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A Candidate Gene Study of Tardive Dyskinesia in the CATIE Schizophrenia Trial

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Abstract

Tardive dyskinesia (TD) is a movement disorder characterized by involuntary oro-facial, limb, and truncal movements. As a genetic basis for inter-individual variation is assumed, there have been a sizeable number of candidate gene studies. All subjects met diagnostic criteria for schizophrenia and were randomized to receive antipsychotic medications as participants in the Clinical Antipsychotic Trials of Intervention Effectiveness project (CATIE). TD was assessed via the Abnormal Involuntary Movement Scale at regular intervals. Probable TD was defined as meeting Schooler–Kane criteria at any scheduled CATIE visit (207/710 subjects, 29.2%). A total of 128 candidate genes were studied in 710 subjects—2,580 SNPs in 118 candidate genes selected from the literature (e.g., dopamine, serotonin, glutamate, and GABA pathways) and composite genotypes for 10 drug-metabolizing enzymes. No single marker or haplotype association reached statistical significance after adjustment for multiple comparisons. Thus, we found no support for either novel or prior associations from the literature.

Keywords

schizophrenia; tardive dyskinesia; antipsychotic medication; adverse drug reaction; genetic; candidate gene association

Tardive dyskinesia (TD) is a movement disorder characterized by involuntary oro-facial, limb, or truncal movements. A crucial TD risk factor is exposure to antipsychotic medications (particularly at higher doses and for longer durations) [Morgenstern and Glazer, 1993] and individual with schizophrenia who receive these medication are at increased risk. A major hypothesis is that TD is a “pharmacogenetic disease” where the interaction of conventional antipsychotic exposure with individual genetic variation mediates risk. This hypothesis is plausible (although the supposition that TD has a genetic basis is based on a few limited family studies) [Yassa and Ananth, 1981; Youssef et al., 1989; Muller et al., 2001] and led to a number of candidate gene studies (e.g., for often single variants in COMT, CYP2D6, DRD2, DRD3, HTR2A, and SOD2) [Lerer et al., 2002, 2005; Patsopoulos et al., 2005; Bakker et al., 2008]. An important limitation of the prior literature is that most studies genotyped only a small number of genetic markers. Using structured and

repeated assessments of TD in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, we genotyped haplotype tag SNPs and functional variants in subjects in a comprehensive set of 128 candidate genes.

All subjects were participants in the CATIE project [Lieberman et al., 2005]. Briefly, CATIE was a multi-phase randomized controlled trial of antipsychotic medications involving 1,460 unrelated persons with schizophrenia followed for up to 18 months, ascertained from a range of distinct clinical settings across US [Stroup et al., 2003; Lieberman et al., 2005]. Written informed consent (including an additional consent for genetic studies) was provided by all participants and the complete study protocol was reviewed by IRBs at UNC and at participating study sites. Inclusion criteria were: definite diagnosis of schizophrenia [American Psychiatric Association, 1994; First et al., 1994], age 18–65 years, clinical decision that oral medication was appropriate, adequate decisional capacity, and provision of written informed consent. Briefly, patients were excluded if they had received a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; a history of serious adverse reactions to the proposed treatments; in a first episode of schizophrenia; a history of treatment resistance; pregnant or breastfeeding; or a serious and unstable medical condition. Individuals with psychoactive drug use disorders were included but only when there was positive evidence that schizophrenia was an independent diagnosis. Peripheral venous blood samples were obtained and sent to the Rutgers University Cell and DNA Repository (RUCDR) where cell lines were established. DNA concentrations were quantified and normalized via the use of Picogreen Kits (Molecular Probes, Eugene, OR).

As described previously [Miller et al., 2005], TD was assessed in a standardized manner during the CATIE study using the Abnormal Involuntary Movement Scale (AIMS) [Guy, 1976]. The AIMS measures the severity of oro-facial, limb, and truncal involuntary movements on a 0–4 scale for 7 items representing different anatomic regions, and was measured for each subject at baseline, every 3 months thereafter, and at the end of each treatment phase. Similar to prior reports from this sample [Miller et al., 2005, 2008], we used Schooler–Kane criteria [Schooler and Kane, 1982] to classify the presence or absence of TD which requires a rating of three (moderate) on at least one item or a rating of two (mild) on at least two items of the AIMS scale at two separate assessments. A crucial complexity of TD is that it may fluctuate between assessments, may be suppressed or “masked” by administration of antipsychotic drugs, or become apparent only after withdrawal or switching of antipsychotic drugs. Therefore, to capture all patients with TD with a high degree of sensitivity, the analysis was conducted using modified Schooler–Kane criteria which requires meeting the AIMS criteria at any one regularly scheduled CATIE assessment (i.e., at baseline or a subsequent visit). This definition is referred to as “probable” TD [Schooler and Kane, 1982].

We selected 128 candidate genes for study. This list was selected in 2005 by the investigators based on the literature. Most genes were selected because of an association with particular biological pathways or processes and included genes related to: acetylcholine (20 genes), dopamine (17), GABA (4), glutamate (33), histamine (8), serotonin (21), treatment response (10), and other (17). One gene could be in multiple categories. SNPs (2,632) for 118 genes were selected using TAMAL [Hemminger et al., 2006] and haplotype tag SNPs were selected using TagIT (minimum $r^2 \geq 0.85$) [Ahmadi et al., 2005] based on the HapMap Phase 1 CEU data [Altshuler et al., 2005]. Genotyping was conducted using Illumina GoldenGate technology per standard protocol. To be used in analysis, we required each SNP to have a valid dbSNP v129 mapping, minor allele frequency ≥ 0.01 , and genotyping completion of $\geq 95\%$. Polymorphisms sufficient to classify predicted activity (i.e., composite genotypes estimating the number of copies of dysfunctional alleles) were

genotyped in 10 drug-metabolizing enzymes (DMEs) as described elsewhere [Grossman et al., 2008]. Subjects were dropped if missingness exceeded 5%. After filtering, 2,580 SNPs, 10 DME composite genotypes, and 710 subjects were included in the analyses.

For population substructure, 75 ancestry informative SNPs selected using HapMap panels were genotyped in CATIE study subjects. We have demonstrated empirically that this method has reasonable performance for controlling population stratification effects [Sullivan et al., 2008]. We used structure [Pritchard et al., 2000] to determine the posterior probability of each study subject being classified into one of three main sources of human ancestry (African, East Asian, and European) with the use of the three HapMap panels as prototypes for continental ancestry. These three probabilities sum to unity. The probabilities of European and East Asian ancestry were used as covariates given that their correlation was the lowest.

We used PLINK [Purcell et al., 2007] to conduct logistic regressions of TD status against SNP genotype (coded as the number of copies of the minor allele for a 1 df additive test) plus two ancestry covariates (to control for population stratification), age at CATIE baseline (a proxy for both increased TD liability due to aging and cumulative exposure to typical antipsychotics), sex, and a multi-modal measure of current drug abuse (based on subject report, informant report, clinician impression, and urine/hair laboratory assessments) [Swartz et al., 2006]. There is no direct measure of amount/duration of previous antipsychotic exposure in CATIE. We used q-values to control the false discovery rate [Storey and Tibshirani, 2001]. Statistical power was estimated using QUANTO [Gauderman, 2002] assuming two independent variables, $N = 710$, TD prevalence of 30%, and a log-additive genetic model. (a) If this experiment were considered independently, a Bonferroni-corrected alpha of 1.8×10^{-5} yields 80% power to detect a genetic relative risk of 2.45 for $MAF = 0.10$, 1.85 for $MAF = 0.25$, and 1.75 for $MAF = 0.40$. (b) As we discuss below, it is more appropriate to use a genomewide association alpha of 2.5×10^{-8} which yields 80% power to detect a genetic relative risk of 2.95 for $MAF = 0.10$, 2.20 for $MAF = 0.25$, and 2.05 for $MAF = 0.40$. Under either scenario, power was adequate only for strong genetic effects.

Association analyses of the DME composite genotypes with a different TD measure than that used here were presented briefly elsewhere [Grossman et al., 2008]. The candidate gene-based SNP results presented here preceded and were independent from the genomewide association genotype data generated in this sample [Sullivan et al., 2008]. It is conservative to assume that the appropriate significance level is that for genomewide significance (i.e., $\sim 5 \times 10^{-8}$) [Pe'er et al., 2008].

We found that 207 of 710 subjects (29.2%) met modified Schooler–Kane criteria for probable TD at the CATIE baseline assessment or on subsequent visits. The majority of the sample was male (524/710, 73.8%), and the mean subject age was 40.9 (SD 11.1) years. Self-reported “race” was 56% European-American, 29% African-American, and 15% other/mixed. Only 40% of the sample did not have current clinically significant illicit drug or alcohol use. Subject genotyping completeness was high (median 100% 10th percentile 99.93%, and minimum 98.9%). SNP missingness was low (median 0%, 90th percentile was 0.14%, and the maximum was 1.4%). The median minor allele frequency was 0.23 with inter-quartile range of 0.11–0.36.

The probable TD measure was analyzed in a series of logistic regression models with each of 2,580 SNPs and 10 composite DME genotypes as independent variables and 5 covariates (age, sex, two ancestry covariates, and a multi-modal index of substance use). The logistic regression beta coefficients for the SNP effects were symmetric and centered on zero

(median 0), a lambda-like estimate was 1.12, the minimum P-value was 0.0001, and the minimum q-value was 0.25. These results are not consistent with large inflations of observed test statistics consequent to stratification effects or with the presence of statistical significance beyond the chance level.

A selected set of associations plus markers widely studied in the literature are shown in Table I. The strongest association was for SLC18A2/rs2015586. A number of the more widely studied polymorphisms in the TD association literature are also shown in the lower portion of Table I.

Given that haplotype tagging guided SNP selection, we conducted haplotype analyses using 3-SNP sliding windows in subjects reporting European ancestry. For both TD phenotypes, the minimum omnibus test for association was 0.002. Haplotype analyses thus did not reveal stronger or more compelling associations in comparison with the single SNP analyses.

These findings of no significant associations are consistent with null findings in the TD literature of TD and inconsistent with previously reported associations in meta-analyses (e.g., COMT, DRD2, and SOD2) [Zai et al., 2007; Bakker et al., 2008]. The most likely reason for differences is the greater power in many meta-analyses.

Elucidating the genetic basis of TD is a worthy goal—a clinical test to identify individuals at high risk for TD with high sensitivity and specificity would enable the safer use of antipsychotic drugs, especially the older, higher risk conventional antipsychotics. This is particularly salient given that conventional antipsychotics are generally inexpensive and as efficacious as many newer antipsychotics [Lieberman et al., 2005].

In this study of 710 individuals with schizophrenia from the CATIE study who were comprehensively genotyped to capture common genetic variation in 128 candidate genes, no single or multi-marker statistical test reached statistical significance after correction for multiple comparisons. These analyses do not provide support for measured genetic variation in any of these candidate genes as important in the etiology of TD.

Although these results are consistent with the generally poor performance of candidate gene studies for complex human phenotypes [Altshuler and Daly, 2007], the negative findings should be considered in the context of the following limitations. First, the sample size was sufficient only to detect genetic variants of strong effect and detection of variants in the range typical for complex traits was unlikely. Second, causal genetic variation could exist in these candidate genes but was not directly or indirectly measured by the genetic variants analyzed here (e.g., less common SNPs, copy number variation, or other types of non-SNP genetic variation). Third, despite the use of standardized and repeated assessments of TD, it is possible that the phenotype or an important covariate was not measured with sufficient precision.

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TABLE I

Selected Associations With Probably Tardive Dyskinesia

Gene	Marker	Chr	Base pair	Alleles		Gene product	Probable TD			
				Ref	Alt		OR	Statistic	P-value	q-value
<i>GRM7</i>	rs1564843	3	7592158	T	C	Glutamate receptor, metabotropic 7	0.5739	-3.366	0.000762	0.47
<i>GRM7</i>	rs7614915	3	7595382	T	C	Glutamate receptor, metabotropic 7	0.5674	-3.311	0.00093	0.47
<i>GRM7</i>	rs1485174	3	7595828	T	C	Glutamate receptor, metabotropic 7	0.5633	-3.353	0.000799	0.47
<i>GRM8</i>	rs6957435	7	126628326	C	T	Glutamate receptor, metabotropic 8	0.6936	-2.861	0.004229	0.81
<i>GRM8</i>	rs3808117	7	126631770	C	A	Glutamate receptor, metabotropic 8	0.6109	-2.814	0.004886	0.81
<i>ADCY8</i>	rs16904354	8	131858802	A	G	Adenylate cyclase 8 (brain)	0.455	-3.026	0.002474	0.79
<i>SLC18A2</i>	rs2619097	10	118982574	G	T	Solute carrier family 18 (vesicular monoamine), member 2	0.6042	-2.919	0.003508	0.81
<i>SLC18A2</i>	rs2015586	10	119011727	C	T	Solute carrier family 18 (vesicular monoamine), member 2	0.5971	-3.894	9.858e-5	0.25
<i>CREBBP</i>	rs129968	16	3731262	G	A	cAMP responsive element binding protein 1	0.658	-3.028	0.002464	0.79
<i>SLC17A7</i>	rs11672810	19	54635590	A	G	Solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7	0.6255	-3.567	0.000361	0.46
<i>PRNP</i>	rs6052778	20	4637236	C	T	Prion protein	1.692	3.065	0.002177	0.79
<i>CACNG2</i>	rs738977	22	35338874	T	C	Calcium channel, voltage-dependent, gamma subunit 2	0.6689	-2.803	0.005067	0.81
<i>CACNG2</i>	rs2267348	22	35343113	C	G	Calcium channel, voltage-dependent, gamma subunit 2	0.6051	-2.816	0.004859	0.81
<i>GRIA3</i>	rs2187797	X	122154922	T	G	Glutamate receptor, ionotropic, AMPA 3	0.5936	-2.862	0.004215	0.81
<i>GRIA3</i>	rs4825838	X	122160374	G	A	Glutamate receptor, ionotropic, AMPA 3	1.622	2.807	0.005006	0.81
<i>DRD3</i>	rs6280	3	115373505	C	T	Dopamine receptor D3	0.9727	-0.205	0.84	0.97
<i>SOD2</i>	rs732498	6	160011550	A	G	Superoxide dismutase 2, mitochondrial	1.113	0.773	0.44	0.93
<i>SOD2</i>	rs8031	6	160020630	A	T	Superoxide dismutase 2, mitochondrial	0.9713	-0.221	0.82	0.97
<i>SOD2</i>	rs5746151	6	160021310	A	G	Superoxide dismutase 2, mitochondrial	1.005	0.019	0.98	0.98
<i>SOD2</i>	rs5746105	6	160032628	C	T	Superoxide dismutase 2, mitochondrial	1.156	1.114	0.27	0.90
<i>HTR2A</i>	rs6313	13	46367941	T	C	5-Hydroxytryptamine receptor 2A	1.153	1.152	0.25	0.90
<i>CYP2D6</i>	Composite	22	40856827	Wt	Mut	Cytochrome P450, family 2, subfamily D, polypeptide 6	0.9363	-0.394	0.69	0.95
<i>HTR2C</i>	rs6318	X	113871991	C	G	5-Hydroxytryptamine receptor 2C	1.227	1.117	0.26	0.90

The upper half (rows 1–15) of the table shows the 15 associations with the smallest *P*-values. The lower half (rows 16–23) contains polymorphisms that have been widely studied in the literature. Genomic positions are per UCSC hg18/NCBI build 36. OR is odds ratio from logistic regression. Statistic is the 1 df Wald test along with its corresponding *P*- and *q*-values.