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*Brief Research Communication*

# Systematic Screening for Mutations in the 5′-Regulatory Region of the Human Dopamine $D_1$ Receptor (DRD1) Gene in Patients With Schizophrenia and Bipolar Affective Disorder

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**A possible dysregulation of dopaminergic neurotransmission has been implicated in a variety of neuropsychiatric diseases. In the present study we systematically searched for the presence of mutations in the 5′-flanking region of the dopamine $D_1$ receptor (DRD1) gene. This region has previously been shown to contain a functional promoter [Minowa et al., 1992: Proc Natl Acad Sci 89:3045–3049; Minowa et al., 1993: J Biol Chem 268:23544–23551]. We investigated 119 unrelated individuals (including 36 schizophrenic patients, 38 bipolar affective patients, and 45 healthy controls) using single-strand conformation analysis (SSCA). Eleven overlapping PCR fragments covered 2,189 bp of DNA sequence. We identified six single base substitutions: −2218T/C, −2102C/A, −2030T/C, −1992G/A, −1251G/C, and −800T/C. None of the mutations was found to be located in regions which have important influence on the level of transcriptional activity. Allele frequencies were similar in patients and controls, indicating that genetic variation in the 5′-regulatory region of the DRD1 gene is unlikely to play a frequent, major role in the genetic predisposition to either schizophrenia or bipolar affective disorder.** © 1996 Wiley-Liss, Inc.

**KEY WORDS: dopamine D1 receptor gene, polymorphism, mutation, promoter, schizophrenia, manic depression**

## INTRODUCTION

Dopamine receptors belong to the family of G-protein-coupled receptors, which as common features display seven highly-conserved hydrophobic transmembrane domains, as well as coupling to intracellular effectors via G-proteins. The dopamine receptors so far cloned can be subdivided into two biochemically and pharmacologically distinct subtypes: the dopamine $D_1$ (DRD1) and $D_5$ (DRD5) receptors which belong to the $D_1$-like subtype, and the dopamine $D_2$ (DRD2), $D_3$ (DRD3), and $D_4$ (DRD4) receptors which belong to the $D_2$-like subtype. Complex synergistic and antagonistic interactions between the $D_1$-like and $D_2$-like dopamine receptors have been described at the cellular and molecular levels [reviewed in Nestler, 1994]. Because of a possible role of dysregulation of dopaminergic transmission in neuropsychiatric diseases, including schizophrenia and affective disorder, we undertook a direct search for mutations in the 5′-regulatory region of the DRD1 gene. We hypothesized that mutations in this region might cause an altered level of expression of the receptor and thereby contribute to development of disease.

Hess et al. [1987] reported a significant reduction of the amount of DRD1 in postmortem striatal tissues of schizophrenic persons, using radioligand binding. Using similar techniques other authors have found normal or only slightly reduced DRD1 densities [Cross et al., 1981, 1983; Seeman and Lee, 1982; Pimoule et al., 1985; Seeman et al., 1987; Reynolds and Czudek, 1988; Joyce et al., 1988]. By applying positron emission tomography (PET) to young drug-naive schizophrenic

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patients, Karlsson et al. [1994] reported a significant reduction of the amount of DRD1 in the basal ganglia of patients when compared with healthy age-matched controls. In a PET study of bipolar patients, a decrease in DRD1 binding was observed in the frontal cortex [Suhara et al., 1992].

The coding sequence of the human DRD1 gene was independently reported by three groups [Zhou et al., 1990; Dearry et al., 1990; Sunahara et al., 1990], and the gene was subsequently mapped to chromosome 5q35.1 [Grandy et al., 1990]. The 5′-flanking region of the DRD1 gene has been characterized by Minowa et al. [1992, 1993] using multiple deletion experiments. The main activator was localized to two regions: nucleotide (nt) region −1154−−1137 relative to the first ATG codon increases promoter activity fourfold, and nt region −1197−−1154 confers an additional twofold increase in transcriptional activity. The presence of a negative modulator was suggested to be located between −1730−−1341. The region between −1197−−1152 has no consensus sequences for known transcription factors but binds to several novel transcription factors as a complex and confers cell specificity; −1154−−1116 has consensus sequences for Sp1 and AP2 binding sites. Minowa et al. [1993] investigated the nuclear factors binding to −1154−−1116 in nuclear extracts from neuroblastoma cell line NS20Y. They showed that proteins interacting with this region bind as a complex that includes SP1 or an SP1-like protein, as well as a novel nuclear factor, but no AP2.

We investigated 119 unrelated individuals (including 36 schizophrenic patients, 38 bipolar affective patients, and 45 healthy controls) using single-strand conformation analysis (SSCA). Eleven overlapping polymerase chain reaction (PCR) fragments covered 2,189 bp of the 5′-flanking region of the DRD1 gene, including all sequences with known modulatory effect.

The schizophrenic and bipolar patients were interviewed using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) [Endicott and Spitzer, 1978]. Lifetime diagnoses were assigned on the basis of the interview and medical records according to DSM-III-R criteria [American Psychiatric Association, 1987]. In addition, 45 healthy probands were recruited among laboratory staff and students and used as controls. Before blood was taken they were questioned closely as to whether they themselves or first-degree relatives had had psychiatric disturbances or previous psychiatric treatment. Only unaffected subjects with no history of psychiatric disorders in first-degree relatives were included in the study. The age range of the control subjects was 23–52 years (mean 28.23 years, SD 5.20). Even though the age of a significant number of control subjects was below peak-onset ages for schizophrenia and bipolar affective disorder, respectively, population frequency of ≈1% for each of these diseases would mean that it is unlikely for more than 1 or 2 of the control subjects to develop disease later in life. All probands were unrelated and of German origin.

Primer pairs were designed from the published sequence of the human DRD1 5′-flanking region [Minowa et al., 1992]. The primers were chosen to produce overlapping fragments spanning nucleotides −2457−−268 relative to the adenosine of the first methionine codon. Primer sequences and fragment sizes are given in Table I. Standard PCR was carried out in a 25-μl volume containing 40 ng genomic DNA, 10 pmol of each primer, 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 1.5 mM $MgCl_2$, 0.01% gelatine, 200 μM of each dNTP, and 1 U Taq polymerase (Life Technologies, Eggenstein, Germany). PCR of primer pairs D1P.1, D1P.3, D1P.4, D1P.5, and D1P.7 contained an additional 10% glycerol and 5% deionized for-

TABLE I. Oligonucleotide Primers for Analysis of the 5′-Flanking Region of the Human DRD1 Gene

| Primer designation | Sequence | Nucleotide position[a] | PCR fragment | PCR additive |
|---|---|---|---|---|
| 5′-D1P.1 | 5′-ACAGGAAGGCACCACAGTGT-3′ | −2457→−2438 | 244 | 10% glycerol |
| 3′-D1P.1 | 5′-AGTCACACAGCTCACGCG-3′ | −2214→−2231 | | 5% formamide |
| 5′-D1P.2 | 5′-TGTACCACATGCGGTGAGTT-3′ | −2281→−2262 | 249 | |
| 3′-D1P.2 | 5′-CGAGACGCAAGCCTTACTCT-3′ | −2033→−2052 | | |
| 5′-D1P.3 | 5′-ACCCTTGTGAGTGAGGTTGG-3′ | −1808→−1789 | 204 | 10% glycerol |
| 3′-D1P.3 | 5′-CGAGGGGACTCACTCCTTC-3′ | −1605→−1623 | | 5% formamide |
| 5′-D1P.4 | 5′-GAGACTGGCGAGGTAACCAG-3′ | −1276→−1257 | 249 | 10% glycerol |
| 3′-D1P.4 | 5′-TCAGGAGCCTGTGGCAAT-3′ | −1029→−1046 | | 5% formamide |
| 5′-D1P.5 | 5′-ACTCTGCCTGTCAAGCGAG-3′ | −1172→−1155 | 250 | 10% glycerol |
| 3′-D1P.5 | 5′-TCTTGGCTTCCTTTCGAGA-3′ | −924→−943 | | 5% formamide |
| 5′-D1P.6 | 5′-TCCTCAACGTTTCGGAGC-3′ | −683→−666 | 250 | |
| 3′-D1P.6 | 5′-TGTCTTCTCGCTCCTCCAAG-3′ | −434→−453 | | |
| 5′-D1P.7 | 5′-TCTTTGAGAGTAAGGCTTGCG-3′ | −2058→−2033 | 271 | 10% glycerol |
| 3′-D1P.7 | 5′-ACCAACCTCACTCACAAGGG-3′ | −1788→−1807 | | 5% formamide |
| 5′-D1P.8 | 5′-GGGGAAGGAGTGAGTCCC-3′ | −1626→−1604 | 221 | |
| 3′-D1P.8 | 5′-GGACCCAAAGCCCTAAGC-3′ | −1406→−1423 | | |
| 5′-D1P.9 | 5′-CCCTAGTTAGGGGACACTTGG-3′ | −1516→−1496 | 261 | |
| 3′-D1P.9 | 5′-CCTGGTTACCTCGCCAGTCT-3′ | −1256→−1275 | | |
| 5′-D1P.10 | 5′-CTCTCGAAAGGAAGCCAAGA-3′ | −944→−925 | 281 | |
| 3′-D1P.10 | 5′-CGGCTCCGAAACGTTGAG-3′ | −664→−681 | | |
| 5′-D1P.11 | 5′-ACCGTGTGTTTTCCTTTTGC-3′ | −511→−492 | 244 | |
| 3′-D1P.11 | 5′-CCTGAATTCCCCAAATAAAGC-3′ | −268→−288 | | |

[a] Nucleotide position is given according to Minowa et al. [1992].

mamide to enhance specificity of primer annealing. Samples were processed in a Perkin Elmer (Norwalk, CT) 9600 thermocycler. After an initial denaturation of 5 min at 95°C, 35 cycles of amplification of 30 sec at 94°C, 30 sec at 57°C, and 30 sec at 72°C were performed, followed by a final extension step of 5 min at 72°C.

For SSCA, 5 μl of PCR product were mixed with 7 μl of denaturing solution containing 85% formamide, 1.1% Ficoll 400, 0.001% bromphenol blue, and 0.14 × Tris/borate buffer (TBE), and denatured for 5 min at 95°C. Samples were subsequently chilled on ice and then loaded on a nondenaturing 10% polyacrylamide (PAA) gel (acrylamide:bisacrylamide, 49:1; 110 mm × 120 mm × 1.0 mm, Multigel Long Biometra) containing 0.5 × TBE. Gels were allowed to run for 16–18 hr at 7 V/cm at room temperature and +4°C. Bands were visualized by silver staining as described in Budowle et al. [1991].

PCR products from heterozygous individuals were cloned into pUC 18 *Sma*I/BAP vector (Pharmacia). Single colonies were lysed in 10 μl Tris/EDTA (TE) buffer by boiling for 10 min. The lysates were used as a template for PCR with insert-specific primer pairs. SSCA of PCR products allowed the identification of clones containing different alleles. From selected colonies a hemibiotinylated PCR product was generated, using one biotinylated vector primer and one normal vector primer. PCR product was incubated with streptavidine Dynabeads (Dynal Ltd.), and magnetic beads were collected with a magnetic concentrator. After washing and denaturing, both strands of DNA were sequenced using Sequenase Version 2.0 (U.S. Biochemicals).

When the mutation altered a natural restriction site, we confirmed presence of the mutation using a PCR-based restriction fragment length polymorphism (RFLP) assay. Digestion of PCR fragments with appropriate restriction enzymes (Table II) was performed following the manufacturer's protocol. Digested PCR products were separated on 10% PAA gels (acrylamide:bisacrylamide, 29:1) containing 1 × TBE at 15 V/cm. Restriction profiles were visualized by silver staining.

Among the 238 chromosomes, six sequence changes were identified (Table II). None of these mutations was found to be located in regions which have important influence on the level of transcriptional activity. Therefore, the identified variants are unlikely to be of functional relevance. However, direct comparison of transcriptional activity using, for example, reporter gene assays, is needed before conclusions can be made in this matter. Allele frequencies were determined in patients suffering from bipolar affective disorder (n = 38) and schizophrenia (n = 36), as well as in healthy control probands (n = 45), using either SSCA (D1P.4) or specific restriction enzyme assays (D1P.1, D1P.2, D1P.3, D1P.5, and D1P.6). No significant differences were observed between patients and controls (Table III).

We and others have previously failed to detect naturally-occurring structural variants of human DRD1 by investigating 288 unrelated individuals (including 174 schizophrenics, 60 bipolars, 8 alcoholics, and 46 controls) [Ohara et al., 1993; Cichon et al., 1994a,b; Shah et al., 1995; Liu et al., 1995]. We also found no association with either schizophrenia or bipolar affective disorder using anonymous RFLP markers from flanking regions [Nöthen et al., 1992, 1993]. These results do not support a causal contribution of DRD1 to the development of these psychiatric diseases. Nevertheless, an involvement of DRD1 still remains possible, because regions affecting the expression of DRD1 have not systematically been screened. In fact, there are precedents of disease-causing mutations affecting promoter elements of human genes [Crossley and Brownlee, 1990; Sakai et al., 1991; Koivisto et al., 1994].

Our study, based on mutation screening of substantial numbers of unrelated patients, does not provide evidence that variation in the 5′-flanking region of the DRD1 gene, including the promoter, plays a significant role in the genetic predisposition to schizophrenia or bipolar affective disorder. If no further sequences with regulatory function are identified, the DRD1 gene will be the first of the so-called candidate genes which can be excluded as a common cause of schizophrenia and bipolar affective disorder, based on systematic screening of both coding and regulatory sequences. Only if a mutation is present in rare cases may we have missed such individuals. Our sample size of 36 schizophrenic and 38 bipolar patients would have allowed a 90% chance of finding a mutation if the frequency of the mutation was at least 6.2% (for schizophrenia) or 5.9% (for bipolar disorder) in the patient sample. Finally,

TABLE II. DNA Sequence Variants in the 5′-Flanking Region of the Human DRD1 Gene

| Polymorphism | Nucleotide substitution | Nucleotide position[a] | Primer | PCR fragment (bp) | Restriction enzyme | Alleles | Restriction fragments (bp) |
|---|---|---|---|---|---|---|---|
| D1P.1 | T→C | −2218 | 5′-D1P.2 | 249 | *Tsp451* | A1 | 249 |
| | | | 3′-D1P.2 | | | A2 | 187 + 62 |
| D1P.2 | C→A | −2102 | 5′-D1P.2 | 249 | *Hpa*II | B1 | 130 + 69 + 50 |
| | | | 3′-D1P.2 | | | B2 | 130 + 119 |
| D1P.3 | T→C | −2030 | 5′-D1P.7 | 271 | *Aci*I | C1 | 174 + 97 |
| | | | 3′-D1P.7 | | | C2 | 145 + 97 + 29 |
| D1P.4 | G→A | −1992 | 5′-D1P.7 | 271 | | D1 | |
| | | | 3′-D1P.7 | | | D2 | |
| D1P.5 | G→C | −1251 | 5′-D1P.4 | 249 | *Hae*III | E1 | 191 + 58 |
| | | | 3′-D1P.4 | | | E2 | 166 + 58 + 25 |
| D1P.6 | T→C | −800 | 5′-D1P.10 | 281 | *Hae*III | F1 | 169 + 112 |
| | | | 3′-D1P.10 | | | F2 | 143 + 112 + 26 |

[a] Nucleotide position is given according to Minowa et al. [1992].

TABLE III. Allele Frequencies in Patients and Controls*

| | Polymorphism | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D1P.1 | | D1P.2 | | D1P.3 | | D1P.4 | | D1P.5 | | D1P.6 | |
| Allele | A1 | A2 | B1 | B2 | C1 | C2 | D1 | D2 | E1 | E2 | F1 | F2 |
| Schizophrenic patients ($n$ = 36) | 1.00 | 0.00 | 0.98 | 0.02 | 1.00 | 0.00 | 1.00 | 0.00 | 0.87 | 0.13 | 0.49 | 0.51 |
| | $P$ = 0.497 | | $P$ = 0.682 | | $P$ = 0.246 | | $P$ = 1.000 | | $P$ = 1.000 | | $P$ = 0.232 | |
| Bipolar affective patients ($n$ = 38) | 1.00 | 0.00 | 0.98 | 0.02 | 1.00 | 0.00 | 1.00 | 0.00 | 0.90 | 0.10 | 0.42 | 0.58 |
| | $P$ = 0.497 | | $P$ = 0.682 | | $P$ = 0.246 | | $P$ = 1.000 | | $P$ = 0.644 | | $P$ = 0.764 | |
| Control persons ($n$ = 45) | 0.98 | 0.02 | 0.96 | 0.04 | 0.97 | 0.03 | 0.99 | 0.01 | 0.87 | 0.13 | 0.39 | 0.61 |

* $P$ values were calculated using Fisher's exact test (two-tailed).

there remains the possibility that we have missed a mutation by relying on SSCA as a mutation-screening procedure, because the sensitivity is not 100% [Hayashi and Yandell, 1993]. Sensitivity can depend substantially on the region analyzed and the conditions utilized. Unless a substantial series of sequence variants is known in the region, sensitivity cannot be estimated. Thus, it is possible that one or more common mutations were missed.

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