International Journal of Neuropsychopharmacology (2007), **10**, 631–637. Copyright © 2006 CINP
doi:10.1017/S146114570600719X

ARTICLE

CINP

The relationship between the therapeutic response to risperidone and the dopamine D_2 receptor polymorphism in Chinese schizophrenia patients

Qinghe Xing[1,2], Xueqing Qian[1,2], Huafang Li[3], Shiming Wong[3], Shengnan Wu[1,2], Guoyin Feng[3], Shiwei Duan[1,2], Mingqing Xu[1,2], Rui Gao[1,2], Wei Qin[1,2], Jianjun Gao[1,2], Junwei Meng[1,2] and Lin He[2,4]

[1] *Bio-X Centre, Shanghai Jiao Tong University, Shanghai, PR China*
[2] *Institute for Nutritional Sciences, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, Shanghai, PR China*
[3] *Shanghai Institute of Mental Health, Shanghai, PR China*
[4] *NHGG, Bio-X Center, Shanghai Jiao Tong University, Shanghai, PR China*

Abstract

Antipsychotic drugs exert both therapeutic and adverse effects through dopamine D_2 receptor (DRD2) antagonism. Genetic variants of this receptor may be responsible for individual variations in neuroleptic response and may therefore be useful in predicting response. In this study we evaluated the role of six polymorphisms of the *DRD2* gene in 125 risperidone-treated Chinese schizophrenia patients following the hypothesis that variation in the *DRD2* gene could affect drug response. Response was categorized as a change of $>40\%$ on the Brief Psychiatric Rating Scale (BPRS). Our results show that genotyping A-241G may help to predict the efficacy of risperidone treatment on the basis that patients with the A allele showed greater improvement than those with the G allele on the overall BPRS ($\chi^2 = 7.19$, $p = 0.007$, $p = 0.031$ after correction by the program SNPSpD), while other polymorphisms, including −141C Ins/Del, *Taq*IB, rs1076562, T939C and *Taq*IA, did not show any association with the response to risperidone. These data suggest that the *DRD2* A-241G polymorphism or, alternatively, another genetic variation that is in linkage disequilibrium, may influence response to risperidone in schizophrenia patients.

Received 1 February 2006; Reviewed 22 April 2006; Revised 30 June 2006; Accepted 26 July 2006; First published online 14 November 2006

Key words: Association, dopamine D_2 receptor, haplotype, polymorphism, response, risperidone.

Introduction

Risperidone is one of the most commonly used novel antipsychotic drugs. It has many clinical advantages over classic neuroleptics, including a lower incidence of extrapyramidal symptoms (EPS); a more frequent clinically significant improvement; a lower risk of relapse; and a favourable effect on both positive and negative symptoms (Csernansky et al., 2002; Heck et al., 2000; Peuskens, 1995). Risperidone causes less weight gain, but can increase prolactin levels and cause EPS dependent on dosage. In a variety of pharmacoeconomic analyses, it has proven to be a cost-effective addition to the antipsychotic armoury (Love and Nelson, 2000). As with all antipsychotics, there are wide individual differences in response to risperidone, both regarding therapeutic effects and adverse effects. This inter-individual variability in response to risperidone imposes some limitations with respect to the therapeutic use of the drug. In particular, the selection of both initial and final doses of risperidone for individual patients becomes difficult, as the same dose of risperidone may have markedly different efficacy and adverse reaction in different patients (Freudenreich and Goff, 2002). It is therefore important to determine the sources of inter-individual variation in response and to predict the clinical response before treatment with risperidone begins.

Correspondence should be addressed to: Dr Lin He or Dr Qinghe Xing, Shanghai Jiao Tong University, Bio-X Centre, Hao Ran Building, 1954 Hua Shan Road, Shanghai 200030, China; or Institute for Nutritional Sciences, SIBS, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai 200031, China.
Tel.: 86-21-62822491 *Fax*: 86-21-62822491
E-mail: helin@nhgg.org

Risperidone is a benzisoxazole derivative with combined dopamine D_2 (DRD2) and serotonin 5-HT_2 receptor-blocking properties (Kane, 1996). DRD2 blockade is believed to be the central mechanism by which conventional atypical antipsychotic drugs (APDs) achieve their effects and probably plays a key role in response to newer atypical antipsychotics (Kapur and Remington, 2001). In-vitro studies show that all antipsychotics bind to the DRD2, and in most cases the clinical doses correlate with their affinity for the DRD2 receptor. Recent studies have demonstrated that the blockade of DRD2 is associated with the response to antipsychotic medication, EPS and elevation of prolactin levels. The degree of receptor occupancy can predict clinical improvement, hyperprolactinaemia, and EPS (Kapur et al., 2000). Therefore, *DRD2* genetic variants which influence D_2 receptor density and/or function may be important in explaining variability in response to risperidone.

The human *DRD2* gene is located on chromosome 11q22–23, and consists of eight exons separated by seven introns. To date, several SNPs in the *DRD2* gene have been identified as being associated with DRD2 density and/or function:

(1) −141C Ins/Del polymorphism. Previous studies have demonstrated a lower density of DRD2 in subjects with no Del alleles of the −141C Ins/Del polymorphism in the *DRD2* gene promoter region than in those with one or two Del alleles (Arinami et al., 1997).
(2) *Taq*IA polymorphism. This polymorphism is related to dopaminergic function in the human brain (Pohjalainen et al., 1998; Thompson et al., 1997). In particular, the T (A1) allele has been reported to be associated with lowered density and diminished function. Recently this SNP has been shown to reside in the coding region of a novel kinase gene called ankyrin repeat and kinase domain containing 1 (*ANKK1*) and causes an amino-acid substitution in the last ankyrin repeat (Dubertret et al., 2004; Neville et al., 2004). It is possible that the *Taq*IA polymorphism is linked to *DRD2* either by being on the same haplotype as a functional polymorphism or because *ANKK1* affects the dopaminergic system via signal transduction response.
(3) rs6277 (C957T). Most recently, it has been demonstrated that the 957T, rather than being 'silent', alters the predicted mRNA folding, leading to a decrease in mRNA stability and translation, and dramatically changing dopamine-induced upregulation of *DRD2* expression (Duan et al., 2003; Hirvonen et al., 2004).
(4) *Taq*IB. The C (B1) allele of the *Taq*IB polymorphism, has been associated with reduced D_2 density in the striatum in both in-vitro and in-vivo studies (Ritchie and Noble, 2003).

Up to now, the relationship between DRD2 polymorphisms and therapeutic response to antipsychotics has been controversial (Scharfetter, 2001, 2004). We therefore examined the effects of the polymorphisms spanning the full length of the *DRD2* gene on risperidone response in schizophrenia patients to clarify whether these polymorphisms would modify dopaminergic function in the central nervous system.

Materials and methods

Clinical sample

Clinical data from 125 in-patients diagnosed as schizophrenic according to DSM-IV criteria were recruited from the Shanghai Mental Health Centre. The patients involved in this study were Han Chinese patients from Shanghai and were included if they satisfied the following criteria: (1) had no physical complications or other psychiatric disorders such as alcoholism or other substance abuse; (2) had no history suggesting that antipsychotics treatment would be contraindicated; (3) satisfied the DSM-IV criteria for schizophrenia; (4) had not received any medication for 4 wk; (5) had never received atypical antipsychotics before. All subjects gave signed, informed consent to participate in the study, which was approved by the Ethics Committee of Shanghai Jiaotong University.

All patients received risperidone at a daily dose ranging from 3 to 6 mg/d given orally in two separate daily administrations. Patients' compliance was confirmed by the nursing stuff. No other drugs were given except biperiden for extrapyramidal side-effects, flunitrazepam for insomnia and sennoside for constipation. Clinical response was assessed on the Brief Psychiatric Rating Scale (BPRS; Lachar et al., 1999). BPRS ratings were conducted at 0, 4, 8 wk respectively by two fully qualified psychiatrists who were blind to the genotype of the patients. The definitions of a responder based on BPRS always differ across studies. A reduction of at least 20, 30, 40 or 50% of the initial BPRS score has been frequently used as a cut-off to define response (Lachar et al., 1999; Zalsman et al., 2003). However, the results of linking analysis between CGI-I (clinical global impression – improvement) score and percentage BPRS change from baseline showed that rating of much improved

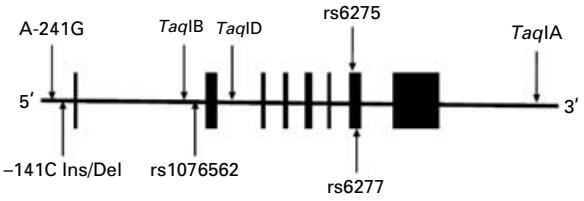

Figure 1. Human dopamine D_2 receptor gene structure and marker sites studied.

(CGI-I = 2) corresponded to percentage BPRS reductions of 41% in the present study. Therefore, we considered the following frequently used cut-off to define a response: a $\geqslant$40% reduction of the BPRS total score at baseline if the definition of response was CGI-I $\geqslant$2.

Laboratory methods

Drug assays

Blood samples for the determination of risperidone and 9-OH-risperidone concentrations were drawn at 6–8 wk after initiation of the risperidone treatment, between 08:00 and 09:00 hours, $\sim$12 h after the bedtime dose. The plasma concentrations of risperidone and 9-OH-risperidone were ascertained using a validated, previously published high performance liquid chromatography method (Llerena et al., 2003).

Genotyping

Genomic DNA was extracted from venous blood using a modified phenol/chloroform method. The determination of the genotypes was performed after the clinical assessment and was completed by researchers who were blind to the results of this assessment. Genotyping was performed by direct sequencing using an ABI BigDye terminator Sequencing kit 3.1 (PerkinElmer, Foster City, CA, USA), and results were confirmed by two researchers. We genotyped eight polymorphisms spanning the full length of the *DRD2* gene. Primer sequences and PCR conditions are available on request. From the 5′ end to the 3′ end of *DRD2*, the eight polymorphisms were: A-241G (rs1799978), −141 Ins/Del C, *Taq*IB (rs17294542), rs1076562, *Taq*ID (rs1800498), T939C (rs6275), C957T (rs6277), and *Taq*IA (rs1800497). The marker locations are shown in Figure 1.

Statistical methods

Statistical analyses were carried out using SPSS for Windows, version 11.0 (SPSS Inc., Chicago, IL, USA). A *t* test was used for group comparisons of age, gender, baseline BPRS scores, dosage of risperidone, plasma concentration of risperidone and 9-OH-risperidone. Linkage disequilibrium (LD) statistics were computed using Arlequin software (Excoffier et al., 2005). Comparisons of the genotypic or allele frequencies between different groups were performed using χ^2 tests. The limit of significance was set to 0.05. Odds ratios (OR) and their 95% confidence intervals (CI) were estimated for the effects of alleles. The program SNPSpD (http://genepi.qimr.edu.au/general/daleN/SNPSpD/), which takes marker LD information into consideration, was used to correct for multiple testing performed on each individual SNP. Haplotype distribution was estimated on EH plus and SHEsis (Shi and He, 2005; Zhao et al., 2000). The numbers of observations for each haplotype were compared using χ^2 tests. Bonferroni correction was applied for haplotype analysis.

Results

The study group consisted of 125 patients. At the end of 8 wk treatment, 72 patients (57.6%) showed a decrease in total BPRS scores >40% and were classified as responders (R) while 53 patients were non-responders (NR). No significant differences were found with respect to gender (R, 22M/50F; NR, 21M/32F), onset age (R, 31.1 $\pm$ 9.9; NR, 30.1 $\pm$ 11.0), the mean risperidone doses (R, 3.15 $\pm$ 1.01; NR, 3.37 $\pm$ 0.98 mg/d), mean plasma concentrations of risperidone (R, 7.52 $\pm$ 6.16; NR, 8.00 $\pm$ 6.69 ng/ml) or 9-OH-risperidone (R, 22.40 $\pm$ 14.77; NR, 24.83 $\pm$ 18.54 ng/ml) between risperidone responders and non-responders. However, there were significant differences in baseline BPRS scores between the responders and non-responders (R, 46.1 $\pm$ 13.1; NR, 37.5 $\pm$ 9.6; $p < 0.001$), signifying that patients with more severe symptoms at baseline showed more improvement, and those with less severe symptoms showed less improvement.

In the study, eight polymorphisms were genotyped successfully. Since both *Taq*ID (minor allele frequency <1%) and C957T (minor allele frequency 2.4%) had low heterozygosity in our subjects, we did not analyse their effects on risperidone response (data not presented). For six other polymorphisms, including A-241G (rs1799978), −141C Ins/Del, qIB (rs17294542), rs1076562, T939C (rs6275) and *Taq*IA (rs1800497), no significant deviation from Hardy–Weinberg equilibrium was observed in our subjects (data not presented). Pairwise LD between the six SNPs are presented in Table 1. Based on linkage disequilibrium determinations, *Taq*IB (rs17294542), rs1076562, T939C (rs6275) and *Taq*IA (rs1800497) were shown to be

Table 1. Pairwise polymorphisms linkage disequilibrium analysis

	D′ value					
	A-241G rs1799978	−141C Ins/Del	*Taq*IB rs17294542	rs1076562	C939T rs6275	*Taq*IA rs1800497
A-241G rs1799978		0.698	0.208	0.314	0.085	0.127
−141C Ins/Del	0.018		0.159	0.092	0.140	0.200
*Taq*IB rs17294542	0.017	0.005		1.000	0.904	1.000
rs1076562	0.031	0.001	0.784		0.931	1.000
T939C rs6275	0.002	0.003	0.684	0.813		0.960
*Taq*IA rs1800497	0.007	0.008	0.936	0.733	0.721	
			r^2 value			

Table 2. Results of individual polymorphisms of *DRD2* gene analyses: frequencies and significance levels

A-241G (rs1799978)	AA	AG	GG		A	G	
N	27	20	6	6.42	74	32	7.19
R	52	17	3	0.040 (0.176)	121	23	0.007 (0.031)
−141C Ins/Del	CC	CD	DD		C	D	
N	43	10	0	1.20	96	10	0.84
R	54	17	1	0.548	125	19	0.359
*Taq*IB (rs17294542)	AA	AG	GG		A	G	
N	7	27	19	0.85	41	65	0.48
R	14	34	24	0.654	62	82	0.487
rs1076562	CC	CT	TT		C	T	
N	11	26	16	0.27	48	58	0.27
R	17	36	19	0.872	70	74	0.602
T939C (rs6275)	CC	CT	TT		C	T	
N	9	25	19	1.82	43	63	1.88
R	18	35	19	0.402	71	73	0.170
*Taq*IA (rs1800497)	CC	CT	TT		C	T	
N	21	26	6	1.53	68	38	1.08
R	25	33	14	0.466	83	61	0.298

N, Non-responder; R, responder.
The numbers in parentheses represent the *p* value after correction by the program SNPSpD.

tightly linked with each other, but not with the other two promoter polymorphic sites studied in this investigation. A-241G (rs1799978) and −141C Ins/Del were in moderate LD, consistent with previous reports (Arinami et al., 1997).

Responder/non-responder groups were compared for genotype and allele frequencies across the other six DRD2 polymorphisms (see Table 2). The results indicated that A-241G genotype frequencies differed significantly between responders and non-responders ($\chi^2 = 6.42$, $p = 0.040$). After adjusting for multiple testing by the program SNPSpD, the result was not considered statistically significant ($p = 0.176$). Allele frequency analysis revealed that even after correction for multiple testing, allele A was associated with responders [$\chi^2 = 7.19$, $p = 0.007$ ($p = 0.031$ after correction by the program SNPSpD); OR 2.3, 95% CI 1.2–4.2]. No significant differences in allele and genotype frequencies of the other polymorphisms [−141C Ins/Del, *Taq*IB (rs17294542), rs1076562, T939C (rs6275), *Taq*IA (rs1800497)] between the responder and the non-responder groups were observed. Additionally,

Table 3. Frequencies of estimated haplotypes composed of six polymorphisms of the *DRD2* gene and test statistics between responder and non-responder groups

Haplotypes	Responders ($n=144$)	Non-responders ($n=106$)	p value	OR (95% CI)
ACACCT	0.221	0.233	0.812	1.1 (0.6–2.0)
ACGCCC	0.022	0.037	0.475	1.8 (0.4–8.4)
ACGTTC	0.353	0.424	0.253	1.4 (0.8–2.3)
ADACCT*	0.089	0.012	0.010	7.8 (1.3–47.7)
			0.087	
ADGTTC*	0.062	0.030	0.215	0.5 (0.1–1.6)
GCACCT	0.106	0.102	0.903	1.0 (0.4–2.2)
GCACTC	0.038	0.007	0.086	0.2 (0.02–1.6)
GCGTTC	0.039	0.103	0.042	0.4 (0.1–1.0)
			0.374	
Global			0.028	
			0.250	

Only haplotypes with a frequency >3% are listed. The haplotype frequencies defined were A-241G (rs1799978), −141C Ins/Del, *Taq*IB (rs17294542), rs1076562, T939C (rs6275), *Taq*IA (rs1800497).
Numbers in bold represent p values after Bonferroni correction.
OR, Odds ratio; CI, confidence interval.
*D, Del allele of −141.

there were no significant differences between different genotypic groups of DRD2 polymorphisms in the risperidone dosages, plasma levels of risperidone and 9-OH-risperidone ($p>0.05$) (data not presented). The present results suggested that there were no significant drug × genotype interaction with any genotypic subgroup.

Since, haplotype analysis is a powerful strategy for resolving the controversial issue of association studies based on individual polymorphisms (Kidd et al., 1998), haplotypes containing all six markers described above were analysed in order to determine whether or not the SNPs would have greater predictive value when analysed together. The results indicated that the estimated haplotype frequencies with different combinations of all six polymorphisms were significantly different in the responder group compared with the non-responder group ($p=0.028$). Haplotype ADACCT ($p=0.010$; OR 7.8, 95% CI 1.3–47.7) was associated with responders and haplotype GCGTTC ($p=0.042$; OR 0.4, 95% CI 0.1–1.0) was associated with non-responders (see Table 3). This resulted from an excess of the A(−241)D(−141) haplotype and a deficit of the G(−241)C(−141) haplotype in the responder group. However, when a Bonferroni correction for multiple testing was employed, neither global nor individual haplotype association remained significant at the 0.05 level; small sample size might be a reason for this observation.

Discussion

Given the similarity of patient characteristics (age, gender, age at onset), and drug factors (type, dose, plasma drug concentration and concomitant drugs) in both groups we were able to focus on the effects of DRD2 polymorphisms on therapeutic response to risperidone in our sample of Chinese schizophrenia patients. A total of six SNPs spanning *DRD2* were analysed. Our individual SNP analyses found that the A-241G polymorphism was related to patients' therapeutic response to risperidone. Patients with the A allele of A-241G had a better risperidone response than patients with the G allele [$p=0.007$ ($p=0.031$ after correction by the program SNPSpD)]. Up to now, the function of −241 SNP has not been clear, and it is possible that the −241 SNP is directly responsible for the regulation of *DRD2* expression or is in LD with an unidentified functional DRD2 polymorphism, which confers response/non-response to antipsychotics. By contrast, we found no association between the *Taq*IB (rs17294542), rs1076562, T939C (rs6275) or *Taq*IA (rs1800497) polymorphisms and risperidone response.

Among the functional polymorphisms of the *DRD2* gene, the most extensively examined have been −141C Ins/Del and *Taq*IA. With regard to −141C Ins/Del, our findings differ from those of Malhotra et al. (1999) and Suzuki et al. (2001a), who found a

positive association between the −141C Ins/Del and therapeutic responses with 72 and 49 patients respectively. However, our results are in agreement with three other studies which found no association between −141C Ins/Del and antipsychotic response (Arranz et al., 1998; Hwang et al., 2005; Ohara et al., 1998). As regards the *Taq*IA (rs1800497) polymorphism, our results concur with Suzuki et al. (2001b), but fail to replicate the positive results of Dahmen et al. (2001) and Kondo et al. (2003), who found that the A1 allele was associated with favourable response after investigating 18 and 49 patients respectively.

There are several explanations for these conflicting results. First, the positive associations might have been due to chance positive findings. Second, the observed odds ratios for association of the −241A allele with risperidone response were small, indicating that the genetic variation contributes only a limited amount to the inter-individual variability of response to risperidone. Third, the discrepancies may be attributable to the slight difference in pharmacological properties between the different drugs. Fourth, in the present study, the statistical power for detecting differences between the genotype groups was calculated to be <0.80 to detect a medium effect size (0.50) according a two-tailed α value of 5%, raising the possibility that the negative results might be attributable to small sample size. Fifth, the discrepancies may be explained by the ethnic differences between the different studies. Sixth, the failure of some of the previous genetic-response studies to collect covariates (ancestry, sex, and age at onset, etc.) may have contributed to the conflicting results in the case-control association studies.

In conclusion, the A-241G polymorphism in the *DRD2* promoter was found to be related to risperidone response in Chinese schizophrenia patients. The −241A allele carriers had a better therapeutic response to risperidone than the G allele carriers. This finding may help us to target the use of risperidone to those with a more favourable response. However, it should be emphasized that these findings are still preliminary because of the small number of subjects in each group and further replicated studies with a larger number of subjects will be necessary to provide a more definitive answer.

Acknowledgements

This work was supported by grants from the Shanghai Municipal Commission for Science and Technology, the national 973 and 863 programmes, and the National Natural Science Foundation of China.

Statement of Interest

None.

References

Arinami T, Gao M, Hamaguchi H, Toru M (1997). A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Human Molecular Genetics 6*, 577–582.

Arranz MJ, Li T, Munro J, Liu X, Murray R, Collier DA, Kerwin RW (1998). Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. *Pharmacogenetics 8*, 481–484.

Csernansky JG, Mahmoud R, Brenner R, Risperidone-USA-79 Study Group (2002). A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *New England Journal of Medicine 346*, 16–22.

Dahmen N, Muller MJ, Germeyer S, Rujescu D, Anghelescu I, Hiemke C, Wetzel H (2001). Genetic polymorphisms of the dopamine D2 and D3 receptor and neuroleptic drug effects in schizophrenic patients. *Schizophrenia Research 49*, 223–225.

Duan J, Wainwright MS, Comeron JM, Saitou N, Sanders AR, Gelernter J, Gejman PV (2003). Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. *Human Molecular Genetics 12*, 205–216.

Dubertret C, Gouya L, Hanoun N, Deybach JC, Ades J, Hamon M, Gorwood P (2004). The 3′ region of the DRD2 gene is involved in genetic susceptibility to schizophrenia. *Schizophrenia Research 67*, 75–85.

Excoffier L, Laval G, Schneider S (2005). Arlequin version 3.0: an integrated software package for population genetics data analysis. *Evolutionary Bioinformatics Online 1*, 47–50.

Freudenreich O, Goff DC (2002). Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatrica Scandinavica 106*, 323–330.

Heck AH, Haffmans PM, de Groot IW, Hoencamp E (2000). Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: a double-blind, multi-center trial. *Schizophrenia Research 46*, 97–105.

Hirvonen M, Laakso A, Nagren K, Rinne JO, Pohjalainen T, Hietala J (2004). C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. *Molecular Psychiatry 9*, 1060–1061.

Hwang R, Shinkai T, De Luca V, Muller DJ, Ni X, Macciardi F, Potkin S, Lieberman JA, Meltzer HY, Kennedy JL (2005). Association study of 12 polymorphisms spanning the dopamine D(2) receptor gene and clozapine treatment response in two treatment refractory/intolerant populations. *Psychopharmacology (Berlin) 181*, 179–187.

Kane JM (1996). Schizophrenia. *New England Journal of Medicine 334*, 34–41.

Kapur S, Remington G (2001). Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biological Psychiatry 50*, 873–883.

Kapur S, Zipursky R, Jones C, Remington G, Houle S (2000). Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *American Journal of Psychiatry 157*, 514–520.

Kidd KK, Morar B, Castiglione CM, Zhao H, Pakstis AJ, Speed WC, Bonne-Tamir B, Lu RB, Goldman D, Lee C, et al. (1998). A global survey of haplotype frequencies and linkage disequilibrium at the DRD2 locus. *Human Genetics 103*, 211–227.

Kondo T, Mihara K, Suzuki A, Yasui-Furukori N, Kaneko S (2003). Combination of dopamine D2 receptor gene polymorphism as a possible predictor of treatment-resistance to dopamine antagonists in schizophrenic patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry 27*, 921–926.

Lachar D, Bailley SE, Rhoades HM, Varner RV (1999). Use of BPRS – a percent change scores to identify significant clinical improvement: accuracy of treatment response classification in acute psychiatric inpatients. *Psychiatry Research 89*, 259–268.

Llerena A, Berecz R, Dorado P, De la Garza CS, Norberto MJ, Cáceres M, Gutierrez JR (2003). Determination of risperidone and 9-hydroxyrisperidone in human plasma by liquid chromatography: application to the evaluation of CYP2D6 drug interactions. *Journal of Chromatography B 783*, 213–219.

Love RC, Nelson MW (2000). Pharmacology and clinical experience with risperidone. *Expert Opinion on Pharmacotherapy 1*, 1441–1453.

Malhotra AK, Buchanan RW, Kim S, Kestler L, Breier A, Pickar D, Goldman D (1999). Allelic variation in the promoter region of the dopamine D2 receptor gene and clozapine response. *Schizophrenia Research 36*, 92–93.

Neville MJ, Johnstone EC, Walton RT (2004). Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Human Mutation 23*, 540–545.

Ohara K, Nagai M, Tani K, Nakamura Y, Ino A, Ohara K (1998). Functional polymorphism of −141C Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. *Psychiatry Research 81*, 117–123.

Peuskens J (1995). Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. *British Journal of Psychiatry 166*, 712–726; discussion 727–733.

Pohjalainen T, Rinne JO, Nagren K, Lehikoinen P, Anttila K, Syvälahti EKG, Hietala J (1998). The A1 allele of the human D_2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Molecular Psychiatry 3*, 256–260.

Ritchie T, Noble EP (2003). Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. *Neurochemical Research 28*, 73–82.

Scharfetter J (2004). Pharmacogenetics of dopamine receptors and response to antipsychotic drugs in schizophrenia – an update. *Pharmacogenomics 5*, 691–698.

Scharfetter J (2001). Dopamine receptor polymorphisms and drug response in schizophrenia. *Pharmacogenomics 2*, 251–261.

Shi YY, He L (2005). SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Research 15*, 97–98.

Suzuki A, Kondo T, Mihara K, Yasui-Furukori N, Ishida M, Furukori H, Kaneko S, Inoue Y, Otani K (2001a). The −141C Ins/Del polymorphism in the dopamine D2 receptor gene promoter region is associated with anxiolytic and antidepressive effects during treatment with dopamine antagonists in schizophrenic patients. *Pharmacogenetics 11*, 545–550.

Suzuki A, Kondo T, Mihara K, Yasui-Furukori N, Otani K, Furukori H, Kaneko S, Inoue Y (2001b). Association between *Taq*I A dopamine D2 receptor polymorphism and therapeutic response to bromperidol: a preliminary report. *European Archives of Psychiatry and Clinical Neuroscience 251*, 57–59.

Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry EK, Morris CM, Perry RH, Ferrier IN, Court JA (1997). D2 dopamine receptor gene (DRD2) *Taq*1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics 7*, 479–484.

Zalsman G, Frisch A, Lev-Ran S, Martin A, Michaelovsky E, Bensason D, Gothelf D, Nahshoni E, Tyano S, Weizman A (2003). DRD4 exon III polymorphism and response to risperidone in Israeli adolescents with schizophrenia: a pilot pharmacogenetic study. *European Neuropsychopharmacology 13*, 183–185.

Zhao JH, Curtis D, Sham PC (2000). Model-free analysis and permutation test for allelic associations. *Human Heredity 50*, 133–139.