Possible impact of *ADRB3* Trp64Arg polymorphism on BMI in patients with schizophrenia

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Abstract

Background: The β3-adrenoceptor (*ADRB3*) gene Trp64Arg polymorphism has been shown to be associated with obesity as well as type 2 diabetes and cardiovascular disease. The incidence of overweight and the risks of type 2 diabetes and cardiovascular disease are also increased in major depression and schizophrenia. We hypothesized that the Trp64Arg polymorphism may be associated with increased risk of schizophrenia and depression.

Methods: The Trp64Arg was genotyped in 504 patients with schizophrenia, 650 with major depressive disorder (MDD), and 1170 healthy controls. Of these participants, body mass index (BMI) data were available for 125 patients with schizophrenia, 219 with MDD, and 261 controls.

Results: No significant difference in genotype or allele distribution was found across the diagnostic groups. No significant difference in BMI was observed between the Arg allele carriers and the non-carriers in the MDD and the control groups. However, patients with schizophrenia carrying the Arg allele had significantly higher BMI (Mean (*SD*): Arg carriers: 26.5 (6.9), Arg non-carriers: 23.8 (4.3); $P = 0.019$) and a higher rate of being overweight (BMI of 25 or more) compared to their counterparts (Trp/Trp group) (%overweight (*SE*): Arg carriers: 52.3 (7.5), Arg non-carriers: 32.1 (5.2); $P = 0.027$).

Conclusions: We obtained no evidence for the association of *ADRB3* Trp64Arg with the development of MDD or schizophrenia. However, the Arg allele was found to be associated with higher BMI and being overweight in patients with schizophrenia. This

may imply that genotyping *ADRB3* is of clinical use to detect schizophrenic individuals at risk for developing obesity.

Keywords: β3 adrenoreceptor; schizophrenia; depression; genetic polymorphism

Abbreviations

ADRB3, β3-adrenoceptor; ANCOVA, analysis of covariance; BMI, body mass index; HWE, Hardy-Weinberg equilibrium; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MDD, major depressive disorder; SD, standard deviation; SE, standard error

1. Introduction

The β3-adrenoceptor is mainly expressed in adipose tissue and mediates the physiologic actions of endogenous catecholamines. Its actions include enhancement of lipolysis in the white adipose tissue and increase of thermogenesis in the brown adipose tissue. Trp64Arg is a missense polymorphism in the β3-adrenoceptor (*ADRB3*) gene and is associated with lower lipolytic activities (Umekawa et al. , 1999). The Arg allele of this polymorphism has been shown to be associated with obesity as well as type 2 diabetes and cardiovascular disease (Clement et al. , 1995, Gjesing et al. , 2008, Iwamoto et al. , 2011, Oizumi et al. , 2001, Walston et al. , 1995, Widen et al. , 1995).

Adipocytes in the white adipose tissue secrete a variety of adipocytokines such as leptin, adiponectin, and resistin. These adipocytokines have a central role in the regulation of insulin resistance, as well as in many aspects of inflammation and immunity (Tilg and Moschen, 2006). Adipocytes also secrete chemokines, particularly monocyte chemoattractant protein 1 (MCP-1). MCP-1 attracts leukocytes such as monocytes, T lymphocytes, and dendritic cells (Carr et al. , 1994, Xu et al. , 1996), which then secrete inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α. MCP-1 is also known to play a critical role in the development of cardiovascular disease and obesity-induced insulin resistance (Niu and Kolattukudy, 2009).

These inflammatory factors are also implicated in the pathogenesis of psychiatric disorders including schizophrenia and depression. An increased IL-6 level is one of the most robust findings in the study of inflammatory markers in schizophrenia

(Potvin et al. , 2008, Sasayama et al. , 2011b) and in depression (Dowlati et al. , 2010). Increased levels of IL-1β in the cerebrospinal fluid of patients with first-episode schizophrenia (Soderlund et al. , 2009) and depression (Levine et al. , 1999) have also been reported. Furthermore, some studies reported significant associations of *IL-1β* polymorphisms with schizophrenia (Hanninen et al. , 2008, Papiol et al. , 2004, Sasayama et al. , 2011a, Zanardini et al. , 2003) and with depression (Borkowska et al. , 2011).

The incidence of overweight as well as the risks of type 2 diabetes and cardiovascular disease is increased in major depressive disorder (MDD) and schizophrenia (De Hert et al. , 2009). A recent meta-analysis showed that depression was found to be predictive of developing obesity and that obesity also increases the risk of depression (Luppino et al. , 2010). The activation of inflammatory factors related to obesity may be one of the possible explanations for the relationship between obesity and psychiatric illnesses. Based on these findings, we examined whether the Trp64Arg polymorphism in *ADRB3* confers susceptibility to developing schizophrenia and depression. Furthermore, the association of the Trp64Arg polymorphism with being overweight in these disorders was examined.

2. Materials and methods

2.1 Subjects

Trp64Arg was genotyped in 504 patients with schizophrenia (274 men and 230 women; mean age (standard deviation: *SD*): 43.1 (14.0) years, 650 patients with MDD

(309 men and 341 women; 45.1 (14.5) years), and 1170 healthy controls (395 men and 775 women; 46.0 (16.2) years). Self-reported body weight and height were obtained from a portion of the participants. Thus, body mass index (BMI) data were available for 125 patients with schizophrenia (74 men and 51 women; mean age: 39.8 (11.7) years), 219 patients with major depressive disorder (MDD) (97 men and 122 women; 42.0 (12.4) years), and 261 healthy controls (71 men and 190 women; 48.5 (15.4) years). Most of the patients with schizophrenia were on chronic treatment of antipsychotic medication; the average (*SD*) chlorpromazine equivalent converted from daily doses of antipsychotics (American Psychiatric Association, 1997, Inagaki et al. , 1999) was 574.5 (509.9) mg/day, and the average duration of treatment was 14.1 (10.7) years. All subjects were biologically unrelated Japanese and were recruited from the outpatient clinic of the National Center of Neurology and Psychiatry Hospital, Tokyo, Japan or through advertisements in free local information magazines and by our website announcement. Consensus diagnosis by at least 2 psychiatrists was made for each patient according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria (American Psychiatric Association, 1994), on the basis of unstructured interviews and information from medical records. The controls were healthy volunteers with no current or past histories of psychiatric treatment and were screened using the Japanese version of the Mini International Neuropsychiatric Interview (Otsubo et al. , 2005, Sheehan et al. , 1998) by a research psychiatrist to eliminate the possibility of any axis I psychiatric disorders. Participants were excluded if they had prior medical histories of central nervous system diseases or severe head injury or if they met the

criteria for substance abuse or dependence or mental retardation. None of the participants were under treatment for cardiovascular diseases or diabetes at the time of assessment. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan. After describing the study, written informed consent was obtained from every subject.

2.2 Genotyping

Genomic DNA was prepared from venous blood according to standard procedures. The Trp64Arg polymorphism was genotyped using the TaqMan 5′-exonuclease allelic discrimination assay (assay ID: C___2215549_20). The thermal cycling conditions for polymerase chain reaction were as follows: 1 cycle at 95°C for 10 min followed by 50 cycles of 92°C for 15 s and 60°C for 1 min. The allele-specific fluorescence was measured with ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster City, CA). Ambiguous genotype data were not included in the analysis.

2.3 Statistical analysis

Deviations of genotype distributions from Hardy-Weinberg equilibrium (HWE) were assessed using the χ^2 test for goodness of fit. Genotype and allele distributions were compared between patients and controls by using the χ^2 test for independence. Comparison of BMI between genotypes was analyzed using two-way analysis of covariance (ANCOVA) with genotype and diagnosis as independent variables and age and gender as covariates. For patients with schizophrenia, ANCOVA was also performed adding the chlorpromazine equivalent dose as a covariate to control for use of antipsychotics. Because the frequency of Arg/Arg homozygotes in the general population is low, we combined the heterozygotes and variant homozygotes into one group to assess the effect of the polymorphism on the degree of obesity, as in previous studies (Clement, Vaisse, 1995, Kurokawa et al. , 2003, Widen, Lehto, 1995). Statistical analyses were performed using the Statistical Package for the Social Sciences version 11.0 (SPSS Japan, Tokyo, Japan). All statistical tests were two-tailed, and $P < 0.05$ indicated statistical significance.

Power calculation for the genetic association analysis was performed using the Power Calculator for Genetic Studies (http://www.sph.umich.edu/csg/abecasis/CaTS/). Assuming a genotype relative risk of 1.3 under an additive model, a disease prevalence of 1% for schizophrenia and 10% for MDD, and a minor allele frequency of 20%, our sample size had 79% and 91% power, respectively, to detect disease associations with an alpha of 0.05. Similarly, assuming a relative risk of 1.3 under a multiplicative model, the power to detect disease associations was 83% and 94% for schizophrenia and depression, respectively.

Power calculation for ANCOVA in subjects with BMI data was performed using G*Power 3.1.3 (Faul et al. , 2007). Assuming that frequency of Arg/Arg homozygotes is 0.671 as in the HapMap data (http://www.hapjmap.org/), the present study provided a power of greater than 0.80 to detect an effect size of 0.38, 0.41, and 0.55 for healthy controls, MDD patients, and schizophrenic patients, respectively.

3. Results

The genotype and allele distributions of the Trp64Arg are shown in Table 1. The genotype and allele distributions did not significantly deviate from the HWE. No significant difference in genotype or allele distribution was found across the three diagnostic groups.

BMI was compared between Arg carriers and non-carriers using ANCOVA with Arg allele carrier status and diagnosis as independent variables and age and gender as covariates. The results showed a significant interaction effect between genotype and diagnosis (F(2,597) = 5.34, P = 0.005). Therefore, we further compared the BMI between Arg carriers and non-carriers in each diagnostic group separately, with Arg allele carrier status as the independent variable and age and gender as covariates. No significant difference in BMI was observed between the Arg carriers and the non-carriers in the MDD and the control groups. However, patients with schizophrenia carrying the Arg allele had significantly higher BMI compared to their Trp/Trp homozygous counterparts (mean (*SD*): Arg carriers: 26.5 (6.9), Arg non-carriers: 23.8 (4.3); F(1,121) = 5.69, P = 0.019). The difference remained significant even after including the chlorpromazine equivalent dose as a covariate (F(1,120) = 4.97, P = 0.028). The categorical analysis also showed that schizophrenic patients carrying the Arg allele were more likely to be overweight (BMI of 25 or more) than their Trp/Trp homozygous counterparts (%overweight (standard error: *SE*): Arg carriers: 52.3 (7.5), Arg non-carriers: 32.1 (5.2); χ^2 = 4.87, df = 1, P = 0.027; odds ratio = 2.32 (95%

confidence interval: 1.09 to 4.92); sensitivity of 0.47 and specificity of 0.72). As shown in Table 2, no significant difference between Arg carriers and non-carriers in age, gender rate, antipsychotic equivalent dose, or treatment duration was observed in patients with schizophrenia. Figure 1 shows the rate of being overweight for the Arg allele carriers and the non-carriers in each diagnostic group.

4. Discussion

The present study had sufficient power to detect a relatively modest effect of the *ADRB3* gene Trp64Arg on the development of schizophrenia and MDD. Thus, our findings suggest that the Trp64Arg polymorphism is unlikely to have a major role in the development of schizophrenia or MDD. The hypothesized effect of Trp64Arg variant on development of schizophrenia and MDD, however, was due to an indirect action, mediated by the inflammatory process. Therefore, the association may have been too weak to be detected by the sample size used in this study. The observed effect of the Trp64Arg on BMI was not significant in healthy controls and patients with MDD. In patients with schizophrenia, however, the Arg allele was associated with higher BMI, which was in line with the evidence that Arg allele is associated with lower lipolytic activities (Umekawa, Yoshida, 1999).

Previous studies carried out in Japanese (Oizumi, Daimon, 2001) and in Finnish subjects (Widen, Lehto, 1995) reported that the Arg allele of the Trp53Arg polymorphism was associated with obesity. However, some studies failed to find such an association (Buettner et al. , 1998, Gagnon et al. , 1996, Gjesing, Andersen, 2008, Oeveren van-Dybicz et al. , 2001). The inconsistency between studies may be partially explained by the population differences between samples. A meta-analysis suggests that the effect of this polymorphism on BMI is greater in East Asians than in Europeans (Kurokawa et al. , 2008). The Trp64Arg may play a particularly important role in the Japanese population, since the minor allele frequency is higher in Japanese than in other populations in the HapMap data (http://www.hapjmap.org/).

The genetic homogeneity of the Japanese population was a major strength of the present study. However, contrary to the results of the meta-analysis in Japanese subjects (Kurokawa, Young, 2008), our results showed no significant association between the Trp64Arg and the BMI in healthy subjects. These negative results may have arisen by the small number of subjects in the present study. Intriguingly, however, the patients with schizophrenia carrying the Arg allele had significantly higher BMI compared to their Trp/Trp homozygous counterparts. Obesity is highly prevalent in patients with schizophrenia due to illness-related factors and use of antipsychotic medications (Kolotkin et al. , 2008). Our results suggest that schizophrenic patients carrying the Arg allele especially have a greater tendency to gain weight. Clement et al (Clement, Vaisse, 1995) demonstrated that although the frequency of the Arg allele was similar in the morbidly obese patients and the normal subjects, the obese patients with Arg allele had higher capacity to gain weight. Taken together, the Trp64Arg variant may enhance the weight gain in individuals already at risk for obesity.

The major limitation of this study was that the effects of medication could not be fully controlled due to the variability in types and doses. Particularly, antipsychotic medications are known to induce metabolic abnormalities such as obesity, hyperglycemia, and metabolic syndrome (De Hert et al. , 2011). Therefore, the use of antipsychotics in patients with schizophrenia may have confounded the results. However, the chlorpromazine equivalent dose did not differ between Arg carriers and non-carriers in patients with schizophrenia. Furthermore, using the chlorpromazine equivalent dose as a covariate in an ANCOVA still resulted in significantly higher BMI in Arg carriers of schizophrenic patients. Thus, controlling for total chlorpromazine equivalent dose did not affect the findings of the present study. Nevertheless, the influence of the Trp64Arg on BMI may differ in non-medicated patients or may depend on the type of antipsychotics used. Further investigations are required to elucidate the effects of antipsychotics. Another limitation of the study is that BMI data relied on self-reports of the participants. However, previous studies show that self-reported BMI is satisfactorily accurate for the assessment of the prevalence of overweight (Craig and Adams, 2009, Dekkers et al. , 2008).

In conclusion, we obtained no evidence for the association of *ADRB3* Trp64Arg with the development of MDD or schizophrenia. However, the Arg allele of the Trp64Arg polymorphism was found to be associated with higher BMI in patients with schizophrenia. This may imply that genotyping *ADRB3* is of clinical use to detect schizophrenic individuals at risk for developing obesity, which is an important issue in the antipsychotic medication. Further studies are warranted to elucidate the influence of the *ADRB3* gene variation on the development of psychiatric disorders and also to understand the factors that contribute to the risk of obesity in patients with psychiatric disorders.

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Figure legend

Figure 1: Percentage overweight in Arg carriers and non-carriers of the Trp358Ala

The rate of being overweight (BMI of 25 or more) is shown for the Arg carriers and the non-carriers in healthy controls and in patients with schizophrenia and MDD. Error bars indicate 1 standard error. In patients with schizophrenia, Arg carriers were significantly more likely to be overweight than the non-carriers.

* $P < 0.05$

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Table 1: The results of the association analysis of theTrp64Arg polymorphism

Subjects	N	Genotype			Allele		χ^2 test		HWE *P*-value	Allelic OR versus controls (95% CI)
		Arg/Arg	Trp/Arg	Trp/Trp	Arg	Trp	Genotype	Allele		
Schizophrenia	504	21 (0.04)	148 (0.29)	335 (0.66)	190 (0.19)	818 (0.81)			0.37	1.06 (0.87 - 1.28)
MDD	650	26 (0.04)	198 (0.30)	426 (0.66)	250 (0.19)	1050 (0.81)	χ^2 = 1.89 *df* = 4 *P* = 0.76	χ^2 = 0.87 *df* = 2 *P* = 0.65	0.62	1.08 (0.91 - 1.29)
Controls	1170	36 (0.03)	350 (0.30)	784 (0.67)	422 (0.18)	1918 (0.82)			0.68	

HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval; MDD: major depressive disorder; *df* : degree of freedom.
Numbers in the parentheses in the genotype and the allele columns represent the frequencies of genotypes and alleles.

Table 2: Demographic and clinical characteristics of Arg carriers and non-carriers in patients with schizophrenia

	Arg carriers	Arg non-carriers	Analysis
Age (years)	39.9 (11.4)	39.8 (11.9)	ANOVA: $F(1,123) = 0.0$, $P = 0.98$
Gender (M/F)	31/13	43/38	χ^2 test: $\chi^2 = 3.56$, $df = 1$, $P = 0.06$
CP equivalent dose (mg/day)	663.2 (613.2)	526.3 (440.7)	ANOVA: $F(1,123) = 2.1$, $P = 0.15$
Treatment duration (years)	15.4 (11.2)	13.2 (10.5)	ANOVA: $F(1,123) = 1.2$, $P = 0.27$

Values are shown as mean (standard deviation).

BMI: body mass index; CP: chlorpromazine; ANOVA: analysis of variance; *df* : degree of freedom

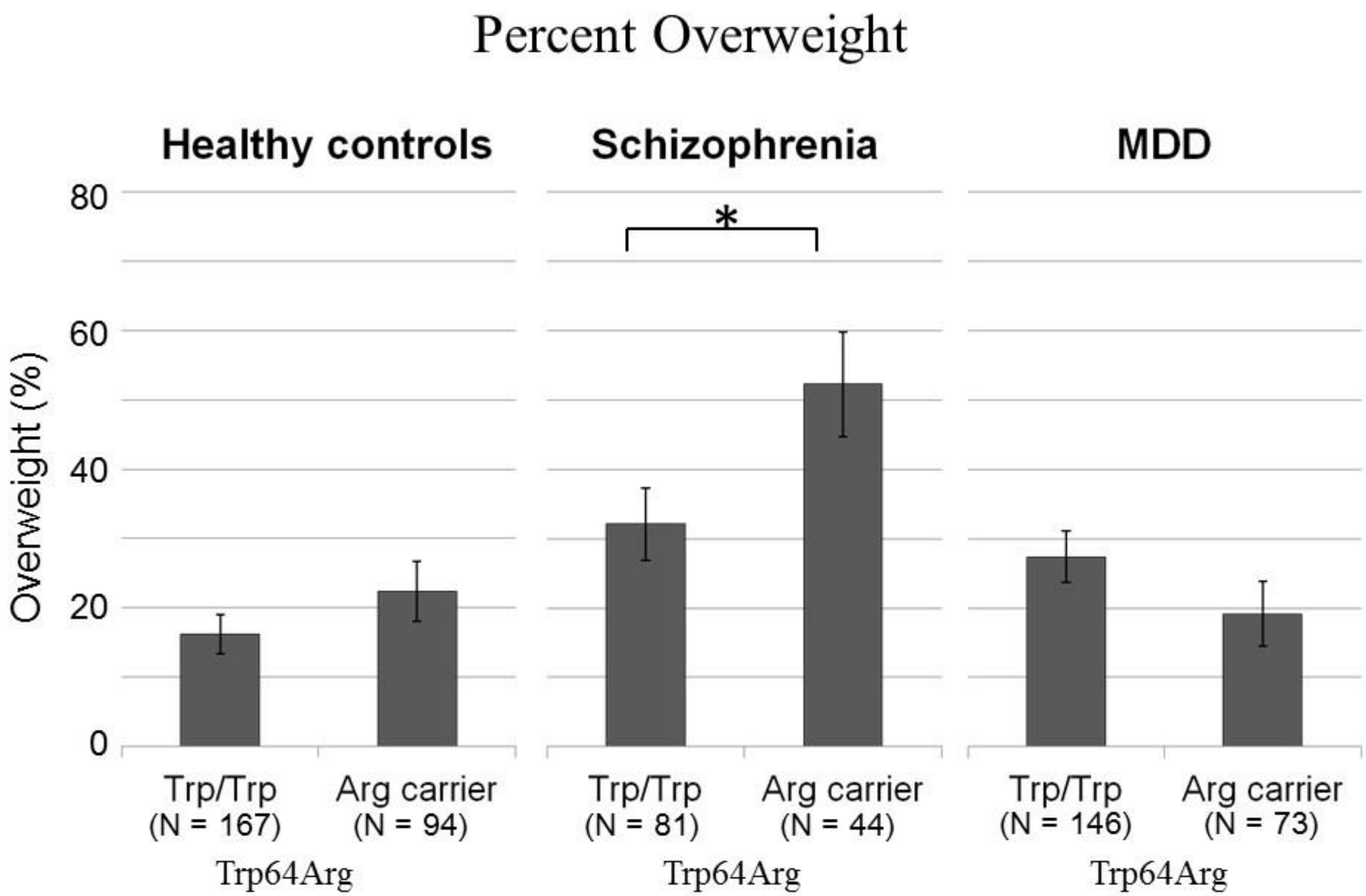
Percent Overweight
Healthy controls
Schizophrenia
MDD
Overweight (%)
80
60
40
20
0
*
Trp/Trp
(N = 167)
Arg carrier
(N = 94)
Trp64Arg
Trp/Trp
(N = 81)
Arg carrier
(N = 44)
Trp64Arg
Trp/Trp
(N = 146)
Arg carrier
(N = 73)
Trp64Arg

Figure 1