HTR2C promoter polymorphisms are associated with risperidone efficacy in Chinese female patients

Aims: A number of studies demonstrate that the polymorphisms in the 5′ region of *HTR2C* play a pivotal role in antipsychotic drug efficacy. Since risperidone is an antagonist of *HTR2C*, polymorphic variations in *HTR2C* may explain variability in response to risperidone treatment. We analyzed *HTR2C* polymorphisms for association with efficacy of risperidone monotherapy. **Materials & methods:** We genotyped five SNPs distributed throughout the *HTR2C* gene and examined them for association using the Brief Psychiatric Rating Scale score in 130 Chinese schizophrenic patients following an 8-week period of risperidone monotherapy. All the patients were receiving the atypical antipsychotic drug treatment for the first time and had a 4-week medication-free period before research began. **Results:** We found rs518147, rs1023574 and rs9698290 were significantly associated with risperidone treatment in female patients ($F = 4.75$, degrees of freedom = 2 and $p = 0.011$; $F = 4.329$, degrees of freedom = 2 and $p = 0.016$; $F = 4.188$, degrees of freedom = 2 and $p = 0.019$, respectively) and they were also found to be in one linkage disequilibrium block. **Conclusion:** Our results indicate that variants in the *HTR2C* promoter region are likely to affect the risperidone therapeutic effect in female mainland patients. It may be helpful to investigate a combination of other clinical factors to predict atypical antipsychotic efficacy.

KEYWORDS: ***HTR2C*** ▪ **pharmacogenomics** ▪ **risperidone** ▪ **schizophrenia** ▪ **treatment response**

Bao-Cheng Liu[1,2,3], Jing Zhang[1,2,3], Lei Wang[1,2,3], Xing-Wang Li[1,2,3], Yang Wang[1,2,3], Zhi-Yun Wei[1,2,3], Jue Ji[1,2,3], Feng-Ping Yang[1,2,3], Chun-Ling Wan[1,2,3], Yi-Feng Xu[4], Guo-Yin Feng[4], Lin He[2,3,5] & Guang He[†1,2,3]

[1]Bio-X Center, Key Laboratory for the Genetics of Developmental & Neuropsychiatric Disorders (Ministry of Education), Shanghai Jiao Tong University, Shanghai 200030, PR China
[2]Institutes of Biomedical Sciences, Fudan University, 138 Yixueyuan Road, Shanghai 200032, PR China
[3]Institute for Nutritional Sciences, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, 320 Yueyang Road, Shanghai 200031, PR China
[4]Shanghai Institute of Mental Health, 600 South Wan Ping Road, Shanghai 200030, PR China
[5]Bio-X Life Science Center, Shanghai Jiao Tong University, 1954 Huashan Road, Shanghai 200030, PR China
[†]Author for correspondence:
Tel.: +86 216 282 2491
Fax: +86 216 282 2491
heguang@sjtu.edu.cn

Schizophrenia is a psychiatric disorder with a prevalence of approximately 1% of the world population and is characterized by psychotic symptoms, such as hallucinations, delusions and thought disturbances. Both living environment and genetic factors could influence patients psychiatric susceptibility. Heritability measurements vary from 68–89% based on different populations [1,2].

Risperidone, a bensisoxazole derivative with a high affinity for the serotonin receptors, was one of the first medicines of the second-generation antipsychotics (SGA) to be introduced into the market [3,4]. Compared with typical antipsychotics, SGAs are less likely to cause extrapyramidal side effects (EPS). The current trend is to gradually replace the first-generation antipsychotic drugs by SGAs. However, therapeutic outcomes vary based on individual genetic background [5,6]. Therefore, there is an urgent need to investigate the relationship between specific polymorphisms of the relevant genes and the response to risperidone medication.

Serotonin (5-hydroxytryptamine [5-HT]) is an essential neurotransmitter, synthesized from dietary tryptophan. The serotonergic system has been studied extensively in the context of psychiatric conditions, including depression, eating disorders, motor behavior and schizophrenia [7]. The potent serotonin receptor, as well as the relatively weaker dopamine D2 antagonists are significant SGA pharmaceutical targets for clozapine, quetiapine, risperidone, sertindole and ziprasidone [8]. The serotonin receptors have been classified into seven families (5-HT_{1-7}). The human *HTR2C* receptor gene is localized in sex chromosome Xq24. It is a post-synaptic G-protein-linked receptor that activates both cyclic GMP and cerebrospinal fluid formation [9]. Animal research has focused on its effect in alcoholism, depression and neuropathic pain [10–12]. Among the SNPs identified in *HTR2C*, previous studies have focused on the association of rs3813929 (-759C/T), rs518147 (-697G/C) and rs6318 (Ser23Cys) with schizophrenia, antipsychotic-induced obesity, metabolic syndrome and antipsychotic efficacy [13–19]. Reynolds *et al.* found that the promoter polymorphism was associated with improvement in the Positive and Negative Syndrome Scale [19], while Ikeda *et al.* fail to replicate their findings [20]. We have summarized the recent finding of risperidone treatment response in schizophrenia patients (see Table 1). To further evaluate the importance of *HTR2C* polymorphisms in Asian schizophrenia patients. we performed

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Table 1. Summary of recent papers on risperidone treatment response in schizophrenia and autism patients.

Study	Sample number	Drug(s) treatment	SNPs in *HTR2C*	Statistical method	Results	Ref.
Reynolds *et al.*	117 Chinese patients (58 males and 59 females)	Chlorpromazine (n = 66), risperidone (n = 43), clozapine (n = 4), fluphenazine (n = 3) and sulpiride (n = 1) for 10 weeks	-759C/T (rs3813929)	Clinical response was defined as 50% improvement from baseline in total PANSS χ^2-goodness-of-fit test used to compare allele and genotype frequencies between categorical clinical subgroups Regression analysis used to determine the influence of clinical and demographic factors on symptom measures T-test was used to determine any association of *HTR2C* genotype with the percentage change in total PANSS score, as they only have CC and CT of rs3813929 in female and C or T in male	-759C/T is associated with the percentage change in PANSS score, especially the negative and general subscore	[19]
Ikeda *et al.*	120 unrelated ethnically Japanese (58 male and 62 female)	Risperidone monotherapy for 8 weeks	-759C/T (rs3813929) and -697C/T (rs518147)	Improvement of patients under risperidone therapy measured by the reduction rate in PANSS scores Dominant genetic model to the following regression analysis: wild-type homozygote and the combined group of heterozygtes and mutant homozygotes, ANOVA test and stepwise regression. The following is true: a dominant model is coded as 1 for any genotype that contains an A allele and 0 otherwise (i.e., AB, AA = 1, BB = 0); a recessive model is coded as 1 for the homozygous AA genotype and 0 otherwise (i.e., AA = 1, AB, BB = 0)	Both of the SNPs are found to lack association with risperidone in ANOVA test and regression analysis	[20]
Correia *et al.*	31 Portuguese autism patients	Risperidone monotherapy for 1 year	rs6318, rs3813928 and rs3813929	Improvement of the patients under risperidone therapy measured by the decline in ATEC scores Multiple linear regression analysis with generalized estimating equation method	Patients with the rs3813928 variant genotype (A in man, AA or AG in women) had 4.1% higher ATEC scores compared with the most common genotype (G or GG) rs6318 and rs3813929 lack association with risperidone treatment	[25]
This paper	130 unrelated ethnically Chinese (45 male and 85 female)	Risperidone monotherapy for 8 weeks	rs3813929, rs518147, rs1023574, rs9698290 and rs6318	Improvement of patients under risperidone therapy measured by the reduction rate in BPRS scores ANOVA test for the genetic association with risperidone efficiency in the female and male group, respectively Dominant genetic model to the following regression analysis: wild-type homozygote and the combined group of heterozygotes and mutant homozygotes	rs518147, rs1023574 and rs9698290 were significantly associated with risperidone treatment in the female group, and G allele in rs518147 may have some effect in drug response rs6318 and rs3813929 lack association with risperidone treatment	

ANOVA: Analysis of variance; ATEC: Autism Treatment Evaluation Checklist; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale.

an association study on the polymorphism sites of the 5′ region of this gene in a relatively large sample of Chinese schizophrenia patients following 8 weeks of risperidone treatment.

Materials & methods

Clinical sample

A total of 145 Chinese Han schizophrenia patients were recruited from the Shanghai Mental Health Center (Shanghai, China). Subjects were chosen based on the following criteria:

- No physical disease or history of substance abuse;
- No history suggesting resistance to antipsychotic treatment.

They were diagnosed as schizophrenic, and this was confirmed by at least two independent experienced psychiatrists who conducted clinical interviews based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [21]. All the patients provided written informed consent and received atypical antipsychotic drug treatment for the first time. All the experiments were in accordance with the Declaration of Helsinki and approved by the Shanghai Ethical Committee of Human Genetic Resources.

Clinical protocols

Before treatment with risperidone, all the patients had been medication-free as a 'washout' period for at least 4 weeks. Risperidone was given at an initial dose of 2 mg/day and gradually increased to 4 mg/day within the first 7 days, then maintained until day 14, at which point the dosage increased or decreased on the basis of each patient's clinical response. Medication compliance was closely supervised and confirmed by nursing staff. During this study period, all the patients were in monotherapy, with no other drugs being given other than flunitrazepam for acute insomnia and biperiden for moderate EPS. The plasma concentration of the drug and prolactin were measured as indicators of compliance to treatment, details of which can be found in our previous publications [22,23]. The psychopathological condition of the patients was assessed by experienced psychiatrists according to the Brief Psychiatric Rating Scale (BPRS) [24] during 8 weeks of monotherapy. All BPRS ratings were conducted independently by two qualified psychiatrists who were blind to the genotype of each patient. Antipsychotic efficacy was evaluated in terms of the percentage change in BPRS scores.

Genotyping

Genomic DNA was prepared from venous blood using standard phenol chloroform extraction. SNPs were selected based on positive reported variants in previous studies. Five SNPs that are located in the 5′ region of *HTR2C*, including rs3813929 (-759C/T) [19], rs518147 (-697G/C) [20], rs1023574, rs9698290 and rs6318 (Ser23Cys) [25] were included. SNPs rs3813929 and rs518147 are located in the promoter region of *HTR2C*. SNP rs6318 is in the coding sequence of the *HTR2C* receptor gene, resulting in an amino acid substitution of serine for cysteine at position 23 (Ser23Cys). Rs1023574 and rs9698290 are found in the noncoding region between rs518147 and rs6318.

All SNPs were genotyped using the ABI 7900 DNA detection system (Applied Biosystems, CA, USA) and TaqMan® technology (Applied Biosystems). All probes were designed by the Applied Biosystems service. The standard 5 µl PCR reaction was carried out using TaqMan Universal PCR Master Mix reagent kits under the guidelines provided. All genotypes were blind tested to assess the clinical outcome of antipsychotic treatment.

Statistical analysis

Genotype frequencies were calculated using SPSS for Windows (version 13.0). Deviations from Hardy–Weinberg equilibrium for each polymorphism were calculated using GENEPOP 3.4 [26]. Linkage disequilibrium (LD) and allele distribution were estimated for each pair of five polymorphisms using the HAPLOVIEW software [27]. Differences were evaluated for continuous variables using one way analysis of variance (ANOVA) followed by the Tukey test for comparison among groups.

To substantiate the results, allele and genotype association and odds ratios were recalculated using software available online [28,101].

Results

Participant characteristics

All 130 patients were available for further assessment at the end of the 8-week treatment. Of them, 67 were drug naive and the remainder had been primarily treated with a typical antipsychotic. A total of 15 patients dropped out of this research owing to noncompliance (n = 6) or emergent somatic illness (n = 3), and six patients quit the study after their psychotic symptoms were not relieved after 14 days of risperidone treatment. Their clinical profiles are shown in Table 2. Since the *HTR2C* gene is

Table 2. Baseline features of schizophrenia patients treated with risperidone.

Patients	Total (n = 130)	Male (n = 45)	Female (n = 85)	p-value
Age (years)	36.3 ± 11.2	35.9 ± 12.8	36.4 ± 10.4	0.80
Age of onset (years)	30.3 ± 10.3	28.4 ± 10.6	31.3 ± 10.1	0.13
Duration of illness (years)	6.0 ± 8.6	7.4 ± 10.1	5.3 ± 7.8	0.72
Plasma risperidone levels (ng/ml)	7.0 ± 5.6	24.9 ± 21.9	26.4 ± 30.2	0.77
Plasma 9-hydrorisperidone levels (ng/ml)	22.6 ± 13.1	12.3 ± 34.9	14.5 ± 49.4	0.80
Total BPRS score				
Baseline BPRS score	42.4 ± 12.4	42.2 ± 12.6	42.5 ± 12.3	0.88

Data expressed as mean ± standard deviation.
BPRS: Brief Psychiatric Rating Scale.

located in the X chromosome, the patients were divided into two different groups based on their gender. Regression analysis shows that there were no significant differences between gender groups in age, age of onset, duration of illness, steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone, or in the baseline BPRS score on admission. This indicated that our sample had no gender bias in terms of clinical indices. No statistical differences in demographic characteristics or in plasma levels of risperidone and 9-hydroxyrisperidone were observed between these two groups ($p > 0.05$) (data not shown).

Genotyping

All genotypes were blind tested to assess the clinical outcome of antipsychotic status. The genotype frequencies of the five SNPs showed no significant deviation from Hardy–Weinberg equilibrium in female patients. We evaluated therapeutic response on the basis of percentage reduction in total BPRS scores before and after the 8-week-period of monotherapy using the ANOVA test. There was no statistical relationship between the coding region SNPs, rs6318 and rs3813929, and the BPRS reduction percentage. However the promoter region in rs518147 and the proximate SNPs (rs1023574 and rs9698290) were found to be associated with changes in BPRS scores in female patients (fixation indices [F] = 4.75, degrees of freedom [df] = 2, $p = 0.011$; $F = 4.329$, $df = 2$ and $p = 0.016$; $F = 4.188$, $df = 2$, $p = 0.019$, respectively) (Table 3). To further compare allele frequencies in the female patients, all the SNPs were tested separately under dominant and recessive genetic models, using the ANOVA test, as the single allele may be the risk/protective allele in response to treatment [29]. We found female patients with the CC genotype in rs518147 and rs1023574 had a better effect

Table 3. Comparison of percentage change in Brief Psychiatric Rating Scale score between female groups with different genotypes after the 8-week treatment.

SNP ID	Genotype	Frequency (%)	p-value for HWE	Percentage reduction in BPRS score (female)	p-value
rs3813929	CC	63 (77)	0.15	44.8 ± 14.5	0.062
5′ near gene	CT	16 (19)		37.7 ± 16.6	
	TT	3 (4)		57.3 ± 19.7	
rs518147	CC	5 (6)	0.14	61.5 ± 16.2	0.011†
5′ UTR	CG	21 (26)		39.7 ± 13.3	
	GG	56 (68)		43.9 ± 14.3	
rs1023574	CC	4 (5)	0.10	62.0 ± 18.7	0.016†
Intron	CG	18 (22)		38.4 ± 13.8	
	GG	61 (73)		43.9 ± 14.7	
rs9698290	CC	60 (73)	0.11	44.5 ± 14.0	0.019†
Intron	CT	18 (22)		39.9 ± 12.2	
	TT	4 (5)		62.0 ± 18.7	
rs6318	CC	0	0.87	0	0.369
Coding SNP	CG	3 (4)		51.1 ± 25.3	
	GG	80 (96)		43.1 ± 14.8	

†Significant p-value (<0.05)
BPRS: Brief Psychiatric Rating Scale; HWE: Hardy–Weinberg equilibrium.

Table 4. Allele carrier frequencies of SNPs in females with different genotypes after the 8-week treatment.

SNP ID		Allele carrier frequency (%)	Percentage reduction in BPRS score	p-value
rs518147 (G/C)	G-	5 (6)	61.5 ± 16.2	0.006†
	G+	77 (94)	42.8 ± 14.1	
rs1023574 (G/C)	G-	4 (5)	62.0 ± 18.7	0.012†
	G+	79 (95)	42.7 ± 14.6	
rs9698290 (T/C)	C-	4 (5)	62.0 ± 18.7	0.011†
	C+	78 (95)	43.4 ± 13.7	

†*Significant p-value (<0.05).*
BPRS: Brief Psychiatric Rating Scale.

than the ones with the GC or GG genotype, while for rs9698290 this improvement was observed in the patients with TT genotype rather than the ones with CC or CT genotype (Table 4, other data not shown). No corresponding correlation was found in the male patients (Table 5).

Linkage disequilibrium analysis

Pairwise LD between the five markers was estimated in terms of r^2, which ranged between 0.8 and 1.0, indicating strong intermediate LD between the markers. As shown in Figure 1, strong LD was observed between the promoter region of rs518147, rs1023574 and rs9698290. The rs3813929 and rs6318 SNPs were in relatively weak LD with any other SNP. Our results indicate that the three SNPs, rs518147, rs1023574 and rs9698290, were in one LD block. Classical haplotype analysis was not adopted, as we did not divide our sample into two or more groups according to the BPRS reduction rate scores; therefore, it did not fit the haplotype criterion.

Discussion

The *HTR2C* gene has been postulated to have a significant role in mediating drug effects, reducing the liability of EPS and affecting therapeutic efficiency against negative symptoms [30]. In our study, five polymorphisms spanning the 5′ region of the *HTR2C* gene were genotyped and investigated for their possible correlation with risperidone response in 130 unrelated Chinese mainland schizophrenia patients. We found that rs518147, rs1023574 and rs9698290 are significantly associated with risperidone efficacy in female patients.

Recent studies have mainly focused on the *HTR2C* polymorphisms with higher risk of both antipsychotic-induced obesity and metabolic syndrome [16,17,31,32]. Rare studies of *HTR2C* and psychotic treatment response were carried out and the outcomes were not consistent. Sodhi *et al.* reported that the Ser allele was more frequent in clozapine responders [33], while following studies failed to replicate this finding [34,35]. We have summarized recent papers on risperidone treatment response

Table 5. Comparison of percentage change in Brief Psychiatric Rating Scale score between male groups with different alleles after the 8-week treatment.

SNP ID	Allele	Frequency (%)	Percentage reduction in BPRS score (male)	p-value
rs3813929	C	36 (90)	35.0 ± 21.2	0.676
5′ near gene	T	4 (10)	39.6 ± 15.9	
rs518147	C	5 (12)	29.1 ± 27.3	0.533
5′-UTR	G	34 (87)	43.9 ± 14.3	
rs1023574	C	4 (9)	39.6 ± 15.9	0.651
Intron	G	37 (90)	35.0 ± 21.2	
rs9698290	C	36 (90)	35.0 ± 21.2	0.654
Intron	T	4 (10)	39.6 ± 15.9	
rs6318	C	0	0	–
Coding SNP	G	44 (0)	35.0 ± 21.2	

BPRS: Brief Psychiatric Rating Scale.

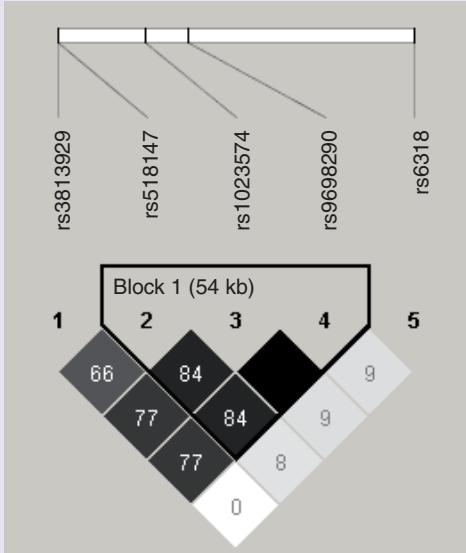

Figure 1. Linkage disequilibrium between SNPs. r^2 between marker pairs is indicated by the shaded matrices. This figure shows that strong linkage disequilibrium was observed between rs518147, rs1023574 and rs9698290.

in schizophrenia patients in TABLE 1. Our results are consistent with those of Hong *et al.,* that the low frequency of 23Ser in rs6318 in the Chinese ethnic population suggests that it may not be an useful marker in this current study [36]. Furthermore, we found that the three variations (rs518147, rs1023574 and rs9698290) may be potential predictors of Asian population risperidone response, as their allele frequencies in Chinese populations all exceed 10% (the frequency of the C allele [$f_{\text{allele C}}$] in rs518147 is 0.18; $f_{\text{allele C}}$ in rs1023574 is 0.18; $f_{\text{allele T}}$ in rs9698290 is 0.15, other data not shown). In addition, our results also support the results of Reynolds *et al.,* that the effect of variations in the *HTR2C* gene might be associated with the therapeutic efficacy of atypical antipsychotics, although their study only tested the rs3813929 (-759C/T) [19].

It is worth noting that we also found that female patients carrying the G allele in rs518147 had a worse response than the ones without the G allele. The rs518147 polymorphism is associated with the decrease in *HTR2C* promoter activity and has an association with the side effect of antipsychotic drugs [32,37]. The mechanisms underlying changes in promoter activity are still unclear. One hypothesis could be that the single nucleotide variation could alter the affinity for transcription factors, especially in the case of rs518147 [38]. Furthermore, antipsychotic drugs also influence the gene promoter activity [39]. They both may include some unknown interactions; therefore, further functional research is needed to validate this hypothesis.

The current trend in pharmacogenomic studies is to identify the genetic contributors to clinical variability in drug response; however, other factors, such as demographic, clinical and environmental variables, can confound the pharmacogenetic association results. Our study had three advantages which help to minimize the effect of such nongenetic factors. Firstly, all the inpatients who participated in this study were treated with only risperidone for the first time, and they all had a washout period before beginning the experiment. The nature of our sample minimized the effects of medical history on risperidone response, as the long-term effects of atypical antipsychotic treatment could selectively decrease the number of dopamine neurons and neuron activity [40]. Secondly, all the patients were provided with a relatively uniform hospital environment for the period of the investigation, avoiding confounding environmental factors. Thirdly, our patients were given an optimal dose of 4 mg/day rather than 6 mg/day. This lower dose meant a lower risk for EPS being observed among all the patients [41]. Therefore, we were able to maintain a uniform dosage schedule for most patients for 8 weeks, which may have reduced the possible effect of this variable on medical response.

There are, however, several limitations. Owing to the exploratory nature of this paper, we did not correct for multiple testing since the genetically complex association between genotype and phenotype had not been established. Furthermore, conservative corrections may increase the likelihood of type II error [42]. More SNP probes spanning the *HTR2C* gene could be included in a comprehensive evaluation study (e.g., haplotype study). Although this study included the highest number of patients treated with one antipsychotic drug in monotherapy so far, we only enrolled the patients who had completed the whole 8-week open-label study, so it may raise a bias in our primary findings. Therefore, further studies with larger sample numbers and functional research of the promoter region of *HTR2C* are needed to replicate and validate our results.

Conclusion

In summary, we conducted a detailed study of the association between the *HTR2C* gene and therapeutic response to risperidone. Our results indicate that variants in the promoter region are likely to affect the therapeutic efficacy in

the Chinese female population. This study here was one of the few that used risperidone monotherapy, and included the highest number of patients treated. However, owing to the shortcomings discussed above, more studies, especially functional research, are needed to elucidate the role of *HTR2C* and to replicate our results in different ethnic populations with larger samples.

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Financial & competing interests disclosure

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Ethical conduct of research

The authors stated that they have obtained appropriate institutional review board approval or have followed the principles outlined in the declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Introduction

- Risperidone is widely used in treating psychiatric disease, while therapeutic outcomes vary based on individual genetic background.
- This study was one of the few that used risperidone monotherapy and enrolled the highest number of patients treated.

Methods

- Five SNPs (rs3813929, rs518147, rs1023574, rs9698290 and rs6318) of *HTR2C* were genotyped in Chinese mainland schizophrenia patients.
- All 130 patients received risperidone for the first time and finished an 8-week risperidone monotherapy after at least a 4-week 'washout' period. Brief Psychiatric Rating Scale changes of patients before and after this period of treatment were used to evaluate drug efficacy.

Conclusion

- We found that one linkage disequilibrium block, including rs518147, rs1023574 and rs9698290, is significantly associated with risperidone efficacy in Chinese female patients.
- Female patients with the CC genotype in rs518147 and rs1023574 had an improved effect compared with the patients with the GC or GG genotype, while for rs9698290, the improvement was more clearly observed in the patients with the TT genotype than in the patients with the CC or CT genotype.

Unresolved issues & future perspective

- Although we have enrolled the largest number of patient in this pharmocogenetic study so far, it is still lacks statistic power and more samples are needed to replicate our findings.
- Future research with function study and gene–gene interaction could give us a more clear picture of mechanism of risperidone treatment efficacy.

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