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ORIGINAL ARTICLE

Association study between the *MDR1* gene and clinical characteristics in schizophrenia

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Objective: Schizophrenia is a complex psychiatric disorder, characterized by disturbed patterns of thought and affecting 0.3-2.0% of the world population. Previously, the multidrug resistance 1 (*MDR1*) gene has been associated with schizophrenia in treatment response studies in psychotic patients. The aim of this study was to determine the association between *MDR1* gene polymorphisms and clinical characteristics in patients with schizophrenia.
Methods: Positive and negative symptoms of schizophrenia were assessed with the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) in 158 Mexican patients with schizophrenia. Analyses of *MDR1* gene polymorphisms were performed using TaqMan technology. A multivariate ANOVA was performed with *MDR1* polymorphisms and gender as independent variables.
Results: Males with the G/G genotype of *MDR1* rs2032582 presented significantly higher levels of delusions ($p = 0.02$). When comparing female vs. male groups, the difference was statistically significant ($p = 0.0003$). Analyses of the *MDR1* gene rs1045642 variant showed no significant differences.
Conclusion: Our findings suggest that male carriers of the G allele of variant rs2032582 exhibit greater severity of delusions; however, these results should be taken as preliminary, and replication studies in other populations of different ethnic origins are required to confirm these findings.

Keywords: Schizophrenia; MDR1 gene; polymorphism; Mexican population; SANS; SAPS

Introduction

Pharmacogenetics is the study of polymorphic genes that encode proteins involved in the mechanism of action, transport, and metabolism of drugs, aiming to uncover genotypes that might affect the response to drugs.[1,2] The main genes investigated are those that encode drug-metabolism enzymes[3]; study of the expression of P-glycoprotein (P-gp), which contributes to the multidrug resistance phenotype, is a clear example (for a review, see Lopes-Rodrigues et al.[4]). P-gp is a transmembrane drug transporter encoded by the multidrug resistance 1 (*MDR1*) gene; it acts as an efflux pump that works in an adenosine triphosphate (ATP)-dependent fashion. The *MDR1* gene is located on chromosome 7q21, and consists of 28 exons encoding a 1280-amino acid protein. The presence of a highly conserved ATP-binding site in two homologous halves, as well as the linker region, make this protein a member of the so-called ATP-binding cassette (ABC) transporter superfamily.[5] More than 170 single nucleotide polymorphisms (SNPs) have been identified along the gene. Mainly, the polymorphisms rs2032582 and rs1045642 have been studied in relation to treatment response in psychotic patients and associated with schizophrenia.[6,7] The rs2032582 variant is a non-synonymous mutation characterized by a change of G to T or A at position 2677 on exon 21 (G2677T/A), which is located on the intracellular side of P-gp, after transmembrane region 10, and related to an amino acid change at codon 893 from Ala to either Ser or Thr. In contrast, the C→T transition (rs1045642) at position 3435 on exon 26 (C3435T) does not change the amino acid sequence.[5]

Multidrug resistance (MDR) and/or P-gp are expressed in drug-resistant tumor cells and could contribute to the development of multidrug resistance[8]; they are also known to be expressed in a wide variety of human tissues, such as the gastrointestinal mucosa, nasal respiratory mucosa, kidneys, liver, adrenal cortex, and placenta.[9-12]

P-gp regulates the distribution of substrate drugs through the blood-brain barrier and into the brain; therefore, a reduction in P-gp function and expression could lead to an abnormal accumulation of prescribed drugs in the brain.[3] Based on the role of P-gp as a drug

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transporter, the *MDR1* gene has been subject to many pharmacogenetics and genetics studies. This gene has been associated with Parkinson's disease,[12,13] Alzheimer's disease,[14] Creutzfeldt-Jakob disease,[15] and tardive dyskinesia.[16] In heroin dependence, MDR variants may influence the methadone dose required to prevent withdrawal symptoms.[17] However, in bipolar patients, no association between antidepressant induced mania and *MDR1* has been found.[18] In schizophrenia, pharmacogenetic studies have yielded discrepant results.[19] In this context, recent investigations have shown no association between *MDR1* and ultra-resistant schizophrenia,[19] or with treatment response during short-term use of risperidone.[20] Nevertheless, alternative results have been encountered in other studies.[21,22] Differences between *MDR1* polymorphisms and clozapine plasma levels have been observed; for example, carriers of two C alleles in the rs1045642 polymorphism require higher clozapine doses to achieve the same plasma concentrations as C/T or T/T carriers[22]; similar results have been found with risperidone.[23] *MDR1* variants have also been associated with weight gain in female schizophrenic patients,[24] and may confer susceptibility to polydipsia in schizophrenia.[25] However, the relationship between *MDR1* and clinical variables is still unclear. Therefore, the aim of this study was to determine the association between *MDR1* polymorphisms and clinical characteristics in patients with schizophrenia, in a relatively ethnically homogeneous cohort. A second objective was to determine whether gender differences could be observed.

Methods

Sample

A total of 158 patients were consecutively recruited from the outpatient service of the Ramón de la Fuente National Institute of Psychiatry in Mexico City. This is a different sample from previous publications.[26,27] All subjects provided written informed consent to participate in the study after they were given verbal and written explanations of the research objectives. To reduce ethnic variation and stratification effects, only Mexican subjects descending from Mexican parents and grandparents participated in this study. The study was approved by the Institute ethics committee in accordance with the ethics standards laid down in the 1975 Declaration of Helsinki.

Clinical evaluation

Psychiatric diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[28] The exclusion criteria were age younger than 15 or older than 60 years; current substance abuse; history of substance dependence; concomitant medical or neurological illness; or intellectual disability.

Positive and negative psychotic symptoms were evaluated with the Scale for the Assessment of Negative Symptoms (SANS)[29] and the Scale for the Assessment of Positive Symptoms (SAPS).[30] The SANS scale comprises 25 items designed to assess five categories: 1) affective flattening; 2) alogia; 3) avolition/apathy; 4) anhedonia; and 5) attention. The SAPS scale consists of 30 items grouped into four categories: 1) hallucinations; 2) delusions; 3) bizarre behavior; and 4) positive formal thought disorder. Both scales have a scoring range from 0 to 5, where "0" denotes the absence of a particular symptom and "5" the most severe form. Clinical symptomatology was measured before pharmacological treatment. SANS and SAPS were administered by the same person (IV).

Age at onset of illness was defined as the age when patients experienced overt positive symptoms (hallucinations and delusions) for the first time. This parameter was obtained by a clinical interview with the patient and his/her relatives. The duration of untreated psychosis (DUP) was defined as the time in weeks from the first continuous psychotic symptom to the initiation of adequate antipsychotic drug treatment.[31] Likewise, this parameter was calculated on the basis of a clinical interview with the patient and his/her relatives.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a standard protocol. Analyses of *MDR1* gene polymorphisms were performed using TaqMan SNP genotyping assays made to order for rs2032582 (Assay C_11592758_10) and rs1045642 (Assay C_11592757_20). The total reaction volume consisted of 20 ng of genomic DNA, 2.5 μL of TaqMan Master Mix, and 0.125 μL of genotyping assay. The amplification was performed in 96-well plates using the TaqMan Universal Thermal Cycling Protocol. After the polymerase chain reaction (PCR) endpoint was reached, fluorescence intensity was measured with the 7500 real-time PCR system using SDS v2.1 software (Applied Biosystems). All genotyping was performed blind to patient outcome. As a quality control for our genotyping analyses, we used random blind duplicates.

Statistical analysis

The chi-square test or Fisher's exact test were used to compare genotype and allele frequencies between subjects.

A multivariate general linear model (MANOVA) was performed to identify differences in the quantitative variables of interest (affective flattening, alogia, avolition/apathy, anhedonia, attention impairment, hallucinations, delusions, bizarre behavior, and formal thought disorder were used as the dependent variables) between genotypes, avoiding the effects of multiple comparisons.[26] The rs2032582 and rs1045642 genotypes and gender were used as factors to identify potential genotype-gender interactions and to control the effects of gender on *MDR1* activity. For post-hoc calculation of statistical power in the *t* test for delusions in male and female subjects, we used the G*Power 3.0.10 software (Franz Faul, Universität

Table 1 SNP genotype distribution and allele frequencies

SNP	n (%)	Allele frequency (%)	Male (%)	Allele frequency (%)	Female (%)	Allele frequency (%)
rs2032582						
G/G	49 (31.0)	T (24.1)	29 (18.4)	T (28.5)	20 (12.7)	T (16.9)
G/T	55 (34.8)		43 (27.2)		12 (7.6)	
T/T	10 (6.3)	A (13.3)	7 (4.4)	A (11.2)	3 (1.9)	A (18.8)
G/A	42 (26.6)		22 (13.9)		20 (12.7)	
T/A	2 (1.3)	G (62.6)	1 (0.6)	G (60.3)	1 (0.6)	G (64.3)
Total	158		102		56	
rs1045642						
C/C	43 (27.2)	C (55.0)	25 (15.8)	C (55.8)	18 (11.4)	C (53.5)
C/T	88 (55.7)	T (45.0)	64 (40.5)	T (44.2)	24 (15.2)	T (46.5)
T/T	27 (17.1)		13 (8.2)		14 (8.9)	
Total	158		102		56	

SNP = single nucleotide polymorphism.

Kiel, Germany). The power was calculated as 0.39 (effect size 0.24, $\alpha = 0.05$, two-tailed).

Results

A total of 158 patients (102 male, 56 female) were included in this study. The mean age of the sample was 34.3 years (range, 17-59). The DUP was 129.90 weeks (standard deviation [SD], 238.7). The mean educational attainment was 11.98 years (SD, 3.36). As additional information, 90 participants (56.96%) were drug users (recreational drugs) and 48 (30.4%) had a history of suicidal behavior. The patients were distributed by genotype for the rs2032582 variant as follows: 49 G/G, 55 G/T, 10 T/T, 42 G/A, and 2 T/A. Likewise, for the rs1045642 genotype, patients were distributed as follows: 43 C/C, 88 C/T, and 27 T/T. The distribution of alleles and genotypes is presented in Table 1.

Relevant sociodemographic and clinical characteristics distributed by rs2032582 genotype are displayed in Table 2. When we evaluated total SANS scores, no significant differences were observed (p = 0.76) (Table 2) (we did not assess individual negative symptoms). In contrast, significant differences were observed in SAPS total (p = 0.01), hallucinations (p = 0.001), and bizarre behavior (p = 0.03) scores (Table 2). When the analysis was performed for rs1045642, no significant differences were observed on sociodemographic variables or positive or negative symptoms (data available upon request).

The results of the multivariate analysis were statistically significant for *MDR1* genotype rs2032582; for this variant, the between-subjects effects for *MDR1*, gender, and *MDR1*-gender interaction using MANOVA are shown in Table 3. *MDR1* genotypes showed statistically significant differences in between-subjects effects analysis for hallucinations (F = 4.28, p = 0.001) and bizarre behavior (F = 3.90, p = 0.02). Subsequently, we assessed whether symptom severity could be exacerbated by DUP by using DUP as a covariate. Statistical significance remained for hallucinations (F = 4.76, $p \leqslant 0.0001$) and bizarre behavior (F = 3.98, p = 0.002). In addition, the interaction between rs2032582 genotypes and gender gave significant differences for delusions (F = 3.09, p = 0.01); this was also observed with DUP as a covariate (F = 2.99, p = 0.02).

On post-test analysis, male carriers of genotype G/G exhibited a higher intensity of delusions; results are given as genotype and mean (SD) value as follows: G/A, 1.64 (1.29); G/G, 1.97 (1.29); G/T, 1.07 (0.91); T/T, 0.71 (0.75) (p = 0.02). In the female group, no significance was observed: G/A, 1.15 (0.93); G/G, 0.70 (0.73); G/T, 0.83

Table 2 Sociodemographic and clinical characteristics of patients distributed according to rs2032582 genotype

	G/G (49)	G/T (55)	T/T (10)	G/A (42)	T/A (2)	Total sample	F	p-value
Educational attainment (mean, SD)	12.21 (4.05)	12.17 (3.52)	11.40 (2.95)	11.62 (2.45)	12.50 (0.70)	11.99 (3.36)	0.28	0.88
Age (mean, SD)	35.33 (9.72)	33.84 (10.53)	33.40 (7.69)	33.71 (10.87)	38.00 (2.82)	34.29	0.72	0.89
Age of onset (mean, SD)	23.78 (8.97)	23.45 (8.17)	25.70 (8.70)	21.00 (6.35)	21.50 (4.95)	23.02 (8.03)	1.11	0.35
DUP (mean in weeks)	123.50 (198.86)	117.02 (269.21)	56.20 (83.69)	177.23 (263.00)	58.00 (65.05)	129.90 (238.73)	0.70	0.58
SANS, total	6.90 (3.39)	7.40 (4.00)	6.80 (3.58)	7.14 (3.23)	10.00 (1.41)	7.17 (3.56)	0.46	0.76
SAPS, hallucinations	1.10 (1.00)	0.65 (0.70)	0.40 (0.69)	1.38 (1.01)	1.00 (1.41)	0.97 (0.94)	5.17	0.001
SAPS, delusions	1.45 (1.25)	1.02 (0.87)	1.00 (1.05)	1.40 (1.14)	1.00 (1.41)	1.25 (1.10)	1.38	0.24
SAPS, bizarre behavior	0.49 (0.73)	0.40 (0.68)	0.30 (0.67)	0.83 (0.82)	0	0.53 (0.75)	2.73	0.03
SAPS, positive formal thought disorder	0.57 (0.93)	0.42 (0.71)	0.40 (0.514)	0.45 (0.63)	0	0.47 (0.75)	0.50	0.73
SAPS, total	3.61 (3.09)	3.61 (3.09)	2.10 (2.02)	4.07 (2.74)	2.00 (2.82)	3.23 (2.65)	3.08	0.01

Results of multivariate ANOVA.
ANOVA = analysis of variance; DUP = duration of untreated psychosis; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation.

Table 3 Results of between-subjects effects analysis using multivariate ANOVA

Factor/dependent variable	F	p-value	Power
rs2032582			
SANS, total	0.639	0.67	0.22
SAPS, total	2.15	0.06	0.69
SAPS, hallucinations	**4.28**	**0.001**	**0.95**
SAPS, delusions	0.90	0.47	0.31
SAPS, bizarre behavior	**3.90**	**0.02**	**0.93**
SAPS, positive formal thought disorder	0.27	0.92	0.11
Gender			
SANS, total	0.01	0.90	0.05
SAPS, total	< 0.001	0.98	0.05
SAPS, hallucinations	0.10	0.74	0.06
SAPS, delusions	0.18	0.66	0.07
SAPS, bizarre behavior	0.03	0.86	0.05
SAPS, positive formal thought disorder	0.56	0.45	0.11
rs2032582 x gender interaction			
SANS, total	0.44	0.81	0.16
SAPS, total	2.13	0.06	0.69
SAPS, hallucinations	1.40	0.22	0.48
SAPS, delusions	**3.09**	**0.01**	**0.86**
SAPS, bizarre behavior	0.99	0.42	0.34
SAPS, positive formal thought disorder	1.62	0.15	0.55

Bold type denotes significant values.
SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms.

(0.71); T/T, 1.67 (1.52) (p = 0.17). However, when we compared the female vs. male groups, differences were statistically significant in the G/G group (t = 3.94, p = 0.0003). The associations between the interaction effect for gender and delusions in *MDR1* variant rs2032582 are displayed in Figure 1.

Discussion

We investigated the association between *MDR1* polymorphisms (rs2032582 and rs1045642) and severity of clinical characteristics in patients with schizophrenia. To our knowledge, this was the first study to do so.

Regarding the rs2032582 polymorphism, we observed that patients with a G homozygous genotype exhibited greater severity of hallucinations and delusions. The mechanism by which synonymous gene variants predispose for higher severity in these symptoms remains unknown. It might be that the tridimensional structure of P-gp is modified when a hydrophilic amino acid (Ser or Thr) replaces the lipophilic one (Ala), making P-gp less substrate-specific.[12,32,33]

MDR1 gene variant rs2032582 has been associated with treatment response to olanzapine and risperidone in schizophrenic patients.[34] Moreover, one study has associated the rs2032582 variant with treatment response to olanzapine in female schizophrenic patients; the major response occurred in females with the T/T genotype, and this was not observed in the male group.[35] In our study, we observed minor severity of delusions in carriers of the T allele and major severity in male G/G carriers (Figure 1); this suggests that a specific genotype of *MDR1* rs2032582 may play a gender-dependent role in schizophrenia. However, more studies are needed to propound conclusive results.

Some general observations can be drawn from these data: 1) the rs2032582 variants of *MDR1* can be associated with severity of hallucinations and delusions in schizophrenic patients; and 2) particularly, male carriers of the G/G genotype of the rs2032582 variant exhibited more delusions.

It is possible that *MDR1* only has an effect on some of the symptoms of schizophrenia (positive and negative); furthermore, the influence may not be seen in all schizophrenic patients, but rather in certain subtypes of

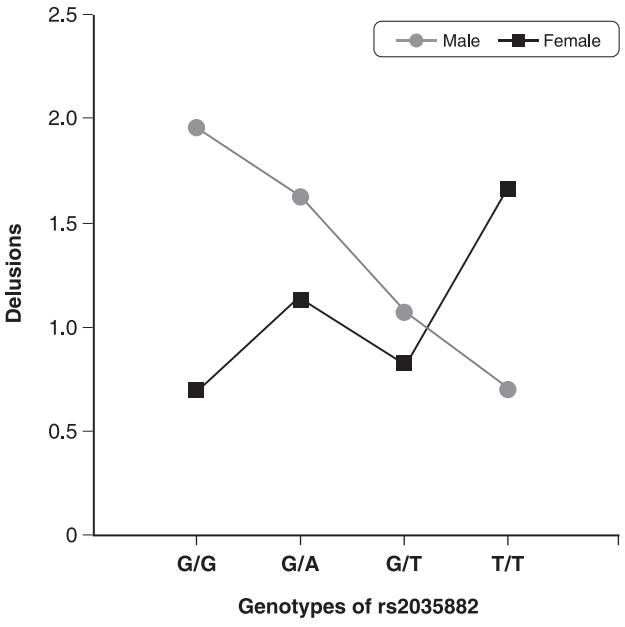

Figure 1 Interaction between delusions and *MDR1* polymorphism according to gender

this condition. This constitutes a limitation of our study, as we did not divide our sample into subtypes. Another limitation is that we did not consider other factors that could exert an influence on negative and positive symptoms, such as smoking or drug abuse. In addition, we did not consider the total variation of SANS and SAPS over a given period. The fourth limitation is the relatively small sample of the populations studied. Finally, we did not analyze response to any drugs (pharmacogenetics) in these schizophrenic patients. In contrast, a positive point to consider is that we used a relatively ethnically homogeneous cohort; nonetheless, we recognize that the Mexican population is itself heterogeneous.

In conclusion, we found a significant association of the *MDR1* rs2032582 polymorphism with the severity of hallucinations and delusions in schizophrenia. Male carriers of allele G of the rs2032582 variant may exhibit greater severity of delusions. However, because of the limitations of our sample, these results should be taken as preliminary. Replication studies in populations of different ethnic origins are required to support these findings and continue the search for alternative and improved treatments for schizophrenic patients.

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Disclosure

The authors report no conflicts of interest.

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