Trp64Arg Polymorphism of the *ADRB3* Gene Predicts Hyperuricemia Risk in a Population from Southern Spain

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ABSTRACT. ***Objective.*** To study the role of Trp64Arg polymorphism of the *ADRB3* gene in the risk of developing hyperuricemia in 1051 subjects from southern Spain, with a followup of 6 years. The inclusion of plasma levels of uric acid as a diagnostic criterion to define the metabolic syndrome is under discussion. Genes responsible for insulin resistance could contribute to the development of hyperuricemia. Previous cross-sectional studies have suggested *ADRB3* as a possible candidate gene in the development of hyperuricemia and insulin resistance.

Methods. A prospective, population-based, cohort study of 1051 persons examined in 1997-98 and reassessed at a second examination 6 years later. The metabolic phenotype was assessed at baseline and again at the followup. Insulin resistance was measured by homeostasis model assessment. The Trp64Arg polymorphism of *ADRB3* was detected by real-time polymerase chain reaction. Subjects were considered normouricemic if their serum uric acid levels were ≤ 7 mg/dl for men or ≤ 6 mg/dl for women.

Results. Carriers of the Arg64 allele who were normouricemic at baseline had a higher risk of developing hyperuricemia 6 years later (p = 0.017, OR 2.3, 95% CI 1.1–4.6). Multivariate logistic regression analysis showed that the OR of having hyperuricemia at the 6-year followup was significantly associated with the Arg64 allele, after adjusting for age, weight gain, baseline levels of triglycerides, serum uric acid, and insulin resistance (OR 3.1, 95% CI 1.3–7.1).

Conclusion. Trp64Arg polymorphism of the *ADRB3* gene predicted the risk of developing hyperuricemia in this adult population. (First Release Dec 15 2009; J Rheumatol 2010;37:417–21; doi:10.3899/jrheum.090637)

Key Indexing Terms:
ADRB3 GENE URIC ACID POLYMORPHISM HYPERURICEMIA

The great individual variation in uric acid concentrations is partly explained by genetic factors, with an estimated inheritability of 0.25–0.73[1]. Although uric acid levels are not currently included among the diagnostic criteria for the definition of the metabolic syndrome, many studies have nevertheless found an association between uric acid concentrations and the metabolic syndrome, or certain of its components[2-4]. Data suggest that uric acid is an important risk factor for cardiovascular disease, especially in association with the other components of the metabolic syndrome[5-8]. Renal clearance of urate is inversely related with the degree of insulin resistance[9]. Human studies have found that increased uric acid levels predict the development of hyperinsulinemia, obesity, and diabetes[8,10-12]. As insulin resistance is partly determined by genetics[13], genes responsible for insulin resistance might also contribute to the development of hyperuricemia; possible candidate genes include the beta-3 adrenergic receptor (*ADRB3*)[14,15]. However, only a few studies have detected an association between Trp64Arg polymorphism of *ADRB3* and hyperuricemia[16,17]. Rho, *et al*[16], in a case-control study in men (203 normouricemic and 203 hyperuricemic), showed that the Arg64 variant was associated with the onset of hyperuricemia. Strazzullo, *et al*[17] undertook a cross-sectional study, again in men, and found an association between Trp64Arg polymorphism and the presence of hyperuricemia, although this association disappeared in a retrospective study. The persons followed in this latter study were a nonrandomly selected subgroup from a study undertaken in a factory 20 years earlier.

We undertook a prospective study in a population-based

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cohort to determine the presence of an association between *ADRB3* and the risk for hyperuricemia.

MATERIALS AND METHODS

Baseline study. In 1997-98 a study was undertaken in Pizarra, a town in the province of Malaga (Andalusia, southern Spain)[18-20]. A total of 1051 persons completed the baseline study, giving a participation index of 70.3%. Persons were selected randomly from the municipal census. The inclusion age was 18–65 years, and persons were excluded from the study if they were institutionalized for any reason, pregnant, or had a severe clinical or psychological disorder that impeded their attendance.

The subjects were requested by mail to attend their local health center for a medical examination. Those who failed to attend their first appointment were sent a second letter giving them another appointment, and all those still not attending were visited at home to ascertain the reason. The final sample distribution by age and sex was not significantly different from the population distribution.

Followup. The cohort was reevaluated in 2003-2004. All those who had completed the baseline study (n = 1051) were invited by letter or telephone to attend for another clinical and anthropometric examination and to take another oral glucose tolerance test (OGTT). In total, 824 persons completed the followup study (78.4%). Of the 227 who did not complete the study, 19 had died, 90 could not be traced, and 118 no longer wished to take part in the study.

The at-risk sample involved the 835 persons who were normouricemic and did not have type 2 diabetes at the baseline study, of whom 691 (245 men and 446 women) completed the followup study (82.7%).

All the participants were informed of the objective of the study and gave their written consent. Similarly, the participants and their family doctors were informed of the most relevant clinical results, whether they were normal or not. The study was approved by the Ethics and Clinical Research Committee of Carlos Haya Regional University Hospital, Malaga.

Procedures. The same methods were used for both the prevalence study and the incidence study. All the participants underwent an interview and standardized clinical examination[21]. Prior to starting the study, a seminar was held for the research team in order to standardize procedures. Standardized measurements were made of weight, height, body mass index (BMI), blood pressure, waist and abdominal circumferences, and waist-to-hip ratio. The increase in weight was calculated as the difference between the weight at followup and the baseline measurement.

Laboratory measurements. The serum was stored at –70°C for later analysis. Glycemia was measured in both studies using the glucose oxidase method (Bayer, Leverkusen, Germany) at fasting and 120 minutes after an OGTT with 75 g of glucose. Insulinemia at baseline and 120 min after an overload was measured by radioimmunoassay (Coat-a-Count Insulin, DPC, Los Angeles, CA, USA).

Insulin resistance was determined with the formula for the homeostasis model assessment (HOMA IR)[22]:

Fasting insulin (pmol/l) × fasting glucose (mmol/l)/22.5

Enzymatic methods were used to measure total cholesterol, triglycerides, and high-density lipoprotein cholesterol in each sample. Uric acid was measured at baseline and 120 min after the OGTT (Dimension autoanalyzer; Dade Behring Inc., Deerfield, IL, USA).

Genotyping. DNA was isolated from whole blood by the salting-out method of Miller, modified by Queipo-Ortuño[23]. Detection of the Trp64Arg polymorphism (rs4994) of the *ADRB3* gene (NM 000025) was done with LightCycler technology (Roche Molecular Biochemicals, Mannheim, Germany). The primers and hybridization probes were designed by TIB Molbiol (Berlin, Germany). The hybridization probes were designed to have melting temperatures higher than the primers. The sensor probe, complementary to the mutated sequence, was labeled with LC-red 640 at its 5' end and was phosphorylated at its 3' end to block extension. The anchor probe was labeled with fluorescein at its 3' end. All the polymerase chain reaction mixtures had 3 mM $MgCl_2$, 0.2 μM of each of the probes, 0.5 μM of each primer, 1 μl of LightCycler FastStart DNA Master Hybridization Probes (Taq DNA polymerase, reaction buffer, dNTP mix, and 10 mM $MgCl_2$; Roche Diagnostics), 100–150 ng of DNA in a final volume of 10 μl. A negative control with water instead of DNA was always included.

Classification criteria. The World Health Organization 1998 criteria were used to classify the persons with diabetes or carbohydrate metabolism disorders[24]. Persons were considered to be obese if their BMI was ≥ 30[25], and normouricemic if their uric acid concentrations were ≤ 7 mg/dl for men or ≤ 6 mg/dl for women[6].

Statistical analysis. The continuous variables are shown as the mean and standard deviation and the classification variables as proportions. Calculation of the statistical difference between the means of the continuous variables was done by 1-way ANOVA and the qualitative variables by the chi-squared test. Hardy-Weinberg equilibrium was tested using the chi-squared test. The data were analyzed with the gene analysis program R (version 1.2.1) of the R statistical software, version 2.6.1 (Department of Statistics, University of Auckland, Auckland, NZ; http://www.r-project.org/). The strength of association between variables was measured by calculating the OR and 95% confidence intervals (95% CI) by logistic regression model. The multivariate logistic regression model was controlled for potential confounders such as age, weight gain, triglyceride concentrations, uric acid, and insulin resistance. In all cases the level of rejection of a null hypothesis was $\alpha = 0.05$ for 2 tails.

RESULTS

The frequencies of the Trp64Arg polymorphism were in Hardy-Weinberg equilibrium. The sample characteristics at baseline and at followup were not significantly different depending on the presence or absence of the Arg64 variant of the Trp64Trp homozygous genotype of the *ADRB3* gene, except for the presence of hyperuricemia. Of the persons who were normouricemic at baseline, 9% had developed hyperuricemia after 6 years. Those who were not hyperuricemic at baseline and who had the Arg64 allele were more likely to develop hyperuricemia than those who had the Trp64Trp genotype (p = 0.017, OR 2.3, 95% CI 1.1–4.6; Table 1).

After adjusting the multivariate logistic regression model for baseline data concerning age, weight gain, triglyceride concentrations, uric acid, and insulin resistance (measured by the HOMA), the Arg64 variant was still significantly associated with the risk for having hyperuricemia at 6 years (Table 2). This was seen in the codominant model, the dominant model (this model has a greater N as the heterozygotes and homozygotes with the Arg64 variant are grouped together), the recessive model, and the log-additive model. After inclusion in the model of alcohol intake, hypertension, and diabetes developing during the followup, the polymorphism remained significantly associated with the incidence of hyperuricemia (p = 0.003, OR 3.7, 95% CI 1.6–8.9; data not shown).

DISCUSSION

The main finding of this study is that Trp64Arg polymorphism of the *ADRB3* gene was significantly and independently associated with the incidence of hyperuricemia in the study population.

Table 1. Characteristics of the study population depending on the Trp64Arg polymorphism of the ADB3 gene (normouricemic persons in the baseline study who completed the followup.

	Baseline Characteristics			Characteristics at 6 Years		
	Trp64Trp, n = 603	Carriers of the Arg64 Allele, n = 88	p*	Carriers of the Trp64Trp, n = 603	Arg64 Allele, n = 88	p*
Age, yrs	38.7 ± 13.0	39.2 ± 13.9	NS	44.8 ± 13.4	44.7 ± 13.8	NS
BMI (weight/height^2)	27.1 ± 4.7	26.6 ± 5.6	NS	28.2 ± 5.1	27.6 ± 5.2	NS
Baseline glycemia, mg/dl	90.3 ± 9.3	91.6 ± 7.4	NS	91.1 ± 14.6	91.8 ± 14.2	NS
Glycemia at 120 min, mg/dl	113.6 ± 26.3	118.3 ± 30.0	NS	116.4 ± 36.8	120.4 ± 35.4	NS
HOMA-IR	2.27 ± 1.5	2.4 ± 1.5	NS	2.2 ± 2.0	1.8 ± 1.1	NS
Total cholesterol, mg/dl	196.0 ± 41.2	197.1 ± 43.6	NS	202.0 ± 39.5	203.6 ± 40.3	NS
Triglycerides, mg/dl	98.6 ± 72.4	89.4 ± 45.9	NS	96.9 + 68.1	89.2 ± 42.6	NS
Uric acid, mg/dl	4.3 ± 1.1	4.4 ± 1.1	NS	4.4 ± 1.3	4.5 ± 1.2	NS
Systolic BP, mm Hg	130.8 ± 17.4	130.6 ± 17.5	NS	131.2 ± 21.2	130.8 ± 25.1	NS
Diastolic BP, mm Hg	81.0 ± 10.7	80.8 + 11.7	NS	80.4 + 13.3	79.8 ± 14.5	NS
Obesity, %	23.6	26.7	NS	31.7	32.9	NS
Hyperuricemic, %	0	0	NS	7.6	16.0	0.017

Data are means ± standard deviation or proportions (%). * Based on ANOVA for continuous variables and chi-square for categorical variables. The rejection level for a null hypothesis was alpha = 0.05 for 2 tails. BMI: body mass index; BP: blood pressure; NS: not significant; HOMA-IR: homeostasis model assessment. To convert to SI units, multiply total cholesterol by 0.0259 (result in mmol/liter), triglycerides by 0.0113 (result in mmol/liter), and uric acid by 59.48 (result in μmol/liter).

Table 2. Simple and multivariate logistic regression for testing the association between Trp64Arg polymorphism and hyperuricemia.

Model	Normouricemic (%)	Hyperuricemic (%)	OR (unadjusted)	95% CI	p	OR (adjusted)	95% CI	p*
Codominant								
T/T	557 (88.2)	46 (76.5)	1.0		0.002	1.0		< 0.0001
T/A	70 (11.2)	10 (15.7)	1.6	0.7–3.6		2.07	0.8–5.2	
A/A	3 (0.6)	5 (7.8)	16.1	3.4–74.5		29.5	4.9–177.2	
Dominant								
T/T	557 (88.2)	46 (76.5)	1.0		0.02	1.0		0.0084
T/A, A/A	73 (11.8)	15 (23.5)	2.3	1.1–4.6		3.15	1.39–7.15	
Recessive								
T/T-T/A	627 (99.4)	56 (92.2)	1.0		0.001	1.0		0.0005
A/A	3 (0.6)	5 (7.8)	15.1	3.2–69.3		25.90	4.4–152.3	
Overdominant								
T/T–A/A	560 (88.8)	51 (84.3)	1.0		NS	1.0		NS
T/A	70 (11.2)	10 (15.7)	1.4	0.66–3.27		1.78	0.72–4.44	
Log-additive								
0, 1, 2	630 (91.3)	61 (8.7)	2.5	1.4–4.4	0.002	3.35	1.73-6.50	0.0006

The codominant model compared heterozygous T/A and homozygous A/A genotypes to the homozygous for the most frequent allele T/T. The dominant model compared a combination of T/A-A/A genotypes to the homozygous T/T. The recessive model compared a combination of T/T-T/A genotypes to the homozygous A/A. The log-additive model is equivalent to calculating the odds ratio for the risk A allele. Data are number of subjects, percentage of subjects with each genotype for each group (normouricemic and hyperuricemic). * p values adjusted for age, weight gain, triglyceride concentrations, uric acid, and insulin resistance.

The strength of the study is that it was undertaken prospectively in a population-based sample. As far as we are aware, this is one of the first longitudinal studies to examine the risk of hyperuricemia in carriers of the Arg64 allele of the *ADRB3* gene. To date, very few studies have found an association between this polymorphism and hyperuricemia[16,17].

Numerous genome-wide studies have been performed in recent years in order to find regions or genes that may explain the genetic variability in the concentrations of uric acid[26]. A recent metaanalysis identified 3 genetic loci that are associated with uric acid concentrations[27]. Others have identified a region on chromosome 6 that is also related with the variability in uric acid concentrations[1].

The *ADRB3* gene is expressed mainly in adipose tissue and it is responsible for an increase in lipolysis and the delivery of free fatty acids into the portal vein. An increase in visceral fat mass, in turn, correlates with resistance to insulin in skeletal muscle[28]. In humans, visceral obesity is associated with the enhanced sensitivity of visceral fat to catecholamine-induced lipolysis, primarily mediated through effects on the beta-3-adrenergic receptor. Visceral

obesity is also associated with decreased uptake of free fatty acids by muscle and with insulin resistance in skeletal muscle — in particular, impaired synthesis of insulin-stimulated glycogen[14].

The products of lipolysis, such as fatty acids, inhibit the signaling pathway of the insulin receptor, which in turn leads to insulin resistance. Insulin resistance could be the link between uric acid levels and the metabolic syndrome. Several studies have associated Trp64Arg polymorphism of the *ADRB3* gene with obesity and insulin resistance[28-30], although others have failed to find such associations[31].

For our study we selected persons who were normouricemic and who did not have type 2 diabetes, as the degree of hyperglycemia is related with uric acid levels[32]. The Trp64Arg polymorphism was associated with the risk of developing hyperuricemia, independently of the baseline levels of uric acid and triglycerides, both factors that are directly associated with the onset of hyperuricemia[33], as well as increases in weight and insulin resistance.

Hyperuricemia is considered a complex disease involving both genetic and environmental factors[34]. Several epidemiological studies have also found that alcohol intake or nutritional variables are associated with raised uric acid levels[35,36]. The inclusion in our analysis of alcohol consumption and intake of proteins or dairy products did not change the significance of the Arg64 variant with hyperuricemia.

Our study of an adult population, including both men and women, with a followup period of 6 years, supports the role of Trp64Arg polymorphism in the development of hyperuricemia independently of insulin resistance.

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