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Interaction of FTO and physical activity level on adiposity in African-American and European American adults: The ARIC Study

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Abstract

Physical inactivity accentuates the association of variants in the FTO locus with obesity-related traits but evidence is largely lacking in non-European populations.

Methods—Here we tested the hypothesis that physical activity (PA) modifies the association of the FTO single-nucleotide polymorphism (SNP) rs9939609 on adiposity traits in 2,656 African Americans (AA) (1,626 women and 1,030 men) and 9,867 European Americans (EA) (5,286 women and 4,581 men) aged 45-66 years in the Atherosclerosis Risk in Communities (ARIC) study. Individuals in the lowest quintile of the sport activity index of the Baecke questionnaire were categorized as low PA. Baseline BMI, waist circumference (WC), and skinfold measures were dependent variables in regression models testing the additive effect of the SNP, low PA, and their interaction, adjusting for age, alcohol use, cigarette use, educational attainment, and percent European ancestry in AA adults, stratified by sex and race/ethnicity.

Results—rs9939609 was associated with adiposity in all groups other than AA women. The SNPxPA interaction was significant in AA men ($p \leq 0.002$ for all traits) and EA men ($p \leq 0.04$ for all traits). For each additional copy of the A (risk) allele, WC in AA men was higher in those with low PA (β_{lowPA} : 5.1 cm, 95% C.I. 2.6-7.5) than high PA (β_{highPA}: 0.7 cm, 95% C.I. −0.4 – 1.9); p (interaction) = 0.002). The interaction effect was not observed in EA or AA women.

Conclusion—FTO SNP x PA interactions on adiposity were observed for AA as well as EA men. Differences by sex require further examination.

Keywords

Genetics; genotype; FTO; obesity; adiposity; BMI; physical activity; exercise; African-American; interaction; environment

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Introduction

Studies in twins have long suggested that physical activity may reduce the influence of genetic factors on the development of obesity (1); (2). A growing number of studies suggest that while common genetic variants in FTO (fat mass and obesity associated gene) are consistently associated with obesity and adiposity level in individuals of European descent (3); (4); (5); (6); (7), their associations depend on the level of physical activity (PA) (6); (8); (9); (10). Specifically, the association of FTO variants on adiposity appears to be greater among individuals with low physical activity level and significantly weaker (or not significant) in individuals with higher PA (reviewed in 11); (12). This finding has public health implications, as it is a proof of principle that increased physical activity, a core strategy for chronic disease prevention, has the potential to counteract the effects of a putatively deleterious genotype on obesity.

The finding of gene-by-environment interactions for obesity loci also has implications for the likelihood of detecting genetic associations in environmentally and genetically heterogeneous study populations. The first recently-published genome-wide association (GWA) study for anthropometric traits in a large sample of individuals of African ancestry found no genetic loci that exceeded the threshold of genome-wide significance, and of the 15 obesity loci previously shown to be associated with BMI and adiposity traits in numerous European populations, only MC4R was replicated in the African-derived populations (13). The authors noted that their sample lacked sufficient statistical power to detect variants with small effect sizes like FTO, and less extensive linkage disequilibrium in African ancestry populations also makes it less likely to detect association using GWA. However, it has been suggested that environmental variation between and within study cohorts may also mask genetic effects when those differences are not accounted for (11); (13);. We have recently confirmed that obesity-related variants in FTO identified in European populations showed significantly weaker (or non-significant) main effects on BMI, waist circumference, and diabetes mellitus in African American as compared to European American subjects in the ARIC (Atherosclerosis Risk in Communities) study (14), despite adequate statistical power to detect modest associations in both groups. We suggested that FTO action is context dependent, and that in addition to population differences in genetic architecture (e.g., allele frequency, linkage disequilibrium), attention to environmental heterogeneity may clarify the differences in results for European and non-European populations.

In this analysis, we examined the association of the widely replicated obesity-associated FTO SNP rs9939609 and adiposity in African American and European American adults accounting for physical activity level and possible interactions between physical activity (PA) and rs9939609 on variation in BMI, waist circumference (WC), and subcutaneous skinfold thickness (SKF). Our hypotheses were that 1) the association of rs9939609 with adiposity is greater among individuals with low self-reported physical activity, and 2) that accounting for PA and its interaction with rs9939609 may resolve some the discrepancies in FTO-obesity associations in African American and European American adults.

Methods

Population

The ARIC Study is a prospective cohort study of cardiovascular disease risk in four US communities (15). Between 1987 and 1989, 7,082 men and 8,710 women aged 45–64 years were recruited from Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); suburban Minneapolis, Minnesota; and Washington County, Maryland. The ARIC Study protocol was approved by the institutional review board of each participating university. After written informed consent was obtained, including that for

genetic studies, participants underwent a baseline clinical examination (Visit 1). Follow-up examinations of the cohort occurred three times, but only data from Visit 1 is used in this analysis.

Measurements and Questionnaires

Anthropometrics were taken with the subject wearing a scrub suit and no shoes. Body mass index (BMI) was calculated (weight in kilograms/height in meters squared), waist circumference (WC) was taken at the level of the umbilicus, and triceps and subscapular skinfolds were obtained with a Lange calipers using standard techniques (16) and summed for analysis (SKF). Visit 1 (baseline) anthropometric measures were used for all analyses.

Questionnaires assessed education, history and frequency of cigarette smoking (coded as current/not current), history and frequency of alcohol consumption (coded as current/ not current), and medical history. Level of physical activity was assessed at baseline using the sport index of the Baecke Questionnaire (17). Sport activity scores range in whole and half increments from 1 – 5, with values <2 indicative of physical inactivity (18). We ranked sport activity scores within race and sex groups and defined low physical activity ("low PA") as the lowest sex- and race-specific quintile, with the remainder of subjects classified as "high PA". The rationale for this cut point is that previous work on the interaction of FTO variants with PA on adiposity suggest the effects of FTO variants are most apparent at very low levels of PA with very infrequent participation in moderate-to-high intensity (e.g., sports) activities (6); (8); (9).

Genotyping

The rs9939609 SNP is located in intron 1 of the FTO gene (Chr. 16q12.2). Genotyping of the FTO polymorphism was performed using the TaqMan assay (Applied Biosystems, Foster City, CA, USA). Sequences for primers and TaqMan probes are available upon request. Allele detection was performed using the ABI Prism 7700 Sequence Detection System (Applied Biosystems). The genotype call rate was 94.4% for rs9939609. The proportion of missing genotype data in the final study sample did not exceed 2.5%. Concordance between genotypes for pairs of blind duplicates was determined using the Kappa coefficient (20) and was high ($\kappa = 0.97$).

Data analysis and statistical methods

From the original ARIC cohort (n = 15,792 (4,266 African Americans), we excluded participants who denied permission for DNA testing, or had missing DNA or FTO genotype (n=1,033), or who were missing covariates (n=497), or who had prevalent diabetes, defined as a fasting glucose ≥ 126 mg/dl (21), non-fasting glucose ≥ 200 mg/dl, or a self-reported history of or treatment for diabetes (n=1,739), leaving 12,523 individuals in the analysis: 2,656 African Americans (1,626 women and 1,030 men) and 9,867 European Americans (5,286 women and 4,581 men). We excluded subjects with prevalent diabetes mellitus from this primarily cross-sectional analysis because while diabetes may be considered an outcome of FTO genotype possibly via increased obesity, diagnosis of diabetes is often subsequently associated with changes in diet and exercise and in intentional or unintentional weight loss which would obscure the association of interest between FTO and adiposity.

Our hypothesis was that the positive statistical association of the rs9939609 A (obesity risk) allele on adiposity traits would be greater in individuals with low habitual physical activity than in those with higher physical activity levels. First, the presence of race and sex interactions between rs9939609 and PA on the dependent variables BMI, WC, and SKF was tested in the entire sample using general linear regression models that included main effect terms for race, sex, rs9939609, and PA, all two-way interactions between these four

variables, as well as age, ARIC study center, education, current smoking, and current alcohol consumption as covariates. There were significant race and sex interactions with our primary exposures of interest on adiposity traits (e.g., for SKF, SNP x Sex, p =0.0073; PA x Race, p <0.0001; and Race x Sex, p<0.0001). Therefore, the sample was then stratified by race and sex for subsequent analysis. SNP and PA main effects and their interaction with one another on adiposity traits were tested assuming an additive model and using a 1 df test for the SNP in multivariate linear regression models, adjusting for all covariates above, and additionally for percent European ancestry in the African-Americans. Percentage European ancestry was determined using a panel of 1,350 ancestry informative markers and the Illumina BeadLab platform (Illumina, San Diego, CA, USA). Global ancestry was estimated using ANCESTRYMAP software (22). Where the SNP x PA interaction effect was significant, we plotted the estimated effects for the SNP in inactive and active groups using the parameter estimates and standard errors obtained by specifying that contrast in the general linear models. Finally, in place of baseline adiposity values, we tested the hypothesis that the effect of the SNP on annualized changes in BMI, WC, and SKF differed by PA level using the same linear regression models as above. Statistical analysis was performed using SAS software (SAS Institute, Inc. version 9.2, Cary, North Carolina), with an alpha value for significance of p<0.05. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Sample Characteristics

Study subjects had a mean BMI in the overweight to obese range (Table 1). All adiposity traits and covariates were significantly different in men and women (p<0.001 for all traits in EA adults and p<0.002 for all traits in AA adults), except for smoking status, which did not differ between EA men and EA women (p=0.44), and educational attainment, which did not differ between AA men and AA women (p=0.24). In women, all race/ethnicity differences in adiposity traits, current alcohol use, and sport score were statistically significant (p<0.0001), but current smoking status (p=0.44) and educational attainment (p=0.66) did not differ between EA women and AA women. In men, all race/ethnicity differences in most adiposity traits, current smoking status, current alcohol use, and educational attainment were statistically significant (p<0.01), but BMI (p=0.95), hip circumference (p=0.47), and sport score (p=0.76) did not differ between EA men and AA men. The minor allele frequencies for rs9939609 in European American and African American subjects were similar to those in the corresponding HapMap populations (0.40 in European ancestry populations and 0.49 in African ancestry populations) (23); http://hapmap.ncbi.nlm.nih.gov HapMap Genome Browser Phase 1, 2, 3 Merged Genotypes and Frequencies, accessed May 20, 2010). There was no evidence that the SNP was not in Hardy-Weinberg equilibrium (p=0.22 in African Americans and p=0.68 in European Americans).

Main effect of rs9939609 genotype on baseline adiposity in non-diabetic adults

Each additional copy of the rs9939609 risk (A) allele was associated with, on average, a 0.49 kg/m^2 greater multivariate-adjusted BMI in European American men (p<0.0001), 0.33 kg/m^2 greater BMI in European American women (p=0.0035), and 0.60 kg/m^2 greater BMI in African-American men (p=0.0071), as well as a ~1-2 cm greater WC per allele, and a ~1-2 mm greater SKF per allele, in these groups. However, rs9939609 was not associated with variation in adiposity traits in African-American women (Table 2).

Interaction of PA and rs9939609 genotype on baseline adiposity in non-diabetic adults

In multivariate-adjusted models with sex and race groups combined, a significant interaction of rs9939609 with PA was identified for BMI (p=0.004) and SKF (p=0.006), and weaker for

WC (p=0.15). Because these associations were found in the presence of numerous other interaction effects including significant race x PA, sex x PA, and SNP x sex interactions, the interaction between the SNP and PA was further explored in race and sex-stratified models (Table 3). The interaction of rs9939609 x PA on BMI was significant in both African American men (p=0.001) and European American men (p=0.036). The interaction of rs9939609 x PA was also significant for WC (p=0.0016 in African American men and p=0.029 in European American men) and for SKF (p=0.0005 in African American men and p=0.012 in European American men). No interaction of PA x rs9939609 on BMI, WC, or SKF was observed in either African-American or European American women. The main effect term for snp genotype was no longer significant for African American men, once the snp*PA term was added. The estimated PA stratum-specific statistical effects (beta-coefficients) of the snp from these significant interaction models are plotted by race in Figure 1. The SNP had a stronger association with adiposity traits in men with low PA than in men with high PA. In African American men in particular, the additive per allele effect of the SNP was nearly 10 times greater in those with low PA than in those with high PA.

European ancestry

In African American women, percent European ancestry was negatively associated with BMI (β= −4.44; 95% CI= −7.32, −1.55) and WC (β= −8.54; 95% CI= −15.80, −1.29). In African American men, percent European ancestry was not associated with adiposity (p>0.15 for all).

Sensitivity analysis

To test whether inclusion of extremely high BMI values may have biased the results, we performed a sensitivity analyses and removed individuals with BMI>50 (N=29) and did not observe any meaningful change in either the p values or the beta coefficients for the main effect terms or for the interaction terms in any race or sex group.

Discussion

FTO and Obesity

Intensive lifestyle intervention in adults, such as that conducted in the Diabetes Prevention Program trial, where subjects achieved at least 150 min/week of moderate-intensity activity, and significantly reduced their dietary fat and caloric intake, can achieve a 6-8% reduction in BMI over one year (24). In comparison, common variants in the FTO gene explain only 1-2% of phenotypic variance in BMI, but because of their typically high allele frequencies, they have been reported to explain a sizeable (~12%-22%) proportion of obesity cases in some populations (3); (5); (25). These observations have lead to intense interest in determining FTO's function and possible modification of its effects in humans. FTO encodes a 2-oxoglutarate-dependent nucleic acid demethylase (26) and is widely expressed, particularly so in the human brain and hypothalamus (27) where it is thought to maintain energy homeostasis by regulating energy expenditure (28); (29). In mice, *Fto* loss of function leads to higher basal energy expenditure and decreased weight and adiposity, perhaps through sympathetic nervous system activation (28); (30). FTO variants may also be involved in energy intake, as they have been found to predict child appetite and satiety and food intake behavior (31).

FTO variants in African Americans

A number of recent studies have found significant associations between FTO variants and obesity-related traits in African American adolescents and adults (32); (33); (34); (35), but others have found weaker, or non-significant associations in this race/ethnic group (14);

(25); (4); (36); (37). In the case of rs9939609, a significant association with BMI was shown in the Insulin Resistance Atherosclerosis Study (IRAS) in a sample of 604 related African-American men and women genotyped for 27 variants in intron 1 of FTO (37), and rs9939609 was also associated with BMI and WC in a sample of 1,025 African-American adolescents (33). In contrast, there was no evidence for association of rs9939609 with BMI in a study of 1,101 African-American participants in the GenNet study (4), with obesity, BMI, or WC in African-American post-menopausal women in the Women's Health Initiative-Observational Study (25), or in 2,208 predominantly lean Gambians (36). None of these studies examined covariate effects of PA or SNP x PA interactions in their analyses, and so it is unknown whether these factors may help to explain the discrepancies in results.

Interaction between FTO and PA on Adiposity

To our knowledge, the present study is the largest examination to date of the FTO x physical activity interaction on adiposity in individuals of African descent, and it provides support for the hypothesis that FTO x PA interaction may help to explain the inconsistent association of FTO variants with adiposity in non-European populations. Among inactive African-American men, each additional copy of the rs9939609 A allele was associated with an approximately 2.0 unit higher BMI, a 5.0 cm higher WC, and a 8 mm increase in SKF, while among more active African-American men, the increases per A allele were largely non-significant, averaging 0.2 kg/m^2 BMI per allele, 0.5 cm WC per allele, and 1.0 mm SKF per allele (p values for interaction: all ≤0.002). It is therefore possible that the lack of consistent association of FTO variants with body fatness in African ancestry individuals could be partly due to this strong interaction, which makes the main effect of FTO difficult to detect unless PA is very low.

We also replicated in European American men (although less dramatically than in African American men) the FTO x PA interaction on adiposity that was first identified in 5,554 Danish adults (8), and then also found in 704 Old Order Amish adults (9), in 20,374 individuals in the EPIC-Norfolk study (6), in 752 European-ancestry adolescents (31), and in other populations (38). The growing literature showing the dependence of FTO effects on PA level has been recently reviewed(11); (12);. While a significant SNP x PA interaction existed in European American men in this study, it was not as dramatic as seen in African American men, which may be one factor in explaining why the main effect of FTO has been more consistently found in European populations.

Sex as a Modifier of the Interaction between FTO and PA on Adiposity

There is yet little discussion of possible sex differences in the FTO x PA interaction on adiposity. In our study, we found no FTO x PA interaction in European American women, and both FTO main effect and interaction effect estimates were non-significant in African American women. These findings are supported by a number of recent observational studies, exercise intervention studies, and by animal models. Quantitative genetic analyses have shown that some genetic effects on BMI are shared by men and women, while others are unique to each sex (39); (40). Rankinen and colleagues recently reported greater resistance to fat loss in predominantly European-ancestry FTO risk-allele carriers than major allele homozygotes in response to a 20 week endurance training program, but the FTO main effect at baseline (sedentary state) was only significant in men (SNP x sex interaction $p = 0.0053$) (41). In contrast, a six-month moderate intensity exercise intervention study in European ancestry women, did observe FTO main effects on adiposity, but no genotype x exercise interaction. In our previous work in a combined sample of diabetic and non-diabetic adults in ARIC, there were no sex differences in the association of FTO with quantitative adiposity traits, but there was a significant interaction between sex and the rs9939609 SNP on the risk of obesity in African Americans, where, as here, the SNP association was significant in men,

but not women (14). FTO-by-sex interactions were also suggested by Jacobsson and colleagues, although in that pediatric study, the association of the rs9939609 variant was associated with morbid obesity in girls but not boys (42). Finally, in a murine model of *Fto* deficiency, post-natal weight and fat gain were diminished and energy expenditure was greater in $Fto^{-/-}$ compared to $Fto^{-/+}$ and $Fto^{+/+}$ mice, but the effect on males was greater than in females (3.5 g less fat in $Fto^{-/-}$ in males compared to 1 g less fat in $Fto^{-/-}$ females), and on a high fat chow, the male *Fto* deficient males had faster fat gains than females (28). In total, our findings and previously published work suggests that sex as well as PA may modify the statistical associations of common FTO variants and therefore should be considered in future GWA and fine-mapping efforts. Exercise intervention studies in men and women of African ancestry may clarify the sex- and race-specificity found in observational studies.

Limitations

The primary limitation of this analysis is the reliance on self-reported physical activity data. Objective measures of activity (e.g., accelerometry) and energy expenditure would have provided more unbiased and precise estimates of PA main effects and therefore increased the power to detect FTO x PA interactions on adiposity in European American women, where the FTO main effect was weaker than in men. In addition, for this gene-environment interaction analysis, we chose to examine a single, well-replicated SNP in high LD with multiple other FTO SNPs and having equally high allele frequency in both African Americans and European Americans, permitting sufficient statistical power to examine sex and race-stratified associations. However, BMI-associated SNPs in FTO lie within a large 47 kilobase (kb) linkage disequilibrium (LD) block encompassing multiple intronic and exonic regions of the gene (34); (43);. It is therefore likely that the intronic SNP rs9939609 examined here is not the causal functional variant but rather is associated with adiposity due to correlation between it and variation elsewhere in the gene or control elements near other genes. As larger genome-wide association studies of African-ancestry individuals are published and sequencing efforts progress, the gene's structure and biology in humans will be clarified, and additional sources of genetic heterogeneity will be revealed that may further explain population differences in the effect of FTO on human health. Finally, while this study did present information on subcutaneous adiposity (the sum of triceps and subscapular skinfold thicknesses), in addition to the more commonly-used anthropometric measures of adiposity (BMI and waist circumference), it remains true that a measure of total body fat mass such as can be obtained from dual energy x-ray absorptiometry would ideally be used, as it may more accurately reflect total body composition across ethnic groups.

In conclusion, our study is the first to confirm a significant difference by activity level in the association of FTO variants with adiposity in African American, as well as European American men, which may, in part, explain some of the inconsistencies in the observed effects of FTO in African-ancestry populations, as the rs9939609 SNP examined here had no significant effect in African American men unless physical activity was low. That this relationship was not found in European American or African American women requires replication and suggests the need for exercise trials in large multi-ethnic samples of men and women to determine whether men and women require different levels or types of exercise in order to counteract the genetic susceptibility to obesity.

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References

1. Plomin R, DeFries JC, Loehlin JC. Genotype-environment interaction and correlation in the analysis of human behavior. Psychol Bull. Mar; 1977 84(2):309–322. [PubMed: 557211]
2. Perusse L, Bouchard C. Genotype-environment interaction in human obesity. Nutr Rev. May; 1999 57(5 Pt 2):S31–7. discussion S7-8. [PubMed: 10391023]
3. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. May 11; 2007 316(5826):889–894. [PubMed: 17434869]
4. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. Jul.2007 3(7):e115. [PubMed: 17658951]
5. Dina C, Meyre D, Gallina S, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet. Jun; 2007 39(6):724–726. [PubMed: 17496892]
6. Vimaleswaran KS, Li S, Zhao JH, et al. Physical activity attenuates the body mass index-increasing influence of genetic variation in the FTO gene. Am J Clin Nutr. Aug; 2009 90(2):425–428. [PubMed: 19553294]
7. Cornes BK, Lind PA, Medland SE, Montgomery GW, Nyholt DR, Martin NG. Replication of the association of common rs9939609 variant of FTO with increased BMI in an Australian adult twin population but no evidence for gene by environment (G x E) interaction. Int J Obes (Lond). Jan; 2009 33(1):75–79. [PubMed: 19030008]
8. Andreasen CH, Stender-Petersen KL, Mogensen MS, et al. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes. Jan; 2008 57(1): 95–101. [PubMed: 17942823]
9. Rampersaud E, Mitchell BD, Pollin TI, et al. Physical activity and the association of common FTO gene variants with body mass index and obesity. Arch Intern Med. Sep 8; 2008 168(16):1791–1797. [PubMed: 18779467]
10. Ruiz JR, Labayen I, Ortega FB, et al. Attenuation of the effect of the FTO rs9939609 polymorphism on total and central body fat by physical activity in adolescents: the HELENA study. Arch Pediatr Adolesc Med. Apr; 2010 164(4):328–333. [PubMed: 20368485]
11. Hetherington MM, Cecil JE. Gene-environment interactions in obesity. Forum Nutr. 2010; 63:195–203. [PubMed: 19955787]
12. Rankinen T, Roth SM, Bray MS, et al. Advances in exercise, fitness, and performance genomics. Med Sci Sports Exerc. May; 2010 42(5):835–846. [PubMed: 20400881]
13. Kang SJ, Chiang CW, Palmer CD, et al. Genome-wide association of anthropometric traits in African- and African-derived populations. Hum Mol Genet. Jul 1; 2010 19(13):2725–2738. [PubMed: 20400458]
14. Bressler J, Kao WH, Pankow JS, Boerwinkle E. Risk of type 2 diabetes and obesity is differentially associated with variation in FTO in whites and African-Americans in the ARIC study. PLoS One. 2010; 5(5):e10521. [PubMed: 20502638]
15. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. Apr; 1989 129(4):687–702. [PubMed: 2646917]
16. Lohman, TG.; Roche, AF.; Martorell, R. Anthropometric standardization reference manual. Abridged, editor. Human Kinetics Books; Champaign, Ill: 1991.
17. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. Nov; 1982 36(5):936–942. [PubMed: 7137077]
18. Meyer AM, Evenson KR, Couper DJ, Stevens J, Pereria MA, Heiss G. Television, physical activity, diet, and body weight status: the ARIC cohort. Int J Behav Nutr Phys Act. 2008; 5:68. [PubMed: 19091124]

19. ARIC Investigators. [cited 2008 Janary 17] ARIC Study Website. Available from:http://www.cscc.unc.edu/aric/
20. Cohen J. A Coefficient of agreement for nominal scales. Educational and psychological measurement. 1960; 20:37–46.
21. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. Jul; 1997 20(7):1183–1197. [PubMed: 9203460]
22. Patterson N, Hattangadi N, Lane B, et al. Methods for high-density admixture mapping of disease genes. Am J Hum Genet. May; 2004 74(5):979–1000. [PubMed: 15088269]
23. The International HapMap Project. Nature. Dec 18; 2003 426(6968):789–796. [PubMed: 14685227]
24. Fujimoto WY, Jablonski KA, Bray GA, et al. Body size and shape changes and the risk of diabetes in the diabetes prevention program. Diabetes. Jun; 2007 56(6):1680–1685. [PubMed: 17363740]
25. Song Y, You NC, Hsu YH, et al. FTO polymorphisms are associated with obesity but not diabetes risk in postmenopausal women. Obesity (Silver Spring). Nov; 2008 16(11):2472–2480. [PubMed: 18787525]
26. Gerken T, Girard CA, Tung YC, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. Nov 30; 2007 318(5855):1469–1472. [PubMed: 17991826]
27. Willer CJ, Speliotes EK, Loos RJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. Jan; 2009 41(1):25–34. [PubMed: 19079261]
28. Fischer J, Koch L, Emmerling C, et al. Inactivation of the Fto gene protects from obesity. Nature. Apr 16; 2009 458(7240):894–898. [PubMed: 19234441]
29. Fredriksson R, Hagglund M, Olszewski PK, et al. The obesity gene, FTO, is of ancient origin, up-regulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain. Endocrinology. May; 2008 149(5):2062–2071. [PubMed: 18218688]
30. Church C, Lee S, Bagg EA, et al. A mouse model for the metabolic effects of the human fat mass and obesity associated FTO gene. PLoS Genet. Aug.2009 5(8):e1000599. [PubMed: 19680540]
31. Wardle J, Carnell S, Haworth CM, Farooqi IS, O'Rahilly S, Plomin R. Obesity associated genetic variation in FTO is associated with diminished satiety. J Clin Endocrinol Metab. Sep; 2008 93(9): 3640–3643. [PubMed: 18583465]
32. Bollepalli S, Dolan LM, Deka R, Martin LJ. Association of FTO Gene Variants With Adiposity in African-American Adolescents. Obesity (Silver Spring). Apr 8.2010
33. Liu G, Zhu H, Lagou V, et al. FTO variant rs9939609 is associated with body mass index and waist circumference, but not with energy intake or physical activity in European- and African-American youth. BMC Med Genet. 2010; 11:57. [PubMed: 20377915]
34. Adeyemo A, Chen G, Zhou J, et al. FTO genetic variation and association with obesity in West Africans and African Americans. Diabetes. Jun; 2010 59(6):1549–1554. [PubMed: 20299471]
35. Grant SF, Li M, Bradfield JP, et al. Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. PLoS One. 2008; 3(3):e1746. [PubMed: 18335027]
36. Hennig BJ, Fulford AJ, Sirugo G, et al. FTO gene variation and measures of body mass in an African population. BMC Med Genet. 2009; 10:21. [PubMed: 19265514]
37. Wing MR, Ziegler J, Langefeld CD, et al. Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study. Hum Genet. Jun; 2009 125(5-6):615–626. [PubMed: 19322589]
38. Karasawa S, Daimon M, Sasaki S, et al. Association of the common fat mass and obesity associated (FTO) gene polymorphism with obesity in a Japanese population. Endocr J. 2010; 57(4):293–301. [PubMed: 20051647]
39. Harris JR, Tambs K, Magnus P. Sex-specific effects for body mass index in the new Norwegian twin panel. Genet Epidemiol. 1995; 12(3):251–265. [PubMed: 7557347]
40. Pietilainen KH, Kaprio J, Rissanen A, et al. Distribution and heritability of BMI in Finnish adolescents aged 16y and 17y: a study of 4884 twins and 2509 singletons. Int J Obes Relat Metab Disord. Feb; 1999 23(2):107–115. [PubMed: 10078843]

41. Rankinen T, Rice T, Teran-Garcia M, Rao DC, Bouchard C. FTO genotype is associated with exercise training-induced changes in body composition. Obesity (Silver Spring). Feb; 2010 18(2): 322–326. [PubMed: 19543202]

42. Jacobsson JA, Danielsson P, Svensson V, et al. Major gender difference in association of FTO gene variant among severely obese children with obesity and obesity related phenotypes. Biochem Biophys Res Commun. Apr 11; 2008 368(3):476–482. [PubMed: 18249188]

43. Fawcett KA, Barroso I. The genetics of obesity: FTO leads the way. Trends Genet. Jun; 2010 26(6):266–274. [PubMed: 20381893]

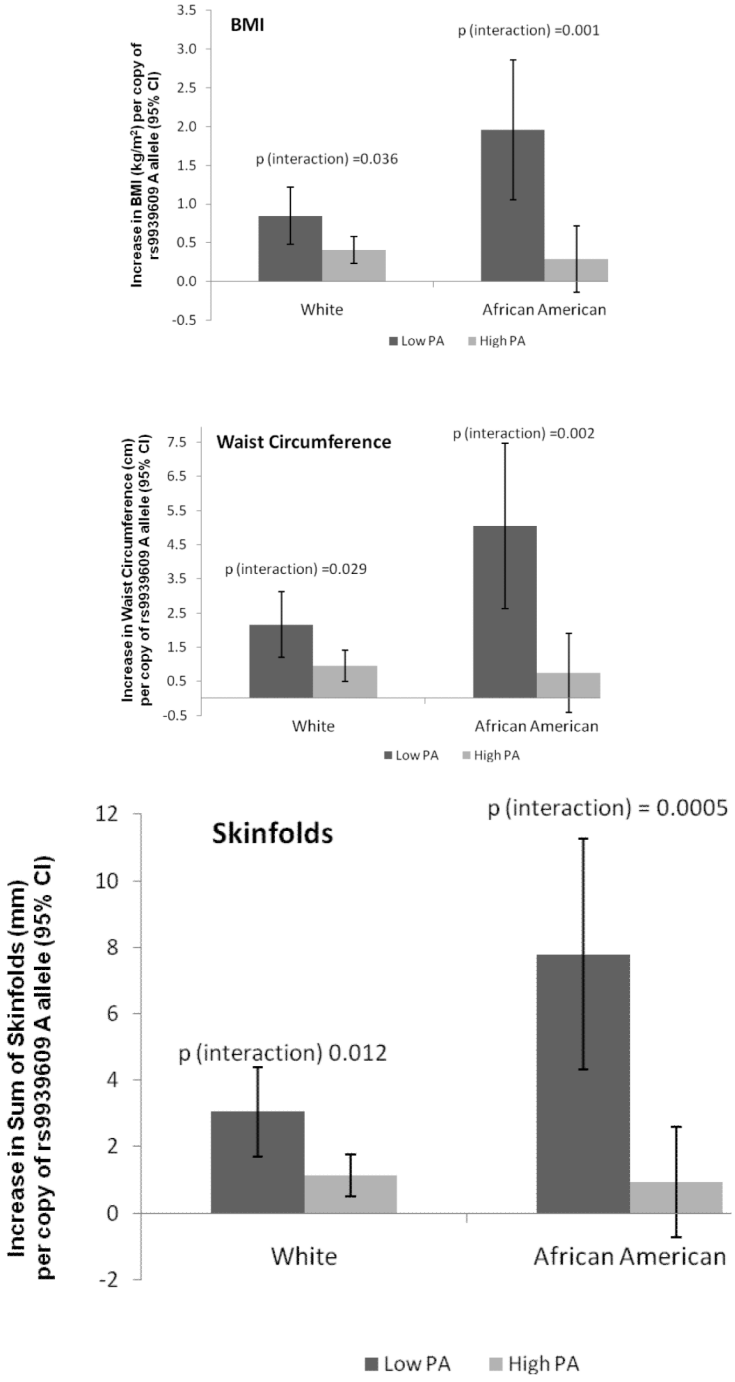

Figure 1.
Association of FTO SNP rs9939609 with Adiposity Traits Depends on Physical Activity Level in European American and African American Men

Table 1

Description of Study Sample

	African American		European American	
	Men	**Women**	**Men**	**Women**
	Mean (SD), [range]			
N	1,030	1,626	4,581	5,286
Age	53.5 (6.0), [44-66]	52.8 (5.7), [44-65]	54.6 (5.7), [44-66]	53.8 (5.7), [44-65]
Baecke Sport Activity Score	2.3 (0.8), [1-5]	2.1 (0.7), [1-4.75]	2.7 (0.8), [1-5]	2.4 (0.8), [1-5]
BMI (kg/m^2)	27.2 (4.7), [15.6-52.4]	30.1 (6.4), [14.2-65.9]	27.2 (3.9), [16.1-56.3]	26.2 (5.2), [14.4-52.8]
Waist (cm)*	95.6 (12.4), [63-178]	98.3 (16.0), [54-178]	99.0 (10.1), [66-171]	91.9 (14.0), [52-157]
Hip (cm)*	102.1 (9.6), [59-192]	109.7 (12.2), [78-179]	102.4 (7.4), [61-165]	103.5 (10.3), [56-173]
Skinfolds (mm)*	41.4 (18.0), [7.5-130]	67.3 (23.0), [8.5-134]	40.0 (14.0), [10-112.5]	50.3 (16.5), [7-115]
Percent European Ancestry†	18.0% (10.8), [1.3-95.8)		18.1% (11.1), [0.9-95.6]	
	N (%)			
Low PA‡	199 (19.3%)	397 (24.4%)	866 (18.9%)	868 (16.4%)
Smoking (N, % current)	458 (39.0%)	487 (26.4%)	1131 (24.7%)	1341 (25.4%)
Alcohol (N, % current)	613 (52.2%)	435 (23.5%)	3213 (70.1%)	3309 (62.6%)
Education (N, % >High School)	372 (31.7%)	612 (33.1%)	2006 (43.8%)	1800 (34.1%)
rs9939609 (N, %)				
TT	317 (27.0%)	513 (27.7%)	1667 (36.4%)	1877 (35.5%)
TA	566 (48.2%)	907 (49.1%)	2153 (47.0%)	2568 (48.6%)
AA	292 (24.8%)	428 (23.2%)	761 (16.6%)	841 (15.9%)
Minor allele (A) frequency	0.48		0.40	

*Sample sizes for waist and hip circumferences (N=1,029 for African-American men), and for sum of skinfolds (N=1,025 for African-American men, N=1,621 for African –American women, N=4,564 for White men, and N=5,280 for White women).

†Percentage European ancestry was determined in African Americans using a panel of 1,350 ancestry informative markers and the Illumina BeadLab platform and estimated using ANCESTRYMAP software (22).

‡Individuals with Low PA were those in the lowest sex- and race/ethnicity-specific quintiles of the Baecke Sport Activity Score, an ordinal variable that takes values from 1.0 to 5.0 at 0.25 increments. Due to the ordinal nature of this variable, the lowest quintile sometimes more or less than exactly 20% of the subjects per group.

Table 2

Main Effect Estimates of FTO rs9939609 on Adiposity Traits, by Race/Ethnicity and Sex, in Non-Diabetic Adults

		African American		European American	
		Men	**Women**	**Men**	**Women**
		Mean (95% CI)			
BMI (kg/m^2)	N	1,030	1,626	4,581	5,286
	TT	26.3 (25.6 – 27.0)	28.9 (28.2 – 29.6)	26.8 (26.5 – 27.0)	25.8 (25.5 – 26.1)
	TA	26.6 (26.0 – 27.2)	28.8 (28.2 – 29.5)	28.4 (27.0 – 27.4)	26.2 (25.9 – 26.4)
	AA	27.5 (26.8 – 28.2)	29.0 (28.2 – 29.7)	28.8 (27.4 – 28.0)	26.4 (26.1 – 26.8)
	p†	0.0071	0.9299	<0.0001	0.0035
	β (95% CI)*	0.60 (0.21 – 0.99)	0.024 (−0.40 – 0.45)	0.49 (0.33 – 0.64)	0.33 (0.14 – 0.52)
Waist (cm)	N	1,029	1,626	4,580	5,286
	TT	93.9 (92.0 – 95.8)	97.0 (95.1 – 98.8)	98.6 (98.0 – 99.1)	91.2 (90.4 – 91.9)
	TA	94.6 (93.1 – 96.2)	97.0 (95.4 – 98.6)	99.7 (99.2 – 100.2)	92.4 (91.7 – 93.1)
	AA	97.0 (95.1 – 96.9)	96.9 (94.9 – 98.8)	100.9 (100.1 – 101.7)	93.0 (92.0 – 94.1)
	p†	0.0093	0.9931	<0.0001	0.0006
	β (95% CI)*	1.54 (0.49 – 2.59)	−0.04 (−1.12 — 1.03)	1.16 (0.75 – 1.58)	1.00 (0.48 – 1.50)
Skinfolds (mm)	N	1,025	1,621	4,564	5,280
	TT	38.5 (35.8 – 41.2)	61.2 (58.6 – 63.8)	39.2 (38.4 – 40.1)	48.6 (47.7 – 49.5)
	TA	39.2 (37.0 – 41.5)	61.4 (59.1 – 63.7)	40.3 (39.6 – 41.1)	50.0 (49.2 – 50.8)
	AA	43.0 (40.2 – 45.7)	62.6 (59.6 – 65.4)	42.3 (41.2 – 43.4)	50.5 (49.3 – 51.7)
	p†	0.0064	0.9731	<0.0001	0.0036
	β (95% CI)*	2.21 (0.71 – 3.72)	0.66 (−0.88 – 2.19)	1.49 (0.92 – 2.06)	1.04 (0.41 – 1.67)

All models included baseline values for age, level of education, current alcohol use status, current cigarette smoking status, physical activity status, study center, and percent European admixture (in African Americans only) as covariates.

†p value from F test of difference in means by genotype (2 df test)

*β (95% CI) indicates the difference in the adiposity trait per copy of the rs9939609 A allele in an additive model (1 df).

Table 3

Interactions of FTO rs9939609 and Physical Activity on Adiposity, by Race/Ethnicity and Sex

		African American		European American	
Variable		**Men**	**Women**	**Men**	**Women**
		β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
BMI (kg/m^2)	rs9939609 (per A allele)	0.29 (0.14, 0.72)	0.14 (−0.35, 0.64)	0.41 (0.24, 0.58)	0.26 (0.04, 0.469)
	PA (Low vs High)	−2.28 (−3.45, −1.07)	0.60 (−0.58, 1.78)	0.50 (0.07, 0.94)	0.73 (0.18, 1.28)
	rs9939609 x PA*	1.67 (0.67, 2.67)	−0.46 (−1.44, 0.52)	0.44 (0.03, 0.85)	0.45 (−0.08, 0.98)
	χ^2 , p for interaction†	10.8, 0.001	0.80, 0.371	4.4, 0.036	2.8, 0.094
Waist (cm)	rs9939609 (per A allele)	0.74 (−0.41, 1.90)	0.30 (0.94, 1.55)	0.94 (0.49, 1.40)	1.01 (0.44, 1.59)
	PA (Low vs High)	−5.20 (−8.47, −1.95)	2.54 (0.43, 5.51)	1.99 (0.85, 3.14)	3.03 (1.55, 4.51)
	rs9939609 x PA*	4.31 (1.62, 7.00)	−1.36 (−3.82, 1.10)	1.21 (0.14, 2.29)	−0.07 (−1.49, 1.35)
	χ^2 , p for interaction†	10.0, 0.0016	1.2, 0.270	4.8, 0.029	0.0, 1.00
Skinfolds (mm)	rs9939609 (per A allele)	0.94 (0.73, 2.60)	1.02 (−0.76, 2.80)	1.15 (0.52, 1.78)	0.98 (0.29, 1.67)
	PA (Low vs High)	−8.20 (−12.88, −3.53)	1.49 (2.77, 5.74)	1.38 (−0.21, 2.96)	2.77 (0.99, 4.56)
	rs9939609 x PA*	6.85 (2.99, 10.71)	−1.43 (−4.96, 2.10)	1.91 (0.43, 3.40)	0.36 (−1.35, 2.07)
	χ^2 , p for interaction†	12.2, 0.0005	0.6, 0.439	6.36, 0.012	0.20, 0.655

All models included baseline values for age, level of education, alcohol use (current/not current), smoking status (current/not current), and study center as covariates, and in African Americans, percent European ancestry was included as an additional covariate, in addition to rs9939609, PA, and rs9939609xPA.

*Parameter estimate for the interaction is the additive effect of each copy of the A allele when PA is low, compared to when PA is high

†The χ^2 and associated p values are for the likelihood ratio tests (LRT) between the model for each trait and ethnicity/sex group that included the rs9939609 x PA interaction and the model that did not include this interaction term but was identical in all other respects.

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