Psychiatry Research 209 (2013) 110–113

Contents lists available at ScienceDirect

Psychiatry Research

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

Brief report

Polymorphisms in schizophrenia candidate gene *UFD1L* may contribute to cognitive deficits

Vanessa K. Ota [a,b,*,1], Arthur A. Berberian [b,c,**,1], Ary Gadelha [b,c], Marcos L. Santoro [a,b], Gustavo L. Ottoni [d], Camila T. Matsuzaka [c], Jair J. Mari [c], Maria I. Melaragno [a], Diogo R. Lara [d], Marília A.C. Smith [a], Sintia I. Belangero [a,b,c], Rodrigo A. Bressan [b,c]

[a] Disciplina de Genética, Departamento de Morfologia e Genética, Universidade Federal de Sao Paulo (UNIFESP), Rua Botucatu 740, Edifício Leitao da Cunha, 1° Andar, CEP 04023-900 Sao Paulo, Brazil
[b] Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Departamento de Psiquiatria, Universidade Federal de Sao Paulo (UNIFESP), Sao Paulo, Brazil
[c] Departamento de Psiquiatria, Universidade Federal de Sao Paulo (UNIFESP), Sao Paulo, Brazil
[d] Faculdade de Biociências, Pontifícia Universidade do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

ARTICLE INFO

Article history:
Received 16 December 2012
Received in revised form
19 March 2013
Accepted 30 March 2013

Keywords:
Executive functions
Cognition
Gene

ABSTRACT

We aimed to investigate *UFD1L* polymorphisms in schizophrenia and in relation to cognition. A total of 299 cases and 363 controls were genotyped, and 130 patients completed nine neuropsychological tests. We found that rs5992403 AA-genotype carriers showed lower scores on the set-shifting task. Therefore, *UFD1L* may participate in the core cognitive deficits observed in schizophrenia.

1. Introduction

Schizophrenia is a heterogeneous disorder with a worldwide prevalence of 0.3–1.6% (Kessler et al., 2005; Saha et al., 2005). It is considered a multifactorial disease that results from a complex interaction of genetic and environmental elements (Sullivan et al., 2003).

In the last decade, several studies have suggested cognitive deficits as a core feature of schizophrenia (Andreasen et al., 1998; Mesholam-Gately et al., 2009). These cognitive deficits are usually present in all phases of the illness, even beginning before the onset of psychotic symptoms (Seidman et al., 2010) Moreover, unaffected first-degree relatives of patients present similar patterns of cognitive deficits, but at a more attenuated level (Szoke et al., 2005; Trandafir et al., 2006).

Data from studies using different methodologies, such as functional and structural imaging, postmortem techniques and neurocognition, converge in showing several brain alterations related to schizophrenia. Such abnormalities are thought to be an effect of genetic liability and environmental factors implicated in schizophrenia (Gur et al., 2007).

Copy number variations in 22q11 are among the most important and replicated known genetic risk factors for developing schizophrenia (Levinson et al., 2011). One gene located at this region is ubiquitin fusion degradation 1-like (UFD1L) protein, which encodes the human homolog of the yeast ubiquitin-fusion-degradation 1 protein (UFD1) (Yamagishi et al., 1999). Deficiency of this protein might result in cell death or aberrant differentiation (Meyer et al., 2000). In humans, *UFD1L* expression is increased in a sensitive phase for neurodevelopment (Novelli et al., 1998). Moreover, *UFD1L* single nucleotide polymorphisms (SNPs) have been associated with schizophrenia (De Luca et al., 2001; Xie et al., 2008; Ota et al., 2010).

We aimed to investigate the association of three *UFD1L* SNPs (rs5992403, rs1547631 and rs5746744) with: (1) schizophrenia in a case-control analysis and (2) neuropsychological performance in a comprehensive battery of tasks within a sample of patients.

* Corresponding author at: Genetics Division, UNIFESP, Morphology and Genetics, Rua Botucatu 740, Edifício Leitão da Cunha 1°, Andar, CEP 04023-900 São Paulo, SP, Brazil. Tel.: +55 115576 4260, +55 1155764264.
** Corresponding author at: Psychiatry Department, UNIFESP, Rua Borges Lagoa, no. 570 Vila Clementino, São Paulo, SP CEP 04038-020, Brazil. Tel.: +55 11 5576 4845.
E-mail addresses: vanessakaota@gmail.com (V.K. Ota), a.berberian@unifesp.br (A.A. Berberian), aryararipe@yahoo.com.br (A. Gadelha), santorogen@gmail.com (M.L. Santoro), ottonigl@gmail.com (G.L. Ottoni), camila.tm@gmail.com (C.T. Matsuzaka), jamari@attglobal.net (J.J. Mari), melaragno.morf@epm.br (M.I. Melaragno), drlara@pucrs.br (D.R. Lara), macsmith.morf@epm.br (M.A.C. Smith), sintia.morf@epm.br (S.I. Belangero), rodrigoabressan@gmail.com (R.A. Bressan).
[1] Both authors contributed equally to this work.

0165-1781/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2013.03.035

2. Methods

2.1. Subjects

A total of 299 patients and 363 healthy controls were recruited from two Brazilian cities (Sao Paulo and Porto Alegre) through the Programa de Esquizofrenia (PROESQ) and Laboratório de Neurociências Clínicas (LiNC), both at the Universidade Federal de Sao Paulo (UNIFESP), and Pontifícia Universidade do Rio Grande do Sul (PUCRS), which selected the sample from Porto Alegre. The diagnosis of schizophrenia was confirmed by the Structured Clinical Interview for DSM-IV, applied by trained psychiatrists. Healthy controls had no family history of severe psychiatric illness or current or previous psychiatric disorders. Characteristics of these study populations are described in Supplementary Table 1.

All subjects underwent blood collection for genetic analyses, and a sample of 130 patients from São Paulo Center was assessed with the Positive and Negative Syndrome Scale (PANSS) and neuropsychological tests. Symptom clusters were classified according to PANSS ratings (Levine and Rabinowitz, 2007). Treatment-resistant (TR) status was defined following the International Psychopharmacological Criteria (IPAP) (www.ipap.org).

The Research Ethics Committee of UNIFESP approved the research protocol, and participants entered the study after giving written informed consent.

2.2. UFD1L genotyping

The *UFD1L* rs5992403 polymorphism was genotyped by Taq-Man probe-based real-time polymerase chain reaction (PCR) assays (Life Technologies, Carlsbad, CA, USA), whereas rs1547931 (G/C) and rs5746744 (G/C) polymorphisms were genotyped using the restriction fragment length polymorphism (RFLP) technique. PCR primers and conditions are available upon request.

Linkage disequilibrium and haplotypes were assessed using Haploview (Barrett et al., 2005).

2.3. Neuropsychological tests

We considered two criteria for selection of the data: the measures should tap some of the core dimensions of the cognitive deficits of schizophrenia (Nuechterlein et al., 2004; Barch et al., 2009) and also represent cognitive skills that are potential endophenotypic vulnerability markers (Gur et al., 2007). Thus, eight tests assessing different aspects of executive functions, working memory, and verbal memory were administered to 130 patients by trained psychologists. The IQ of each participant was also determined. Previous studies have shown that these tasks are sensible choices for discriminating the cognitive performance of subjects with schizophrenia and healthy comparison individuals (Berberian et al., 2009) (Supplementary Table 4). A full description of all tests is available on Supplementary Material 1 and 2.

2.3.1. Working memory/updating

- Letter memory task, adapted from Morris and Jones (1990);
- Keep track task, adapted from Yntema (1963).

2.3.2. Inhibition

- Victoria computerized Stroop test (Seabra et al., in press).

2.3.3. Set-shifting tasks

- Trail Making Test (Arbuthnott and Frank, 2000).
- Plus–minus task, adapted from Jersild (1927).
- Letter-number task, adapted from Rogers and Monsell (1995).

2.3.4. Verbal learning and memory

- Hopkins Verbal Learning Task Revised (HVLT-R; Brandt, 1991).

2.3.5. Complex executive functions

- The Wisconsin Card Sorting Task with 64 trials (Kongs et al., 2000).

2.3.6. Non-verbal intelligence test

- The non-verbal intelligence task (R-1) (Oliveira, 2002) was developed to allow measurement of intelligence in low literacy populations.

2.4. Statistics

The Hardy–Weinberg equilibrium was verified using the Chi-squared test. Next, a logistic regression and a chi-squared test were performed to associate each genotype and haplotype, respectively, with schizophrenia.

For the cognitive analysis, we grouped the heterozygotes with minor allele homozygotes. An analysis of variance (ANOVA) was applied to evaluate the associations between each group and cognitive measures. Levene's test indicated that the homogeneity of variance could not be presumed for all tasks. Thus, the performances of the patients required square root transformations. Statistical analyses were performed using SPSS v.15.0, and significance was considered at the $p < 0.05$ level, after Bonferroni correction.

3. Results

3.1. Sample description

The patients and control group differed in gender ($\chi^2 = 11.16$; d.f. = 1; $p < 0.001$), age ($t = 3.43$; d.f. = 643.88; $p = 0.001$) and ethnicity ($\chi^2 = 10.23$; d.f. = 2; $p = 0.006$); hence, these variables were inserted as covariates in the first analysis that compared patients and controls.

3.2. Effect of UFD1L SNPs in schizophrenia diagnosis

Genotype distributions of both SNPs were in accordance with the Hardy–Weinberg equilibrium ($p > 0.05$).

Because these SNPs were in linkage disequilibrium (rs1547931/rs5746744: $D' = 0.981$; rs5746744/rs5992403: $D' = 0.983$; and rs1547931/rs5992403: $D' = 0.953$), we performed haplotype analyses. Genotype and haplotype frequencies are reported in Supplementary Table 2.

We could not find any association between genotypes and schizophrenia (rs5992403: $p = 0.344$; rs1547931: $p = 0.734$; and rs5746744: $p = 0.496$). Similarly, no associations with haplotypes were found ($p > 0.05$).

3.3. Association between UFD1L SNPs and neurocognitive performance

There were no differences in demographic variables and clinical data between genotype groups for those individuals that had both neuropsychological and genotype data (Supplementary Table 3).

The results concerning each SNP and neurocognitive performance are summarized in Table 1. Briefly, an ANOVA revealed an association of the rs5992403 AA genotype with poorer performance in the WCST Perseverative Errors score (evaluates set-shifting ability) after Bonferroni correction for multiple comparisons (Table 1).

No association was found for both rs1547931 and rs5746744 (Table 1).

4. Discussion

This is the first study to explore the influence of *UFD1L* SNPs on different aspects of executive functions and memory in schizophrenia.

4.1. Association studies of UFD1L SNPs in schizophrenia

First, we found no association of any of the three *UFD1L* SNPs with schizophrenia. Previous studies have suggested that these three SNPs were positively associated with schizophrenia (De Luca et al., 2001; Xie et al., 2008), but with some discrepancies. One possible reason for these inconsistent results may be ethnic background differences. De Luca et al. (2001) investigated Caucasian and Canadian samples, whereas Xie et al. (2008)