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Brief report

The rs1801278 G > A polymorphism of IRS-1 is associated with metabolic syndrome in healthy nondiabetic men. Modulation by cigarette smoking status

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ABSTRACT

Aims: To explore associations between IRS-1 rs1801278 G > A polymorphism and metabolic syndrome (MS).
Methods: rs1801278 G > A was genotyped in 610 healthy Argentinian men.
Results: GA carriers had lower risk of MS (OR = 0.52, $P = 0.045$), particularly among smokers (OR = 0.10, $P = 0.006$).
Conclusions: rs1801278 GA carriers had lower risk of MS, especially among smokers.

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1. Introduction

The metabolic syndrome (MS), a cluster of cardiovascular risk factors, is associated with insulin resistance (IR) and obesity, and plays a role in the pathogenesis of T2D. Although MS is partially genetically determined, their genetic factors remain mostly unknown [1].

Insulin receptor substrate-1 (IRS-1) is a major substrate for the insulin receptor in insulin-sensitive tissues, and has been considered a candidate gene for T2D and IR [2]. IRS-1 polymorphisms, especially the allele A of rs1801278 G > A, could impair beta-cell function [3] and, especially, insulin sensitivity [4]. However, associations between rs1801278 G > A and IR disorders [5–7] were not consistently replicated. Inconsistency may be explained by strong environmental influences, and unknown gene–environment interactions [8]. Recently we found an association between *Pro12Ala* PPARG polymorphism and MS modulated by smoking [9]. Additionally, little is known about whether rs1801278 G > A is associated with MS in healthy nondiabetic population. The purpose of this study was to analyze whether rs1801278 G > A is associated with MS in healthy men from Argentina.

2. Research design and methods

610 unrelated Argentinian healthy blood donor men were recruited at the Hospital ''José de San Martín'', University of Buenos Aires. This study was approved by the ethic committee of our hospital. Anthropometric measurements (BMI, waist circumference [WC]), systolic (SBP) and diastolic (DBP) blood pressure, and fasting levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), glucose (FPG) and insulin were determined as previously [9]. MS was assessed using the revised NCEP/ATP III criteria [10], and IR with fasting insulin, TG/HDL-C, HOMA-IR (www.dtu.ox.ac.uk/index.php?maindoc=/homa/) and QUICKI [11].

The rs1801278 G > A genotypes were scored using PCR-RFLP analysis as previously [12].

Differences in rs1801278 G > A distribution among the groups for qualitative variables were assessed with χ^2 test. Gene–environmental interaction was explored with ANCOVA, and comparing the difference between two estimates from associations between rs1801278 G > A and MS in absence vs. presence of an environmental factor. A *P* value less than 0.05 was considered significant, except for interaction when $P < 0.1$ was considered significant.

3. Results

The average age of the individuals was 37.0 ± 10.9 years (range: 18–65 years). The prevalence of NCEP/ATP III-MS and obesity was 27.5 and 29.0%, respectively. The frequency of current smokers was 33.9%.

541 individuals were carrying the *GG*, 69 the *GA*, and none the *AA* genotype. The distribution was in Hardy–Weinberg equilibrium ($P > 0.1$).

GA carriers, and individuals carrying the allele *A*, had lower risk of MS (OR = 0.52, $P = 0.045$), especially current smokers (OR = 0.10, $P = 0.006$). These findings were found among current smokers aged >36 years (median value, $P = 0.0094$) but not among current smokers aged ≤36 years ($P = 0.69$). Individuals aged ≤36 years had lower smoking prevalence than those aged >36 years ($P < 0.0001$).

Interaction was confirmed comparing the associations between allele *A* and MS in absence (OR = 0.82) vs. presence of smoking (OR = 0.11, *P* for interaction = 0.036).

Multivariate logistic analysis confirmed that rs1801278 G > A was associated with MS ($P = 0.034$), particularly current smokers ($P = 0.008$) but not never/former smokers ($P = 0.47$).

In age- and BMI-adjusted ANCOVA, current smokers aged >36 years showed an interaction with rs1801278 G > A for WC ($P = 0.086$) and systolic BP ($P = 0.077$), and *GA* carriers had lower WC (91.1 cm vs. 99.0 cm, $P = 0.031$). TG was lower in *GA* current smokers carriers (107.2 mg/dl vs. 143.2 mg/dl, $P = 0.045$). *GA* carriers showed higher HDL-C (44.3 mg/dl vs. 40.4 mg/dl, $P = 0.016$), and lower risk of overweight/obesity (OR = 0.51, $P = 0.012$), especially current smokers (OR = 0.30, $P = 0.0045$).

GA carriers had lower TG/HDL-C (3.1 vs. 4.0, $P = 0.048$) especially current smokers (2.7 vs. 4.1, $P = 0.043$), but not different HOMA-IR (*P* = NS). Among individuals with FPG >99 mg/dl, *GA* carriers had lower fasting insulin (13.16 μU/ml vs. 23.71 μU/ml, $P = 0.019$) and higher QUICKI (0.355 vs. 0.303, $P = 0.0003$).

4. Discussion

This is the first report that demonstrates an association between the IRS-1 rs1801278 G > A polymorphism and the risk for MS modulated by cigarette smoking, in healthy men. *GA* carriers had, especially current smokers aged >36 years, lower risk for NCEP/ATPIII-MS and overweigh/obesity. Current smoking showed an interaction with rs1801278 G > A for MS and central obesity. The *GA* genotype was modestly associated with reduced levels of measures of IR such as TG/HDL-C. We hypothesize that *GA* genotype carriers had, compared to *GG* carriers, lower risk for MS due to a synergistic protective effect of allele *A* and smoking on central obesity. Current smokers, especially aged >36 years, had lower WC, BMI and FPG (data not shown). This is highlighted by several [13] but not all [14] studies that reported reduced BMI and central obesity in smokers, probably associated to greater fat utilization, in part due to higher resting metabolic rate, adrenergic-induced thermogenesis and fat oxidation, as well as appetite inhibition [15]. The level of leptin has been shown to be higher in smokers although there are discrepancies [16]. Cigarette smoking was associated with overexpression of AZGP1, a fat-depleting gene [17], and inhibition of adipocyte differentiation through endoplasmic reticulum stress and downregulation of PPARG [18]. We reported, in a similar sample, an association between *Ala12* of the *Pro12Ala* PPARG polymorphism and higher risk of MS among non-smokers [9]. We found that *GA* + *Pro12Pro* carriers had, compared to *GG* + *Pro12Ala* carriers, lower risk for MS and central obesity (data not shown).

Genome-wide association studies confirmed rs2943641 C > T [19] and rs7578326 A > G [20] IRS-1 polymorphisms,

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but not rs1801278 G > A, as new loci for T2D. rs2943641 C > T showed an interaction with rs1801278 G > A for IR [19]. rs1801278 G > A is not in linkage disequilibrium with either of the above SNPs.

In conclusion, the IRS-1 *GA* genotype of rs1801278 G > A polymorphism was associated with lower risk for MS, especially among current smokers, in healthy men from Argentina. Haplotype-based analyses in larger samples are necessary to confirm these findings.

Conflict of interest

There are no conflicts of interest.

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