Journal of Affective Disorders 168 (2014) 91–97

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

DISC1-TSNAX and DAOA genes in major depression and citalopram efficacy

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ARTICLE INFO

Article history:
Received 26 February 2014
Received in revised form
25 June 2014
Accepted 27 June 2014
Available online 5 July 2014

Keywords:
Major depression
Gene
DISC1
DAOA
TSNAX
Antidepressant

ABSTRACT

Background: Major depressive disorder (MDD) is a common disease with high morbidity and still unsatisfying treatment response. Both MDD pathogenesis and antidepressant effect are supposed to be strongly affected by genetic polymorphisms. Among promising candidate genes, distrupted in schizophrenia 1 (DISC1), translin-associated factor X (TSNAX) and D-amino acid oxidase activator (DAOA) were suggested since their regulator role in neurodevelopment, neuroplasticity and neurotransmission, and previous evidence of cross-involvement in major psychiatric diseases.
Methods: The present paper investigated the role of 13 SNPs within the reported genes in MDD susceptibility through a case-control ($n=320$ and $n=150$, respectively) study and in citalopram efficacy ($n=157$). Measures of citalopram efficacy were response (4th week) and remission (12th week). Pharmacogenetic findings were tested in the STAR*D genome-wide dataset ($n=1892$) for replication.
Results: Evidence of association among rs3738401 (DISC1), rs1615409 and rs766288 (TSNAX) and MDD was found ($p=0.004$, $p=0.0019$, and $p=0.008$, respectively). A trend of association between remission and DISC1 rs821616 and DAOA rs778294 was detected, and confirmation was found for rs778294 by repeated-measure ANOVA ($p=0.0008$). In the STAR*D a cluster of SNPs from 20 to 40 Kbp from DISC1 findings in the original sample was associated with citalopram response, as well as rs778330 (12,325 bp from rs778294).
Limitations: Relatively small size of the original sample and focus on only three candidate genes.
Conclusions: The present study supported a role of DISC1-TSNAX variants in MDD susceptibility. On the other hand, genetic regions around DAOA rs778294 and DISC1 rs6675281-rs1000731 may influence citalopram efficacy.

1. Introduction

Major depressive disorder (MDD) is a common disease involving high functional morbidity, an increased rate of suicide, high risk of recurrence, and considerable health service utilization (Judd et al., 2000). Currently only half of patients shows a satisfying response to pharmacotherapy (Kemp et al., 2008), which is partly due to the lack of reliable predictors of response. Both MDD pathogenesis and mechanisms of antidepressant action are thought to have a strong genetic component. Indeed, the prevalence of MDD in proband first-degree relatives is 15%, against the 5.4% of the general population (Gershon, 1992), and antidepressant response shows a familiar clustering (Franchini et al., 1998). Interestingly, several genes were identified as putative predictors of both MDD susceptibility and antidepressant response (Lekman et al., 2008; Tsai et al., 2008), consistently with the hypothesis that antidepressants reverse the biological unbalances involved in MDD. Among these genes, distrupted in schizophrenia 1 (DISC1), translin-associated factor X (TSNAX) and D-amino acid oxidase activator (DAOA) seem to have a cross-sectional role among major psychiatric diagnosis.

Composed of 13 alternatively spliced exons, DISC1 gene is expressed most highly during periods of neurogenesis (Lipska et al., 2006). In the adult mammalian brain it plays a critical role in

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http://dx.doi.org/10.1016/j.jad.2014.06.048
0165-0327/

neurite outgrowth and neuronal migration, particularly in the hippocampus (Carless et al., 2011). Interestingly, non-synonymous SNPs rs821616 (Cys704Ser) and rs6675281 (Leu607Phe) were associated with the expression of DISC1 splice variants, that encode truncated proteins. In particular, rs6675281 predicted higher expression of these transcripts in the hippocampus (Nakata et al., 2009) and was associated with altered hippocampal structure and function in healthy subjects (Callicott et al., 2005). DISC1 was firstly identified as a candidate gene for schizophrenia (St Clair et al., 1990), but following studies suggested it may be a factor influencing phenotypes related to several psychiatric diseases. Indeed, DISC1 sequence variations were associated with brain-related phenotypes (e.g. hippocampal gray matter volume and function (Di Giorgio et al., 2008), recall and memory, verbal and visuospatial ability, psychomotor processing (Palo et al., 2007)), MDD (Hashimoto et al., 2006; Schosser et al., 2010; Carless et al., 2011; Thomson et al., 2014) and bipolar disorder (Palo et al., 2007; Hennah et al., 2009). Furthermore, DISC1 SNPs have been associated with anxiety, depression, emotional stability and neuroticism (Harris et al., 2010). DISC1 knockdown leads to a reduction of VGF (i.e. nerve growth factor inducible, that has potent antidepressant effects), suggesting a possible molecular mechanism explaining the role of DISC1 in MDD (Ramos et al., 2014).

TSNAX gene is located immediately upstream of DISC1, and has been shown to undergo intergenic splicing with DISC1 (Millar et al., 2000). TSNAX protein is known to form a brain enriched complex with translin, that can bind single-stranded DNA and RNA through which it is involved in protein regulation (Finkenstadt et al., 2000). The TSNAX–DISC1 region was found associated with the risk of schizophrenia and bipolar disorder (Thomson et al., 2005; Palo et al., 2007), but some studies suggested it may be involved also in MDD risk (Hashimoto et al., 2006; Okuda et al., 2010), even if one negative study exists (Schosser et al., 2010).

DAOA (or G72) gene encodes for a protein that binds to and activates the D-serine amino acid oxidase that acts as a coactivator of the glycine binding site on the glutamatergic N-methyl D-aspartate (NMDA) receptor (Mustafa et al., 2004). Subsequently, it influences NMDA excitatory transmission (Panatier et al., 2006) and several lines of evidence suggested a strong role of the glutamatergic system in MDD pathogenesis (Drago et al., 2011). Further interesting issues are that DAOA gene generates several splice variants expressed in the brain (Grigoroiu-Serbanescu et al., 2010) and influences neuronal dendritic arborization (Kvajo et al., 2008). DAOA gene overlaps with G30 building a complex described as a susceptibility locus for various neuro-psychiatric disorders (Abou Jamra et al., 2006), i.e. schizophrenia and bipolar disorder (Grigoroiu-Serbanescu et al., 2010), history of affective episodes in bipolar disorder and schizophrenia (Williams et al., 2006; Corvin et al., 2007), panic disorder (Schumacher et al., 2005), and MDD (Rietschel et al., 2008; Gawlik et al., 2010; Chen et al., 2012). On the other hand, a recent meta-analysis did not demonstrate any evidence of involvement of rs2391191, rs947267 and rs3918342 in MDD risk (Tan et al., 2014), calling into question the hypothesis of DAOA contribution to the disease.

Given the well-established familial clustering of MDD, schizophrenia, bipolar disorder, and anxiety disorders (Gershon et al., 1988; Alonso et al., 2004; Kessler et al., 2005) and previous findings about DISC1, TSNAX and DAOA, association between these genes and MDD is plausible but still needs to be confirmed. Even fewer data are available about the role of these genes in antidepressant efficacy, that remains to be investigated. Indeed, only some negative findings were reported for TSNAX (Okuda et al., 2010) and DAOA (Chiesa et al., 2012).

The aims of the present paper are therefore to investigate the role of DISC1, TSNAX and DAOA variants in MDD risk through a case-control study and their possible effect on citalopram efficacy in a pharmacogenetic subsample. The possible impact of these genes on citalopram efficacy was then validated in an independent sample (Sequenced Treatment Alternatives to Relieve Depression or STAR*D).

2. Methods

2.1. Samples

2.1.1. Spanish sample

320 MDD outpatients were recruited at the Centre de Salut Mental Esquerre de Eixample (Hospital Clinic I Provincial de Barcelona, Spain). All patients fulfilled DSM-IV criteria for a current MDD episode. Exclusion criteria were diagnosis of bipolar disorder, substance abuse or dependence, mental retardation and medical diseases that could impair evaluation. The 21-item Hamilton Depression Rating Scale (HDRS) was used to evaluate clinical severity at recruitment. Detailed data about severity clinical features were collected, particularly the presence of melancholic features, psychotic symptoms, seasonal pattern and previous suicidal attempts.

A control sample consisting of 150 healthy individuals with no personal history of mental illness was recruited. The Spanish version of the 28-item General Health Questionnaire (GoldbergandHillier, 1979) was used to assess their current mental condition.

All the individuals included were of Spanish origin as stated through the birthplace of their four grandparents. Ethical approval was obtained from Spanish local research ethic committee; all patients signed informed consent after adequate explanations about methods and objectives of the study.

A MDD subsample ($n=157$) followed a 12 week pharmacogenetic protocol. All patients included were treated with citalopram (20–40 mg/day) and HDRS was used to evaluate clinical severity at baseline and every 4 weeks until week 12. Clinical response to treatment was defined as a decrease of at least 50% in the baseline HDRS score at the 4th week (Baumann et al., 1996) and remission as a HDRS score equal to or less than 7 by the end of 12th week (Frank et al., 1991). Before their inclusion in the study, a 2-week washout was carried out with those patients who were being treated with different drugs. In case it was necessary, low dose concomitant treatments with drugs such as other psychotropics (10% of the sample) or benzodiazepines at bedtime (55.4% of the sample) were allowed. Citalopram plasma levels were measured at the 6th week by means of high-performance liquid chromatography to assess treatment compliance (Olesen and Linnet, 1996).

2.1.2. Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Detailed descriptions of the study design and study population are detailed elsewhere (Howland, 2008). In brief, non psychotic MDD (DSM-IV criteria) patients were enrolled from primary care or psychiatric outpatient clinics and a current 17-item Hamilton Depression Rating score of ≥ 14 by independent raters was obtained. Severity of depression was assessed using the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C) (Trivedi et al., 2004) at baseline, weeks 2, 4, 6, 9, and 12. All patients received citalopram in level 1.

2.2. Genotyping in the Spanish sample

Genomic DNA was extracted from blood samples by using a standard phenol–chloroform method. The following SNPs were selected according to earlier literature: rs3738401 (A/G), rs6675281