University of Groningen

Pharmacogenetics of parkinsonism, rigidity, rest tremor, and bradykinesia in African-Caribbean inpatients

Al Hadithy, Asmar F.; Wilffert, Bob; Stewart, Roy E.; Looman, Nicole M.; Bruggeman, Richard; Brouwers, Jacobus R.; Matroos, Glenn E.; van Os, Jim; Hoek, Hans W.; van Harten, Peter N.

Publication date:
2008

Link to publication in University of Groningen/UMCG research database

Pharmacogenetics of Parkinsonism, Rigidity, Rest Tremor, and Bradykinesia in African-Caribbean Inpatients:
Differences in Association With Dopamine and Serotonin Receptors

Asmar F. Al Hadithy,[1,2,4*] Bob Wilffert,[1,2] Roy E. Stewart,[3] Nicole M. Looman,[1] Richard Bruggeman,[1,4] Jacobus R. Brouwers,[1,2] Glenn E. Matroos,[5] Jim van Os,[6] Hans W. Hoek,[4,7] and Peter N. van Harten[4,8]

[1]Department of Pharmacotherapy and Pharmaceutical Care, GUIDE, University of Groningen, Groningen, The Netherlands
[2]Department of Clinical Pharmacy and Pharmacology, Zorggroep Noorderbreedte and De Tjongerschans, Leeuwarden, The Netherlands
[3]Department of Public Health, University Medical Center Groningen, Groningen, The Netherlands
[4]Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands
[5]Dr. D.R. Capriles Clinic, Curaçao, Netherlands Antilles, The Netherlands
[6]Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands
[7]Parnassia Psychiatric Institute, The Hague, The Netherlands
[8]Symfora Group Psychiatric Centre, Amersfoort, The Netherlands

We studied the association between polymorphisms of genes coding for dopamine D_2 (DRD2), dopamine D_3 (DRD3), serotonin 2_a (HTR2A), and serotonin 2_c (HTR2C) receptors and Antipsychotic-Induced Parkinsonism (AIP), rigidity, bradykinesia, and rest-tremor in African-Caribbeans treated with antipsychotics. Polymorphisms of DRD2 (-141CIns/Del, *Taq*IA, 957C > T), DRD3 (Ser9Gly), HTR2A (-1438A > G, 102T > C, His452-Tyr), and HTR2C (-759C > T, Cys23Ser) genes were determined according to standard protocols. The Unified Parkinson Disease Rating Scale was used for the measurement of AIP, rigidity, bradykinesia, and rest-tremor. Chi-squared or Fisher's exact tests were applied for the association analyses. The *t*-test was applied for continuous data. Ninety nine males and 27 females met the inclusion criteria (Schizophr Res 1996, 19:195). In males, but not in females, there were significant associations between *-141CDel*-allele carriership (DRD2) and rigidity (Fisher's Exact Test: P = 0.021) and between *23Ser*-allele carriership (HTR2C) and bradykinesia (P = 0.026, χ^2 = 5.0) or AIP (P = 0.008, χ^2 = 7.1). Rest-tremor was not associated with any of the polymorphisms studied. Analyses of the age, chlorpromazine equivalents, benztropine equivalents, the number of patients using anticholinergic medication, and the utilization patterns of the antipsychotic medication did not show statistically significant differences between patients with and without AIP, rigidity, bradykinesia, rest-tremor. Conducting the analysis without gender stratification did not affect our findings considerably, except for the association between bradykinesia and *23Ser*-allele which failed to reach statistical significance in the total sample (P = 0.0646, χ^2 = 3.41). Since AIPs subsymptoms (rigidity, bradykinesia, and rest-tremor) may differ pharmacogenetically, our data strongly support symptom-specific analysis of AIP. However, further research is warranted to confirm our findings.   © 2008 Wiley-Liss, Inc.

KEY WORDS: parkinsonism; tremor; rigidity; bradykinesia; antipsychotics

INTRODUCTION

Antipsychotic-induced parkinsonism (AIP) is an acute movement disorder that may appear in 15–40% of patients within the first few weeks following the start of an antipsychotic and may adversely affect therapeutic compliance, self-esteem, and quality of life [Fleischhacker et al., 1994; Gerlach, 1999; Hofer et al., 2004; Hirose, 2006].

Several risk factors have been suggested to predispose to AIP, such as old age, female gender, and high doses of antipsychotics [Metzer et al., 1989; Ebadi and Srinivasan, 1995; Caligiuri et al., 1999, 2000; Jabs et al., 2003; Hirose, 2006]. However, these factors only partially explain the variance in the occurrence of AIP and hereditary predisposition is, therefore, possible [Galdi et al., 1981; Lencer et al., 2004].

Although the pharmacogenetics of movement disorders has been examined extensively, many studies tend to generalize multiple forms of drug-induced movement disorders (e.g., tardive dyskinesia, AIP, akathisia, dystonia) as being one single clinical syndrome [Armstrong et al., 1997; Inada et al., 1999; Nakazono et al., 2005; Gunes et al., 2007; Guzey et al.,

2007]. It is however plausible that these movement disorders do differ in their genetic liability, since each movement disorder has a distinct clinical presentation, time to onset, prognosis, and medical management [Trosch, 2004].

AIP may be caused by the antagonistic effects of antipsychotics on nigrostriatal dopamine D2 receptors (DRD2 gene) [Gerlach, 1999; Lidow, 2000; Reynolds, 2004], which are modulated by serotonin 2_A and 2_C receptors (HTR2A and HTR2C genes, respectively) [Lidow, 2000; Alex et al., 2005; Di et al., 2006; Haleem, 2006].

DRD2, HTR2A, and HTR2C are therefore plausible candidate genes for the study of the pharmacogenetics of AIP. Studies focusing on HTR2A and HTR2C pharmacogenetics and AIP are currently scarce [Hamdani et al., 2005; Gunes et al., 2007]. Furthermore, there are currently only a few studies evaluating extensive sets of DRD2-polymorphisms in connection with AIP [Kaiser et al., 2002; Nakazono et al., 2005; Wu et al., 2006] and none were conducted in Negroid patients.

In contrast to akathisia [Eichhammer et al., 2000] and tardive dyskinesia [Segman et al., 2000; Lerer et al., 2002; Bakker et al., 2006], the pharmacogenetics of dopamine D3 receptor (DRD3 gene) and AIP is still poorly understood [Chong et al., 2003; Gunes et al., 2007; Guzey et al., 2007].

The goal of the present study is to investigate the association between several polymorphisms of DRD2, DRD3, HTR2A, and HTR2C genes and AIP and three of its subsymptoms (rigidity, bradykinesia, and rest-tremor) in African-Caribbean inpatients on chronic antipsychotic treatment.

Currently, there are no studies published on the pharmacogenetics of AIP in Negroid populations. Since African-Caribbean subjects may have ethnic roots similar to those of native Africans [Page, 1997], the present study may also be of relevance for other Negroid populations.

METHODS
Subjects

In this study we utilized data obtained from predominantly African-Caribbean subjects (Negroid or Mixed), who previously had participated in an epidemiological study on antipsychotic-induced movement disorders [van Harten et al., 1996]. All of the study subjects were inpatients from the Dr. D.R. Capriles Clinic (Curaçao, Netherlands Antilles) and had received nearly all of their psychiatric care from that hospital.

The study protocol was approved by the Curaçao institutional review board. Informed consent was obtained from each patient after full explanation of the purpose of the study and subjects were requested to provide peripheral blood for DNA genotyping.

Patients were included in this pharmacogentic study regardless the presence or absence of AIP and regardless the type or severity of their mental illness. Inclusion criteria were: (i) absence of organic and neurological disorders that could cause movement disorders, (ii) a history of neuroleptic use for at least 3 months, and (iii) informed consent.

Clinical Data

AIP and its subsymptoms were measured with the motor examination part of the Unified Parkinson Disease Rating Scale [Martinez-Martin et al., 1994]. All of the ratings were dichotomized in presence/absence of AIP, rigidity, rest-tremor. Since rest-tremor and rigidity are typical of AIP, a 'mild' involvement on one of these items led to case definition [van Harten et al., 1996]. If no tremor or rigidity was present, then the cut-off point for the presence of AIP was at least one 'moderate' or two 'mild' scores on the other items [van Harten et al., 1996].

To reduce the risk of false positives, we chose to categorize the presence/absence of bradykinesia by the use of a more stringent cut-off point of at least one 'moderate' or two 'mild' scores on the items speech, facial expression, hand movements, alternating hands, foot agility, arising from chair, posture, gait, postural stability, body bradykinesia, and hypokinesia.

Furthermore, 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 as well as other co-medications (anticholinergics and benzodiazepines).

The dose of the antipsychotic medication was converted into chlorpromazine equivalents and the dose of anticholinergics into benztropine equivalents [Davis, 1976; Moleman, 1992].

DNA Genotyping

Genomic DNA was extracted from EDTA whole-blood samples [Miller et al., 1988]. We genotyped the patients for several polymorphisms of DRD2 (-141CIns/Del, TaqIA, 957C > T), DRD3 (Ser9Gly), HTR2A (-1438A > G, 102T > C, His452Tyr), and HTR2C (-759C > T, Cys23Ser) genes. The genotyping was conducted blind to the clinical status of the patients.

Fluorogenic 5'-exonuclease TaqMan® assays were applied for the determination of all of the polymorphisms except three polymorphisms (102T > C, Cys23Ser, and Ser9Gly), which were determined by standard restriction fragment length polymorphism (RFLP) protocols [Lannfelt et al., 1992; Warren et al., 1993; Ebstein et al., 1997]. All of the TaqMan-assays, except one (-141C Ins/Del), were ordered from Applied Biosystems (Nieuwerkerk aan den IJssel, the Netherlands) as Assay-On-Demand. The -141C Ins/Del polymorphism was performed by the use of user-designed TaqMan primers and probes, kindly provided by Xu et al. [2004].

In relation with the 957C > T polymorphism of DRD2 gene [Hirvonen et al., 2004], we genotyped additionally any subject with the homozygous 957TT genotype for the 1101G > A polymorphism of DRD2, since it has been reported that the effects of the 957T-allele are annulated in presence of the 1101A-allele [Duan et al., 2003]. The genotyping of 1101G > A polymorphism was conducted by a PCR-RFLP protocol, as kindly provided by Hirvonen et al. [2004].

Statistics

The associations between allele-positivity (allele carriership status) and AIP, rigidity, bradykinesia, and rest-tremor were analyzed by the use of Chi-squared or Fisher's exact tests (2×2 contingency tables). Chi-squared or Fisher's exact tests were also applied for the analyses of other dichotomous variables (e.g., anticholinergics and polypharmacy use).

Logistic regression was applied for the calculation of the Odds Ratio (OR) and adjusted OR (OR_adj) for polymorphisms with a significant association. For analyses of age, chlorpromazine- and benztropine equivalents the t-test was applied. The analyses were conducted twice; with and without gender-stratification. P values <0.050 were regarded as significant. In our study we endeavored to replicate data from previous studies (some of which not reporting an association) rather than to explore new genetic targets. Since our approach is hypothesis driven, we did not correct for multiple testing.

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; accessed October 28th 2007).

RESULTS

Demographic and Clinical Features of the Subjects

One hundred twenty six African-Caribbean subjects (99 males and 27 females) met the inclusion criteria. Table I presents the distribution (mean ± standard deviation) of age (years), DSM-III-R diagnosis, ethnicity, polypharmacy (number of patients using no, single, or multiple antipsychotics simultaneously), lifetime exposure to antipsychotics (kilogram chlorpromazine equivalents), age on first neuroleptic use (years), daily dose of antipsychotics (mg/day chlorpromazine equivalents) and anticholinergics (mg/day benztropine equivalents) as well as the number and percentage of subjects using anticholinergic medication. Table I also presents the number of cases of AIP, rigidity, bradykinesia, and rest-tremor in the total sample and per gender.

Genotype Distribution, Hardy–Weinberg Equilibrium (HWE), and Allele-Carriership Frequencies

None of the polymorphisms tested deviated from the HWE (Table II). For some polymorphisms we failed to genotype 1 (DRD2 -141CIns/Del, HTR2A His452Tyr, and -1438G > A) or 2 (HTR2C -759C > T) DNA samples, due to insufficient DNA quality or quantity.

Of the five subjects with the homozygous 957TT genotype (DRD2 957C > T polymorphism), none had the 1101AA genotype (DRD2 1101G > A).

Since we found in the total sample that for some polymorphisms the frequency of homozygote subjects could be as low as 3.2%, and becomes even lower after stratification by gender, we chose to characterize subjects either as carriers or non-carriers of an allele, if they were heterozygote, hemizygote, or homozygote for that particular allele. However, it should be noted that this conservative approach does not reflect any specific hypothesis regarding the mode of inheritance (i.e., we do not suggest a dominant inheritance mode).

Genotype and allele-carriership frequencies are shown in Table II.

Comparison of Allele-Carriership Frequencies in Cases and Non-Cases

AIP. As shown in Table III, χ^2 test in the total sample indicates significant associations between AIP and HTR2C 23Ser-allele carriership ($\chi^2 = 5.35$, **P = 0.021**). All other polymorphisms were not significantly associated with AIP (data not shown).

The frequency of AIP in patients carrying the 23Ser-allele of HTR2C gene is 1.7 times higher than in non-carriers (50.0 vs. 29.5%). Furthermore, the OR for having AIP in 23Ser-allele carriers was significant (OR = 2.39, **P = 0.022**). Adjustment of the OR for age, chlorpromazine- and benztropine equivalents daily used, did not affect the results adversely (OR_adj = 2.61, **P = 0.017**).

After gender stratification, the association between carriership of 23Ser-allele and AIP remained significant in males ($\chi^2 = 7.05$, **P = 0.008**), but not in females (Fisher's Exact Test:

TABLE I. The Distribution of Age, Diagnosis (DSM-III-R), Ethnicity, Polypharmacy, Daily Use of Antipsychotics (mg/Day Chlorpromazine Equivalents, CPZeq) on the Day of Assessment of the UPDRS, Lifetime Exposure to Antipsychotics (kg CPZeq), Age First Neurolerptic use (Years), Daily use of Anticholinergics (mg/Day Benztropine Equivalents, BNZeq) on the Day of Assessment of the UPDRS, and the Number (n) and Percentage (%) of Subjects Using Anticholinergics or Benzodiazepines as well as AIP, Rigidity, Bradykinesia, and Rest-Tremor Cases

	All (126)	Male (99)	Female (27)
Age (years)	49.2 ± 13.4	47.5 ± 13.0	55.4 ± 13.3
Diagnoses[a,b], n (%)			
Schizophrenia[c]	88 (80.7)	—	—
Affective disorder	5 (4.6)		
Dementia	3 (2.8)		
Other	13 (11.9)		
Ethnicity, n (%)[d]			
Negroid or mixed	108 (95.6)	—	—
Caucasian	3 (2.7)		
Other	2 (1.8)		
Polypharmacy, number of patients using			
0 antipsychotics	12	—	—
1 antipsychotic	85		
2 antipsychotics	27		
3 antipsychotics	2		
Daily use of antipsychotics (mg CPZeq/day)	686.0 ± 740.6	692.4 ± 676.8	662.5 ± 953.8
Lifetime exposure to antipsychotics (kg CPZeq)[e]	3.9 ± 3.2	3.9 ± 3.2	4.0 ± 3.2
Age first neurolerptic use (years)[e]	29.8 ± 10.9	28.6 ± 10.2	33.7 ± 12.6
Daily use of anticholinergics (mg BNZeq/day)	1.4 ± 2.1	1.6 ± 2.2	0.7 ± 1.4
Patients on anticholinergics, N (%)	49 (38.9%)	42 (33.3%)	7 (5.6%)
Patients on benzodiazepines, N (%)	28 (22.2%)	23 (23.2%)	5 (18.5%)
AIP present, n (%)	47 (37.3)	35 (35.4)	12 (44.4)
RIG present, n (%)	14 (11.1)	11 (11.1)	3 (11.1)
TREM present, n (%)	21 (16.6)	18 (18.2)	3 (11.1)
BRAD present, n (%)	33 (26.2)	23 (23.2)	10 (37.0)

[a]Data from 109 patients.
[b]A patient can have several diagnosis, thus the total number exceeds 100%.
[c]Includes 295.1, 295.2, 295.3, 295.4, 295.6, 296.7, 295.9.
[d]Data from 113 patients.
[e]Data from 93 patients (72 males + 21 females).

TABLE II. Genotype Distribution, Hardy–Weinberg Equilibrium Chi-Squared (χ^2) Values, the Number (n) and Percentage of Allele Carriers

Genotype	% of total sample (n)	χ^2 value	Genetic variation	Total sample, % (n)	Males, % (n)	Females, % (n)
DRD2 -141CIns/Del						
Ins/Ins	42.4 (53)	0,003	*Carriers of the -141CDel allele*	57.6 (72)	56.6 (56)	61.5 (16)
Ins/Del	45.6 (57)					
Del/Del	12.0 (15)					
DRD2 *Taq*IA						
A2/A2	38.1 (48)	0.016	*Carriers of the TaqIA A1 allele*	61.9 (78)	59.6 (59)	70.4 (19)
A2/A1	46.8 (59)					
A1/A1	15.1 (19)					
DRD2 957C > T						
957C/C	68.3 (86)	0.356	*Carriers of 957T allele*	31.8 (40)	33.3 (33)	25.9 (7)
957C/T	27.8 (35)					
957T/T	4.0 (5)					
DRD3 Ser9Gly						
Gly9/Gly9	39.7 (50)	0,004	*Carriers of the 9Ser allele*	60.3 (76)	60.6 (60)	59.3 (16)
Gly9/Ser9	46.8 (59)					
Ser9/Ser9	13.5 (17)					
HTR2A -1438G > A						
-1438G/G	44.8 (56)	0.127	*Carriers of the -1438A allele*	55.2 (69)	52.5 (52)	65.4 (17)
-1438G/A	43.2 (54)					
-1438A/A	12.0 (15)					
HTR2A His452Tyr						
His/His	76.0 (95)	1.651	*Carriers of the 452Tyr allele*	24.0 (30)	28.3 (28)	7.7 (2)
HisTyr	20.8 (26)					
Tyr/Tyr	3.2 (4)					
HTR2A 102C > T						
102C/C	42.1 (53)	1.446	*Carriers of the 102T allele*	57.9 (73)	54.5 (54)	70.4 (19)
102C/T	49.2 (62)					
102T/T	8.7 (11)					
HTR2C -759C > T						
-759C/C	96.8 (120)	—	*Carriers of the -759T allele*	3.2 (4)	4.0 (4)	0.0 (0)
-759C/T	0.0 (0)					
-759T/T	3.2 (4)					
HTR2C Cys23Ser						
Cys23/Cys23	61.9 (78)	—	*Carriers of the 23Ser allele*	38.1 (48)	29.3 (29)	70.4 (19)
Cys23/Ser23	11.1 (14)					
Ser23/Ser23	27.0 (34)					

$P = 1.000$). The OR and OR_adj were also significant in males (OR $= 3.30$, **$P = 0.009$** and OR_adj $= 3.91$, **$P = 0.005$**), but not females (OR $= 0.73$, $P = 0.707$ and OR_adj $= 0.75$, $P = 0.763$).

Rigidity. As shown in Table III, χ^2 test in the total sample indicates significant associations between rigidity and DRD2 -*141CDel*-allele carriership ($\chi^2 = 8.02$, **$P = 0.005$**). All other polymorphisms were not significantly associated with rigidity (data not shown). The frequency of rigidity in patients carrying the -*141CDel* allele of DRD2 gene was 9.5 times higher, compared to non-carriers (18.1 vs. 1.9%). The OR and OR_adj for having rigidity in -*141CDel* carriers was significant (OR $= 11.46$, **$P = 0.021$** and OR_adj $= 13.21$, **$P = 0.018$**).

After gender stratification, Fisher's Exact Test indicated a significant association between carriership of -*141CDel*-allele and rigidity in males (**$P = 0.021$**), but not in females ($P = 0.262$).

The OR and OR_adj were also significant in males (OR $= 9.13$, **$P = 0.039$** and OR_adj $= 8.98$, **$P = 0.049$**), but not females (OR, OR_adj, and P values not rateable).

Bradykinesia. As shown in Table III, χ^2 test in the total sample indicated a non-significant trend towards an association between bradykinesia and HTR2C *23Ser*-allele carriership ($\chi^2 = 3.41$, $P = 0.065$, OR $= 2.13$, $P = 0.067$ and OR_adj 2.27, $P = 0.054$). In the total sample, the frequency of bradykinesia in *23Ser*-allele carriers was 1.7 times higher than in non-carriers (35.4 vs. 20.5%). All other polymorphisms were not significantly associated with bradykinesia (data not shown). After gender stratification, the association between carriership of *23Ser*-allele and bradykinesia became significant in males ($\chi^2 = 5.0$, **$P = 0.026$**, OR $= 2.95$, **$P = 0.029$** and OR_adj $= 3.40$, **$P = 0.018$**), but not in females (Fisher's Exact Test: $P = 0.415$, OR $= 0.46$, $P = 0.370$ and OR_adj $= 0.44$, $P = 0.380$).

Rest-tremor. Rest-tremor was not associated with any of the polymorphisms studied, as determined by χ^2 test, Fisher's Exact Test, and logistic regression (data not shown).

Comparison of Age and the use of Antipsychotics, Anticholinergics and Benzodiazepines

Mean age (years), mean chlorpromazine and benztropine equivalents (mg/day), and the proportion of patients using anticholinergic medication did not differ significantly neither between subjects with and without AIP, rigidity, bradykinesia, and tremor nor between carriers and non-carriers of *23Ser* (HTR2C) and -*141CDel* (DRD2) alleles (data not shown). Furthermore, the frequency of patients using benzodiazepines did not differ significantly between cases (18.2%) and non-cases (23.7%) of bradykinesia ($\chi^2 = 0.42$, $P = 0.516$) or between carriers (18.8%) and non-carriers (24.4%) of *23Ser* allele of the Cys23Ser polymorphism ($\chi^2 = 0.54$, $P = 0.462$).

TABLE III. Cross Tabulation of Antipsychotic-Induced Parkinsonism (AIP), Rigidity, and Bradykinesia in Relation With *23Ser* (HTR2C), *-141CDel* (DRD2), and *23Ser* (HTR2C) Allele Carriership, Respectively

Genetic variation			Significance
Total sample (n = 126)	AIP = no n (%)	AIP = yes n (%)	
23Ser non-carriership	55 (70.5)	23 (29.5)	χ^2 = **5.35**, *P* = **0.021; OR** = **2.39** [**CI: 1.13–5.04**], *P* = **0.022;**
23Ser carriership	24 (50.0)	24 (50.0)	**OR_adj** = **2.61** [**CI: 1.19–5.74**], *P* = **0.017;**
Males (n = 99)			
23Ser non-carriership	51 (72.9)	19 (27.1)	χ^2 = **7.05**, *P* = **0.008; OR** = **3.30** [**CI: 1.34–8.14**], *P* = **0.009;**
23Ser carriership	13 (44.8)	16 (55.2)	**OR_adj** = **3.91** [**CI: 1.50–10.23**], *P* = **0.005;**
Females (n = 27)			
23Ser non-carriership	4 (50.0)	4 (50.0)	Fisher's exact test: *P* = 1.000; OR = 0.73 [CI: 0.14–3.82],
23Ser carriership	11 (57.9)	8 (42.1)	*P* = 0.707; OR_adj = 0.75 [CI:0.12–4.87], *P* = 0.763;
	Rigidity = no n (%)	Rigidity = yes n (%)	
Total sample (n = 125)			
-141CDel non-carriership	52 (98.1)	1 (1.9)	χ^2 = **8.02**, *P* = **0.005; OR** = **11.46** [**CI: 1.45–90.60**], *P* = **0.021;**
-141CDel carriership	59 (81.9)	13 (18.1)	**OR_adj** = **13.21** [**CI: 1.57–111.07**], *P* = **0.018;**
Males (n = 99)			
-141CDel non-carriership	42 (97.7)	1 (2.3)	**Fisher's exact test**: *P* = **0.021; OR** = **9.13**, [**CI: 1.12–74.36**];
-141CDel carriership	46 (82.14)	10 (17.9)	*P* = **0.039 OR_adj** = **8.98** [**CI: 1.01–79.52**], *P* = **0.049;**
Females (n = 26)			
-141CDel non-carriership	10 (100.0)	0 (0.0)	Fisher's exact test: *P* = 0.262; infinite OR, OR_adj, and *P*
-141CDel carriership	13 (81.2)	3 (18.8)	values due to many zero values
	Bradykinesia = no n (%)	Bradykinesia = yes n (%)	
Total sample (n = 126)			
23Ser non-carriership	62 (79.5)	16 (20.5)	χ^2 = 3.41, *P* = 0.065; OR = 2.13 [CI: 0.95–4.77], *P* = 0.067;
23Ser carriership	31 (64.6)	17 (35.4)	OR_adj = 2.27 [CI: 0.99–5.21], *P* = 0.054;
Males (n = 99)			
23Ser non-carriership	58 (82.9)	12 (17.1)	χ^2 = **5.0**, *P* = **0.026; OR** = **2.95** [**CI: 1.12–7.82**], *P* = **0.029;**
23Ser carriership	18 (62.1)	11 (37.9)	**OR_adj** = **3.40** [**CI: 1.23–9.41**], *P* = **0.018;**
Females (n = 27)			
23Ser non-carriership	4 (50.0)	4 (50.0)	Fisher's exact test: *P* = 0.415; OR = 0.46 [CI: 0.09–2.50],
23Ser carriership	13 (68.4)	6 (31.6)	*P* = 0.370; OR_adj = 0.44 [CI: 0.07–2.79], *P* = 0.380;

Significant results are printed in bold. CI, 95% confidence interval; n, number of subjects; %, percentage within carriership status; OR, odds ratio; OR_adj, odds ratio adjusted for age, dose of the antipsychotic medication, and dose of anticholinergic medication.

Gender stratification did not alter any of the abovementioned findings (data not shown), except for the male DRD2 -*141CDel* allele non-carriers who had a significantly (*P* = **0.014**) higher mean chlorpromazine equivalents than male carriers of that allele (892 vs. 539 mg/day, respectively).Furthermore, we analyzed the type of the antipsychotics used. Most of the patients (n = 114) used antipsychotics on the day of examination. Of whom, 7 patients were using an atypical antipsychotic as monotherapy (risperidone in all cases), and 1 patient was using risperidone in combination with a classical neuroleptic. On the day of examination 75% of the users of antipsychotics were on monotherapy and 25% used 2 or more antipsychotics simultaneously. Of the patients using two or more antipsychotics, only two were using three antipsychotics simultaneously. To test whether polypharmacy has affected our finding, we applied 2 × 2 contingency tables to compare subjects without prescribed antipyschotics on the day of UPDRS-assessment versus those using at least 1 antipsychotic as well as those using 2 or 3 antipsychotics versus those with 1 or none antipsychotics in relation to AIP, rigidity, tremor, bradykinesia, and carriership of the Cys23Ser and -141C Ins/Del polymorphisms (HTR2C and DRD2 genes, respectively). In all of the comparisons made, we do not find any significant difference in the utilization patterns of the antipsychotic medication (data not shown).

DISCUSSION

The present study suggests that rigidity, bradykinesia, and rest-tremor may have different genetic vulnerability, because these neurological phenomena did differ in their association with polymorphisms of HTR2A, HTR2C, DRD2, and DRD3 genes. We found for example in males that the Cys23Ser (HTR2C) and the -141CIns/Del (DRD2) polymorphisms are associated with bradykinesia, AIP and rigidity, respectively, but none is associated with rest-tremor. This symptom-specific relationship may probably reflect a difference in the genetic predisposition for the different parkinsonian phenomena. Of the published pharmacogenetic studies dealing with AIP as a discrete clinical entity only few [Mihara et al., 2000, 2001] dissect AIP into its subsymptoms (e.g., rigidity, tremor, bradykinesia, etc.).

In fact, it is plausible that some of these symptoms have distinct neurological circuits, etiology, pathophysiology, and/

or genetic liability. For example it has been shown that stimulation of certain brain regions in patients with Parkinson Disease (which has symptoms similar to those of AIP) may lead to differential effects on rigidity and tremor [Bejjani et al., 1997; Krack et al., 1998; Gross et al., 1999]. Furthermore, the symptomatic treatment of the Parkinson Disease is symptom-dependent [Siemers, 1992; Koller, 1992]. Anticholinergic preparations for instance are generally considered effective for tremor and rigidity but not for bradykinesia, which is better treated with Levodopa.

Recent work [Lerer et al., 2005] on another movement disorder (tardive dyskinesia) supports this approach too, because two subclasses of tardive dyskinesia (orofacial- and limbotruncal tardive dyskinesias) differ in their association with particular genetic markers.

Moreover, examination of the published papers in this field reveals that the majority of the pharmacogenetic papers do not even assess AIP as a discrete clinical syndrome, but rather pool this syndrome with other antipsychotic-induced movement disorders. Although there is some overlap between the different types of antipsychotic-induced movement disorders (tardive dyskinesia, AIP, akathisia, and dystonia) [van Harten et al., 1997], these different types of movement disorders do differ considerably from each other in many points [Trosch, 2004]. Pooling these different types of movement disorders may, therefore, be detrimental for the analyses.

The significant associations observed in this study were exhibited in males, but not in females. Although gender-related effects can not be excluded, the lack of associations in the female sample is probably due to the small number of female subjects included in our study (i.e., insufficient power).

In the current study we find a significant association between bradykinesia or AIP and HTR2C Cys23Ser polymorphism, which—although debated [Jonsson et al., 2004; Fentress et al., 2005]—has been suggested to be functional [Okada et al., 2004]. This finding is completely in line with the findings of the only other published study [Gunes et al., 2007]. In our sample, the minor-allele frequency of the Cys23Ser polymorphism (Ser allele) was 0.26, which is higher than that of Asians (0.03) and Europeans (0.16) (www.genecards.org; accessed October 28th 2007).

In relation with HTR2A gene, we find no evidence for any association with its polymorphisms (-1438A > G, 102T > C, and His452Tyr). This lack of association between AIP and -1438A>G polymorphism has also been reported by Hamdani et al. [2005]. Gunes et al. [2007] reported a higher 102C allele frequency in 25 Estonian patients with either parkinsonism (n = 23) or akathisia (n = 2). However, the utilization of allele frequencies, instead of allele-positivity (as in our study), may has led to biased conclusions as discussed by Ohashi and Tokunaga [1999] and Ohashi et al. [2001]. Indeed, when Gunes et al. [2007] compared the median SAS scores between the three genotype classes of 102T > C polymorphism, there was no significant difference observed. Furthermore, Gunes et al. [2007] reported that the frequency of the 452Tyr allele (His452Tyr polymorphism) was not significantly different in cases as compared to non-cases. Taken all together, currently, there is no strong evidence for an association between these polymorphisms and AIP.

Notably, our data do not support the view that genetic variations of the DRD2 gene significantly predispose to AIP—when measured as a total syndrome—and hence do replicate findings of three other studies in German [Kaiser et al., 2002] and Asian [Chong et al., 2003; Wu et al., 2006] patients, respectively. However, we do find a significant association between rigidity and the DRD2 promoter variant -141CIns/ Del, which—although debated [Pohjalainen et al., 1999; Ritchie and Noble, 2003]—has been suggested to be functional [Arinami et al., 1997; Jonsson et al., 1999] or in linkage

disequilibrium with another functional polymorphism [Duan et al., 2003]. This relationship with rigidity was not reported by the only co-existing study on 52 Japanese subjects [Mihara et al., 2001], who are ethnically different from African-Caribbeans. The frequency of the minor allele of this polymorphism (the Del allele) was 0.35 in our sample, which is 2–3 times higher than that of Asians (0.16) and Europeans (0.11) (SZGene, www.schizophreniaforum.org; accessed October 28th 2007).

Two other studies did report an association between the -141CIns/Del polymorphism and extrapyramidal symptoms [Inada et al., 1999; Nakazono et al., 2005]. However, these studies are probably biased due to pooling of parkinsonism with other types of movement disorder (akathisia, dyskinesia, and dystonia).

We chose DRD3 gene because many studies have shown that it may be associated with tardive dyskinesia [Lerer et al., 2002; Bakker et al., 2006]. Our study however provides no evidence for a relationship between this polymorphism and symptoms of AIP, which is in agreement with the literature [Chong et al., 2003; Gunes et al., 2007; Guzey et al., 2007]. This finding suggests that the genetic vulnerability for tardive dyskinesia may differ from that for antipsychotic-induced parkinsonism.

A limitation of our study is that we did not correct for variation in the psychopathology of the patients. However, our study sample can be considered as homogenous, since the majority of the patients was of African-Caribbean origin and had schizophrenia. Furthermore, the presence of organic and neurological disorders that may cause movement disorders was a stringent exclusion criterion. Since we followed our patients for 10 years [van Harten et al., 2006], neurological diseases such as Morbus Parkinson would have been detected [Hausner, 1983].

Factors other than genetic polymophisms (i.e., confounders) may also cause the parkinsonian symptoms. Tremor for example may be an essential tremor or may be induced by other drugs (such as antidepressants or antiepileptics). However, these tremors are predominantly postural, whereas we examined our patients for rest tremor, which is more specifically related to antipsychotics and AIP.

Furthermore, we compared the means of age, chlorpromazine and benztropine equivalents as well as the number of patients using anticholinergic medication and the number of antipsychotics used per patient (polypharmacy) in cases and non-cases of AIP, rigidity, bradykinesia, and rest-tremor and in carriers and non-carriers of 23Ser (HTR2C) and -141CDel (DRD2) alleles. Overall there were no statistically significant differences between the compared groups, except for male carriers of the -141CDel allele (DRD2) who had significantly lower mean chlorpromazine equivalents than non-carrier male patients (a fact which may only reinforce our findings). Of note, the majority of the patients were using typical (first generation) antipsychotics. There is, therefore, no indication for biased findings due to difference in the utilization patterns of antipsychotics.

Bradykinesia might be caused by psychiatric symptoms or sedation. We therefore chose a more stringent cut-off point (see Methods Section). Additionally, we evaluated the utilization of benzodiazepines in our sample and found that the number of patients using benzodiazepines does not differ significantly between bradykinesia cases and non-cases or between carriers and non-carriers of 23Ser allele (HTR2C).Another limitation of the present study is that the UPDRS is not developed specifically to measure AIP. However, the UPDRS is a reliable and a valid instrument that has been extensively tested and used for Parkinson's disease. Since the phenomenology of Morbus Parkinson is not essentially different from the phenomenology of drug-induced parkinsonism, we assume that the UPDRS is able to measure AIP. In fact, several studies

have utilized the UPDRS for the measurement of drug-induced parkinsonism [van Harten et al., 1996, 2006; Lera and Zirulnik, 1999; Hassin-Baer et al., 2001; Jamora et al., 2007]. Additionally, the UPDRS is far more comprehensive and balanced than the often used Simpson-Angus Scale (SAS), which has been criticized for overemphasizing rigidity items (6 out 10 items measure rigidity, while only 1 item measures tremor) as well as other shortcomings recently highlighted by Loonen and van Praag [2007].

In our study we have endeavored to replicate data from previous studies rather than to explore new genetic targets. Since our approach is hypothesis driven, we did not correct for multiple testing. In fact, the issue of correction for multiple testing is a subject of ongoing debate. The European Society of Human Genetics states that "How to correct for this [multiple testing for genetic association] is still under debate. The Bonferroni correction could overcorrect for the inflated false-positive rate, and as a consequence, valid information would be discarded . . . What is even more concerning than the incidence of false-positives is the potential lack of detecting genuine effects" (http://www.eshg.org; accessed November 11th 2007). To give an example, since we tried to replicate a number of studies simultaneously in the same sample, correction for multiple testing would obviously lower the chance of statistically significant confirmation of studies investigating only 1 SNP.

CONCLUSIONS

The present study does support an association between the -141CIns/Del (DRD2) polymorphism and rigidity and between the Cys23Ser (HTR2C) polymorphism and AIP or bradykinesia in African-Caribbeans. However, this study does not provide evidence for a genetic association between rest-tremor and any of the polymorphisms studied.

Since our data suggest that AIP and its more specific subsymptoms rigidity, rest-tremor, and bradykinesia may differ pharmacogenetically, our data strongly support symptom-specific approach in contrast to recent pharmacogenetic studies that pool even the different extrapyramidal symptoms in their analyses. Further research is however warranted to confirm our findings.

ACKNOWLEDGMENTS

REFERENCES

Alex KD, Yavanian GJ, McFarlane HG, Pluto CP, Pehek EA. 2005. Modulation of dopamine release by striatal 5-HT2C receptors. Synapse 55:242–251.

Arinami T, Gao M, Hamaguchi H, Toru M. 1997. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum Mol Genet 6:577–582.

Armstrong M, Daly AK, Blennerhassett R, Ferrier N, Idle JR. 1997. Antipsychotic drug-induced movement disorders in schizophrenics in relation to CYP2D6 genotype. Br J Psychiatry 170:23–26. 23–26.

Bakker PR, van Harten PN, van Os J. 2006. Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: A meta analysis. Schizophr Res 83:185–192.

Bejjani B, Damier P, Arnulf I, Bonnet AM, Vidailhet M, Dormont D, Pidoux B, Cornu P, Marsault C, Agid Y. 1997. Pallidal stimulation for Parkinson's disease. Two targets? Neurology 49:1564–1569.

Caligiuri MP, Lacro JP, Jeste DV. 1999. Incidence and predictors of drug-induced parkinsonism in older psychiatric patients treated with very low doses of neuroleptics. J Clin Psychopharmacol 19:322–328.

Caligiuri MR, Jeste DV, Lacro JP. 2000. Antipsychotic-induced movement disorders in the elderly: Epidemiology and treatment recommendations. Drugs Aging 17:363–384.

Chong SA, Tan EC, Tan CH, Mythily Chan YH. 2003. Polymorphisms of dopamine receptors and tardive dyskinesia among Chinese patients with schizophrenia. Am J Med Genet Part B 116:51–54.

Davis JM. 1976. Comparative doses and costs of antipsychotic medication. Arch Gen Psychiatry 33:858–861.

Di GG, Di MV, Pierucci M, Benigno A, Esposito E. 2006. Serotonin involvement in the basal ganglia pathophysiology: Could the 5-HT2C receptor be a new target for therapeutic strategies? Curr Med Chem 13:3069–3081.

Duan J, Wainwright MS, Comeron JM, Saitou N, Sanders AR, Gelernter J, Gejman PV. 2003. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. Hum Mol Genet 12:205–216.

Ebadi M, Srinivasan SK. 1995. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. Pharmacol Rev 47:575–604.

Ebstein RP, Segman R, Benjamin J, Osher Y, Nemanov L, Belmaker RH. 1997. 5-HT2C (HTR2C) serotonin receptor gene polymorphism associated with the human personality trait of reward dependence: Interaction with dopamine D4 receptor (D4DR) and dopamine D3 receptor (D3DR) polymorphisms. Am J Med Genet 74:65–72.

Eichhammer P, Albus M, Borrmann-Hassenbach M, Schoeler A, Putzhammer A, Frick U, Klein HE, Rohrmeier T. 2000. Association of dopamine D3-receptor gene variants with neuroleptic induced akathisia in schizophrenic patients: A generalization of Steen's study on DRD3 and tardive dyskinesia. Am J Med Genet 96:187–191.

Fentress HM, Grinde E, Mazurkiewicz JE, Backstrom JR, Herrick-Davis K, Sanders-Bush E. 2005. Pharmacological properties of the Cys23Ser single nucleotide polymorphism in human 5-HT2C receptor isoforms. Pharmacogenomics J 5:244–254.

Fleischhacker WW, Meise U, Gunther V, Kurz M. 1994. Compliance with antipsychotic drug treatment: Influence of side effects. Acta Psychiatr Scand Suppl 382:11–15.

Galdi J, Rieder RO, Silber D, Bonato RR. 1981. Genetic factors in the response to neuroleptics in schizophrenia: A psychopharmacogenetic study. Psychol Med 11:713–728.

Gerlach J. 1999. The continuing problem of extrapyramidal symptoms: Strategies for avoidance and effective treatment. J Clin Psychiatry 60(Suppl 23):20–24.

Gross RE, Lombardi WJ, Lang AE, Duff J, Hutchison WD, Saint-Cyr JA, Tasker RR, Lozano AM. 1999. Relationship of lesion location to clinical outcome following microelectrode-guided pallidotomy for Parkinson's disease. Brain 122:405–416.

Gunes A, Scordo MG, Jaanson P, Dahl ML. 2007. Serotonin and dopamine receptor gene polymorphisms and the risk of extrapyramidal side effects in perphenazine-treated schizophrenic patients. Psychopharmacology (Berl) 190:479–484.

Guzey C, Scordo MG, Spina E, Landsem VM, Spigset O. 2007. Antipsychotic-induced extrapyramidal symptoms in patients with schizophrenia: Associations with dopamine and serotonin receptor and transporter polymorphisms. Eur J Clin Pharmacol 63:233–241.

Haleem DJ. 2006. Serotonergic modulation of dopamine neurotransmission: A mechanism for enhancing therapeutics in schizophrenia. J Coll Physicians Surg Pak 16:556–562.

Hamdani N, Bonniere M, Ades J, Hamon M, Boni C, Gorwood P. 2005. Negative symptoms of schizophrenia could explain discrepant data on the association between the 5-HT2A receptor gene and response to antipsychotics. Neurosci Lett 377:69–74.

Hassin-Baer S, Sirota P, Korczyn AD, Treves TA, Epstein B, Shabtai H, Martin T, Litvinjuk Y, Giladi N. 2001. Clinical characteristics of neuroleptic-induced parkinsonism. J Neural Transm 108:1299–1308.

Hausner RS. 1983. Neuroleptic-induced parkinsonism and Parkinson's disease: Differential diagnosis and treatment. J Clin Psychiatry 44:13–16.

Hirose G. 2006. Drug induced parkinsonism: A review. J Neurol 253 (Suppl 3):22–24.

Hirvonen M, Laakso A, Nagren K, Rinne JO, Pohjalainen T, Hietala J. 2004. C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. Mol Psychiatry 9:1060–1061.

Hofer A, Kemmler G, Eder U, Edlinger M, Hummer M, Fleischhacker WW. 2004. Quality of life in schizophrenia: The impact of psychopathology, attitude toward medication, and side effects. J Clin Psychiatry 65:932–939.

Inada T, Arinami T, Yagi G. 1999. Association between a polymorphism in the promoter region of the dopamine D2 receptor gene and schizophrenia in Japanese subjects: Replication and evaluation for antipsychotic-related features. Int J Neuropsychopharmcol 2:181–186.

Jabs BE, Bartsch AJ, Pfuhlmann B. 2003. Susceptibility to neuroleptic-induced parkinsonism–age and increased substantia nigra echogenicity as putative risk factors. Eur Psychiatry 18:177–181.

Jamora D, Lim SH, Pan A, Tan L, Tan EK. 2007. Valproate-induced Parkinsonism in epilepsy patients. Mov Disord 22:130–133.

Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, Sedvall GC. 1999. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry 4:290–296.

Jonsson EG, Bah J, Melke J, Abou JR, Schumacher J, Westberg L, Ivo R, Cichon S, Propping P, Nothen MM, Eriksson E, Sedvall GC. 2004. Monoamine related functional gene variants and relationships to monoamine metabolite concentrations in CSF of healthy volunteers. BMC Psychiatry 4:4.

Kaiser R, Tremblay PB, Klufmoller F, Roots I, Brockmoller J. 2002. Relationship between adverse effects of antipsychotic treatment and dopamine D(2) receptor polymorphisms in patients with schizophrenia. Mol Psychiatry 7:695–705.

Koller WC. 1992. Initiating treatment of Parkinson's disease. Neurology 42:33–38.

Krack P, Pollak P, Limousin P, Hoffmann D, Benazzouz A, Le Bas JF, Koudsie A, Benabid AL. 1998. Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann Neurol 43:180–192.

Lannfelt L, Sokoloff P, Martres MP, Pilon C, Giros B, Jonsson E, Sedvall G, Schwartz JC, Berger R. 1992. Amino acid substitution in the dopamine D3 receptor as a useful polymorphism for investigating psychiatric disorders. Psychiatr Genet 2:249–256.

Lencer R, Eismann G, Kasten M, Kabakci K, Geithe V, Grimm J, Klein C. 2004. Family history of primary movement disorders as a predictor for neuroleptic-induced extrapyramidal symptoms. Br J Psychiatry 185:465–471.

Lera G, Zirulnik J. 1999. Pilot study with clozapine in patients with HIV-associated psychosis and drug-induced parkinsonism. Mov Disord 14:128–131.

Lerer B, Segman RH, Fangerau H, Daly AK, Basile VS, Cavallaro R, Aschauer HN, McCreadie RG, Ohlraun S, Ferrier N, Masellis M, Verga M, Scharfetter J, Rietschel M, Lovlie R, Levy UH, Meltzer HY, Kennedy JL, Steen VM, Macciardi F. 2002. Pharmacogenetics of tardive dyskinesia: Combined analysis of 780 patients supports association with dopamine D3 receptor gene Ser9Gly polymorphism. Neuropsychopharmacology 27:105–119.

Lerer B, Segman RH, Tan EC, Basile VS, Cavallaro R, Aschauer HN, Strous R, Chong SA, Heresco-Levy U, Verga M, Scharfetter J, Meltzer HY, Kennedy JL, Macciardi F. 2005. Combined analysis of 635 patients confirms an age-related association of the serotonin 2A receptor gene with tardive dyskinesia and specificity for the non-orofacial subtype. Int J Neuropsychopharmacol 8:411–425.

Lidow MS. 2000. Neurotransmitter receptors in actions of antipsychotic medications. Florida: CRC Press LLC. p 256.

Loonen AJ, van Praag HM. 2007. Measuring movement disorders in antipsychotic drug trials: The need to define a new standard. J Clin Psychopharmacol 27:423–430.

Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F. 1994. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord 9:76–83.

Metzer WS, Newton JE, Steele RW, Claybrook M, Paige SR, McMillan DE, Hays S. 1989. HLA antigens in drug-induced parkinsonism. Mov Disord 4:121–128.

Mihara K, Suzuki A, Kondo T, Nagashima U, Ono S, Otani K, Kaneko S. 2000. No relationship between Taq1 a polymorphism of dopamine D(2) receptor gene and extrapyramidal adverse effects of selective dopamine D(2) antagonists, bromperidol, and nemonapride in schizophrenia: A preliminary study. Am J Med Genet 96:422–424.

Mihara K, Kondo T, Suzuki A, Yasui N, Ono S, Otani K, Kaneko S. 2001. No relationship between -141C Ins/Del polymorphism in the promoter region of dopamine D2 receptor and extrapyramidal adverse effects of selective dopamine D2 antagonists in schizophrenic patients: A preliminary study. Psychiatry Res 101:33–38.

Miller SA, Dykes DD, Polesky HF. 1988. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215.

Moleman P. 1992. Praktische psychofarmacologie. Houten: Bohn Stafleu Van Loghum. p 264.

Nakazono Y, Abe H, Murakami H, Koyabu N, Isaka Y, Nemoto Y, Murata S, Tsutsumi Y, Ohtani H, Sawada Y. 2005. Association between neuroleptic drug-induced extrapyramidal symptoms and dopamine D2-receptor polymorphisms in Japanese schizophrenic patients. Int J Clin Pharmacol Ther 43:163–171.

Ohashi J, Tokunaga K. 1999. Selecting a contingency table in a population-based association study: Allele frequency or positivity? J Hum Genet 44:246–248.

Ohashi J, Yamamoto S, Tsuchiya N, Hatta Y, Komata T, Matsushita M, Tokunaga K. 2001. Comparison of statistical power between 2×2 allele frequency and allele positivity tables in case-control studies of complex disease genes. Ann Hum Genet 65:197–206.

Okada M, Northup JK, Ozaki N, Russell JT, Linnoila M, Goldman D. 2004. Modification of human 5-HT(2C) receptor function by Cys23Ser, an abundant, naturally occurring amino-acid substitution. Mol Psychiatry 9:55–64.

Page WF. 1997. The Dutch Triangle: The Netherlands and the Atlantic Slave Trade,1621-1664. New York: Garland. p 262.

Pohjalainen T, Nagren K, Syvalahti EK, Hietala J. 1999. The dopamine D2 receptor 5′-flanking variant, -141C Ins/Del, is not associated with reduced dopamine D2 receptor density in vivo. Pharmacogenetics 9:505–509.

Reynolds GP. 2004. Receptor mechanisms in the treatment of schizophrenia. J Psychopharmacol 18:340–345.

Ritchie T, Noble EP. 2003. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. Neurochem Res 28:73–82.

Segman RH, Heresco-Levy U, Finkel B, Inbar R, Neeman T, Schlafman M, Dorevitch A, Yakir A, Lerner A, Goltser T, Shelevoy A, Lerer B. 2000. Association between the serotonin 2C receptor gene and tardive dyskinesia in chronic schizophrenia: Additive contribution of 5-HT2Cser and DRD3gly alleles to susceptibility. Psychopharmacology (Berl) 152:408–413.

Siemers E. 1992. Recent progress in the treatment of Parkinson's disease. Compr Ther 18:20–24.

Trosch RM. 2004. Neuroleptic-induced movement disorders: Deconstructing extrapyramidal symptoms. J Am Geriatr Soc 52:S266–S271.

van Harten PN, Matroos GE, Hoek HW, Kahn RS. 1996. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia The Curacao Extrapyramidal Syndromes Study: I. Schizophr Res 19:195–203.

van Harten PN, Hoek HW, Matroos GE, Koeter M, Kahn RS. 1997. The inter-relationships of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia: The Curacao Extrapyramidal Syndromes Study II. Schizophr Res 26:235–242.

van Harten PN, Hoek HW, Matroos GE, van OJ. 2006. Incidence of tardive dyskinesia and tardive dystonia in African Caribbean patients on long-term antipsychotic treatment: The Curacao extrapyramidal syndromes study V. J Clin Psychiatry 67:1920–1927.

Warren JT Jr, Peacock ML, Rodriguez LC, Fink JK. 1993. An MspI polymorphism in the hyman serotonin receptor gene (HTR2): Detection by DGGE and RFLP analysis. Hum Mol Genet 2:338.

Wu SN, Gao R, Xing QH, Li HF, Shen YF, Gu NF, Feng GY, He L. 2006. Association of DRD2 polymorphisms and chlorpromazine-induced extrapyramidal syndrome in Chinese schizophrenic patients. Acta Pharmacol Sin 27:966–970.

Xu K, Lichtermann D, Lipsky RH, Franke P, Liu X, Hu Y, Cao L, Schwab SG, Wildenauer DB, Bau CH, Ferro E, Astor W, Finch T, Terry J, Taubman J, Maier W, Goldman D. 2004. Association of specific haplotypes of D2 dopamine receptor gene with vulnerability to heroin dependence in 2 distinct populations. Arch Gen Psychiatry 61:597–606.