ANOVA function for each regression model suggested that genotype and age accounted for the largest proportion of the variation. The other variables did not explain a significant part of the variation. Genotype and allele frequencies for the 15 SNPs are provided in the supplementary materials.

Statistically significant differences in genotype frequency were observed for 8 SNPs: *OXT* rs2740210 ($P = .03$); *OXTR* rs2228485 ($P < .01$); *CNR1* rs806368 ($P < .01$), rs1049353 ($P < .01$), rs806379 ($P < .01$), and rs806380 ($P < .01$); *DDC* rs10499696 ($P = .001$); and *DRD2* rs1799978 ($P = .005$) (Figure 3). Of note, statistical differences between SZ patients and controls were

Table 1. Results for 4 markers significantly associated with treatment response in Chilean patients with schizophrenia

SNP	Genotype	P	FDR	OR	95% CI
OXTR rs2228485	A/A Reference	–	–	–	–
	A/G	0.015*	0.0643	0.13	0.02 - 0.57
	G/G	0.0039*	0.02*	0.07	0.01 - 0.37
CNR1 rs806368	T/T Reference	–	–	–	–
	T/C	0.07	0.2625	0.11	0.01 - 0.84
	C/C	0.0001*	0.001*	0.01	0.0005 - 0.07
CNR1 rs1049353	G/G Reference	–	–	–	–
	G/A	0.004*	0.02*	0.07	0.01 - 0.35
	A/A	0.0001*	0.001*	0.02	0.002 - 0.10
DDC rs10499696	A/A Reference	–	–	–	–
	A/G	0.002*	0.015*	0.09	0.01 - 0.39
	G/G	1.1E-05*	0.0003*	0.002	0.0 - 0.02

Abbreviations: CI, confidence interval; FDR, false discovery rate; OR, odds ratio; SNP, single-nucleotide polymorphism.

Table 2. Psychotic symptom scale scores

Symptoms sub-scale	Second-generation antipsychotics	Clozapine	P *
Total BPRS	35.9 (10.39)	39.72 (17.83)	0.78
Positive symptoms	7.39 (3.54)	10.01 (5.39)	0.005*
Negative symptoms	9.68 (4.11)	10.78 (4.18)	0.15

Abbreviation: BPRS, Brief Psychiatric Rating Scale.

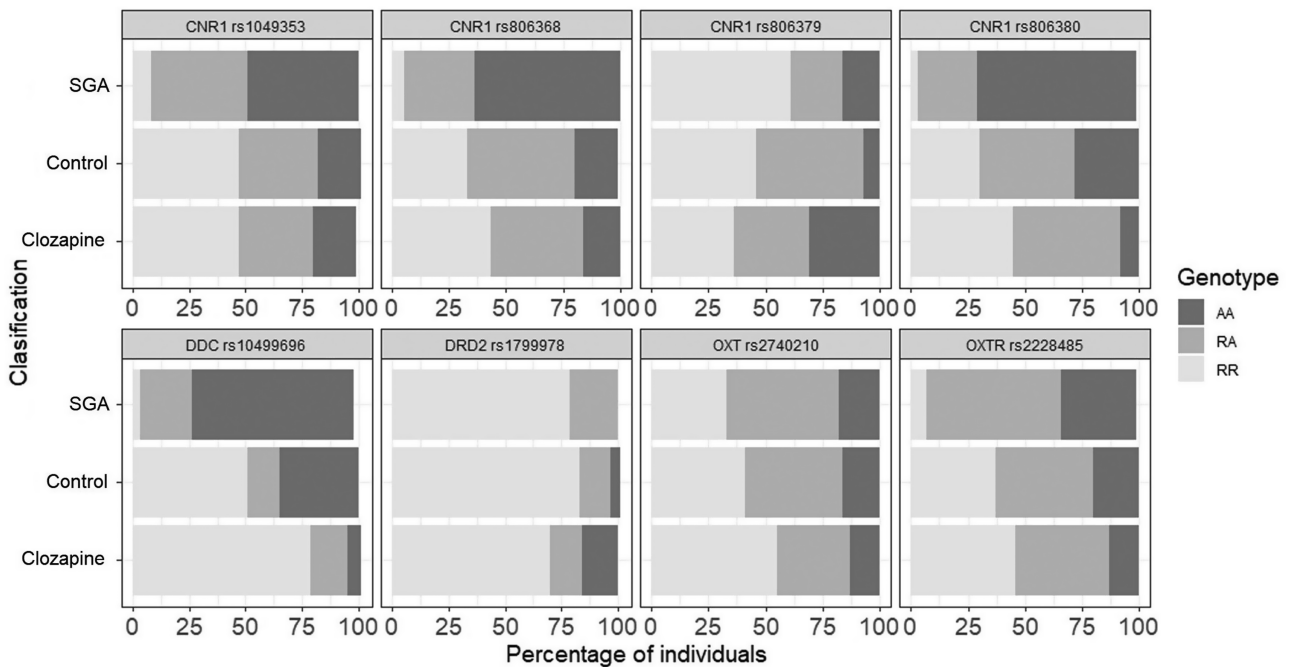


Figure 3. Single-nucleotide polymorphism (SNPs) with significant differences in the clozapine vs. second-generation antipsychotics groups.

detected only for the SNP *CNR1* rs806379 ($P = .001$). Statistically significant differences in allele frequencies were observed for *OXT* rs877172 ($P = .02$) and rs2740210 ($P = .02$); *OXTR* rs2254298 ($P = .02$) and rs2228485 ($P < .001$); *CNR1* rs806368 ($P < .001$), rs1049353 ($P < .001$), rs806379 ($P = .0004$), and rs806380 ($P < .001$); *DDC* rs11283133 ($P = .04$) and rs10499696 ($P < .001$); and *DRD2* rs1799978 ($P = .01$) (Supplementary Table 2).

For all 8 SNPs with significant differences in genotype frequency, allele frequencies were also found to differ. On the other hand, some of the SNPs with significant differences in allele frequency (*OXT* rs877172, *OXTR* 2254298, and *DDC* rs11283133) showed no statistical differences in genotype frequency. Allele frequency differed significantly between SZ individuals and controls for 3 SNPs: *CNR1* rs1049353 ($P = .04$) and

rs806379 ($P < .001$) and DRD2 rs1799978 ($P = .01$) (Supplementary Table 3).

Associations Between Variants and Clozapine Response

No significant differences in genotype frequency were observed for any of the SNPs (Supplementary Table 4). For CNR1 rs806379, the frequency of the C-allele was higher in refractory individuals (0.41 vs. 0.27, $P = .025$), as was the frequency of the rs1043953 A-allele (0.43 vs. 0.23, $P = .021$). For DRD2 rs1799978, the frequency of the G-allele was lower in refractory individuals (0.05 vs. 0.23, $P = .008$) (Supplementary Table 4).

When all TRS individuals were compared, we found that GG-homozygous DRD2 rs1799978 individuals had significantly lower total ($P = .038$), negative symptom ($P = .039$), and positive symptom ($P = .015$) BPRS scores. We did not find any associations between the other genotypes and BPRS scores (Figure 4).

Discussion

Because of the impact of early treatment response on long-term outcome, timely recognition of TRS and refractoriness is a pressing need in clinical practice. This is the first study in our admixed Chilean population to test for associations between SZ-related genes and the full treatment response spectrum. The historically poor representation of Latin American individuals in genetic variation studies is progressively improving in new cohorts. The Psychiatric Genetics Consortium of SZ included the largest Latino cohort to date, with 1234 cases and 3090 controls. Results from this consortium suggest that previously identified SNPs may increase SZ risk across groups with different ancestries. This is a major step in clarifying the application of GWAS results to SZ risk estimation (Bigdeli et al., 2020). On the other hand, the evidence regarding the applicability of SZ polygenic risk scores to prediction of TRS is controversial, as results have been

inconsistent (Gasse et al., 2019; Werner et al., 2020; Wimberley et al., 2017).

Our study contributes to defining potential genetic predictors of treatment response, with great potential clinical utility in decision-making regarding standard antipsychotic therapies. In addition, our findings may lead to a better characterization of individuals who may benefit from novel therapies, such as oxytocin and cannabinoids, which have been proposed for SZ in recent years (Hamdani et al., 2008; Souza et al., 2010).

Furthermore, by studying the biological underpinnings of TRS and refractoriness, we contribute to a better understanding of the relationship between these 2 phenomena. We identified SNPs predictive of TRS harbored in OXTR, CNR1, and DDC. Variants in OXTR, as well as epigenetic changes affecting this gene, have been previously linked to SZ (Haram et al., 2016). A single prior study found an association between this gene and treatment response (Souza et al., 2010). Oxytocin is involved in issues such as flattened affect and social withdrawal, negative symptoms that are less responsive to antipsychotic drugs. Therefore, one might expect that variations in oxytocin function might be associated with response to this family of drugs. As oxytocin has been proposed as a potential treatment, variations in oxytocin function should be assessed when deciding who could benefit most from this novel treatment. In our study, the OXT rs2740210 C-allele and OXTR rs2228485 A-allele were predictors of poor response.

The issue of whether refractory SZ is a distinct category or a more severe form of TRS remains unresolved. Some authors propose that these are biologically different forms of the disease (Schennach et al., 2012) while others do not; to the best of our knowledge, we do not have sufficient evidence to exclude either approach. Therefore, we first analyzed our sample of patients undergoing clozapine treatment as a whole and then separated the sample into 2 extreme groups based on their response to clozapine. This latter approach is advantageous for studying heterogeneous, complex phenotypes. However, we must also acknowledge this step markedly reduced the sample size.

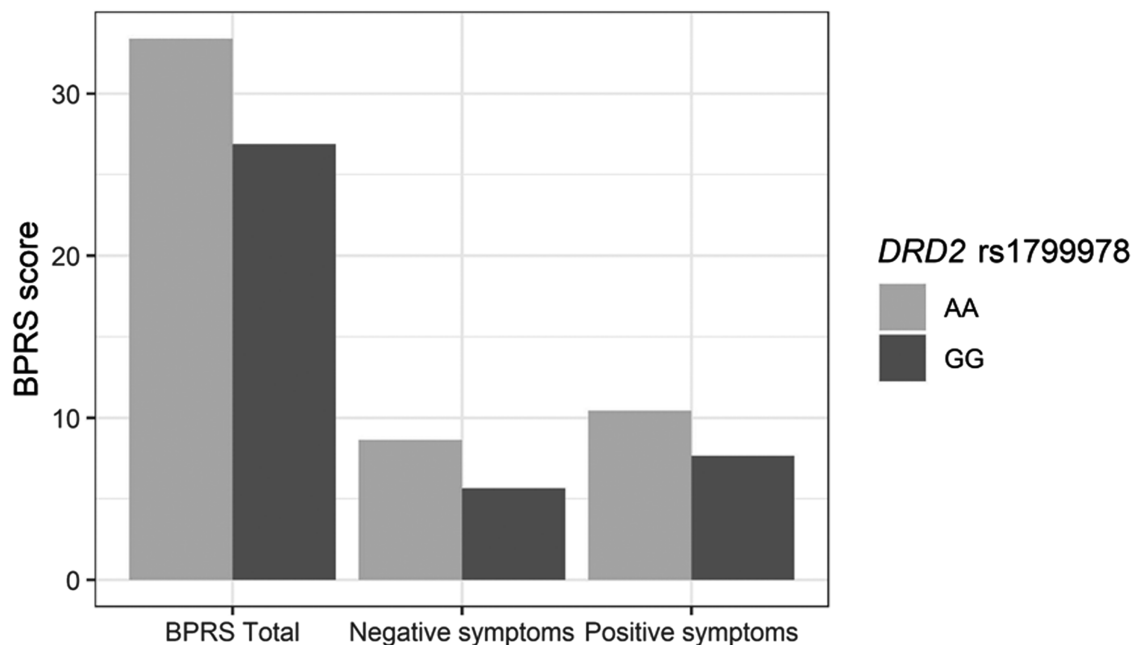


Figure 4. Brief Psychiatric Rating Scale (BPRS) scores for the whole treatment-resistant schizophrenia (TRS) group by DRD2 rs1799978 variant.

Therefore, this second analysis must be viewed as exploratory. Nevertheless, within the refractory group, we did find a higher frequency of the T allele of *CNR1* rs806379, the A allele of *CNR1* rs1043953, and the T allele of *DRD2* rs1799978 compared with the responsive group. This finding is compatible with distinct biological underpinnings for refractoriness and resistance in SZ. This distinction is relevant for defining management protocols, as there are already proven treatment strategies beyond those whose main target is the dopaminergic system and others are in development.

Limitations of the Study

The main limitations related to the clinical interpretation of the study stem from the fact that this was carried out retrospectively using a sample of individuals who presented primarily for treatment purposes. Thus, the study's clinical data records are not exhaustive, and information regarding potential confounding factors was not available for analysis. This includes objective measures of concomitant use of alcohol, presence of polypharmacy, and treatment compliance. Even in the face of these limitations of the research records, we are confident that our clinical interpretation is sound, because the study took place in the context of the Chilean mental health system in which health care for persons with severe mental disorders is provided in a sectorized, community-based, comprehensive fashion. Dedicated teams use national, evidence-based guidelines for the differentiation of cases with TRS from those with treatable conditions that negatively impact their clinical outcome (Ministerio de Salud, Chile, 2009). Thus, we consider that the presence of environmental causes of TRS as confounders is not a systemic problem in our sample, but we must acknowledge that we are not able to rule out all nongenetic factors that may influence TRS because we did not purposefully record them in our recruitment. A rough approximation to this would be through observing the socioeconomic status, which is linked to lower quality of life, increased stress, and less access to general health services, and that in this study did not show an effect.

We defined TRS by the use of clozapine, which is a common problem in these types of studies because of the lack of consensus regarding standardization of diagnosis and follow-up criteria for TRS (Kane et al., 2019). The average age of our SGAP group was younger; therefore, some of these patients may have been in an earlier stage of the disorder and will develop TRS later. However, because the vast majority of TRS patients show signs of resistance early in treatment, we do not expect that our results would be affected even if a minor proportion of this group goes on to develop secondary resistance after their initially favorable response.

Regarding the genetic design, we present here the results from a proof-of-concept study aimed to analyze a small number of markers in a relatively large sample of patients with severe mental disorders in Hispanic countries. Whereas genomic research in Chile has been steadily growing in the past decade, genetic studies of severe mental disorders are still scarce. Because feasibility was a key concern, our selection of genetic markers was limited. Considering this, our SNP selection was necessarily biased, and our choice was made with our current research focus in mind (see [supplementary Table 5](#) for information on each marker) (Sherry et al., 2001). We acknowledge that we did not perform a systematic search for the best candidates ranked according to functional or statistical data, knowing that this information would be of limited value

because the Hispanic population in these studies is strongly under-represented. We are confident that with the present study we have established the viability of our approach and we can proceed in the future to study a wider selection of SNPs. Although candidate gene studies have produced some lasting contributions to the field of pharmacogenomics in psychiatry (Corponi et al., 2018), they are progressively being abandoned because of the poor replicability of many initial results. The more promising strategy is the estimation of polygenic risk scores, constructed from a subsample of all the risk SNPs for a complex trait, which are extracted from genome-wide association studies. The usefulness of polygenic risk scores will depend on the frequency and effect size of each SNP on the target population; therefore, understanding the distribution of gene frequencies in a local sample is relevant for the implementation of personalized medicine. In this sense, the study sample does not reflect the resistance/responsiveness ratio in the general population; in fact, our sample of TRS patients was twice as large as the SGAP group. To adequately estimate the proportion of the TRS risk captured, our findings should be replicated in a sample with the expected 1:3 proportion of TRS to responsive individuals.

Conclusions

In our study, we have identified potential genetic predictors of AP treatment resistance in a Chilean population of individuals with SZ, a relevant first step to establishing a precision medicine strategy for facing this relevant health problem. In our country, patients with severe mental disorders are treated in a protocolized fashion in a community-based context. We consider that this setting is ideal for searching to replicate the present findings in a new study using prospective collection for clinical and demographic data and an unbiased genetic approach. The nature of our existing resources for the care of persons with severe mental health disorders makes it a promising environment for testing pharmacogenetic applications, toward which our study contributes a preliminary step.

Supplementary Materials

Supplementary data are available at International Journal of Neuropsychopharmacology (IJNPPY) online.

A.Z. and T.C. contributed equally to the present work.

Acknowledgments

The authors are indebted to all patients who participated in the study.

Miss Jennifer Rengachary proofread the article for language correction; she did not participate in the scientific writing.

This work was supported by the Biomedical Neuroscience Institute (ICM MINECOM ICMP09) and NuMIND (ICM MINECOM NC130011), Hospital Clínico de la Universidad de Chile, Clínica Los Tiempos, Centro Interdisciplinario de Neurociencia de Valparaíso (ICM-ANID Grant no. ICN09-022), and Fondecyt Grant no. 1190833.

Statement of Interest: None.

References

Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR (2005) Remission in schizophrenia: proposed

- criteria and rationale for consensus. *Am J Psychiatry* 162:441–449.
- Barozet E, et al. (2021) The Chilean socio-ethno-genomic cline. *Biodemography Soc Biol* 66(2). <https://doi.org/10.1080/19485565.2021.1879626>
- Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Ser B (Methodological)* 57(1). <https://doi.org/10.1111/j.2517-6161.1995.tb02031.x>
- Bigdeli TB, et al.; Consortium on the Genetics of Schizophrenia (COGS) Investigators; Genomic Psychiatry Cohort (GPC) Consortium (2020) Contributions of common genetic variants to risk of schizophrenia among individuals of African and Latino ancestry. *Mol Psychiatry* 25:2455–2467.
- Brenner HD, Dencker SJ, Goldstein MJ, Hubbard JW, Keegan DL, Kruger G, Kulhanek F, Liberman RP, Malm U, Midha KK (1990) Defining treatment refractoriness in schizophrenia. *Schizophr Bull* 16:551–561.
- Buckley PF, Gaughran F (2014) Treatment-refractory schizophrenia: a clinical conundrum. Berlin: Springer. <https://doi.org/10.1007/978-3-642-45257-4>
- Cavieres A, Campos-Estrada C, Moya Y, Maldonado R, González-Vargas R, Bustamante ML, Moya PR (2019) Lack of association between the IL6R gene Asp358Ala variant (rs2228145), IL-6 plasma levels, and treatment resistance in Chilean schizophrenic patients treated with clozapine. *Schizophr Res Treatment* 2019:5601249.
- Corponi F, Fabbri C, Serretti A (2018) Pharmacogenetics in psychiatry. *Adv Pharmacol* 83:297–331.
- Gasse C, Wimberley T, Wang Y, Mors O, Børghlum A, Als TD, Werge T, Nordentoft M, Hougaard DM, Horsdal HT (2019) Schizophrenia polygenic risk scores, urbanicity and treatment-resistant schizophrenia. *Schizophr Res* 212:79–85.
- Hamdani N, Tabeze JP, Ramoz N, Ades J, Hamon M, Sarfati Y, Boni C, Gorwood P (2008) The CNR1 gene as a pharmacogenetic factor for antipsychotics rather than a susceptibility gene for schizophrenia. *Eur Neuropsychopharmacol* 18:34–40.
- Haram M, Bettella F, Brandt CL, Quintana DS, Nerhus M, Bjella T, Djurovic S, Westlye LT, Andreassen OA, Melle I, Tesli M (2016) Contribution of oxytocin receptor polymorphisms to amygdala activation in schizophrenia spectrum disorders. *Bjpsych Open* 2:353–358.
- Hasan A, et al (2012) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry* 13:318–378.
- Hong EP, Park JW (2012) Sample size and statistical power calculation in genetic association studies. *Genomics Inform* 10:117–122.
- Ihaka R, Gentleman R (1996) R: a language for data analysis and graphics. *J Comput Graph Stat* 5(3). <https://doi.org/10.1080/10618600.1996.10474713>
- Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, O'Donovan M, Correll CU, Kane JM, van Os J, Insel TR (2015) Schizophrenia. *Nat Rev Dis Primers* 1. <https://doi.org/10.1038/nrdp.2015.67>
- Kane JM, Agid O, Baldwin ML, Howes O, Lindenmayer JP, Marder S, Olfson M, Potkin SG, Correll CU (2019) Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry* 80(2). <https://doi.org/10.4088/JCP.18com12123>
- Kay SR, Fiszbein A, Opler LA (1987) The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 13:261–276.
- Ministerio de Salud, Chile (2009) Guía clínica para el tratamiento de personas desde primer episodio de esquizofrenia. Chile: Ministerio de Salud, Subsecretaría de Salud Pública.
- Nucifora FC Jr, Woznica E, Lee BJ, Cascella N, Sawa A (2019) Treatment resistant schizophrenia: clinical, biological, and therapeutic perspectives. *Neurobiol Dis* 131:104257.
- Schennach R, Riedel M, Musil R, Möller HJ (2012) Treatment response in first-episode schizophrenia. *Clin Psychopharmacol Neurosci* 10:78–87.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20:22–33;quiz 34.
- Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, Sirotkin K (2001) dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res* 29:308–311.
- Souza RP, de Luca V, Meltzer HY, Lieberman JA, Kennedy JL (2010) Schizophrenia severity and clozapine treatment outcome association with oxytocinergic genes. *Int J Neuropsychopharmacol* 13:793–798.
- Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M, Fujiwara Y, Sakai A, Kuroda S (2002) CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Mol Psychiatry* 7:515–518.
- Werner MCF, Wirgenes KV, Haram M, Bettella F, Lunding SH, Rødevand L, Hjell G, Agartz I, Djurovic S, Melle I, Andreassen OA, Steen NE (2020) Indicated association between polygenic risk score and treatment-resistance in a naturalistic sample of patients with schizophrenia spectrum disorders. *Schizophr Res* 218:55–62.
- Wimberley T, Gasse C, Meier SM, Agerbo E, MacCabe JH, Horsdal HT (2017) Polygenic risk score for schizophrenia and treatment-resistant schizophrenia. *Schizophr Bull* 43:1064–1069.
- Yoshida K, Müller DJ (2019) Pharmacogenetics of antipsychotic drug treatment: update and clinical implications. *Mol Neuropsychiatry* 5(1). <https://doi.org/10.1159/000492332>
- Zhang JP, Malhotra AK (2011) Pharmacogenetics and antipsychotics: therapeutic efficacy and side effects prediction. *Expert Opin Drug Metab Toxicol* 7:9–37.