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LETTER TO THE EDITOR

Association of *ABCB1* Gene Polymorphisms with Efficacy and Adverse Reaction to Risperidone or Paliperidone in Han Chinese Schizophrenic Patients

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Dear editor,

P-glycoprotein (P-gp, also known as ATP-binding cassette transport sub-family B member 1, ABCB1) is a potent ATP-dependent efflux pump for a wide variety of drugs. Although studies of its substrates are abundant [1, 2], and *ABCB1* is a well-conserved gene, there is increasing evidence that its polymorphisms affect substrate specificity [3]. A previous study reported that the synonymous single nucleotide polymorphism (SNP) C3435T (rs1045642) affects the timing of co-translational folding and insertion of P-gp into the membrane, and alters the structure of the substrate and inhibitor interaction sites [4]. Some studies have also reported an association between *ABCB1* genotypes and antipsychotics [5, 6]. Bozina *et al.* [5] found that the T allele and TT genotype of G2677T (rs2032582) are associated with a better treatment response to olanzapine in female schizophrenic patients. Qinghe Xing *et al.* [6] reported that the TT genotype of locus rs1128503 in the *ABCB1* gene is associated with a better response to risperidone treatment. Most such studies have focused on the effects of the genotypes, and loci are limited to the commonly-studied rs2235048, rs1045642, and rs2032582, and the results are not consistent. Risperidone is one of the atypical antipsychotics, its main metabolic product is 9-hydroxyriperidone (9-OH-risperidone or paliperidone), and they are both substrates of P-gp [2, 7].

In order to investigate the relationships of *ABCB1* gene polymorphisms (genotype, haplotype, and risk alleles) and the clinical efficacy of risperidone and paliperidone in the treatment of schizophrenia, we recruited 201 Han Chinese schizophrenic patients treated with risperidone or paliperidone from Jan/2008 to Jan/2009. Among them, 133 were randomized to take paliperidone palmitate (50–150 mg/4 weeks) or risperidone long-acting injection (risperidone LAI, 25–50 mg/2 weeks) for 12 weeks. The efficacy and safety were assessed every two weeks. In the other 68 inpatients or outpatients who were treated with risperidone tablets (2–6 mg/day) for 4 weeks, the efficacy and security were assessed every week. The main effect assessment used the final and baseline Positive and Negative Syndrome Scale (PANSS) total score reduced rate (PANSS reduced rate = (baseline score − final score) / (baseline score) ×100%). Five milliliters of venous blood was taken at the baseline visit, centrifuged, and stored at −70°C. Based on previous studies, we chose the commonly-studied

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loci rs2235048, rs1045642, and rs2032582, while adding another two loci, rs1128503 and rs12535512. The genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) or direct sequencing (Table S1). The biomedical statistical software SPSS16.0 (SPSS Inc., Chicago, IL) was used for analysis. The prediction of haplotypes was completed using the online software 'Haplotype resolution using imperfect phylogeny' (http://research.calit2.net/hap/) [8]. The protocol was approved by the Ethics Committee of the Peking University Institute of Mental Health, and written informed consent was given by all participants.

We found that all SNPs were in Hardy-Weinberg equilibrium and the pairwise linkage disequilibrium of the 5 SNPs was calculated (Table S2). The demography and clinical data of the patients are listed in Table S3. Logistic analysis showed that gender, years from onset, age, dosage, and dosage form had no impact on the PANSS reduced rate (none were entered into the equation). ANOVA did not reveal significant associations between each genotype and the PANSS reduced rate (Table S4), but *t*-tests of alleles and PANSS reduced rate revealed that carriers of the C allele (CT+CC) of rs2235048 had a lower PANSS reduced rate (Table 1), and TT genotype carriers had better clinical efficacy ($P < 0.05$, 95% CI: −0.139, −0.006). There were no significant associations between the remaining loci and PANSS reduced rate. In the analysis of association of haplotypes and PANSS reduced rate, we found that the haplotype T-C (rs2235048-rs1045642) was significantly associated with a higher PANSS reduced rate ($P < 0.05$, 95% CI: 0.0007, 0.133; Table 1), so T-C carriers might have better clinical efficacy.

We also found that *ABCB1* gene polymorphisms influenced the extrapyramidal symptom (EPS) incidence rate and the increased prolactin level. C allele carriers of rs1128503 had a higher total EPS incidence rate than TT carriers ($P < 0.05$). GT/GA carriers of rs2032582 had a higher total EPS incidence rate than the other genotype carriers (AA/GG/AT/TT, $P < 0.05$, $n = 201$). EPS symptoms can be divided into dysmyotonia, dyskinesia (movement disorder), and tremor. GG genotype carriers of rs2032582 had a lower dyskinesia incidence rate than the other genotypes ($P < 0.05$). The tremor incidence rate was higher in C-G-C haplotype carriers (rs1045642–rs2032582–rs1128503) than in non-carriers ($P < 0.05$, $n = 201$; Tables S5–S7). The mean blood prolactin increase was (284.22 ± 1076.19) μIU/L (mean ± SD) (the normal upper limit of prolactin in this study was 424 μIU/L in males and 530 μIU/L in females), but gender and drug dosage form did not influence the degree of prolactin increase. C allele (CT+CC) carriers of rs2235048 were associated with a lower degree of prolactin increase ($P < 0.01$). T-A-T haplotype (rs1045642–rs2032582–rs1128503) carriers had a lower prolactin level ($P < 0.05$, $n = 201$; Table S8).

The SNP rs2235048 is reported for the first time in our study. SNP is located on the 27th intron of the 3'-end of the gene, and although it is a synonymous SNP, it may influence the structure of P-gp as has been reported [4]. This study also provides cues about the haplotype effects on P-gp function; different SNPs may have combined effects that differ from the effect of each SNP, but our results are not consistent with previous studies [4, 9]. In conclusion, our study indicates a probable association between *ABCB1* gene polymorphisms and clinical efficacy/safety in Han

Table 1 Alleles and haplotype analysis for the association between *ABCB1* and PANSS reduced rate (mean ± SD).

Loci/haplotypes	rs2235048	rs1045642	rs2032582	rs1128503	rs12535512	T-T-A-T-C (rs2235048-rs1045642-rs2032582-rs1128503-rs12535512)	T-A-T (rs1045642-rs2032582-rs1128503)	T-C (rs2235048-rs1045642)
Alleles or haplotype (*n*)	CC/CT(114)*	CC(59)	AA/TT/AT/AG/GT(138)	CC/CT(97)	CC/CT(130)	T-T-A-T-C carrier (55)**	T-A-T carrier (97)	T-C carrier (58)
	0.29 ± 0.21	0.35 ± 0.22	0.31 ± 0.20	0.31 ± 0.19	0.33 ± 0.21	0.31 ± 0.19	0.30 ± 0.21	0.36 ± 0.20
Percentage PANSS reduction (mean ± SD)	TT(57)	CT/TT(112)	GG(34)	TT(73)	TT(43)	T-T-A-T-C non-carrier (118)	T-A-T non-carrier (76)	T-C non-carrier (115)
	0.36 ± 0.19	0.29 ± 0.20	0.31 ± 0.24	0.32 ± 0.24	0.28 ± 0.22	0.32 ± 0.22	0.34 ± 0.21	0.29 ± 0.21
T	4.647	1.756	0.002	−0.276	1.467	−0.328	−1.221	1.993
P	0.033	0.081	0.998	0.783	0.144	0.744	0.224	0.048
95% CI	−0.139, −0.006	−0.007, 0.125	−0.080, 0.080	−0.074, 0.056	−0.019, 0.126	−0.079, 0.056	−0.102, 0.024	0.0007, 0.133

*Number in brackets stands for the number in the special allele group.

**Number in brackets stands for the number in the special haplotype group.

Chinese schizophrenic patients treated with risperidone or paliperidone.

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