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ORIGINAL ARTICLE

Association and synergistic interaction between promoter variants of the *DRD4* gene in Japanese schizophrenics

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Abstract Recent association studies suggest that polymorphisms in the promoter and exon 1 upstream region of the dopamine D4 receptor (*DRD4*) gene play a functional role in the development of common psychiatric illnesses, although there are also conflicting results. In this study, we re-sequenced this region to identify all genomic variants, and tested them for association with schizophrenia. A total of 570 Japanese schizophrenic cases with matched controls were studied by genotyping all identified/validated common polymorphisms (–1106T>C, –906T>C, –809G>A, –616G>C, –521T>C, –376C>T, –291C>T and 12-bp repeat) and a known microsatellite (120-bp tandem duplication) in the upstream region. A single nucleotide polymorphism (SNP) –809G>A in the promoter region was found to be significantly associated with disease (*P*=0.018 and 0.032 for allelic and genotypic comparisons, respectively), although not surviving after Bonferroni correction. Logistic regression analysis showed that a combination of the four polymorphisms, –809G>A, –616G>C, –291C>T and the 12-bp repeat, conferred a susceptibility to schizophrenia. These results suggest that the upstream variants have a primary functional effect in the etiology of schizophrenia in the Japanese population.

Keywords Dopamine D4 receptor · Re-sequencing · Promoter region · Linkage disequilibrium · Haplotype block · Logistic regression analysis

The nucleotide polymorphism data reported is available in the DDBJ/EMBL/GenBank databases under the accession number ss61570833.

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Introduction

Disturbances in the dopamine neurotransmitter system have long been suggested to play a crucial role in the pathogenesis of schizophrenia (Prasad et al. 2002). However, involvement of dopamine-related genes in the manifestation of this disorder has been difficult to determine. The dopamine D4 receptor (*DRD4*) gene, located at chromosome 11p15.5 (Gelernter et al. 1992; Petronis et al. 1993), has received considerable interest because clozapine, a neuroleptic which is often effective against treatment-resistant symptoms, has a high affinity for this receptor (Sanyal and Van Tol 1997;

Van Tol et al. 1991). Also, DRD4 is up-regulated in postmortem brain tissue from schizophrenic patients (Murray et al. 1995; Seeman et al. 1993; Stefanis et al. 1998; Sumiyoshi et al. 1995).

To investigate its genetic association with schizophrenia, many groups have examined polymorphisms of the *DRD4* gene. Early studies focused on a 48-bp variable number of tandem repeat (VNTR) in exon 3. This tandem repeat comprises 2 (2R) to 11 (11R) 48-bp repeat units and codes for the third intracellular loop of the receptor protein (Van Tol et al. 1992). There is growing genetic evidence linking the VNTR with psychiatric traits or illnesses, such as novelty-seeking (Benjamin et al. 1996; Ebstein et al. 1996), attention-deficit hyperactivity disorder (ADHD) (Faraone et al. 2001; LaHoste et al. 1996), and schizophrenia (Hwu et al. 1998; Jonsson et al. 1996; Kaiser et al. 2000; Sanak et al. 2005; Serretti et al. 2001), but the results are still variable.

In recent years, promoter region polymorphisms of the *DRD4* have also received particular attention because of their possible role in the regulation of gene transcription. To date, two polymorphisms in the promoter, T allele of the single nucleotide polymorphism (SNP) –521T>C and a 120-bp tandem duplication (1.2 kb upstream from the initiation codon), are reported to reduce transcriptional efficiency (D'Souza et al. 2004; Okuyama et al. 1999). Numerous studies have examined the association of upstream (promoter region and exon 1) polymorphisms with schizophrenia and some have shown a positive association (Okuyama et al. 1999; Xing et al. 2003), although not all were in full agreement (Hong et al. 1998; Jonsson et al. 2001; Kohn et al. 1997; Lung et al. 2006; Mitsuyasu et al. 2001; Petronis et al. 1995).

Since previous studies focused primarily on individual polymorphisms, allelic heterogeneity and/or a relatively weak effect of the variants may partly explain these inconsistencies. When haplotype construction is difficult because of a weakness or absence of linkage disequilibrium (LD) in a genomic interval, as is the case for the promoter region of *DRD4*, it may be important to test for a synergistic interaction between genetic variants in addition to performing single SNP analysis. Haplotype analysis is a reasonable strategy, assuming that the causative allele arises from a specific ancestral haplotype. However, this method is inadequate when there is an accumulation of multiple causative variants in a restricted genomic stretch. Additionally, haplotypic analysis is further compromised in regions where LD is decayed, because of the low statistical power to detect association due to inflated degrees of freedom. Therefore, clusters of potentially functional variants in genomic region with tenuous LD are better analyzed using a logistic regression framework that provides a powerful test of SNP etiology.

In this study, we examined the 5′ upstream region of *DRD4*, by first re-sequencing the region to identify all genomic variants. We then tested the association of all identified/validated common variants individually, as well as performing synergistic interaction analyses between them and schizophrenia.

Materials and methods

Subjects

Samples from 570 unrelated cases of schizophrenia (285 men, 285 women; mean age 47.0±11.4 years), and 570 age and sex matched controls (285 men, 285 women; mean age 46.7±11.1 years) were analyzed. The diagnosis of schizophrenia was made by consultation according to DSM-IV criteria with consensus from at least two experienced psychiatrists. All available medical records were taken into consideration. Control subjects were recruited from hospital staff and volunteers who showed no evidence of present or past psychoses during brief interviews with psychiatrists. All subjects were from central Japan. The study was approved by the Ethics Committees of RIKEN, Hamamatsu University and Chiba University. All participants provided written informed consent.

Sequence analysis

The upstream region encompassing the promoter region and exon 1 of the *DRD4* gene (from 1,216 bp upstream of "A" in the start codon to 293 bp downstream of this "A") was analyzed by the direct sequencing of PCR amplification from the genomic DNA of 30 unrelated Japanese schizophrenics. Primer sequences and detailed information on the reaction conditions are available upon request. Sequencing was performed using the DYEnamic ET terminator cycle sequencing kit (Amersham Biosciences, Piscataway, N.J., USA) and the ABI PRISM 3730 Genetic Analyzer (Applied Biosystems, Foster City, Calif., USA). Polymorphisms were detected by the SEQUENCHER program (Gene Codes Corporation, Ann Arbor, Mich., USA).

Genotyping

SNPs were typed by the TaqMan system (Applied Biosystems). PCR was performed using an ABI 9700

thermocycler and fluorescent signals were analyzed by an ABI 7900 sequence detector single point measurement and SDS v2.0 software (Applied Biosystems). Conflicts or flagged alleles were resolved by re-genotyping. Two microsatellite marker loci, the 120-bp tandem duplication and the 12-bp repeat polymorphism (Fig. 1), were amplified by PCR using fluorescently labeled primers. PCR fragments were analyzed on an ABI PRISM 3730 Genetic Analyzer (Applied Biosystems). Genotypes were determined using GeneScan 3.5.2 and Genotyper 3.6 software (Applied Biosystems).

Statistical analyses

The allelic and genotypic distributions were tested for association by Fisher's exact test for biallelic markers (SNPs, the 120-bp tandem duplication and the 12-bp repeat polymorphism).

Haplotypic association analysis was performed using COCAPHASE in the UNPHASED package (http://www.rfcgr.mrc.ac.uk/~fdudbrid/software/unphased/) (Dudbridge 2003). We employed a 2- and 3-marker sliding window analysis using COCAPHASE. To estimate the degree of LD between pairs of loci, the standardized disequilibrium coefficient (D') was calculated and haplotype blocks were defined using the Haploview program (http://www.broad.mit.edu/mpg/haploview/) (Barrett et al. 2005).

Logistic regression analysis

To test the multiple polymorphisms in the upstream region for a synergistic effect, stepwise logistic regression analysis was performed using the SPSS Software (Release 11.0J) (SPSS Japan, Tokyo, Japan). We employed a procedure of backward selection in which we started with all the markers genotyped in the present study. According to the approach of Cordell and Clayton (2002), we set dummy variables, x_1 and x_2, taking values x_1=–1, 0 and 1, x_2=–0.5, 0.5 and –0.5, for genotypes w/w, w/m and m/m, respectively (w: wild-type, m: mutant).

Results

We re-sequenced the upstream region of the *DRD4* gene, and identified a total of eleven SNPs: –1106T>C, –930C>G, –906T>C, –873G>A, –809G>A, –616G>C, –603G>T, –595G>del, –521T>C, –376C>T, and –291C>T, and a 12-bp repeat polymorphism (Fig. 1). One novel variant, –930C>G (deposited into GenBank as ss61570833), was detected in only 1 out of 58 chromosomes. The remaining variants were already present in the public databases and were validated in Japanese subjects during the course of this study.

The eight markers, –1106T>C, –906T>C, –809G>A, –616G>C, –521T>C, –376C>T, –291C>T, and the 12-bp repeat polymorphism in exon 1, were selected for genotyping using the criterion of a minor allele frequency >0.05 from our sequencing data. We also typed the size of the 120-bp tandem duplication (bi-allelic polymorphism with either one or two repeat alleles). The information on markers is shown in Table 1. The 12-bp repeat polymorphism was mostly bi-allelic with the exception of four chromosomes (three from schizophrenics and one from controls) that contained a three-repeat allele.

Allelic and genotypic distributions of the promoter SNP –809G>A differed significantly between cases and controls (P=0.018 and 0.032 for allelic and genotypic comparisons, respectively). In the exploratory haplotype window analysis, the two-SNP haplotype

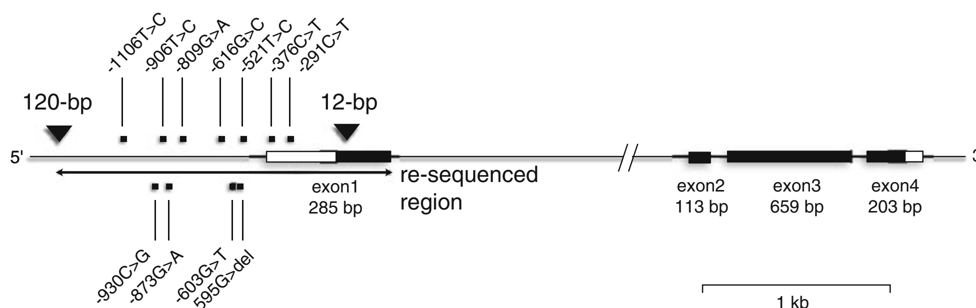

Fig. 1 Genomic structure and location of polymorphic sites within *DRD4*. Exons are denoted by *boxes*, with untranslated regions in *white* and translated regions in *black*. The sizes of exons and a scale are also shown. SNPs and microsatellites are indicated by *solid squares* and *triangles*, respectively. Re-sequencing was performed on the upstream region (from 1.2 kb upstream of the initiation codon to the 3′ end of exon 1)

Table 1 Genotype distributions of bi-allelic polymorphisms from the upstream region of *DRD4*

Marker	dbSNP ID	Physical position	Case or control	*n*	Genotype frequencies			*P* value for allelic association	*P* value for genotypic association
–1.2 kb	–	625826–626065			1/1	1/2	2/2		
120-bp repeat			Case	569	0.04	0.32	0.64	0.202	0.377
			Control	570	0.06	0.34	0.61		
–1106 T>C	rs936460	626199			T/T	T/C	C/C		
			Case	569	0.79	0.20	0.02	0.522	0.644
			Control	570	0.76	0.22	0.02		
–906 T>C	rs3758653	626399			T/T	T/C	C/C		
			Case	569	0.66	0.31	0.03	0.116	0.223
			Control	569	0.62	0.34	0.05		
–809 G>A	rs936461	626496			A/A	A/G	G/G		
			Case	562	0.03	0.33	0.64	**0.018**	**0.032**
			Control	564	0.06	0.35	0.59		
–616 G>C	rs747302	626689			C/C	C/G	G/G		
			Case	565	0.09	0.44	0.47	0.769	0.257
			Control	568	0.10	0.39	0.50		
–521 T>C	rs1800955	626784			T/T	T/C	C/C		
			Case	566	0.34	0.48	0.19	0.371	0.377
			Control	569	0.34	0.50	0.16		
–376 C>T	rs916455	626929			T/T	T/C	C/C		
			Case	561	0.01	0.18	0.81	0.732	0.838
			Control	562	0.01	0.19	0.80		
–291 C>T	rs916457	627014			T/T	T/C	C/C		
			Case	565	0.01	0.21	0.79	0.518	0.080
			Control	566	0.02	0.19	0.79		
Exon 1	rs4646983	627392–627391			1/1[a]	1/2[a]	2/2[a]		
12-bp repeat			Case	568	0.02	0.25	0.73	0.512	0.248
			Control	569	0.03	0.21	0.76		

[a] Alleles are coded by the number of repeats. Four subjects (three from the schizophrenia and one from the control group) with three repeats are omitted from this table. Significant results are shown in bold type

[(–1106C) – (–906C)] tended to be over-represented in schizophrenia (frequencies in cases and in controls were 0.70 and 0.66, respectively, P=0.0656) (data not shown).

In LD analysis, D' values were close to 1 in the distal [(120-bp repeat) – (–1106T>C) – (–906T>C)] and proximal [(–376C>T) – (–291C>T) – (–12-bp)] segments of the upstream region, with each defined as a haplotype block, but it did not hold for the region in between (Fig. 2). Decay of LD in this short stretch (1.2 kb) may imply a high local recombination rate. Therefore, in addition to conventional haplotype-window analysis, we employed logistic regression analysis, which can test a combinatorial effect of multiple SNPs simultaneously. A combination of four polymorphisms (–809G>A, –616G>C, –219C>T and 12-bp repeat) appeared to affect susceptibility to schizophrenia (Table 2).

Discussion

In this study of the *DRD4* gene, we focused on the upstream region, where associations with psychiatric phenotypes have been previously reported. However, genetic variants in this region do not show consistent association with schizophrenia. This may have been due to insufficient statistical power or inadequate interrogation of genomic variations in some studies. In addition, the differences in marker sets between studies increase the ambiguity when interpreting data. To minimize these problems, we adopted the thorough approach of re-sequencing and genotyping all validated polymorphisms.

Both upstream region variants, the single marker –809G>A and a multi-marker combination, displayed association with schizophrenia in this study. The SNP –521T>C, which was previously reported to show association with schizophrenia in an independent Japanese sample set (Okuyama et al. 1999), was not significant in our data set, as in other population data sets (Ambrosio et al. 2004; Jonsson et al. 2001; Segman et al. 2003). Since it is conceivable that particular combinations of multiple variants may confer an enhanced susceptibility to schizophrenia, we performed a logistic regression analysis to test all SNPs in the upstream region for association. This

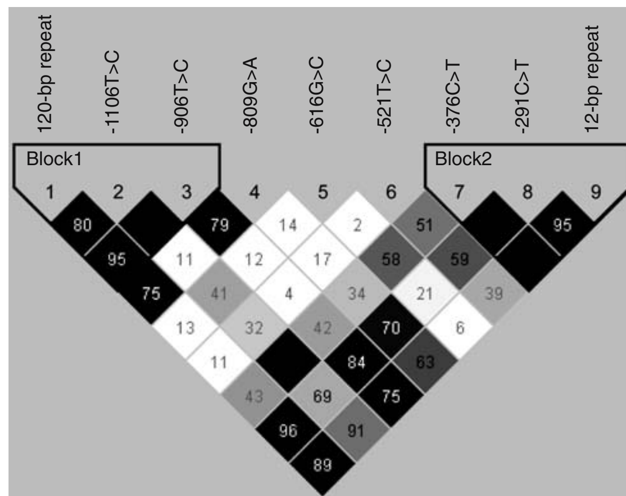

Fig. 2 Haplotype organization of *DRD4* in Japanese. The haplotype block pattern was constructed by the Haploview program using the genotype data from both case and control samples (1,140 subjects). The number in each cell represents the LD parameter D' (×100), blank cells mean D'=1. Each cell color is graduated relative to the strength of LD between markers, which is defined by both the D' value and confidence bounds on D'. Strong LD was observed in the discrete distal [(120-bp repeat) – (–1106T>C) – (–906T>C)] and proximal [(–376C>T) – (–291C>T) – (12-bp repeat)] segments, but not in the intervening region

Table 2 Logistic regression analysis in the upstream region of *DRD4*

Marker	β	SE	Wald's χ^2	P value	OR	OR 95% CI
–809G>A	0.346	0.127	7.384	0.007	1.414	1.10–1.82
–616G>C	0.247	0.125	3.872	0.049	1.280	1.00–1.64
–291C>T	1.031	0.400	6.649	0.010	2.804	1.28–6.24
12-bp repeat	–0.725	0.274	6.988	0.008	0.484	0.28–0.83

β Logistic regression coefficient in the model, *SE* standard error of the coefficient, *Wald* χ^2 Wald statistic to test significance of the coefficient, *OR* the odds ratio, *CI* 95% confidence interval of the odds ratio

approach may be more appropriate than conventional haplotype analysis, when examining the upstream region of the *DRD4* gene where there is evidence of LD decay in a relatively short genomic stretch and most markers do not correlate with each other. Results appear to indicate a synergistic interaction among the four promoter polymorphisms in the *DRD4* gene. These results should be treated with caution since there are limitations to the present association study. Firstly, this is a case-control study, where false positive findings due to population stratification can occur. Analysis of this sample set using STRUCTURE software (Pritchard et al. 2000) detected no evidence of population stratification (Shimizu et al. 2006). To address this issue further, we also performed a transmission disequilibrium test. This testing failed to replicate the association of –809G>A in a sample set of 80 complete schizophrenic trios (data not shown). This sample size would have only a limited statistical power to detect true association. Secondly, the significance of the –809G>A polymorphism in the promoter region disappeared after Bonferroni correction for multiple testing. Thirdly, the sample size is obviously limited and so the insignificant result for –521T>C needs to be interpreted cautiously. The sample size in this study had a power of 0.59 to detect a susceptibility variant with a relatively small effect (relative risk = 1.2 and 1.44 for heterozygotes and homozygotes, respectively), when the allele frequency is 0.41. This frequency equals that of SNP –521C, whose association with schizophrenia has been previously reported (Purcell et al. 2003; Xing et al. 2003).

In conclusion, to our knowledge, this is the first study that highlights a possible combinatorial effect of promoter SNPs in the *DRD4* gene. It will be interesting to determine whether this multi-marker association can be confirmed in independent data sets, where samples are well-defined in terms of clinical variables such as symptoms, age-at-onset, severity, medication type, and response to antipsychotic treatment. Furthermore, it will be important to examine the functional effects of variant combinations, to understand the mechanisms by which they increase or decrease susceptibility to schizophrenia.

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