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Association Between the 1291-C/G Polymorphism in the Adrenergic α-2a Receptor and the Metabolic Syndrome

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Abstract: The prevalence of the metabolic syndrome is increased in patients with schizophrenia compared with the general population. The strong interindividual differences in susceptibility to developing the metabolic syndrome suggests that the genetic makeup is a modulating factor. Part of the genetic puzzle can possibly be explained by variations in the gene coding for the adrenergic α-2a receptor (ADRA2A) because this receptor plays an important role in lipolysis.

Three studies have found an association between the α-2a 1291-C/G polymorphism and antipsychotic induced weight gain, with conflicting results between whites and Asians. No studies have been published investigating the association between the 1291-C/G polymorphism and the metabolic syndrome.

The primary objective of this cross-sectional study was to investigate the association between the ADRA2A 1291-C/G polymorphism and the metabolic syndrome in 470 patients using antipsychotic drugs.

There was no significant association between carriership of the variant 1291-G allele and prevalence of the metabolic syndrome (odds ratio, 0.73; 95% confidence interval, 0.49–1.15). Exploratory analysis showed an association between carriership of the variant 1291-G allele and a reduced prevalence of the metabolic syndrome in patients not currently using antipsychotics (odds ratio, 0.05; 95% confidence interval, 0.003–0.97; $P = 0.048$).

In conclusion, this study shows that the ADRA2A 1291-C/G polymorphism does not seem to be a strong predictor for long-term occurrence of the metabolic syndrome in antipsychotic using patients. Studies investigating this association using a prospective, or retrospective, design, as well as studies investigating this association in a nonpsychiatric population, are warranted.

Key Words: ADRA2A, antipsychotics, metabolic syndrome, schizophrenia, 1291-C/G

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It has been shown that the prevalence of the metabolic syndrome is increased in patients with schizophrenia compared with the general population.[1] Although controversy exists about the causal mechanisms, it is most likely that metabolic adverse effects of antipsychotic drugs including lipid abnormalities, disturbed glucose metabolism, and weight gain are important determinants for this increased prevalence. These metabolic disturbances, like insulin resistance, can still be present for more than a year after treatment with the antipsychotic drugs has ended.[2]

The mechanism behind antipsychotic-induced metabolic abnormalities is not entirely clear. The high interindividual differences suggest that genetic makeup is a modulating factor.

One of the potential genetic determinants is genetic variation in the gene coding for the adrenergic α-2 receptor, because of its effects on the breakdown of fat (lipolysis) and the fact that antipsychotics such as clozapine, which are associated with metabolic abnormalities, have a high affinity for the α-2 receptors. Studies have shown that stimulation of the G protein–coupled α-2 adrenergic receptor leads to an inhibition of lipolysis.[3] Weight loss during hypocaloric diets was associated with a decreased α-2 adrenoceptor sensitivity.[4]

Three different subtypes of the α-2 adrenoceptor have been discovered: α-2a, α-2b, and α-2c.[5] Data from the HERITAGE Family study showed an association between the 1291-C/G polymorphism (rs1800544) in the gene coding for the α-2a receptor (*ADRA2A*) and accumulation of (predominantly abdominal) body fat.[6] Black male patients carrying the variant 1291-G allele had a higher trunk-to-extremity skin fold ratio than black male patients without the variant allele. No association was found in white subjects. Recently, overexpression of the α-2a receptor and the rs553668 polymorphism in the *ADRA2A* gene have also been associated with type 2 diabetes.[7]

To our knowledge, 3 studies have been published investigating the potential role of the *ADRA2A* 1291-C/G polymorphism in explaining interindividual differences in antipsychotic-induced weight gain.

The study by Wang et al,[8] in 93 Asian patients with a follow-up of 14 (SD, 6) months, showed that patients carrying the 1291-G/G genotype experienced more weight gain during treatment with clozapine than did carriers of the 1291-C/C genotype (8.5 [SD, 7.2] kg vs 2.8 [SD, 6.1] kg, respectively; $P = 0.023$). The 1291-GG genotype or carriership of the variant G allele was also associated with a more than 7% increase in body weight during treatment with clozapine (odds ratio [OR], 4.21; 95% confidence interval [CI], 1.58–11.19; and OR, 3.45; 95% CI, 1.87–6.35, respectively). The study by Park et al,[9] in 62 Asian patients with a minimum follow-up of 3 months, showed that patients carrying the G allele more often experienced a more than 10% increase in body weight during treatment with olanzapine (OR, 2.58; 95% CI, 1.21–5.51). A recent study by Sickert et al,[10] in 129 patients with a follow-up of 6 to 14 weeks, showed that European Americans carrying the 1291-C allele gained more weight compared with subjects homozygous for the G allele (3.7 [SD, 4.1] kg vs 0.2 [SD, 2.9] kg, respectively; $P = 0.01$). These results suggest that ethnicity may

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play a role in the effect of the *ADRA2A* 1291-C/G polymorphism on antipsychotic-induced weight gain, with the 1291-G allele being protective for weight gain in whites and the 1291-C allele being protective for weight gain in Asians. A basis for this discrepancy between ethnicities may lie in a differential gene expression caused by genetic and/or environmental factors.

To our knowledge, no studies investigating the possible association between the *ADRA2A* 1291-C/G polymorphism and prevalence of the metabolic syndrome have been published.

The primary objective of this study was to investigate the association between the *ADRA2A* 1291-C/G polymorphism and prevalence of the metabolic syndrome in patients using antipsychotics. Secondary objectives were associations between the *ADRA2A* 1291-C/G polymorphism and individual parameters contributing to the metabolic syndrome as well as effects of individual antipsychotics.

MATERIALS AND METHODS

Setting

This study included patients from 3 pooled comparable patient populations. Two of these populations (n = 114 and n = 170) were used before in previous studies investigating the association between HTR2c polymorphisms and antipsychotic-induced metabolic syndrome. The study designs of these studies have been described in detail elsewhere.[11–13] The third sample (n = 186) came from an ongoing "Pharmacotherapy Monitoring and Outcome Survey" (PHAMOUS). PHAMOUS is an initiative from the Rob Giel Research Centre, a number of mental health care institutions, and the Department of Pharmacotherapy and Pharmaceutical Care from the University of Groningen. PHAMOUS combines a yearly somatic screening with routine outcome assessment in patients using antipsychotics. Risk factors for cardiovascular and metabolic complications are monitored, and effectiveness of antipsychotic treatment is evaluated in this survey, with the goal of improving health care for people with psychosis. Patients included in this study originated from the northern part of The Netherlands. A detailed description of the study design can be found on www.phamous.eu (Dutch).

Design and Patients

A cross-sectional design was used to assess the association between ADRA2A 1291-C/G genotype and the metabolic syndrome. Patients were eligible for inclusion in this study if they were 18 years or older and with a diagnosis of schizophrenia, schizoaffective or schizophreniform disorder, or psychotic disorder. After complete description of the study to the patients, written informed consent was obtained, and blood was drawn.

Outcome Measures

Primary end point of the study was the presence of the metabolic syndrome. The metabolic syndrome was defined according to the new definition by the National Cholesterol Education Program's Adult Treatment Panel IIIa (ATPIIIa).[14] The metabolic syndrome was diagnosed in all patients when 3 or more of the following 5 metabolic criteria were met: waist circumference 102 cm or greater (male) or 88 cm or greater (female); triglycerides 1.7 mmol/L or greater or use of a fibrate; high-density lipoprotein (HDL) cholesterol less than 1.0 mmol/L (male) or less than 1.3 mmol/L (female) or use of a statin; blood pressure 130/85 mm Hg or greater or use of an antihypertensive drug; and finally fasting glucose 5.6 mmol/L or greater or hemoglobin A_{1c} (HbA_{1c}) greater than 6.1% or use of an antidiabetic. Hemoglobin A_{1c} was used when fasting glucose level data were not available. The cutoff value used for HbA_{1c} is based on a review by Bennett et al.[15] With respect to triglyceride-lowering therapy or HDL-increasing therapy, a choice was made to allocate fibrates specifically to the triglyceride category and statins to the HDL category. Allocating both fibrates and statins to both triglyceride and HDL categories would have led to an overestimation of the metabolic syndrome, because treatment with a statin or a fibrate would have led to a diagnosis of the metabolic syndrome almost immediately. Secondary end points were the separate metabolic parameters as mentioned above.

Determinants

Primary determinant was the genotype of the 1291-C/G (rs1800544) polymorphism located in the *ADRA2A* gene. It should be noted with regard to ADRA2A polymorphism nomenclature that, for reasons of clarity, we use the nomenclature and nucleotide numbering at the genomic level according to the guidelines of the Human Genome Variation Society (www.hgvs.org) as well as the "traditional" nomenclature and numbering used in previous publications. We regarded the 1291-G allele as the dominant allele, based on the studies by Wang et al,[8] Park et al,[9] and Sickert et al.[10]

DNA Isolation and Genotyping

Genomic DNA of patients was isolated from EDTA blood using the X-tractor Gene (Corbett Robotics; Corbett Life Science, Westburg, Leusden, The Netherlands) with X-tractor Gene Liquid Sample Reagent Pack (XTR1, Sigma-Aldrich, Westburg, Leusden, The Netherlands).

Rs1800544 was determined with allelic discrimination using a predeveloped assay (C_7611979_10; Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands) according to a standard protocol provided by Applied Biosystems. The reaction was carried out in TaqMan universal polymerase chain reaction master mix (Applied Biosystems) in a TaqMan 7500 apparatus. The genotyping of this assay was conducted blind to the clinical status of the patients.

Data Analyses and Statistics

The association between the metabolic syndrome or the individual metabolic parameters and the ADRA2A genotype, or presence or absence of the ADRA2A 1291-G allele, was investigated with logistic regression. Data were investigated for potential confounding effects of age, HTR2c rs1414334 and rs3813929 genotypes, ethnicity, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis, sex, and antipsychotic drugs prescribed. We included these variables in the multivariate model if they were univariately associated with the primary end point metabolic syndrome at a significance level of $P < 0.20$.[16] Unless otherwise stated, results are expressed as adjusted ORs. More exploratory analyses included a stratified analysis for individual antipsychotic drugs used at the moment of evaluation as well as an investigation of the association between the 1291-C/G polymorphism and the metabolic syndrome in a small group of schizophrenic patients not currently using antipsychotic drugs. $P \leq 0.05$ or less was regarded as significant. Data were analyzed using SPSS 17.0 (SPSS Inc, Chicago, Ill).

RESULTS

In total, 497 patients were recruited for this study. Twenty-seven patients did not take any antipsychotic drug at the moment of evaluation, and data from these patients were used only in the exploratory analysis. Therefore, the data from 470 patients were used for primary data analysis.

TABLE 1. ADRA2A 1291C/G Genotype and Metabolic Syndrome

Genotype	Patients (n = 408)	Metabolic Syndrome	Crude OR* (95% CI; *P*)	Adjusted OR*† (95% CI; *P*)
Patients with antipsychotics				
1291-CC	215	43%	1	1
1291-GC	165	36%	0.74 (0.49–1.13; 0.17)	0.77 (0.48–1.23; 0.27)
1291-GG	28	29%	0.54 (0.23–1.27; 0.16)	0.49 (0.18–1.33; 0.16)
1291-GG+GC‡	193	35%	0.71 (0.48–1.06; 0.095)	0.73 (0.49–1.15; 0.18)
Patients without antipsychotics (n = 25)§				
1291-GG+GC	9	11%‖	0.097 (0.01–0.97; 0.047)	0.05 (0.003–0.97; 0.048)

*Data were analyzed with the common genotype (1291-CC) as reference.

†Data were adjusted for age, sex, carriership of variant HTR2c rs1414334 C allele, ethnicity, *DSM-IV* diagnosis and prescribed antipsychotic drug.

‡Analysis for carriership of the variant allele.

§Data could be investigated only for an association between carriership of the variant allele and the metabolic syndrome because of sample size.

‖Compared with 56% in group with 1291-CC genotype.

Most patients were male (68%), with a diagnosis of schizophrenia (78%) or schizoaffective disorder (17%), with a mean age of 38 (SD, 10) years. Prevalence of the metabolic syndrome was 39%.

Of these patients, 442 were of white origin, 14 were of Asian origin, 9 were of African origin, and the remainder was of unknown origin. Olanzapine (n = 106 [23%]), risperidone (n = 103 [22%]), and clozapine (n = 102 [22%]) were the most frequently prescribed atypical antipsychotic drugs. The remaining 23% of the patients used aripiprazole (n = 21), quetiapine (n = 12), or typical antipsychotics (n = 69) or used a combination of antipsychotics (n = 57).

The ADRA2A 1291-CC genotype was most prevalent (51%), followed by the 1291-CG (41%) and 1291-GG genotypes (8%). Genotype frequencies of the 1291-C/G polymorphism did not deviate from those expected under Hardy-Weinberg equilibrium ($P = 0.59$).

Ethnicity, *DSM-IV* diagnosis, carriership of the variant HTR2C rs1414334 C allele, age, sex, and prescribed antipsychotic drug were associated with the metabolic syndrome at a $P < 0.20$ significance level and were therefore included as covariates in the multivariate analysis. We did not find any confounding effects of statin and/or fibrate use. Multivariate analysis using only the data from patients of white origin did not influence the results either.

Table 1 shows that the ADRA2A 1291-C/G polymorphism was not significantly associated with an increased risk for the metabolic syndrome in patients using antipsychotics. Analysis based on genotypes as well as carriership of the variant G allele did not show a significant association with the metabolic syndrome, although the point estimate decreases by the number of variant 1291-G alleles.

Table 2 shows that an analysis of the association between the ADRA2A polymorphism and the 5 components of the metabolic syndrome showed a trend for an association with lower triglyceride levels. Carriership of the variant G allele was protective for reaching the triglyceride cutoff point of 1.7 mmol/L (OR, 0.67; 95% CI, 0.44–1.00; $P = 0.05$).

A stratified analysis for the individual antipsychotic drugs showed no association or trend between carriership of the variant 1291-G alleles and prevalence of the metabolic syndrome in any of the antipsychotics (Table 3).

The exploratory analysis in the group of schizophrenic patients not currently using any antipsychotic drugs (n = 27, with 25 patients evaluable) showed that patients carrying the variant 1291-G allele had a lower chance of having the metabolic syndrome than patients not carrying the variant 1291-G allele (nonadjusted OR, 0.10; 95% CI, 0.01–0.97; $P = 0.047$). This lowered risk was still significant after correction for the 2 significant ($P < 0.2$) covariables, age and sex (OR, 0.05; 95% CI, 0.003–0.97; $P = 0.048$; Table 1).

DISCUSSION

In this study, we did not find a significant association between the 1291-C/G polymorphism in the *ADRA2A* gene and prevalence of the metabolic syndrome in psychiatric patients using antipsychotics. However, we found that the point estimate

TABLE 2. Association Between Carriership of the Variant 1291-G Allele and Individual ATPIIIa Parameters Contributing to the Metabolic Syndrome

Determinant*	Patients†	Crude OR (95% CI; *P*)	Adjusted OR (95% CI; *P*)‡
HDL cholesterol	440	1.00 (0.69–1.46; 0.99)	1.07 (0.71–1.62; 0.75)
Triglycerides	442	0.60 (0.41–0.88; 0.008)	0.67 (0.44–1.00; 0.05)
Waist circumference	446	1.18 (0.82–1.71; 0.38)	1.43 (0.92–2.21; 0.11)
Hypertension	357	0.93 (0.61–1.41; 0.73)	0.95 (0.60–1.52; 0.84)
Glucose	408	0.97 (0.59–1.61; 0.91)	0.87 (0.49–1.55; 0.64)

*HDL cholesterol <1.0 mmol/L (male) or <1.3 mmol/L (female) or use of a statin. Triglycerides ≥1.7 mmol/L or use of a fibrate. Waist circumference ≥102 cm (male) or ≥88 cm (female). Hypertension = blood pressure ≥130/85 mm Hg or use of an antihypertensive drug. Glucose = fasting glucose ≥5.6 mmol/L, or HbA_{1c} > 6.1% or use of an antidiabetic.

†Patient number varies because of missing values.

‡Data were adjusted for age, sex, carriership of variant HTR2c rs1414334 C allele, ethnicity, *DSM-IV* diagnosis and prescribed antipsychotic drug.

TABLE 3. Association Between Carriership of the Variant 1291-G Allele and the Metabolic Syndrome for Individual Antipsychotics

Antipsychotic	n	MS	Crude OR (95% CI)	Adjusted OR* (95% CI)
Clozapine	91	44%	0.89 (0.47–1.71)	0.99 (0.47–2.07)
Olanzapine	99	33%	0.50 (0.23–1.08)	0.49 (0.18–1.39)
Risperidone	87	31%	1.03 (0.48–2.19)	0.44 (0.15–1.32)
Quetiapine	16	38%	1.30 (0.25–6.74)	NA
Aripiprazole	10	30%	0.21 (0.01–3.13)	NA
Typical antipsychotic	56	45%	1.03 (0.46–2.30)	1.37 (0.49–3.89)
Multiple antipsychotic	49	33%	0.39 (0.13–1.16)	0.32 (0.09–1.22)

*Data were adjusted for age, sex, carriership of variant HTR2c rs1414334 C allele, ethnicity, and *DSM-IV* diagnosis.
MS indicates metabolic syndrome; NA, not applicable.

for an association between the 1291-C/G genotype and the metabolic syndrome decreased as the number of variant 1291-G alleles in the genotype increased (Table 1). This inverse relation is suggestive for a gene-dose effect, although this was not significant possibly because of the limited power of this study. A trend was found for an association between the ADRA2A 1291-C/G polymorphism and triglyceride levels, in which the variant 1291-G allele was protective for reaching the triglyceride cutoff point of 1.7 mmol/L (OR, 0.67; 95% CI, 0.44–1.00; $P = 0.05$). An exploratory analysis in a group of patients not currently using antipsychotics showed a protective effect of carriership of the variant 1291-G allele on prevalence of the metabolic syndrome (OR, 0.05; 95% CI, 0.003–0.97; $P = 0.048$).

There are some limitations to these results. First, although our sample is relatively large with 470 patients, still only 37 patients carrying the 1291-G/G genotype were included. Because most effect of the 1291-C/G polymorphism is expected in this group (Sickert et al,[10] Wang et al[8]), it is possible that the sample size was too small to find significant results.

Second, we recognize that a cross-sectional design has its limitations because data on metabolic parameters of the patients at the initiation of antipsychotic drug treatment were not available to us. Therefore, we were unable to analyze data for changes in these parameters over time related to the use of antipsychotic drugs.

This limitation makes it difficult to compare our results to prospective follow-up studies investigating the association between the *ADRA2A* 1291-C/G polymorphism and metabolic disturbances (weight gain) in psychiatric patients using antipsychotics.[8–10]

Third, some variables contributing to a patient's risk of the metabolic syndrome, for example, smoking behavior, exercise, and diet, were not taken into account. Fourth, in most of the patients, no values for fasting plasma glucose were available in this study. Therefore, we used HbA_{1c} instead, with a cutoff value of greater than 6.1%. Using HbA_{1c} instead of fasting glucose possibly has some effect on the diagnosis of the metabolic syndrome, thereby affecting our results. However, the review study by Bennett et al[15] showed that a recommended HbA_{1c} cutoff point of greater than 6.1% had similar accuracy as fasting plasma glucose 6.0 mmol/L for predicting type 2 diabetes (sensitivity, 72.7%; specificity, 94.7%). Based on these results, and the fact that we did not even see a trend toward a positive association between the ADRA2A polymorphism and HbA_{1c}, we believe that using HbA_{1c} instead of fasting plasma glucose did not influence our results.

Fifth, although predominantly white, our sample was of mixed ethnic origin. Ethnicity could be an important confounder in data analysis because the studies in Asians and whites have shown opposite results. However, we corrected for ethnicity in our multivariate analysis, and moreover, using only the data from white patients (n = 440) did not affect our results.

Waist circumference is one of the most relevant determinants for insulin resistance and cardiovascular morbidity in the ATPIIIa definition of the metabolic syndrome.[17,18] Because the adrenergic α-2a receptor (ADRA2A) has an important function in lipolysis and therefore in waist circumference, as was shown by Garenc et al,[6] one would expect an association between the ADRA2A 1291-C/G polymorphism and waist circumference and the metabolic syndrome. In this study, we could not find these associations, although the mean waist circumference did decrease with an increasing number of variant G alleles in the genotype (CC: 101 cm, CG: 100.0 cm, GG: 98.0 cm). However, because the average SD was around 14 cm, these differences were not significant. The trend we found for an association between the 1291-C/G polymorphism and triglyceride levels is suggestive for an association with lipolysis nevertheless (Table 2).

It is possible that drugs with an antagonistic action for ADRA2As, such as antipsychotics, mask the effects of the 1291-C/G genotype (protective effect of the 1291-G allele) on waist circumference and prevalence of the metabolic syndrome. This would explain why we found no association in the group of patients currently using antipsychotics, but did find an association in the group of patients not currently using antipsychotics.

Following this lead, we divided our study sample in a group of patients using antipsychotics with a high affinity for the α-2 receptors (clozapine, quetiapine, and risperidone) and a group of patients using antipsychotics with a lower affinity for the α-2 receptors based on the study by Matsui et al.[19] The resulting analysis showed no association between the 1291-C/G polymorphism and prevalence of the metabolic syndrome (results not shown).

It is possible that even antipsychotics with a lower affinity for α-2a receptors still mask the protective effect of the 1291-G allele, but given the fact that the "antipsychotic-naive" group of patients was small, the results found in this group could also be a type I error. To further explore the impact of the 1291-C/G polymorphism on lipolysis and prevalence of the metabolic syndrome, we are currently investigating this association in a larger antipsychotic-naive population.

This is the first study in which the association between the ADRA2A 1291-C/G polymorphism and prevalence of the metabolic syndrome was investigated. Insight in the factors responsible for the metabolic syndrome can have implications for daily clinical psychiatric practice, because there is a strong association between the metabolic syndrome and cardiovascular

morbidity and mortality. A pharmacogenetic tool to predict a patient's chance of developing the metabolic syndrome would be helpful in psychiatric practice because this could identify patients at risk, offering an opportunity to choose an alternative treatment.

In conclusion, this study shows that the ADRA2A 1291-C/G polymorphism does not seem to be a strong predictor for long-term occurrence of the metabolic syndrome in patients using antipsychotics. However, the use of antipsychotics with antagonistic ADRA2A activity may mask the possible protective effect of the 1291-G allele as shown in patients not currently using antipsychotics.

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AUTHOR DISCLOSURE INFORMATION

The authors have no conflicts of interest to declare.

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