Brief report

Associations between polymorphisms of LSAMP gene and schizophrenia

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1. Introduction

Schizophrenia (SCZ) is a devastating psychiatric disorder with a median lifetime prevalence of 4.0 per 1000 and a lifetime morbidity risk of 7.2 per 1000 persons (Saha et al., 2005). Recent review of 18 genome-wide association studies of SCZ concluded that most of the relevant genes in these studies are associated with various aspects of neurodevelopment, including neuroplasticity, synapse maturation and neurogenesis (Hosak et al., 2012). Limbic system-associated membrane protein (LSAMP) is a member of the IgLON subfamily of cell adhesion molecules (Eagleson et al., 2003). The product of LSAMP gene is a 64–68-kDa glycoprotein that is found on the somata and dendrites of neurons in cortical and subcortical regions comprising the adult mammalian limbic system (Levitt, 1984; Horton and Levitt, 1988). LSAMP gene is located in 3q13.2–q21 region and consists of seven exons (Pimenta et al., 1996). Linkage studies have shown associations between long arm of chromosome 3 and SCZ (Maziade et al., 2001; Devlin et al., 2002; Kaneko et al., 2007). Additionally, the dorsolateral prefrontal cortex (DLPFC) is strongly implicated in the pathogenesis of SCZ and LSAMP expression was found to be increased in samples of DLPFC derived from patients with SCZ (Behan et al., 2009).

2. Materials and methods

2.1. Subjects and genotyping

Patients with schizophrenia (n=127; mean age ± S.D. 51.5 ± 11.6 years; 54% female) and matched healthy controls (n=171; mean age ± S.D. 50.0 ± 8.4 years; 56% female) were enrolled in the study. All subjects were of white European ancestry living in Estonia. The Research Ethics Committee of the University of Tartu had approved the study, and written informed consent was obtained from all subjects. Twenty-two SNPs were genotyped using the SNPlexTM Genotyping System (Applied Biosystems, Foster City, USA) and the tetra-primer ARMS-PCR method (Ye et al., 2001).

2.2. Statistical analysis

Allelic association, linkage disequilibrium (LD), haplotype analyses between the groups of patients and controls, Hardy–Weinberg equilibrium (HWE) calculations in control group, and 10,000 permutations to correct P values for multiple testing were performed using Haploview 4.0 software (Barrett et al., 2005). The significance level for all statistical tests was 0.05. The algorithm for defining haplotype blocks was internally developed method Solid Spine of LD (D' > 0.75).

3. Results

SNP rs4831129 was excluded from the further analysis due to a bias from HWE in control group. The results showed significant allelic and haplotype associations between LSAMP gene and schizophrenia.
significant associations – rs7634137, rs1461131, rs4831089, rs16824691, and rs9874470 (P values 0.041, 0.039, 0.02, 0.001, and <0.001, respectively). For the last two SNPs, P values remained statistically significant after permutations (odds ratios (OR), 95% confidence intervals (CI), and permutation P values 0.44, 0.27–0.70, 0.018 and 0.45, 0.30–0.67, 0.003, respectively).

LD and haplotype analyses revealed six haplotype blocks. Haplotypes of block 4 (rs16824691, rs4831089, and rs9874470) remained statistically significant across cases and controls. Haplotype TAT emerged as a risk haplotype with OR, 95% CI, and P value of 1.53, 1.05–2.24, 0.027, respectively. Haplotype CCGA appeared protective with P value of 1.53, 1.05–2.24, 0.027, respectively. Haplotype block No. 4 was formed from the three forenamed SNPs (rs16824691, rs4831089, and rs9874470) giving two significantly associated haplotypes: TAT being risk and CCGA protective. Thus, our findings indicate that LSAMP gene may be related to SCZ. In a previously published study SNP rs2918217 from LSAMP was suggestively associated with SCZ (Jungierius et al., 2008). This SNP was not significantly associated in our study. Possible associations between LSAMP polymorphisms and male suicidal behaviour (Must et al., 2008) and major depressive disorder (MDD) and panic disorder (PD) (Koido et al., 2012) have been formerly reported. These preliminary findings suggest that LSAMP gene polymorphisms may play a role in the expressions of emotional dysregulation shared across different psychiatric disorders, such asanhedonia and anxiety, which are common in SCZ as well as in MDD and PD (van Os and Kapur, 2009; Pallanti et al., 2013).

Several limitations of our study should be recognized. The sample sizes were small. Not all associations survived correction for multiple testing and we cannot exclude false positive results. Therefore, replication association studies in independent samples are needed to confirm and extend our findings. Also, further functional research is required to determine the relevance of LSAMP function to the molecular mechanisms of psychiatric disorders.

4. Discussion

We detected significant allelic associations between five LSAMP SNPs and SCZ. Two SNPs out of five contributed to the increased risk (rs1461131 and rs4831089) and three were protective (rs7634137, rs16824691, and rs9874470). Haplotype block No. 4 was formed from the three forenamed SNPs (rs16824691, rs4831089, and rs9874470) giving two significant haplotypes: TAT being risk and CCGA protective. Thus, our findings indicate that LSAMP gene may be related to SCZ. In a previously published study SNP rs2918217 from LSAMP was suggestively associated with SCZ (Jungierius et al., 2008). This SNP was not significantly associated in our study. Possible associations between LSAMP polymorphisms and male suicidal behaviour (Must et al., 2008) and major depressive disorder (MDD) and panic disorder (PD) (Koido et al., 2012) have been formerly reported. These preliminary findings suggest that LSAMP gene polymorphisms may play a role in the expressions of emotional dysregulation shared across different psychiatric disorders, such as anhedonia and anxiety, which are common in SCZ as well as in MDD and PD (van Os and Kapur, 2009; Pallanti et al., 2013).

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