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ORIGINAL PAPER

HTR2A is Associated with SSRI Response in Major Depressive Disorder in a Japanese Cohort

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Abstract Several recent investigations reported that the serotonin 2A receptor gene (*HTR2A*) was associated with selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder. There have also been two reported association analyses of *HTR2A* with SSRI response in Japanese MDD patients, but the results were rather inconsistent and both studies had the problem of small sample sizes. Therefore, we conducted a replication association study using a sample larger than those in the two original Japanese studies (265 MDD patients), and found that four SNPs, two functional SNPs (-A1438G: rs6311 and T102C: rs6313) and two SNPs (rs7997012 and rs1928040) in *HTR2A*, were associated with the therapeutic response to SSRIs. *HTR2A* was associated with the therapeutic response SSRIs in Japanese MDD patients in a haplotype-wise analysis ($P_{\text{all markers}} = 0.0136$), and a significant association between rs1928040 in *HTR2A* and SSRI response was detected in MDD ($P_{\text{allele-wise analysis}} = 0.0252$). However, this significance disappeared after Bonferroni correction ($P_{\text{allele-wise analysis}} = 0.101$). In conclusion, we suggest that *HTR2A* may play an important role in the pathophysiology of the therapeutic response to SSRIs in Japanese MDD patients. However, it will be important to replicate and confirm these findings in other independent studies using large samples.

Keywords Serotonin 2A receptor gene (*HTR2A*) · SNPs · Major depressive disorder · Selective serotonin reuptake inhibitor (SSRI) response

Introduction

Several investigations have suggested that serotonin 2A receptor gene (*HTR2A*) might be a factor in the therapeutic response in major depressive disorder (MDD). The evidence for this relation is discussed in more detail in the reviews (Kato and Serretti 2008; Kato 2007; Serretti and Artioli 2004a, b; Serretti et al. 2007a, b; Serretti and Mandelli 2008). Other recent investigations reported that *HTR2A* was associated with selective serotonin reuptake inhibitors (SSRIs) treatment response in MDD. McMahon et al. (2006) reported an association between rs7997012 and rs1928040 in *HTR2A* and the outcome of citalopram treatment in a very large sample of outpatients with MDD. Peters et al. (2009) replicated those findings in a study showing that rs7997012 was associated with citalopram response in MDD. However, Perlis et al. (2009) reported that rs7997012 and rs1928040 were not associated with duloxetine treatment outcome in MDD. In Japan, there have been two reported association analyses of *HTR2A* with SSRIs response in MDD patients, but the results were rather inconsistent and both studies had the problem of small sample sizes (Kato et al. 2006; Sato et al. 2002).

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A recent meta-analysis reported that -A1438G (rs6311), which is known to be a functional SNP in *HTR2A*, was associated with SSRI response in Asian MDD patients (Kato and Serretti 2008).

In our previous study, we found no association between *HTR2A* and mood disorders, including MDD and bipolar disorder, in the Japanese population (Kishi et al. 2009c). Here, we conducted a replication association study using a sample larger than those in the two Japanese original studies (265 MDD patients), and found that four SNPs, two functional SNPs (-A1438G: rs6311 and T102C: rs6313) and two SNPs (rs7997012 and rs1928040) in *HTR2A*, were associated with the therapeutic response to SSRIs.

Materials and Methods

Subjects

Two hundred and sixty-five MDD patients participated in this study. These patients had been diagnosed according to DSM-IV criteria with the consensus of at least two experienced psychiatrists on the basis of a review of medical records and assessment with the Structured Interview Guide for Hamilton Rating Scale for Depression (SIGH-D) (Williams 1988). None had severe medical complications such as cirrhosis, renal failure, heart failure, or other Axis-I disorders according to DSM-IV.

Participating patients took fluvoxamine two or three times a day and sertraline and paroxetine one or two times a day for 8 weeks. Fluvoxamine, sertraline, and paroxetine were increased gradually to a maximum of 150, 100, and 40 mg, respectively, depending on the patients' condition. Patients with insomnia and severe anxiety were prescribed benzodiazepine drugs, but no other psychotropic drugs were permitted during the study. The study was described to subjects and written informed consent was obtained from each. This study was approved by the Ethics Committee at Fujita Health University and University of Occupational and Environmental Health.

Data Collection

The scores of the 265 MDD patients in this study on the 17 items of the SIGH-D were 12 or higher (Peveler and Kendrick 2005). We defined a clinical response as a decrease of more than 50% in baseline SIGH-D within 8 weeks, and clinical remission as a SIGH-D score of less than 7 at 8 weeks. Detailed information on data collection was described in a previous article (Saito et al. 2006). The clinical characteristics of the patients in this study, classified according to these definitions, can be seen Table 1.

Table 1 Clinical characteristics of the patients in both definition groups

	N			Patients permitted SSRIs, *n* (%)[c]			Age (mean ± SD)	Baseline SIGH-D (avg ± SD)	Number of previous episodes (avg ± SD)	Patients permitted anxiolytics/hypnotics, *n* (%)
	Total	Male	Female	FLV	STL	PAX				
Overall	265	121	144	129 (48.7)	72 (27.2)	64 (24.2)	48.2 ± 16.3	20.6 ± 5.16	1.77 ± 0.787	116 (43.9)
Clinical response group[a]										
Responders	150	75	75	68 (25.7)	47 (17.7)	35 (13.2)	48.6 ± 15.6	21.3 ± 5.30	1.76 ± 0.750	70 (26.5)
Nonresponders	115	46	69	61 (23.0)	25 (9.43)	29 (10.9)	47.7 ± 17.2	19.7 ± 4.87	1.79 ± 0.842	46 (17.4)
P value	0.105			0.208			0.662	**0.0161**	0.745	0.305
Clinical remission group[b]										
Remitters	103	53	50	53 (20.0)	32 (12.1)	18 (6.79)	48.4 ± 15.9	19.6 ± 4.47	1.67 ± 0.686	42 (15.9)
Nonremitters	162	68	94	76 (28.7)	40 (15.1)	46 (17.4)	48.1 ± 16.6	21.2 ± 5.48	1.84 ± 0.843	74 (28.0)
P value	0.131			0.109			0.880	**0.0136**	0.122	0.407

[a] Clinical response was defined as a 50% or greater decrease in the baseline SIGH-D score

[b] Clinical remission was defined as a final SIGH-D score of less than 7

[c] *FLV* fluvoxamine, *STL* sertraline, *PAX* paroxetine

SNP Selection and Linkage Disequilibrium (LD) Evaluation

We selected two biologically functional SNPs (T102C: rs6313 and -A1438G: rs6311; Myers et al. 2007; Spurlock et al. 1998). Because we detected r^2 less than 0.800 for all phenotypes (r^2 = healthy controls: 0.719 and MDD: 0.709; Kishi et al. 2009c), we selected two biologically functional SNPs (-A1438G: rs6311 and T102C: rs6313) in this study (Myers et al. 2007; Spurlock et al. 1998). In addition, we also included rs7997012 and rs1928040 in *HTR2A* because McMahon et al. (2006) reported an association between these two SNPs and outcome of citalopram treatment in a very large sample of outpatients with MDD. These four SNPs were used in the following association analysis. Detailed information about SNP selection was described in our previous article.

SNP Genotyping

We used TaqMan assays (Applied Biosystems, Inc., Foster City, CA,) for all SNPs. One allelic probe was labeled with FAM dye and the other with fluorescent VIC dye. The plates were heated for 2 min at 50 and 95°C for 10 min, followed by 45 cycles of 95°C for 15 s and 58°C for 1 min. Please refer to ABI for the primer sequence. Detailed information, including primer sequences, and reaction conditions, is available on request.

Statistical Analysis

Genotype deviation from the Hardy–Weinberg equilibrium (HWE) was evaluated by chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan).

Marker-trait association analysis was used to evaluate allele- and genotype-wise association with the chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan), and haplotype-wise association analysis was evaluated with a likelihood ratio test using the COCA-PHASE2.403 program (Dudbridge 2003). In the haplotype analysis, we determined that the cutoff for testing haplotype frequency was 0.05. We used the permutation test option as provided in the haplotype analysis to avoid spurious results and correct for multiple testing. Permutation test correction was performed using 1,000 iterations (random permutations). In addition, Bonferroni's correction was used to control inflation of the type I error rate in the single marker association analysis and in the individual haplotype-wise analysis. For Bonferroni correction, we employed the following numbers of multiple tests: 4 for each sample set in allele- and genotype analysis (4 examined SNPs); and 3 for each sample set in the individual haplotype-wise analysis (3 common haplotypes).

The significance level for all statistical tests was 0.05. Power calculation was performed using the Genetic Power Calculator (Purcell et al. 2003).

Results

Among the clinical characteristics of patients in this pharmacogenetic study, significant differences between either responders or nonresponders and remitters or nonremitters were detected in total SIGH-D score at the baseline ($P_{\text{response}} = 0.0161$ and $P_{\text{remission}} = 0.0136$; Table 1). Genotype frequencies of all SNPs were in HWE (Table 2). We found *HTR2A* to be associated with SSRI therapeutic response and remission in Japanese MDD patients in an all markers haplotype-wise analysis ($P_{\text{response}} = 0.0136$ and $P_{\text{response}} = 0.0400$) (Tables 3 and 4). When we performed a haplotype-wise analysis using the sliding window fashion method, a three-marker haplotype (rs6311-rs6313-rs1928040) showed the strongest association with the SSRI therapeutic response in MDD (P value = 0.000707; Tables 3 and 5). Also, this three-marker haplotype (rs6311-rs6313-rs1928040) showed the strongest association with remission in MDD (P value = 0.0324) (Tables 4 and 6). We also detected a significant association between rs1928040 in *HTR2A* and SSRI response and remission in MDD in an allele-wise analysis ($P_{\text{response}} = 0.0252$ and $P_{\text{remission}} = 0.0418$), but the significance disappeared after Bonferroni correction ($P_{\text{response}} = 0.101$ and $P_{\text{remission}} = 0.167$) (Table 2).

In addition, regarding genotyping quality control measures, we added 32 randomly selected samples that were genotyped again as a measure of genotyping quality control, and the genotype consistency rates for all four SNPs were 100%.

We obtained power of more than 80% for the detection of association when we set the genotype relative risk at 1.65–1.78 in all 265 samples, under a multiplicative model of inheritance (Purcell et al. 2003).

Discussion

We performed an association study for the SSRI therapeutic response in Japanese MDD patients using a larger sample than in two original Japanese studies. In one of those studies, Kato et al. (2006) reported an association between -A1438G (rs6311) and the SSRI therapeutic response in Japanese MDD, whereas Sato et al. (2002) found no such association. In this study, we found an association between *HTR2A* and the SSRI therapeutic response and remission in MDD in the haplotype-wise analysis.

Table 2 Genotype and allele distributions of *HTR2A* in both definition groups

SNPs[a]	Phenotype	MAF[b]	*N*	Genotype distribution[c]			*P* value[e]			Corrected *P* value[f]	
				M/M	M/m	m/m	HWE[d]	Genotype	Allele	Genotype	Allele
rs6311	Responders	0.410	150	47	83	20	0.0784				
(-1438A/G)	Nonresponders	0.428	115	40	53	22	0.743	0.567	0.670		
Intronl	Remitters	0.389	103	36	54	13	0.293				
	Nonremitters	0.432	162	51	82	29	0.690	0.502	0.319		
rs6313	Responders	0.493	150	35	82	33	0.252				
(102T/C)	Nonresponders	0.487	115	31	56	28	0.875	0.624	0.884		
Exonl	Remitters	0.495	103	24	56	23	0.375				
	Nonremitters	0.488	162	42	82	38	0.869	0.827	0.867		
rs 1928040	Responders	0.323	150	64	75	11	0.0806				
T>C	Nonresponders	0.235	115	66	44	5	0.487	0.0540	**0.0252**		0.101
Intron2	Remitters	0.335	103	42	53	8	0.116				
	Nonremitters	0.253	162	88	66	8	0.323	0.0910	**0.0418**		0.167
rs7997012	Responders	0.177	150	99	49	2	0.132				
G>A	Nonresponders	0.186	115	74	39	2	0.215	0.938	0.761		
Intron2	Remitters	0.189	103	65	37	1	0.0840				
	Nonremitters	0.176	162	108	51	3	0.275	0.664	0.696		

[a] Major allele > minor allele, SNP position

[b] *MAF* minor allele frequency

[c] *M* major allele, *m* minor allele

[d] Hardy–Weinberg equilibrium

[e] Bold numbers represent significant *P* value

[f] Calculated by Bonferroni's correction

Table 3 Haplotype-wise analysis between *HTR2A* and SSRIs response in MDD

	Global *P* value[a]		
	2 window	3 window	4 window
rs6311	0.518		
rs6313	**0.0101**	**0.000707**	**0.0136**
rsl928040	0.0535	0.106	
rs7997012			

[a] Bold numbers represent significant *P* value

Table 4 Haplotype-wise analysis between *HTR2A* and SSRIs remission in MDD

	Global *P* value[a]		
	2 window	3 window	4 window
rs6311	0.736		
rs6313	**0.0451**	**0.0324**	**0.0400**
rsl928040	0.0604	**0.0423**	
rs7997012			

[a] Bold numbers represent significant *P* value

Haplotype analysis to investigate SSRI response and resmissin in MDD indicated three common haplotypes (rs6311- rs6313-rs1928040: A-T-T, G-C-T and G-C–C). The G-C-T haplotype was less prevalent in subjects with an SSRI therapeutic response (corrected $P = 0.00723$), while G-C–C was very prevalent in subjects with an SSRI therapeutic response (corrected $P = 0.00864$). Therefore, we considered that *HTR2A* was associated with SSRI therapeutic response in MDD in the Japanese population. On the other hand, The G-C-T haplotype was less prevalent in subjects with remission on SSRIs (uncorrected $P = 0.0200$). This significance disappeared after Bonferroni correction (corrected $P = 0.0600$). As a result, there are possibilities of type I errors in an association between *HTR2A* and SSRI therapeutic remission in MDD of the haplotype-wise analysis statistically.

In this study, we detected a marginal association between rs1928040 and SSRI therapeutic response in Japanese MDD in the allele-wise analysis (uncorrected $P_{response} = 0.0252$ and uncorrected $P_{remission} = 0.0418$). Therefore, we considered that an association between haplotype in *HTR2A* and SSRI response in this study might

Table 5 Haplotype-wise analysis between rs6311-rs6313-rs1928040 in *HTR2A* and SSRIs response in MDD

rs6311-rs6313-rs1928040	Phenotype	Individual haplotype frequency	OR[a]	95% CI[b]	Individual *P* value[c]	Corrected *P* value[d]
A-T-T	Responders	0.551	1.00	1.00–1.00	0.816	
	Nonresponders	0.539				
G-C-T	Responders	0.267	1.84	1.07–3.15	**0.00241**	**0.00723**
	Nonresponders	0.142				
G-C-C	Responders	0.182	0.558	0.337–0.924	**0.00288**	**0.00864**
	Nonresponders	0.319				

[a] *OR* odds ratio

[b] *95% CI* 95% confidence interval

[c] Bold numbers represent significant *P* value

[d] Calculated by Bonferroni's correction (3 tests)

Table 6 Haplotype-wise analysis between rs6311-rs6313-rs1928040 in *HTR2A* and remission in MDD

rs6311-rs6313-rs1928040	Phenotype	Individual haplotype frequency	OR[a]	95% CI[b]	Individual *P* value[c]	Corrected *P* value[d]
A-T-T	Remitters	0.538	1.00	1.00–1.00	0.741	
	Nonremitters	0.556				
G-C-T	Remitters	0.237	1.76	3.16–5.41	**0.0200**	0.0600
	Nonremitters	0.139				
G-C-C	Remitters	0.225	0.759	0.466–1.24	0.0791	
	Nonremitters	0.306				

[a] *OR* odds ratio

[b] *95% CI* 95% confidence interval

[c] Bold numbers represent significant *P* value

[d] Calculated by Bonferroni's correction (3 tests)

be reflected rs1928040. According to the HapMap database, MAFs of rs7997012 and rs1928040 in Caucasians were different to those in Japanese. Haplotype frequencies and LD between rs6313, rs6311, rs1928040 and rs7997012 in Caucasians were significantly different than in Japanese.

Because we detected r^2 less than 0.800 for all phenotypes (r^2 = Control 0.719 and MDD 0.709) (Kishi et al. 2009c), we selected two biologically functional SNPs (T102C: rs6313 and -A1438G: rs6311) in this study (Myers et al. 2007; Spurlock et al. 1998). Although Wilkie and colleagues recently reported an association between rs6314 (C1354T) in *HTR2A* and both response and remission to paroxetine in MDD (Wilkie et al. 2008), this SNP was shown to have "minor allele frequencies: 0%" in the HapMap database (Japanese population).

A few points of caution should be noted in interpreting our results. First, our sample sizes were small, and there is a possibility of statistical errors in our results. Secondly, because we did not perform an association analysis based on LD and a mutation scan of *HTR2A*, a replication study using a larger sample and based on LD may be required for conclusive results. Thirdly, we measured plasma levels of administered sertraline and paroxetine excepting fluvoxamine. However, these effects should be minimal because no correlation between plasma SSRI concentration and clinical response has been reported (Kasper et al. 1993; Saito et al. 2006). Fourthly, because we investigated SSRIs response in MDD patients who were able to take each SSRIs without side effects during the treatment protocol, we did not examine the number of drop out patients due to side effects in this study. Fifthly, we did not investigate several demographic informations (education, income, etc.) of the participated patients in this study. Finally, our subjects did not undergo structured interviews. MDD patients who are not diagnosed by structured interview may develop bipolar disorder in the future (Bowden 2001; Stensland et al. 2008). Also, we did not perform a screening to exclude Axis II disorders. However, in this study patients were carefully diagnosed according to DSM-IV criteria with consensus of at least two experienced

psychiatrists on the basis of a review of medical records (Kishi et al. 2008, 2009a, b, c, d). In addition, when we found a misdiagnosis, we promptly excluded the misdiagnosed case in consideration of the precision of our sample.

In conclusion, we suggest that *HTR2A* may play an important role in the pathophysiology of the SSRI therapeutic response in Japanese MDD patients. However, it will be important to replicate and confirm these findings in other independent studies using large samples.

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