Neurosci. Bull. December, 2019, 35(6):1102–1105
https://doi.org/10.1007/s12264-019-00432-2

www.neurosci.cn
www.springer.com/12264

LETTER TO THE EDITOR

Interaction Between Variations in Dopamine D2 and Serotonin 2A Receptor is Associated with Short-Term Response to Antipsychotics in Schizophrenia

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Received: 8 May 2019 / Accepted: 12 July 2019 / Published online: 30 September 2019

Dear Editor,

Schizophrenia is a chronic and debilitating brain disorder, which has a strong genetic component with heritability ranging from 66% to 85% [1, 2]. Currently, antipsychotic drugs remain the most effective treatment for the psychotic symptoms of schizophrenia [3]. Because of the severe side-effects of first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs) have become more widely used in the treatment of schizophrenia. However, due to differing clinical, demographic, environmental, and genetic factors, the treatment response to SGAs shows considerable differences among patients. Most SGAs are antagonists of dopamine D2 (DRD2) and serotonin 2A (5-HT2A) receptors. It has been reported that DRD2 and 5-HT2A receptors play critical roles in antipsychotic effects. Several studies have shown that polymorphisms of the DRD2 and 5-HT2A receptor genes are associated with the antipsychotic response in schizophrenia. However, findings remain inconsistent and even contradictory.

Therefore, we expanded the sample size to include 1664 patients with schizophrenia to determine whether

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12264-019-00432-2) contains supplementary material, which is available to authorized users.

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variations in the *DRD2* and *5-HT2A* genes contribute to the therapeutic effect of SGAs. All patients were diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and received 6 weeks of treatment with 5 types of SGA (risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone), randomly allocated using the table of random numbers generated by computer. The patients were assessed using the Positive and Negative Syndrome Scale (PANSS) at baseline and the end of week 6. The demographic and clinical characteristics of patients are listed in Table S1. Based on previous studies, three SNPs (rs1799932, rs1799978, and rs1800497) in *DRD2*, and two SNPs (rs6313 and rs7997012) in *5-HT2A*, were selected as candidates and genotyped by PCR and Sanger sequencing (the rationale for SNP selection is detailed in Supplementary Material).

After Bonferroni correction, the percentage change in the positive symptoms differed significantly among the rs7997012 genotypes (Table 1). Pair-wise comparisons showed that patients with the AA genotype had better improvement of positive symptoms than those with the AG genotype ($P = 3.78 \times 10^{-3}$, Fig. S1). We further investigated the interaction effect between variations in *DRD2* and *5-HT2A* in response to antipsychotic treatment. A significant interaction effect between rs1800497 in *DRD2* and rs6313 in *5-HT2A* was found for the percentage change in the total PANSS score (Table 2, $F = 4.46$, $P = 1.37 \times 10^{-3}$). Moreover, we found that individuals with the rs1800497 AA genotype together with the rs6313 AG genotype had better responses to antipsychotic treatment (Fig. S2). The interaction effect between rs1799732 in *DRD2* and rs6313 in *5-HT2A* was also found for the percentage change in the total PANSS score (Table 2, $F = 3.29$, $P = 0.011$). However, this result was no longer significant after correction for multiple comparisons.

We found a coupling effect of *DRD2* and *5-HT2A* on the treatment response to antipsychotics in schizophrenia. Blasi and colleagues reported that rs1076560 T carrier and rs6314 CC genotype individuals responded better to antipsychotic treatment in two independent samples of patients with schizophrenia ($n = 63$ and 54). This study provides the first large randomized clinical trial in Chinese patients ($n = 1664$). More specifically, we found that individuals with the rs1800497 AA/rs6313 AG genotype responded better to antipsychotic treatment. The *TaqIA* single-nucleotide polymorphism (SNP, rs1800497) is a functional marker located 10 kb downstream of the *DRD2* gene and located in exon 8 of the Ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene, leading to a Glu713-to-Lys substitution in the ANKK1 protein [4]. Its minor allele (T) is associated with a reduced number of dopamine binding sites in the brain [5]. The expression data from the BRAINEAC project (Brain eQTL Almanac, http://www.braineac.org/) revealed this SNP as an expression quantitative trait locus (eQTL) that significantly regulates DRD2/ANKK1 expression in the brain (frontal cortex, $P = 0.003$ and hippocampus, $P = 0.00089$) and strongly associated with the pathology of schizophrenia. This SNP has been investigated in several studies of the antipsychotic treatment response in different populations, with inconsistent conclusions. Furthermore, a meta-analysis by Zhang *et al*. indicated no significant association between rs1800497 and treatment response to antipsychotics [6]. We found an interaction effect of rs1800497 × rs6313, rather than a main effect of rs1800497, and this was significantly associated with the percentage change in the total PANSS score. This finding suggested an alternative hypothesis in which the role of rs1800497 or DRD2/ANKK1 in the pathology of schizophrenia and its treatment deserves further exploration.

Rs6313 is also a functional marker (102T > C) located in exon 1 of *5-HT2A*; this has been a critical target of psychotropic agents such as antidepressants and SGAs. The GTEx (Genotype-Tissue Expression) database identified rs6313 as a *cis*-eQTL regulating *5-HT2A*, and homozygosity of its alternative allele (T) is associated with lower expression of *HTR2A* than the homozygosity of its reference allele (C, $P < 0.001$) [7]. Similar to rs1800497, previous association studies of rs6313 in antipsychotic treatment response have also generated inconsistent conclusions [8, 9]. To the best of our knowledge, this is the first time an interaction effect of rs1800497 × rs6313 on antipsychotic treatment response has been reported. This interaction effect provides a perspective from which to investigate the complexity of interactions between different neurotransmitters in the pharmacokinetics of antipsychotics.

We found a single intronic SNP, rs7997012, in *5-HT2A* associated with improvement of positive symptoms in patients with schizophrenia treated with antipsychotics. This SNP is primarily associated with the treatment response to antidepressants [10–14], but few studies have focused on the response to antipsychotic medication.

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Table 1 Associations of five SNPs with drug response.

Gene	SNP	Genotype	ΔPANSS total	ΔPANSS positive	ΔPANSS negative
DRD2	rs1800497	A/A	0.47 ± 0.36	0.56 ± 0.40	0.22 ± 0.90
		G/A	0.47 ± 0.34	0.61 ± 0.33	0.20 ± 1.01
		G/G	0.48 ± 0.34	0.59 ± 0.38	0.23 ± 0.93
		P value	0.42	0.13	0.84
		F value	0.87	2.01	0.18
	rs1799978	C/C	0.54 ± 0.24	0.65 ± 0.26	0.26 ± 1.00
		T/C	0.48 ± 0.34	0.59 ± 0.35	0.17 ± 1.04
		T/T	0.49 ± 0.35	0.60 ± 0.36	0.23 ± 0.92
		P value	0.33	0.43	0.31
		F value	1.11	0.84	1.18
	rs1799732	DEL/DEL	0.50 ± 0.26	0.68 ± 0.20	0.28 ± 0.44
		G/DEL	0.48 ± 0.37	0.59 ± 0.38	0.28 ± 0.80
		G/G	0.49 ± 0.34	0.60 ± 0.35	0.19 ± 1.01
		P value	0.91	0.45	0.26
		F value	0.10	0.81	1.35
5-HT2A	rs6313	A/A	0.48 ± 0.36	0.59 ± 0.37	0.20 ± 0.97
		A/G	0.50 ± 0.32	0.61 ± 0.35	0.23 ± 0.94
		G/G	0.47 ± 0.36	0.59 ± 0.35	0.19 ± 1.01
		P value	0.42	0.48	0.66
		F value	0.86	0.73	0.41
	rs7997012	A/A	0.43 ± 0.38	0.51 ± 0.41	0.25 ± 0.84
		G/A	0.50 ± 0.33	0.63 ± 0.34	0.19 ± 1.04
		G/G	0.48 ± 0.34	0.58 ± 0.36	0.22 ± 0.92
		P value	0.08	0.001*	0.61
		F value	2.56	6.66	0.49

*Significance after correction for 4 independent SNPs and 2 independent symptom (positive symptom and negative symptom), with adjusted *P* value at 0.05 level being 6.25×10^{-3}.

Table 2 Interaction between *DRD2* and *5-HT2A* SNPs.

Gene	SNP	Gene	SNP	Total		Positive		Negative	
				F	*P*	*F*	*P*	*F*	*P*
DRD2	rs1800497	*5-HT2A*	rs6313	4.46	1.37×10^{-3}*	1.65	0.491	1.45	0.215
	rs1799732		rs6313	3.29	0.011	1.97	0.096	0.81	0.519
	rs1799978		rs6313	0.47	0.758	1.25	0.289	0.59	0.668
	rs1800497		rs7997012	0.85	0.496	1.98	0.094	1.11	0.352
	rs1799732		rs7997012	1.59	0.174	0.35	0.843	0.61	0.654
	rs1799978		rs7997012	0.50	0.735	0.46	0.769	0.70	0.592

*Significance after correction for 6 SNP pairs and 2 independent symptoms (positive symptom and negative symptom), with adjusted *P* value at 0.05 level being 4.17×10^{-3}.

Unlike FGAs, SGAs generally have a more expanded profile of neurotransmitter targeting, including dopaminergic, serotoninergic, and glutamatergic transmitters. Although it is generally thought that positive symptoms arise from dopamine imbalance in the relevant brain region, both animal model and post-mortem studies have demonstrated a probably equal contribution of serotonin to psychosis [15, 16]. Although future replication is required, our findings provide further evidence of a potential moderating role of SGAs on *5-HT2A* in psychosis.

The present study provides preliminary evidence that *DRD2* and *5-HT2A* together affect the response to the treatment of schizophrenia with SGAs, however, there were still some limitations. The SNPs we found associated

with the response to antipsychotic medication were only the markers of genes. The relationship among these variations and the expression of genes remains unclear. Besides, the affinity for neurotransmitter receptors differs among SGAs, although they all mainly bind to *DRD2* and *5-HT2A*. In addition, although the sample size in the present study was relatively large, the statistical power was still small when a threshold was set to 0.00625 (adjusted *P* value at the 0.05 level). It should be cautioned that the negative results may be due to the probability of false-negative errors. Further studies with a single antipsychotic drug and a large sample size focusing on the biological functions of SNPs and gene expression are needed to confirm these findings and identify the mechanisms.

Acknowledgements This work was supported by the National Basic Research Development Program (2016YFC0904300), the National Natural Science Foundation of China (81630030 and 81461168029), and the 1.3.5 Project for Disciplines of Excellence of West China Hospital, Sichuan University (ZY2016103 and ZY2016203), China.

Conflict of interest All authors claim that there are no conflicts of interest.

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