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Association of tardive dyskinesia with variation in *CYP2D6*: Is there a role for active metabolites?

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Abstract

Background—The aim of this study was to examine whether there was an association between tardive dyskinesia (TD) and number of functional *CYP2D6* genes.

Methods—A Caucasian sample of 70 patients was recruited in 1996–1997 from South London and Maudsley National Health Service (NHS) Foundation Trust, UK. Subjects had a DSM-III-R diagnosis of schizophrenia and were treated with typical antipsychotics at doses equivalent to at least 100 mg chlorpromazine daily for at least 12 months prior to assessment. All patients were genotyped for *CYP2D6* alleles*3–5, *41, and for amplifications of the gene.

Results—There were 13 patients with TD. The mean (standard deviation (SD)) years of duration of antipsychotic treatment in TD-positive was 15.8 (7.9) vs TD-negative 11.1 (7.4) ($p=0.04$). Increased odds of experiencing TD were associated with increased ability to metabolize *CYP2D6*, as measured by genotypic category (odds ratio (OR)=4.2), increasing duration in treatment (OR=1.0), and having drug-induced Parkinsonism (OR=9.7).

Discussion—We found a significant association between *CYP2D6* genotypic category and TD with the direction of effect being an increase in the number of functional *CYP2D6* genes being associated with an increased risk of TD. This is the first study to examine the association between

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Conflicts of interest

KJ Aitchison has received consultancy fees from companies including Johnson and Johnson, Roche Diagnostics and Roche Molecular Systems, and has previously sat on advisory boards for various companies including Johnson and Johnson. All other authors declare no conflict of interest.

TD and *CYP2D6* in Caucasians with this number of genotypic categories. In the future, metabolomics may be utilized in the discovery of biomarkers and novel drug targets.

Keywords

Cytochrome P450; genotype; antipsychotic; tardive dyskinesia; Parkinsonism

Introduction

Tardive dyskinesia (TD) is an abnormal involuntary movement disorder associated with sustained exposure to antipsychotics, characterized by orofacial dyskinesia and choreoathetoid movements of the trunk and limbs. TD is a particularly concerning adverse drug reaction of antipsychotic medication, as it may be irreversible, and hence may impact on the long-term quality of life of patients with schizophrenia (Kane, 1999). The occurrence of TD is thought to be influenced by genetic susceptibility (Morgenstern and Glazer, 1993), as well as by factors such as increasing age (Quinn et al., 2001), female gender (Smith and Baldessarini, 1980), duration of treatment with antipsychotic medication (Jeste and Kelsoe, 1997), and drug-induced Parkinsonism (DIP) (Muscettola et al., 1999). DIP resembles idiopathic Parkinson's disease, which is characterized by the triad of bradykinesia, rigidity and tremor, except that asymmetrical distribution and the classical pill-rolling tremor are less common in the drug-induced form. The prevalence of TD from antipsychotic treatment TD is approximately 20% (Kane and Smith, 1982). Other studies have shown point-prevalence of 5–45% in psychiatric inpatients and 30% among psychiatric outpatients (Jeste and Wyatt, 1981).

CYP2D6 is involved in the metabolism of most typical antipsychotic drugs, including haloperidol (Llerena et al., 1992), fluphenazine (Shin et al., 1999), and zuclopenthixol (Jaanson et al., 2002). It is encoded by the *CYP2D6* gene, which is located on chromosome 22 (22q13). There are over 100 allelic variants of the enzyme (see www.cypalleles.ki.se), resulting in four different phenotypes with respect to *CYP2D6* metabolizer status. Poor metabolizers (PMs) have two alleles that do not encode active *CYP2D6* enzyme (non-functional or null alleles), intermediate metabolizers (IMs) have one reduced activity allele and one non-functional allele or two reduced activity allele, extensive metabolizers (EMs) have at least one functional allele, and ultrarapid metabolizers (UMs) possess excess enzymatic activity due to multiple copies of functional alleles (3–13) resulting from gene amplification (Ingelman-Sundberg, 2005). The distribution of *CYP2D6* functionality shows ethnic differences; for example, up to 10% of European Caucasians are PMs, in comparison to only 1% of Asians (Aitchison et al., 2000).

A meta-analysis of 12 studies reported on the impact of *CYP2D6* variants on TD risk in various ethnicities, and concluded that lack of *CYP2D6* functionality may predispose patients with schizophrenia treated with antipsychotics to TD (Patsopoulos et al., 2005). A non-significant association between the *CYP2D6* PM phenotype and TD was shown in 516 severely mentally ill patients in North America (De Leon et al., 2005). Further studies on Chinese patients with schizophrenia rated for TD concluded that the *CYP2D6*10IM* allele may be associated with TD (Liou et al., 2004); whereas a study on Slovenian Caucasians

found no association between TD and other antipsychotic-induced extrapyramidal disorders with *CYP2D6* genotype (Plesnicar et al., 2006). Finally, in 110 TD-positive and 92 TD-negative Korean patients with schizophrenia, males with 1 PM or IM *CYP2D6* allele had greater odds of TD than males with wild-type alleles (OR=2.10, 95% CI 0.93–4.74, p=0.07) (Nikoloff et al., 2002). In view of these conflicting results, we examined the association between all four categories of *CYP2D6* functionality and TD in an English Caucasian sample from South London, UK.

Methods

Subjects

This was a cross sectional study of all consecutive outpatients from a clinic in a particular catchment area of Bethlem, South London and Maudsley NHS Foundation Trust, UK. Recruitment included some current patients but was mostly from records and contact by letter, via the National Schizophrenia Fellowship through letters to branches, talks at meetings and contact with patients directly or through parents. Seventy patients were enrolled over a one-year period (1996–1997). Subjects had a DSM-III-R diagnosis (American Psychiatric Association, 1987) of schizophrenia determined by the Structured Clinical Interview for DSM Disorders (Spitzer et al., 1990). They were treated with typical antipsychotics at doses equivalent to at least 100 mg chlorpromazine daily for at least 12 months prior to assessment. No changes in treatment regimen were made for at least three months prior to assessment. The study was approved by the local Research Ethics Committee. Of 70 patients, 68 had information on antipsychotics: 23 (32.9%) were on haloperidol decanoate, 16 (22.9%) on flupentixol decanoate, 16 (22.9%) on fluphenazine decanoate, 6 (8.6%) on thioridazine, 5 (7.1%) on chlorpromazine, 1 (1.4%) on zuclopenthixol decanoate and oral pimozide and another person (1.4%) was on fluphenazine decanoate and oral sulpiride. All 70 patients were examined for the presence of TD by the Abnormal Involuntary Movements Scale (AIMS) (US Department of Health, Education and Welfare, 1974), and the Schooler and Kane criteria were employed to make a research diagnostic criteria (RDC) diagnosis of probable TD (Schooler and Kane, 1982). Our sample consisted of English Caucasian patients treated with typical antipsychotics with antipsychotic-induced adverse reactions including movement disorders. This involved a history of at least three months' total cumulative antipsychotic exposure, the presence of at least 'moderate' abnormal, involuntary movements in one or more body areas or at least 'mild' movements in two or more body areas (face, lips, jaw, tongue, upper extremities, lower extremities, trunk), and absence of other conditions that might produce abnormal involuntary movements. For the 66 patients with DSM-III-R schizophrenia, a further assessment using the AIMS was made between two and six weeks after the initial assessment, and persistent TD was confirmed if the above criteria were still fulfilled. These sixty-six subjects were also examined for the presence of DIP by Webster's Rating Scale for Parkinsonism (WRSP) (Webster, 1968).

CYP2D6 genotyping

DNA was extracted from blood collected in EDTA tubes using the Nucleon II kit (then supplied by Nucleon Biosciences, UK; current kit equivalent the Nucleon BACC2 kit, GE

Health Care Europe, Amersham, UK). All genotyping was performed blind to the patients' clinical status. Genotyping for all the functional allelic variants common in Caucasians was undertaken. These comprised the following: *CYP2D6*41* (IM), *CYP2D6*3* (PM), *CYP2D6*4* (PM), *CYP2D6*5* (PM), and gene amplification (UM if a functional variant is amplified). Genotyping for the *CYP2D6*2* allele with promoter variant was undertaken by KBiosciences Ltd (Hoddesdon, UK), providing the company with the sequence surrounding the 2850C>T (rs16947) and -1584C>G single-nucleotide polymorphisms (SNPs). The three non-functional alleles (*3, *4, and *5) comprise the large majority of the mutant alleles responsible for the PM phenotype (Zanger et al., 2004) in Caucasians, and these and *CYP2D6* gene amplifications were performed as previously described (Aitchison et al., 1999). In addition, for cases positive on both the *CYP2D6* gene amplification assay and the *CYP2D6*4* polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, a further nested PCR followed by restriction enzyme digestion was employed, also as previously described (Aitchison et al., 1999).

In the eight cases where, following this genotyping, it was not possible to resolve calls between allelic variants (*CYP2D6*35*, *CYP2D6*41*, or *CYP2D6*2A*), the AmpliChip CYP450 Test (Roche Molecular Systems, Alameda, California, USA) was also employed. The AmpliChip CYP450 Test uses Affymetrix technology, with the original Affymetrix CYP450 array having been made more comprehensive (e.g. including *CYP2D6*5* and gene amplifications) by work conducted by Roche Molecular Systems, Inc. It detects 33 polymorphisms and mutations in *CYP2D6*, using multiple assays for the same variant, thereby generating a high specificity and sensitivity. The assay was conducted according to the manufacturer's instructions (Roche Molecular Systems, Inc., 2005). Data analysis was performed by the GeneChip Operating Software (GCOS) and the AmpliChip CYP450 Data Analysis Software was used to generate a report summarizing the genotype call and listing the corresponding identified alleles. The report was checked by hand versus the output detailing the call for each variant detectable by the array, in order to generate calls for subtypes of alleles such as *CYP2D6*35*.

Statistical analysis

All the analyses were performed using STATA 12.0 and SPSS version 13.0 for Windows. Independent *t*-tests were used to test differences in age and duration of antipsychotic treatment between those with TD (TD-positive) and those without (TD-negative), while the Chi-square test was utilized to test differences in proportions between groups for sex and DIP. A logistic regression tested the association between TD and genotypic category controlling for age, gender, duration of antipsychotic treatment, and DIP. The distributions were skewed to the left, yet both groups had similar medians and variances, thus we performed the more appropriate Wilcoxon rank-sum (Mann-Whitney) test, which found a statistically significant difference in the underlying distribution of duration of treatment between persons who had TD and those that did not ($z = -2.075$, $p = 0.0379$). The group of patients that had TD had higher ranks of duration of treatment. Genotypic category was treated as a continuous variable with the following levels: PM/PM=0, PM/IM=0.5, EM/PM=1, EM/IM=1.5, EM/EM=2, UM/IM=2.5, UM/EM=3, as the ability to metabolize

CYP2D6 is hypothesized to incrementally increase across these allelic combinations. A *p* value of 0.05 was interpreted as significant for all analyses.

Results

Patients with TD did not differ from those without TD in terms of sex or age; however, they did have a significantly longer duration of antipsychotic treatment ($t=-2.05$, $df=68$, $p=0.04$), and also had a greater proportion with DIP ($X^2=7.65$, $df=1$, $p=0.006$). Thirtyfive out of 70 patients (50.0%) met the criteria for DIP, and 13 of 70 (18.6%) met the criteria for TD. These results are summarized in Table 1.

The main predictor of interest was *CYP2D6* genotypic category, with alleles being classified according to the Human Cytochrome P450 (CYP) Allele Nomenclature Committee (www.cypalleles.ki.se). Seven genotypic categories were created, each representing ascending levels of functional alleles. The frequencies of the *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*3* (PMs) *CYP2D6*2* (varies) and *CYP2D6*41* (IM) alleles were 0.221, 0.014, 0.021, 0.229, and 0.20 respectively. All of the calls made by the CYP450 Test were consistent with the presence of a *CYP2D6*2* variant as determined by the prior genotyping. Three out of 70 (4.3%) of cases were UMs, of which none was positive for the null alleles tested.

After adjusting for known predictors of TD, each level increase in genetic category (ability to metabolize *CYP2D6*) increased the odds of experiencing tardive dyskinesia by 4.04 (95% confidence interval (CI): 1.09–14.95). As hypothesized, duration of antipsychotic treatment (odds ratio (OR)=1.248, 95% CI: 1.033–1.507) and DIP (OR=9.71, 95% CI: 1.38–68.37) were also significantly associated with TD. These results are summarized in Table 2. The association between *CYP2D6* genotypic category and TD is shown in Figure 1.

Discussion

We found a significant association between greater ability to metabolize *CYP2D6*, as measured by increasing number of functional alleles, and tardive dyskinesia. This is the first study to examine the association between TD and *CYP2D6* in Caucasians when genotyped comprehensively enough to generate the genotypic category as described. The allele frequencies found in our sample were consistent with those reported previously for European Caucasians (Sachse et al., 1997). The prevalence of TD in our sample is 19% (13/70) which is also consistent with other studies (Jeste and Wyatt, 1981; Kane and Smith, 1982).

Consistent with our study, there are studies which found an association between *CYP2D6* and TD (Fu et al., 2006). In contrast to our study, there are other studies which have shown no association between *CYP2D6* and TD (De Leon et al., 2005). Poor metabolizers were 1.6 times more likely to suffer from TD compared to other patients with schizophrenia, although it was not significant in a meta-analysis of 12 studies (Patsopoulos et al., 2005). One possible interpretation of our findings is that metabolism of typical antipsychotics by *CYP2D6* produces toxic metabolites that are associated with increased risk of TD, such that individuals with a greater number of functional *CYP2D6* genes produce more such

metabolites. This hypothesis is only a speculation. The pharmacodynamic effects of most metabolites of typical antipsychotics have not been established; however, in the case of thioridazine, it is known that *CYP2D6* catalyzes the formation of mesoridazine, which has D2 blocking activity. Furthermore, in addition to generating active metabolites of antipsychotic drugs, *CYP2D6* also generates toxic metabolites. For example, with haloperidol, *CYP2D6* is involved in the production of haloperidol pyridinium, a highly neurotoxic metabolic product (Fang et al., 1995) which has been proposed to play a role in the emergence of haloperidol-induced extrapyramidal side-effects (Fang et al., 1997). Of note, the most commonly prescribed antipsychotic in our study was haloperidol. Moreover, *CYP2D6* is found in the nigrostriatal pathway. It is therefore possible that increased oxidative metabolism resulting from higher *CYP2D6* activity may be responsible for higher plasma or local neuronal levels of neurotoxic antipsychotic drug metabolites, and hence, increased risk for the development of TD and there is evidence of *CYP2D6* activity in various brain regions in the rat (Aitchison et al., 2010). Authors who have not found an association between TD and *CYP2D6* PM status have suggested that this may be explained by *CYP2D6* PMs having a low level of lifetime exposure to antipsychotics metabolized by *CYP2D6* due to severe intolerance (Kapitany et al., 1998). Similarly, it is possible that an association with UM status has been previously missed owing to *CYP2D6* UM individuals not remaining on antipsychotics associated with tardive dyskinesia.

Other cytochrome P450 enzymes such as *CYP1A2* (Basile et al., 2000) or *CYP3A5* (De Leon et al., 2005) are also involved in the metabolism of typical antipsychotics, and have been implicated in TD. However, subsequent studies investigating the putative association between *CYP1A2* and TD were negative (Schulze et al., 2001). In a published abstract there was no association between the *CYP1A2* C_{-164A} polymorphism and TD (Tsapakis et al., 2002). Other factors, e.g. the Ser9Gly SNP in the dopamine D3 receptor (Bakker et al., 2006), and polymorphisms in the serotonin (5-HT_{2A}) and 5-HT_{2C} receptors may also contribute to a vulnerability to TD, possibly in interaction with pharmacokinetic factors such as *CYP2D6*, *CYP1A2*, and *CYP17* (Segman et al., 2002). Movement disorders may be part of the pathophysiology of schizophrenia (Owens et al., 1982; Waddington et al., 1995) and hence one might expect overlap between genes associated with schizophrenia and genes associated with TD. The associations found with the *DRD3* (Bakker et al., 2006; Ebstein et al., 1997; Segman et al., 1999; Williams et al., 1998) are an example of such overlap. Drug availability may also be influenced by other factors such as plasma protein binding, drug transporters, nutrition, hormones and inflammatory cytokines (Morgan et al., 1998).

In agreement with previous findings, duration of treatment with antipsychotic medication differed between TD-positive and TD-negative groups (Smith and Baldessarini, 1980; Woerner et al., 1998), and DIP was significantly associated with TD (Kane et al., 1986; Woerner et al., 1998), but there was no apparent effect of age and sex on the presence of persistent TD in this sample. This may be attributable to the short duration of follow-up (six weeks). In the multicenter GENDEP pharmacogenomics trial (*n*=790), *CYP2D6* UM genotype was associated with a significantly lower dose of escitalopram, and a higher rate of a specific adverse drug reaction (nausea) on escitalopram (Keers et al., 2010).

In HIV-infected patients, oral metabolites have been found to be useful biomarkers for monitoring immune status (Ghannoum et al., 2013). The advantages include, but are not limited to, this being an easy to collect, noninvasive technique, and safer than blood to handle. Such methodology may well be useful to explore in patients with psychiatric diagnoses and treatment.

The limitations of this study include the following. First and foremost, the relatively small number affected with TD means that our finding may be false positive. Secondly, the fact that the sample was collected in 1996–1997, and clinical notes from many of the patients are no longer available to us, means that for these patients we are unable to establish the exact doses of the antipsychotics, nor other relevant clinical parameters, such as use of anticholinergic medications. With 13 patients with TD on seven different typical antipsychotics and seven genotypic categories, we do not have the power to test for a difference. The one patient with UM/IM was prescribed chlorpromazine, while one of the two patients with UM/EM was on flupentixol decanoate while the other was on haloperidol decanoate. Finally, patients were heterogeneous in terms of medication received (seven different antipsychotics being in the dataset). There were no data on the following: drug plasma concentrations, concomitant medication which could have increased the risk for TD either pharmacokinetically and/or pharmacodynamically (e.g. selective serotonin reuptake inhibitor, inhibitors of CYP2D6), and previous treatment with other antipsychotics. None of the patients was a ‘true’ PM. Those categorized as PM were actually heterozygotes as shown in Figure 1. There may be important overlap in the final expression of alleles. And part of the reason for analyzing like this was the small size. However, there are papers that have analyzed the data in the same way we did (for example, Huezo-Diaz et al., 2012). The strength of this study is that it is the first to examine the association of CYP2D6 genotype with tardive dyskinesia so comprehensively in Caucasians, including the relatively common IM and UM alleles.

In conclusion, in our sample, the number of functional *CYP2D6* genes was positively associated with an increased risk of TD, and we suggest that this could be due to the generation of neurotoxic metabolites. However, this hypothesis is only a speculation and requires replication, ideally with a larger prospective sample collection, in which clinical data collection includes complete drug histories and plasma levels of antipsychotic medications, and in which genotyping is performed in a similar, comprehensive manner.

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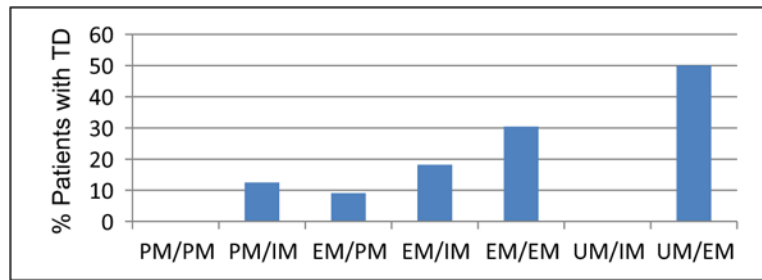


Figure 1.

Association between CYP2D6 genotypic category and tardive dyskinesia.

Genotypic category was treated as a continuous variable with the following levels: PM/PM=0, PM/IM=0.5, EM/PM=1, EM/IM=1.5, EM/EM=2, UM/IM=2.5, UM/EM=3, as the ability to metabolize CYP2D6 is hypothesized to incrementally increase across these allelic combinations. The risk of tardive dyskinesia (TD) increases with increasing CYP2D6 metabolizer status. Of those with UM alleles, 0/1 with UM/IM and 1/2 with UM/EM developed TD. EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer.

Table 1

Sociodemographic and clinical characteristics.

Clinical characteristic	TD positive, <i>n</i> =13	TD negative, <i>n</i> =57	Test statistic for difference between groups
Sex			$\chi^2=0.34$, <i>df</i> =1, <i>p</i> =0.561
Males, <i>n</i> (%)	8 (61.5%)	30 (52.6%)	
Females, <i>n</i> (%)	5 (38.5%)	27 (47.4%)	
Age, years, mean (SD)	39.6 (11.6)	42.0 (18.5)	<i>t</i> =0.45, <i>df</i> =68, <i>p</i> =0.653
Duration of antipsychotic treatment, years, mean (SD)	15.8 (7.9)	11.1 (7.4)	<i>z</i> = -2.075, <i>p</i> = 0.0379
Drug-induced Parkinsonism, <i>n</i> (%)	11 (84.6%)	24 (42.1%)	$\chi^2=7.65$, <i>df</i> =1, <i>p</i> = 0.006

TD: tardive dyskinesia; SD: standard deviation.

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Table 2

Association between tardive dyskinesia and clinical variables using logistic regression.

Variables	OR (95% CI)	<i>p</i> value
Genotypic category	4.2 (1.1–15.7)	0.032
Females	0.5 (0.08–2.6)	0.371
Age	0.9 (0.8–1.0)	0.141
Duration of treatment	1.248 (1.033–1.507)	0.022
Drug-induced Parkinsonism	9.7 (1.4–68.4)	0.022
constant	0.04 (0.0007–2.7)	0.135

CI: confidence interval; OR: odds ratio.

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