Journal of Psychiatric Research 45 (2011) 588–595

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Dysbindin (*DTNBP1*) – A role in psychotic depression?

Katharina Domschke [a,*], Bruce Lawford [b,c], Ross Young [c], Joanne Voisey [c], C. Phillip Morris [c], Tilmann Roehrs [a], Christa Hohoff [a], Eva Birosova [d], Volker Arolt [a], Bernhard T. Baune [d]

[a] Dept. of Psychiatry, University of Muenster, Albert-Schweitzer-Strasse 11, D-48143 Muenster, Germany
[b] Division of Mental Health, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
[c] Institute for Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia
[d] Dept. of Psychiatry, School of Medicine, James Cook University, Queensland, Australia

ARTICLE INFO

Article history:
Received 8 June 2010
Received in revised form
10 August 2010
Accepted 22 September 2010

Keywords:
Major depression
Psychotic depression
Genetic
Dysbindin
DTNBP1
Glutamate

ABSTRACT

Previous studies yielded evidence for dysbindin (*DTNBP1*) to impact the pathogenesis of schizophrenia on the one hand and affective disorders such as bipolar or major depressive disorder (MDD) on the other. Thus, in the present study we investigated whether *DTNBP1* variation was associated with psychotic depression as a severe clinical manifestation of MDD possibly constituting an overlapping phenotype between affective disorders and schizophrenia.

A sample of 243 Caucasian inpatients with MDD (SCID-I) was genotyped for 12 SNPs spanning 92% of the *DTNBP1* gene region. Differences in *DTNBP1* genotype distributions across diagnostic subgroups of psychotic ($N = 131$) vs. non-psychotic depression were estimated by Pearson Chi^2 test and logistic regression analyses adjusted for age, gender, Beck Depression Inventory (BDI) and the Global Assessment of Functioning Scale (GAF).

Overall, patients with psychotic depression presented with higher BDI and lower GAF scores expressing a higher severity of the illness as compared to depressed patients without psychotic features. Four *DTNBP1* SNPs, particularly rs1997679 and rs9370822, and the corresponding haplotypes, respectively, were found to be significantly associated with the risk of psychotic depression in an allele-dose fashion.

In summary, the present results provide preliminary support for dysbindin (*DTNBP1*) gene variation, particularly SNPs rs1997679 and rs9370822, to be associated with the clinical phenotype of psychotic depression suggesting a possible neurobiological mechanism for an intermediate trait on the continuum between affective disorders and schizophrenia.

1. Introduction

Psychotic major depression (PMD) is conceptualized as a severe clinical subphenotype of major depressive disorder (MDD) presenting with psychotic features such as feelings of worthlessness or guilt, delusions or hallucinations (APA, 2004; Coryell et al., 1984; Glassman and Roose, 1981; Lykouras et al., 1986; Thakur et al., 1999). PMD is diagnosed in 19–25% of depressed patients (Coryell et al., 1984; Ohayon and Schatzberg, 2002). Psychotic depression is associated with greater illness severity, higher rates of illness chronicity, relapse, more frequent hospitalizations and a higher risk of suicide (for review see Gaudiano et al., 2008) as well as higher levels of dopamine (Schatzberg and Rothschild, 1992). By some authors PMD has thus been suggested to possibly constitute a distinct clinical entity (e.g., Glassman and Roose, 1981; Schatzberg and Rothschild, 1992). Given a number of clinical and biological characteristics apparently being specific for psychotic depression, one might assume a particular genetic risk profile predisposing to the development of major depression with psychotic features (cf. Serretti et al., 1999). Identification of risk genes of psychotic depression could contribute to a better understanding of the underlying pathomechanism of this particular subtype of depression and consequently possibly also to the development of more targeted treatment options for PMD (cf. Schatzberg, 2003).

In the context of psychotic symptoms, dysbindin is a promising candidate molecule: dysbindin binds to alpha- and beta-dystrobrevin as components of the dystrophin-associated protein complex (DPC) (Benson et al., 2001). Dysbindin is involved in glutamatergic neurotransmission by influencing exocytotic glutamate release (Numakawa et al., 2004; Straub et al., 2002) with high levels of dysbindin in cells of the intrinsic glutamatergic pathways of the hippocampus as well as an inverse correlation with vesicular glutamate transporter-1 (Talbot et al., 2004). Glutamatergic

* Corresponding author. Tel.: +49 251 8356601; fax: +49 251 8356612.
E-mail address: katharina.domschke@ukmuenster.de (K. Domschke).

0022-3956/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2010.09.014

neurotransmission as partly driven by dysbindin has been shown to mediate noradrenergic and serotonergic drug effects in antidepressant response (Yagasaki et al., 2006; Yoshimizu et al., 2006) and in addition to play a major role in the pathogenesis of schizophrenia as well as in the mediation of neuroleptic treatment (for review see: Goff and Coyle, 2001; Numakawa et al., 2004; Heresco-Levy, 2005). This renders dysbindin a prime candidate in the investigation of the overlapping phenotype of psychotic major depression.

The gene coding for dysbindin (dystrobrevin-binding protein 1; *DTNBP1*) is located on chromosome 6p22.3, a consistently replicated susceptibility region in schizophrenia as well as affective disorders (cf. Lewis et al., 2003; Park et al., 2004). Besides converging evidence for a major role of *DTNBP1* gene variants in the pathogenesis of schizophrenia (Straub et al., 2002; Schwab et al., 2003; van den Bogaert et al., 2003; van den Oord et al., 2003; Funke et al., 2004; Kirov et al., 2004; Bray et al., 2005; Pae et al., 2008, 2009), *DTNBP1* gene variation has also been implicated in psychotic features associated with bipolar disorder (Raybould et al., 2005) as well as in the aetiology of major depression (Kim et al., 2008). Additionally, in a sample of patients with schizophrenia some evidence for association between *DTNBP1* gene variants and anxiety/depression symptoms was observed (Wirgenes et al., 2009). These findings underline a potential role of *DTNBP1* in the well-known shared genetic susceptibility to psychotic and affective disorders (for review see Maier, 2008; Van Den Bogaert, 2006; Wildenauer et al., 1999) as possibly captured by the phenotype of psychotic depression comprising both affective and psychotic symptoms.

Thus, in the present study the role of dysbindin in the pathogenesis of psychotic depression was further investigated by analyzing a representative number of *DTNBP1* polymorphisms for association with the clinical phenotype of psychotic depression.

2. Materials and methods

2.1. Sample

A sample of 243 (mean age: 47.8 ± 14.6; $f = 143$, $m = 100$) unrelated Caucasian patients with Major Depressive Disorder (MDD) admitted for inpatient treatment were consecutively recruited at the Department of Psychiatry, University of Muenster, Germany, between 2004 and 2006 (cf. Baune et al., 2008). A subsample of $N = 131$ was diagnosed with psychotic depression (mean age: 47.2 ± 13.9; $f = 82$, $m = 49$). Patients under the age of 18 and patients with schizoaffective disorders or comorbid substance abuse disorders, mental retardation, pregnancy and neurological, neurodegenerative disorders or other clinically unstable medical illnesses impairing psychiatric evaluation were not included in this analysis. In order to minimize the risk of ethnic stratification, Caucasian descent was ascertained by Caucasian background of both parents. Patients were treated in a naturalistic setting with a variety of antidepressant medication (mirtazapine: $N = 26$ (10.7%), citalopram/escitalopram: $N = 44$ (18.1%), venlafaxine: $N = 45$ (18.5%), mirtazapine plus citalopram/escitalopram: $N = 35$ (14.4%); mirtazapine plus venlafaxine: $N = 58$ (23.9%), other (TCA, MAO inhibitors, lithium): $N = 24$ (9.9%)). As co-medication atypical antipsychotics (quetiapine, olanzapine, risperidone; $N = 118$, 48.5%) as well as mood stabilizers (lithium, valproate acid; $N = 82$, 33.7%) were used in addition to antidepressant treatment. None of the included patients had received electroconvulsive therapy within six months before the present investigation. The treatment regime as described above was not significantly different for patients with or without psychotic depression.

The ethics committees of the University of Muenster, Muenster, Germany, and James Cook University, Townsville, Australia, approved the present study. Written informed consent was obtained from all participating subjects.

2.2. Assessment

Patients' diagnoses were ascertained by the use of a structured clinical interview (SCID-I) according to the criteria of DSM-IV. The diagnosis of psychotic depression was made based on SCID-I item A7 (feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)) and the psychotic symptoms module (psychotic and associated symptoms). History of suicide attempts was recorded upon admission. Severity of depression was measured by lifetime duration of depression, number of lifetime episodes of depression and number of lifetime admissions to inpatient treatment for depression. Furthermore, clinical severity of depression at admission was assessed with the Hamilton Depression (HAM-D-21) scale, the Beck's Depression Inventory (BDI), the Clinical Global Impression (CGI) scale and the Global Assessment of Functioning (GAF) scale.

2.3. SNP selection and genotyping

The selection of SNPs used in this analysis was initially described in a paper by Voisey et al. (2010). Details of the selected *DTNBP1* SNPs are described in Table 2. The entire sequence of the *DTNBP1* gene contains more than 917 single nucleotide polymorphisms (SNPs) of which 182 SNPs have a minor allele frequency (MAF) > 5% (International HapMap, 2003). We used various techniques to limit the number of SNPs assessed to the most relevant. We initially constructed the linkage disequilibrium (LD) pattern of the CEPH population of the HapMap Phase II genotype data (see Fig. 1) to identify tagging SNPs by an aggressive tagging approach (MAF>5% and $r2>0.8$) using Gevalt v2 software package (Davidovich et al., 2007). The region analyzed included about 140.2 kb of the *DTNBP1* gene between the positions 15,523,038 and 15,663,271 at chromosome 6 (human genome coordinates hg18). Ultimately, we reduced SNP numbers by assessing the ability of limited numbers of the tagging SNPs to predict the total SNP population using Stampa algorithm (Halperin et al., 2005). With this approach, 92.0% of the variation in the gene was captured using 12 tagging SNPs (rs1047631, rs17470454, rs1997679, rs2743857, rs3829893, rs4236167, rs4712253, rs742106, rs7758659, rs9370822, rs9370823, rs9476886). The mean r^2 of individual tagging SNPs in conjunction with one or more tagged SNPs was 0.984 (see Table 2 for details).

Genotyping was carried out following published protocols applying the multiplex genotyping assay iPLEX™ for use with the MassARRAY platform (Oeth et al., 2008), yielding a genotyping completion rate of 92% for *DTNBP1* SNPs for all included patients. Genotyping failures resulted in a total genotype availability of $N = 205$ for rs1047631, $N = 231$ for rs17470454, $N = 221$ for rs1997679, $N = 217$ for rs2743857, $N = 217$ for rs3829893, $N = 232$ for rs4236167, $N = 229$ for rs4712253, $N = 231$ for rs742106, $N = 220$ for rs7758659, $N = 227$ for rs9370822, $N = 231$ for rs9370823 and $N = 222$ for rs9476886. Genotypes were determined by investigators blinded for clinical diagnoses.

2.4. Statistical analysis

Differences in *DTNBP1* genotype distribution for all 12 SNPs across gender and diagnostic subgroup of psychotic depression were estimated by Pearson Chi^2 test. Odds ratios were calculated using logistic regression analyses for the association between psychotic depression and genotypes of *DTNBP1* SNPs. Logistic regression analyses were adjusted for age, gender and BDI and GAF