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The role of dopamine D3, 5-HT2A and 5-HT2C receptor variants as pharmacogenetic determinants in tardive dyskinesia in African-Caribbean patients under chronic antipsychotic treatment: Curacao extrapyramidal syndromes study IX

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The role of dopamine D₃, 5-HT₂ₐ and 5-HT₂c receptor variants as pharmacogenetic determinants in tardive dyskinesia in African-Caribbean patients under chronic antipsychotic treatment

Curaçao extrapyramidal syndromes study IX

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Abstract

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. One hundred and twenty-six patients under 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 the respective orofaciolingual dyskinesia (TDof) (sum of the items 1–4 of the AIMS), limb-truncal dyskinesia (TDlt) (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. 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. The study clearly shows that the African-Caribbean population differs from the Caucasian population with regard to the association of TD with the polymorphisms studied and suggests that the association of TD with the studied polymorphisms of the 5-HT₂c and probably of the 5-HT₂ₐ receptor are the result of a changed susceptibility of the patients, independent of the action of the antipsychotics on these receptors.

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

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 (for review see Bakker et al. (2006)) and other forms of movement disorders (Eichhammer, et al., 2000; Mihara, et al., 2002; Chong, et al., 2003; Coffey, et al., 2005).

The serotonergic system interacts with the dopaminergic system and therefore 5-HT2A and 5-HT2C receptors (HTR2A and HTR2C, 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; Segman, et al., 2001; Tan, et al., 2001; Herken, et al., 2003; Lattuada, et al., 2004; Lerer, et al., 2005) and HTR2C (Segman, et al., 2000; Zhang, et al., 2002; Werge, et al., 2003; Reynolds, et al., 2005) genes have been studied in relation to antipsychotic-induced movement disorders or TD. However, since the 102T>C polymorphism of the 5-HT 2A 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 (Spurlock, et al., 1998; Kouzmenko, et al., 1999; Segman, et al., 2001; Eillingrod, et al., 2003)

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 in African-American patients versus white Americans (Morgenstern and Glazer, 1993). As far as we know, there are no pharmacogenetic studies of TD in African-Caribbean patients.

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

Methods and Materials

Subjects

In this study, we used data from predominantly African-Caribbean inpatients of the Psychiatric Hospital of the Dutch Antilles in Curacao. 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, which has been 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 TDof and TDlt (American Psychiatric Association – Task force on tardive dyskinesia, 1992). For the measurement of TDof and TDlt, we summed items 1–4 and items 5–7 of the AIMS score, respectively. Furthermore, we calculated TDsum, which is the sum of both TDo 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 whole-blood samples to which EDTA was added, 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 (Lannfelt, et al., 1992; Warren, Jr. et al., 1993; Ebstein, et al., 1997).
Genotyping for the polymorphic −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 labelled 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 emphasised 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 in 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+23Ser (DRD3 and HTR2C), 9Ser+−1438A (DRD3 and HTR2A) and 23Ser+−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, hypothesis-driven corrections for multiple testing were not applied.

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

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

*Data available from only 93 patients (72 males + 21 females).
The effects of the age on TDof, TDlt and TDsum

There was no significant correlation between age and TDlt in both males and females. However, TDsum 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 $= 0.46$; $P = 0.016$).

On the basis of these findings, we chose to make corrections for age effects in ANCOVA analysis.

The effects of allele carrierships on TDof values

After adjustment was made for age, 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 analyzed separately. However, male patients carrying both 9Ser and 23Ser alleles had significantly higher TDof-values than those without these two alleles (3.26 and 1.30, respectively; $P = 0.051$).

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

Furthermore, those carrying 23Ser and −1438A alleles simultaneously exhibited significantly higher AIMS orofaciolinguinal 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 those in 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 (4.18 versus 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 values.

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 of allele carrierships on TDlt values

After adjustment was made for age, there were no statistically significant differences in both genders between the TDlt values of carriers or those of 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 analyzed 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, carrierships of 9Ser (DRD3), −1438A (HTR2A) and 23Ser (HTR2C) alleles were not accompanied by significantly different age-adjusted TDsum values both in males and in females.

However, in males, 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.

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 (Segman, et al., 2000; Liao, et al., 2001; Lerer, et al., 2002; Chong, et al., 2003; Lerer, et al., 2005). This is the first published pharmacogenetic study of TD in predominantly African-Caribbeans.

The present study suggests that the pharmacogenetic associations of TD in African-Caribbeans are different 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 genotypic studies might be clinically significant.

The antipsychotics used have a low affinity to 5HT2C and to 5HT2A receptors. Therefore, our data suggest that in the population studied, the association of TD with Cys23Ser polymorphism of the 5HT2C receptor and probably also with the −1438G>A polymorphism of the 5HT2A 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 (Morgenstern and Glazer, 1993; Eastham, et al., 1996). Most of the patients investigated in this study were African-Caribbeans 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 TDof and TDlt must be considered as two distinct phenotypes (Lerer, et al., 2005), we analyzed 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 TDlt.

Lerer et al. (2002) summarised data obtained from 780 patients, whereas Bakker et al. (2006) analyzed the data of 695 patients with TD and 915 without TD. Both concluded that TD was significantly associated with the 9Gly allele carrier status, also when controlling for age and gender. However, it seems that the effect of Ser9Gly is opposite in direction in our African-Caribbean sample. In females, 9Ser carrier was associated with higher AIMS scores. Furthermore, in males 9Ser carrier was combined with either 23Ser or 1438A carrier 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. In addition, Lerer et al. (2002) have also reported an overrepresentation of the 9Ser allele 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 TDlt, but not TDOf, and the 102T>C polymorphism of the 5HT2A receptor, with an increasing risk for C-allele carriers in older, but not in younger patients. In addition to the 102T>C polymorphism, Segman et al. (2001) studied the −1438G>A polymorphism and found an excess of both 102C and −1438G alleles in patients with TDlt.

Since the 102T>C polymorphism is non-functional and is in linkage disequilibrium with the −1438G>A polymorphism, we analyzed our data with the former polymorphism. However, in our African-Caribbean population, the −1438A carriers (whose carrier was fully associated with carrier of 102T allele) if combined with 9Ser or 23Ser carriership showed higher TDOf scores in men only in the whole age group. In females, the effect of the −1438G>A polymorphism could not be demonstrated. However, the size of the female population in our study is a limitation. The effects of the −1438G>A polymorphism were comparable between TDOf and TDlt, but did not reach statistical significance in the latter.

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 (linkage disequilibrium) the polymorphisms we studied. It is well known that the extent of linkage disequilibria varies with ethnicity and therefore in other populations the 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 high binding affinities for 5-HT2A receptors, seems to indicate that there is possibly an intrinsic change in the 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 based on the study of larger samples, which, however, especially for this African-Caribbean population with its restricted size might be difficult.

Acknowledgements

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Reference


