CHAPTER 2

THE ROLE OF DOPAMINE D3, 5-HT2A AND 5-HT2C RECEPTOR VARIANTS AS PHARMACOGENETIC DETERMINANTS FOR TARDIVE DYSKINESIA IN AFRICAN-CARIBBEAN PATIENTS WITH CHRONIC ANTIPSYCHOTIC TREATMENT

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ABSTRACT

Background: Tardive dyskinesia (TD) is associated with polymorphisms of the dopamine D3, serotonin 2A and 2C receptors (DRD3, HTR2A, and HTR2C respectively). This study investigated the possible relationship between TD and the polymorphisms Ser9Gly (DRD3), 102T>C (HTR2A), -1438G>A (HTR2A) and Cys23Ser (HTR2C) in African-Caribbean inpatients.

Methods: 126 patients with chronic antipsychotic treatment were genotyped. The assessment of TD was carried out with the Abnormal Involuntary Movement Scale (AIMS). The relationships between the carriership of the least frequent alleles and respectively orofaciolingual dyskinesia (sum of the items 1-4 of the AIMS), limb-truncal dyskinesia (sum of items 5-7 of the AIMS) and TD (sum of items 1-7 of the AIMS) were analyzed with ANCOVA comparing means with age as a covariate and stratification for carriers and non-carriers of the mutations. In addition, we conducted pre-planned t-tests to compare AIMS values of carriers of the combinations of alleles versus the corresponding non-carriers.

Results: In the study population, females with 9Ser carriership exhibited higher AIMS values than non-carriers. Male subjects with 9Ser carriership in combination with 23Ser or –1438A carriership exhibited higher AIMS values. In male patients also the combination of 23Ser and –1438A carriership increased TD.

Conclusion: The study clearly shows that the African-Carribean population differs form the Caucasian population in the association of TD with the polymorphisms studied and suggests that the associations of TD with the polymorphisms studied of the serotonin 2C and probably serotonin 2A receptors are the result of a changed susceptibility of the patients independent of the action of the antipsychotics on these receptors.

INTRODUCTION

Up to 75% of patients chronically exposed to typical antipsychotics may develop antipsychotic-induced movement disorders such as tardive dyskinesia (TD), tardive dystonia, parkinsonism, and akathisia [Gerlach 2002; Gerlach 1999]. Drug-induced movement disorders can produce physical handicaps; however, more often patients feel embarrassed about the abnormal movements. TD is often a reason for medication non-compliance and increases the risk of psychotic relapse [Gerlach 2002; Strejilevich et al., 2005]. TD is potentially irreversible and has a prevalence of around 30% in patients chronically exposed to antipsychotics [Glazer 2000; Kane et al., 1988]. Several risk factors have been suggested such as age, female gender, Negroid race, and co-morbidity with akathisia have been reported to predispose to TD [Glazer 2000; Kane et al., 1988; Morgenstern and Glazer 1993; van Harten et al., 1998; Wonodi et al., 2004]. However, this only accounts for a small amount of the variance in the occurrence of TD [Basile et al., 2002; Jeste and Caligiuri 1993] and hereditary predisposition may play a role as well [Muller et al., 2001; Rosengarten et al., 1994; Weinhold et al., 1981; Yassa and Ananth 1981; Youssef et al., 1989].

The dopamine D3 receptor (DRD3) is involved in TD in an experimental primate model [Malik et al., 2004] and its pharmacogenetics has been investigated in relation to TD [Bakker et al., 2006] and other forms of Movement Disorders [Chong et al., 2003; Coffey et al., 2005; Eichhammer et al., 2000; Mihara et al., 2002].

The serotonergic system interacts with the dopaminergic system and therefore 5-HT2A and 5-HT2C receptors (HTR2A and HTR2C gene, respectively) may be responsible for some of the dyskinetic effects of antipsychotics [Segman et al., 2000]. Indeed, genetic variations of HTR2A [Basile et al., 2001; Herken et al., 2003; Lattuada et al., 2004; Lerer et al., 2005; Segman et al., 2001; Tan et al., 2001] and HTR2C [Reynolds et al., 2005; Segman et al., 2000; Werge et al., 2003; Zhang et al., 2002] have been studied in relation to Antipsychotic-induced Movement Disorders or TD. However, since the 102T>C polymorphism of the 5-HT2A receptor is non-functional we also genotyped for the -1438G>A polymorphism, which is functional and in complete linkage disequilibrium with the 102T>C polymorphism [Ellingrod et al., 2003; Kouzmenko et al., 1999; Segman et al., 2001; Spurlock et al., 1998]

Ethnicity can be an important pharmacogenetic determinant [Frackiewicz et al., 1997] and a relative two-fold increase in risk for developing TD has been found for African-American patients versus white Americans [Morgenstern and Glazer 1993]. As far as we know there are no pharmacogenetic studies of TD in African-Caribbeans.

In the present study, we hypothesized that the carriership of a variant allele of the polymorphisms Ser9Gly (DRD3), -1438G>A (HTR2A), and Cys23Ser (HTR2C) would affect the severity of orofaciolingual and limb-truncal dyskinesias. Furthermore, we hypothesized that there might be additive effects of the polymorphisms.

METHODS

Subjects

In this study we used data from predominantly African-Caribbean inpatients of the Psychiatric Hospital of the Dutch Antilles in Curaçao. The results of this epidemiological study have previously been reported [van Harten et al., 1996]. One hundred and twenty six subjects (99 males, mean age 47.5 years; 27 females, mean age 55.4 years) met the inclusion criteria described elsewhere [van Harten et al., 1996], gave oral informed consent after full explanation of the study, and provided DNA for genotyping. The study protocol was approved by the local Curacao review board. Four trained raters assessed the patients and each patient was examined in the same way by two raters simultaneously. After the examination a joint decision was reached regarding the presence or absence of each EPS and, if present, the ratings were established by consensus. Furthermore, two medical doctors, blinded for the existence of antipsychotic-induced movement disorders, extracted clinical and demographic data from the patients' medical files.

TD was assessed with the Abnormal Involuntary Movement Scale (AIMS), which includes items for orofaciolingual and limb-truncal dyskinesias[American Psychiatric Association.Task force on tardive dyskinesia 1992]. For the measurement of orofaciolingual dyskinesia (TDof) and limb-truncal dyskinesia (TDlt) we summed items 1-4 and items 5-7 of the AIMS score, respectively. Furthremore, we calculated TDsum, which is the sum of both TDof and TDlt scores (AIMS 1-7).

Medication

Two junior medical doctors, who were not aware of the existence of movement disorders in the subjects, assessed patients' medical files for information on the type, dose, and duration of the antipsychotic treatment[van Harten et al., 1998]. The dose of the antipsychotic medication was converted into chlorpromazine equivalents (CPZEQ), as described by Davis [Davis 1976].

DNA genotyping

Genomic DNA was extracted from EDTA whole-blood samples, as described previously [Miller et al., 1988]. Genotyping for Ser9Gly (DRD3), 102T>C (HTR2A), and Cys23Ser (HTR2C) was performed using standard polymerase chain reaction (PCR) protocols in combination with restriction fragment length polymorphism (RFLP) analysis, as described in the literature [Ebstein et al., 1997; Lannfelt et al., 1992; Warren, Jr. et al., 1993].

Genotyping for the polymorphism -1438G>A (HTR2A) was conducted by a fluorogenic 5'-exonuclease TaqMan® assay, ordered from Applied Biosystems as an Assay-On-Demand (C___8695278_10).

We labeled subjects heterozygous, hemizygous, or homozygous for a particular allele as carriers of that allele, because of the sample size of our study population. It should, however, be emphasized that no assumptions were made regarding the inheritance mode.

Statistics

Pearson Correlation was applied to study the correlations between age and TDof, TDlt, and TDsum. ANCOVA analyses were applied to compare the mean AIMS-values in carriers and non-carriers of 9Ser-, -1438A-, and 23Ser-alleles using age as a covariate. In addition, we conducted pre-planned t-tests to compare AIMS values of carriers of the following combinations of alleles versus the corresponding non-carriers. The combinations studied were 9Ser plus 23Ser (DRD3 and HTR2C), 9Ser plus -1438A (DRD3 and HTR2A), and 23Ser plus -1438A (HTR2C and HTR2A). P-values < 0.05 were regarded as significant.

Departure from Hardy-Weinberg Equilibrium was calculated for all polymorphisms except those of the X–chromosomal HTR2C gene. An online tool was applied for the Chi-square goodness-of-fit test (http://www.kursus.kvl.dk/shares/vetgen/_Popgen/genetik/applets/kitest.htm).

Since our analyses were replications of previously published findings in other populations and therefore hypothesis-driven corrections for multiple testing were not applied.

RESULTS

Demographic and clinical features of the subjects

One hundred and twenty six African-Caribbean subjects (99 males and 27 females) met the inclusion criteria. Table 1 shows the distribution (mean ± standard deviation) of age (years), and the current (mg /day chlorpromazine equivalents) and lifetime dose of antipsychotics (kg chlorpromazine equivalents). Table 1 also presents the various AIMS values for the total sample and per gender.

Table 1. The distribution of the age, daily use of antipsychotics (mg/day chlorpromazine equivalents, CPZ), life time dose of antipsychotics (kg chlorpromazine equivalents, CPZLIFE), and the AIMS values (presented as mean ± standard deviation).

	Male (99)	Female (27)	All (126)
Age (years)	47.5±13.0	55.4±13.3	49.2±13.4
CPZ (mg chlorpromzaine equivalents /day)	692.4±676.8	662.5±953.8	686.0±740.6
CPZLIFE (kg chlorpromzaine equivalents)*	3.90±3.21	4.00±3.21	3.92±3.19
Orofaciolingual AIMS (TDof)	2.9±3.5	3.1±3.5	2.9±3.5
Limb-truncal AIMS (TDlt)	0.9±1.4	0.7±1.3	0.8±1.4
AIMS 1-7 (TDsum)	3.7± 4.5	3.9±4.0	3.8±4.4

* Data available from only 93 patients (72 males + 21 females).

Genotype distribution and carriership frequencies

The distribution of the different genotypes is shown in Table 2. All genotypes were in Hardy-Weinberg equilibrium. Carriership is assessed as being carrier of the variant-alleles defined as the alleles of the least frequent homozygotes. Since all carriers except for 2 of the 102T-allele were also carrier of the -1438A-allele (data not shown), further analyses were only made with the functional polymorphism -1438G>A.

Table 2. Genotype distribution, χ^2-values for Hardy-Weinberg equilibrium, as well as the number (n) and percentage of allele positive subjects (carriers) in African-Caribbean patients.

Genotype	% of the total sample (n)	χ^2 value	Genetic variation	Total sample, % (n)	Males, % (n)	Females, % (n)
DRD3 Ser9Gly						
Gly9/Gly9	39.7 (50)	0.004	*non-carriers of 9Ser allele*	39.7 (50)	39.4 (39)	40.7 (11)
Gly9/Ser9	46.8 (59)		*carriers of the 9Ser allele*	60.3 (76)	60.6 (60)	59.3 (16)
Ser9/ Ser9	13.5 (17)					
HTR2C Cys23Ser						
Cys23/Cys23	61.9 (78)	–	*non-carriers of 23Ser allele*	61.9 (78)	70.7 (70)	29.6 (8)
Cys23/Ser23	11.1 (14)		*carriers of the 23Ser allele*	38.1 (48)	29.3 (29)	70.4 (19)
Ser23/Ser23	27.0 (34)					
HTR2A -1438G>A						
-1438G/G	44.8 (56)	0.127	*non-carriers of -1438A allele*	44.8 (56)	47.5 (47)	34.6 (9)
-1438G/A	43.2 (54)					
-1438A/A	12.0 (15)		*carriers of the -1438A allele*	55.2 (69)	52.5 (52)	65.4 (17)

HTR2C is localized on the X-chromosome; males can therefore only be hemizygous for the Cys23Ser polymorphism. For males, the hemizygosities for the 23Cys and the 23Ser alleles are denoted as Cys23/Cys23 and Ser23/Ser23, respectively.

The effects of antipsychotic medications

The majority (n=114) of the patients used antipsychotics on the day of examination. Of these 114 patients, only 7 patients were using an atypical antipsychotic as monotherapy (risperidone in all cases). In addition to those 7 patients, there was also 1 patient who used risperidone, however in combination with a classical neuroleptic.

All patients used antipsychotics for at least 245 days. The lifetime dose of antipsychotics (CPZLIFE) amounted in males to 3.90±3.21 and in females to 4.00±3.21 kgm chlorpromazine equivalents (mean ± SD).

The daily use of antipsychotics (as expressed by CPZ) as well as the lifetime exposure to antipsychotics (as expressed by CPZLIFE) did not differ significantly between the different classes analysed (data not shown).

The effects of the age on TDof, TDlt, and TDsum

There was no significant correlation between age and TDlt neither in males nor in females.

TDsum however correlated significantly with age in females (Pearson's correlation coefficient=0.46; p=0.017). Furthermore, there was a positive correlation between age and TDof in males which however did not reach statistical significance (p=0.058) and in females (Pearson's correlation coefficient=0.46; p=0.016).

Based on these findings we chose to correct for age effects in ANCOVA analysis.

The effects of allele carrierships on TDof values

After adjustment for age in male patients there were no statistically significant differences between the TDof values of carriers or non-carriers of the 9Ser allele of the Ser9Gly polymorphism (DRD3), of the -1438A-allele of the -1438G>A polymorphism (HTR2A), and of the 23Ser allele of the Cys23/Ser23-polymorphism (HTR2C) if analysed separately. However, male patients carrying both 9Ser- and 23Ser-alleles had almost significantly higher TDof-values than those without these two alleles (3.26 and 1.30, respectively; p=0.050).

Subjects carrying both 9Ser and -1438A alleles also exhibited higher AIMS values when compared to the non-carriers of these alleles. The difference was however not significant (1.76 and 3.51 for non-carriers and carriers, respectively; p=0.062).

Furthermore, those carrying 23Ser- and -1438A-alleles simultanously exhibited significantly higher AIMS orofaciolingual values than the corresponding non-carriers (4.55 and 2.39, respectively; p=0.026).

After adjustment for age in female patients carriers of the 9Ser-, -1438A-, and 23Ser- alleles (DRD3, HTR2A and HTR2C genes, respectively) exhibited higher TDof values than the corresponding non-carriers. However, of these three genetic variations only carriers of the 9Ser-allele of the Ser9Gly polymorphism (DRD3) had significantly higher TDof values than non-carriers (4.17 vs. 1.66; P =0.042).

Carriership of the -1438A-allele or the 23Ser-allele on top of carriership of the 9Ser-allele did not lead to an additional statistically significant increase in TDof .

Moreover, the combined carriership of the -1438A- and the 23Ser-alleles did not lead to a statistical significant increase in TDof. An overview of these data is given in Table 3.

The effects allele carrierships on TDlt values

After adjustment for age there were no statistically significant differences in both genders between the TDlt values of carriers or non-carriers of the 9Ser-allele of the Ser9Gly polymorphism of the DRD3 gene, of the -1438A-allele of the -1438G>A-polymorphism of the HTR2A gene and of the Ser23-allele of the Cys23Ser polymorphism of the HTR2C gene if analysed separately.

However, males carrying both the 9Ser- and the 23Ser-alleles exhibited higher TDlt-values than the corresponding non-carriers, with the difference being almost statistically significant (1.20 versus 0.41 AIMS points; p=0.057), but not for patients carrying both the 9Ser- and -1438A- alleles or both the 23Ser- and -1438A-alleles.

In females there were no statistically significant differences between TDlt-values in patients carrying either one of the following allelic combinations 9Ser/23Ser, 9Ser/-1438A, or 23Ser/-1438A. An overview of these data is given in Table 3.

The effects of allele carrierships on TDsum values

When analyzed separately, carriership of 9Ser- (DRD3), -1438A- (HTR2A), and 23Ser- (HTR2C) alleles were not accompanied with significantly different age-adjusted TDsum values; neither in males nor in females.

In males, however, statistically significant higher TDsum-values were found in male patients carrying the combinations: 9Ser- and 23Ser-alleles (4.45 and 1.71 for carriers and non-carriers of this combination, respectively; p=0.036), 9Ser- and -1438A-alleles (4.49 and 2.09 for carriers and non-carriers of this combination, respectively; p=0.048), and 23Ser- and -1438A- alleles (5.77 and 3.08 for carriers and non-carriers of this combination, respectively; p=0.034).

In females, we observed no statistically significant differences in TDsum-values between carriers and non-carriers of the 9Ser-/23Ser- or the 23Ser-/-1438A-allelic combinations. However, female carriers of the 9Ser-/-1438A-allelic combination exhibited significantly higher TDsum values than the corresponding non-carriers (5.63 versus 0.23, respectively; p=0.032) . An overview of these data is given in Table 3.

Table 3. An overview of the effects of the carriership of polymorphisms on TDof, TDlt and TDsum scores. TD values are presented for carriers versus non-carriers with the corresponding p-values. See text for further details.

Genetic variation	TDof	TDlt	TDsum
Males			
9Ser/23Ser combination Carriers (N=19) Non-carriers (N=28)	**3.26 *vs* 1.30; p=0.050**	1.20 *vs* 0.41; p=0.057	**4.45 *vs* 1.71; p=0.036**
9Ser/-1438A combination Carriers (N=36) Non-carriers (N=22)	3.51 *vs* 1.76; p=0.062	0.98 *vs* 0.33; p=0.082	**4.49 *vs* 2.09 ; p=0.048**
23Ser/-1438A combination Carriers (N=19) Non-carriers (N=37)	**4.55 *vs* 2.39 ; p=0.026**	1.22 *vs* 0.69; p=0.182	**5.77 *vs* 3.08; p=0.034**
Females			
9Ser allele carriership Carriers (N=16) Non-carriers (N=11)	**4.17 *vs* 1.66; p=0.042**	0.39 vs 1.16; p=0.140	4.56 *vs* 2.81; p=0.223
9Ser/23Ser combination Carriers (N=12) Non-carriers (N=4)	4.46 *vs* 1.98; p=0.178	0.56 *vs* 0.47; p=0.901	5.02 *vs* 2.45; p=0.244
9Ser/-1438A combination Carriers (N=9) Non-carriers (N=3)	**5.34 vs 0.21; p=0.015**	0.29 vs 0.03; p=0.753	**5.63 vs 0.23; p=0.032**
23Ser/-1438A combination Carriers (N=14) Non-carriers (N=4)	3.62 *vs* 1.34; p=0.222	0.97 *vs* 0; p=0.208	4.59 *vs* 1.30; p=0.125

DISCUSSION

Several studies have reported the relationship between TD and Ser9Gly, 102T>C, and Cys23Ser polymorphisms of dopamine D3, serotonin 2A, and 2C receptors, respectively, in different populations [Chong et al., 2003; Lerer et al., 2005; Lerer et al., 2002; Liao et al., 2001; Segman et al., 2000]. This is the first published pharmacogenetic study of TD in predominantly African-Caribbean.

The present study suggests that the pharmacogenetic associations of TD are different in African-Caribbeans from those in Caucasians, specifically regarding polymorphism of dopamine D3 (Ser9Gly polymorphism), serotonin 2A

(102T>C and -1438G>A polymorphisms) and 2C receptors (Cys23Ser polymorphism). Furthermore, our data suggest that the effects of the genotypes studied might be clinically significant.

The antipsychotics used have a low affinity to serotonin 2C and (in majority) to 2A receptors. Therefore, our data suggest that in the population studied the association of TD with Cys23Ser polymorphism of the 5-HT2C receptor and probably also with the -1438G>A polymorphism of the 5-HT2A receptor is likely to be independent of the direct action of the antipsychotics on these receptors.

The association observed is probably the result of a distinct endogenous susceptibility of the patients. In other words, these patients seem to have a higher susceptibility for TD independent of the antipsychotic used. Notably, African-Americans in the Yale study, which also included white Americans, displayed an almost doubled relative risk for TD [Eastham et al., 1996; Morgenstern and Glazer 1993]. Most of the patients investigated in this study were African-Caribbean from the Netherlands Antilles (Curaçao). African-Caribbeans have ethnic roots similar to those of native Africans [Page 1997].

The data support a gender specific analysis, although stratified analysis reduces the power of the study by lowering the number of patients in each group. Since it has been advocated that orofaciolingual and limb-truncal dyskinesias must be considered as two distinct phenotypes [Lerer et al., 2005], we analysed these forms of TD separately. However in our limited study population we did not find different genetic effects except for the fact that the effects did not reach statistical significance for limb-truncal dyskinesia.

Lerer et al. [2002] summarized data obtained from 780 patients, whereas Bakker et al. [2006] analysed the data of 695 patients with TD and 915 without TD. Both concluded that tardive dyskinesia was significantly associated with the 9Gly-allele carrier status, also when controlling for age and gender. It seems, however, that the effect of Ser9Gly is opposite in direction in our African-Caribbean sample. In females 9Ser carriership was associated with higher AIMS scores. Furthermore in males 9Ser carriership combined with either 23Ser or –1438A carriership increased AIMS scores. Also, in the Chinese population Ser9/Ser9 [Lerer et al., 2005] was found to be associated with TD; however, no gender-effect was described. Additionally, Lerer et al. [2002] have also reported an overrepresentation of the 9Ser alelle in TD patients in their Vienna subsample.

Lerer et al. [2005] performed a combined analysis of a large multicentre patient sample and found an association between limb-truncal, but not orofaciolingual TD, and the 102T>C polymorphism of the 5-HT2A receptor with an increasing risk for C-allele carriers in older, but not in younger patients. Segman et al. [2001] studied additional to the 102T>C polymorphism the -1438G>A polymorphism and found an excess of both 102C- and -1438G-alleles in patients with limb-truncal TD.

Since the 102T>C polymorphism is non-functional and is in linkage disequilibrium with the -1438G>A polymorphism we analysed our data with the former polymorphism. In our African-Caribbean population, however, the –1438A carriers

(whose carriership was fully associated with carriership of 102T allele) if combined with 9Ser or 23Ser carriership showed higher orofaciolingual dyskinesia scores in men only in the whole age group. In females the effect of the -1438G>A polymorphism could not be demonstrated. The size of the female population in our study is, however, a limitation. The effects of the -1438G>A polymorphism were comparable between orofacial and limb-truncal TD, but did not reach statistical significance in the latter.

Segman et al. [2000] described for the Cys23Ser polymorphism of the 5-HT2C receptor an excess of 23Ser alleles in orofaciolingual dyskinesia cases in females only. For orofaciolingual dyskinesia our data are so far in accordance with the study of Segman et al. [2000] that 23Ser carriership (HTR2C) in combination with 9Ser carriership (DRD3) increases the magnitude of the effect (with approximately 2 AIMS points), however only in male patients. In females we found no statistically significant effects, but this may result from the low number of female patients. (27 vs. 55 in the study of Segman et al. [2000]). The additivity of the effects of the DRD3 and HTR2C polymorphisms in our male patients is therefore similar to what has been reported by Segman et al.[2000]. However, in our population the 9Ser carriership –but not 9Gly carriership– showed higher TDof scores.

This study in African-Caribbeans shows for the first time that this population appears to show different associations between TD and the Ser9Gly polymorphism of the D3 receptor and the -1438G>A polymorphism of the 5-HT2A receptor. For the Cys23Ser polymorphism of the 5-HT2C receptor predominantly a different gender effect compared to Segman et al. [2000] was observed, although both studies have limited sample sizes.

Since the effects of Ser9Gly, -1438G>A, and Cys23Ser polymorphisms on the susceptibility for TD vary in different ethnic groups, it might be speculated that polymorphisms other than these polymorphisms confer the susceptibility for TD. In fact, these hypothetical key-polymorphisms for TD in our population might be inherited together with the polymorphisms we studied (through linkage disequilibrium). It is well-known that the extent of linkage disequilibria varies with ethnicity and therefore in other populations these causal key-polymorphisms may be inherited together with other polymorphisms.

Furthermore, the effects of the polymorphisms of the 5-HT2C and probably also the 5-HT2A receptors observed in this study in patients using neuroleptics, agents with low binding affinities for 5-HT2C and in the majority for 5-HT2A receptors, seems to indicate that there is possibly an intrinsic change in sensitivity of the patient rather than a drug specific effect. Independent of the theoretical explanation, the results of this study might assist in the future development of pharmacogenetic testing for predicting TD in African-Caribbean schizophrenic patients.

Because of the small sample size, the results of the present study should be considered as preliminary and require confirmation in larger samples, which however, especially for this African-Carribean population with its restricted size might be difficult.

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