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Letter to the Editor

Correlation between neurocognitive impairment and DNA methylation of *MMP-9* gene in patients with deficit schizophrenia

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Dear Editor

Deficit schizophrenia (DS) is defined as a homogeneous subtype of schizophrenia characterized by primary and persistent negative symptoms (Carpenter et al., 1988; Kirkpatrick and Galderisi, 2008). Compared to non-deficit schizophrenia (NDS), DS patients exhibited uniqueness in clinical characteristics, such as a higher rate in males, summer birth, poorer treatment responses, and long-term functional outcome. Most evidence suggested more severe neurocognitive impairments were observed in patients with DS relative to NDS (Cascella et al., 2008). However, the distinct pathophysiological foundation of neurocognitive deficit in DS patients remains unclear.

Matrix metalloproteinase 9 (MMP-9), the member of extracellular proteolytic family of enzymes, recently emerged as an important molecule that contributed to physiological processes and brain pathologies (Vafadari et al., 2016). The expression pattern and specific dendritic localization suggested MMP-9s involvement in synaptic plasticity, learning, and memory (Lepeta and Kaczmarek, 2015). MMP-9 plays a prominent role in the critical developmental period (Aujla and Huntley, 2014), during which snaptic circuits are formed and mature. Sinece DS demonstrated a peculiar developmental trajectory with poorer premorbid adjustment relative to NDS (Bucci et al., 2016), this drawn significant attention to the potential association of MMP-9 in the pathogenesis of DS subtype. Previous studies have already indicated that *MMP-9* might be one potential candidate gene related to schizophrenia (Lepeta et al., 2017; Rybakowski et al., 2009). DNA methylation is one of the most common epigenetic factors occurring at cytosine residues in C-phosphate-G (CpG) dinucleotides within particular sequences, resulting in altered genomic expression. However the association between *MMP-9* methylation and behavior in schizophrenia has not yet been reported. Thus, the present study was aimed to characterize *MMP-9* methylation and investigate the correlations with multiple indices of neurocognition in DS patients.

A total of 97 male schizophrenic patients, including 46 DS and 51 NDS, and 44 age- and gender-matched healthy controls (HC) were recruited. The overall patients were divided into DS and NDS subgroups according to the Chinese version of the Schedule for the Deficit Syndrome (SDS) (Wang et al., 2008). A battery of neurocognitive tests, including Spatial Processing Block Design, Trail Making Test-A, B (TMT-A, B), and the Stroop Color-Word test (SCWT), were employed to assess multiple neurocognitive domains for all participants. Pyrosequencing approach was performed to determine the methylation status in the sequence of interest that contained 9 CpG sites in exon 4 and exon 5 in *MMP-9* (Fig. 1A). For each CpG site, the percentage of methylation was analyzed as a C/T single nucleotide polymorphism using the following equation: $C\ (\%) = C/(C + T)$.

ANCOVA analyses were employed to identify differences among three groups for DNA methylation and neurocognitive assessments using years of education as a covariant. Partial correlation analyses were used to determine the relationships between methylation percentage of each *MMP-9* CpG site and specific neurocognitive impairments. For multiple comparisons among three groups for 9 CpG sites, a Bonferroni-corrected p value of 0.0056 (0.05/9) was applied. In all other cases, $p < 0.05$ was considered statistically significant.

The results indicated DS patients demonstrated more severe impairment in each neurocognitive test compared to NDS and HC subjects (all ps < 0.05). The percentage of methylation across the 9 CpG sites in *MMP-9* gene was significantly different among three groups. All individual CpG site in DS patients had a significantly lower methylation status when compared to HC subjects (all adjusted ps < 0.001). When compared to NDS patients, lower methylation in CpG4-4, CpG4-5, CpG5-1, CpG5-2, CpG5-3, and CpG5-4 (all adjusted ps < 0.001) were observed in DS patients. No significant differences were observed in CpG4-2, CpG4-3 between DS and NDS patient groups, and DS patients demonstrated a higher level of CpG4-1 (Fig. 1B).

Partial correlation analyses were performed to determine the association between methylation of CpG sites and neurocognitive measurements in DS and NDS patients, controlling for influence factors (See stepwise regression analyses in supplementary material). The results indicated a significant correlation between deteriorated visuospatial abilities and declined methylation level of CpG5-4, and a significant positive correlation between the time-consuming of TMT-B and methylation status of CpG4-5 site in DS patients (Fig. 1C). None of these neurocognitive functional measures indicated a significant correlation with individual CpG site methylation in NDS patients.

In present study, we focused on the methylation of candidate gene *MMP-9*, for it has been considered to have pathological importance in schizophrenia (Lepeta and Kaczmarek, 2015; Lepeta et al., 2017). Our results revealed the individual hypo-methylation CpG site of *MMP-9* in DS patients might be correlated with neurocognitive impairments such as visual spatial memory, working memory, and executive function. These corresponding associations were not observed in NDS patients, highlighting the unique role for epigenetic processes of *MMP-9* in the pathophysiology of DS. This was the first study to provide evidence that methylation of *MMP-9* was involved in neurocognitive impairments in DS, contributing to our understanding of this unique schizophrenia subtype.

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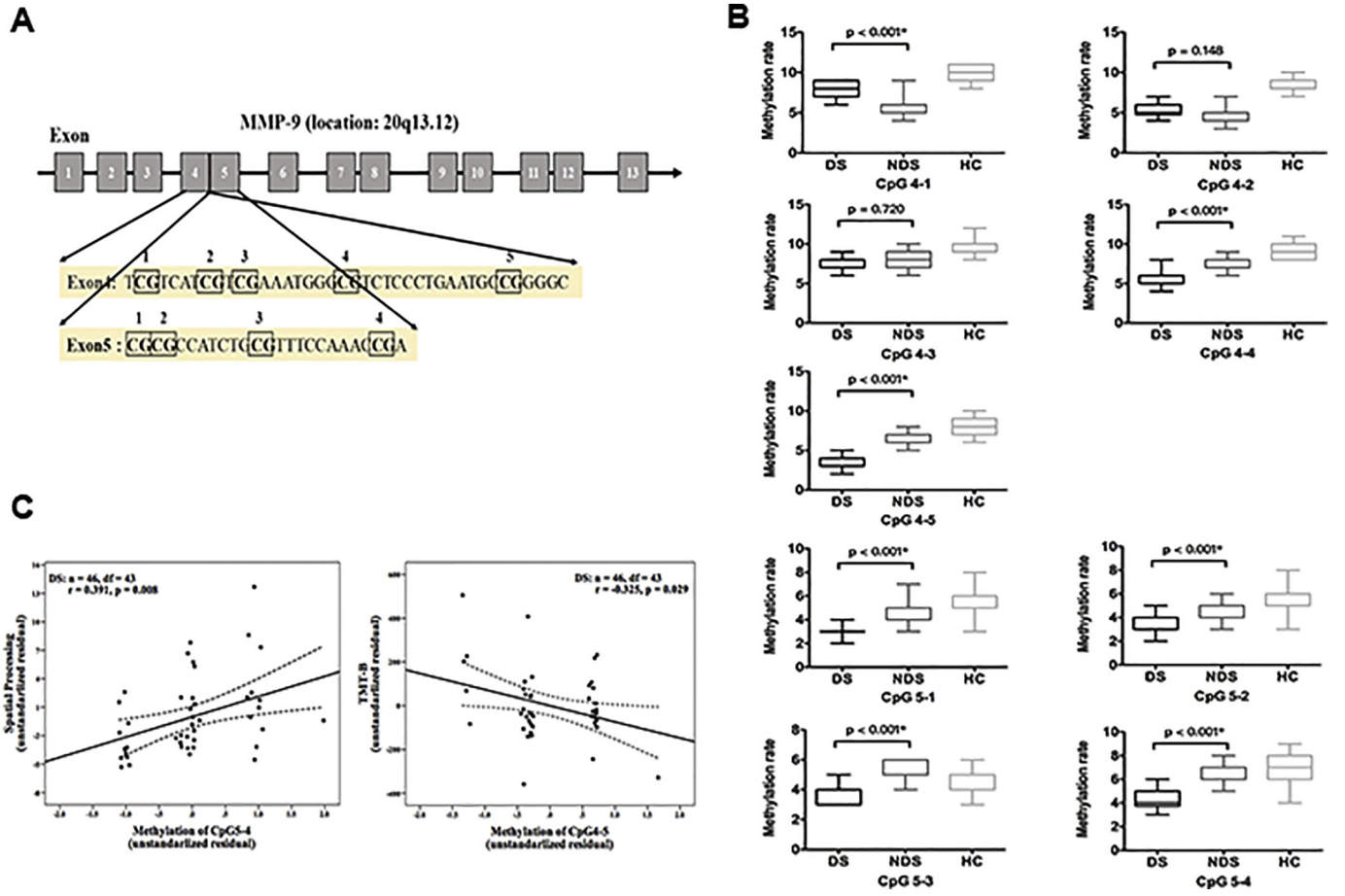

Fig. 1. A) Location of the *MMP-9* gene and the 9 CpG sites for pyrosequencing. B) The comparisons of DNA methylation in individual CpG site in the *MMP-9* gene among DS, NDS, and HC groups. Data are shown as the mean ± standard error of the mean. * = DS vs. NDS $p < 0.0056$ (0.05/9). C) Scatter plots of the CpG site methylation and scores of the neurocognitive performance in the DS group. Data are presented in unstandardized residual form. DS, deficit schizophrenia; NDS, non-deficit schizophrenia; HC, healthy controls; TMT—B, trail making test-B.

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Contributions

All authors reviewed and contributed to the final version of the manuscript. Additional contributions are stated below.

Ju Gao was responsible for data analyses and preparation of the manuscript. Xiaowei Tang and Ju Kang performed experiments, analyzed the data. Chunming Xie and Miao Yu contributed to the interpretation of findings and preparation of the manuscript. Weiwei Sha and Xiaobin Zhang were responsible for obtaining ethical approval and performing the neurocognitive assessments. Xiang Wang offered the Chinese version of SDS. Xiangrong Zhang and Hongwei Yi came up with the hypothesis, designed the experimental strategy and obtained funding for the study.

Conflict of interest

All authors declare there are no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.10.005.

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