

Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population

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Risperidone non-compliance is often high due to undesirable side effects, whose development is in part genetically determined. Studies with genetic variants involved in the pharmacokinetics and pharmacodynamics of risperidone have yielded inconsistent results. Thus, the aim of this study was to investigate the putative association of genetic markers with the occurrence of four frequently observed adverse events secondary to risperidone treatment: sleepiness, weight gain, extrapyramidal symptoms and sexual adverse events. A series of 111 schizophrenia inpatients were genotyped for genetic variants previously associated with or potentially involved in risperidone response. Presence of adverse events was the main variable and potential confounding factors were considered. Allele 16Gly of *ADRB2* was significantly associated with a higher risk of sexual adverse events. There were other non-significant trends for *DRD3* 9Gly and *SLC6A4* S alleles. Our results, although preliminary, provide new candidate variants of potential use in risperidone safety prediction.

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Introduction

Since 1959 when Vogel coined the term pharmacogenetics, there is increasing evidence that therapeutic outcome is influenced genetically.¹ One of the most important applications might be schizophrenia management because of the high prevalence of this illness (1% approximately across countries and cultures) and the non-compliance often seen with the antipsychotic treatment.² Risperidone is a widely prescribed antipsychotic for the treatment of schizophrenia, with a relatively high rate of non-effectiveness or intolerable side effects.² In fact, extensive research has been devoted to elucidate the genetic underpinnings of risperidone response to reduce its adverse effects.³

Risperidone pharmacogenetic studies have focused on clinical improvement and adverse events, such as the frequently observed extrapyramidal symptoms (EPS),⁴ hyperprolactinemia,⁵ hyperlipidemia,⁶ weight gain⁷ and metabolic syndrome.⁸ Candidate genes to be involved in the above mentioned events have been *CYP2D6* and *MDR1*, related to pharmacokinetics and *DRD2*,⁹ *DRD3*,⁴ *HTR2A* or *HTR2C*,⁷ all of them coding risperidone targets. Additionally, others like *BDNF*,⁷ *COMT*,¹⁰ *HTR1A*,¹¹ *HTR6*⁷ or *LEP*¹² have been explored in relation with risperidone effectiveness or side effects. However, all of them have yielded

conflicting results, so no definitive genetic marker predictive of risperidone response exists currently.

Thus, the aim of this study was to examine the putative association of several genetic markers related to risperidone pharmacokinetics and pharmacodynamics or potentially involved, with four of the most frequent and discomforting adverse events secondary to risperidone treatment (sleepiness, weight gain, EPS and sexual dysfunction)² in a sample of acutely ill schizophrenic inpatients.

Subjects and methods

Subjects

As a part of a larger pharmacogenetic schizophrenia project, 111 acutely ill schizophrenic patients were recruited at the Department of Psychiatry of Fundacion Jimenez Diaz Hospital between 2004 and 2009. All subjects were adult patients hospitalized in an Acute Psychiatric Unit, unrelated and Caucasian. DSM-IV diagnosis was obtained by means of a brief structured psychiatric interview, the Spanish version of the Mini International Neuropsychiatric Interview version 4.4 (MINI 4.4).¹³ The study was approved by the Research Ethics Committee of Fundacion Jimenez Diaz Hospital and conducted according to the tenets of the Declaration of Helsinki. All participants signed an informed consent form after the explanation of the study objective and procedures.

Clinical data

All subjects were inpatients with variable length of hospital stay. They were all treated with risperidone. Treatment dosage was established according to patient's clinical state. Concurrent treatments, such as other antipsychotics, anticholinergics, antidepressants, antiepileptics or benzodiazepines, were used. Sex, age, risperidone dosages, length of hospitalization and concomitant treatments were considered as potential confounding factors for the association with the genetic variants. The main variables, sleepiness, weight gain, EPS and sexual adverse events, were assessed with the UKU scale¹⁴ at the hospital discharge by psychiatrists trained in the UKU evaluation.

Variant selection and genotyping

Genomic DNA was extracted from 7 ml of peripheral blood samples using an automatic DNA extractor (BioRobot EZ1, Qiagen, Hilden, Germany). Genes, variants and the rationale for the selection are summarized in Table 1. All genetic variants investigated were either previously related to risperidone outcome or potentially involved (Table 1). Some of them were included in PHARMACHip,¹⁵ a commercially available tool whose suitability in pharmacogenetic genotyping has been previously described,^{16,17} and others were determined by allelic discrimination or sequencing (Table 1). Allelic discrimination was performed using TaqMan Pre-Designed SNP genotyping assays (Applied Biosystems, Foster City, CA, USA) in a LightCycler 480 (Roche Diagnostics, Mannheim, Germany). Sequencing was used to genotype *BDNF* Val66Met and to verify the truthfulness of the allelic discrimination results with a BigDye

Terminator Cycle Sequencing Kit and an ABI Prism 3130xl DNA sequencer (Applied Biosystems). Primer sequences and conditions are available upon request.

Data and statistical analysis

All genetic variants were tested for Hardy-Weinberg equilibrium (HWE) deviation using Pearson Chi-squared test (χ^2). The association of the genetic variants with the dependent variable was performed through the codominant genetic model in all cases except *CYP2D6*, whose genotypes were grouped based on the number of functional alleles into poor metabolizers (two defective alleles), intermediate metabolizers (one defective allele), extensive metabolizers (two functional alleles) and ultra rapid metabolizers (more than two functional alleles), according to a previous report by Gaedigk *et al.*³¹

The presence of all four adverse events (sleepiness, weight gain, EPS and sexual adverse events), notwithstanding their severity, was the main variable. EPS category consisted of the UKU items akathisia, hyperkinesia, hypokinesia, rigidity or tremor. The sexual adverse event category included the following items: diminished sexual desire, dry vagina and erectile, ejaculatory and orgasmic dysfunctions. For both EPS and sexual adverse effects, 'presence' was considered as the occurrence of at least one of the signs or symptoms.

For continuous variables, mean and standard deviations were calculated and also data distributions were tested for normality. In case of non-adjustment, they were categorized for the statistical analysis.

Logistic regression was used to examine the association of the genotypes with the presence of the adverse events, adjusting for covariates. The strength of the association was measured with the odds ratio (OR) and its 95% CI (confidence interval). The effect of the genetic variant on the outcome was adjusted by those demographic and clinical variables (covariates) either associated with the outcome ($P < 0.05$) or modifying the risk (change in putative OR > 20%) of the genetic variant on the outcome. Hence, the effect of the covariates on the risk to develop the adverse events was also investigated.

Because of the multiple testing, Bonferroni correction was applied and the cutoff value was set as $P \leq 0.003$ ($P = 0.05/19$ hypothesis tested).

Statistical analysis was carried out using the STATA v10 software (Stata Corp, TX, USA).

Results

Clinical and genetic data

None of the continuous variables were normally distributed, so they were categorized for the analysis as shown in Table 2. Age of the patients (45 ± 13 years) was grouped into <40 years, 40–59 years and ≥ 60 years; and length of hospital stay (13 ± 9 days) was transformed considering the median of data distribution (12 days).

Patients were prescribed oral (mean dosage = 8.1 ± 3.3 mg) and intramuscular (25–100 mg biweekly) risperidone. 73% ($n = 81$) were taking oral risperidone, 6.3% intramuscular

Table 1 Genetic variants included in the pharmacogenetic study

Gene	Gene name	Genetic variant	Function	Previous associations ^{ref.}
<i>Pharmacokinetics</i>				
<i>CYP2D6</i> ^a	Cytochrome P450 2D6	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *40, *41; *1XN, *2XN, *4XN, *10XN, *17XN, *35XN, *41XN	Risperidone metabolism	Risperidone plasma levels, effectiveness and adverse events ^{18,19}
<i>CYP3A4</i> ^a	Cytochrome P450 3A4	*1B	Risperidone metabolism	Risperidone plasma levels and effectiveness ²⁰
<i>MDR1</i> ^a	Multidrug resistance 1	3435C>T	Risperidone active transporter	Risperidone induced adverse events and response ^{21,22}
<i>Pharmacodynamics</i>				
<i>ADRA1</i> ^b	Adrenergic receptor α 1	−4884A>G −4155C>G −563C>T	Risperidone target	Atypical antipsychotic response (negative findings) ²³
<i>ADRB1</i> ^a	Adrenergic receptor β 1	Arg389Gly	Members of the adrenergic pathway	Potentially involved in risperidone response
<i>ADRB2</i> ^a	Adrenergic receptor β 2	Arg16Gly	Related to serotonin pathway	Risperidone effectiveness and adverse events ^{7,24}
<i>BDNF</i> ^b	Brain-derived neurotrophic factor	Val66Met	Member of dopaminergic pathway	Risperidone effectiveness ²⁵
<i>COMT</i> ^a	Catechol-o-Methyl transferase	Val108Met	Risperidone target	Risperidone effectiveness and adverse events ^{9,26}
<i>DRD2</i> ^b	Dopamine receptor D2	Taq1A	Risperidone target	Risperidone effectiveness and adverse events ^{4,27}
<i>DRD3</i> ^a	Dopamine receptor D3	Ser9Gly	Risperidone target	System previously associated to risperidone outcome ²⁸
<i>GRIN2B</i> ^a	Glutamatergic receptor 2B	2667C>T	Member of serotonergic pathway	Effectiveness (negative findings) ²⁶
<i>HTR1A</i> ^b	Serotonin receptor 1A	−1019C>G	Risperidone target	Effectiveness and adverse events ^{27,29}
<i>HTR2A</i> ^a	Serotonin receptor 2A	102C>T His452Tyr	Risperidone target	Effectiveness and adverse events ²⁷
<i>HTR2C</i> ^b	Serotonin receptor 2C	−759C>T	Risperidone target	Effectiveness and adverse events ²⁷
<i>HTR6</i> ^b	Serotonin receptor 6	267T>C	Member of serotonergic pathway	Effectiveness ³⁰
<i>SLC6A4</i> ^a	Serotonin transporter	Promoter VNTR		

Abbreviation: VNTR, variable number tandem repeat.

^aGenotyped with PHARMACHip genotyping array.^bAllelic discrimination or sequencing.

($n=7$) and 20.7% were taking both forms ($n=23$). Risperidone dosages were grouped according to the terciles of data distribution (11 missing data), if administered orally, and in three categories in the case of intramuscular administration (2 missing data). Concomitant treatments were classified according to the therapeutic group (Table 2).

All genetic variants investigated were in HWE except *ADRB2* 16Gly ($P=0.002$). When grouping *CYP2D6* according to the number of defective alleles, 3 subjects were classified as poor metabolizers and 3 as ultra rapid metabolizers (0.294), 32 as intermediate metabolizers (0.314) and 64 as extensive metabolizers (0.628) (there were 9 subjects, which genotype was missing). For the X chromosome *HTR2C* −759C>T variant, CC accounted for

84 subjects (0.764) and allele T was present in 26 patients (0.236) (1 genotype was missing). Genotype frequencies of the remaining variants are summarized in Table 3. In one sample, no genotyping results for the PHARMACHip variants could be obtained because of the low quality of the DNA. Additionally, there were 5 missing genotypes for *SLC6A4*, also included in the array. For variants determined by allelic discrimination, there were 4 missing genotypes for *ADRA1* −4884G>A, 9 for *BDNF* Val66Met and 3 in case of *HTR1A* −1019C>G.

Regarding the four adverse events investigated, the most frequent was sleepiness in 66 patients (56.7%), weight gain and EPS were observed in 40 patients each (36%) and 25 patients had sexual adverse events (22.5%).

Genetic associations with adverse events

When the genotype significantly associated with the outcome was the heterozygous one, dominant genetic model

Table 2 Frequency of patients according to the demographic and clinical variables

Variable	Category	n (%)
Sex	Males	62 (55.8)
	Females	49 (44.2)
Age	< 40 years	38 (34)
	40–59 years	61 (55)
	≥ 60 years	12 (11)
Hospital stay	≤ 12 days	57 (62)
	> 12 days	35 (38)
Oral risperidone dosages	< 6 mg per day	44 (47)
	6–9 mg per day	28 (30)
	> 9 mg per day	21 (23)
Intramuscular risperidone dosages	0 mg	81 (73)
	< 50 mg per 2 weeks	9 (8.1)
	≥ 50 mg per 2 weeks	19 (17.1)
Concomitant treatments	Anticholinergics	21 (21)
	Antidepressants	10 (9)
	Antiepileptics	12 (10.8)
	Atypical antipsychotics	7 (6.3)
	Benzodiazepines	54 (48.6)
	Classical antipsychotics	12 (10.8)
	Lithium	2 (1.8)

There were missing data for hospital stay (19) and risperidone dosages (11 for oral and 2 for intramuscular).

was also evaluated. The only association that remained significant after Bonferroni correction was that of *ADRB2* 16Gly as a risk factor for developing risperidone-induced sexual adverse events (Table 4). Furthermore, as shown in Table 4, there were also some non-significant trends: *DRD3* 9Gly was present with a higher incidence in those patients who developed risperidone-induced sleepiness and, conversely, it appeared less frequently in patients with EPS. Additionally, allele S of *SLC6A4* was underrepresented in patients with weight gain (S/S) and also in those with sexual adverse events (L/S).

Besides considering the demographic and clinical variables as potential confounding factors, it was also evaluated whether they could influence the development of the four adverse events investigated. Only anticholinergic consumption was associated with a higher incidence of weight gain (OR = 3.28; 95% CI: 1.02–10.54; *P* = 0.046).

Discussion

The present study sought to evaluate the possible association of genetic variants related to risperidone pharmacokinetics and pharmacodynamics, and others with potential involvement, with the risk of developing four of the most frequent adverse events secondary to risperidone treatment.

The investigation of the genetic basis of risperidone safety has traditionally focused on weight gain and EPS, considered as the most handicapping adverse effects.³² However, to our knowledge, no report has examined sleepiness or sexual

Table 3 Allelic and genotypic frequencies of the genetic variants investigated

Genetic variant	Allele (N(p))		Genotype (N (p))		
	A	B	AA	AB	BB
<i>ADRA1</i> –563C>T	123 (0.554)	99 (0.446)	33 (0.297)	57 (0.513)	21 (0.189)
<i>ADRA1</i> –4155C>G	109 (0.491)	113 (0.509)	26 (0.234)	57 (0.514)	28 (0.252)
<i>ADRA1</i> –4884A>G	167 (0.780)	47 (0.220)	65 (0.607)	37 (0.346)	5 (0.047)
<i>ADRB1</i> Arg381Gly	58 (0.264)	162 (0.736)	10 (0.091)	38 (0.345)	62 (0.564)
<i>ADRB2</i> Arg16Gly	169 (0.768)	51 (0.232)	75 (0.682)	19 (0.173)	16 (0.145)
<i>BDNF</i> Val66Met	161 (0.789)	43 (0.211)	65 (0.637)	31 (0.304)	6 (0.059)
<i>COMT</i> Val108Met	116 (0.527)	104 (0.473)	29 (0.264)	58 (0.527)	23 (0.209)
<i>CYP3A4</i> *1B	116 (0.527)	104 (0.473)	6 (0.054)	104 (0.945)	0 (0.000)
<i>DRD2</i> Taq1A	181 (0.815)	41 (0.185)	75 (0.676)	31 (0.279)	5 (0.045)
<i>DRD3</i> Ser9Gly	147 (0.668)	73 (0.332)	48 (0.436)	51 (0.464)	11 (0.100)
<i>GRIN2B</i> 2664C>T	174 (0.791)	46 (0.209)	69 (0.627)	36 (0.327)	5 (0.045)
<i>HTR1A</i> –1019C>G	103 (0.477)	113 (0.523)	29 (0.268)	45 (0.417)	34 (0.315)
<i>HTR2A</i> His452Tyr	196 (0.891)	24 (0.109)	86 (0.782)	24 (0.218)	0 (0.000)
<i>HTR2A</i> 102C>T	123 (0.559)	97 (0.441)	38 (0.345)	47 (0.427)	25 (0.227)
<i>HTR2C</i> –759C>T	179 (0.821)	39 (0.179)	80 (0.734)	19 (0.174)	10 (0.092)
<i>HTR6</i> 267C>T	188 (0.847)	34 (0.153)	81 (0.730)	26 (0.234)	4 (0.036)
<i>MDR1</i> 3435C>T	113 (0.514)	107 (0.486)	34 (0.309)	45 (0.409)	31 (0.282)
<i>SLC6A4</i> L/S	126 (0.613)	86 (0.387)	38 (0.358)	50 (0.472)	18 (0.170)

A refers to wild-type allele and B to the mutant one. For *HTR2C* –759C>T AA=CC (females)+C (males); AB=CT (females) and BB=TT (females)+T (males). N=Absolute frequency and P=relative frequency.

Table 4 Association of the genetic variants with the adverse events

Adverse event (n (%))	Genetic variant	Genotypic frequencies (n (%))		OR (95% CI)	P
		Cases	Controls		
Sexual adverse events (25 (22.5%))	<i>ADRB2</i> 16Gly	14 (56%)	21 (25%)	4.58 (1.72–12.20)	0.002*
	<i>SLC6A4</i> L/S	6 (25%)	44 (53.6%)	0.22 (0.06–0.75)	0.015
Sleepiness (66 (56.7%))	<i>DRD3</i> 9Gly	40 (64.5%)	22 (45.8%)	2.47 (1.00–6.09)	0.050
EPS (40 (36%))	<i>DRD3</i> 9Gly	18 (45%)	44 (62.8%)	0.29 (0.11–0.79)	0.015
Weight gain (40 (36%))	<i>SLC6A4</i> S/S	1 (2.7%)	17 (24.6%)	0.07 (0.01–0.66)	0.020

Significant findings (*; $P < 0.003$) and non-significant trends ($P < 0.05$) from the genetic association study after adjusting with the potential confounding variables.
* $P < 0.003$.

adverse events, which are reported by patients to be as frequent and discomforting as the formers.²

This pharmacogenetic study describes for the first time the association between *ADRB2* 16Gly and a greater susceptibility of developing sexual adverse events in schizophrenic patients under risperidone treatment, considering potential demographic and clinical confounding factors. The elevated frequency of sexual dysfunction among schizophrenia patients treated with antipsychotics has been reported to reduce patients' quality of life.³³ Even though the incidence of these adverse events can reach as much as 50% of patients and that usually lead to treatment non-compliance,³³ to our knowledge no pharmacogenetic study concerning sexual adverse events secondary to risperidone therapy has been performed until date. Sexual normal function involves several neurotransmitter systems, such as dopaminergic, adrenergic and serotonergic, involved in processes like erection, ejaculation and orgasm.³⁴ Therefore, the disruption of any of these systems might lead to sexual side effects and would support our findings about *ADRB2* 16Gly as a risk factor, which has been linked to lower β 2 adrenergic receptor density and efficiency.³⁵ It should be noted that although *ADRB2* 16Gly did not meet HWE it was not removed from the study to prevent from the possibility of being out of HWE because of a linkage with the disease. All patients were ascertained by their disease status and so, the subject selection was not random, which is one of the premises of HWE for genotypic frequencies to reach a fixed value.

We are aware that genotyping errors should also be considered as a cause of HWE departure. In this regard, two relatively recent reports have demonstrated the accuracy of *PHARMACHip* in genotyping, one of them performed by our group.^{16,17} Nevertheless, our previously mentioned study also reports this variant deviating from HWE in the Spanish control population.¹⁶ However, it has been demonstrated that this typically occurs in several European populations, suggesting this variant is subject to selective forces, such as parental selection or epistasis, leading to oscillations in genotype frequencies.³⁶

Therefore, considering all the above explanations, although preliminary, this result should be taken into account and be further validated in an independent sample.

Although *ADRB2* 16Gly was the only variant that met Bonferroni cutoff value, there were some non-significant

trends that should be highlighted. Although multiple comparison adjustment is necessary in order to avoid type-I error, it significantly increases type II and therefore the likelihood of false negatives, and Bonferroni correction is especially conservative in this regard. The consequence of the adjustment is a decrease in the statistical power, which was already low because of the population sample size, and the increase in the rate of false negative findings. Indeed, for the association of the event with the higher incidence and the genotype with the higher frequency, it is only possible to detect, with 80% statistical power, ORs greater than 4 (or lower than 0.25), which is higher than expected. It is suggested that the risk that genetic variants confer to the complex phenotypes, such as risperidone response, range from low to moderate.³⁷ In consequence, it would require substantially larger sample sizes to detect associations with lower ORs, for genotypes with lower frequencies or for adverse events with lower incidence. In any case, the study was performed through a candidate gene approach, where the rationale for the variant selection was to be linked to risperidone pharmacokinetic and/or pharmacodynamic pathways. Additionally, among all possible variants, we chose from the literature those with the higher likelihood of being involved in the occurrence of the outcomes, because of the existence of previous positive findings. Hence, given that the study was hypothesis-driven and due to the small sample size of the population included, the non-significant trends found should not be completely ruled out, but considered as exploratory findings that need to be further confirmed.

One of those non-significant trends was the higher incidence of sleepiness in patients carrying allele 9Gly of *DRD3*. *DRD3* Ser9Gly variant has been extensively studied with regard to many antipsychotics' effectiveness and safety, but with inconsistent results.^{38,39} In the present study, the higher propensity observed to sleepiness among patients with the *DRD3* 9Gly allele suggests that disruption of the dopaminergic neurotransmission might contribute to the sleep disturbances experienced by schizophrenic patients, as it is well established that dopaminergic system participates in the wake-sleep cycle.⁴⁰ Conversely, the same allele was linked to a lower incidence of EPS. Although the atypical antipsychotics are known to be safer concerning motor side effects compared with the classical ones, risperidone treatment is known to have a relatively high rate of EPS.³²

Whereas data on the possible relevance of the Ser9Gly variant of *DRD3* in EPS are still controversial,^{4,41} our study reports a trend to a protective effect of the 9Gly allele. That effect could be explained by the role that D3 receptors have in motor control,⁴² with their agonists exerting an inhibitory effect.⁴³ This, together with the higher affinity and effectiveness that dopamine shows for D3 receptors with the 9Gly variant⁴⁴ could be in line with the observed effect.

On the other hand, patients carrying the *SLC6A4* S/S genotype were less likely to gain weight secondarily to risperidone treatment. Currently, there is an increasing concern regarding weight gain in schizophrenia patients, as it significantly impacts the antipsychotic compliance.⁴⁵ Although the exact mechanism for antipsychotic-related weight gain remains unclear, the serotonergic system has emerged as a strong candidate.⁴⁵ Specifically and based on the large body of evidence that supports the role of serotonin in regulating feeding behavior, variants in genes involved in serotonergic neurotransmission, such as *HTR2A*, *HTR2C*, *HTR6* or *BDNF*, have been previously associated with weight gain secondary to risperidone treatment.⁷ Despite our failure to replicate the above-mentioned associations, the lower incidence of weight gain in *SLC6A4* S/S carriers is in consonance with the recent report by Bah *et al.*,⁴⁶ who found this genotype to be more prevalent in underweight control individuals.

Further, the L/S genotype was observed to predispose patients to lower incidence of sexual adverse events. As previously mentioned, the serotonergic system participates in normal sexual function and so carrying the *SLC6A4* short allele could protect patients from developing sexual dysfunction secondary to risperidone treatment.

Overall, none of the previous associations were replicated. Strikingly, variants in *CYP2D6* and *MDR1*, which have been reported to influence risperidone plasma concentrations^{18,47} did not yield significant results. *CYP2D6* is involved in the hydroxylation of risperidone to 9-OH risperidone⁴⁷ and there is increasing evidence about the correlation between the number of functional *CYP2D6* alleles and both risperidone and 9-OH risperidone plasma concentrations.^{18,47} Similarly, *MDR1*, involved in risperidone transportation through the blood-brain barrier,⁴⁸ has been several times associated with risperidone plasma concentrations,⁴⁹ effectiveness and safety.^{21,22} *MDR1* encodes P-glycoprotein, a drug transporter that works limiting risperidone entry to the brain.⁵⁰ The 3435T allele of *MDR1* results in lower P-glycoprotein expression,⁵¹ which may result in higher brain risperidone concentrations. According to their role in risperidone pharmacokinetics, it was expected for *CYP2D6* and *MDR1* to impact significantly the development of adverse events. However, once again, the small sample size studied could have been responsible for the negative findings.

The non-replication and the lack of association found for most of the genetic variants investigated point out the complexity of risperidone response, which is determined by the interaction of several genetic and environmental factors³⁷ and whose contribution to the antipsychotic response is difficult to establish. In addition, there are other factors, intrinsic to psychiatric patients management, and

hence, to pharmacogenetic studies on antipsychotics, that makes complex the search of the genetic basis of drug response. Such factors are the uncertainty of the psychiatric phenotype, the variety of treatments administered in psychiatric patients and the large number of confounding factors affecting the antipsychotic response, what conforms a heterogeneous subject sample. All these factors, typically common to all pharmacogenetic studies on antipsychotics, together with the small sample size here investigated, could have been responsible for the negative findings yielded in this study and for the general inconsistencies of pharmacogenetic studies in schizophrenia. The consequence is the inexistence of a definitive predictive factor of risperidone response until date.

In conclusion, although further replication in an independent sample with adequate statistical power is needed, this study provides new candidate genetic variants of potential use in risperidone safety prediction. Additionally, it points out the importance adrenergic, dopaminergic and serotonergic disruption might have in the risk of developing four of the most handicapping adverse events secondary to risperidone treatment, namely sleepiness, weight gain, EPS and sexual adverse events.

Conflict of interest

The authors declare no conflict of interest.

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