Tardive dyskinesia and DRD3, HTR2A and HTR2C gene polymorphisms in Russian psychiatric inpatients from Siberia

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ARTICLE INFO

ABSTRACT

Background: Pharmacogenetics of tardive dyskinesia and dopamine D3 (DRD3), serotonin 2A (HTR2A), and 2C (HTR2C) receptors has been examined in various populations, but not in Russians.
Purpose: To investigate the association between orofaciolingual (TDof) and limb-truncal dyskinesias (TDlt) and Ser9Gly (DRD3), -1438G>A (HTR2A), and Cys23Ser (HTR2C) polymorphisms in Russian psychiatric inpatients from Tomsk, Siberia.
Methods: In total, 146 subjects were included. Standard protocols were applied for genotyping. TDof and TDlt were assessed with AIMS items 1–4 and 5–7, respectively. Two-part model, logistic and log-normal regression analyses were applied to assess different variables (e.g., allele-carriership status, age, gender, and medication use).
Results: TDlt, but not TDof, exhibited an association with Ser9Gly and Cys23Ser (with 9Gly and 23Ser alleles exhibiting opposite effects). However, -1438G>A was not associated with TDof and Dlt.
Conclusions: This is the first pharmacogenetic report on tardive dyskinesia in Russians. Subject to further replication, our findings extend and support the available data.

1. Introduction

Tardive dyskinesia (TD) is a potentially irreversible antipsychotic-induced movement disorder with a prevalence of about 20–30% in psychiatric patients chronically exposed to antipsychotics. Older age, female gender, race, and family history are several risk factors for the development of TD (Glazer, 2000; Kane et al., 1988; Muller et al., 2001; Rosengarten et al., 1994; Wonodi et al., 2004).

Phenotypically, TD can be dissected into two distinct subsyndromes; orofaciolingual (TDof) and limb-truncal dyskinesias (TDlt). TDof involves movements of mouth and face muscles and may impair eating and swallowing, whereas TDlt involves purposeless choreiform movements of trunk and/or limbs and may cause gait disturbances and falls.

Accumulating evidence suggest that TDof and TDlt are two distinct clinical entities with different clinical features, different risk factors, different prognosis, and probably even different genetic liability (Gureje, 1988, 1989; Inada et al., 1990; Paulsen et al., 1996; Waddington et al., 1987; Wilffert et al., in press).

Dopamine D3, serotonin 2A, and 2C receptors (encoded by DRD3, HTR2A, and HTR2C genes, respectively) are involved, at least partially, in the therapeutic and adverse effects of antipsychotics and genetic variations in these receptors may affect the individual sensitivity to TD (Reynolds 2004). Several studies suggest, for example, that Ser9Gly polymorphism of DRD3 gene may be associated with TD in humans (Bakker et al., 2006; Lerer et al., 2005; Wilffert et al., in press) and even in non-human primates (Werge et al., 2003). Furthermore, accumulating evidence suggests that HTR2A and HTR2C genes may be

pharmacogenetically important for TD (Arranz and de Leon, 2007; Lerer et al., 2005; Segman et al., 1999; Segman et al., 2001; Segman et al., 2003; Segman and Lerer, 2002; Wilffert et al., in press).

Ethnicity is an important, but often underestimated, demographic and pharmacogenetic determinant of the response to antipsychotics (Frackiewicz et al., 1997; Swartz et al., 1997). African-Americans for instance have been found to be more sensitive to TD (Eastham et al., 1996; Morgenstern and Glazer, 1993).

Several studies have examined TD pharmacogenetics in relation to DRD3, HTR2A, and HTR2C gene polymorphisms in various ethnic groups (Liou et al., 2004; Segman et al., 1999; Segman et al., 2000; Segman et al., 2001), but not in Slavonic Caucasians from Siberia. Anthropologically, Siberia forms an important geographic link between the European and Asian continents and between North Asia and the Japanese Archipelago (Karafet et al., 2002). Southern Siberia particularly is an area where the most ancient contacts occurred between Caucasoid and Mongoloid people, which may have affected the genetic architecture of Eastern Slavonic populations generally and Russian Siberians particularly (Derenko et al., 2006; Karafet et al., 2002; Shorokhova et al., 2005; Verbenko et al., 2005).

In the present study, we report for the first time the association between certain polymorphisms in DRD3, HTR2A, and HTR2C (Ser9Gly, -1438G>A, and Cys23Ser, respectively) and TD including its two main forms (TDof and TDlt) in Russian psychiatric patients from Siberia.

2. Methods

2.1. Subjects

Informed consent was obtained from each subject after explanation of the study after approval of the study protocol by the institutional bioethics committee. Subjects were included from two psychiatric departments (for permanent and temporal hospitalization) of the Mental Health Research Institute in Tomsk, Siberia (Russia).

We included subjects with informed consent and clinical diagnosis of schizophrenia or schizotypal disorder (ICD-10: F20 and F21, respectively), and excluded subjects with non-Caucasian physical appearance (e.g., Mongoloid, Buryats, or Khakassians), subjects on clozapine but without TD (clozapine may ameliorate TD), subjects with clinically relevant withdrawal symptoms, and those with organic disorders.

Clinical and demographic data were extracted from patients' medical files.

In total, 153 Russian Caucasian patients met the inclusion criteria. Of these, 7 subjects used clozapine but did not exhibit TD (assessed by having an AIMS item ≥2 points). Since clozapine may ameliorate TD, these subjects were excluded from the analysis. Therefore, a total of 146 subjects (91 males, 55 females) were included in the analysis.

2.2. Assessment instruments

TD was assessed cross-sectionally by the use of the Abnormal Involuntary Movement Scale (AIMS) (Gardos et al., 1977), which scores 7 dyskinesia items (face, lips, jaw, tongue, arms, legs, and trunk) on a 5-point scale (0 = none, 1 = minimal or extreme normal, 2 = mild, 3 = moderate, and 4 = severe). Four trained raters assessed the presence of TD and, when present, the rating of TD was established by consensus with either one of the two senior doctors. The presence of TDof and TDlt was established by a cutoff score of ≥2 (mild but definite) on any of the items 1 through 4 and 5 through 7 of AIMS, respectively. The sum of the first four items and the sum of items 5 through 7 were used as TDof and TDlt severity proxies, respectively. Additionally, we have conducted a full AIMS analyses (i.e., presence of TDof and/or TDlt) by examining items 1–7 of AIMS. In analogy, the sum of these 7 items was used as a proxy of the severity of TD as one entity (TDsum).

2.3. Medication

On the day of TD assessment, a complete documentation of the medications utilized was compiled by the raters. The dose of the antipsychotic medication was converted into chlorpromazine equivalents (CPZEQ), according to the literature (Davis, 1976; Rey et al., 1989; Schulz et al., 1989; Woods, 2003).

2.4. Genotyping

Blind to the clinical status of the subjects, genomic DNA was extracted from EDTA whole-blood and genotyped with standard TaqMan® Assays-On-Demand ordered from Applied Biosystems (Ser9Gly, C____949770_10; -1438G>A, C___8695278_10; Cys23Ser, C___2270166_10). To reduce the number of classes studied, we chose to underestimate the effects of the polymorphisms by classifying the subjects as carriers or non-carriers of the minor allele, as previously suggested (Al Hadithy et al., 2008).

2.5. Statistics

Initially, we applied logistic regression (LR) analysis to investigate the genetic effects on the probability of presence of TDof and TDlt.

Because dichotomizing the data is not reflective of the severity, we also examined the association between these polymorphisms and the severity proxies. However, since clustering of zeros and skewness of data distributions are common problems in psychiatric research (Delucchi and Bostrom, 2004), we first examined the distributions of the sums of AIMS items 1–4 (TDof), 5–7 (TDlt), and 1–7 (TDsum) to determine the most appropriate and well-fitting theoretical distribution and to apply an appropriate parametric method thereafter.

To handle the clumping of zeros, we utilized a two-part model (TPM) approach (Delucchi and Bostrom, 2004). In the first part of the TPM analyses we used LR analysis to estimate the probability of having TDof, TDlt, and TDsum sum scores above 0. In the second part of the TPM approach, we used multivariate parametric regression to study the effects of the above mentioned variables on the non-zero part TDof, TDlt, and TDsum variables. Since is it reasonable to consider subjects with zero AIMS values as dyskinesia-free cases, the TPM may explain the difference in the proportion of subjects with and without dyskinesia in relation to allele-carriership status (part 1), and, for those subjects with possible dyskinesia (AIMS-sum>0), whether there is an association between the severity and the carriership of a certain allele (part 2).

Since the separation of zeros from non-zeros in TPM analysis may decrease the sample-size and hence the statistical power, we have also conducted parametric regression analyses on the whole sample to overcome that disadvantage. To make the transformation possible, we chose to add 1 to all of the untransformed sums and transform thereafter (Sokal and Rohlf, 1994).

In all of these three approaches, we applied a stepwise selection procedure (by means of Akaike's Information Criterion) to select variables (allele-carriership, age, gender, type of psychiatric clinic, use of anticholinergic and antipsychotic medication) that offer the highest explanatory power to the model.

Since there is accumulating evidence suggesting additive effects of these polymorphisms (Segman et al., 2000; Wilffert et al., in press), we chose to study the effects of 2 genes simultaneously in each model (i.e., Ser9Gly plus -1438G>A, Ser9Gly plus Cys23Ser, or -1438G>A plus Cys23Ser).

For the calculations, the statistical software "R" was used. Where needed, we utilized Fisher's exact test for 2×2 contingency tables. Departure from the Hardy–Weinberg Equilibrium was calculated for all of the polymorphisms, except for Cys23Ser polymorphism (X-chromosomal), using an online tool (http://www.tufts.edu/~mcourt01/Documents/Court%20lab%20-%20HW%20calculator.xls).