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Linkage and Association Between Serotonin 2A Receptor Gene Polymorphisms and Bipolar I Disorder

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Several inconsistent associations between bipolar I disorder (BD1) and polymorphisms of the genes encoding the serotonin 2A receptor (*HTR2A*) have been published. We conducted the Transmission Disequilibrium Test (TDT) and case-control comparisons involving nine single nucleotide polymorphisms at the serotonin 2A receptor gene (four SNPs of HTR2A exons and five flanking SNPs). Comparison of BD1 cases (n = 93) with a group of unrelated population based controls (n = 92) revealed associations with SNPs on exons 2 and 3 (516C/T and 1354C/T, respectively), consistent with haplotype-based differences. Analysis of the cases and their available parents using the TDT suggested significant linkage and associations with 1354C/T, as well as haplotypes bearing this SNP. Our results support an etiological role for *HTR2A* in BD1. In view of the relatively small sample, replicate studies using large samples are needed.

KEY WORDS: **serotonin 2A; genetics; linkage; association; bipolar disorder**

INTRODUCTION

The mode of inheritance of BD1 is complex and individual genes may contribute only a small fraction of the liability [Craddock and Jones, 1999]. In this setting, candidate gene studies may be required because they can detect loci with relatively small effect]Risch and Merikangas, 1996]. Genes encoding proteins involved in serotonergic transmission have been logical targets for such analyses, because of considerable evidence implicating serotonin (5-HT) in mood regulation [Veenstra-VanderWeele et al., 2000]. Among the numerous serotonergic candidates, the serotonin 2A receptor (HTR2A, localized to chromosome 13q14-q21) has been investigated extensively, as it may mediate the beneficial therapeutic effects of serotonin re-uptake inhibitors, a popular class of antidepressants [Veenstra-VanderWeele et al., 2000].

Five *HTR2A* polymorphisms have been tested in association studies (Table I). Three significant associations have been published. In the earliest report, the frequency of allele C102 at the 102T/C single nucleotide polymorphism (SNP) was elevated among Caucasian cases compared with unrelated controls (odds ratio, OR 1.79). Recently, an association has also been observed at −1438A/G in a French sample (OR for A-1438: 1.59) [Bonnier et al., 2002]. Association with this SNP has also been reported in a Korean sample, albeit with the G-1438 allele [Chee et al., 2001]. However, the majority of studies did not detect associations at *HTR2A* (Table I). To our knowledge, only one study utilized family-based controls. This study tested one SNP (T102C) using the haplotype relative risk method and did not detect an association among 58 case-parent trios [Murphy et al., 2001].

There are several explanations for the lack of consensus for the *HTR2A* associations. First, the sample sizes are relatively small and therefore each study had limited power by itself to detect small effects on liability. Second, most studies have examined one or a relatively small number of polymorphisms, which limits power to detect association if the measured polymorphisms are only in linkage disequilibrium with polymorphisms having a direct effect on liability. Since the majority of

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TABLE I. Published Association Studies Using *HTR2A* Polymorphisms Among BD1 Cases and Unrelated Controls

Reference	Ethnicity	Cases	Controls	Diagnostic criteria	SNPs	Comment	*P*
Mahieu et al. [1997]	Caucasian	83	129	RDC	102T/C	NS	1.0
Gutierrez et al. [1997]	Caucasian	88	113	DSM-III-R	102T/C	NS	0.39
					516C/T		
					1354C/T		
					74C/A		
Massat et al. [2000]	Caucasian	309	309	RDC	102T/C	NS	0.82
Tut et al. [2000]	Chinese	72	74	RDC DSM-III-R	102T/C	NS	0.93
Vincent et al. [1999]	Sample 1: mixed*	103	103	RDC	102T/C	Sample 1: association with C102 (OR 1.79)	0.01
	Sample 2: Caucasian	109	109		1354C/T	Sample 2: NS	0.47
Arranz et al. [1997]	Caucasian	GS: 129	GS: 252		74C/A	NS	0.31
					102T/C		0.19
		BS: 176	BS: 183		516C/T		0.06
					1354C/T		0.46
Serretti et al. [1999]	Caucasian	149	—	DSM-IV	102T/C	NS	0.07
Blairy et al. [2000]	Caucasian	40	89	RDC	102T/C	NS	>0.05
Chee et al. [2001]	Korean	142	148		—	Association with G-1438	0.007
					1438G/A		
Bonnier et al. [2002]	Caucasian	127	142	DSM-IV	—	Association with A-1438	0.015
					1438G/A		

NS, not significant; GS, sample from Germany; BS, British sample; RDC, research diagnostic criteria; DSM, diagnostic and statistical manual for mental disorders.
*95% Caucasian, 3% Oriental, and 2% Native Canadian.

studies employed unrelated controls, varying levels of population sub-structure could also explain the inconsistencies [Devlin et al., 2001a,b]. To evaluate these possibilities, we investigated multiple polymorphisms using the TDT. The TDT investigates preferential transmission of alleles from heterozygous parents to affected probands and is therefore not prone to artifacts induced by population sub-structure. Significant transmission distortion suggests association in the presence of linkage, providing further credence to the results. To increase the informativeness of the available polymorphisms, we conducted additional haplotype based analyses. The requirement for heterozygous parents restricts the number of family units that can be used for TDT analyses. The TDT also has reduced power when only one parent is available for analyses [Sham and Curtis, 1995; Sun et al., 1999; Lange and Laird, 2002]. Since a significant fraction of our sample included single parent units, we also compared our cases with unrelated controls.

MATERIALS AND METHODS

Clinical Report

Cases and parents. Probands with Bipolar Disorder I (DSM IV Criteria) and available parents were included. The sample included inpatients and outpatients receiving treatment at Western Psychiatric Institute and Clinic, Pittsburgh (WPIC). WPIC is a tertiary care institution that also serves as a catchment area facility. In addition, we sought participants from 30 other regional treatment facilities. Consenting probands were interviewed using the Diagnostic Interview for Genetic Studies (DIGS), a structured diagnostic interview schedule [Nurnberger et al., 1994]. Additional clinical information was obtained from available clinical records and from relatives as required. This information was synthesized and a consensus diagnosis assigned using DSM-IV criteria. Available parents of the probands were also recruited, but did not complete a diagnostic interview.

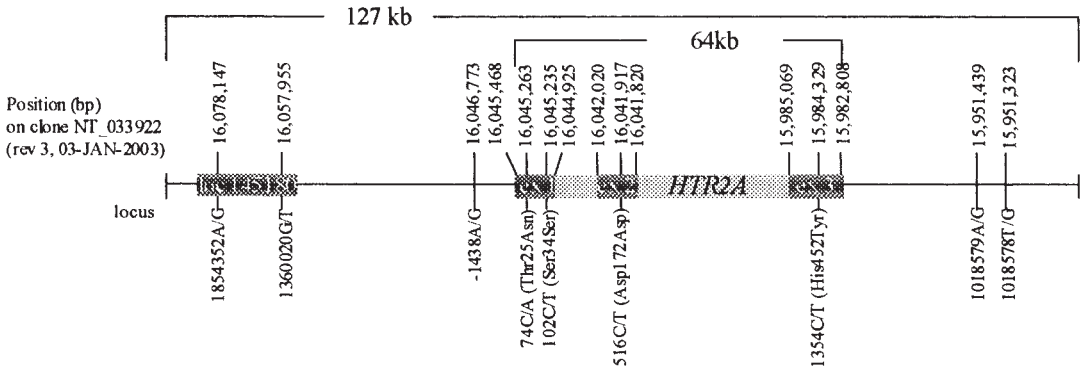
Unscreened controls. Cord blood samples were obtained from live births at Magee-Women's Hospital, Pittsburgh and served as unscreened, population based controls. No information apart from ethnicity was available for these samples.

All participants reported Caucasian ethnicity (maternal report for neonatal samples). We obtained written informed consent from participants, according to the guidelines of the University of Pittsburgh Institutional Review Board (IRB).

Laboratory

Genomic DNA was extracted from venous blood samples using the phenol chloroform method.

HTR2A SNPs. Nine SNPs were investigated (Fig. 1). Three SNPs were assayed using PCR based assays with allele specific primers; namely 102T/C, 74C/T (Thr25Asn), and 1354C/T (His452Tyr) [Marshall et al., 1999]. SNPs 516C/T and −1438G/A were assayed with restriction enzymes following PCR amplification



The genomic region under investigation is shown, with the position of each SNP shown above the line and the SNP identification below the line. ex: exon

Fig. 1. Structure of *HTR2A* and surrounding region.

[Erdmann et al., 1996; Basile et al., 2001]. We investigated 17 additional SNPs flanking *HTR2A*, listed in public databases (1360020T/G, 1410659T/C, 1854352G/A, 2149436G/A, 1410655T/C, 1410656G/A, 2503314G/A, 754325A/G, 1018578T/G, 1051064A/G, 2230948A/C, 6312A/G, 2298086T/C, 912125C/A, 2298085T/A, 2298084T/C, and 1886221T/C. Further details are available online at http://www.pitt.edu/~nimga/research/htr2a/data/). The genomic sequence flanking these SNPs was used to design primers and amplicons ~500 bp generated for genomic DNA pooled from 93 cases. The amplified fragments were sequenced using an ABI 3700 DNA sequencer to identify potentially informative SNPs. Four SNPs flanking *HTR2A* were selected for analysis, based on informativeness, LD patterns in a panel of six case-parent trios and assay availability (SNPs 1854352, 1360020, 1018578, and 1018579). These SNPs were assayed in the entire sample using Fluorescence Polarization following PCR amplification [Chen et al., 1999].

We denoted alleles at each polymorphism as '1' or '2' for convenience during haplotype based analyses. Allele 1 refers to A1854352, G1360020, A-1438, C74, C102, C516, C1354, A1018579, and T1018578 for the *HTR2A* markers. Allele 2 refers to the converse alleles at these markers. All genotypes were read by two individuals blind to the clinical status of the respective individual. Inconsistencies were resolved by repeating assays.

Statistical Analysis

Genotype data were tested for Mendelian inconsistencies using PEDCHECK software [O'Connell and Weeks, 1998]. Linkage disequlibrium (LD) was evaluated using published software [Abecasis and Cookson, 2000]. The Chi square test was employed for comparisons between cases and unrelated neonatal controls. Haplotype frequencies among the cases and neonatal controls were estimated using and EM based algorithm and compared using SNPEM software [Fallin and Schork, 2000]. In case of discrepancy, samples were retyped. The software program GENEHUNTER (GH) was used for TDT analysis [Lander and Kruglyak, 1995]. GH relies on asymptotic theory, which does not hold for a small number of transmissions/non-transmissions. Therefore, exact P values were calculated using standard binomial analysis when the total number of transmissions were less than 20. We also used TRANSMIT for global tests of association involving multiple haplotypes in the family-based sample [Clayton and Jones, 1999].

RESULTS

The family-based sample included 93 cases; both parents were available for 38 families, while a single parent was available for the remaining 55 families. Among the cases there were 28 men and 65 women (median age at onset 20 years, range 3–54; current median age 38 years, range 15–63). All genotype distributions were in Hardy-Weinberg equilibrium for cases, parents and neonatal controls, with the exception of 516C/T. A heterozygote deficit was noted for this SNP in the neonatal sample ($P = 0.0007$).

The relative position of the SNPs and their allele frequencies are displayed in Figure 1. Pair-wise linkage disequilibrium (LD) analysis among the neonatal controls suggested three sets of SNPs (Table II). Significant LD was observed among SNPs localized to exon 1 (102 T/C and 74 C/A) and those 5′ to *HTR2A* (SNPs −1438G/A, 1360020, 1854352). SNP 516C/T, localized to exon 2, was not in significant LD with any other SNP and constituted the second set. Significant LD was also observed in a third set of SNPs, composed of 1354C/T in exon3 and the SNPs localized 3′ to *HTR2A* (1018578 and 1018579). Significant LD was not consistently observed across members of these sets of SNPs. These data could be interpreted as evidence for three haplotype 'blocks' (Table II). However, a graphical plot suggested a linear decline in LD across this region (data not shown).

When genotype distributions for individual SNPs were compared among the cases and neonatal controls, significant differences were noted for 516C/T and 1354C/T (located in the second and third exons, respectively; Fig. 1). At 1354C/T, allele 1 was also significantly more common among the cases (OR 3.38). Haplotypes incorporating two to four contiguous haplotypes were next compared between the cases and the neonatal

TABLE II. Pair-Wise Linkage Disequilibrium Estimates for *HTR2A* SNPs

	5′ Untranslated region			Exon 1		Exon 2	Exon 3	3′ Untranslated region	
	1854352A/G	1360020G/T	−1438A/G	74C/A	102C/T	516C/T	1354C/T	1018579A/G	1018578T/G
1854352A/G		<0.001	0.001	0.243	<0.001	0.483	0.171	0.09	0.796
1360020G/T	0.738		<0.001	0.253	<0.001	0.975	0.6	0.784	0.776
−1438A/G	0.596	0.554		0.019	<0.001	0.724	0.099	0.308	0.282
74C/A (Thr25Asn)	0.551	0.999	1.0		0.015	0.543	0.569	0.1	0.835
102C/T (Ser34Ser)	0.665	0.782	0.824	1.0		0.547	0.167	0.824	0.969
516C/T (Asp172Asp)	0.267	0.015	0.151	1.0	0.237		0.014	0.668	0.561
1354C/T (His452Tyr)	0.352	0.197	0.502	0.13	0.35	0.534		0.001	0.001
1018579A/G	0.282	0.037	0.148	1.0	0.038	0.191	1.0		0.0
1018578T/G	0.044	0.041	0.181	0.135	0.005	0.242	1.0	0.895	

Caucasian neonatal controls (n = 91) were used to estimate linkage disequilibrium. The figures below the diagonal represent D′ and estimates for statistical significance (*P* values) are above the diagonal.

controls, in order to understand the pattern of associations across the *HTR2A* locus and flanking regions. Consistent with the association at 1354C/T, significant differences were observed overall for haplotypes bearing this SNP. Interestingly, significant overall case-control differences were also observed for haplotypes that encompassed −1438G/A and 1360020, i.e., SNPs located in the first exon and those 5′ to *HTR2A* (Fig. 2).

In agreement with the case-control analyses, TDT analysis of individual SNPs revealed significant increased transmission of allele 1 at 1354C/T, located in exon 3 ($P = 0.016$). A trend for increased transmission of allele 1 at 74C/A, the SNP localized to exon 1 was also observed ($P = 0.06$; Table III). When the 74C/A and 1354C/T SNPs were considered together, increased transmission of haplotypes bearing allele 1 at these SNPs was also noted, consistent with the TDT involving the individual SNPs ($P = 0.00048$, df = 1). These analyses were uncorrected for multiple comparisons. Even ignoring the correlation among the tests, however, the Bonferroni corrected critical value, $0.05/25 = 0.002$, is larger than the *P*-value for the haplotype based on 74C/A and 1354C/T (total number of haplotypes analyzed = 25). 'Moving window' haplotype analyses using two to four contiguous SNPs was next conducted [Nair et al., 2000]. Increased transmission of haplotypes bearing allele 1 at 1354C/T and allele 1 at 516C/T was noted ($P = 0.0039$, df = 1; Fig. 2). Details of other haplotype based TDT analyses are available online (http://www.pitt.edu/~nimga/research/htr2a/data/).

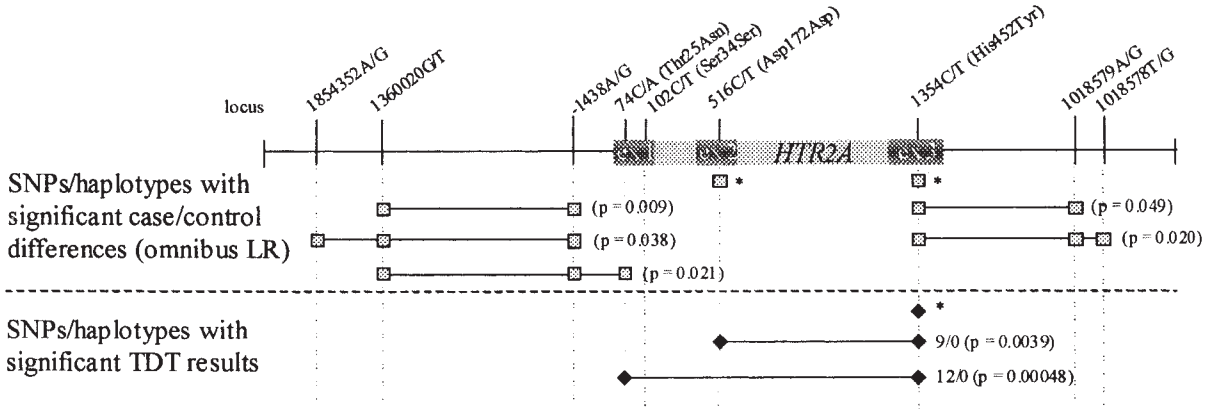
The statistically significant TDT analyses incorporated relatively small numbers of families, because the software we used for TDT analysis excludes case-parent duo families if SNPs are used. Therefore, we also analyzed the data using TRANSMIT. This computer program includes case-parent families of all configurations, while providing robust tests of association. TRANSMIT also provides global tests involving all haplotypes for sets of SNPs [Clayton, 1999; Clayton and Jones, 1999]. Global tests involving sets of four adjacent SNPs revealed significant association for haplotypes encompassing SNPs located in the first exon and further upstream (SNPs 1360020, −1438G/A, 74C/A and 102T/C; $\chi^2 = 19.8$, df = 11, $P = 0.048$). Global tests involving sets of 2–3 adjacent SNPs revealed significant association for haplotypes incorporating 102T/C, 516C/T, 1354C/T ($\chi^2 = 12.9$, df = 6, $P = 0.045$) and −1438G/A, 74C/A ($\chi^2 = 8.14$, df = 3, $P = 0.043$).

POWER ANALYSIS

The case-control differences in allele frequencies for SNP 1354C/T were used to evaluate power. The observed differences suggest a moderate effect size (w = 0.35). A sample composed of 120 cases and controls would have over 90% power to detect such a difference ($\alpha = 0.05$) [Cohen, 1988].

DISCUSSION

Our results, based on both case-control and family-based analyses support association and linkage at



*significant individual SNPs, see Table III for details
Associated SNPs/haplotypes, alleles not specified
family based analyses: ◆Allele 1, represents C74, C516 and C1354. Only statistically significant increased transmissions to cases are shown. Two sided binomial tests were used to assess significance due to the small number of observations.

Fig. 2. Haplotype analysis using family based and cases/neonatal control samples.

HTR2A. The family-based results are more persuasive, as they are not prone to artifacts related to ethnic admixture. When TDT analysis of nine SNPs was conducted individually, transmission distortion was noted at 1354C/T. The differential transmission is supported by haplotype based analyses. The TDT results may not be attributed to a general transmission bias in this chromosomal region because consistent case-control differences for individual SNPs and related haplotypes were also observed. The results are also unlikely to reflect LD with another gene, as TDT and case-control analyses were not significant using flanking individual SNPs localized approximately 30 kb from HTR2A.

There are several plausible functional explanations for the observed associations. SNP 1354C/T (His452 Tyr), the SNP localized to the third exon was implicated by the TDT as well as the case-control analyses. This SNP leads to a non-synonymous change, as does 74C/A (Thr25Asn), the SNP from the first exon included in some of the associated haplotypes. Differential expression of 102C/T has been demonstrated in post-mortem brain samples from unaffected heterozygous individuals [Polesskaya and Sokolov, 2002]. Though significant association with 102 C/T was not observed in our sample, this SNP is in significant LD with 74C/A (Thr25Asn, $D' = 1.0$, $P = 0.015$) in our sample. It is possible that more than one SNP may confer risk in our sample. For example, TDT analysis of haplotypes based on SNPs 74C/A and 1354C/T suggested a cumulative effect (Table III).

Two point LD analyses among the controls suggest three sets of SNPs at *HTR2A*, members of each set being in strong LD. The first set encompasses SNPs in the first exon and the 5′ end. The second involves a SNP in the second exon and the third set involves SNPs in the third exon and 3′ end of *HTR2A*. It is tempting to speculate on the basis of the present results that there are discrete

TABLE III. Allele Frequencies and TDT Transmissions

	Case/control analysis		Family based analysis
	Frequency		
SNP	Cases	Controls	Transmitted/ not transmitted
1854352A/G	0.32/0.68	0.36/0.64	15/16
1360020G/T	0.43/0.57	0.51/0.49	13/20
−1438A/G	0.39/0.61	0.43/0.57	13/19
74C/A (Thr25Asn)	0.99/0.01	0.97/0.03	5/0
102C/T (Ser34Ser)	0.65/0.35	0.61/0.39	18/18
516C/T (Asp172Asp)	0.95/0.05	0.97/0.03*	3/1
1354C/T (His452Tyr)	0.96/0.04	0.89/0.11**	7/0***
1018579A/G	0.43/0.57	0.51/0.49	13/18
1018578T/G	0.41/0.59	0.47/0.53	17/18

For the case-control analyses, allele frequencies are listed in the order stated in the first column. Transmission of alleles in the family based analyses refer to allele 1 at each SNP; i.e., A1854352, G1360020, A-1438, C74, C102, C516, C1354, A1018579, and T1018578.
*Significant genotype-wise difference from controls ($\chi^2 = 7.9$, $P = 0.02$, df = 2).
**Significant genotype-wise ($\chi^2 = 6.2$, $P = 0.04$, df = 2) and allele-wise ($\chi^2 = 6.2$, $P = 0.01$, df = 1) differences.
***$P = 0.016$ (binomial test).

haplotype 'blocks,' each associated with the disorder. We felt it was inappropriate to make such a claim because a plot of D′ values for pairs of SNPs against their physical distance suggested a linear decline in LD, consistent with expectations for a relatively small genomic distance. These disparities illustrate difficulties in interpreting results from pair-wise LD analysis.

Though our results are internally consistent, caution is necessary in view of the limited sample size and the relatively small magnitude of the associations. The presence of single parent family units further reduced the number of informative transmissions for the conventional TDT analyses. Reassuringly, analyses involving TRANSMIT, which exploited the entire family-based sample were consistent with the initial TDT analyses. Even so, our results need to be investigated using independently ascertained samples. Only two association studies have reported on 74C/A and three others analyzed 1354C/T (Table I). Only one of the studies conducted haplotype based analyses among cases and unrelated controls [Gutierrez et al., 1997]. Significant associations were not detected in these studies. More reliable information may be obtained using parental genotypes.

In summary, differential transmission of one SNP at *HTR2A*, as well as related haplotypes was detected among Caucasian BD1 cases and their parents. Case-controls analyses also support the associations and suggest *HTR2A* as a susceptibility gene for BD1. Our analyses illustrate the benefits of analyses involving multiple SNPs at candidate genes, as many prior studies which examined solitary SNPs failed to detect associations. Replicate studies using large samples, as well as studies to investigate the functional impact of variations at SNPs 74C/A and 1354C/T are needed.

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