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ORIGINAL ARTICLE

Serotonin 1A receptor gene and major depressive disorder: an association study and meta-analysis

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Several genetic studies have shown an association between the 5-HT1A receptor gene (*HTR1A*) and major depressive disorder (MDD); however, results have been rather inconsistent. Moreover, to our knowledge, no association study on *HTR1A* and MDD in the Japanese population has been reported. Therefore, to evaluate the association between *HTR1A* and MDD, we conducted a case–control study of Japanese population samples with two single-nucleotide polymorphisms (SNPs), including rs6295 (C-1019G) in *HTR1A*. In addition, we conducted a meta-analysis of rs6295, which has been examined in other papers. Using one functional SNP (rs6295) and one tagging SNP (rs878567) selected with the HapMap database, we conducted a genetic association analysis of case–control samples (331 patients with MDD and 804 controls) in the Japanese population. Seven population-based association studies, including this study, met our criteria for the meta-analysis of rs6295. We found an association between rs878567 and Japanese MDD patients in the allele-wise analysis, but the significance of this association did not remain after Bonferroni's correction. We also did not detect any association between *HTR1A* and MDD in the allele/genotype-wise or haplotype-wise analysis. On the other hand, we detected an association between rs6295 and MDD in the meta-analysis ($P(Z)=0.0327$). In an explorative analysis, rs6295 was associated with Asian MDD patients after correction for multiple testing ($P(Z)=0.0176$), but not with Caucasian MDD patients ($P(Z)=0.138$). Our results suggest that *HTR1A* may not have a role in the pathophysiology of Japanese MDD patients. On the other hand, according to the meta-analysis, *HTR1A* was associated with MDD patients, especially in the Asian population.
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Keywords: case–control study; functional SNP; major depressive disorder (MDD); meta-analysis; serotonin 1A receptor gene (*HTR1A*); tagging SNP

INTRODUCTION

Altered serotonergic neural transmission is hypothesized to be a susceptibility factor for major depressive disorder (MDD). The evidence for such an association is discussed in more detail in reviews.[1,2]

Several genetic studies have shown an association between the serotonin 1A (5-HT1A) receptor gene (*HTR1A*) and MDD; however, results have been rather inconsistent. A recent meta-analysis showed no association between *HTR1A* and MDD.[3] However, two very recent studies reported that rs6295 (C-1019G) in the promoter region of *HTR1A*, which regulates *HTR1A* transcription,[4,5] was associated with MDD in the Chinese population.[6,7] Moreover, to our knowledge, no association study of *HTR1A* and MDD in the Japanese population has been reported.

Therefore, we examined the association between *HTR1A* and MDD in the Japanese, using the recently recommended strategy of 'gene-based' association analysis.[8] Moreover, we conducted an updated meta-analysis of rs6295, which has been intensively investigated in other studies.

MATERIALS AND METHODS

Subjects

The subjects in the association analysis were 331 patients with MDD (162 men and 169 women; mean age ± s.d. 44.3 ± 14.2 years) and 804 healthy controls (352 men and 452 women; mean age ± s.d. 38.6 ± 12.9 years). The patients were diagnosed according to the DSM-IV criteria with the consensus of at least two experienced psychiatrists on the basis of unstructured interviews and a review of medical records. In addition, at least 125 of the 331 MDD patients had been diagnosed according to the 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 SIGH-D (Structured Interview Guide for Hamilton Rating Scale for Depression). All subjects were unrelated to each other, ethnically Japanese and lived in the central area of Japan. All healthy controls were also psychiatrically screened on the basis of unstructured interviews. None of them had severe medical complications, such as cirrhosis, renal failure, heart failure

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or other Axis-I disorders according to DSM-IV. No structured methods were used to assess psychiatric symptoms in the controls, which included hospital staff, their families and medical students.

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 Nagoya University School of Medicine.

SNP selection and linkage disequilibrium (LD) evaluation

We first consulted the HapMap database (release no. 23.a. phase2, March 2008, http://www.hapmap.org, population: Japanese Tokyo: minor allele frequencies (MAFs) of more than 0.05) and included three SNPs (rs6449693, rs878567 and rs1423691) covering *HTR1A* (5′-flanking regions including ~1 kb from the initial exon and ~2 kb downstream (3′) from the last exon: HapMap database contig number chr5: 63287418.63291774) (Figure 1). One tagging SNP was then selected with the criteria of an r^2-threshold >0.8 in 'pairwise-tagging-only' mode using the 'Tagger' program (Paul de Bakker, http://www.broad institute.org/tagger-0) of the HAPLOVIEW software.[9]

HTR1A has also been reported to have one biologically functional SNP (C-1019G: rs6295).[4,10,11] rs6295 (C-1019G) in the promoter region regulates *HTR1A* transcription.[4,5] The C allele is a part of a 26 palindrome that connects transcription factors (Deaf-1, Hes1 and Hes5) by NUDR (nuclear deformed epidermal auto regulatory factor), whereas the G allele turns off repression by NUDR.[4,5] This would lead to elevated levels of 5-HT1A receptor in the presynaptic raphe nucleus in GG genotypes, compared with the CC genotype.[4,5] As no information about rs6295 was shown in the HapMap database, we included this SNP. These two SNPs were then used for the following association analysis.

SNP genotyping

We used TaqMan assays (Applied Biosystems, Foster City, CA, USA) for both SNPs. Detailed information, including primer sequences and reaction conditions, is available on request.

Statistical analysis

Case–control association study based on LD. Genotype deviation from the Hardy–Weinberg equilibrium (HWE) was evaluated by χ^2 test (SAS/Genetics, release 8.2, SAS Japan, Tokyo, Japan).

Marker-trait association analysis was used to evaluate allele- and genotype-wise association with the χ^2 test (SAS/Genetics, release 8.2, SAS Japan), and haplotype-wise association analysis was conducted with a likelihood ratio test using the COCAPHASE2.403 program.[12] Power calculation was performed using the Genetic Power Calculator.[13] Bonferroni's correction was used to control inflation of the type I error rate. The significance level for all statistical tests was 0.05.

Meta-analysis. To identify studies eligible for the meta-analysis, we searched PubMed citations through March 2009 using the terms '*HTR1A*,' 'serotonin 1A receptor gene,' 'major depressive disorder' and 'MDD' as key words.

As criteria selected for eligible studies, we referred to the study by López-León *et al.*[3] In summary, eligible studies had to meet all of the following criteria: (1) be published in peer-reviewed journal, (2) have cases not selected by questionnaires assessing symptoms of depression, (3) contain independent data, (4) have distribution of genotypes in the control population that was in the HWE, (5) be case–control association studies investigating one or more of the three polymorphisms, (6) have MDD patients diagnosed according to ICD and DSM and (7) use healthy individuals as controls in case–control studies.

Cochran's χ^2-based *Q*-statistic test was applied to assess between-study heterogeneity. The significance of the pooled odds ratio (OR) was determined using a *Z*-test. Overall, ORs and their 95% confidence intervals (95% CIs) were estimated under both the Mantel–Haenszel[14] fixed-effects and DerSimonian–Laird[15] random-effects models. The random-effects model is more conservative than is the fixed-effects model and produces a wider CI. When there is no evidence of heterogeneity, the random-effects model will yield similar results to the fixed-effects model. Therefore, if it is confirmed that there was no heterogeneity, we could calculate pooled ORs and *P*-values according to the Mantel–Haenszel fixed-effects model. If there was evidence of heterogeneity, we could calculate pooled ORs and *P*-values according to the DerSimonian and Laird random-effects model. Publication bias was evaluated using a funnel plot asymmetry with Egger's test. The statistical significance was set at 0.05. All data were analyzed using Comprehensive Meta Analysis (Version 2.0). More detailed information about the meta-analysis method is given in our previous papers. Bonferroni's correction was used to control inflation of the type I error rate. The significance level for all statistical tests was 0.05.

RESULTS

The LD from rs6449693, rs878567 and rs1423691 was tight, according to the HapMap database samples (r^2=1.00). However, the LD structure of rs6295 (functional SNP) and rs878567 (tagging SNP) in our control samples was not tight (r^2=0.160). Genotype frequencies of all SNPs were in the HWE. We found an association between rs878567 and Japanese MDD patients in the allele-wise analysis (*P*=0.0448), but this significance did not remain after Bonferroni's correction (*P*=0.0896). We also did not detect any association between *HTR1A* and MDD in the allele/genotype-wise (Table 1) or in the haplotype-wise analysis (*P*=0.126).

In the meta-analysis, seven population-based association studies, including this study, met our criteria for rs6295[4,6,16–19] (Table 2). We found significant heterogeneity among ORs (*Q*=16.2, df=6, *P*(*Q*)=0.0119). The pooled OR derived from all studies comprising

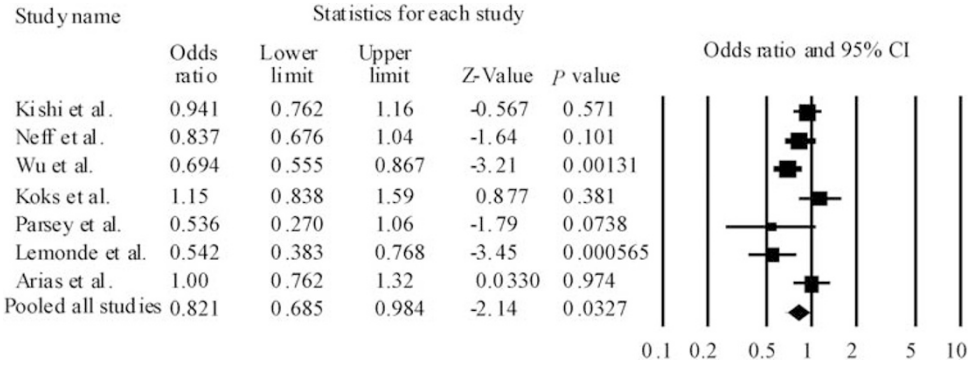

Figure 1 Forest plots of odds ratio (OR) with 95% confidence interval (95% CI) for rs6295. Results of all pooled studies are shown. We found significant heterogeneity among ORs (*Q*=16.2, df=6, *P*(*Q*)=0.0119). Therefore, we could calculate pooled ORs and *P*-values according to the DerSimonian and Laird random-effects model.

Table 1 Tagging SNPs and association analysis of *HTR1A*

SNP	Phenotype[a]	MAF	N	Genotype distribution[b]			P-value[d]			Corrected P-value
				M/M	M/m	m/m	HWE[c]	Genotype	Allele	Allele
rs6295	Controls	0.235	804	474	282	48	0.484			
	MDD	0.246	331	190	119	22	0.567	0.851	0.571	
rs878567	Controls	0.115	804	634	155	15	0.131			
	MDD	0.145	331	243	80	8	0.645	0.138	**0.0448**	0.0896

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; MDD, major depressive disorder; SNP, single-nucleotide polymorphism.
[a]MDD.
[b]M: major allele, m: minor allele.
[c]HWE.
[d]Bold numbers represent significant *P*-value.

Table 2 Studies included in meta-analysis for rs6295

Authors	Year	Ethnicity	Diagnostic system	N[a,b]		C[a,c]		G[a,d]		OR[e]	CI[f]	P(Z)[g]
				MDD	CON	MDD	CON	MDD	CON			
Kishi		Asian	DSM-IV	331	804	499	1230	163	378	0.941	0.761–1.16	0.571
Wu	2008	Asian	DSM-IV	400	400	558	615	242	185	0.694	0.555–0.867	**0.00131**
Neff	2008	Caucasian	DSM-IV-TR	344	336	338	360	350	312	0.837	0.676–1.04	0.101
Koks	2006	Caucasian	DSM-IV	177	160	141	132	163	176	1.15	0.838–1.59	0.381
Parsey	2006	Caucasian	DSM-IV	28	42	24	49	32	35	0.536	0.270–1.06	0.0738
Lemonde	2003	Caucasian	DSM-IV	129	134	123	168	135	100	0.542	0.383–0.768	**0.000565**
Arias	2002	Caucasian	DSM-III-R	249	170	232	158	266	182	1.00	0.762–1.32	0.974
Pooled all studies[h]				1658	2046	1915	2712	1351	1368	0.822	0.685–0.984	**0.0327**

Abbreviations: CI, confidence interval; CON, controls; MDD, major depressive disorder; OR, odds ratio.
[a]MDD, CON.
[b]*N*: number of samples.
[c]C: allele C.
[d]G: allele G.
[e]OR.
[f]CI.
[g]*P*(*Z*): *Z*-test was used to detect the significance of the overall OR. Bold numbers represent significant *P*-value.
[h]We found significant heterogeneity among ORs (Q=16.2, df=6, $P(Q)$= 0.0119). Therefore, we could calculate pooled ORs and *P*-values according to the DerSimonian and Laird random-effects model.

1658 patients and 2046 control subjects indicated a significant association (random model: OR=0.821, 95% CI=0.695–984, $P(Z)$=0.0327) (Table 2) (Figure 1). Next, to limit ethnic heterogeneity, we included an explorative analysis with either Caucasian or Asian samples. We did not observe significant heterogeneity among ORs in the Asian population (Q=4.30, df=1, $P(Q)$=0.133). However, we found significant heterogeneity among ORs in the Caucasian population (Q=13.1, df=4, $P(Q)$=0.0108). We detected a significant association between rs6295 and MDD in the Asian population (fixed model: pooled OR=0.815, 95% CI=0.699–0.950, $P(Z)$=0.00878) (Figure 2). Moreover, these associations were still significant after correction for multiple testing (fixed model: $P(Z)$=0.0176) (Figure 2). In addition, rs6295 was not associated with MDD in the Caucasian population (random model: OR=0.819, 95% CI=0.629–1.066, $P(Z)$=0.138) (Figure 1). No publication bias was found (t=0.685, P=0.524).

DISCUSSION

We detected an association between rs6295 and MDD in the meta-analysis. However, because significant heterogeneity among ORs was found (P=0.0119), we carried out an explorative analysis with either Caucasian or Asian samples. We detected a significant association between rs6295 and MDD in the Asian population, but did not observe significant heterogeneity among ORs (P=0.133). On the other hand, we observed significant heterogeneity among ORs in the Caucasian population (P=0.0108). The heterogeneity may result from (1) different ancestries (Asian population versus Caucasian population), (2) incomplete genotyping rates or genotyping error rates in different studies. Although the studies by Arias *et al.*[16] and Koks *et al.*[18] reported that the major allele was 'G', other studies showed that the major allele was 'C'. We contacted the corresponding authors with regard to the genotype data in these studies. They and Kato *et al.*[20] informed us that there were no genotyping errors. (3) The overall sample size included in the meta-analysis was relatively small (1658 patients and 2046 control subjects).[21] To overcome these limitations, a replication study using larger samples or samples of other populations will be required for conclusive results.

In our case–control study, no association was found. Although the Japanese and Chinese populations are both classified as Asian populations, rs6295 was associated with Chinese MDD patients,[6,7] but not with Japanese MDD patients. Several reasons may explain these inconsistent findings, including allelic heterogeneity, true variation in disease association between populations, modifying genetic and/or environmental factors and statistically underpowered small sample sizes. In rs6295, the MAFs in MDD in the Japanese population (0.246)

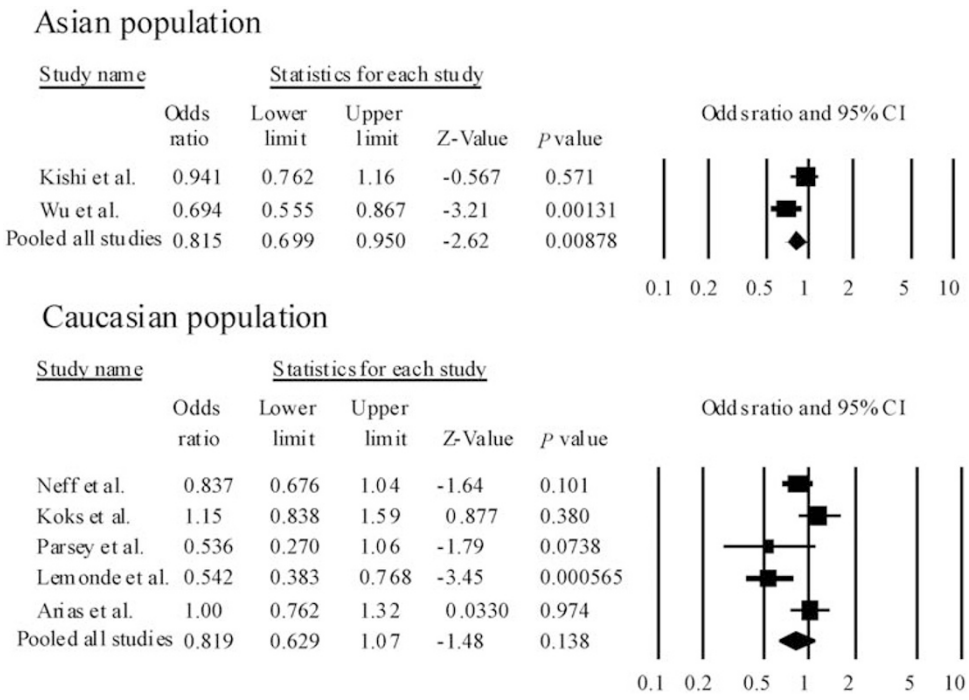

Figure 2 Forest plots of odds ratio (OR) with 95% confidence interval (95% CI) for rs6295. Results of subgroup analysis are shown. We did not observe significant heterogeneity among ORs in the Asian population (Q=4.30, df=1, $P(Q)$=0.133). Therefore, we could calculate pooled ORs and P-values according to the Mantel–Haenszel fixed-effects model. However, we found significant heterogeneity among ORs in the Caucasian population (Q=13.1, df=4, $P(Q)$=0.0108). Therefore, we could calculate pooled ORs and P-values according to the DerSimonian and Laird random-effects model.

seem to be smaller compared with those in the Chinese population (0.303).[6] The MAFs in Japanese controls were similar to those in Chinese controls (0.231).[6] Although classified in the same Asian population, the susceptibility genes for MDD might be not common. Recent evidence supports this hypothesis. The serotonin 2A gene was associated with MDD in the Korean population,[22] but not in Japanese population.[23] rs6295 (C-1019G) in the promoter region regulates *HTR1A* transcription.[4,5] The C allele is part of a 26 palindrome that connects transcription factors (Deaf-1, Hes1 and Hes5) by NUDR, whereas the G allele turns off repression by NUDR.[4,5] This would lead to elevated levels of 5-HT1A receptor in the presynaptic raphe nucleus in GG genotypes compared with the CC genotype.[4,5] In several studies, these variants were associated with responses including the antidepressant response in MDD.[24–29] Recently, Kato and Serretti[30] reported a meta-analysis between rs6295 and antidepressant efficacy in MDD. The authors showed that the pooled OR derived from six studies comprising 893 patients was not significant.[30] The pooled OR of studies in Caucasian populations only was also not significant.[30] However, the pooled OR of the studies in Asian studies only did show a significant association.[30] Therefore, the authors suggested that the rs6295 genotype may be a predictor of antidepressant treatment response in MDD in the Asian population.[30]

A few points of caution should be mentioned with respect to our results. First, our sample sizes were small. In the power analysis, we obtained power of more than 80% for the detection of association when we set the genotype relative risk at 1.33–1.51 in MDD for *HTR1A*, under a multiplicative model of inheritance. As our samples were small, type II errors are possible in the results of these statistical association analyses. Second, we did not perform a mutation scan of *HTR1A*. As we consider it to be difficult to evaluate the association of such extremely rare variants from the viewpoint of statistical power, a replication study using a larger sample is required for conclusive results. Finally, our subjects did not undergo structured interviews. MDD patients who are not diagnosed by structured interview may develop bipolar disorder in the future.[31] However, in this study, patients were carefully diagnosed according to the DSM-IV criteria with the consensus of at least two experienced psychiatrists on the basis of a review of medical records. In addition, when we found a misdiagnosis in a patient, we promptly excluded the misdiagnosed case in consideration of the precision of our sample. Detailed information on our samples was provided in previous papers.[32–35]

In conclusion, our results suggest that *HTR1A* may not have a role in the pathophysiology of Japanese MDD patients. On the other hand, according to the meta-analysis, *HTR1A* was associated with MDD patients, especially in the Asian population. As our sample and the overall sample size included in the meta-analysis were relatively small, statistical errors are possible in the results of these statistical association analyses. To overcome these limitations, a replication study using a larger sample may be required for conclusive results.

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