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Association Study of Bipolar Disorder With Candidate Genes Involved in Catecholamine Neurotransmission: DRD2, DRD3, DAT1, and TH Genes

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Despite strong evidence for genetic involvement in the etiology of affective disorders (from twin adoption and family studies), linkage and association methodologies are still exploring the nature of genetic factors in these diseases. Interesting testable hypotheses have been described, including candidate genes involved in catecholamine neurotransmission. We studied 69 bipolar patients and 69 matched controls (for age, sex, and geographical origin) for association and linkage disequilibrium with DNA markers at the following genes: the tyrosine hydroxylase gene, dopamine transporter gene, and dopamine D2 and D3 receptor genes. Association and linkage disequilibrium were excluded between bipolar affective disorder and these four candidate genes in our sample. © 1996 Wiley-Liss, Inc.

KEY WORDS: bipolar affective disorder, candidate genes, catecholamine neurotransmission, linkage disequilibrium

INTRODUCTION

Implication of the catecholamine neurotransmitter system in the etiopathogenesis of affective disorders (AD) was hypothesised nearly 30 years ago [Schildkraut, 1965]. Evidence in favor of this hypothesis in AD initially relied on the effects of drugs such as tricyclic antidepressants and monoamine oxydase inhibitors on catecholaminergic transmission. These observations were supported by several molecular biological studies in depression and mania [reviewed in Schatzberg and Schildkraut, 1995].

Tyrosine hydroxylase (TH) catalyses the enzymatic conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-dopa), the first and rate-limiting step in the biosynthesis of dopamine (DA), norepinephrine (NE), and epinephrine (E). It has been shown that TH activity differs in NE and DA neurons in the central nervous system [Reis et al., 1974], illustrating the extreme complexity of this pathway. Five different DA receptors have been identified (DRD_1–DRD_5). The dopamine transporter (DAT1) terminates dopaminergic transmission by reuptake of DA into presynaptic terminals. DAT-mediated recapture of released DA is generally thought to be the primary mechanism for limiting the extent, duration, and area of DA receptor activation. The cDNA encoding DAT1 was recently cloned and located on chromosome 5p15.3 [Vandenbergh et al., 1992].

Traditional methodologies such as twin, adoption, and family studies have implicated genetic vulnerability factors in the etiology of AD and their various subtypes [Mendlewicz, 1994]. However, from these methods, it is difficult to delineate the type of genetic variables involved and the precise mode of transmission. In searching for underlying genes and their mechanism of action, linkage and allelic association methodologies are being applied to mood disorders, in particular to the bipolar form of the disease (BPAD), considered the "core phenotype" in genetic studies of the AD spectrum.

Candidate genes encoding enzymes and receptors involved in the metabolism of catecholamines have been investigated through linkage and association studies in AD. Chromosome 11 has been the subject of multiple

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linkage studies. This location is of great interest, since the tyrosine hydroxylase (TH) gene is situated on the short arm of chromosome 11 (11p15) [Egeland et al., 1987]. For reasons mentioned above, the TH gene is considered a candidate gene in AD. The majority of linkage studies with the TH gene excluded linkage between this gene and BPAD [Souery et al., 1996b]. However, weak positive lod-scores (below significant threshold) were observed for the TH locus in some pedigrees from different populations [Pakstis et al., 1991; Byerley et al., 1992; Lim et al., 1993; Sidenberg et al., 1994].

A possible role for the TH gene was also examined in case-control designed association studies in BPAD. Some reports described a significant association between BPAD and TH polymorphisms [Leboyer et al., 1990; Kennedy et al., 1993; Cauli et al., 1995; Meloni et al., 1995]. This observation could not be replicated using the same TH polymorphisms, or with other TH polymorphisms in other studies [Todd and O'Malley, 1989; Nöthen et al., 1990; Körner et al., 1990, 1994; Gill et al., 1991; Inayama et al., 1993; Cavazzoni et al., 1995].

Other candidate genes involved in the catecholamine pathway, including D_2–D_4 dopamine receptors genes (DRD_2–DRD_4), are located on other regions of chromosome 11 (11q22–23 and 11p15.5, respectively). Almost all recent linkage studies searching for autosomal susceptibility loci in AD excluded linkage with DNA markers located on this chromosome, including the two candidate genes mentioned above [Byerley et al., 1990; Mendlewicz et al., 1991; Holmes et al., 1991; Mitchell et al.; 1992; Gejman et al., 1993; Coon et al., 1993; Gerhard et al., 1994; De Bruyn et al., 1994; Detera-Wadleigh et al., 1994; Ewald et al., 1994]. Shinichiro et al. [1994] could not definitely exclude linkage for the DRD_4 locus in four Japanese pedigrees, while they excluded linkage for DRD_2. A weak positive lod score of 1.16 for this marker was also observed in the Old Order Amish pedigree 00A110 [Sidenberg et al., 1994].

The DRD_3 gene, located on chromosome 3 (3q 13.3), was investigated for linkage in BPAD families. Linkage was excluded for this marker in two reports [Shinichiro et al., 1994; Mitchell et al , 1993]. Two BPAD Belgian families were recently investigated for linkage with candidate genes involved in dopaminergic neurotransmission (DAT1, DBH, DRD_2, DRD_3, and DRD_5) [De Bruyn et al., 1996]. No evidence of linkage was found in these families for these markers.

Some of these candidate genes were also investigated in association studies. Lack of association was observed between the DRD_2 gene and BPAD [Craddock et al., 1995]. This was also the case for DRD_3 on chromosome 3 in two studies [Shaikh et al., 1993; Rietschel et al., 1993]. A statistically significant association of allele 1 of DRD_3 with BPAD was found using the transmitted vs. nontransmitted allele relative-risk method in one study [Parsian et al., 1995]. In the same report, lack of association with the same marker was observed using the case-control design.

From these numerous reports, it is difficult to specify the exact implication of these genetic markers in the etiology of AD. Inconclusive results with both linkage and association methodologies, as well as some preliminary positive findings, may once again be partially explained by genetic heterogeneity. It is then of interest to further investigate genetic markers of the metabolism of catecholamines in AD, with special attention to the possible bias encountered in association and linkage methodologies.

In the present study, we investigated the possible role in BPAD of four candidate genetic markers, all involved in catecholamine neurotransmission. An association study, using a case-control design, was conducted with simple tandem repeat polymorphisms in the genes coding for TH, DAT1, DRD_2, and DRD_3 between BPAD patients and normal controls. Special attention was devoted to stratification bias. Patients and controls were carefully matched for age, sex, and geographical origin.

MATERIALS AND METHODS

Subjects

Sixty-nine unrelated BPAD patients (34 females and 35 males) and 69 healthy controls (34 females and 35 males) were randomly selected from a larger sample of 95 BPAD patients and 145 controls recruited at Erasme Hospital for genetic studies. The 69 patients and 69 controls included in the present study were carefully matched pairwise for sex and geographical origin, leading to 69 patient-control pairs. The mean age difference between patients (46.17 ± 14.9) and controls (47.48 ± 14.7) was not significantly different ($P = 0.606$). For the patient group, mean age-at-onset was 28.19 (SD, 11.02) years. The mean for number of affective episodes was 3.07 (SD, 2.88) depressive episodes, and 3.35 (SD, 3.90) manic or hypomanic episodes.

The patients were ascertained from admissions to the in- or outpatient units of the Department of Psychiatry of Erasme Hospital and from families included in previous linkage studies (probands only). The controls were recruited from among the staff of the department and friends, and via an announcement in hospital.

Subjects were interviewed using the Schedule for Affective Disorders and Schizophrenia-Lifetime Versions (SADS-LA). Diagnosis was established according to Research Diagnostic Criteria (RDC). All patients met the diagnosis of BPAD. Within the control group, subjects with a positive personal and family history (assessed by the Family History-Research Diagnostic Criteria) of minor or major affective disorder were not included.

DNA Analysis

Genomic DNA was isolated from heparinized blood using a standard phenol-chloroform extraction method. An automated DNA synthesiser was used to generate primers for the four polymorphisms tested. Table I gives information on these polymorphisms.

Standard polymerase chain reaction (PCR) was done in a 25-μl volume containing 100 ng genomic DNA, with 200 μM each of dATP, dCTP, dTTT, dGTP, and 30 pmol of each primer. One primer was end-labelled before PCR with T4 polynucleotide kinase and [γ-^{32}P] ATP. The mixture was denaturated at 94°C for 5 min, followed by 22 cycles consisting of denaturation at 94°C for 1 min, amealing at appropriate temperature for 1.5 min, and

TABLE I. Candidate Genes Analyzed

Gene	Localization	Polymorphism (Restriction Enzyme)	Reference
DRD2	11q22–q23	$(CA)_n$	Hauge et al., 1991
DRD3	3q13.3	RFLP (*BalI*)	Lannfelt et al., 1992
TH	11p15	$(TCAT)_n$	Polymeropoulos et al., 1991
DAT1	5p15.3	VNTR	Vandenbergh et al., 1992

extension at 72°C for 1 min. The final elongation step was performed at 72°C for 5 min. The polymorphisms at DRD2, TH, and DAT1 were detected by separating the PCR products on a polyacrylamide gel and exposure to X-ray film. The restriction fragment length polymorphism (RFLP) at DRD3 was detected by digestion with *Msc*I (isoschizomer, *Bal*I) following nonradioactive PCR. Fragments were visualized by ethidium bromide staining after 3% agarose gel electrophoresis.

Data Analysis

The analysis of allelic association consisted of comparison of allele and genotype frequencies for the four markers investigated between patients and controls. Homozygote-heterozygote distribution was also evaluated. Chi-square statistics were applied. The EH (estimate haplotype) frequencies program for case-control association studies [Terwilliger and Ott, 1994] was also applied for each marker. Allele and haplotype frequencies between disease and marker alleles were calculated by the EH program under specified parameters for disease-gene frequency (0.02), phenocopy rate (0.01), and penetrance (0.80). Deviation from linkage equilibrium between alleles at disease and marker loci was quantified from chi-square values calculated by the program.

RESULTS AND DISCUSSION

Tables II–V display the allele and genotype frequencies as well as the homozygote-heterozygote distribution for TH, DAT1, DRD_2, and DRD_3 polymorphisms in patients and controls. The total number of subjects analyzed differs for each marker according to available genetic information. No significant differences were observed between BPAD patients and controls for DAT1, DRD_2, DRD_3, and TH polymorphisms regarding allele frequencies, genotype frequencies, and homozygote-heterozygote distributions. No evidence of linkage disequilibrium between disease and the four marker alleles was found when the EH was program applied ($P > 0.05$ for TH, DAT1, DRD_2, and DRD_3).

In this sample of 69 BPAD patients and 69 controls matched pairwise for sex and geographical origin, no association was found between BPAD and four candidate genes coding for receptors and enzymes involved in catecholamine neurotransmission. These results indicate that, in our sample, DRD_2 and DRD_3 receptor genes, as well as DAT1 and TH genes, are not directly implicated in the etiology of BPAD.

As reviewed in the Introduction, all of the association studies with DRD_2 and DRD_3 receptors genes in BPAD were negative and are in agreement with our findings. Except for a few studies, all linkage reports excluded

TABLE II. Allele Frequencies, Genotype Counts, and Homozygote-Heterozygote Distribution for TH Polymorphism in BPAD Patients and Control Subjects†

	Controls (n = 67)	BPAD (n = 66)
Alleles*		
1	45 (33.6)	34 (25.8)
2	17 (12.7)	27 (20.5)
3	16 (12)	17 (12.9)
4	15 (11.1)	25 (18.9)
5	41 (30.6)	29 (22)
Genotypes**		
1-1	9 (13.4)	6 (9.1)
1-2	5 (7.5)	7 (10.6)
1-3	4 (5.9)	1 (1.5)
1-4	7 (10.4)	3 (4.5)
1-5	12 (17.9)	11 (16.6)
2-2	0 (0)	3 (4.5)
2-3	1 (1.4)	5 (7.6)
2-4	3 (4.5)	5 (7.6)
2-5	7 (10.4)	4 (6.0)
3-3	1 (1.4)	0 (0)
3-4	0 (0)	5 (7.6)
3-5	8 (11.9)	6 (9.1)
4-4	1 (1.4)	3 (4.5)
4-5	3 (4.5)	6 (9.1)
5-5	6 (8.9)	1 (1.5)
Homozygote-heterozygote***		
Homozygote	17 (25.4)	13 (19.7)
Heterozygote	50 (74.6)	53 (80.3)

† Frequencies expressed in percentages in parentheses for alleles, genotypes, and homozygote-heterozygotes distribution. Number for each allele represents total number of times allele is observed (n × 2).
*$P = 0.063$.
**$P = 0.057$.
***$P = 0.434$.

TABLE III. Allele Frequencies, Genotype Counts, and Hemozygote-Heterozygote Distribution for DAT1 Polymorphism in BPAD Patients and Control Subjects†

	Controls (n = 48)	BPAD (n = 54)
Allele*		
1	0 (0)	2 (1.9)
2	72 (75)	73 (67.6)
3	24 (25)	33 (30.5)
Genotypes**		
1-1	0 (0)	0 (0)
1-2	0 (0)	1 (1.9)
1-3	0 (0)	1 (1.9)
2-2	27 (56.3)	24 (44.4)
2-3	18 (37.5)	24 (44.4)
3-3	3 (6.2)	4 (7.4)
Homozygote-Heterozygote***		
Homozygote	30 (62.5)	28 (51.8)
Heterozygote	18 (37.5)	26 (48.2)

† Frequencies expressed in percentages in parentheses for alleles, genotypes, and homozygote-heterozygote distribution. Number for each allele represents total number of times allele is observed (n × 2).
*$P = 0.255$.
**$P = 0.586$.
***$P = 0.278$.

TABLE IV. Allele Frequencies, Genotype Counts, and Homozygote-Heterozygote Distribution for DRD2 Polymorphism in BPAD Patients and Control Subjects†

	Controls (n = 67)	BPAD (n = 69)
Allele*		
1	1 (0.7)	0 (0)
2	25 (18.7)	28 (20.3)
3	83 (61.9)	81 (58.7)
4	15 (11.2)	11 (8.0)
5	10 (7.5)	18 (13.0)
Genotypes**		
1-3	1 (1.5)	0 (0)
2-2	4 (6)	3 (4)
2-3	13 (19.4)	18 (26)
2-4	2 (3)	1 (1)
2-5	2 (3)	3 (4)
3-3	26 (39)	21 (30)
3-4	9 (13)	9 (13)
3-5	8 (12)	12 (17)
4-4	2 (3)	0 (0)
4-5	0 (0)	1 (1)
5-5	0 (0)	1 (1)
Homozygote-heterozygote***		
Homozygote	32 (47.8)	25 (36.2)
Heterozygote	35 (52.2)	44 (63.8)

† Frequencies expressed in percentages in parentheses for alleles, genotypes, and homozygote-heterozygote distribution. Number for each allele represents total number of times allele is observed (n × 2).
*P = 0.401.
**P = 0.650.
***P = 0.173.

linkage with these markers in BPAD families. A possible explanation for these findings could be that these genes act as genetic susceptibility genes for BPAD in limited samples of patients and families (genetic heterogeneity). In this context, and given genetic heterogeneity, association studies have more power than linkage studies to detect predisposing genes and may be the best way to identify the genes contributing to psychiatric disorders [Crowe, 1993; Commings, 1994]. This effect has been confirmed by simulation studies, showing that once the number of genes involved exceeds 4–6, the linkage approach has a very limited power compared to association studies [Propping et al., 1993]. One should also consider phenotypic (clinical) heterogeneity when studying genetic factors in AD. Indeed, candidate genes such as the ones mentioned above may play a role only in particular subgroups of patients. Phenotypic definition and clinical characteristics may then have important implications for association and linkage studies in AD. Recent findings in schizophrenia [Nanko and Hattori, 1995; Shaikh et al., 1995] and major psychosis [Serreti et al., 1995] suggest that for the severe form of the disease, response to atypical antipsychotic (clozapine) or clinical factors such as mania, delusion, depression, and disorganization appeared to be more relevant than diagnosis for detecting genetic factors, including DA receptors genes. This methodology (using different clinical parameters) should be applied to large samples of BPAD patients with candidate genes of DA neurotransmission in order to formally exclude their implication in the disease.

TABLE V. Allele Frequencies, Genotype Counts, and Homozygote-Heterozygote Distribution for DRD3 Polymorphism in BPAD Patients and Control Subjects†

	Controls (n = 62)	BPAD (n = 62)
Allele*		
1	90 (72.6)	81 (65.3)
2	34 (27.4)	43 (34.7)
Genotypes**		
1-1	36 (58)	27 (44)
1-2	18 (29)	27 (44)
2-2	8 (13)	8 (13)
Homozygote-Heterozygote***		
Homozygote	44 (71)	35 (56.5)
Heterozygote	18 (29)	27 (43.5)

† Frequencies expressed in percentages in parentheses for alleles, genotypes, and homozygote-heterozygotes distribution. Number for each allele represents total number of times allele is observed (n × 2).
*P = 0.217.
**P = 0.214.
***P = 0.093.

Association and linkage studies with the TH gene in AD provide more encouraging data. In our study, the only suggestive trend towards association was observed with the TH gene. Weak positive lod scores have been observed with this marker in some families [Pakstis et al., 1991; Lim et al., 1993; Byerley et al., 1992; Sidenberg et al., 1994]. These observations, as well as some positive association findings with TH in BPAD [Leboyer et al., 1990; Kennedy et al., 1993; Cauli et al., 1995; Meloni et al., 1995] and UPAD [Souery et al., 1996a], constitute enough evidence to suggest the implication of this gene in AD. Negative findings may be explained by genetic heterogeneity or the presence of phenotypic diversity.

In conclusion, our association data provide additional evidence against a possible implication of DAT1, DRD_2, DRD_3, and TH in BPAD. Linkage disequilibrium was excluded between BPAD and these four genetic markers. However, these candidate genes should be further investigated in AD using larger samples and phenotypic models in parametric and nonparametric methodologies. It is expected that significant advances in finding the hereditary causes of major psychosis will arise from large multicenter projects.

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