



# Education modulates the association of the FTO rs9939609 polymorphism with body mass index and obesity risk in the Mediterranean population

D. Corella<sup>a,b,\*</sup>, P. Carrasco<sup>a,b</sup>, J.V. Sorlí<sup>a,b</sup>, O. Coltell<sup>c</sup>, C. Ortega-Azorín<sup>a,b</sup>, M. Guillén<sup>a,b</sup>, J.I. González<sup>a,b</sup>, C. Sáiz<sup>a,b</sup>, R. Estruch<sup>b,d</sup>, J.M. Ordovas<sup>b,e,f</sup>

<sup>a</sup> Genetic and Molecular Epidemiology Unit, School of Medicine, University of Valencia, Blasco Ibañez, 15, 46010 Valencia, Spain

<sup>b</sup> CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid, Spain

<sup>c</sup> Department of Computer Languages and Systems, University Jaume I, Castellón, Spain

<sup>d</sup> Department of Internal Medicine, Hospital Clinic, Barcelona, Spain

<sup>e</sup> Nutrition and Genomics Laboratory, JM-USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA

<sup>f</sup> Department of Cardiovascular Epidemiology and Population Genetics, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

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## KEYWORDS

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Educational level;  
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**Abstract** *Objective:* To define whether the rs9939609 FTO (fat mass and obesity associated) single nucleotide polymorphism (SNP) is associated with anthropometric measurements and its modulation by educational level in a Mediterranean population.

*Methods:* We studied 3 independent adult samples: a random sample ( $n = 1580$ ) from the general population (GP), obese hospital patients (OHP) ( $n = 203$ ) and elderly subjects ( $n = 1027$ ) with high cardiovascular risk (HCR). Weight and height were directly measured. Education and physical activity (PA) were measured using questionnaires.

*Results:* The rs9939609 presented heterogeneous associations with BMI. In the GP, the minor A-allele was significantly associated with greater BMI, following a co-dominant pattern ( $P = 0.009$ ), whereas in the OHP this association was recessive ( $P = 0.004$ ). Conversely, we did not find a significant association with BMI in the HCR group ( $P < 0.596$ ). In the GP we found a significant interaction between the FTO SNP and education ( $P = 0.048$ ). In the stratified analysis, no association of the FTO SNP with greater BMI in university subjects was detected ( $P = 0.786$ ), whereas the association was observed in non-university subjects ( $P = 0.001$ ). The FTO  $\times$  education interaction ( $P = 0.020$ ) was also observed in determining obesity risk in the GP. A-allele carriers had a greater risk of being obese only if they had no university

\* Corresponding author. Genetic and Molecular Epidemiology Unit, School of Medicine, University of Valencia, Blasco Ibañez, 15, 46010 Valencia, Spain. Tel.: +34 963864417; fax: +34 963864166.

E-mail address: [dolores.corella@uv.es](mailto:dolores.corella@uv.es) (D. Corella).

education (OR: 1.56; 95%CI: 1.09–2.23 for TA and OR: 2.01; 95%CI: 1.27–3.26 for AA subjects). The interaction of the FTO with education remained significant even after adjustment for PA. *Conclusions:* The association of the FTO SNP with greater BMI and obesity risk in the GP was strongly modulated by education.  
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## Introduction

Within the complex etiology of cardiovascular diseases and obesity, it has long been known that lower educational level is a shared risk factor [1–3]. Especially notable has been the recent increasing prevalence of obesity in subjects of lower educational level/socioeconomic status [4–7]. Although several studies have been carried out to investigate the differences in diet, exercise and other environmental variables among subjects with different educational level that may influence the risk of obesity [8–10], there have been very few studies that have investigated the genetic influence on the association between education and obesity-related variables, most of them being heritability studies conducted on twins [11,12]. Thus, a study undertaken on Danish twins [12], investigated how genetic and environmental variance in physical health differed with level of education, and concluded that education reduced the influence of genetic susceptibility to poor health, suggesting that this might take place because more educated people manage their environments better to protect their health. Concerning the analysis of specific loci, there is one study showing that a low educational level aggravated the association between the rs3809508 neuro-medin B single nucleotide polymorphism (SNP) and the risk of obesity in the HELENA study [13].

Genetic variation, namely the rs9939609 SNP, at the fat mass and obesity associated (FTO) gene has been frequently associated with common obesity [14–18]; however, not all the studies undertaken have found statistically significant associations between the FTO variant alleles and greater body mass index (BMI) [19–21]. Even in studies which have found significant associations between the rs9939609 and BMI, differences have been detected in the magnitude of the association depending on the population analyzed [14–18,22–24]. These studies are done with different ethnical backgrounds as well as with different demographic characteristics. Among the demographic characteristics, some studies have suggested that the effect could be greater in children and adolescents and lesser in elderly people [22–24]. Among the environmental interactions that may modulate the association of the FTO SNP with BMI, physical activity (PA) has been the most commonly studied. Several studies have found that low PA accentuates the effects of FTO risk-allele, whereas, high PA attenuates the association of that allele with greater BMI [24–26]. Nevertheless, not all the studies have been able to observe that modulation [27,28]. Although PA has been related to education in some studies [29] [for example, participation in exercise and sports was positively associated with educational level in Eurobarometers [29]], there is no published study that has examined the interaction between the FTO gene variation and education in determining the risk of obesity.

Taking into account the diversity of effects of the FTO SNP on BMI depending on the characteristics of the population as well as the gap in knowledge regarding the modulation of this association by education status, our aims were: 1) To study the association between the FTO rs9939609 SNP and BMI in three independent samples of the same Mediterranean population that differ in socio-demographic and anthropometric characteristics in order to estimate the homogeneity/heterogeneity of the association; 2) To study the interaction of educational level on the association of the rs9939609 SNP with BMI and obesity in these samples.

## Methods

### Subjects and study design

We included Caucasian subjects from three independent Mediterranean samples 1580 subjects from the general population (GP), 203 severely obese patients from a hospital (OHP) and 1027 elderly subjects with high cardiovascular risk (HCR). All participants gave their informed consent. The ethics committee of the University of Valencia approved the studies.

#### Subjects from the GP

We studied 1580 unrelated subjects (757 men and 823 women) participating in a previous study (EPIGEM Study) aimed at ascertaining the prevalence of both genetic and environmental cardiovascular risk factors in this Mediterranean population [30]. Participants (aged 18–70 y; mean age: 41.2±13.8 y) were apparently healthy, unrelated subjects residing or working in the Valencia region (East Mediterranean coast of Spain), recruited between 2000 and 2006.

#### OHP

We studied 203 unrelated obese patients (37 men and 166 women), aged 18–68 y (mean age: 46.3±14.7 y) referred to the Endocrinology Unit of the University General Hospital in Valencia (from May 2001 to June 2003), for diagnostic and weight reduction treatments related to obesity and who agreed to take part in the study, as previously described [31]. Prevalence of morbid obesity (BMI ≥ 40 kg/m<sup>2</sup> in this sample was 51%).

#### Elderly subjects with HCR

1027 unrelated subjects (325 men and 582 women), aged 55–80 y (mean age: 67.3±6.4 y) who participated in the PREDIMED (Prevención con Dieta Mediterránea) study and were consecutively recruited in the Valencia Region from October 2003 to December 2008 were included. Details of

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