Psychiatry Research 240 (2016) 47–52

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Sex-specific association between the albumin D–element binding protein gene and metabolic syndrome in patients with bipolar disorder and schizophrenia

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ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form
22 February 2016
Accepted 25 March 2016
Available online 30 March 2016

1. Introduction

A substantial body of research has shown that patients with bipolar disorder and schizophrenia are at high risk for metabolic syndrome (MetS), as evidenced by data showing that the odds ratio for MetS is twice as high among patients with these conditions than among the age- and sex-matched general population (Lee et al., 2010; Vancampfort et al., 2013). Metabolic adversity leads to increased somatic comorbidity and premature mortality, particularly from cardiovascular disorders (CVDs) in this population (Capasso et al., 2008). The co-occurrence of MetS with bipolar disorder and schizophrenia has become a major concern in treatment because it is linked with a poor quality of life, poor functional outcomes (Vancampfort et al., 2011). and noncompliance with medication (Weiden et al., 2004). Cardiometabolic adversity has also been associated with negative clinical outcomes, such as more complex illness presentations and less favorable responses to treatment (McIntyre et al., 2010).

The adverse effects of medications, particularly atypical antipsychotics such as clozapine or olanzapine, or mood stabilizers have been considered major risk factors for metabolic disturbances (De Hert et al., 2012; Thase, 2012). Genetic factors have also been reported to play a role in variations in the prevalence of MetS or in individual differences in the susceptibility to the metabolic side effects of medication in patients with bipolar disorder and schizophrenia (Adkins et al., 2011). In a previous twin and sibling study, high inter-individual variability was observed in antipsychotic-induced weight gain, with a heritability of $h^2=0.6$ (Gebhardt et al., 2010). Additionally, previous studies have documented that the distribution of the abnormality of MetS components or CVD risk factors differentially affects male and female patients with serious mental illnesses, indicating that sex may be an important modifier of metabolic risk (Baskaran et al., 2014; Carliner et al., 2014). The association between obesity and related metabolic traits and genetic polymorphisms can also differ by sex in patients with schizophrenia (Gregoor et al., 2009) or bipolar disorder (Kim et al., 2012).

The D site of albumin promoter (albumin D-box) binding protein (DBP) is a member of the conserved proline and acidic amino acid-rich basic leucine zipper (PAR bZip) transcription factor family (Gachon et al., 2004; Khatib et al., 1994). DBP is an activator of the transcriptional circuit in mammalian circadian clocks (Ukai-Tadenuma et al., 2008) and is among the genes showing the strongest cyclic patterns (Li et al., 2013). The expression of DBP shows robust oscillation with circadian rhythm in tissues with

Abbreviations: MetS, metabolic syndrome; CVDs, cardiovascular disorders; DBP, D site of albumin promoter (Albumin D-Box) binding protein; BP, blood pressure; WC, waist circumference; TG, triglycerides; HDL, high-density lipoprotein

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http://dx.doi.org/10.1016/j.psychres.2016.03.040
0165-1781/

high amplitudes of clock gene expression, like the suprachiasmatic nucleus, and maintains constant levels in cerebral regions with stable clock gene expression (Gachon et al., 2004). Circadian rhythms are seen in many metabolic pathways, such as glucose and lipid metabolism, and disturbances in insulin secretion and circadian rhythm affect key aspects of metabolic adversity (Bass, 2012). Preclinical studies have suggested that DBP plays a key role in the metabolism of lipids, cholesterol, and glucose in the liver by influencing the rhythmic expression and activity of the nuclear receptor peroxisome proliferator-activated receptor-α (PPARα) (Gachon et al., 2011). DBP is also involved in adipose tissue development and function (Dankel et al., 2014). Furthermore, it has been implicated in pancreatic β-cell dysfunction and type 2 diabetes (Nakabayashi et al., 2013). Circadian rhythm dysregulation is common in patients with schizophrenia (Wulff et al., 2012) or bipolar disorder (Gonzalez, 2014). DBP polymorphisms are related to the diurnal phenotype of experiencing a worse mood in the afternoon/evening among patients with bipolar disorder (Shi et al., 2008). Microarray studies of brains and blood have suggested that DBP is a potential candidate gene for bipolar disorder or psychosis (Le-Niculescu et al., 2007; Niculescu et al., 2000), although no association was confirmed (Mansour et al., 2009). DBP may be involved in the pathophysiology of metabolic disturbance and bipolar disorder and schizophrenia, but this possibility has not yet been explored.

This study used a cross-sectional design to assess the relationship between DBP and the severity of MetS in patients with bipolar disorder and schizophrenia who were receiving medication, after controlling for potential confounding factors. We present our results separately by sex to explore sex-specific genetic associations.

2. Materials and methods

2.1. Participants

Patients who visited the outpatient psychiatry clinic at Seoul National University Hospital between June 2007 and January 2014 and who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for bipolar disorder and schizophrenia (types I and II) were recruited for participation in this study. The patients were interviewed individually by trained researchers using the Korean version of the Diagnostic Interview for Genetic Studies (Joo et al., 2004). Meetings with more than three psychiatrists were held regularly to arrive at consensual decisions regarding participants' final diagnoses. Subjects with a history of any kind of organic brain abnormality, substance dependence, drug abuse, or other general medical condition that may manifest as psychiatric symptoms were excluded from this study. A total sample of 391 patients (177 males and 214 females) who provided fasting laboratory test results and anthropometric data for assessing the presence of metabolic syndrome were included in analysis of the association between DBP polymorphisms and metabolic adversities. The protocol was approved by the Ethics Committee of Seoul National University Hospital, and this study was conducted in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from each patient prior to enrollment.

2.2. Metabolic parameters

Anthropometric and sitting blood pressure (BP) measurements were performed. Waist circumference (WC) was measured midway between the lowest rib and the iliac crest. Blood glucose and lipid levels were measured and evaluated after overnight fasting. The presence of MetS was assessed according to the guidelines of the American Heart Association and the National Heart, Lung, and Blood Institute's adaptation of the National Cholesterol Education Program Adult Treatment Panel III, with modified WC criteria provided by the Korean Society for the Study of Obesity. MetS was defined by three or more of the following criteria: (1) fasting plasma glucose $\geq$ 5.6 mmol/L (100 mg/dL) or drug treatment for elevated glucose, (2) serum triglycerides (TG) $\geq$ 1.7 mmol/L (150 mg/dL) or drug treatment for elevated TG, (3) high-density lipoprotein (HDL)-cholesterol $<$ 1.0 mmol/L (40 mg/dL) in males and $<$ 1.3 mmol/L (50 mg/dL) in females, (4) systolic BP $\geq$ 130 mmHg or diastolic BP $\geq$ 85 mmHg or drug treatment for hypertension, and (5) WC $>$ 90 cm for males and $>$ 85 cm for females.

2.3. SNPs selection and genotyping

Tag SNPs were selected for SNPs across DBP, including 5 kilobases (kb) upstream and 5 kb downstream of the coding sequence in the international HapMap database (Data release #27, http://hapmap.ncbi.nlm.nih.gov/). Downloaded genotypes were restricted to those of the Japanese population of Tokyo, Japan (JPT) because the genetic backgrounds of Korean and Japanese populations are closely related (Ader et al., 2005; Tian et al., 2008). One tag SNP (rs3848543) had minor allele frequencies greater than 5% in Japanese populations, with correlation between SNPs below a predetermined threshold ($r^2 > 0.8$) (de Bakker et al., 2005) implemented in Haploview ver. 4.2 (Barrett et al., 2005). Deoxyribonucleic acid (DNA) was extracted from whole blood samples using a DNA isolation kit (Roche Applied Science, Indianapolis, IN, USA). Genotyping assays were performed using the TaqMan method (Applied Biosystems, Foster City, CA, USA) (McGuigan and Ralston, 2002).

2.4. Statistical analyses

Tests for differences between groups were based on analysis of variance (ANOVA) or independent-sample *t*-tests for continuous measures and on χ^2-tests for categorical data using the Cochran–Armitage test for trends. To examine the relationship between SNP in the DBP gene and the severity of MetS, a multivariate ordinal logistic regression model was constructed treating the cumulative number of MetS components as the dependent variable and SNP, age, duration of illness, diagnosis, use of weight-gain-associated antipsychotic agents, use of mood stabilizers (lithium or valproic acid) as independent variables. Subjects currently receiving olanzapine or clozapine were classified as receiving weight-gain-associated antipsychotic agents. *Chi*-square tests were performed to compare the allele frequencies of male and female subjects. Hardy–Weinberg equilibrium was assessed using the Haploview software ver. 4.2. All *p*-values were two-tailed, and a value of $p < 0.05$ was taken to indicate statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences ver. 20.0 for Windows (SPSS, Chicago, IL, USA) and R software.

3. Results

3.1. Baseline characteristics

Table 1 presents the demographic and clinical characteristics of the population, 45.3% (177/391) of whom were male. We found no significant differences between the males and females regarding the following demographic and clinical characteristics, except the use of clozapine or olanzapine and diagnosis. Male patients were more likely to use clozapine or olanzapine (t=18.720, df=1, p < 0.001) and to have received a diagnosis of schizophrenia (t=25.241, df=1, p < 0.001). In terms of metabolic parameters, BMIs and all components MetS were significantly higher in male than in female patients. In additional analyses conducted according to diagnosis (schizophrenia vs. bipolar disorder), there were significant differences between the groups in marital status, medication, and the number of antipsychotics by gender. In females, the patients with schizophrenia showed a higher rate of MetS than those with bipolar disorder, but not in males. The distributions of DBP gene polymorphisms were in Hardy–Weinberg equilibrium. No significant difference in the genotype distributions of the DBP gene polymorphism between male and female patients was observed (χ^2=0.648, *df*=1, *p*=0.421). The proportions of all patients with the CC, CT, and TT genotypes were 36.1% (*n*=141), 46.8% (*n*=183), and 17.1% (*n*=67), respectively. The frequencies of the C and T alleles were 59.5% (*n*=465) and 40.5% (*n*=317), respectively.

3.2. Associations of DBP polymorphism with various components of MetS

Table 2 shows significant differences among the genotypes regarding several metabolic adversities in male patients but not in females. The CC genotype was significantly associated with a higher mean BMI, mean TG level, mean WC, and number of