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ORIGINAL RESEARCH

Association study between *COMT*, *DRD2*, and *DRD3* gene variants and antipsychotic treatment response in Mexican patients with schizophrenia

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Purpose: The efficacy of schizophrenia treatments using antipsychotics (APs) has long been established, but the benefit obtained by several patients using conventional APs (typical or atypical) has not been enough. Currently, the genetic study of the primary mechanisms of action of the APs has been focused on the dopaminergic pathways. The objective of this study was to determine if the response phenotypes (responder, resistance to treatment, and ultra-resistance to treatment groups) are associated with six single-nucleotide polymorphisms: *COMT* (Val158Met), *DRD2* (A-241G, C376G, C939T, Taq1A), and *DRD3* (Ser9Gly).

Patients and methods: We classified the patients through a retrospective/prospective methodology to define response phenotypes.

Results: *COMT*/Val158Met and *DRD3*/Ser9Gly were associated with the responder group ($P<0.05$). The single-nucleotide polymorphism A-241G of *DRD2* gene was related with the resistant-to-treatment group ($P<0.001$). Finally, Met/Met of *COMT* and Ser/Gly of *DRD3* genes showed a predictive effect associated with the resistant-to-treatment phenotype.

Conclusion: Further analyses should be performed to validate these genetic markers as mediators for the response to APs.

Keywords: pharmacogenetics, dopamine, resistant to treatment, ultraresistant to treatment

Introduction

Schizophrenia is a chronic and profoundly disabling mental health condition, characterized by positive, negative, and cognitive symptoms.[1] Although the etiology of schizophrenia is unknown, it appears to be a multifactorial disorder originated by biological and environmental factors.[2] The treatment of schizophrenia is based on the use of typical and atypical antipsychotic (AP) drugs.[3] There is evidence that genetic factors play a central role in response to APs. Twin and family studies have reported a high rate of concordance in response to pharmacological treatment.[4,5]

Pharmacogenetic biomarkers aim to predict which patients could improve with certain drugs according to genetic variants; this could allow optimizing the AP treatment.[6] The dopaminergic pathways, one of the primary mechanisms of action of APs, have been the main focus of pharmacogenetic studies on schizophrenia. The most common methodology to identify genetic predictors of AP treatment outcomes are candidate gene studies, using single-nucleotide polymorphisms (SNPs) located in genes involved in the dopaminergic transmission.[6,7] The *DRD2* is one of the critical targets in pharmacogenetic studies. *DRD2* polymorphisms have been associated with the AP response. In particular, −141C Ins/Del showed that patients who have at least

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one copy of the Ins allele respond better to treatment than those with the Del/Del genotype, and this variant has also been related with a milder symptomatology.[8] In contrast, Del carriers have been associated with responding to conventional APs and with a poor response to treatment with clozapine in resistant patients.[9] One study with the *DRD2*/Taq1A polymorphism reported an association between the A1 allele and a better response to APs than the A2 allele.[10] However, Hwang et al[11] and Vijayan et al[12] found that patients with the A2/A2 genotype presented a good response. Nonetheless, Zhang et al[13] failed to replicate these results and did not observe any association. Four studies analyzed the association between the A-241G (rs1799978) polymorphism and the risperidone response, showing conflicting findings in Han-Chinese, Japanese, African American, and Thai patients.[14–17] It has also been reported that C939T (rs6275) and C376G (rs6279) SNPs might be associated with an increase of prolactin in female patients treated with olanzapine.[18] The distribution of gene variants has shown significant variation worldwide; therefore, findings cannot be extrapolated a priori across populations.

DRD3 is another of the primary targets for AP drugs. The Ser9Gly SNP has been one of the most studied SNPs regarding response to AP. The Ser allele has been related to resistance to clozapine,[19,20] and it has been associated with the response to negative symptoms in patients treated with risperidone.[21] Concerning the response to typical APs, the Gly allele has been associated with a poor response, although the Gly/Gly genotype has been associated with a satisfactory response to olanzapine.[22] It has been proposed that the Ser allele could have a role as a mediator of the response for typical APs and the Gly allele for the atypical AP response.[23,24]

COMT enzyme has an essential role in the metabolism of dopamine. The functional Val158Met polymorphism has been related with different levels of enzyme activity. The Val/Val genotype is associated with three to four times increased activity compared to the Met/Met genotype.[25] The Met allele has been associated with symptom severity, poorer response to APs, and higher maintenance doses compared with Val carriers.[26] However, a meta-analysis conducted by Huang et al[27] found that patients with the Met/Met genotype had the best response to atypical AP treatment.

Since the 1990s, there have been different studies regarding pharmacogenetics in schizophrenia, mostly in Caucasian and Asian populations.[9] However, to date, there are few studies in Latin American populations. The aim of this study was to analyze the previously reported association between *DRD2*, *DRD3*, and *COMT* gene polymorphisms and the AP treatment response in Mexican patients with schizophrenia.

Materials and methods

Sample

The sample was formed by 218 Mexican patients with schizophrenia, diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*-Fifth Edition (DSM-V) through the mini international neuropsychiatric interview (MINI),[28] corroborated by at least two certified psychiatrists from the Schizophrenia Clinic at the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz. Patients were excluded from the study if they had a comorbid medical condition or if they had a substance-related disorder that could influence the response to AP. The study was approved by the Ethics Committee of the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, and written informed consent was obtained from the patients or the responsible caretakers. Demographic and clinical information was collected. We used the O'Donnell et al[29] criteria to assess compliance to AP treatment. Other instruments such as Clinical Global Impression and Positive and Negative Syndrome Scale (PANSS) were used to assess response to treatment.[30,31] Data were retrospectively collected, including all reliable AP assays from medical files and through interviews with the attending psychiatrist of each patient. By using this information, we allocated the patients of each group, according to their level of AP response. If these data were not conclusive, a mandatory follow-up period with scheduled ratings was added, to obtain reliable data for the classification of each patient into one of the three main phenotypes, according to the following definitions.[32]

Responder group was defined as patients who responded to treatment with an AP other than clozapine. The response was defined as at least a 30% reduction of PANSS total score at 12 weeks. Resistance to treatment group was defined as a documented clinical history of treatment failure with ≥2 AP (minimum doses of 600 mg/d of chlorpromazine equivalents, for ≥6 weeks) but with a response for clozapine. Ultra-resistance to treatment group was defined as patients who failed at least two trials of APs and a trial of clozapine (at least for 6 months, within a dose range between 250 and 600 mg/d). They presented persistent positive symptoms, rating ≥4 (moderate or higher) in at least two items of the PANSS positive subscale.[33]

Genotyping

DNA was extracted from whole blood using the Flexigene DNA kit (Qiagen, Minneapolis, MN, USA). A total of six polymorphisms in three candidate genes were analyzed in the present study: *COMT*/Val158Met, *DRD2* (A-241G, C376G, C939T, Taq1A), and *DRD3*/Ser9Gly using allelic discrimination with TaqMan probes (5-exonuclease fluorogenic assay). The final volume of the reaction was 7 µL with the following reaction conditions: 100 ng DNA, 2.5 µL TaqMan Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), 2.367 µL water for PCR, and a 0.125 µL 20× probe (https://dx.doi.org/10.17504/protocols.io.rtwd6pe).

The power analysis was performed using the QUANTO V.1.2 program (https://bio.tools/QUANTO). The sample had a power of 0.98 to detect a 2-fold increased risk, assuming an additive genetic model, a risk allele frequency of 0.46, a population prevalence 0.1, and an α level of 0.05. The Bonferroni correction was taken into consideration. Thus, the significance level for the specific analysis of each polymorphism was fixed in $P \leq 0.0083$ (0.05/6 SNPs). A logistic regression analysis was performed to determine if *COMT*/Val158Met and *DRD3*/Ser9Gly SNPs were predictive for the resistant-to-treatment group. After this, regression model was performed; age of illness onset and duration of untreated psychosis were included in a second regression model to identify the role of nongenetic factors in the resistance to treatment in this sample.

Results

Clinical and demographic characteristics of the sample

The study included a sample of 170 patients with schizophrenia. From these, 88 (52%) patients were classified in the responder group, 49 (29%) in resistance to treatment group, and 33 (19%) in the ultra-resistance to treatment group. There were no differences between groups concerning sex, or occupation. However, there were differences in age and education (Table 1). In the responder group, the APs used were: risperidone (30%), olanzapine (20%), sulpiride (18%), haloperidol (15%), trifluoperazine (7%), amisulpride (6%), perphenazine (2%), and zuclopenthixol (2%). All the patients in the resistance to treatment group were under treatment with clozapine. Regarding the clinical characteristics, an earlier age of onset for schizophrenia, the most extended durations of untreated psychosis, and evolution were observed in the ultra-resistance to treatment group. When comparing the average equivalent doses of chlorpromazine for each group,

Table 1 Clinical and demographic characteristics of the sample

Characteristics	Responders (n=88)		Resistance to treatment (n=49)		Ultra-resistance (n=33)		Statistics
	N	%	n	%	N	%	
Gender							
Male	60	68	32	65	19	58	χ^2=1.19, *df*=1, *P*=0.551
Female	28	32	17	35	14	42	
Marital status							
Without partner	73	83	46	94	29	88	χ^2=3.35, *df*=1, *P*=0.187
With partner	15	17	3	6	4	12	
Occupation							
Unemployed	34	39	32	65	30	91	
Housekeeping	15	17	2	4	2	6	χ^2=34.06, *df*=3, *P*=0.27
Student	7	8	6	12	0	0	
Employed	32	36	9	19	1	3	
	Mean	SD	Mean	SD	Mean	SD	Statistics
Age (years)	38.3	10.3	37.9	9.8	43.6	12.8	*F*=3.416, *df*=167, *P*=0.035
Education (years)	9.8	2.8	11.3	2.6	11.5	2.7	*F*=6.625, *df*=167, *P*=0.002
Age of onset (years)	23.7	6.8	20.4	4.9	19.8	4.0	*F*=5.51, *df*=114, *P*=0.005
DUP (weeks)	53.1	65.3	72.7	64.9	88.4	56.6	*F*=4.13, *df*=167, *P*=0.018
Time evolution (weeks)	738.3	396.0	924.8	462.5	1,193.5	568.9	*F*=3.57, *df*=114, *P*=0.033
ED chlorpromazine (mg/d)	322.0	242.4	508.8	241.8	723.4	300.0	*F*=31.35, *df*=167, *P*<0.001

Abbreviations: DUP, duration of untreated psychosis; ED, equivalent doses.

the responder group reported the lowest doses and the ultra-resistance to treatment group the highest. Differences were found in the overall PANSS scores among the three groups (Table 1). The mean decrease in the PANSS total score for the responder group was 55% (SD 10).

Genetic analyses

DRD2 gene

Four SNPs were analyzed: Taq1A, C939T, C376G, and A-241G. Regarding A-241G, the resistant-to-treatment group showed a higher frequency of the G allele in comparison with the other two groups (χ^2=15.84, P=0.00036) (Table 2). We did not find an association between Taq1A, C939T, and C376G polymorphism and AP response in Mexican patients with schizophrenia (Table 2).

COMT gene

In regard to Val158Met, the comparison of genotypes between the response phenotypes did not show differences. On the contrary, the allelic distribution differed between groups: the responder group presented a higher frequency in the Val allele in comparison with the ultra-resistance to treatment group (χ^2=10.24, P=0.00137) (Table 2).

DRD3 gene

Ser9Gly. The analysis of genotype frequencies between groups exhibited a trend for the ultra-resistance to treatment group had a higher percentage of Ser/Gly (χ^2=8.50, P=0.0142) (Table 2) and a higher percentage (67%) carrying the Gly allele in comparison to the responder group (44%) (χ^2=5.77, P=0.016) (Table 3).

One final analysis, a logistic regression model showed that Met/Met genotype of *COMT*/Val158Met and Ser/Gly genotype of *DRD3*/Ser9Gly were predictive for the resistant-to-treatment group, with an adequate classification for 66.0% of subjects. However, when clinical variables were included, a younger age of illness onset was the most important predictor for resistance, while the Ser/Gly genotype of *DRD3*/Ser9Gly was no longer part of the prediction model (Table 4). This second model identified 71.4% of participants.

Table 2 Genotype and allele frequencies of *DRD2*, *COMT*, and *DRD3* genes

Gene polymorphism	Genotype frequencies			Allele frequencies	
DRD2/A-241G (rs1799978)	AA	AG	GG	A	G
Responders (n=93)	61 (0.66)	16 (0.17)	16 (0.17)	138 (0.74)	48 (0.26)
Resistance to treatment (n=46)	24 (0.52)	5 (0.11)	17 (0.37)	53 (0.58)	39 (0.42)
Ultra-resistance (n=34)	27 (0.75)	4 (0.17)	3 (0.08)	58 (0.85)	10 (0.15)
DRD2/C376G (rs6279)	CC	CG	GG	C	G
Responders (n=78)	38 (0.49)	32 (0.41)	8 (0.10)	108 (0.69)	48 (0.31)
Resistance to treatment (n=39)	18 (0.46)	16 (0.41)	5 (0.13)	52 (0.67)	26 (0.33)
Ultra-resistance (n=29)	13 (0.45)	15 (0.52)	1 (0.03)	41 (0.71)	17 (0.29)
DRD2/C939T (rs6275)	CC	CT	TT	C	T
Responders (n=58)	12 (0.21)	27 (0.46)	19 (0.33)	51 (0.44)	65 (0.56)
Resistance to treatment (n=39)	6 (0.15)	16 (0.41)	17 (0.44)	28 (0.36)	50 (0.64)
Ultra-resistance (n=29)	1 (0.04)	14 (0.48)	14 (0.48)	16 (0.28)	42 (0.72)
DRD2/Taq1A (rs1800497)	CC	CT	TT	C	T
Responders (n=78)	20 (0.26)	37 (0.47)	21 (0.27)	77 (0.50)	79 (0.50)
Resistance to treatment (n=51)	16 (0.31)	24 (0.47)	11 (0.22)	56 (0.55)	46 (0.45)
Ultra-resistance (n=33)	7 (0.21)	18 (0.55)	8 (0.24)	32 (0.48)	34 (0.52)
COMT/Val158Met (rs4680)	Val/Val	Val/Met	Met/Met	Val	Met
Responders (n=81)	38 (0.47)	30 (0.37)	13 (0.16)	106 (0.65)	56 (0.35)
Resistance to treatment (n=45)	17 (0.38)	17 (0.38)	11 (0.24)	51 (0.57)	39 (0.43)
Ultra-resistance (n=32)	8 (0.25)	11 (0.35)	13 (0.40)	27 (0.42)	37 (0.58)
DRD3/Ser9Gly (rs6280)	Ser/Ser	Ser/Gly	Gly/Gly	Ser	Gly
Responders (n=95)	54 (0.58)	34 (0.34)	7 (0.08)	142 (0.75)	48 (0.25)
Resistance to treatment (n=45)	23 (0.51)	21 (0.47)	1 (0.02)	67 (0.74)	23 (0.26)
Ultra-resistance (n=36)	12 (0.33)	23 (0.64)	1 (0.03)	47 (0.65)	25 (0.35)

Table 3 Frequency of Gly carriers of *DRD3* gene

Phenotype	Gly carriers	Non-Gly carriers
Responders (n=95)	41 (0.44)	54 (0.58)
Resistance to treatment (n=45)	22 (0.49)	23 (0.51)
Ultra-resistance (n=36)	24 (0.67)	12 (0.33)

Notes: Non-Gly carriers = Ser/Ser.Gly carriers = Gly/Gly, Ser/Gly.

Discussion

The identification of resistant-to-treatment patients from the start would prevent multiple unsuccessful trails and avoid the deterioration caused by the lack of response. In our sample, there were no differences by sex. Seeman[34] and Canuso[35] reported gender differences, having higher possibilities of developing resistance to treatment being observed in males. The ultra-resistance patients were the oldest, probably due to a longer evolution time with an incomplete control of the disorder, poor response to treatment, an earlier age of onset, and longer duration of untreated psychosis, which, consistently with our results, have been associated with lack of response and resistance to the treatment.[36] For this study, the ultra-resistance group received the highest doses (equivalent conversions of chlorpromazine) followed by the resistance to treatment group. Increasing dose is a common practice to achieve an adequate response. Pharmacogenetic studies identifying the genetic variants might guide the prediction of who would benefit from specific AP treatment. In our study, the responders presented a higher frequency of the Val allele in comparison with the patients in the ultra-resistance group, which showed a higher frequency of Met allele, associated with a reduced degradation of dopamine.[25] Higher availability of dopamine at the mesolimbic circuit is correlated with positive symptoms.[36] These findings are consistent with the studies using next-generation sequencing which reported associations with the Met allele and severe psychopathology, poor response, resistance to conventional APs, and the need to use higher doses of drugs in resistant patients.[25,37,38] On the other hand, Molero et al[39] reported an association between Val/Val and a poor response; meanwhile, Kang et al[40] and a recent meta-analysis carried out by Hwang et al[20] reported an association between response and the Met/Met genotype. There is also a series of studies that did not find any association between Val158Met and the response to treatment.[41,42] For SNP A-241G, the resistance to treatment group, in comparison with the other groups, showed a high frequency of the G allele. Interestingly, there were reported associations between the A allele and response and the G allele and the lack of response.[14,15] Also, Lencz et al[43] reported an association between the G allele and an early response in patients with first episode of schizophrenia; meanwhile, Hwang et al[11] failed to find any association between A-241G and patients resistant or intolerant to conventional APs. Recently, consistently with our results, a meta-analysis reported an association between A allele and a significant greater improvement with risperidone treatment.[44] Finally, we did not replicate the association between Taq1A, C939T, and C376G and the AP response in schizophrenia patients.

The analysis of the Ser9Gly of *DRD3* gene showed a trend for significance, showing a high frequency of the Ser/Gly genotype and the Gly allele in the ultra-resistance group compared with the responder group; one current study using next-generation sequencing reported an association between Gly allele and a poorer response.[37] In contrast, Shaik et al,[45] Scharfetter et al,[19] and one recent meta-analysis (Gressier et al[46]) found an association between ultra-resistant patients and the Ser allele. Similarly, Hwang et al[47] found a gene × gene interaction between the Gly allele/*DRD3* and the G allele/*DRD1* in ultraresistant patients with schizophrenia. Ebstein et al,[48] Lane et al,[21] and Ma et al,[44] in three different ethnic groups, established an association between response to conventional APs and the Ser allele. However, other studies have reported an association between the response and the Gly allele.[23,24,49] Shi et al[37] successfully incorporated Ser9Gly into a four-locus model in order to predict an AP response; otherwise, our logistic regression model, which included Ser9Gly and Val158Met, could predict resistant-to-treatment patients.

Table 4 Logistic regression models for the prediction of resistance to treatment

Model	β	SD β	(β) Exp	CI 95% (β) Exp	*P*-value
Initial model: genetic factors					
DRD3 Ser/Gly	0.64	0.32	1.90	1.0–3.6	0.048
COMT Met/Met	0.86	0.39	2.38	1.1–5.1	0.026
Final model: genetic and clinical factors					
COMT Met/Met	0.83	0.41	2.30	1.03–5.17	0.042
Younger age of illness onset	0.91	0.35	2.49	1.24–4.97	0.010
Longer duration of untreated psychosis	0.008	0.003	1.008	1.002–1.014	0.010

All the patients in the responder group complied with a follow-up period of evaluation. The subjects in the resistance to treatment group, at least one retrospective and one prospective trial were consistently documented. The response phenotype is complex; the differences in the associations between genotypes or alleles and the different response phenotypes could be related to the heterogeneity of definitions or criteria. Usually, there is no distinction of the intermediate phenotype, and so the resistant-to-treatment group patients (exclusive response to clozapine) are included within the responder or nonresponder groups.[9,32] The limitations of this study included the fact that only a few SNPs were selected and that the sample size was small, which is why it was not possible to perform stratification of other groups for analysis (eg, APs individually). The classification of patients in the phenotypes of resistant-to-treatment and ultraresistant-to-treatment groups was based on a retrospective methodology. Association studies between resistant and ultraresistant patients offer a new opportunity to explore an explanation for its action mechanisms from the genetic and biologic points of view. The dopaminergic hypothesis continues to be the best explanation for the development of the positive symptoms of schizophrenia. The definitions of response/resistance/ultra-resistance continue to focus heavily on the persistence of these symptoms. It is possible that the dopaminergic system is not the only one involved in response to AP therapy, which becomes fundamental when evaluating the rest of the symptomatic dimensions, mainly negative and cognitive symptoms. Some of the results agree with the different polymorphisms that might affect the general response, and others could have predictive power to a specific type of response. Each one may have a lesser role individually, but together they may have a more significant contribution to the variation of the whole spectrum of response.

Conclusion

Summarizing the response phenotypes, the responders to treatment could be associated with the Val (*COMT*/Val158Met) and Ser (*DRD3*/Ser9Gly) alleles. Meanwhile, the resistant-to-treatment patients could be have a function associated with the G allele (*DRD2*/A-241G). Finally, ultra-resistant-to-treatment patients can have a linkage with the Met allele (*COMT*/Val158Met) and Gly allele from Ser9Gly (*DRD3*). This type of study could offer the possibility of an individual genetic assessment before the beginning of a new AP trial, decreasing the cost of long-term treatments and increasing the chances to achieve a better level of response in a shorter period.

Disclosure

The authors report no conflicts of interest in this work.

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