TPH, SLC6A2, SLC6A3, DRD2 and DRD4 Polymorphisms and Neuroendocrine Factors Predict SSRIs Treatment Outcome in the Chinese Population with Major Depression

Authors L. Yin[1,3], Y. Y. Zhang[1,3], X. Zhang[1], T. Yu[1,2], G. He[2], X. L. Sun[1]

Affiliations Affiliation addresses are listed at the end of the article

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Correspondence
Prof. X. Sun
Department of Psychiatry
West China Hospital of Sichuan University
Chengdu
Sichuan Province 610041
People's Republic of China
sunxueli58@163.com

Dr. T. Yu
Bio-X Institute
Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education)
Shanghai Jiao Tong University
Shanghai 200030
People's Republic of China
yutao03d@gmail.com

Abstract

Objective: This study was intended to determine whether antidepressant outcome to SSRIs was associated with catecholamine gene polymorphisms and neuroendocrine factors in patients of Chinese Han ethnicity with MDD.

Method: A total of 290 MDD patients were recruited and received a 6-week randomized double-blinded treatment. Cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), 3′-triiodothyronine (T3), thyroxine (T4), free triiodothyronine (fT3), and free thyroxine (fT4) levels were measured at the baseline. Allele, genotype, and haplotype frequencies of catecholamine genes were compared between responders and non-responders, remission and non-remission groups respectively.

Results: We found that genotype frequency of the rs1800544 polymorphism in the DRD4 gene was significantly different between responders and non-responders ($P<0.05$). Also the frequency of the rs1800544 CG genotype was significantly higher ($P<0.05$) in responders (51.4%) than that in non-responders (35.8%). No significant difference was found between responders and non-responders, remission and non-remission groups in the SNPs polymorphisms in the TPH, SLC6A2, SLC6A3, or DRD2 genes. The combination of all neuroendocrine factors, clinical characteristics and gene polymorphisms predicted 74.8% of the variation in SSRI response and 65.5% in SSRI remission.

Conclusion: Polymorphisms of the DRD4 gene were associated with SSRI response in Chinese Han MDD patients. A combination of clinical characteristics, neuroendocrine factors, and gene polymorphisms might be able to predict the outcome to SSRIs.

Introduction

In a clinical setting, selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant drugs for major depressive disorder (MDD) treatment. Although these antidepressants have proven to be effective [1], the response and remission rates remain unsatisfactory [2,3]. This is partly due to the lack of reliable predictors of treatment outcome [4].

Previous studies have shown that genetic variation may partly explain the inter-individual differences in response to antidepressive drugs [5]. Pathway analysis, which is based on the analysis of variants within genes involved in the same biological pathway, appears to be a particularly promising approach in this regard [6]. Along with rapid developments in the discovery of antidepressants targeting the tyrosine and tryptophan metabolism pathways, pharmacogenetic studies on related gene polymorphisms have received increased attention. In particular, several studies have evaluated the correlation between polymorphisms in the tyrosine and tryptophan metabolism pathway genes and MDD [7]. However, the correlations between these polymorphisms and antidepressant response show controversial results which has limited their clinical application [8,9]. In this study, we hypothesize that SSRI response or remission is significantly associated with the tyrosine or tryptophan metabolism pathways gene polymorphisms.

Dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis and the hypothalamus-pituitary-thyroid (HPT) axis plays a pivotal role in the pathogenesis of depression [10–12]. Corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and cortisol were found to be increased in older depressed patients,

and are restored to normal levels after amitriptyline treatment [13]. Enhanced activities of thyrotropin-releasing hormone (TRH) and blunted thyroid-stimulating hormone (TSH) responses to TRH are commonly found in depressive patients [14]. Higher serum TSH levels were found to be associated with response to paroxetine in patients with MDD and could effectively predict the response to paroxetine treatment [15]. However, it is still controversial whether alterations in the HPA or HPT axes can predict the outcome to SSRI treatment.

In the current study, we examined the effect of tyrosine and tryptophan metabolism pathway gene polymorphisms on the antidepressant treatment outcome to SSRIs and explored whether neuroendocrine factors in the HPA and HPT axes could predict the SSRI treatment outcome in MDD patients of Chinese Han ethnicity.

Patients and Methods

Subjects

The study was approved by the local research ethics committee. Written informed consent was obtained from each patient. A total of 290 depressed patients, aged 18–55 years, fulfilling the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for major depressive disorder, with a minimum 17-item Hamilton Depression Rating Scale (HAMD) score of 18 [16], were recruited for this study from April 2005 to September 2006. All the participants were of unrelated (no blood relationship) Chinese Han origin, and shared similar geographic and sociodemographic characteristics (**Table 1**). The diagnosis of each patient was confirmed in a psychiatric examination performed by an experienced and board-certified psychiatrist. Interrater reliability was evaluated using Kappa coefficients (Kappa value = 0.85). Patients were drug naive, or without any antidepressant treatment for at least 2 weeks (fluoxetine for 4 weeks), and none had received electroconvulsive therapy treatment. Patients with other axis I psychiatric disorders, such as schizophrenia, rapid cycling bipolar disorder, dementia, generalized anxiety disorder, obsessive-compulsive disorder, or substance abuse, and those with axis II disorders (including personality disorders), major medical/neurological disorders, abnormal laboratory baseline values, and pregnancy were excluded.

Treatment

All patients received a 6-week period of treatment. Patients were randomly selected for treatment with fluoxetine, paroxetine, citalopram, or sertralin. The total dose per day ranged from 20 to 60 mg of floxetine, paroxetine, or citalopram, and from 50 to 150 mg of sertraline. No other psychotropic medications were permitted during the study except an acceptable dosage of benzodiazepine at bedtime for insomnia.

Data collection

5 mL of peripheral venous blood were collected from each participant for genotyping upon enrollment. Patients' conditions were assessed by trained psychiatrists blinded to genotypes, who were responsible for determining a detailed objective protocol for each patient. The HAMD rating scale was used to assess the severity of symptoms at the baseline and then at 1, 2, 4, and 6 weeks following the initiation of treatment, respectively. We used a last-observation-carried-forward (LOCF) analysis, missing data were replaced by the last record value. Response was defined as a more than 50% reduction in the total HAMD score at the end of the 6th week. Patients with a reduction of HAMD scores ≤ 50% at the end of the 6th week were assigned to the group of non-responders. Remission was defined as a score of ≤ 7 in the total HAMD score at the end of the 6th week.

Table 1 Demographic and clinical characteristics of patients.

Group	Responders (n = 220)		Non-responders (n = 70)			P-value	Remission (n = 144)		Non-remission (n = 146)			P-value
	Mean	SD	Mean	SD	t/χ^2		Mean	SD	Mean	SD	t/χ^2	
age (years)	35.51	13.62	37.74	12.19	1.119	0.197	33.81	13.42	38.16	12.75	−2.835	0.005 *
number of episodes	1.51	0.859	1.56	1.326	5.124	0.787	1.43	0.687	1.61	1.211	−1.576	0.116
body mass index	21.90	4.37	21.98	3.57	0.023	0.891	21.44	3.49	22.37	4.77	−1.849	0.066
HAMD baseline	24.42	4.89	24.37	4.82	−0.070	0.944	23.43	4.44	25.37	5.09	−3.455	0.001 *
HAMD-6week	5.96	3.46	18.33	7.69	18.640	0.000 *	3.90	2.09	13.38	6.47	−16.719	0.000 *
gender	N	%	N	%	0.229	0.992	N	%	N	%	0.499	0.481
male	107	48.6	34	48.6			67	46.5	74	50.7		
female	113	51.4	36	51.4			77	53.5	72	49.3		
marital status	N	%	N	%	0.622	0.522	N	%	N	%	6.756	0.011 *
single (never married)	82	37.3	21	30.0			63	43.75	40	27.4		
married	122	55.5	44	62.9			72	50.0	94	64.38		
divorced or remarried	16	7.2	5	7.1			9	6.25	12	8.22		
family history	N	%	N	%	2.919	0.094	N	%	N	%	0.421	0.517
yes	29	13.2	15	21.4			23	15.6	21	14.7		
no	191	86.8	55	78.6			124	84.4	122	85.3		
neuroendocrine factor												
CORT (nmol/L)	415.76	88.92	416.68	75.18	1.015	0.937	434.73	135.88	387.72	119.93	1.764	0.081
ACTH (ng/L)	29.52	7.44	28.64	6.72	9.293	0.369	31.69	13.17	28.10	11.71	1.186	0.240
TSH (mU/L)	2.69	1.19	2.85	1.22	0.034	0.316	2.70	1.74	2.91	1.99	−0.561	0.576
fT3 (pmol/L)	4.49	0.52	4.42	0.39	4.535	0.340	4.41	0.75	4.45	0.90	−0.246	0.806
fT4 (pmol/L)	15.95	2.36	15.49	1.43	8.821	0.131	16.13	3.82	15.28	3.17	1.23	0.222
T3 (nmol/L)	1.62	0.16	1.62	0.04	0.713	0.909	1.56	0.31	1.64	0.34	−0.951	0.346
T4 (nmol/L)	91.14	9.88	91.53	6.73	1.061	0.836	86.93	15.42	93.65	25.24	−1.173	0.246

HAMD = Hamilton depression rating scale; * $p < 0.05$

7 neuroendocrine indicators were evaluated, as follows: cortisol, ACTH, TSH, 3′-triiodothyronine (T3), thyroxine (T4), free triiodothyronine (fT3), and free thyroxine (fT4). Cortisol, T3, T4, fT3, and fT4 were measured by electrochemiluminescene quantitative assays. TSH was measured using an electrochemiluminescene double-antibody sandwich method. ACTH was measured by radioimmunoassay. All of the above indicators were detected with a Roche E170 analytical system in the clinical laboratory of the West China Hospital.

Single nucleotide polymorphism (SNP) selection and genotyping

Among the many catecholamine genes, TH, DRD2, DRD4, SLC6A2, and SLC6A3 are the most well-studied in MDD. We used the following criteria for SNP selection of these genes: (1) the SNP is in a functional region of the gene; (2) the SNP was shown to have strong effects on drug response in previous studies, especially genome-wide association studies; and (3) it was a tag SNP.

Genomic DNA was extracted from venous blood leukocytes using the standard phenol-chloroform method. Considering that the coverage of a gene and a minor allele frequency occur at a rate above 0.03, we selected 19 single SNPs for the TH, DRD2, DRD4, SLC6A2, and SLC6A3 genes from the literature and the National Center for Biotechnology Information dbSNP database (http://www.ncbi.nlm.nih.gov/SNP). Of the 19 SNPs, 2 (rs2234689, rs3863145) were downstream, 4 (rs1362621, rs2550948, rs2550956, rs2937639) were upstream, 2 (rs140504, rs6356) were in a coding exon, 4 (rs10743152, rs10770141, rs1800544, rs933399) were in the promoter region, 4 (rs2242446, rs4963126, rs5564, rs7131056) were in introns, 2 (rs2292023, rs27072) were in the 3' untranslated region, and 1 (rs5569) was a synonymous codon. All SNPs were genotyped with a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer using a MassARRAY(R) Analyzer 4 platform (Sequenom; San Diego, CA, USA). All primers were designed by the accompanying software, Spectrodesigner. Polymerase chain reactions (PCRs) were carried out in a total volume of 5 µL with10 ng genomic DNA, under the cycling conditions recommended by the manufacturer. Detailed information about the primers and PCR conditions is available on request. The determination of genotypes was performed by researchers who were blinded to the clinical outcome of the antidepressant treatment.

Statistical analysis

Demographic and clinical variables were compared using the Student's t test (age, body mass index, HAMD scores, number of episodes, neuroendocrine factors) or Pearson's χ^2 test (gender, marital status, family history), and Fisher's exact test was used to compare data between responders and non-responders, remission and non-remission groups. A stepwise logistic regression was used to examine the relationship between genotype, neuroendocrine factors, clinical variables and treatment outcome. All tests were 2-tailed and statistical significance was accepted at $P<0.05$. Statistical analyses were performed using SPSS 17.0. Analysis of allelic and genotypic distributions and pairwise linkage disequilibria were performed using SHEsis software (http://202.120.31.177/myanalysis.php) [17]. The discrepancies in allele and genotype frequency between groups were compared by using a χ^2 test. Odd ratios (ORs) and their 95% confidence intervals (CIs) were also calculated. Deviations from Hardy-Weinberg equilibrium were tested using HaploView version 4.2 [18]. Haplotype construction was initially performed on HaploView and further analysis was carried out with SHEsis software [19].

Results

A total of 303 patients were initially enrolled in this study. Ten patients were removed due to the absence of blood samples or because genotyping failed due to the poor quality of their blood samples. Furthermore, 3 patients dropped out as a result of intolerable adverse effects at their first or second visit. A cohort of 290 patients was used in the final analysis.

Demographic and clinical characteristics

Clinical and demographic characteristics of subjects and the levels of significance of differences in clinical variables between responders and non-responders, remission and non-remission groups are shown in **Table 1**. Of the 290 patients who completed the 6-week SSRI treatment trial, 220 were responders and 70 were non-responders, 144 were in the remission and 146 were in the non-remission groups, for an overall rate of response of 75.9% and remission of 49.7%. There were no significant differences in age, gender, body mass index, HAMD scores at baseline, number of previous episodes of MDD, marital status, or family history ($P=0.197$, 0.992, 0.891, 0.944, 0.787, 0.552, 0.094, respectively) between responders and non-responders. There were no significant differences in gender, body mass index, number of previous episodes of MDD, or family history between the remission and non-remission groups ($P=0.481$, 0.066, 0.116, 0.517). But there were significant differences in age, HAMD scores at baseline, marital status between remission and non-remission groups ($P=0.005$, 0.001, 0.011). No significant differences in neuroendocrine levels were found between responders and non-responders, remission and non-remission groups, i.e., CORT, ACTH, TSH, fT4, fT3, T3, and T4 levels ($P=0.937$, 0.369, 0.316, 0.131, 0.340, 0.909, and 0.836 between responders and non-responders, $P=0.081$, 0.240, 0.576, 0.222, 0.806, 0.346 and 0.246 between remission and non-remission groups, respectively).

Genotype and allele frequencies of DRD4

The genotype and allele frequencies of 14 SNPs in each group are shown in **Table 2**, **3**. 5 SNPs (rs2550948, rs27072, rs2937639, rs5569, and rs933399) were omitted from the analysis because they deviated from the values expected under Hardy-Weinberg equilibrium ($P<0.001$ for all). The frequency of the DRD4 rs1800544 CG genotype was significantly higher ($P<0.05$) in the SSRIs responders (51.4%) than that in the non-responders (35.8%). The frequencies of the DRD4 rs1800544 CC and GG genotypes were significantly lower ($P<0.05$) in the SSRIs responders (7.7%, 40.9%) than that in the non-responders (19.4%, 44.8%). A response rate to SSRIs was strongly associated with the genotype of the DRD4 rs1800544 polymorphism (OR=6.38; 95% CI=1.53–18.71; $P=0.003$, false discovery rate [FDR] $P=0.042$). Allele frequencies of rs1800544 polymorphisms and those of other SNPs (TPH, SLC6A2, SLC6A3, and DRD2) did not differ significantly between responders and non-responders ($P>0.05$).

Referring to the remission and non-remission groups, genotype and allele frequencies did not differ significantly between groups after FDR adjusted ($P>0.05$).

Table 2 Genotype and allele distributions of DRD4, DRD2, SLC6A2, SLC6A3, and TH polymorphisms in responders and non-responders to SSRIs.

Gene	SNP	Genotype frequency (%)			χ^2	P-values (genotype)	FDR adjusted	Allele frequency (%)		χ^2	P-values (allele)	P-values (Hardy-Weinberg)
DRD4	rs1800544	CC	CG	GG				C	G			
	non-responder	13 (0.194)	24 (0.358)	30 (0.448)	10.372	0.003 *	0.042 * *	50 (0.373)	84 (0.627)	0.683	0.408	0.101
	responder	16 (0.077)	107 (0.514)	85 (0.409)				139 (0.334)	277 (0.666)			
	rs3863145	CC	CT	TT				C	T			
	non-responder	63 (0.913)	6 (0.087)	none	0.381	0.537	0.939	132 (0.957)	6 (0.043)	0.367	0.544	0.539
	responder	201 (0.935)	14 (0.065)	none				416 (0.967)	14 (0.033)			
	rs4963126	CC	CT	TT				C	T			
	non-responder	22 (0.324)	32 (0.471)	14 (0.206)	4.682	0.096	0.672	76 (0.559)	60 (0.441)	1.789	0.180	0.088
	responder	43 (0.200)	126 (0.586)	46 (0.214)				212 (0.493)	218 (0.507)			
DRD2	rs7131056	AA	AC	CC				A	C			
	non-responder	12 (0.174)	38 (0.551)	19 (0.275)	3.466	0.176	0.616	62 (0.449)	76 (0.551)	2.860	0.090	0.999
	responder	29 (0.136)	99 (0.465)	85 (0.399)				157 (0.369)	269 (0.631)			
	rs2234689	CC	CG	GG				C	G			
	non-responder	0 (0.000)	4 (0.059)	64 (0.941)	1.411	0.493	0.986	4 (0.029)	132 (0.971)	1.429	0.231	0.720
	responder	1 (0.005)	21 (0.100)	188 (0.895)				23 (0.055)	397 (0.945)			
SLC6A2	rs1362621	AA	AG	GG				A	G			
	non-responder	35 (0.507)	28 (0.406)	6 (0.087)	0.819	0.663	0.844	98 (0.710)	40 (0.290)	0.260	0.610	0.955
	responder	111 (0.521)	90 (0.423)	12 (0.056)				312 (0.732)	114 (0.268)			
	rs2242446	CC	CT	TT				C	T			
	non-responder	6 (0.090)	29 (0.433)	32 (0.478)	0.009	0.995	0.995	41 (0.306)	93 (0.694)	0.008	0.928	0.955
	responder	19 (0.091)	91 (0.438)	98 (0.471)				129 (0.310)	287 (0.690)			
	rs5564	CC	CT	TT				C	T			
	non-responder	2 (0.030)	17 (0.254)	48 (0.716)	0.118	0.942	1.014	21 (0.157)	113 (0.843)	0.014	0.905	0.538
	responder	8 (0.038)	51 (0.245)	149 (0.716)				67 (0.161)	349 (0.839)			
SLC6A3	rs140504	AA	AG	GG				A	G			
	non-responder	14 (0.203)	34 (0.493)	21 (0.304)	0.542	0.762	0.889	62 (0.449)	76 (0.551)	0.424	0.515	0.205
	responder	47 (0.222)	110 (0.519)	55 (0.259)				204(0.481)	220(0.519)			
	rs2292023	AA	AC	CC				A	C			
	non-responder	16 (0.232)	33 (0.478)	20 (0.290)	1.432	0.488	1.139	65 (0.471)	73 (0.529)	0.001	0.981	0.067
	responder	41 (0.190)	121 (0.560)	54 (0.250)				203 (0.470)	229 (0.530)			
	rs2550956	CC	CT	TT				C	T			
	non-responder	53 (0.757)	14 (0.200)	3 (0.043)	0.907	0.635	0.889	120 (0.857)	20 (0.143)	0.069	0.792	0.286
	responder	166 (0.755)	49 (0.223)	5 (0.023)				381 (0.866)	59 (0.134)			
TH	rs10743152	CC	CT	TT				C	T			
	non-responder	64 (0.928)	5 (0.072)	0 (0.000)	1.664	0.435	1.218	133 (0.964)	5 (0.036)	1.646	0.199	0.979
	responder	186 (0.873)	26 (0.122)	1 (0.005)				398 (0.934)	28 (0.066)			
	rs10770141	AA	AG	GG				A	G			
	non-responder	0 (0.000)	5 (0.072)	64 (0.928)	1.218	0.543	0.845	5 (0.036)	133 (0.964)	1.189	0.275	0.912
	responder	1 (0.005)	24 (0.112)	190 (0.884)				26 (0.060)	404 (0.940)			
	rs6356	AA	AG	GG				A	G			
	non-responder	49 (0.710)	15 (0.217)	5 (0.072)	4.034	0.133	0.621	113 (0.819)	25 (0.181)	0.407	0.523	0.960
	responder	150 (0.708)	57 (0.269)	5 (0.024)				357 (0.842)	67 (0.158)			

* $p < 0.05$; * * $p < 0.05$ (FDR correction); FDR = false discovery rate

Table 3 Genotype and allele distributions of DRD4, DRD2, SLC6A2, SLC6A3, and TH polymorphisms in remission and non-remission groups to SSRIs.

Gene	SNP	Genotype frequency (%)			χ^2	P-values (genotype)	FDR adjusted	Allele frequency (%)		χ^2	P-values (allele)	FDR adjusted	P-values (Hardy-Weinberg)
DRD4	rs1800544	CC	CG	GG				C	G				
	non-remission	19 (0.134)	64 (0.451)	59 (0.415)	2.648	0.266	0.466	105 (0.370)	179 (0.630)	1.771	0.183	0.854	0.101
	remission	10 (0.075)	64 (0.481)	59 (0.444)				84 (0.316)	182 (0.684)				
	rs3863145	CC	CT	TT				C	T				
	non-remission	135 (0.931)	10 (0.069)	none	0.010	0.922	0.922	280 (0.966)	10 (0.034)	0.009	0.923	1.175	0.539
	remission	129 (0.928)	10 (0.072)	none				268 (0.964)	10 (0.036)				
	rs4963126	CC	CT	TT				C	T				
	non-remission	39 (0.273)	72 (0.503)	32 (0.224)	4.075	0.130	0.91	150 (0.524)	136 (0.476)	0.566	0.452	0.703	0.088
	remission	26 (0.186)	86 (0.614)	28 (0.200)				138 (0.493)	142 (0.507)				
DRD2	rs7131056	AA	AC	CC				A	C				
	non-remission	19 (0.133)	73 (0.510)	51 (0.357)	0.793	0.673	0.785	111 (0.388)	175 (0.612)	0.001	0.993	0.993	0.999
	remission	22 (0.158)	64 (0.460)	53 (0.381)				108 (0.388)	170 (0.612)				
	rs2234689	CC	CG	GG				C	G				
	non-remission	1 (0.007)	13 (0.091)	129 (0.902)	0.953	0.621	0.869	15 (0.052)	271 (0.948)	0.193	0.661	0.925	0.720
	remission	0 (0.000)	12 (0.089)	123 (0.911)				12 (0.044)	258 (0.956)				
SLC6A2	rs1362621	AA	AG	GG				A	G				
	non-remission	77 (0.538)	54 (0.378)	12 (0.084)	3.230	0.199	0.557	208 (0.727)	78 (0.273)	0.001	0.986	1.062	0.955
	remission	69 (0.496)	64 (0.460)	6 (0.043)				202 (0.727)	76 (0.273)				
	rs2242446	CC	CT	TT				C	T				
	non-remission	14 (0.098)	55 (0.385)	74 (0.517)	3.251	0.197	0.690	83 (0.290)	203 (0.710)	0.995	0.319	0.893	0.955
	remission	11 (0.083)	65 (0.492)	56 (0.424)				87 (0.330)	177 (0.670)				
	rs5564	CC	CT	TT				C	T				
	non-remission	6 (0.043)	29 (0.206)	106 (0.752)	2.836	0.242	0.484	41 (0.145)	241 (0.855)	0.919	0.338	0.789	0.538
	remission	4 (0.030)	39 (0.291)	91 (0.679)				47 (0.175)	221 (0.825)				
SLC6A3	rs140504	AA	AG	GG				A	G				
	non-remission	28 (0.194)	75 (0.521)	41 (0.285)	0.959	0.619	1.075	131 (0.455)	157 (0.545)	0.806	0.369	0.646	0.205
	remission	33 (0.241)	69 (0.504)	35 (0.255)				135 (0.493)	139 (0.507)				
	rs2292023	AA	AC	CC				A	C				
	non-remission	30 (0.208)	75 (0.521)	39 (0.271)	0.446	0.799	0.860	135 (0.469)	153 (0.531)	0.005	0.945	1.103	0.067
	remission	27 (0.191)	79 (0.560)	35 (0.248)				133 (0.472)	149 (0.528)				
	rs2550956	CC	CT	TT				C	T				
	non-remission	113 (0.774)	30 (0.205)	3 (0.021)	0.853	0.653	0.831	256 (0.877)	36 (0.123)	0.834	0.361	0.722	0.286
	remission	106 (0.736)	33 (0.299)	5 (0.035)				245 (0.851)	43 (0.149)				
TH	rs10743152	CC	CT	TT				C	T				
	non-remission	134 (0.931)	10 (0.069)	0 (0.000)	6.074	0.048 *	0.672	278 (0.965)	10 (0.035)	6.046	0.014 *	0.196	0.979
	remission	116 (0.841)	21 (0.152)	1 (0.007)				253 (0.917)	23 (0.083)				
	rs10770141	AA	AG	GG				A	G				
	non-remission	0 (0.000)	11 (0.076)	134 (0.924)	3.336	0.189	0.882	11 (0.038)	279 (0.962)	3.182	0.075	0.525	0.912
	remission	1 (0.007)	18 (0.129	120 (0.863)				20 (0.072)	258 (0.928)				
	rs6356	AA	AG	GG				A	G				
	non-remission	106 (0.746)	30 (0.211)	6 (0.042)	3.218	0.200	0.467	242 (0.852)	42 (0.148)	1.049	0.306	1.071	0.960
	remission	93 (0.669)	42 (0.302)	4 (0.029)				228 (0.820)	50 (0.180)				

$p < 0.05$; FDR = false discovery rate

Table 4 Frequencies of estimated haplotypes and test statistics between the responders and non-responders/remission and non-remission groups.

SNP	Haplotype	Responder/Non-Responder	χ^2	Permutation P-value	P FDR adjusted	OR (95%CI)	Remission/Non-remission	χ^2	Permutation P-value	P FDR adjusted	OR (95%CI)
rs 1362621	AACG	149.80 (0.358)/38.93(0.286)	3.027	0.073	0.146	1.475 (0.963–2.260)	101.67 (0.371)/79.74 (0.285)	6.903	0.038 *	0.051	1.625 (1.130–2.336)
rs 2292023	ACCG	139.09 (0.333)/55.68 (0.409)	1.961	0.161	0.161	0.750 (0.501–1.123)	84.59 (0.309)/121.35 (0.433)	6.878	0.038 *	0.051	0.623 (0.437–0.888)
	ACTA	10.40 (0.025)/1.39 (0.010)	–	–	–	–	7.32 (0.027)/3.20 (0.011)	–	–	–	–
rs10743152	GACG	35.10 (0.084)/21.46 (0.158)	5.523	0.019 *	0.760	0.505 (0.283–0.900)	20.15 (0.074)/44.12 (0.158)	8.315	0.014 *	0.056	0.447 (0.256–0.781)
	GATA	7.29 (0.017)/3.61 (0.027)	–	–	–	–	5.85 (0.021)/3.43 (0.012)	–	–	–	–
	GCCG	66.02 (0.158)/14.93 (0.110)	2.288	0.130	0.173	1.585 (0.869–2.888)	44.59 (0.163)/24.79 (0.089)	8.301	0.014 *	0.056	2.137 (1.264–3.611')
rs10770141	GCTA	3.49 (0.008)/0.00 (0.000)	–	–	–	–	3.51 (0.013)/2.66 (0.009)	–	–	–	–
	AATA	3.82 (0.009)/0.00(0.000)	–	–	–	–	3.32 (0.012)/0.71 (0.003)	–	–	–	–
	ACTG	1.90 (0.005)/0.00(0.000)	–	–	–	–	2.10 (0.008)/0.00 (0.000)	–	–	–	–
	GCTG	1.10 (0.003)/0.00 (0.000)	–	–	–	–	0.90 (0.003)/0.00 (0.000)	–	–	–	–

FDR = false discovery rate; * $p < 0.05$

Haplotype frequencies of SNPs between the responders and non-responders

Pairwise linkage disequilibrium (LD) between the 14 markers was conducted. Strong LD was observed between the 2 haplotype blocks composed of rs2292023-rs1362621 (D' = 0.990; $r^2 = 0.827$; SLC6A2 gene) and rs10743152-rs10770141 (D' = 1.000; $r^2 = 0.904$; TH gene). Therefore, we estimated the haplotype distributions with these SNPs (**Table 4**). Haplotypes were removed from this analysis if their estimated frequencies were less than 3% in either the responder or non-responder group. Neither of these markers remained significant after FDR correction (**Table 4**; FDR $P > 0.05$). Thus, no association was found between either of the haplotype blocks and SSRI treatment response at week 6.

Haplotype frequencies of SNPs between the remission and non-remission groups

LD between the 14 markers was conducted between the remission and non-remission groups. Strong LD was observed between the 2 haplotype blocks composed of rs2292023-rs1362621 (D' = 0.990; $r^2 = 0.827$; SLC6A2 gene) and rs10743152-rs10770141 (D' = 1.000; $r^2 = 0.904$; TH gene). Neither of these markers remained significant after FDR correction (**Table 4**; FDR $P > 0.05$). Thus, no association was found between either of the haplotype blocks and SSRI treatment remission at week 6.

Clinical characteristics, neuroendocrine factors, gene polymorphisms and treatment outcome

We used SSRI response or remission as the dependent factor; genotype of rs1800544, age, gender, baseline scores on the HAMD, number of episodes, family history, marital status, and neuroendocrine indicators (CORT, ACTH, TSH, fT3, fT4, T3, and T4) as covariates in the logistic regression (**Table 5, 6**). None of the factors was a significant predictor of SSRI response when examined independently ($P > 0.05$, respectively). Baseline scores on the HAMD was a significant predictor of SSRI remission when examined independently ($P = 0.015$). We also found the combination of all factors (genotype of rs1800544, age, gender, baseline scores on the HAMD, number of episodes, family history, marital status, and neuroendocrine factors) predicted 74.8% of the variation in SSRI response and 65.5% in SSRI remission (**Table 6**).

Discussion

In our study we found that the rs1800544 polymorphisms of the DRD4 gene were significantly associated with MDD response after 6 weeks of SSRI treatment. No neuroendocrine indicator independently predicted the SSRI response or remission in our study; however, a combination of neuroendocrine factors, some clinical characteristics and rs1800544 polymorphisms predicted 74.8% of the SSRI response and 65.5% of the SSRI remission. There were significant differences in age, HAMD scores at baseline, marital status between remission and non-remission groups.

DRD4 gene polymorphisms are associated with SSRIs response

Our data revealed that the rs1800544 (DRD4 gene) polymorphisms play a major role in the antidepressant response to SSRI treatment. The frequency of the DRD4 rs1800544 CG genotype

Table 5 The logistic regression in which SSRI response (or remission) was the dependent factor.

Covariate	B	S.E.	Wald	df	Sig	Exp (B)	95%CI for Exp (B)
genotype	0.188 (0.320)	0.311 (0.275)	0.363 (1.354)	1	0.547 (0.245)	1.206 (0.726)	0.655–2.22 (0.424–1.245)
age	−0.014 (0.002)	0.017 (0.015)	0.607 (0.025)	1	0.436 (0.874)	0.986 (1.002)	0.953–1.021 (0.973–1.032)
gender	−0.145 (0.360)	0.322 (0.280)	0.202 (1.659)	1	0.653 (0.198)	0.865 (1.434)	0.460–1.627 (0.829–2.480)
HAMD-baseline	0.042 (−0.074)	0.035 (0.030)	1.454 (5.951)	1	0.228 (0.015*)	1.043 (0.929)	0.974–1.117 (0.876–0.986)
number of episodes	0.052 (−0.182)	0.161 (0.166)	0.103 (1.198)	1	0.748 (0.274)	1.053 (0.834)	0.768–1.444 (0.602–1.155)
family history	−0.451 (−0.225)	0.424 (0.386)	1.134 (0.340)	1	0.287 (0.560)	0.637 (0.798)	0.278–1.461 (0.374–1.702)
single	0.598 (0.932)	0.654 (0.614)	0.836 (2.305)	1	0.360 (0.129)	1.818 (2.539)	0.505–6.549 (0.762–8.458)
married	0.576 (0.129)	0.581 (0.558)	0.983 (0.054)	1	0.321 (0.817)	1.779 (1.138)	0.570–5.552 (0.381–3.399)
divorced			1.090 (4.137)	2	0.580 (0.126)		
CORT	0.003 (0.003)	0.003 (0.002)	1.234 (1.779)	1	0.267 (0.182)	1.003 (1.003)	0.998–1.008 (0.998–1.008)
ACTH	−0.002 (0.038)	0.029 (0.027)	0.005 (2.092)	1	0.946 (0.148)	0.998 (1.039)	0.943–1.056 (0.986–1.094)
TSH	−0.214 (−0.167)	0.154 (0.153)	1.931 (1.196)	1	0.165 (0.274)	0.807 (0.846)	0.597–1.092 (0.627–1.142)
fT3	−0.171 (−0.239)	0.368 (0.355)	0.215 (0.453)	1	0.643 (0.501)	0.843 (0.787)	0.410–1.734 (0.392–1.580)
fT4	0.271 (0.238)	0.160 (0.191)	2.878 (1.546)	1	0.090 (0.214)	1.311 (1.269)	0.959–1.792 (0.872–1.846)
T3	0.572 (−1.193)	1.283 (1.342)	0.199 (0.791)	1	0.656 (0.374)	1.771 (0.303)	0.143–21.881 (0.022–4.207)
T4	−0.032 (−0.039)	0.030 (0.032)	1.185 (1.526)	1	0.276 (0.217)	0.968 (0.961)	0.913–1.026 (0.903–1.023)
constant	−1.530 (2.060)	2.794 (2.430)	0.300 (0.719)	1	0.584 (0.397)	0.217 (7.846)	

Genotype of rs1800544 was included in logistic regression which included C allele carrier (CG or CC) or not (GG). The values in the brackets are the results of logistic regression in which SSRI remission was the dependent factor

Table 6 The predictive probability of clinical characteristics, neuroendocrine factors and gene polymorphisms in SSRI treatment outcome.

	Predicted by combination of all factors		
Observed	Negative	Positive	Percentage Correct (%)
non-responder	11	59	15.7
responder	14	206	93.6
overall			74.8
non-remission	95	51	65.1
remission	49	95	66.0
overall			65.5

All factors include age, gender, HAMD baseline, number of episodes of MDD, family history, marital status, rs1800544 genotype and neuroendocrine factors. Neuendocrine factors include CORT, ACTH, TSH, fT3, fT4, TT3, TT4. Negative indicate non-response or non-remission to SSRI treatment predicted by logistic regression. Positive indicate response or remission to SSRI treatment predicted by logistic regression. Number of patients or correct percentage are shown

was significantly higher in the SSRI responders (51.4%) than that in the non-responders (35.8%). Dopamine (DA) is hypothesized to play an important role in MDD pathogenesis and antidepressant effects. DA function is increased after chronic antidepressant treatment [20,21]. Also the antidepressant effects of SSRIs are reversed by acute administration of a D2 receptor-selective antagonist [22]. Nevertheless, the DA system has been poorly investigated in previous pharmacogenetic studies, which have instead focused on dopamine receptors belonging to the D2-like family (D2, D3, and D4). Garriock et al. reported that a variable number tandem repeat (VNTR) polymorphism within exon 3 of DRD4 may modulate the antidepressant efficacy [23], but no association with SSRI response was found in a larger sample [24]. Our results support our primary hypothesis that SSRI response is significantly associated with the DRD4 gene polymorphisms. Genetic make-up of the Asian people is likely to differ from other ethnic groups, which maybe can partly explain the different outcomes of antidepressant treatment with SSRI relative to previous studies. As this genetic subgroup (CG) comprised 59.5% of the present cohort (131/220 cases), this result may prove important for clinical practice. This preliminary finding should be further tested in studies specifically designed to examine the differential response to drug class according to genotype.

TPH, SLC6A2, SLC6A3, and DRD2 gene polymorphisms are not associated with SSRIs response or remission

Our data revealed no association between polymorphisms in the TPH, SLC6A2, SLC6A3, and DRD2 genes and the efficacy of SSRIs. The noradrenaline transporter or the norepinephrine transporter, encoded by the SLC6A2 gene, is a primary target of several antidepressant agents. Previous studies reported that the G allele of the SLC6A2 variant rs5569 (G1287A) might be associated with antidepressant outcome, especially for noradrenergic antidepressants, and that the T allele of rs2242446 (T182C) may predict a better milnacipran response [8,9,25]. On the other hand, negative findings for the association of both of these polymorphisms and patient response have also been reported [26–29].

The SLC6A3 gene encodes the dopamine transporter DAT, which is a membrane-spanning protein whose primary function is to clear DA from the synapses. A 40-bp VNTR in exon 15 has been reported to affect DAT expression [30]. In addition, the 9/10 and 9/9 SLC6A3 genotypes may be associated with the risk of poorer and slower response to various antidepressants [31] and SSRI augmentation with methylphenidate [32]. Another variant in SLC6A3 (rs8179029) was associated with desipramine response in Mexican-Americans, but confirmation of this result is lacking [25]. Thus, given the low number of available studies, no definitive conclusion of the association between this gene and antidepressant outcome can be established.

Associations between polymorphisms of the TPH gene, which encodes tryptophan hydroxylase, and SSRI response were confirmed by pharmacogenetic studies [33–35], but these results have not been replicated for the most part, especially in Asian populations but also in Caucasians [36–42].

Similarly, studies examining the role of the DRD2 gene in antidepressant response are conflicting. Negative results were obtained for the rs1801028 and rs6275 polymorphisms, while a significant association between early improvement and rs4460839/rs2734833 has been reported [24,29,43].

Clinical characteristics, neuroendocrine factors and gene polymorphisms may predict SSRIs response and remission

With respect to the HPA and HPT axes, no neuroendocrine indicator independently predicted SSRI response or remission in this study. However, we found the combination of some clinical characteristics, neuroendocrine factors and rs1800544 polymorphisms predicted 74.8% of the SSRI response and 65.5% of the SSRI remission. This might provide a valuable way which combined with the genetic pathway, neuroendocrine factors and clinical characteristics may be able to predict SSRI treatment outcome in the future. Our findings were different from previous studies that reported higher TSH independently predicted SSRIs response [44].

Additionally, we found that every one point increase in the HAMD baseline scores was associated with a 0.929 fall in the possibility to research remission (**Table 5**) and the remission group had lower baseline HAMD scores relative to the non-remission group. Our finding is consistent with one previous study which stated that higher baseline depressive symptom severity predicted lower probability of remission [45]. In the current study we found that the remission group was younger and had less percent of patients who were married, remarried or divorced relative to the non-remission group. The relationship between age, marital status and antidepressant outcome was also reported by other studies [46].

Limitation

There are some limitations of our study. First, we did not measure the plasma levels of the medications. Some studies have shown no relationship between SNPs and plasma drug concentration; however, there may be indirect effects that influence antidepressant efficacy [47]. Second, the relationships between SNPs and side effects were not explored, and neither were relationships with personality and cognitive functions. Further limitations include the relatively short timeframe of the study, the inability to exclude the possibility of a placebo effect because of the lack of a control group and focusing only on a limited number of genetic polymorphisms.

Conclusion

In conclusion, despite these limitations, this randomized double-blinded study demonstrates that the responses to SSRIs are significantly associated with catecholamine gene polymorphisms. We concluded that polymorphisms of the DRD4 gene accurately predict SSRI responses in Chinese Han individuals suffering from MDD. Therefore, it will be necessary to replicate and further verify this possibility in other independent studies using larger samples. Independently, neuroendocrine factors were not significant predictors for SSRI outcome, and only their combination with clinical characteristics and gene polymorphisms could predict subject response or remission to SSRIs. Therefore, the influence of gene-environment interactions on SSRI response or remission should be explored in future studies.

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Conflict of Interest

The authors declare no conflicts of interest.

Affiliations

[1] Department of Psychiatry, West China Hospital of Sichuan University, Chengdu, Sichuan Province, People's Republic of China
[2] Bio-X Institute, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Shanghai Jiao Tong University, Shanghai, People's Republic of China
[3] Li Yin and Yao Ying Zhang contributed to the work equally

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