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ORIGINAL PAPER

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A search for association between schizophrenia and dopamine-related alleles

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Abstract Dopamine receptor dysfunction and altered tyrosine hydroxylase activity have both been implicated in the pathophysiology of schizophrenia. Schizophrenic patients and control subjects were examined for allele frequencies in the tyrosine hydroxylase and dopamine D_2 and D_4 receptor genes. No significant differences of allele or genotype frequencies were found between the two groups after adjustment for multiple comparisons. Neither were any significant relationships observed between allele frequencies and a number of clinical variables within the schizoprenic subsample. When no adjustment was made for multiple testing a few significant tendencies were obtained which warrant further research in extended patient and control materials. The results are compatible with the view that the tyrosine hydroxylase, dopamine receptor D2 and D4 gene polymorphisms examined are not of major importance in the aetiology or pathophysiology of schizophrenia.

Key words Schizophrenia · Association study · Dopamine receptors (DRD2, DRD4) · Tyrosine hydroxylase

Introduction

Family, twin and adoption studies suggest that genetic factors play a role in the aetiology of schizophrenia (Kety et al. 1968; Onstad et al. 1991; Kendler and Diehl 1993; Kendler et al. 1993 a). The evolution of molecular genetic techniques has provided tools to investigate schizophrenic patients for putative DNA aberrations. Recent findings in linkage studies have suggested susceptibility loci for schizophrenia at the long arms of chromosomes 6 and 22 (Polymeropoulos et al. 1994; Antonarakis et al. 1995; Lasseter et al. 1995; Moises et al. 1995 a, b; Schwab et al. 1995; Straub et al. 1995; Vallada et al. 1995 a, b; Wang et al. 1995; Schizophrenia Collaborative Linkage Group [chromosome 22] 1996). Schizophrenia is likely to be heterogeneous in origin. Data from adoption, twin and family studies can more easily be interpreted to support the existence of a large number of genes producing a high risk of schizophrenia than supporting the occurrence of a single gene disorder as determinant to the disease (McGue and Gottesman 1991). This makes it reasonable to also investigate other loci with methods allowing the detection of genes with small effects. In this context association studies may be useful, especially if there is an a priori hypothesis giving guidelines to the genomic localization. Alterations in dopamine transmission and dopamine receptors have long been hypothesized in the pathophysiology of schizophrenia (van Rossum 1967; Haracz 1982; Davis et al. 1991). Being the rate-limiting enzyme in catecholamine synthesis (Nagatsu et al. 1964), tyrosine hydroxylase (TH) adds as an aspirant gene for schizophrenia. Findings from post-mortem (Lee and Seeman 1980; Hess et al. 1987) and positron emission tomography studies (Wong et al. 1986), although controversial (Farde et al. 1990; Nordström et al. 1995), have highlighted the dopamine D_2 receptor (DRD2) as possibly involved in the pathophysiology of schizophrenia. The dopamine D_4 receptor (DRD4) has been suggested as a candidate gene for schizophrenia on the basis of one report indicating a sixfold increase in receptor levels in post-mortem brains from schizophrenic patients (Seeman et al. 1993). The DRD4 receptor is also of interest due to its high affinity for the atypical neuroleptic drug clozapine (Van Tol et al. 1991). Genetic polymorphisms for these and others enzymes, receptors and transporters involved in brain

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dopamine turnover have been investigated in linkage (Moises et al. 1991; Barr et al. 1993; Coon et al. 1993; Gill et al. 1993; Jensen et al. 1993; Nicolini et al. 1993; Sherrington et al. 1993; Su et al. 1993; Wang et al. 1993; Wiese et al. 1993; Campion et al. 1994; Hallmayer et al. 1994; Li et al. 1994; Macciardi et al. 1994a; Maier et al. 1994; Nanko et al. 1994a; Sabaté et al. 1994; Shaikh et al. 1994b; Maziade et al. 1995; Mulcrone et al. 1995; Persico et al. 1995; Kalsi et al. 1996; Meszaros et al. 1996) and association studies (Comings et al. 1991; Sanders et al. 1992; Crocq et al. 1992; Catalano et al. 1993; Cichon et al. 1993; Hattori et al.1993; Jönsson et al. 1993; Nanko et al. 1993a; Nanko et al. 1993b; Nicolini et al. 1993; Nimgaonkar et al. 1993; Nöthen et al. 1993a; Nöthen et al. 1993b; Sommer et al. 1993; Arinami et al. 1994; Asherson et al. 1994; Campion et al. 1994; Cichon et al. 1994; Daniels et al. 1994; Laurent et al. 1994a; Laurent et al. 1994b; Macciardi et al. 1994b; Mant et al. 1994; Nanko et al. 1994b; Nöthen et al. 1994a; Nöthen et al. 1994b; Sabaté et al. 1994; Shaikh et al. 1994a; Sobell et al. 1994; Daniels et al. 1995; Kennedy et al. 1995; Lee et al. 1995; Meloni et al. 1995; Nakamura et al. 1995; Petronis et al. 1995; Sobell et al. 1995; Tanaka et al. 1995; Wei et al. 1995; Daniels et al. 1996; Griffon et al. 1996; Meszaros et al. 1996; Nimganokar et al. 1996; Rietschel et al. 1996) in schizophrenic pedigrees and samples of unrelated patient and control subjects. No consistent evidence for linkage has been found. Most association studies have also given negative results, with a few exceptions (Comings et al. 1991; Crocq et al. 1992; Nimgaonkar et al. 1993; Arinami et al. 1994; Mant et al. 1994; Griffon et al. 1995; Kennedy et al. 1995; Lee et al. 1995; Nakamura et al. 1995). Allele distributions often vary between different ethnic populations. It is also possible that an association may be present in one ethnic population but not in others. Therefore, in the present study we examined allele frequencies in TH, DRD2 and DRD4 polymorphisms in schizophrenic patients and healthy control subjects from Sweden, representing an ethnic category not investigated previously for these polymorphisms in association studies.

Materials and methods

Subjects

All subjects were unrelated Caucasian individuals living in Stockholm. They were assessed for psychiatric diagnosis (DSM-III-R), family history of psychosis in first- or second-degree relatives and geographic origin as described previously (Jönsson et al. 1993). Patients were also evaluated regarding age at first hospitalization, abuse of alcohol, solvents, or drugs, previous suicide attempts, response to neuroleptic drug treatment, extrapyramidal side effects (EPS) and treatment with anticholinergic drugs. All patients (n = 118) fulfilled a DSM-III-R diagnosis of schizophrenia; 75 were men and 43 women. Their age range was 20–90 years (mean age 45.8 years). They had their first hospitalization at the age of 15–59 years (mean age 25.7 years). Of the schizophrenic patients, 49 (43.8%) had at least one first-degree relative with schizophrenia, schizoaffective disorder, bipolar disorder, recurrent unipolar disorder, other nonorganic psychosis or a history of completed suicide. Genealogical reports indicated that 86 patients were of plain Swedish origin, whereas 33 had to some degree antecedents from other countries. This corresponds to a population gene frequency of 19.7%, of which approximately 69% were Finnish and the remaining were distributed throughout 11 European countries. Of the 78 control subjects, 45 were men and 33 women. All were free from current or prevoius psychiatric morbidity. The age range was 29–56 years (mean age 38.7 years). Genealogical data implicated that 61 of the control subjects were of plain Swedish origin. Seventeen persons had antecedents from other countries, which corresponds to a population gene frequency of 12.5%, of which approximately 48% were Finnish and the remaining were distributed throughout eight European countries.

Laboratory procedure

From all individuals venous blood was taken into EDTA-containing tubes. DNA isolation was performed as described previously (Geijer et al. 1994).

The imperfect tetranucleotide repeat polymorphism (TCAT) in the first intron of the TH gene (Polymeropoulos et al. 1991) was analysed as described previously (Jönsson et al. 1996). Five DNA fragments were observed (260/259, 256, 252, 248 and 244 bp) and denoted K1, K2, K3, K4 and K5, respectively (Polymeropoulos et al. 1991).

The DRD2 TaqI A (Grandy et al. 1989) and B (Hauge et al. 1991) two-allele polymorphisms were determined as described by Geijer et al. (1994). TaqI restriction endonuclease generates a 3.7-kb DNA fragment, defining the A2 allele, or fails to do so resulting in a 6.6-kb DNA fragment instead, defining the A1 allele. TaqI restriction endonuclease cleavage also generates a 4.6-kb DNA fragment (B1) or a 4.1-kb DNA fragment (B2).

A DRD4 48 nucleotide sequence occurs as two to ten repeat units (Lichter et al. 1993) in the DNA sequence that codes for the third cytoplasmic region of the receptor protein. PCR was used to amplify DNA in this region, generating DNA fragments with different sizes depending on the number of 48 bp repeats as described previously (Jönsson et al. 1996). Eight different DNA fragments were denoted C2, C3, C4, C5, C6, C7, C8 and C10 according to their numbers of 48 bp repeats.

Data analysis

Testing of nonparametric variables for significance was performed with the χ^2-test. For the derived 2×2 contingency tables, Yates' correction was applied. Continuous variables (age) were compared by unpaired Student's t-test or analysis of variance (ANOVA). More than 1000 different calculations were performed. To correct for chance significances, we used Boniferroni's correction. The overall level of significance was set to 0.05, leading to a probability significance level of less than 0.00005 for each comparison to be regarded as significant.

Results

When corrected for multiple testing no significant relationships emerged. Some of the tendencies obtained are listed below.

Tyrosine hydroxylase

A tendency for deviant allele distribution was found (Table 1). There were lower K1 allele [$\chi^2(1) = 4.67$, $P = 0.031$] and genotype [$\chi^2(1) = 7.18$, $P = 0.007$] frequencies among schizophrenic patients than controls (Table 1). When comparing the allele distribution with regard to gender,

Table 1 Tyrosine hydroxylase allele and genotype counts and frequencies (given in percent within parentheses) in schizophrenic patients and control subjects

	Schizophrenics (n = 118)	Controls (n = 78)
Allele[a]		
K1[b]	65 (27.5)	60 (38.5)
K2	41 (17.4)	22 (14.1)
K3[c]	24 (10.2)	8 (5.1)
K4	45 (19.1)	33 (21.2)
K5	61 (25.9)	33 (21.2)
Genotype		
K1K1	9 (7.6)	8 (10.3)
K1K2	11 (9.3)	13 (16.7)
K1K3	8 (6.8)	4 (5.1)
K1K4	11 (9.3)	14 (18.0)
K1K5	17 (14.4)	14 (18.0)
K2K2	4 (3.4)	0
K2K3	6 (5.1)	3 (3.9)
K2K4	7 (5.9)	1 (1.3)
K2K5	11 (9.3)	5 (6.4)
K3K3	0	0
K3K4	4 (3.4)	0
K3K5	5 (4.2)	1 (1.3)
K4K4	5 (4.2)	5 (6.4)
K4K5	13 (11.0)	7 (9.0)
K5K5	7 (5.9)	3 (3.9)

[a] $\chi^2(4) = 8.13$, $P = 0.087$
[b] $\chi^2(1) = 4.67$, $P = 0.031$
[c] $\chi^2(1) = 2.55$, $P = 0.111$

schizophrenic men had a deviant distribution [$\chi^2(4) = 10.56$, $P = 0.032$] with lower K1 allele [$\chi^2(1) = 4.26$, $P = 0.039$] and genotype frequencies [$\chi^2(1) = 5.37$, $P = 0.021$] and higher K3 allele [$\chi^2(1) = 3.37$, $P = 0.067$] and genotype frequencies [$\chi^2(1) = 3.56$, $P = 0.059$] than male controls, whereas no difference was found between schizophrenic and control women [$\chi^2(4) = 1.27$, $P = 0.866$]. When comparing schizophrenic patients with regard to presence or absence of suicide attempts, the K5 allele and genotypes were found to be less prevalent in patients who had previously made at least one suicide attempt ($n = 48$) than among patients who had never attempted suicide ($n = 68$) [allelic $\chi^2(1) = 5.50$, $P = 0.019$; genotype $\chi^2(1) = 5.92$, $P = 0.015$]. Schizophrenic patients with the K2K5 genotype were younger at first hospitalization than patients without this allele combination (average 21.0 vs 26.2 years; $t = 2.23$, $P = 0.028$). Patients who had experienced EPS tended to have lower K2K5 genotype frequency than those who had not [$\chi^2(1) = 3.17$, $P = 0.075$].

Dopamine D_2 receptor

The allele and genotype frequencies of the DRD2 TaqI A and TaqI B restriction fragment length polymorphisms (RFLP) were found to be in disequilibrium with each other. This is in accordance with previous studies (Hauge et al. 1991; O'Hara et al. 1993; Geijer et al. 1994; Castiglione et al. 1995). Consequently, the results of all the comparisons made with the TaqI A and TaqI B RFLP allele and genotype frequencies were very similar. Therefore, only the data from calculations with the TaqI A RFLP are presented. There were no statistically significant differences between schizophrenic patients and control subjects (Table 2). The combined subgroups of patients and controls with a family history of major mental illness in first-degree relatives were examined vs subjects without such family history. An association between heterozygosity and family history for mental disorders [$\chi^2(2) = 12.67$, $P = 0.004$ and $\chi^2(1) = 7.87$, $P = 0.005$] was found. Also in

Table 2 Dopamine D_2 receptor TaqI A allele and genotype counts and frequencies (given in percent within parentheses) in schizophrenic patients and control subjects

	Schizophrenics (n = 104)	Controls (n = 67)
Allele		
A1	38 (18.3)	26 (19.4)
A2	170 (81.7)	108 (80.6)
Genotype		
A1A1	4 (3.8)	4 (6.0)
A1A2	30 (28.8)	18 (26.9)
A2A2	70 (67.3)	45 (67.2)

Table 3 Dopamine D_4 receptor allele and genotype counts and frequencies (given in percent within parentheses) in schizophrenic patients and healthy control subjects

	Schizophrenics (n = 118)	Controls (n = 76)
Allele		
C2	16 (6.8)	7 (4.6)
C3	12 (5.1)	15 (9.9)
C4	159 (67.4)	102 (67.1)
C5	2 (0.9)	1 (0.7)
C6	1 (0.4)	1 (0.7)
C7	42 (17.8)	23 (15.1)
C8	3 (1.3)	3 (2.0)
C10	1 (0.4)	0
Genotype		
C2C4	14 (11.9)	7 (9.2)
C2C7	2 (1.7)	0
C3C3	1 (0.9)	0
C3C4[a]	6 (5.1)	13 (17.1)
C3C7	4 (3.4)	2 (2.6)
C4C4	54 (45.8)	31 (40.8)
C4C5	2 (1.7)	1 (1.3)
C4C6	1 (0.9)	1 (1.3)
C4C7	25 (21.2)	17 (22.4)
C4C8	2 (1.7)	2 (2.6)
C4C10	1 (0.9)	0
C7C7	5 (4.2)	1 (1.3)
C7C8	1 (0.9)	1 (1.3)

[a] $\chi^2(1) = 6.26$, $P = 0.012$

schizophrenic patients there was a similar difference between subjects with and without family history for mental disorders [$\chi^2(1) = 6.68$, $P = 0.010$].

Dopamine D_4 receptor

Comparisons of the C3C4 genotype vs all other genotypes indicated a lower frequency of this allele combination in schizophrenic patients than controls [$\chi^2(1) = 6.26$, $P = 0.012$; Table 3]. When the C3C4 genotype was analysed with regard to gender, schizophrenic men displayed a lower frequency than control males [$\chi^2(1) = 8.73$, $P = 0.003$], whereas no differences were found between schizophrenic and control women [$\chi^2(1) = 0.00$, $P = 0.984$]. There was also an increased frequency of C4 alleles in patients who had experienced EPS [allelic $\chi^2(1) = 2.79$, $P = 0.095$; genotype $\chi^2(1) = 4.35$, $P = 0.037$]. Different frequencies of the C7 allele among schizophrenic subdiagnoses were found [allelic $\chi^2(3) = 7.34$, $P = 0.062$; genotype $\chi^2(3) = 9.01$, $P = 0.029$], with higher frequencies in catatonic and paranoid patients.

Discussion

In the present study TH, DRD2 and DRD4 allele and genotype frequencies were compared in schizophrenic patients and healthy control subjects. When Boniferroni's correction was used, no significant relationship was found. However, a number of tendencies between or within the subject groups for each of the polymorphisms investigated were observed. A few of these merit discussion.

A tendency for a different TH allele distribution with lower TH K1 allele and genotype frequencies in schizophrenic patients than in control subjects was found (Table 1). To further evaluate this putative negative association, the control material was enlarged by including another 63 subjects. Of these, 33 were unscreened independently sampled subjects from the same region and with a similar ethnic background. The remaining 30 were excluded from the present study due to lifetime DSM-III-R diagnoses, none with schizophrenia but usually with alcohol, anxiety or depressive disorders. It was considered appropriate to pool the control samples because no significant difference in allele or genotype frequencies was found between the original control material and the two latter samples [allelic $\chi^2(4) = 1.13$, $P = 0.889$ and $\chi^2(4) = 0.32$, $P = 0.988$, respectively]. Together these samples represent an unscreened control population. Uncorrected comparisons of alleles between the schizophrenic sample and all controls then reached significance [$\chi^2(4) = 10.02$, $P = 0.040$]. The probability for difference when the K1 allele were compared vs all other alleles was further strengthened [$\chi^2(1) = 6.07$, $P = 0.014$]. Family and adoption studies suggest relationships between schizophrenia and other psychoses and personality disorders with schizophrenic symptoms (Kety et al. 1978; Kendler et al. 1993b, c; Kendler et al. 1995a, b). In order to evaluate this broader "schizophrenia spectrum" concept, patients ($n = 21$) with schizophrenic symptomatology not fulfilling DSM-III-R criteria for schizophrenia, but mainly schizoaffective disorder, schizophreniform psychosis, psychosis not otherwise specified and personality disorders within cluster A, and who were excluded in the present study, were added to the schizophrenic sample. No significant TH allele difference was found between the patients with "core" DSM-III-R schizophrenia and the remaining 21 patients [$\chi^2(4) = 0.99$, $P = 0.911$]. When patients with schizophrenic symptoms, but not fulfilling a DSM-III-R diagnosis of schizophrenia, were included in the patient group and compared with the extended control group, the probability differences of all TH alleles [$\chi^2(4) = 12.32$, $P = 0.015$], TH K1 alleles [$\chi^2(1) = 8.27$, $P = 0.003$] and genotypes [$\chi^2(1) = 10.86$, $P = 0.001$] culminated. A parallel tendency for increased TH K3 allele frequency in patients as compared with control subjects was recorded [allelic $\chi^2(1) = 3.13$, $P = 0.077$; genotype $\chi^2(1) = 2.44$, $P = 0.120$].

The present results differ from those of Wei et al. (1995) and Meloni et al. (1995). Wei and coworkers did not find any significant difference in allele frequencies between British schizophrenic patients and control subjects. However, without Yates' and Boniferroni's corrections they found a significant excess of the K1K5 genotype in schizophrenic patients. No such association was detected in the present sample. On the contrary, when comparing schizophrenic and control men in the present sample, a trend towards lower K1K5 frequency in schizophrenic subjects was found [$\chi^2(1) = 3.04$, $P = 0.081$]. Similar comparisons of female subjects did not yield any differences [$\chi^2(1) = 0.19$, $P = 0.663$]. The reason for the discrepancy between the two investigations is presently unclear. Chance findings may be an explanation, perhaps the most plausible one. Also, stratification effects may contribute. Wei et al. (1995) did not report origin in their sample; neither did they define schizophrenia. This may mean that the two studies are not fully comparable in these respects.

The K1 allele as measured in the present study refers to two alleles: a rare perfect 10 repeat of the four nucleotides ($TCAT_{10}$), found in an allele frequency of around 1% in a Caucasian population (Puers et al. 1993), and a common (Caucasian population frequency according to Puers: 35%) repeat sequence in which one of the repeats is imperfect lacking a thymine: $(TCAT)_4CAT(TCAT)_5$. In a previous study (Meloni et al. 1995) no significant difference was found between the K1 allele and schizophrenia in a French and a Tunisian sample, although there were small excesses of K1 alleles in both patient samples. These excesses were due to the rare perfect K1 allele, which was found in 5 and 9% of the French and Tunisian schizophrenic subjects, respectively, but was not found among the control samples. The tendency obtained in the present sample points in the opposite direction and most likely reflects the common imperfect K1 allele. However, it cannot be excluded that this putative negative association may hide a positive association to schizophrenia with the rare perfect K1 allele. This possibility is presently under investigation.

We did not find evidence for an association between different DRD2 TaqI alleles and schizophrenia. Our results are accordingly in agreement with those of Sanders et al. (1992), Nöthen et al. (1993b), and Campion et al. (1994), but differ partly from those of Comings et al. (1991) and Lee et al. (1995). Comings and coworkers (1991) found an association between the A1 allele and schizophrenia when compared with controls not suffering from alcoholism. This difference may be partly due to different A1 allele frequencies in the two control groups [0.07 in Comings et al. (1991) vs 0.19 in the present study; $\chi^2(1) = 7.72$, $P = 0.006$]. Because no matching for ethnic origin in controls and patients was reported in the American study, different allele frequencies in groups with different ethnical backgrounds in their samples may explain the discrepant findings. However, this is a less likely explanation for the discrepant findings between the Korean investigation (Lee et al. 1995) and the present study. Chance findings or reflection of a susceptibility gene restricted mainly to the Korean population may be other hypothetical explanations for the association found between the TaqI A1 allele and schizophrenia in the Korean sample (Lee et al. 1995).

Comparisons of DRD4 allele frequencies did not yield statistical significance. This is in accordance with previous investigations (Cichon et al. 1993; Nanko et al. 1993a; Sommer et al. 1993; Daniels et al. 1994; Petronis et al. 1995; Tanaka et al. 1995). As in three of these studies (Sommer et al. 1993; Daniels et al. 1994; Tanaka et al. 1995), although at variance with a Japanese research team (Nakamura et al. 1995), analyses of our schizophrenic sample did not reveal differences between patients with or without family history (data not shown). A small but nonsignificant excess of the C7 allele in schizophrenic patients as compared with controls was found as has previously also been reported by Petronis et al. (1995) and Daniels et al. (1994). However, in two other studies of Caucasian subjects, higher C7 allele frequencies were found among controls (Cichon et al. 1993; Sommer et al. 1993). In the present study, lower C3C4 genotype frequency in schizophrenic patients than in healthy controls was found [$\chi^2(1) = 6.26$, $P = 0.012$]. When analysed for gender, lower C3C4 frequencies were found in schizophrenic men, but not in women, when compared with control men and women, respectively. None of the other groups who reported genotype frequencies found a similar tendency (Sommer et al. 1993; Daniels et al. 1994; Nakamura et al. 1995; Petronis et al. 1995; Tanaka et al. 1995). It is tempting to conclude that the 48-bp repeat polymorphism in the third exon of DRD4 does not reflect a major susceptibility to schizophrenia. However, at least 25 haplotypes exist for this polymorphic region of the DRD4 gene (Lichter et al. 1993). Therefore, involvement of this polymorphism in the genetics of schizophrenia cannot be ruled out. Future studies determining these haplotypes for population studies will require much larger sample sizes.

The present investigation in combination with the studies mentioned herein support the view that the parts of the TH, DRD2 and DRD4 genes examined are not of major importance for the susceptibility to schizophrenia. However, a few nonsignificant trends reported may warrant further studies with larger patient materials to determine whether the polymorphisms reflect minor aetiological contributions to the disease. Also, it cannot be excluded that other nearby locations in linkage equilibrium with the polymorphisms investigated may contribute to the genesis of this disorder.

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