Fat Mass–and Obesity-Associated (FTO) Gene Variant Is Associated With Obesity

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**ORIGINAL ARTICLE**

**Fat Mass– and Obesity-Associated (FTO) Gene Variant Is Associated With Obesity**

**Longitudinal Analyses in Two Cohort Studies and Functional Test**

Lu Qi,1,2 Kihwa Kang,3 Cuilin Zhang,4 Rob M. van Dam,1,2 Peter Kraft,2,5 David Hunter,1,2,5 Chih-Hao Lee,3 and Frank B. Hu1,2,5

OBJECTIVE—To examine the longitudinal association of fat mass– and obesity-associated (FTO) variant with obesity, circulating adipokine levels, and FTO expression in various materials from human and mouse.

RESEARCH DESIGN AND METHODS—We genotyped rs9939609 in 2,287 men and 3,520 women from two prospective cohorts. Plasma adiponectin and leptin were measured in a subset of diabetic men (n = 854) and women (n = 987). Expression of FTO was tested in adipocytes from db/db mice and mouse macrophages.

RESULTS—We observed a trend toward decreasing associations between rs9939609 and BMI at older age (≥65 years) in men, whereas the associations were constant across different age groups in women. In addition, the single nucleotide polymorphism (SNP) rs9939609 was associated with lower plasma adiponectin (log[e]− means, 1.82 ± 0.04, 1.73 ± 0.03, and 1.68 ± 0.05 for TT, TA, and AA genotypes, respectively; P for trend = 0.02) and leptin (log[e]− means, 3.56 ± 0.04, 3.63 ± 0.04, and 3.70 ± 0.06; P for trend = 0.06) in diabetic women. Adjustment for BMI attenuated the associations. FTO gene was universally expressed in human and mice tissues, including adipocytes. In an ancillary study of adipocytes from db/db mice, FTO expression was ~50% lower than in those from wild-type mice.

CONCLUSIONS—The association between FTO SNP rs9939609 and obesity risk may decline at older age. The variant affects circulating adiponectin and leptin levels through the changes in BMI. In addition, the expression of FTO gene was reduced in adipocytes from db/db mice. *Diabetes* 57:3145–3151, 2008

In a recent genome-wide association study, Frayling et al. (1) identified a common variant in fat mass– and obesity-associated (FTO) gene (rs9939609) that was related to higher BMI in both children and adults. In addition, adiposity appeared to mediate the association between FTO variant and the risk of type 2 diabetes (2,3). Several other studies have also observed associations between FTO variants and obesity-related traits in various populations (4–13).

Because most available data are cross-sectional, the longitudinal pattern of the associations between FTO variants and adiposity and age-specific genetic effects are not clearly defined. The primary aim of the present study is to address these issues by assessing the genetic effects in two prospective cohorts. Obesity status affects the endocrine function of adipose tissue by altering the secretion of adipokines, such as adiponectin and leptin, which have been related to ectopic fat accumulation, insulin sensitivity, and diabetes risk in epidemiological studies (14–16). We therefore examined the associations of FTO variant with circulating levels of adiponectin and leptin. In addition to the association analyses, to shed light on its potential functions, we also examined the expression of FTO gene in various tissues from humans and mice and investigated the expression in adipocytes from db/db mice and mouse macrophages in response to inflammatory stimulants.

**RESEARCH DESIGN AND METHODS**

The Nurses’ Health Study (NHS) was established in 1976 when 121,700 female registered nurses aged 30–55 years and residing in 11 large U.S. states completed a mailed questionnaire on their medical history and lifestyle (17). Between 1989 and 1990, 32,826 women provided blood samples. The Health Professional Follow-Up Study (HPFS) is a prospective cohort study of 51,529 U.S. male health professionals aged 40–75 years at study initiation in 1986 (18). Between 1986 and 1989, 18,159 men provided blood samples. Information about health and disease is assessed biennially by self-administered questionnaires in both cohorts.

Diabetes cases were defined as self-reported diabetes confirmed by a validated supplementary questionnaire. For cases occurring before 1998, the diagnosis was made using criteria proposed by the National Diabetes Data Group (19). Medical record review confirmed 98% of the diagnoses. We used the American Diabetes Association diagnostic criteria for diagnosis after the 1998 cycles (20). Subjects for the present study were selected from those who provided blood samples and were free from cardiovascular disease or cancer at baseline. Healthy control subjects were matched on age and the time of blood drawing with diabetic patients. To reduce potential bias due to population stratification, we included only Caucasians of European ancestry.
In total, 1,506 female and 1,076 male diabetic patients and 2,014 female and 1,211 male nondiabetic control subjects were included. **Assessment of adiposity.** At baseline (1976 for the NHS and 1986 for the HPFS), participants were asked to report their height and current body weight; the self-reported weight was then updated every 2 years during the follow-up through 2002 (1976, 1978, 1980, 1982, 1986, 1988, 1990, 1992, 1994, 1996, 1998, 2000, and 2002 in the NHS; and 1986, 1988, 1990, 1992, 1994, 1996, 1998, 2000, and 2002 in the HPFS) using self-administered questionnaires. To assess the adiposity in early adulthood, the 1980 NHS questionnaire asked about weight at 18 years of age (n = 3,337), and the 1986 HPFS questionnaire asked about weight at 21 years of age (n = 2,194). We calculated BMI as weight in kilograms divided by height squared in meters. In 1986–1987, participants in the NHS (n = 2,335) and HPFS (n = 1,888) reported direct measurements of their waists (at the umbilicus) and hips (at the largest circumference) to the nearest quarter of an inch, using a paper tape and detailed measuring directions. The validity of self-reported adiposity measures were assessed in a random sample living in the greater Boston area, with high correlation with measured weight (r ≥ 0.96) and waist (r = 0.95) (21,22). We defined obesity as BMI ≥ 30 kg/m². **Assessment of biomarkers.** Blood samples were collected between 1988 and 1990 in NHS and between 1993 and 1999 in HPFS, as previously described (23,24). Biomarkers were measured in a subset of diabetic men (n = 554) and women (n = 987). Plasma adiponectin concentration was measured by competitive radioimmunoassay (RIA; Linco Research, St. Charles, MO) with a coefficient of variation (CV) of 3.4%. Leptin was assayed by RIA (Linco Research) with intra-assay CV of 3.4–8.3%. A1C values were determined based on turbidimetric immunoinhibition using hemolyzed whole blood or packed red cells. The day-to-day variability at A1C concentrations of 5.5 and 9.1% was 1.9 and 3.0%, respectively. **Single nucleotide polymorphism selection and genotype determination.** To date, five single nucleotide polymorphisms (SNPs) in FTO genes have been reported to be associated with obesity traits. These SNPs are in strong to perfect linkage disequilibrium. We therefore selected one SNP, rs9939606, which was not in linkage disequilibrium with known obesity risk loci in the genome-wide association (GWA) study, as a proxy for other SNPs (pairwise r² with rs9939606: rs17817449, 1.00; rs1421085, 0.97; rs7571812, 1.00; and rs9035066, 0.84; HapMap, Centre d’Etude du Polymorphisme Humain [CEPH]). DNA was extracted from the buffy coat fraction of centrifuged blood using the QiAmp Blood kit (Qiagen, Chatsworth, CA). The SNP was genotyped using TaqMan SNP allelic discrimination by means of an ABI 7900HT (Applied Biosystems, Foster City, CA). The internal quality of genotype data was assessed by typing 10% blinded samples in duplicate; resulting concordance was >99%. The call rate was >95%, and genotype distribution was in Hardy-Weinberg equilibrium (χ² test). **Real-time RT-PCR and analyses of experimental data.** Mouse tissues were collected from wild-type (n = 3; C57BL/6 strain mice obtained from The Jackson Laboratories [Bar Harbor, ME]) and db/db mice (n = 3, 3 months old, male), a genetic model of obesity and type 2 diabetes. Mouse 3T3-L1 adipocytes were differentiated in media containing insulin, dexamethasone, and isobutylmethylxanthine for 8 days. Human adipocytes were differentiated from preadipocytes (obtained from a cell line maintained by Cambrex) in a similar manner. Mouse macrophages were generated from bone marrow of wild-type mice as described previously (25). Macrophages were cultured in Dulbecco’s modification of Eagle’s medium and 10% fetal bovine serum and treated with γ-interferon (IFN-γ) at a dose of 2 ng/ml overnight. Lipopolysaccharide (LPS; 10 ng/ml) was then added for an additional 8 h. RNA was isolated using TRIzol (Invitrogen) and reverse transcribed with the Quantitect RT kit (Qiagen). Human tissue (brain, heart, lung, liver, spleen, intestine, kidney, muscle, leukocytes, preadipocytes, and adipocytes) cDNAs were purchased from Clontech (multiple choice cDNA). SYBR green–based real-time PCRs were conducted using RealMasterMix (Eppendorf) and detected by the 7300 Real-Time PCR system (Applied Biosystems). The expression of the 36B4 gene, which is a housekeeping gene to serve as a control, was used for normalization to obtain relative expression levels. The slope of efficiency curves for human FTO gene is ~3.4 and for mouse is ~3.6 (~4 ± mean PCR product doubles each cycle). Oligo sequences used were as follows: human FTO, 5′-TTAATTCCACCCACGGATGT-3′ and 5′-ACATCTCCAGGCAACACTG-3′; mouse FTO, 5′-ATCAGATTAGAAGCTGTGCG-3′ and 5′-CCAATGCCTACAAGTATCAGG-3′; and 36B4, 5′-AGATGCAGCAGATCGCAT-3′ and 5′-GTCTCTTGCACATGCAGC-3′. For gene expression analyses, values are presented as means ± SE (n = 3), and group means were compared using Student’s t test. The SAS statistical package was used for the analyses (SAS, version 8.2 for UNIX). Statistical significance was set at the 0.05 level, and all tests were two-tailed. **Statistical analyses.** Similar associations between FTO SNP rs9939606 and BMI were previously reported in diabetic patients and control subjects (1) and were also observed in our cohorts. Thus, we pooled diabetic and nondiabetic subjects in the analyses. The geometric means of BMI and waist circumference were compared among the genotypes using general linear models, adjusting for age and diabetes status. In the multivariable analyses, we also adjusted for physical activity (quintiles), smoking (never, past, and current), alcohol intake (non-drinker and drinker [0–4, 5–10, >10 g/day]), family history of diabetes (yes/no), and menopausal status (pre- or postmenopausal [never, past, or current hormone use]; women only). Crude associations between genotype and binary outcomes (obesity and diabetes) were tested using Pearson’s χ² statistic, and unconditional logistic regression was used to test for association after adjusting for covariates. General linear models were used to compare the genotype difference in biomarkers (adiponectin and leptin) among diabetic patients, adjusting for age, BMI, physical activity, smoking, alcohol intake, duration of diabetes, A1C, and menopausal status (women only). Plasma adiponectin and leptin levels were logarithmically transformed to achieve a normal distribution. The geometric means of the back-transformed values were presented. We used generalized estimating equations (GEEs) to analyze the associations between the genotypes and longitudinal BMI values (26,27). The analysis used the biennially collected repeated measurements of BMI from 1976 to 2002 in the NHS and from 1986 to 2002 in the HPFS. We used exchangeable correlation structure to account for the correlation of the repeated measures. Interaction between genotype and age was tested by creating a product term of the two variables in the model. **RESULTS** Table 1 shows the baseline characteristics of the participants by sex and diabetes status. The frequency of rs9939609 allele A in the study populations was 0.44, similar to the HapMap population frequency of 0.45 in the CEPH and other European populations (1,4). **Associations with adiposity at early and middle adulthood.** Table 2 shows the associations of SNP rs9939609 with BMI (n = 2,236 and 3,483 in men and women, respectively) and waist circumference (n = 1,898 and 2,333 in men and women, respectively) in 1986/1987, when both measures were available in the NHS and HPFS, and with BMI at early adulthood (n = 2,194 and 3,337 in men and women, respectively). The SNP was associated

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<th>Women (NHS)</th>
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<td><strong>Participants (n)</strong></td>
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<td>1,211</td>
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<td>Age (years)</td>
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<td>Physical activity*</td>
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<td>Alcohol consumption (g/day)</td>
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<td>Family history of diabetes</td>
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Data are n, means ± SD, and percent. Cohort baseline, 1976 for the NHS and 1986 for HPFS; physical activity and alcohol consumption were obtained from the 1980 questionnaire in NHS. *In hours of physical activity at least moderate intensity per week for women and in MET hours per week for men.
with higher BMI and waist circumference in women, under an additive inheritance model. In men, rs9939609 was associated with a higher BMI. SNP rs9939609 was also associated with higher BMI at early adulthood in men and women (Table 2). Although the genetic effects in men seemed not to fit well with the additive model, testing for the departure from the additive model was not significant. Because smoking may affect adiposity, we excluded current smokers in sensitivity analyses but did not find appreciable changes in the associations.

We further assessed the relation between rs9939609 and obesity risk (in 1986/1987). The AA homozygotes were associated with 1.75 (1.26–2.45) and 1.71 (1.36–2.16) times higher obesity risk (in 1986/1987). The AA homozygotes were associated with 1.57 (1.22–2.03) and 1.84 (1.40–2.40) times higher overweight risk in men and women, respectively. We further assessed whether the associations between SNP rs9939609 and adiposity were consistent across different age groups (Figs. 2 and 3). It appears that the association between the SNP and obesity risk declined with older age especially in men, although tests for interaction between SNPs and age were not significant (Table 3).

**Associations with longitudinal measurements of adiposity.** rs9939609 was associated with higher BMI during the 26 years of follow-up in women (1976–2002) and was associated with BMI at nearly all time points during 16 years of follow-up in men (1986–2002) except in 1988 and 1998 (supplementary Fig. 1, which is available in an online appendix at http://dx.doi.org/10.2337/db08-0006). Similarly, the AA genotype was associated with greater obesity risk during the follow-up in women and men (except at 1992, 1996, and 2000 in men) (supplementary Fig. 2).

In longitudinal analyses using GEEs, associations were observed between rs9939609 and BMI and the obesity risk in both sexes (Table 3). Each allele A was associated with 0.25 (SE = 0.11; P = 0.03) and 0.59 (SE = 0.13; P < 0.0001) kg/m² higher BMI, as well as 1.17 (1.05–1.38)–fold (P = 0.007) and 1.19 (1.07–1.31)–fold (P = 0.0008) higher risk of obesity in men and women, respectively. We further examined whether the associations between SNP rs9939609 and adiposity were consistent across different age groups (Figs. 2 and 3). It appears that the association between the SNP and obesity risk declined with older age especially in men, although tests for interaction between genotypes and age were not significant (P = 0.20 for men and 0.08 for women).

**Case-control studies on type 2 diabetes.** In the crude analyses, the TT and AA genotypes were associated, respectively, with a 1.17 (1.01–1.36)–fold and 1.24 (1.02–1.50)–fold higher risk of type 2 diabetes compared with the TA genotype in women (P for trend = 0.019) (Table 4). The associations between FTO genotypes and diabetes risk became nonsignificant when adjusted for BMI. However, adjusting for other diabetes risk factors, such as age, smoking, alcohol consumption, and physical activity, did not alter the association for diabetes. This SNP was not associated with diabetes risk in men.

**Associations with adipokine concentrations in patients with type 2 diabetes.** We further assessed whether FTO SNP rs9939609 was associated with adipose-secreted adipokines. We measured leptin and adiponectin in a subset of patients with type 2 diabetes (987 women and 854 men). In women, the FTO genotypes were associated with lower leptin concentrations, and higher adiponectin concentrations.
Associated with lower plasma adiponectin levels (log[10]-transformed means: 1.82 \pm 0.04, 1.73 \pm 0.03, and 1.68 \pm 0.05 for TT, TA, and AA genotypes, respectively; \( P = 0.02 \)), adjusting for age (Fig. 4). The association remained when adjusted for smoking, alcohol consumption, physical activity, duration of diabetes, A1C, and menopausal status. Further adjustment for BMI attenuated the association. Allele A tended to be associated with higher leptin levels, with borderline significance. The genotype-associated difference in leptin disappeared when adjusted for BMI. In men, we did not find associations between \( FTO \) genotypes and adipokine levels.

\( FTO \) gene expression profile and in tissues/cells with high metabolic capacities. To shed light on its potential role in adiposity, we conducted expression profiling of the \( FTO \) gene in human and mouse tissues and found similar expression patterns between the two species (supplementary Fig. 3). \( FTO \) was present at high levels in several metabolically active tissues (from humans and wild-type C56BL/6 mice), including brain, heart, kidney, and adipose tissue, with the highest expression in brain from humans and mice. In white adipose tissue isolated from \( db/db \) mice, \( FTO \) expression was reduced by \(-50\%\) compared with lean wild-type controls (Fig. 5A). Interestingly, \( FTO \) is also expressed by macrophages and was induced by inflammatory stimulants, IFN-\( \gamma \), and LPS (Fig. 5B).

**DISCUSSION**
In this study, we confirmed that the SNP rs9939609 was associated with higher BMI and obesity risk (1) in men and women from two independent U.S. cohorts. Frayling et al. (1) observed that the \( FTO \) genotype–associated difference in BMI occurred as early as 7 years old. We observed associations between \( FTO \) SNP and high BMI in early adulthood. The genetic effects were constant across different ages in women but tended to decrease at older ages in men. The mechanisms underlying this observation are not clear. A longitudinal twin study suggests that the metabolic effects may be more pronounced during early childhood.
genetic components regulating body weight may vary throughout life (28) and decrease with advanced age (29,30). Adiposity loss with age may partly explain the reduction in association at senior age. In addition, environmental influences accumulate with age and likely exert stronger influences on later BMI. It appears that the decreasing trend of BMI with advanced age is more pronounced in men than in women, but the test for interaction between sex and \( FTO \) was not statistically significant.

In women, rs9939609 was associated with greater risk of type 2 diabetes. Adjustment for BMI abolished the association. This finding is consistent with the observations from recent GWA studies (2,3), supporting the idea that obesity mediates the effects of \( FTO \) variant on the development of type 2 diabetes.

Adipose tissue acts as endocrine organ through secreting hormone-like adipokines, which mediate the effects of obesity on various metabolic disorders (31). Adiponectin is the most abundant adipokine in the circulation (32). Adiponectin improves insulin action and metabolism of glucose and lipids (33,34). Low blood adiponectin levels have been related to increased risk of obesity and diabetes (35,36). Our data indicated that low adiponectin levels associated with the risk allele A were secondary to the changes in BMI and may partly mediate the genetic effects on diabetes risk. The association between \( FTO \) SNP and adiponectin was observed in diabetic patients. Future studies are warranted to replicate the findings in the general population.

Little is known about the function of \( FTO \) gene. Our data comparing both human and mouse genes confirm high expression of \( FTO \) gene in brain (1). Gerken et al. (37) recently demonstrated that \( FTO \) was highly expressed in arcuate, paraventricular, dorsomedial, and ventromedial nuclei. Of note, all of these sites are of critical importance in controlling energy balance. These data suggest \( FTO \) gene may affect the neuroregulation of energy balance. In addition, \( FTO \) expression was high in heart, kidney, and adipose tissues (particularly brown fat in mice).

The expression of \( FTO \) was moderately increased in adipocytes compared with preadipocytes and was substantially reduced in white adipose tissues of obese, diabetic \( db/db \) mice, indicating that it may play a role in adipocyte function but not adipogenesis. The mechanism underlying the reduced expression of \( FTO \) in adipocytes from the genetic models with direct interruptions of the

![FIG. 4. The geometric means (SEs) of plasma adiponectin and leptin levels (log-transformed) by the genotypes of \( FTO \) SNP rs9939609 among women with type 2 diabetes. The multivariate analyses were adjusted for age, physical activity (quintiles), smoking (never, past, and current), alcohol intake (non-drinker and drinker [0.1–4.9, 5–10, or >10 g/day]), duration of diabetes, A1C, and menopausal status (pre- or postmenopausal [never, past, or current hormone use]).](image)

![FIG. 5. Regulation of \( FTO \) expression by genetic obesity and inflammatory stimulants. A: \( FTO \) is downregulated in adipose tissue of \( db/db \) mice. Adipose tissue was harvested from lean wild-type (\( n = 3 \)) and obese, diabetic \( db/db \) mice (\( n = 3 \)), and gene expression was determined by real-time RT-PCR. B: \( FTO \) is induced by proinflammatory stimulants in the macrophages. Bone marrow–derived wild-type mouse macrophages were incubated with or without 2 ng/ml IFN-\( \gamma \) overnight followed by 10 ng/ml LPS treatment for 8 h. The experiments were done in triplicate. * \( P < 0.05 \).](image)
FTO GENE VARIANT IS ASSOCIATED WITH OBESITY

leptin axis (db/db mice) is not clear. The data suggest that FTO is likely a part of the pathway mediating the neuroregulation (e.g., leptin) of energy metabolism in adipose tissue, and blocking the leptin signal may inhibit the downstream changes in adipose tissue that induce the expression of FTO. Furthermore, FTO was found to be expressed in leukocytes and was drastically upregulated in expression of downstream changes in adipose tissue that induce the genesis of obesity-related metabolic diseases.

SNP rs9939609 is highly correlated with many other SNPs within a 47-kb region encompassing parts of the first two introns and exon 2 of FTO gene. Sequencing the chromosomes did not result in clear candidate functional variants in the FTO coding region, minimal splice sites, or 3′-untranslated region (1). Further work is warranted to explore the genetic mechanism underpinning the observed associations.

Several limitations need to be acknowledged. Population stratification, mostly arising from either ethnic admixture or genetic substructure within an ethnically homogenous group, may cause spurious associations. However, neither is likely to explain the associations observed in the present study. Our study populations are highly homogeneous by including only European whites. In addition, there is no evidence showing regional difference in rs9939609 across European countries (1).

The participants in our study do not represent random samples of U.S. men and women. However, major cohort studies, such as the Framingham Heart Study, have also not relied on national samples. Clearly, data validity is the chief prerequisite that must be fulfilled before the results can be generalized. In previous analyses, the observed genetic and environmental associations for obesity, type 2 diabetes, coronary heart disease, and other diseases in our cohorts are very similar to those found in other broadly based U.S. populations (40–44). Nonetheless, the findings in the present study need to be replicated in other ethnic groups.

Adiposity measures were self-reported in our cohorts. However, self-reported information has been reliably validated, with a high correlation with technician-measured variables (21,22). In addition, previous analyses in NHS and HPFS have demonstrated that self-reported BMI and waist circumference strongly predicted various chronic diseases (40,45,46).

We examined only one SNP, rs9939609, which was reported by the original GWA study (1). Several other SNPs were associated with obesity in subsequent studies (4,5), but these SNPs are all in strong to perfect linkage disequilibrium with rs9939609. Thus, genotyping of these SNPs would have been redundant.

In conclusion, we confirmed associations between the FTO SNP rs9939609 and higher obesity risk. Our data suggest that the genetic association for obesity may decline at older age. In addition, the genetic variant may affect circulating adiponectin levels through the changes in BMI. The expression of FTO gene was reduced in adipocytes from db/db mice. Little is known about the function of FTO gene, and thus, further investigation is warranted to identify the causal genetic variants and potential mechanisms underlying the observed genetic associations.

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