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Effect of an *FTO* polymorphism on fat mass, obesity, and type 2 diabetes mellitus in the French MONICA Study

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Abstract

We investigated the association between the rs9939609 (T>A) polymorphism in the *FTO* (fat mass– and obesity-associated) gene and obesity- and type 2 diabetes mellitus–related phenotypes in the French Multinational MONItoring of Trends and Determinants in CArdiovascular Disease (MONICA) Study (n = 3367). In the study, TA or AA subjects had higher body mass index (BMI) ($P = .017$), waist circumference ($P = .017$), and hip ($P = .01$) circumference in an A allele dose-dependent manner. The A allele was also significantly associated with higher plasma insulin levels ($P = .05$), higher insulin resistance index (homeostasis model assessment) ($P = .02$), and higher systolic blood pressure ($P = .003$); but these associations disappeared after adjustment for BMI. In the study, 598 subjects were obese (BMI $\geq$30 kg/m^2); and 2769 subjects were not obese (BMI <30 kg/m^2). Subjects bearing the A allele of rs9939609 had a higher risk of obesity (adjusted odds ratio [95% confidence interval] = 1.29 [1.06-1.58], $P = .01$) compared with TT subjects. Moreover, the homozygous AA genotype of rs9939609 was associated with a higher risk of type 2 diabetes mellitus (odds ratio = 1.45 [1.05-1.99], $P = .02$, 283 subjects with and 2601 subjects without type 2 diabetes mellitus), independently of BMI. In conclusion, the role of the A allele of the *FTO* rs9939609 polymorphism on the risk of obesity and type 2 diabetes mellitus was confirmed in the French MONICA Study.

1. Introduction

For several decades, obesity and type 2 diabetes mellitus (T2D) have been worldwide issues because of their alarming increased prevalence and their associated morbidity (mainly essential hypertension, dyslipidemia, cardiovascular diseases, etc) and mortality. Today, more than 1.1 billion adults worldwide are overweight; and 312 million of them are obese [1]. In addition, at least 155 million children worldwide are overweight or obese, according to the International Obesity Task Force. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [2]. Although the evidence of the heritable character of these diseases has been established, only few reliable genetic determinants have been discovered. The difficulties in finding these determinants can be explained by the presence of complex and abundant interactions between genes and environment in the development of obesity or T2D and also because the genetic determinants of these diseases are multiple and that each confers modest risk.

Two genomewide association studies for T2D identified a highly significant association between the *FTO* rs9939609 polymorphism and T2D [3,4]. The risk of T2D associated with the A allele of rs9939609 was increased by approximately 50% in a Finnish case-control study [3] and by approximately 25% in the Wellcome Trust Case-Control Consortium collection [4]. Interestingly, this predisposition to diabetes was in fact due to an effect on body mass index (BMI) [5]. The A allele of rs9939609 was indeed associated

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with higher BMI (~0.2-0.4 kg/m^2 per A allele). Adults homozygous for the A allele at rs9939609 were at increased risk of being overweight (odds ratio [OR] = 1.38) and obese (OR = 1.67). Similar results were obtained in children cohorts by the age of 7 years [5,6]. Since then, several publications have confirmed the influence of *FTO* polymorphisms on fat mass in different population samples [7-11]. Lopez-Bermejo et al [12] showed that an *FTO* single nucleotide polymorphism (SNP) was associated with weight and ponderal index as early as 2 weeks of age. Jacobsson et al [13] showed that rs9939609 predisposed to obesity in girls but not in boys in a sample of 450 obese and 512 nonobese Swedish children. In contrast, in Chinese Han or in African American subjects, rs9939609 was not associated with T2D or obesity-related phenotypes despite sufficient power in the studies [7,14]. The minor allele frequency of this SNP being much lower in these ethnic population samples (0.20) than in white subjects (0.40), the absence of replication in these population samples could be due to an evolutionary divergence or genetic drift. It remains also possible that other common variants in the *FTO* gene, especially those with higher minor allele frequency, may contribute to the increased risk for obesity or T2D in Chinese or African Americans, similar to the *TCF7L2* gene [15].

All the described *FTO* polymorphisms associated with T2D or BMI are in tight linkage disequilibrium (HapMap release 23, March 2008), including rs9939609, rs1121980, rs17817449, rs3751812, and rs1421085 (r^2 >0.8). Therefore, we investigated the association between the *FTO* rs9939609 polymorphism and the risk of obesity and T2D as well as clinical and biochemical phenotypes in the French Multinational MONItoring of Trends and Determinants in CArdiovascular Disease (MONICA) population study.

2. Materials and methods

2.1. MONICA Study

Participants were recruited as part of the World Health Organization–MONICA population survey conducted from 1995 to 1997 in 3 different parts of France: the Lille urban community in northern France (n = 1195), the Bas-Rhin county in eastern France (n = 1131), and the Haute-Garonne county in southern France (n = 1182). The protocol was approved by the appropriate independent ethics committee in each center. Subjects (aged 35-64 years) were randomly selected from electoral rolls after stratification by town size, sex, and age to obtain 200 participants for each sex and each 10-year age group (World Health Organization–MONICA Project protocol) [16]. DNA samples were available for 3452 subjects. After providing written informed consent, participants filled out a standard questionnaire; and physical measurements were taken by a specially trained nurse. Details of the study have been described elsewhere [17]. *Physical activity* was defined as at least 15-minute walk a day, and/or lifting or carrying heavy objects at work daily, and/or doing sport or physical exercise for more than 2 hours a week. In terms of smoking exposure, subjects were categorized as never smokers, former smokers, and current smokers (ie, subjects reporting at least 1 cigarette per day). Total alcohol intake was expressed as the sum of milliliters of alcohol per week from wine, beer, cider, and spirits. Anthropometric measurements included body weight (rounded to the nearest even decimal) and waist girth (at a level midway between the lower rib margin and the iliac crest, to the nearest 0.5 cm) and were performed on subjects in light clothing without shoes. Body mass index was calculated according to the Quetelet equation. Subjects having a BMI greater than or equal to 30 kg/m^2 were considered as obese. Blood pressure was measured on the right arm, with the subject in a sitting position and after a minimum 5-minute rest, using a standard mercury sphygmomanometer. The mean value of 2 consecutive blood pressure readings was taken into account. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as the product of fasting plasma insulin (in microunits per milliliter) and fasting plasma glucose (in millimoles per liter), divided by 22.5 [18]. Diabetic subjects (n = 283) were identified by fasting glycemia of at least 7 mmol/L (1.26 g/L) or antidiabetic treatment [19]. Normoglycemic subjects (n = 2601) had fasting glycemia less than 6.1 mmol/L (1.10 g/L) and no specific treatment or diet for T2D, whereas individuals with raised fasting glycemia (n = 261) had fasting glycemia between 6.1 and 7 mmol/L. A total of 222 subjects had type 1 diabetes mellitus, nonfasting blood samples, or missing values and were not used in the T2D analyses.

2.2. Laboratory methods

A 20-mL blood sample was drawn into a disodium EDTA tube (after the subjects had fasted for at least 10 hours), stored at room temperature, and centrifuged within 4 hours. All measurements were performed at the Purpan Hospital Biochemical Laboratory (Toulouse). The quality of biological measures was assessed within the framework of the MONICA Project. Plasma total cholesterol and triglyceride levels were measured using enzyme assays (Boehringer Mannheim, Mannheim, Germany). Plasma high-density lipoprotein (HDL) cholesterol was measured after sodium phosphotungstate/magnesium chloride precipitation (Boehringer Mannheim). Plasma low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald equation. Plasma glucose was measured using the standard glucose hexokinase method (DuPont Dimension, Brussels, Belgium). Plasma insulin was measured by radioimmunoassay (Medgenix Diagnostics, Brussels, Belgium).

2.3. Genotyping

The *FTO* rs9939609 polymorphism was genotyped with a restriction fragment length polymorphism–based method. The 105–base pair polymerase chain reaction product was obtained using the following primers : 5′-GGT TCC TTG

CGA CTG CTG TGA AAT T-3′ and 5′-GCT TTT ATG CTC TCC CAC TC-3′. The forward primer created a forced restriction site for *Apo*I. The T allele of rs399609 was cut by *Apo*I into 2 fragments of 85 and 20 base pairs, whereas the A allele was not cut. Genotyping success rate was 98.4%. Genotypes for rs9939609 were available for 1149, 1049, and 1169 subjects in MONICA Lille, Strasbourg, and Toulouse, respectively.

2.4. Statistical analyses

Analyses were performed with the SAS statistical software release 8 (SAS Institute, Cary, NC). The deviation from the Hardy-Weinberg equilibrium was tested using the χ^2 test (1 *df*). Pearson χ^2 tests were used to compare genotype and allele distributions between groups. Heterogeneity among centers was assessed with the Breslow-Day test. We calculated the association between *FTO* genotypes and risk of obesity or T2D (ORs and 95% confidence intervals) using unconditional logistical regression. Comparison of means among genotype groups was tested using an additive model. Confounding variables were age, sex, physical activity level, smoking habit, alcohol consumption, and center ± BMI. Subjects treated with cholesterol-lowering drugs, oral antidiabetic drugs, insulin, or blood pressure–lowering therapy (n = 801) were excluded when considering quantitative biological variables.

3. Results

The frequencies of the TT, TA, and AA genotypes of rs9939609 were 0.33, 0.49, and 0.18 in MONICA Strasbourg; 0.31, 0.53, and 0.16 in MONICA Toulouse; and 0.33, 0.50, and 0.17 in MONICA Lille, respectively (P = .32 for the comparison between centers). The genotypic distribution did not differ from the expected values of the Hardy-Weinberg equilibrium either in MONICA Lille (P = .34) or in MONICA Strasbourg (P = .99). The distribution of rs9939609 did not respect the Hardy-Weinberg equilibrium in MONICA Toulouse (P = .009), although the minor allele frequency of rs9939609 was similar in Toulouse as in the 2 other centers (0.43, 0.43, and 0.42 in MONICA Strasbourg, Toulouse, and Lille, respectively). The mean BMI was lower in subjects from the Toulouse center compared with the Strasbourg and Lille centers (25.5 ± 4.2 vs 27.0 ± 4.6 and 26.6 ± 5.0 kg/m^2, respectively, P < .0001), and the Hardy-Weinberg equilibrium was respected in the Toulouse center when considering the group of lean subjects (P = .16).

We evaluated the association between rs9939609 and anthropometric (BMI, body weight, waist circumference), biochemical, and clinical variables (plasma glucose, insulin, lipids, and blood pressure) in the MONICA Study (Table 1). The A allele of rs9939609 was significantly associated with higher body weight (P trend = .0009), waist circumference (P trend = .001), hip circumference (P trend = .02), waist-hip ratio (P trend = .02), and BMI (P trend = .005) in an A allele dose-dependent manner (eg, +∼0.3 kg/m^2 per A allele for BMI). These associations persisted for all parameters except waist-hip ratio after adjustment for age, sex, alcohol consumption, smoking habit, physical activity level, and center but became nonsignificant after further adjustment for BMI (Table 1). The associations between rs9939609 and the anthropometric measurements were similar whatever the level of insulin resistance of the subjects (assessed using tertiles of HOMA-IR) (data not shown). The A allele was also significantly associated with higher plasma insulin levels (P trend = .05), higher insulin resistance (HOMA index) (P trend = .03), and higher systolic blood pressure

Table 1
Association between the *FTO* rs9939609 SNP and anthropometric and biochemical variables in the French MONICA Study

	TT 1095	TA 1702	AA 570	Crude *P* trend	Adjusted[a] *P* trend	Adjusted[a] (including BMI) *P* trend
Weight, kg	72.9 ± 14.4	73.8 ± 15.4	75.5 ± 14.9	.0009	.009	.71
Waist, cm	89.3 ± 13.2	90.3 ± 13.8	91.6 ± 13.5	.001	.006	.83
Hip, cm	101.1 ± 9.4	101.7 ± 9.8	102.3 ± 9.6	.02	.004	.45
Waist-hip ratio	0.88 ± 0.10	0.89 ± 0.09	0.89 ± 0.09	.02	.28	.67
BMI, kg/m^2	26.1 ± 4.5	26.4 ± 4.7	26.8 ± 4.7	.005	.005	–
	851	1276	439			
Insulin[b], μU/mL	10.49 ± 6.58	10.58 ± 9.70	11.31 ± 10.09	.05	.055	.32
Glucose[b], mmol/L	5.32 ± 0.81	5.34 ± 1.13	5.44 ± 1.06	.06	.29	.56
HOMA-IR[b]	2.49 ± 1.77	2.57 ± 3.00	2.74 ± 2.35	.03	.05	.30
Triglycerides[b], mmol/L	1.24 ± 0.98	1.23 ± 1.07	1.37 ± 2.11	.48	.90	.37
Cholesterol, mmol/L	5.85 ± 1.00	5.86 ± 1.08	5.82 ± 1.02	.69	.51	.49
HDL cholesterol, mmol/L	1.50 ± 0.43	1.51 ± 0.47	1.47 ± 0.44	.42	.70	.26
LDL cholesterol, mmol/L	3.82 ± 0.96	3.83 ± 1.02	3.81 ± 0.98	.93	.48	.46
SBP, mm Hg	128.3 ± 17.5	128.4 ± 16.6	131.4 ± 18.9	.007	.03	.08
DBP, mm Hg	80.8 ± 11.4	80.9 ± 10.8	82.1 ± 11.5	.08	.15	.40

Data are means ± SD. Subjects treated with cholesterol-lowering drugs, oral antidiabetic drugs, insulin, or blood pressure–lowering therapy were excluded when considering biological variables. SBP indicates systolic blood pressure; DBP: diastolic blood pressure.

[a] P adjusted for age, sex, alcohol consumption, smoking habit, physical activity level, and center.

[b] P values were calculated on log-transformed variables to obtain normal distribution.

(*P* trend = .007); but these associations disappeared after adjustment for BMI. No significant association could be found between rs9939609 and fasting plasma glucose, total cholesterol, LDL and HDL cholesterol, or triglyceride levels.

We next evaluated the association between rs9939609 and obesity risk in the MONICA Study. There was no detectable heterogeneity among centers (*P* = .48). The overall genotype distribution of rs9939609 differed between lean, overweight, and obese subjects (*P* trend = .005) (Table 2). The crude OR [95% confidence interval] of obesity (BMI ≥30 kg/m^2) for A allele carriers was 1.25 [1.03-1.52] (*P* = .024) and was 1.29 [1.06-1.58] (*P* = .01) after adjustment for confounders. The adjusted OR of obesity was 1.46 [1.12-1.90] (*P* = .005) in homozygous AA subjects compared with TT subjects. Physical activity level had no influence on the association, as the adjusted ORs of being obese for A allele carriers were 1.28 [0.92-1.81] or 1.30 [1.02-1.66] in subjects with or without physical activity, respectively. There was no significant interaction with sex (*P* = .60), and the association with the risk of obesity was similar in both men and women (OR = 1.32 [0.99-1.75] and OR = 1.25 [0.95-1.66] in men and women, respectively).

Finally, we evaluated the association between rs9939609 and the risk of T2D. We compared the genotype distribution of rs9939609 among subjects with normal fasting glycemia (n = 2601), raised fasting glycemia (n = 261), or T2D (n = 283) (*P* = .97 for the test of heterogeneity between centers) (Table 2). The genotype distribution was not significantly different between the 3 subject groups (*P* trend = .08). The adjusted OR of T2D for A allele carriers was 1.06 [0.81-1.39] (*P* = .67 compared with TT subjects). Only AA homozygous subjects had a significantly higher risk of T2D than T allele bearers (crude OR = 1.48 [1.10-1.99], *P* = .01 and OR = 1.45 [1.05-1.99], *P* = .02 after adjustment for age, sex, BMI, alcohol consumption, smoking habit, physical activity level, and center).

4. Discussion

In our study, we confirmed the association between the *FTO* rs9939609 polymorphism and a higher risk of obesity in the French MONICA Study. The frequency of the A allele of rs9939609 was 0.42 in our sample, consistent with previous reports [3,5,6]. The A allele was associated with a 30% higher risk of obesity. This association was homogenous between sexes. Moreover, the A allele of rs9939609 was significantly associated with higher BMI, in an A allele dose-dependent manner (BMI +∼0.3 kg/m^2 per A allele), in a magnitude similar as previously described studies (0.2-0.4 kg/m^2 per A allele) [5,6,11]. It was also associated with higher waist and hip circumferences but not with higher waist-hip ratio, suggesting that fat tended to accumulate in all depots in A allele carriers. Andreasen et al [11] showed that physical inactivity accentuated the deleterious effect of *FTO* on fat mass accumulation in Danes; but we could not replicate this finding in the French MONICA Study, although physical activity was self-reported in both studies. Other studies using direct measures of physical activity are needed to evaluate this particular point.

It has been shown that AA subjects had lower whole-body insulin sensitivity than T allele carriers and that a low insulin sensitivity index enhanced the deleterious genotype effect on BMI levels [11]. Like others [8,11,13], we detected significant associations between rs9939609 and insulin-related variables (plasma insulin levels and insulin resistance index) as well as systolic blood pressure values; but these associations were purely the reflection of the effect of *FTO* on BMI, as they became nonsignificant after adjustment for BMI. Moreover, the effect of the rs9939609 A allele on anthropometric phenotypes was similar whatever the tertile of insulin resistance.

FTO is located on chromosome 16q12.2 in humans. It is expressed in many tissues such as adipose tissue, brain, liver, skeletal, β-cells, and muscle [5,6]. Fto is expressed in hypothalamic nuclei governing energy balance and is regulated by fasting and feeding in mice [20]. It has a role in nucleic acid demethylation [20], but more studies are needed to understand the link between nucleic acid methylation status and fat mass regulation. In addition, it has been shown that the A allele of rs9939609 is associated with lower in vitro basal unstimulated adipocyte glycerol release and increased in vivo lipolytic activity in women, suggesting that *FTO* may participate, at least in part, in the regulation of body fat mass through lipolysis [21].

Finally, regarding T2D, only the *FTO* homozygous AA genotype was associated with a 48% higher risk of T2D in the French MONICA Study. The association with T2D was seen only under a recessive model, but the relatively small number of subjects with T2D in the sample (n = 283) might explain this outcome. This risk was in accordance with 2 previous studies (OR ∼1.25 in the United Kingdom Wellcome Trust Case-Control Consortium collection and OR ∼1.50 in Finns) [3,4]. However, unlike the data presented by Frayling et al [5] or others, the present association with T2D persisted after adjustment for BMI (risk still increased by 45%) or waist circumference (data not shown), meaning that the present association with T2D was not purely the reflection of the association with BMI in our

Table 2
Association between the *FTO* rs9939609 SNP and overweight, obesity, or T2D in the French MONICA Study

	TT	TA	AA	*P* trend
BMI <25 (1460)	491 (0.34)	746 (0.51)	223 (0.15)	.005
25 ≤ BMI < 30 (1309)	433 (0.33)	649 (0.50)	227 (0.17)	
BMI ≥30 (598)	171 (0.29)	307 (0.51)	120 (0.20)	
NFG (2601)	844 (0.33)	1327 (0.51)	430 (0.16)	.08
RFG (261)	80 (0.31)	134 (0.51)	47 (0.18)	
T2D (283)	89 (0.31)	130 (0.46)	64 (0.23)	

Data are number (frequency). Crude *P* values are presented. NFG indicates normal fasting glycemia; RFG, raised fasting glycemia.

sample. One can assume that *FTO* polymorphisms could also be associated with diabetes-related phenotypes other than fat mass. Recently, Fisher and colleagues [22] showed that the A allele of rs9939609 was associated with higher plasma C-reactive protein levels in 2415 participants, independently of BMI or waist-hip ratio. This *FTO* polymorphism may enhance the inflammatory state of adipose tissue and may increase systemic inflammation, independently of the degree of adiposity. As C-reactive protein is an independent predictor of risk for the development of T2D [23] and cardiovascular diseases, *FTO* polymorphisms might contribute partly to the development of increased T2D and cardiovascular risk, independently of obesity.

In conclusion, our study confirmed the role of the genetic variability in *FTO* in the modulation of the risk of obesity and T2D in a large French population sample.

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