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Association study of the vesicular monoamine transporter gene SLC18A2 with tardive dyskinesia

Clement C. Zai [a,1], Arun K. Tiwari [a,1], Marina Mazzoco [a,b], Vincenzo de Luca [a], Daniel J. Müller [a,c], Sajid A. Shaikh [a], Falk W. Lohoff [d], Natalie Freeman [a], Aristotle N. Voineskos [a], Steven G. Potkin [e], Jeffrey A. Lieberman [f,2], Herbert Y. Meltzer [g,3], Gary Remington [a], James L. Kennedy [a,*]

[a] Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, ON, Canada
[b] Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil
[c] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[d] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[e] Department of Psychiatry and Human Behavior, 5251 California, Suite 240, University of California, Irvine, Irvine, CA 92617, USA
[f] Department of Psychiatry, Mental Health and Neuroscience Center, University of North Carolina at Chapel Hill School of Medicine, NC, USA
[g] Department of Psychiatry, University Hospitals of Cleveland, Hanna Pavilion, Room B-68, 11100 Euclid Avenue, Cleveland, OH 44106-5000, USA

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ABSTRACT

Tardive dyskinesia (TD) is an involuntary movement disorder that can occur in up to 25% of patients receiving long-term first-generation antipsychotic treatment. Its etiology is unclear, but family studies suggest that genetic factors play an important role in contributing to risk for TD. The vesicular monoamine transporter 2 (VMAT2) is an interesting candidate for genetic studies of TD because it regulates the release of neurotransmitters implicated in TD, including dopamine, serotonin, and GABA. VMAT2 is also a target of tetrabenazine, a drug used in the treatment of hyperkinetic movement disorders, including TD. We examined nine single-nucleotide polymorphisms (SNPs) in the *SLC18A2* gene that encodes VMAT2 for association with TD in our sample of chronic schizophrenia patients ($n = 217$). We found a number of SNPs to be nominally associated with TD occurrence and the Abnormal Involuntary Movement Scale (AIMS), including the rs2015586 marker which was previously found associated with TD in the CATIE sample (Tsai et al., 2010), as well as the rs363224 marker, with the low-expression AA genotype appearing to be protective against TD ($p = 0.005$). We further found the rs363224 marker to interact with the putative functional D2 receptor rs6277 (C957T) polymorphism ($p = 0.001$), supporting the dopamine hypothesis of TD. Pending further replication, VMAT2 may be considered a therapeutic target for the treatment and/or prevention of TD.

1. Introduction

Schizophrenia is a severe neuropsychiatric disorder, with antipsychotics being the mainstay of treatment. However, the use of these medications is often marred by the occurrence of adverse events. Long-term treatment, especially with conventional antipsychotic drugs, is associated with a risk of tardive dyskinesia (TD), an involuntary and potentially irreversible movement disorder with a prevalence rate in the range of 25% (Margolese et al., 2005; Tarsy and Baldessarini, 2006). The presence of TD can be stigmatizing, as well as contributing to treatment nonadherence and lower quality of life (Gerlach, 2002; Marsalek, 2000). While the risk of TD is lower for patients taking the newer "atypical" antipsychotics, the risk, as well as that of other extrapyramidal side effects,

Abbreviations: (TD), tardive dyskinesia; (VMAT2), vesicular monoamine transporter 2; (CATIE), Clinical Antipsychotic Trials of Intervention Effectiveness; (SNP), single-nucleotide polymorphism; (AIMS), Abnormal Involuntary Movement Scale.

* Corresponding author. Rm 129 250 College Street, Toronto, Ontario, Canada M5T1R8. Tel.: +1 416 979 4987; fax: +1 416 979 4666.
E-mail address: james_kennedy@camh.net (J.L. Kennedy).

[1] Equal contribution.

[2] Present address: Department of Psychiatry, College of Physicians and Surgeons, Columbia University and the New York State Psychiatric Institute, New York City, NY 10032, USA.

[3] Present address: Department of Psychiatry & Behavioral Science, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA.

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has not been eliminated (Goumeniouk, 2012). In addition, the use of conventional neuroleptics remains relatively high in developing countries due to their lower cost. Accordingly, predicting those patients who are susceptible to developing TD remains clinically important.

TD etiopathophysiology is complex and remains unclear. A number of mechanisms for TD development have been postulated, including serotonin modulation (Kapur and Remington, 1996; Lerer et al., 2005), GABA insufficiency (Tamminga et al., 1985), oxidative stress (Cho and Lee, 2012; Lohr et al., 2003; Shinkai et al., 2006; Zai et al., 2010a), and dopamine receptor hypersensitivity (Abilio et al., 2003; Gerlach and Casey, 1988; Klawans et al., 1980; Tarsy and Baldessarini, 1977). Observations that TD runs in families indicate a genetic component as well (Müller et al., 2001, 2004). Although the dopamine D_2 receptor *DRD2* gene has been a primary candidate (e.g., (Zai et al., 2007b)), meta-analyses (Bakker et al., 2008; Zai et al., 2007a) have demonstrated only a small risk effect for the markers studied, suggesting additional genetic factors play a role in TD susceptibility.

The vesicular monoamine transporter 2 (VMAT2), which is expressed predominantly in the brain, stores neurotransmitters (dopamine, serotonin, norepinephrine, GABA, etc) from the cytosol into vesicles prior to their release to neuronal synapses (Tritsch et al., 2012). The role of VMAT2 in regulating the release of multiple neurotransmitters makes it an attractive candidate for studying neuropsychiatric disorders where these same systems have been implicated. VMAT2 is a target of the inhibitor tetrabenazine, which is used for the treatment of a number of hyperkinetic movement disorders, including TD (Chen et al., 2012; Ondo et al., 1999). VMAT2 is coded by the *SLC18A2* gene (MIM: 193001) at chromosomal region 10q25.3; the *SLC18A2* gene has been associated with alcohol and nicotine dependence in a family-based study (Schwab et al., 2005). Recently, *SLC18A2* variants have also been associated with nonaffective psychotic disorder and performance in a comprehensive neurocognitive test battery (Simons and van Winkel, 2013). Furthermore, the rs2015586 marker in the *SLC18A2* gene was the top finding in a large association study of 128 candidate genes with TD occurrence in the CATIE sample (Tsai et al., 2010), making it an important gene for further investigation in TD occurrence and severity.

In the present study, we aim to examine the *SLC18A2* gene for possible association with TD occurrence as well as severity as measured by the Abnormal Involuntary Movement Scale (AIMS) in our sample of schizophrenia patients.

2. Materials and methods

2.1. Subjects

For the current study, we included 217 participants for which the sample characteristics have been described previously (Zai et al., 2007b, 2008). Briefly, participants were enrolled from four sites in Canada and the US: Center for Addiction and Mental Health in Toronto, Ontario (Dr. G Remington, $N = 94$); Case Western Reserve University in Cleveland, Ohio (Dr. HY Meltzer, $N = 63$); Hillside Hospital in Glen Oaks, New York (Dr. JA Lieberman, $N = 48$); and University of California at Irvine, California (Dr. SG Potkin, $N = 12$). Participants had DSM-III-R or DSM-IV diagnoses for schizophrenia or schizoaffective disorder (APA, 2000), and individuals with type II diabetes, head injury with loss of consciousness, or seizure disorder were excluded from the study. Patients recruited in the US (HYM, JAL, SGP) had no prior exposure to atypical antipsychotics, while the chronic patients from Canada (GR) may have been on either typical or atypical antipsychotics. Overall, all patients had been exposed to typical antipsychotic medication for at least one year before TD assessment. The rates of TD did not differ significantly between the US (38%) and Canadian (43%) samples ($p = 0.58$), and was lower, albeit not significantly, in males (36%) versus females (49%) in the collective sample ($p = 0.11$). The classification of TD was based on the Schooler and Kane criteria using the Abnormal Involuntary Movement Scale (AIMS) or the modified Hillside Simpson Dyskinesia Scale (HSDS) for the 48 patients recruited from the Hillside Hospital (Basile et al., 1999; Guy, 1976; Schooler and Kane, 1982). Thus, presence of TD included at least one moderate rating or at least two mild ratings on the first seven items of the AIMS (Schooler and Kane, 1982). Because of previous findings of a higher rate of TD in patients of African ancestry compared to those of European ancestry, we analyzed our self-reported African ($N = 30$, 11 of which were classified as having TD) and European ($N = 187$, of which 76 were positive for TD) subjects separately (Jeste, 2000). AIMS scores were available for 155 European patients and 26 African patients. Our European sample has over 80% power to detect an odds ratio of 2.07 ($\alpha = 0.05$, allele frequency = 0.2, additive model; Quanto v1.2.3; (Gauderman and Morrison, 2006)). In accordance to the declaration of Helsinki, we obtained voluntary consent from each study participant after the nature of the study was explained to them, and the study was approved by the individual institutional research ethics boards.

2.2. Genotyping and analysis

We selected single-nucleotide polymorphisms (SNPs) based on the linkage disequilibrium among available SNPs (pairwise r^2 threshold of 0.80, minimum minor allele frequency of 0.20) from 10 kb upstream to 10 kb downstream of the *SLC18A2* gene from the HapMap genome browser. We also included a number of SNPs that have been previously cited: rs393390 in alcohol and nicotine dependence (Schwab et al., 2005); rs2015586 in tardive dyskinesia (Tsai et al., 2010); rs1860404 in risk attitudes (Roe et al., 2009); rs363393 in schizophrenia (Talkowski et al., 2008) and neurocognitive test scores (Simons and van Winkel, 2013). The genotypes for rs2244249 are highly correlated to those for rs363227, a marker recently associated with psychotic disorder and performance in a comprehensive neurocognitive test battery (Simons and van Winkel, 2013). Based on these criteria, we selected a final list of nine SNPs across the *SLC18A2* gene (Fig. 1), and genotyped these

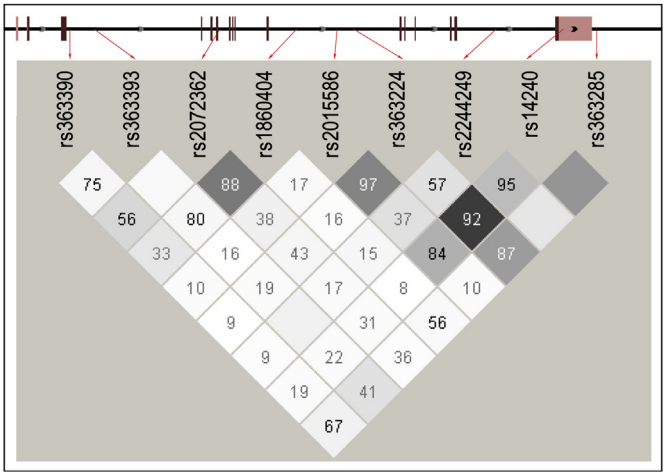

Fig. 1. Schematic diagram of the SLC18A2 gene with the nine single nucleotide polymorphisms we examined for association with tardive dyskinesia and AIMS. The linkage disequilibrium structure of SLC18A2 SNPs is also displayed, with the numbers indicating the pairwise D-prime values, and the intensity of grey relating to the r-squared values between SNP pairs.