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The interaction of *NOS1AP*, *DISC1*, *DAOA*, and *GSK3B* confers susceptibility of early-onset schizophrenia in Chinese Han population

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ABSTRACTS

Although many major breakthrough had identificated potential susceptibility genes for schizophrenia, the aetiology of schizophrenia is still unknown. In the present study, we focused on the *N*-methyl-Daspartate receptors related genes nitric oxide synthase 1 adaptor gene (*NOS1AP*), disrupted in schizophrenia 1 gene (*DISC1*), D-amino acid oxidase activator gene (*DAOA*), and glycogen synthase kinase 3-beta gene (*GSK3B*). A family-based genetic association study (459 Han Chinese subjects in 153 nuclear families) using 3 single nucleotide polymorphisms in *NOS1AP*, 2 in *DISC1*, 1 in *DAOA* and 1 in *GSK3B* was conducted. We found rs12742393 have just positive trend with schizophrenia (SCZ) ($p = 0.07$) after FDR correction. *NOS1AP* mRNA and serum levels were significantly elevated in SCZ patients ($p < 0.001$; $p < 0.001$) compared with healthy control. However, expression Quantitative Trait Loci (eQTL) analysis have demonstrated that rs12742393 genotype were not significantly associated with the *NOS1AP* mRNA expression. GMDR identified a significant seven-locus interaction model involving (*NOS1AP*-rs348624, rs12742393, rs1415263, *DISC1*-rs821633, rs1000731, *DAOA*-rs2391191and *GSK3B*- rs6438552) with a good testing accuracy (0.72). Our finding suggested statistically significant role of interaction of *NOS1AP*, *DISC1*, *DAOA*, and *GSK3B* polymorphisms (*NOS1AP*-rs348624, rs12742393, rs1415263, *DISC1*-rs821633, rs1000731, *DAOA*-rs2391191and *GSK3B*-rs6438552) in EOS susceptibility.

1. Introduction

Schizophrenia (SCZ) is a severe, chronic, neurodevelopmental disorder that affects approximately 1% of the global population (Saha et al., 2005). However, the specific aetiology and underlying pathophysiological mechanisms of SCZ remain unknown. Early-onset schizophrenia (EOS), defined as a diagnosis before the age of 18 years, tends to have a more biologically-based aetiology and persists longer than the late-onset form (Cechnicki et al., 2013; Hilker et al., 2017). An earlier age of SCZ onset in index patients is correlated with a higher prevalence of SCZ in their relatives (Kendler and MacLean, 1990).

Although SCZ tends to run in families, no specific single "gene for SCZ" appears to exist (Howell and Pillai, 2014). Instead, the pattern of inheritance suggests that SCZ is caused by many different genes that have minor effects (Lindholm et al., 2001) but function together to confer susceptibility.

Abbreviation: NMDAR, *N*-methyl-Daspartate receptor; *NOS1AP*, nitric oxide synthase 1 adaptor gene; *DISC1*, disrupted in schizophrenia 1 gene; *DAOA*, D-amino acid oxidase activator gene; *GSK3B*, glycogen synthase kinase 3-beta gene; SCZ, Schizophrenia; EOS, early-onset schizophrenia; GMDR, generalized multifactor dimensionality reduction; NMDA, *N*-methyl-Daspartate; PPI, pre-pulse inhibition; G72Tg, G72 transgenic; SHMC-IRB, Shanghai Mental Health Center-Institutional Review Board; MINI, Mini International Neuropsychiatric Interview; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition; MAF, the minor allele frequency; EDTA, Ethylene Diamine Tetraacetic Acid; qRT-PCR, quantitative reverse-transcription polymerase chain reaction; TDT, Transmission Disequilibrium Test; FDR, false discovery rate; eQTL, expression Quantitative Trait Loci.

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The locations of *NOS1AP*, *DISC1*, *DAOA* and *GSK3B* were previously reported to be linked with *N*-methyl-D aspartate receptors (NMDARs) (Brzustowicz et al., 2000; Gong et al., 2014; Brzustowicz et al., 2004; Singh et al., 2011). Additionally, these four genes were reported to be associated with neuronal death and regeneration or with neuronal differentiation, which are thought to lead to the development of SCZ (Brzustowicz, 2008; Lai et al., 2014; Rajashekaran et al., 2013; NQ and Aizenstein, 2013; Stein et al., 2014; Singh et al., 2010; Wei et al., 2014; Chumakov et al., 2002; He et al., 2004).

Previous reports have indicated that these four genes are associated with SCZ. Regarding *NOS1AP*, a large case-control study conducted by Puri et al. (2006) failed to replicate previous positive findings in a British sample. Furthermore, Puri et al. (2006) suggested that the apparent association between *NOS1AP* and SCZ might be due to the U2AF homology motif kinase 1 (*UHMK1*) gene. However, an analysis of linkage disequilibrium (LD) patterns encompassing *NOS1AP* and *UHMK1* in the European HapMap population revealed no significant LD.

Regarding *DISC1*, Vázquez-Bourgon et al. (2014) found that its variations may modulate the clinical severity of psychosis at the onset of SCZ. Gómez-Sintes et al. (2014) confirmed that the 129*DISC1*(Del) mutation results in alterations in spontaneous locomotor activity (hyperactivity in males and hypoactivity in females), deficits in prepulse inhibition (PPI) and increased despair behaviour in heterozygous 129*DISC1*(Del) mice, thus reproducing typical behaviors associated with psychiatric disorders. Lepagnol-Bestel et al. (2010) found that the *DISC1* gene is associated with the negative dimension of SCZ. However, some studies did not identify an association in Japanese, American, and Korean samples (Ratta-Apha et al., 2013; Hotta et al., 2011; Docherty et al., 2014; Bae et al., 2013; Mathieson et al., 2012; Takahashi et al., 2015; Prata et al., 2011).

Recently, many studies (Ma et al., 2009; Müller et al., 2011) have reported that the *DAOA* gene locus is involved in conferring susceptibility to SCZ. The *DAOA* gene is associated with altered regional homogeneity, distinct cortical thinning and an altered age of SCZ onset (Chen et al., 2013; Schultz et al., 2011; Yue et al., 2006). Pae et al. (2010) examined Korean SCZ patients treated with aripiprazole for 8 weeks and found that individuals carrying the rs2391191 A allele had significantly lower Brief Psychiatric Rating Scale scores than subjects carrying the G allele at every measured time point. Drews et al. (2013) found that G72 transgenic (G72Tg) mice showed several behavioural deficits related to SCZ. However, two studies suggested that the *DAOA* gene was not a susceptibility gene for SCZ in a Taiwanese sample (Tan et al., 2014; Liu et al., 2006).

GSK-3B is one isoform of *GSK3* that is highly expressed in the central nervous system (CNS), indicating that *GSK-3B* plays a prominent role in that system (Benedetti et al., 2010). Benedetti et al. (2010) and Souza et al. (2008) found a direct association between *GSK-3B* polymorphism and SCZ. Overexpression of *GSK-3B* in mice produced mania-like behaviour (Prickaerts et al., 2006). However, some results have indicated that *GSK-3B* may not play a major role in SCZ (Sand et al., 2010).

The inconsistent results of these studies may be attributable to the following causes. First, the studies examined different ethnic populations, resulting in genetic heterogeneity. Second, many candidate endophenotypes in SCZ are neuropsychological markers. Different phenotypes may imply different molecular pathogenetic mechanisms underlying the occurrence of SCZ. Last but not least, SCZ is thought to be caused by multiple genetic variants that exert pleiotropic and epistatic effects. The genetic loci modulating an endophenotype may need to interact with other genetic factors to further move the patient towards the disease state.

Thus, to further investigate the effects of *NOS1AP, DISC1, DAOA* and *GSK-3B* on susceptibility to SCZ, we detected the polymorphisms of these four genes. Several candidate susceptibility genes for schizophrenia have been identified, but for all except one of them, the single-nucleotide polymorphisms found to be associated with the disorder are noncoding. Hence, changes in the expression of the genes (for example, in terms of their splicing or relative abundance), rather than amino acid alterations, are thought to underlie their genetic association with schizophrenia (Harrison and Weinberger, 2005). Studies of gene expression in peripheral blood are required to investigate this possibility. Meanwhile, we also analysed the interactive effects of these four genes on susceptibility to EOS given that any specific individual genetic variant has a minor marginal effect in complex psychiatric disease and that gene–gene interaction is critical for describing the phenotypic effect (Su et al., 2017).

2. Materials and methods

In the exploratory study, we selected the seven polymorphisms based on minor allele frequency (MAF) > 0.2, r^2 > 0.8, using the International HapMap project (http://www.hapmap.org; version 4.1). Previously, the markers rs12742393, rs1000731, rs1415263, rs348624, and rs2391191 attained a level of significance to SCZ, with corrected *p* values of < 0.05 (Wratten et al., 2009), < 0.05 (Ekelund et al., 2004), 0.02 (Brzustowicz et al., 2004), < 0.001 (Zheng et al., 2005), and < 0.001 (Wang et al., 2004), respectively. The rs821633 (p = 0.07) (Hennah et al., 2009) and rs6438552 (p = 0.66) (Souza et al., 2010) variants showed a positive trend for an association with SCZ and TD, respectively. The reference sequence numbers of these seven SNPs were as follows: rs348624, rs12742393, and rs1415263 for *NOS1AP*; rs821633 and rs1000731 for *DISC1*; rs2391191 for *DAOA*; and rs6438552 for *GSK-3B*. The locations, SNP types, alleles, and MAFs of these SNPs are provided in Fig. 1. In the replication study, we selected the top-ranked markers identified in the exploratory study (only one SNP of seven had been genotyped at the time of the replication study).

We used TaqMan genotyping assays (Applied Biosystems, Foster, CA, USA) to genotype the seven SNPs in the exploratory study and the top SNPs in the replication study. Genomic DNA was extracted carefully from whole blood samples preserved with the anticoagulant ethylene diamine tetraacetic acid (EDTA) using Tiangen DNA isolation kits (Tiangen Biotech, Beijing, China). Seven SNPs, namely, rs348624, rs12742393, rs1415263, rs821633, rs1000731, rs2391191 and

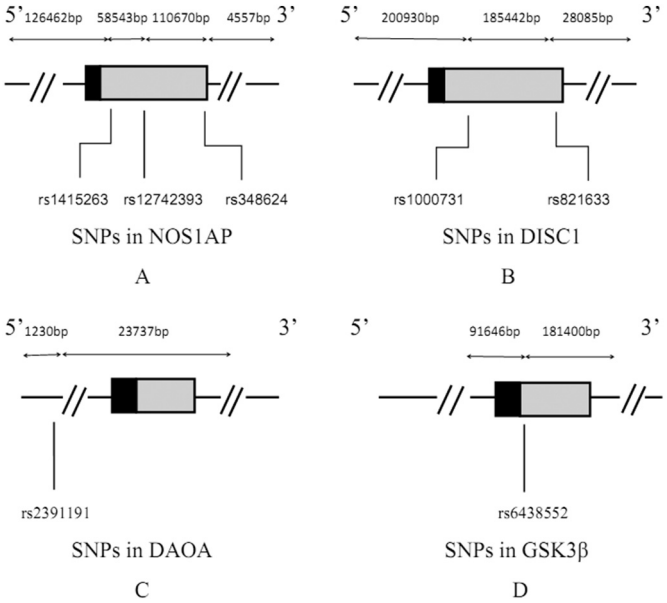

Fig. 1. The sites of SNPs in *NOS1AP*, *DISC1*, *DAOA*, and *GSK3B*. From left to right, the SNPs are aligned from 5′ to 3′. The black boxes represent exons and the gray box represents 3-untranslated region. (A) The sites of three SNPs in *NOS1AP* gene. (B) The sites of two SNPs in *DISC1* gene. (C) The site of one SNPs in *DAOA* gene. (D) The site of one SNPs in *GSK3B* gene.

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