Bipolar affective disorder (BPD), a common severe mood disorder characterised by manic and depressive episodes, has an estimated lifetime prevalence of 0.1%–1% in various populations, including that of Taiwan. Although previous studies have strongly suggested the involvement of genetic factors in the aetiology of BPD, the search for predisposing genes using classical linkage analysis has been fraught with difficulty. Association studies have been shown to be effective in mapping genes for complex diseases and have therefore been widely applied to studies of many psychiatric traits, including BPD. The results suggest that several genes with minor effects might be involved in the pathogenesis of BPD and that genes involved in neurotransmitter metabolism or signal transduction are possible candidates for an association with BPD.

Serotonin (5-hydroxytryptamine; 5-HT), a major neurotransmitter in the central nervous system, is involved in various physiological events, such as mood control, sleep, thermoregulation, learning, and memory. Disruption of serotonergic function has been implicated in the pathogenesis of many psychiatric disorders, including BPD. Serotonin exerts its diverse functions through multiple receptor (HT receptor; HTR) subtypes. These receptors, localised on the post- or pre-synaptic neuronal membrane, bind released serotonin and either transmit the signal to the post-synaptic neurone or regulate serotonin production by the neurone itself. Seven classes of HTRs (HTR1–7), made up of 15 functionally and pharmacologically distinct receptor subtypes, have been identified in mammalian species in the past few years. Except for HTR3, which is a ligand gated ion channel receptor, all known HTR family members are G-protein coupled receptors.

Of these 15 subtypes, several, which are abundantly expressed in the limbic system and have a high affinity for antipsychotic drugs, are related to mood control. Studies on knockout or transgenic mice have shown that impaired mood regulation is caused by dysfunction of certain HTRs. For example, HTR1B knockout mice exhibit more aggressive and reactive behaviour and less anxious behaviour. Conversely, HTR1A knockouts show less reactive behaviour, more anxious behaviour, and possibly less aggressive behaviour. Moreover, mice with mutations in the HTR2C or HTR5A gene exhibit, respectively, an obesity syndrome or a reduced locomotor stimulatory effect. In addition to this strong evidence from animal studies, previous studies have shown that suicidal patients have a higher number of platelet HTR2A and BPD patients have significantly decreased brain levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Furthermore, it has been reported that treatment with HTR1A agonists can affect neurotransmitter release and cause behavioural change. The results of these studies suggest that the HTRs implicated in mood regulation are good candidates for involvement in BPD pathogenesis.
To investigate the role of HTRs in the aetiology of BPD in Taiwan, single nucleotide polymorphisms (SNPs) located in the coding or regulatory regions of six genes, HTR1A, HTR2A, HTR2C, HTR5A, HTR6, and HTR7, were examined in 100 BPD patients and 106 normal controls. Significant differences in both the genotypic and allelic distribution of HTR2C and HTR7 were found between the case and control groups. In addition, a logistic regression model including HTR2C, HTR7, HTR2A, and HTR6 was found to be the best model for predicting disease status. Our results support the idea that HTR2C and HTR7 play important pathophysiological roles in predisposition to BPD, and suggest that the HTR2C C12G and HTR7 G3217A polymorphisms may be valuable as both functional and genetic markers, the products of which affect signalling networks, owing to their abnormal interaction with serotonin.

METHODS
Sample collection and DNA preparation
Starting in 1998, probands were recruited from bipolar outpatients in the Chung Shan Medical University Hospital and the Taichung Rehabilitation Hospital in Taiwan. Controls were local volunteer blood donors, with no family or personal history of major affective disorder, who were matched to cases based on ethnic or geographical origin, sex, and age. Patients and controls were interviewed by experienced psychiatrists after the study procedure had been fully explained, and information on general demographic data, such as age, sex, and ethnicity, was obtained. Patients were assessed solely by direct clinical interview by the treating clinician, according to the procedure described in the DSM-VI (Diagnoses of lifetime major depressive disorder and bipolar I). In addition, information required to reach diagnosis was also obtained from all clinical and hospital records where available. This study was approved by the university ethics committee, and written informed consent was obtained from all participants.

We recruited 100 unrelated BPD subjects and 106 normal control subjects. All participants were ethnic Chinese from Taiwan. Genomic DNA was prepared from peripheral blood by standard salt precipitation methods or using InstaGene Whole Blood kits (BioRad, Hercules, CA, USA) according to the manufacturer’s protocol.

Selection of candidate genes and markers
The candidate gene approach focuses on genes, the products of which are likely to be of functional significance in the disease. To examine whether specific HTRs were involved in the pathology of BPD, we selected those that are abundantly expressed in the limbic system and have a high affinity for antipsychotic drugs. The candidate gene approach focuses on genes, the products of which are likely to be of functional significance in the disease. To examine whether specific HTRs were involved in the pathology of BPD, we selected those that are abundantly expressed in the limbic system and have a high affinity for antipsychotic drugs.

Genotyping procedures and primer design
All primers used for genotyping were designed using OLGIGO 6 Primer Analysis Software (Molecular Biology Insights, Inc., Cascade, CO, USA). Except for HTR2C and HTR7, in which SNPs were genotyped using the multiple single base extension (MSBE) approach, SNP markers were genotyped using the PCR allele specific oligonucleotide (PCR-ASO) method and the amplification refractory mutation system (ARMS).

The PCR-ASO method was modified from the original ASO hybridisation assay by the use of fluorescent primers. Two forward primers for the alternative alleles were labelled with different fluorescent markers and amplified together with one common anti-sense primer, the different fluorescent colours indicating the presence of the alternative alleles. In the ARMS approach, two pairs of primers were designed, each one of the coupled primers having an allele specific oligonucleotide at the 3'-end that targets the polymorphic base for amplification of different products. The two forward primers for the alternative alleles were labelled with the same fluorescent marker and amplified with the paired reverse primer. PCR products of different sizes indicated the presence of the two alleles of a given polymorphism.

MSBE was carried out using an ABI PRISM® SNaPshot™ Kit (Applied Biosystems, Forster City, CA, USA). Paired primers were designed for amplification of the flanking sequence of the SNP sites, and detection was based on the dideoxy single base extension of an unlabelled oligonucleotide primer. Each primer binds to a complementary template in the presence of fluorescent labelled ddNTPs, and the polymerase extends the primer by one nucleotide, adding a single ddNTP to its 3' end. Four different fluorescent dyes were used to label the different ddNTPs. Extension primers with sizes ranging from 18–60 bp were designed to separate the different products and detect multiple SNPs in a single reaction. Using a fluorescence detection system (ABI 310 Genetic Analyzer; Applied Biosystems), extended products with different sizes and colours were detected automatically.

PCR reaction
PCR for ASO and ARMS analyses was performed in a volume of 15 μl containing 50 ng of genomic DNA, 0.2 μmol/l primer, 200 μmol/l dNTP, 1 x buffer, 1.5 mmol/l MgCl2, and 0.5 U of TaqGold DNA polymerase (Applied Biosystems). The PCR program started with 10 min at 95°C, followed by 43 cycles of 94°C for 30 s and 50-62°C for 60–90 s, and a final extension at 60–72°C for 5 min. In the MSBE system, PCR was performed using 0.5 U of Taq polymerase (ABgene, Epsom, Surrey, UK) and the PCR program was 5 min at 95°C, followed by 30 cycles of 94°C for 30 s and 50–55°C for 30–60 s, and a final extension at 60–72°C for 5 min.

Genotype analysis
The PCR and extension products were analysed using an ABI310 Genetic Analyzer. Capillary electrophoresis was performed by mixing 1 μl of the PCR product mix with 11.5 μl of formamide and 0.5 μl of size markers, heating the mixture at 95°C for 5 min, then quickly cooling it on ice. Onto a capillary polymer, 14 μl of each sample was loaded and run for 30 min. Products of different size were separated by polymer capillary electrophoresis, and the length of each PCR product determined from the size markers. Data were collected and analysed using ABI GeneScan software (Applied Biosystems). To avoid genotyping errors, all marker genotypes were scored independently by two investigators and checked for confirmation. In addition, discrepant genotypes were retyped to ensure the correct genotypes for final data analysis.

Statistical methods
Differences in genotype and allele distributions between patients and normal controls were analysed using Fisher’s exact test and χ² test implemented by SAS (version 8; SAS Cary, NC, USA). The Hardy–Weinberg equilibrium in control groups was tested using Haldane’s exact test because of small sample size. As markers might show violation of the Hardy–Weinberg equilibrium, a complementary test for association was also conducted. This complementary test, a
combination of Armitage’s test and Monte Carlo simulation, is robust to the Hardy–Weinberg equilibrium, and can provide a precise statistical inference. In addition, estimation of the relative risk of BPD associated with a particular allele and power analyses were performed using, respectively, the RelRisk program and the Power Analysis and Sample Size (PASS) 2002 software (NCSS, Kaysville, UT, USA).

An additional regression model was used to consider the relative importance of candidate HTR genes to the disease. Because the disease status was dichotomous, we used the SAS program LoGistic to carry out the logistic regression analysis. For model selection, three effect selection methods, forward, backward, and stepwise selection, were used to consider models including all possible combinations of different numbers of the variables (the HTR types). Two other values, the $-2\log L$ and Akaike’s information criterion ($AIC$), which help in determining goodness of fit, were also used. In general, smaller values of $-2\log L$ and $AIC$ are preferred, and a significant difference in the $-2\log L$ between two models of different complexity indicates that the more complex model is better. In addition, the Hosmer and Lemeshow test for goodness of fit was used to confirm the validity of the selected model. A significant $p$ value means that the model fails the goodness of fit test.

**RESULTS**

Six polymorphisms of the targeted HTRs were genotyped to examine the association with BPD in Taiwanese. As the subjects were recruited from multiple centres, DNA quality was difficult to control, thus it varied significantly. The overall genotyping rate was 83.2% and the missing rates of genotyping for the six receptors ranged from 3% to 26% and from 9% to 13% in the patient and control groups, respectively. The frequencies of the alleles and genotypes for the selected markers in the BPD and control groups are shown in table 2. Significant differences in both the genotypic and allelic distribution for HTR1A, HTR2A, HTR2C, and HTR7 were seen between cases and controls (table 2); in the case of HTR2C and HTR7, the differences were still significant after Bonferroni correction. As few markers in the control groups exhibited significant deviations from the Hardy–Weinberg equilibrium (data not shown), a complementary Armitage’s test for association was also conducted. Results from Armitage’s test were consistent with the data obtained from the $\chi^2$ test (table 2). No association was seen between HTR5A and HTR6 gene polymorphisms and BPD.

Logistic regression analyses were used to consider several markers simultaneously to investigate any multiple gene effect. According to all three selection criteria, the chosen model contains markers HTR2C and HTR7 (model 1 in table 3). Under hierarchical modelling, all complex models based on model 1 were examined and three were judged as candidate models (model 2, 3 and 4 in table 3). All $p$ values of likelihood ratio tests for four candidate models showed the significance of gene effects. On the basis of their $-2\log L$ and $AIC$ values, models 2, 3, and 4 were, respectively, the best three, four, or five variable models. The $-2\log L$ value decreased considerably from model 1 to model 2 (31.983) and from model 2 to model 3 (20.14), indicating a significant improvement in model fitting. However, the difference in $-2\log L$ between models 3 and 4 was small (6.04) indicating modest improvement. Based on a conservative viewpoint, the results of the logistic regression analyses suggest that model 3, which included HTR2A, HTR2C, HTR6, and HTR7, was the best model under the selection from multiple gene effects. A $p$ value of 0.8 in the goodness of fit test demonstrated that the model was valid.

**DISCUSSION**

BPD is a common and genetically heterogeneous disease. Many genes involved in serotonin transmission, such as the tryptophan hydroxylase gene coding for the rate limiting enzyme in serotonin biosynthesis, have been studied for an association with BPD. However, the results from previous studies have not been consistent and sometimes even controversial. These findings indicate that BPD is a complex disease involving multiple genetic factors.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP location</th>
<th>Amino acid alteration</th>
<th>Primers and probes†</th>
<th>dbSNP ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR1A</td>
<td>Exon1/G402A</td>
<td>Arg134Arg</td>
<td>WF1 FAM 5’-CGCCATCGCGGTCGACAGCAG-3’</td>
<td>rs139347</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WR1 TET 5’-CGCCATCGCGGTCGACAGCAG-3’</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MF TET 5’-TGAGCAGGAGGGATGTAAGGGA-3’</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MR FAM 5’-TGAGCAGGAGGGATGTAAGGGA-3’</td>
<td></td>
</tr>
<tr>
<td>HTR2A</td>
<td>Exon3/C62428T</td>
<td>–</td>
<td>WF FAM 5’-TCTACAGAATAGCCTAACTGCC-3’</td>
<td>rs6313</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WR FAM 5’-TCTACAGAATAGCCTAACTGCC-3’</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MF TET 5’-TCTACAGAATAGCCTAACTGCC-3’</td>
<td></td>
</tr>
<tr>
<td>HTR2C</td>
<td>Exon4/C12G</td>
<td>Leu4Val</td>
<td>WF FAM 5’-TCTCTCCAGGAGGACGAGA-3’</td>
<td>rs6320</td>
</tr>
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<td></td>
<td></td>
<td>WR FAM 5’-TCTCTCCAGGAGGACGAGA-3’</td>
<td></td>
</tr>
<tr>
<td>HTR5A</td>
<td>Exon1/A12T</td>
<td>–</td>
<td>WF FAM 5’-CTGAGGAGGAGGGATGTAAGGGA-3’</td>
<td>rs180504</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WR FAM 5’-CTGAGGAGGAGGGATGTAAGGGA-3’</td>
<td></td>
</tr>
<tr>
<td>HTR6</td>
<td>Exon1/C734T</td>
<td>–</td>
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<td>rs193547</td>
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<td>WR FAM 5’-CTGAGGAGGAGGGATGTAAGGGA-3’</td>
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<tr>
<td>HTR7†</td>
<td>Exon1/G3217A</td>
<td>–</td>
<td>WF1 FAM 5’-GAGATATTTTGGCTAATGGC-3’</td>
<td>rs2228669</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MR TET 5’-GAGATATTTTGGCTAATGGC-3’</td>
<td></td>
</tr>
</tbody>
</table>

†WF, wild type forward primer; MF, mutation forward primer; WR, wild type reverse primer; MR, mutation reverse primer; P, probe. FAM, HEX, and TET indicate the different fluorescent labels.

Table 1 Sequence of primers and probes for the SNPs used in this study

A significant $p$ value means that the model fails the goodness of fit test.
To characterise the gene effect of HTRs on BPD aetiology, we examined the genetic association between SNPs of several HTRs and BPD in Taiwanese bipolar I disorder patients. The significant allelic and genotypic differences between patients and normal controls for the HTR2C and HTR7 genes (table 2) suggest that genetic variation at these two loci may play important roles in the development of BPD. Although the newly characterised HTR7 has not yet been associated with any diseases, multiple polymorphisms in HTR2C are known to be associated with BPD in various populations.12 34 35 Moreover, the chromosomal regions of HTR2C (Xq24) and HTR7 (10q21–24) have been linked to BPD.36 37 38 The consistent results from different mapping studies in various populations suggest that dysfunction of HTR2C and HTR7 is related to the pathogenesis of BPD.

HTR1A and HTR2A have been implicated in several psychiatric conditions, including BPD.19 30 31 The HTR2A antagonist, clozapine, and the HTR1A partial agonist, buspirone, are used as alternative drugs for the treatment of many psychiatric diseases. Moreover, HTR1A knockout mice exhibit increased anxiety behaviour and decreased aggressive behaviour.31 32 Although the two receptors seem important in regulating behavioural traits, previous association studies of HTR2A using the same polymorphism and HTR1A using a microsatellite marker with BPD have given negative results.33 34 35 In our study, statistical analysis showed significantly genotypic and allelic differences in the frequencies of HTR1A and HTR2A gene polymorphisms between case and control samples before the Bonferroni correction (table 2); however, these associations were weak and were lost after the Bonferroni correction, suggesting that the gene effects of HTR1A and HTR2A are minor. Much less attention has been paid to HTR5A since it was cloned41 and mapped to human chromosome 7q36.1.32 No disease association has been studied, and no association was found between HTR5A gene polymorphism and BPD in our report. This suggests that, although the HTR5A gene appears to be expressed uniquely in the central nervous system,32 the polymorphism probably does not represent a major genetic risk factor of BPD. HTR6 gene polymorphism is not associated with tardive dyskinesia,42 mood disorders,39 or sporadic Alzheimer’s disease.43 As HTR6 was not associated with BPD in our study using the \( \chi^2 \) test, the effect seen in the logistic regression analysis (model 3) might imply that any role of HTR6 in the pathogenesis of BPD involves an interaction with other factors in the regression model. However, models for testing interactions between genes did not fit well due to the small sample size in this study. More samples will be required to study the epistatic effects among these candidate genes.

In genetically complex (polygenic) diseases, susceptibility or resistance variants are expected to be few at each locus, relatively common in the human population, and enriched in the coding and regulatory sequence of genes.44 45 Moreover, these susceptibility or resistance loci are rarely functionally independent, but work together to trigger the disease. Several methodologies and statistical methods have been successfully applied to analyse the effect of several genes on one phenotype.46 47 In this study, we used a logistic regression model to investigate the multiple gene effects of HTRs on the aetiology of BPD in Taiwan. Results from regression analysis showed the best model for predicting disease status was that using HTR2A, HTR2C, HTR6, and HTR7, based on our data.

<table>
<thead>
<tr>
<th>Locus symbol (alternative alleles)</th>
<th>Allele†</th>
<th>p value</th>
<th>Genotype</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR1A (G/A)</td>
<td>1</td>
<td>0.0117</td>
<td>0.0183</td>
<td>0.011</td>
</tr>
<tr>
<td>HTR2A (C/T)</td>
<td>1</td>
<td>0.0421</td>
<td>0.0137</td>
<td>0.044</td>
</tr>
<tr>
<td>HTR2C (G/G)</td>
<td>1</td>
<td>0.0005†</td>
<td>0.0060†</td>
<td>0.007‡</td>
</tr>
<tr>
<td>HTR5A (T/A)</td>
<td>1</td>
<td>0.00961</td>
<td>0.1321</td>
<td>0.261</td>
</tr>
<tr>
<td>HTR7 (G/A)</td>
<td>1</td>
<td>0.00001†</td>
<td>0.00005†</td>
<td>0.00025‡</td>
</tr>
</tbody>
</table>

†The number 1 and 2 indicate, respectively, the major and minor allele.
‡Significant difference in the distribution between the case and control groups after Bonferroni correction.
§The relative risk is 0.39 (95% confidence interval (CI) 0.22 to 0.72) and power for the allele distribution of HTR2C is approximately 87% with \( \alpha = 0.05 \).
∥The relative risk is 0.35 (95% CI 0.20 to 0.59) and power for the allele distribution of HTR7 is about 98% with \( \alpha = 0.05 \).

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables</th>
<th>Likelihood ratio test (p value)</th>
<th>−2logL</th>
<th>AIC</th>
<th>Goodness of fit (p value)</th>
<th>Number of cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HTR2C + HTR7</td>
<td>24.9578 (&lt;0.0001)</td>
<td>192.378</td>
<td>202.378</td>
<td>5.4955 (0.3584)</td>
<td>82/75</td>
</tr>
<tr>
<td>2</td>
<td>HTR2A + HTR2C + HTR7</td>
<td>23.9032 (0.0005)</td>
<td>160.395</td>
<td>174.395</td>
<td>5.2578 (0.5112)</td>
<td>74/60</td>
</tr>
<tr>
<td>3</td>
<td>HTR2A + HTR2C + HTR6 + HTR7</td>
<td>20.9882 (0.0007)</td>
<td>140.255</td>
<td>158.255</td>
<td>3.8390 (0.7981)</td>
<td>70/49</td>
</tr>
<tr>
<td>4</td>
<td>HTR2A + HTR2C + HTR5A + HTR6 + HTR7</td>
<td>23.7910 (0.0008)</td>
<td>134.215</td>
<td>156.215</td>
<td>7.0184 (0.4208)</td>
<td>67/49</td>
</tr>
</tbody>
</table>

†All possible combinations were tested; the four models shown were the best candidates.
‡The test statistic is for testing the difference between the fitted model and the model without gene effects.
Of those SNPs associated with BPD pathophysiology, HTR2C C12G involves a missense amino acid change (Leu4Val), and the HTR7 G3165A polymorphism involves a sequence change in the 5’ regulatory region. The HTR2C missense mutation may contribute to disease by changing the encoded amino acid, thus altering its properties. The substituted site is in the first extracellular domain of HTR2C and, although valine and leucine are both hydrophobic amino acids with similar biochemical properties, valine is smaller and more hydrophilic, which may influence the binding affinity of serotonin for HTR2C. A functional mutagenesis study is in progress to test the biophysical effect of this missense mutation. The HTR7 G3165A polymorphism is in the 5’UTR region of the consensus region of the autonomously replicating sequence binding factor 1 (ABF1) binding site. ABF1 is a multifunctional, site specific DNA binding protein that is essential for cell viability in Saccharomyces cerevisiae.\textsuperscript{46} The human ABF1 gene has been cloned and found to be a member of the basic helix-loop–helix family of transcription factors.\textsuperscript{47} An analysis of the transcription factor binding prediction using the MatInspector program (http://www.gsf.de/biodiv/matinpector.html) indicated that the base change from G to A alters the consensus sequence and abolishes ABF1 binding, thus could cause down-regulation of HTR7 gene expression.

There have been reports that abnormalities in various second messenger systems (that is signal transduction pathways) could be involved in the pathophysiology of affective disorders.\textsuperscript{48–50} These signalling networks rely on membrane receptors to communicate information from the extracellular environment to the interior of the cell through binding to G-proteins. Inside the cell, the information induces changes in gene and protein expression. Of these pathways, the adenylyl cyclase (cyclic adenosine monophosphate; cAMP) and phosphoinositide (protein kinase C) second messenger systems (that is signal transduction pathways) lead to the mobilisation of intracellular calcium and activation of protein kinase C. It is possible that receptors with altered affinity or requirements for binding serotonin will affect signal transmission through these two major second messenger systems, leading to altered gene expression patterns and induction of BPD.

Although some important findings from statistical association analyses have inspired us, some cautionary remarks should be addressed, for example, effects on population stratification and type I and type II errors. Some auxiliary variables (gender, medical history, family register) were analysed to detect the confounding effect and population stratification (data not shown). The results indicate that these factors are not confounders misleading the positive associations obtained in this study. Moreover, the Bonferroni correction and logistic regression partially keep the false positive rate under control. However, the false positive event may still occur due to some intangible factors even after careful statistical treatments. On the other hand, results from the present study cannot exclude completely the non-associated receptors, such as HTR6. These receptors may still contribute minor effects to BPD but it is insufficient to be supported in our study due to the modest sample size. Expanding the sample size and more efforts will be required to reproduce the results of this study in future works.

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