ADRA1A gene is associated with BMI in chronic schizophrenia patients exposed to antipsychotics

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Noradrenaline and adrenaline are neurotransmitters of the sympathetic nervous system that interact with various adrenergic receptor (ADR) subtypes, and this regulates the basal metabolic rate, thermogenesis and efficiency of energy utilization. We examined a possible role of the gene coding for ADRA1A receptor in weight gain in schizophrenia subjects exposed to antipsychotics. A total of 401 schizophrenia in-patients treated with antipsychotics for >2 years were recruited and a final 394 DNA samples were genotyped. Their body mass indexes (BMIs) were recorded for 12 months and parameterized to be correlated in regression. Among the 58 single-nucleotide polymorphisms (SNPs) genotyped, 44 valid SNPs, which had minor allele frequency >0.03, were analyzed in statistics. Linear regression model with age, gender, diabetes, use of typical antipsychotics and use of atypical antipsychotics as covariates, with or without gender interaction, showed evidence of associations between the ADRA1A gene and BMI. Most of the SNPs associated with BMI are located in the promoter and intron regions, and being female appeared to enhance the gene effect. Our study suggests that the ADRA1A gene is involved in weight gain among schizophrenia patients treated with antipsychotics. Further molecular dissection of the ADRA1A gene warrants better understanding on weight gain mechanisms in schizophrenia.

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Introduction

Obesity is common in schizophrenia subjects. Exposure to antipsychotic treatment, especially the atypical antipsychotics, might be a critical cause of obesity in schizophrenia. Atypical antipsychotics offer a number of advantages not seen in typical antipsychotics in the treatment of schizophrenia, notably a reduced incidence of extrapyramidal adverse effects and a better efficacy against negative symptoms. However, ongoing experience with these agents has showed physical morbidity and mortality associated with obesity, including cancers, diabetes, metabolic disturbances, coronary heart disease, and so on.1 Defining body mass index (BMI) >28.6 as severe obesity and >26.4 as obesity, a cross-sectional study investigating 201 Chinese outpatients with schizophrenia-spectrum disorders treated with antipsychotics found that the prevalence rates of obesity among male and female patients were 2.74- and 2.51-fold higher than the reference population (Nutrition and Health Survey in Taiwan from 1993–1996).2 For severe obesity, the prevalence rates among male and female patients were 4.66- and 3.53-fold higher, respectively. It is generally true that,
in comparison with typical antipsychotics, atypical antipsychotics are more effective in gaining weight. In addition, different types of atypicals have different strengths in weight gain. For the common atypical antipsychotics used clinically, clozapine and olanzapine seem to cause larger increase in weight, followed by risperidone and seroquel, and subsequently aripiprazole and ziprasidone. 

Obesity is an outcome of low energy expenditure and high energy intake. Urge of food intake is enhanced by low dopaminergic neuronal activity and at least in part by low hypothalamic serotonergic neuronal activity. The influence of low dopaminergic activity is evident from the weight gain after discontinuation of pharmaceutical dopaminergic overstimulation in rat model. 

A variety of studies in rodents indicate that, at low doses, serotonin (5-HT) or drugs that enhance the release of 5-HT preferentially inhibit the ingestion of carbohydrate. This phenomenon is mediated, in part, by 5-HT receptors located in various medial hypothalamic nuclei. A negative feedback loop exists between the consumption of carbohydrate and the turnover of 5-HT in the hypothalamus, which involves circulating hormones (insulin, corticosterone, adipose tissue-derived hormone, leptin, and so on) and glucose in the process. This is supported by an evidence of interaction between the SHT2C and leptin genes in weight gain and circulating leptin level among schizophrenia subjects. Other literature reviews on studies related to antipsychotic-associated weight gain have summarized the importance of genetics in the phenotype of antipsychotic-induced weight gain, and potential candidate genes have been suggested. Several animal models have shown that low energy expenditure and high energy intake are markers of a blunted sympathetic nervous system (SNS). SNS activation stimulates energy mobilization and utilization in various tissues, including the adipose tissues where high-energy substrate is located. Interestingly, the basal muscle SNS activity of one of the most obese populations in the world, the Pima Indians, was 20–30% lower than that of weight-matched Caucasians. Moreover, SNS reactivity to both stimulatory and inhibitory factors was also blunted in the Pima population. Obesity-related indexes have been reported to be negatively correlated to the improvement of psychiatric symptoms in schizophrenia. We hypothesized that the ADR1A promoter region in the development of schizophrenia was found in an isolated Spanish population, but not in the Chinese population. As the complex modulator effects of noradrenaline and adrenaline on adipose tissues involve various ADR subtypes, it is reasonable to believe that the ADR genes may be involved in the development of obesity-related phenotypes among subjects exposed to antipsychotics. One such study examined the possible contribution of the ADR1A and ADR3 genes in weight gain (estimated by a delta change score: 6 weeks weight minus baseline weight) induced by clozapine in a mixed ethnic subpopulation (58 Caucasians, 22 African Americans). The study found no evidences to support the hypothesis. It was likely that the significance of the ADR genes in weight gain of the mixed ethnic sample was concealed by population difference, small sample size or ignorance of important covariates such as the age factor in statistical analysis. Subsequently, Ujike et al. examined the possible roles of several candidate genes in 164 Japanese schizophrenia patients treated with olanzapine and found an association between the ADR3 gene and weight gain.

We hypothesized that the ADR1A gene is associated with BMI in schizophrenia patients exposed to antipsychotics. To test this hypothesis, we genotyped single-nucleotide polymorphisms (SNPs) at the ADR1A gene and evaluated their associations with BMI.

Materials and methods

As season changes affect weight gain, we took precautions in choosing an appropriate parameter to reflect the situation. In addition, possible statistical biases were avoided by including covariates in the analysis.

Study population

This study was approved by the Institutional Review Board of Yu-Li Hospital, Department of health, Taiwan, file number YLH-93001. A total of 401 patients (300 males and 101 females) meeting the diagnostic and statistical manual of mental disorders criteria of schizophrenia and treated
with antipsychotics for > 2 years were recruited after signing the informed consent forms. The mean age of the patients was 49.3 ± 9.9 years, ranging from 21–84. All patients resided in the open dormitories with medical professionals on duty, and the spaces for leisure and physical activities were commodious. None of the patients received psychiatric therapeutics other than antipsychotics, except hypnotics when medically needed, and co-medication for physical health problems was allowed as usual during the study period. Equivalent doses of antipsychotics were prescribed to the patients according to psychopathological requirements. Finally, 394 DNA samples with good DNA quality were used for the evaluation of a possible association between the ADRA1A gene and BMI in schizophrenia exposed to antipsychotics. The BMIs were measured prospectively from October 2004 to October 2005.

SNPs and genotyping
A small amount of blood was drawn from each patient and DNA was prepared from peripheral blood leukocytes using the GENTRA PUREGENE DNA Purification Kit (Qiagen, Hilden, Germany). Extracted DNAs were measured using picogreen dye (Invitrogen, Carlsbad, CA, USA) and Bio-Tek FLx800 fluorescence-luminescence microplate readers (TiSoft, Mississauga, Ontario, Canada), as instructed by the manufacturers.

It is understood that four isoforms of ADRA1A transcripts are currently known. For an easy access to this report, we described the relative locations of the SNPs using the two exons gene model (mRNA alignment) as shown in the database of National Center for Biotechnology Information. We adopted a round-up-all approach when choosing the SNPs. A total of 58 SNPs at the ADRA1A gene were selected. These included 11 coding SNPs (cSNPs), 17 SNPs in the promoter or activator/suppressor region, 26 TagSNPs and 4 additional intronic SNPs (iSNPs). The 11 cSNPs were 9 cSNPs registered in the single nucleotide polymorphism database (build 126) and 2 cSNPs reported by Lei et al.40 The 17 SNPs in the promoter or activator/suppressor region included 2 variants (SNP1 and SNP17) examined by Clark et al.33 and 15 variants (from SNP2 to SNP16) identified by Razik et al.41 We compared the sequence information of Razik et al. with that of the single nucleotide polymorphism database and confirmed the RefSNP accession IDs (rs numbers) accordingly. The 15 SNPs are located in the sequences with distinct activator and suppressor elements between −2623 and −6194 nucleotide region, as counted from the start codon. The 26 TagSNPs were retrieved from the HapMap database (http://www.hapmap.org). The additional four iSNPs were variants with minor allele frequency (MAF) > 0.05 in the Asian population (Han Chinese in Beijing and Japanese in Tokyo) as recorded in the HapMap database.

Information of these SNPs, including their locations within the gene, chromosomal position, allelic variants and amino acid changes, are summarized in Supplementary Table 1. The overall tagging property of all SNPs included in further statistical analyses was re-estimated and does not necessary include the 28 pre-selected TagSNPs from the HapMap database.

The GenomeLab SNPstream genotyping platform (Beckman Coulter, Fullerton, CA, USA) and the SNPstream software suite were used for genotyping and signal analysis. The genotyping method is based on single base extension on array.12 Currently, the GenomeLab SNPstream genotyping platform is able to genotype maximal 12 SNPs simultaneously. Briefly, 12 pairs of primers for the multiplex PCR and 12 single base extension primers for the SNPs selected were optimally designed by web-based software at http://www.autoprimers.com/. After amplifying the DNA fragments embracing the SNPs of interests, the 3’ portion of the tagged extension primers was extended with single fluorescein-labeled nucleotide terminator reactions and the 5’ portion was hybridized to the complementary oligonucleotides arrayed on the 384-well SNPware Tag array microplates. The individual SNPs were identified by their specific position and fluorescent color in each well according to the position of the tagged oligonucleotides. Individual sample genotype data were generated by computer according to their relative fluorescent intensities for each SNP.

Statistics
Single-nucleotide polymorphisms with genotype distribution deviating from Hardy–Weinberg equilibrium or MAF < 0.03 were excluded from statistical analyses. The Haploview was used for the estimations of linkage disequilibrium, haplotype, Hardy–Weinberg equilibrium and overall tagging property of valid SNPs. The SAS program (SAS, Cary, NC, USA) was used for further statistical analyses.

BMIs were continuously recorded for 12 months (13 visits—baseline, once per month) at the same periods as the major outcomes for all subjects. The overall variation of the 13 BMIs can be attributed to between-subject-variation (at the same period) and with in-subject-variation (among different periods). Conceptually, to evaluate the variation of the 13 BMIs measured over time, each measurement must be correlated to others. To resolve this, we used the Proc Mixed, a SAS procedure based on mixed model methodology, with autoregressive 1 as the covariance structure, so that the 13 BMIs were correlated. Proportions of cigarette use, diagnosis of diabetes, use of typical antipsychotics, use of atypical antipsychotics, and shift use of typical and atypical antipsychotics among schizophrenia patients during the observation period were summarized in Table 1. Contributions of age, gender, diabetes (as recorded in the chart, with the clinical criteria of fasting plasma glucose ≥ 126 mg per 100 ml), use of typical antipsychotics and use of atypical antipsychotics to BMI were evaluated as independent variables by enter method. All the five factors were retained in the model. Use of typical antipsychotics and use of atypical antipsychotics were set as two different variables because the prescribed type of antipsychotics was changed in some patients for medical reasons. Then, the regressions were performed with BMI as dependent variable and each SNP as independent variable; age, gender, diabetes, use of typical antipsychotics and use of atypical antipsychotics...
were covariates in the model and gender interaction was examined.

We also examined the possible effects of calorie intake, activeness (rated in four levels; the first being bedridden, second being working 1–3 h a day, third being working 4–6 h a day and fourth being working >6 h a day), cigarette use (yes/no and also pack per day) to BMI, but these variables did not show significant contributions to the model (details not shown) and thus, excluded from further modeling.

Results

It is generally accepted that BMI cutoff points for defining overweight and obesity should be lower for Asians. The Department of Health, Taiwan, defined BMI ≥24 as overweight for the Taiwan population. The mean monthly BMI (hereafter regarded as mean BMI) of male, female and all patients are shown in Figure 1. On average, our research subjects were overweight. In accordance to the observation in general populations, the mean BMI of female patients was higher than that of the male patients. The trend of mean BMI in all patients rose between December 2004 and April 2005, dropped on May 2005 and maintained at the plain line until October 2005. The mean BMI plateau (March–April 2005) in female patients was shorter than that of male patients (January–April 2005). From the risen trends of mean BMI between September and October 2005 in male, female and all patients, autumn seemed like a period when body weight started to climb. Although our study only collected 13 consecutive BMIs on calendar sequence with one overlap on Octobers, the trends obviously showed that schizophrenia patients in our study tended to have lower BMI weight change and October as the time point of measurement, 9% of the patients (N = 35) lost weight and 11% of the patients (N = 43) gained weight after 12 months. At the level of ± 2.5%, 20% of the patients (N = 79) lost weight and 27% of the patients (N = 107) gained weight after 12 months.

Among the 58 SNPs examined, 13 SNPs had MAF <0.03. None of the genotype distribution deviated from Hardy–Weinberg equilibrium except the SNP44. These 14 SNPs were excluded from further statistics. Linkage disequilibrium strengths in D’ between SNPs and haplобlocks are shown in Figure 2. The linkage disequilibrium plot shows six major haploblocks: block-1 includes SNP54 to SNP58, covering an 8-kb region; block-2 includes SNP36 to SNP43, SNP43, SNP46, and SNP50 to SNP52, covering a 29-kb region; block-3 includes SNP34 to SNP35, covering a 4-kb region; block-4 includes SNP29 to SNP33, covering a 7-kb region; block-5 includes SNP23 to SNP28, covering an 11-kb region and block-6 includes SNP2 to SNP10, SNP14 and SNP16 to SNP 17, covering a 5-kb region. Twenty-four SNPs that theoretically represent the 44 SNPs included in the association tests are marked in Figure 2, as calculated using the SNP tagging tests (cutoff value r² > 0.8). Further information of haplotype frequencies and strengths between blocks are shown in Figure 3.

The significances of SNPs by genotype and allele distributions are summarized in Figures 4a and b, respectively. With gender as covariate without interaction with SNP, genotype distribution of SNP36 (P = 0.0234), SNP39 (P = 0.0287), SNP41 (P = 0.0233), SNP54 (P = 0.009), SNP55 (P = 0.0138), SNP56 (P = 0.023) and SNP57 (P = 0.042) were found significantly associated with BMI. These SNPs are ranged in block-1 and block-2. When gender interaction was concerned in the model, genotype distribution of SNP2 (P = 0.039), SNP55 (P = 0.0082), SNP10 (P = 0.0421), SNP16 (P = 0.0426), SNP25 (P = 0.021), SNP27 (P = 0.0258), SNP28 (P = 0.0263), SNP29 (P = 0.0205), SNP31 (P = 0.0101), SNP32 (P = 0.0202) and SNP33 (P = 0.0007) were found to be associated with BMI. The SNPs are ranged in block-4, block-5 and block-6. Among the genetic variants, SNP2, SNP55, SNP10 and SNP16 are located in the promoter region. It is noteworthy that the SNPs significantly associated with BMI when gender interaction was concerned were totally different from the SNPs identified in the model without gender interaction. These results were summarized in Figure 4a. For allele distributions, SNP2 (P = 0.0484), SNP3 (P = 0.0151), SNP4 (P = 0.0150), SNP5 (P = 0.0072), SNP7 (P = 0.0150), SNP9 (P = 0.0153), SNP10 (P = 0.0376), SNP16 (P = 0.0378), SNP31 (P = 0.0059), SNP32 (P = 0.0287) and SNP33 (P = 0.0070) were found to be associated with BMI, when gender interaction was concerned in the model. The SNPs are ranged in block-4 and block-6. When gender interaction was not concerned, only SNP57 (P = 0.0420) was associated with BMI. SNP57 is ranged in block-1. These results were summarized in Figure 4b. As shown in the two figures (Figures 4a and b), when gender interaction was not concerned in statistical analysis, genotype-wise tests seem to have more SNPs associated with BMI when compared with allele-wise tests. When gender interaction

Table 1 General information on mean age, gender, cigarette use, diagnosis of diabetes, use of typical antipsychotics, use of atypical antipsychotics and shifted use of typical and atypical antipsychotics in male and female patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male (N = 300)</th>
<th>Female (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.5 ± 0.5</td>
<td>48.4 ± 1.1</td>
</tr>
<tr>
<td>Cigarette use (%)</td>
<td>81.7</td>
<td>31.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20.3</td>
<td>32.7</td>
</tr>
<tr>
<td>Use of typical antipsychotics (%)</td>
<td>63.0</td>
<td>56.4</td>
</tr>
<tr>
<td>Use of atypical antipsychotics (%)</td>
<td>51.3</td>
<td>58.4</td>
</tr>
<tr>
<td>Use of typical and atypical antipsychotics (%)</td>
<td>8.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Information on onset age, duration of treatment and duration of illness could not be ascertained reliably for a large proportion of the research subjects before they resided in this hospital, either by clinical assessments or current medical history system. Thus, these variables are not listed here.
was concerned in the model, the number of SNPs associated with BMI was more frequent in the genotype-wise tests than the allele-wise tests. It seems that there is a division region in intron 1 and separate the effect of gender interaction. It is obvious that the gender interaction enhanced the associations in region between SNP2 and SNP33 in both genotype-wise and allele-wise tests. However, the strength of associations was generally repressed by gender interaction in the region between SNP34 and SNP58 in genotype-wise tests, and seemed to have no effects in allele-wise tests. These indicate a further need to dissect the molecular role of gender in ADRA1A gene and BMI in schizophrenia patients exposed to antipsychotics.

None of the SNPs associated with BMI are located in the exons. Almost all significant SNPs are located in the promoter region and intron 1 of the ADRA1A gene, either evaluated by genotype or allele distribution. SNP54 and SNP57 located at the 3’ untranslated region were significantly associated with BMI, either by genotype or allele distribution, in the model without gender interaction.

**Discussion**

Weight increases with age and fluctuates seasonally. The fluctuations shift along with aging, as shown in a follow-up study of a man from 29 to 65 years, which showed that weight tended to rise in summer at younger ages, but in autumn or winter at older ages.37 Women of a nonpregnant rural African female population, the Senegalese women, tended to have higher weight in dry season (March and April), followed by lower weight in rainy season (September–November) at the end of each year, when agricultural labor consumed the stored energy.38 A longitudinal study involving 202 Chinese infants in Chengdu City and 174 Hong Kong infants in their first 2 years of life showed that the weight gained faster in winter and slower in summer.39 Thus, statistical analysis using only one cross-sectional BMI measurement is likely to yield biased conclusion. Averaging the BMIs of a particular period is theoretically more representative than one BMI measurement but still, information related to individual variation is lost. In our study, we collected 13 BMIs for 12 consecutive months and correlated them in statistics. The statistical results should have avoided seasonal biases and loss very few information, if there is any. In addition, the weight changes associated with atypical antipsychotics are not straightforward. Not all subjects receiving atypical antipsychotics gain weight. Tadger and Melamed44 showed that 55% of the patients treated with atypical antipsychotics for ≥1 year increased their weight, whereas 2% remained unchanged and 43% lost weight.
Moreover, some atypicals effectively lead to an increase in BMI than do others. In this study, we had controlled the effect of main classification of antipsychotics, that is, typical or atypical. Further stratification was not conducted because this would lead to an unnecessary reduction in statistical power.
The discrepancy of drug responses between individuals and across populations is a major concern in clinical practice. Difference of allele or genotype frequencies of functional relevant genetic variants partly explains why the prevalence of a defined phenotype (for example, treatment response, treatment efficacy, adverse reaction, and so on) of the same drug exposure can be different across populations. Previous molecular study on ADRA1A receptors carrying the 492Arg/Arg and 492Cys/Cys amino acids showed no differences in binding affinity with agonist or antagonist; both receptors couple to Ca^{2+} signaling, and the dose-response relationships on the noradrenaline-induced rise in intracellular Ca^{2+} concentration were similar. These suggest that the Arg492Cys has little or no effects on the pharmacokinetics and pharmacodynamics of antipsychotics. The possible role of Arg492Cys (SNP46) variant has also been examined in human subjects in previous studies. There is no evidence to support an association of the variant with schizophrenia or treatment responses.46 Likewise, we did not find an association between the Arg492Cys and BMI in our sample.

In the report of Clark et al., associations were found between two SNPs in the promoter region of the ADRA1A gene and schizophrenia/schizoaffective disorder, with odd ratios of 2.05 and 3.84 for −563 C/T (SNP17) and −9625 G/A (SNP1), respectively. In our sample, the SNP was monomorphic for all subjects, whereas SNP17 exhibits an MAF of 0.496, with no association with BMI. Although further expression study in brain tissues with the two nucleotide variations did not identify a change in ADRA1A mRNA level,48 possible effects to differential transcription cannot be ruled out.

Every phenotype is limited to some extents in interpretation. BMI is a simple obesity indicator. Other obesity related indexes, for example, waist circumference, waist-to-hip ratio and conicity index, are not more effective than BMI as a simple reference to the standard dual-energy X-ray absorptiometry trunk fat mass in the Chinese population.49 Unless cardiovascular diseases are the phenotypes of interest, the waist-to-height ratio may be used as it is more sensitive than BMI as a discriminator.50 Another common physiological measurement, blood pressure, which is strongly associated with BMI,51 is inversely related to the strength of ADRA1A receptor antagonism of antipsychotics. This is noteworthy because blood pressures are common indicator to obesity. Almost universally, antipsychotics cause orthostatic hypotension.52 Interestingly, cell model showed much higher (~10-fold) antagonist affinity of sertindole and risperidone than haloperidol for recombinant human ADRA1A, which is consistent with the findings in rat model53 and human post-mortem study.54 The high ADRA1A affinity of sertindole and risperidone explains the relatively high incidence of dizziness in patients taking sertindole55 and risperidone56 compared with those taking haloperidol. Moreover, Gu et al.57 has also reported an evidence of association of ADRA1A gene with essential hypertension in the Chinese population. Clarification of the relations between BMI, blood pressures and the ADRA1A gene may provide further understandings to obesity in schizophrenia.

Current evidences suggest that most stimulatory effects of the sympathetic nerves for glucose uptake in white and
Figure 4 (a) Significance of single-nucleotide polymorphisms (SNPs) in body mass index (BMI) evaluated by genotype distribution. P-values are shown in the form of minus natural logarithm (−ln P). The green line is the significant level of −ln 0.05 (χ² = 2.99). SNP serial numbers correspond with the SNP information in Supplementary Table 1. (b) Significance of SNPs in BMI evaluated by allelle distribution. SNP serial numbers correspond with the SNP information in Supplementary Table 1.
brown adipose tissue are caused by β-adrenergic action.\(^5^8\) It is also evident that pharmacological blockade on α-adrenergic activity effectively potentiates lipolysis and exercise energy expenditure.\(^5^9\) but not glucose-induced thermogenesis.\(^6^0\) Several lines of evidences have provided clues for the observation. Stimulation of ADRA1 subtypes by phenylephrine increases glucose uptake and metabolism in rats\(^6^1\) and human\(^6^2\) white adipose tissue. Exposure of human white fat cells to the ADRA1 agonists norfenefrine and noradrenaline increased the glycerol concentration in the abdominal diastale, showing that ADRA1 receptors are involved in the regulation of lipolysis rate and microcirculation of adipose tissue.\(^6^3\) The evidence of a female gender effect on the ADRA1A gene in BMI in this study supports the existence of an antipsychotic and weight-gain effect through ADRA1A receptor antagonism, possibly regulated by female sex hormones.

The implication of this study is limited by the fact that the research subjects were chronic schizophrenia who had been treated for many years that the antipsychotics-induced weight changes are less obvious than the schizophrenia subjects who were treated for the first time (for example, see Flechtner-Mors et al.\(^6^3\)). The sensitivity for detecting a true association is thus reduced. However, these weaknesses had been reduced to some extents because we collected 13 consequent BMIs so that the nature of change could be included in the statistical model. In addition, other possible confounding factors were also controlled. Further molecular study on the ADRA1A gene, especially the effects of the promoter and intron region on the regulation of lipolysis rate and microcirculation of adipose tissue, warrants a closer understanding to weight gain and other obesity related phenotypes in schizophrenia.

**Conflict of interest**

The authors declare no conflict of interest.

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