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RESEARCH ARTICLE | *Big Data Integration to Understand Complex Disease*

Functional genomic characterization of the *FTO* locus in African Americans

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[1]*Division of Molecular Genetics, Department of Pediatrics, College of Physicians and Surgeons, Columbia University Medical Center, New York, New York;* [2]*Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, New York;* [3]*Genomics Analysis Unit, Amgen Research, Cambridge, Massachusetts;* [4]*The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, New York; and* [5]*Gertrude H. Sergievsky Center, Columbia University, New York, New York*

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Gill R, Stratigopoulos G, Lee JH, Leibel RL. Functional genomic characterization of the *FTO* locus in African Americans. *Physiol Genomics* 51: 517–528, 2019. First published September 18, 2019; doi:10.1152/physiolgenomics.00057.2019.—Background: SNPs in the first intron of the fat mass and obesity-associated (*FTO*) gene represent the strongest genome-wide associations with adiposity [body mass index (BMI)]; the molecular basis for these associations is under intense investigation. In European populations, the focus of most genome-wide association studies conducted to date, the single nucleotide polymorphisms (SNPs) have indistinguishable associations due to the high level of linkage disequilibrium (LD). However, in African American (AA) individuals, reduced LD and increased haplotype diversity permit finer distinctions among obesity-associated SNPs. Such distinctions are important to mechanistic inferences and for selection of disease SNPs relevant to specific populations. Methods: To identify specific *FTO* SNP(s) directly related to adiposity, we performed: *1*) haplotype analyses of individual-level data in 3,335 AAs from the Atherosclerosis Risk in Communities Cohort (ARIC) study; as well as *2*) statistical fine-mapping using summary statistics from a study of *FTO* in over 20 000 AAs and over 1000 functional genomic annotations. Results: Our haplotype analyses suggest that in AAs at least two distinct signals underlie the intron 1 *FTO*-adiposity signal. Fine mapping showed that two SNPs have the highest posterior probability of association (PPA) with BMI: rs9927317 (PPA = 0.94) and rs62033405 (PPA = 0.99). These variants overlap possible enhancer sites and the 5′-regions of transcribed genes in the substantia nigra, chondrocytes, and white adipocytes. Conclusions: We found two SNPs in *FTO* with the highest probability of direct association with BMI in AAs, as well as tissue-specific mechanisms by which these variants may contribute to the pathogenesis of obesity.

adiposity; African Americans; FTO; GWAS; obesity

INTRODUCTION

Genome-wide association studies (GWAS) of obesity [usually quantified by body mass index (BMI)] in people of European, African, and East Asian descent have systematically interrogated common variants, identifying ~100 genome-wide significant associations (13, 17, 25, 32, 33, 40, 55). The biological mechanisms underlying the majority of these associations are unclear, as most obesity-associated single nucleotide polymorphisms (SNPs) do not lie near or within genes previously implicated in obesity. However, the majority of implicated genes are expressed in the central nervous system (25). In addition, SNPs in linkage disequilibrium (LD) with GWAS-identified SNPs generally have indistinguishable statistical associations with disease. A striking example of this situation is the fat mass and obesity-associated (*FTO*) gene, in which SNPs in the first intron have the strongest statistical associations with obesity yet detected (26).

FTO encodes an ortholog to the AlkB family of enzymes that demethylate nucleic acids (15). Manipulation of *Fto* expression in rodents leads to directionally inconsistent changes in body weight (6, 43, 46, 51, 54). The first intronic region of *FTO* is less than 100 bp 3′ from the transcriptional start site of the gene retinitis pigmentosa GTPase regulator-interacting protein-1 Like (*RPGRIP1L*), a ciliary gene (24, 56) that is transcribed in the 5′-direction. Mice hypomorphic for *Rpgrip1l* display hyperphagia, obesity, and diminished response of food intake to leptin administration (45).

The initial obesity GWAS in Europeans identified associations with *FTO* SNPs rs9939609 (12), rs8050136, and rs9930506 (38), all with indistinguishable effects on BMI due to the high degree of LD. rs9939609 alleles do not perturb any regulatory elements and are not correlated with gene expression. We previously showed that rs8050136 resides within a putative binding site for the transcription factor Cut-like Homeobox 1 (CUX1) (46), which regulates expression of *FTO* and *RPGRIP1L* (43, 44). Other groups have shown that rs9930506 is associated with expression of *IRX3* in the brain (39), as well as expression of both *IRX3* and *IRX5* in adipose tissue (7), with apparent biological relevance conveyed by physical interactions (chromosome conformation) with these genes' promoters, although the resolution of this chromatin interaction data was not sufficient to detect (or rule out) interactions with *RPGRIP1L*.

In African populations, rs9930506 is nominally associated with BMI (13), while rs9939609 (2, 13, 34) and rs8050136 (2, 13, 14, 16, 34) are not. Instead, in populations of African ancestry, an independent cluster of linked SNPs is associated with BMI. This cluster includes rs1421085, which is a second SNP within a putative CUX1 binding site (2, 13, 16, 32, 34), as well as rs3751812 (14, 16, 32, 34), rs17817964 (32), and rs1558902, which is associated with obesity in both European and African populations (2, 16, 25, 32, 40). The latter three SNPs do not have proposed functional consequences. Claussnitzer et al. (7) found that CRISPR/Cas9-mediated genome edit-

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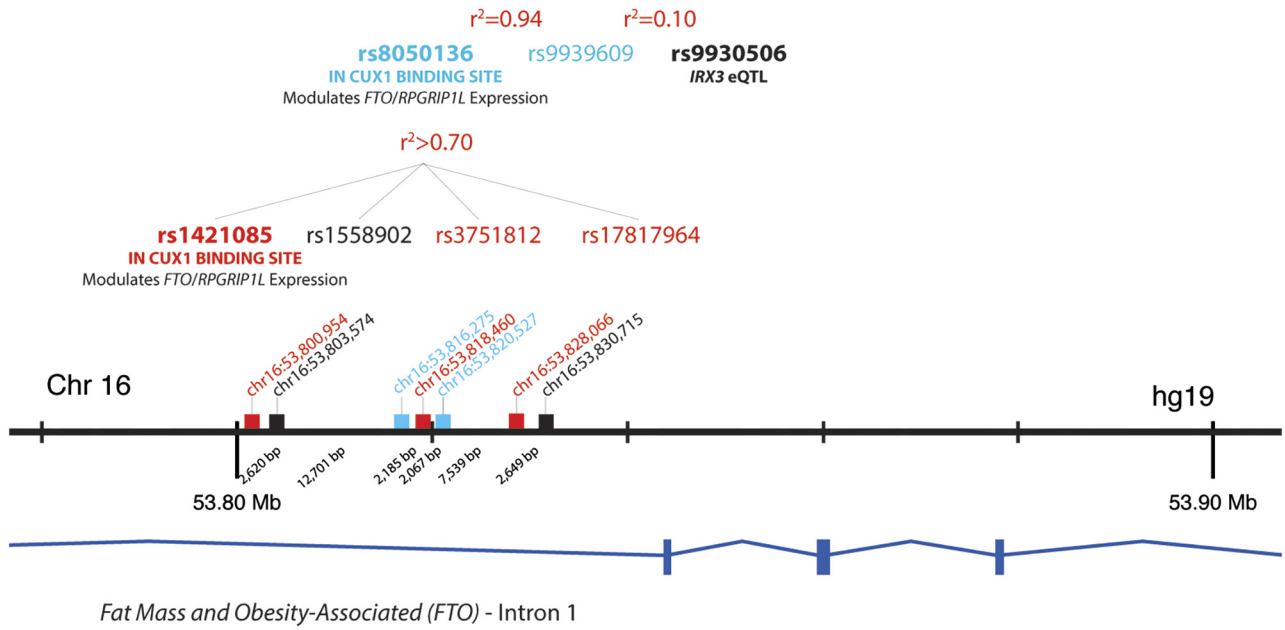

Fig. 1. Obesity-associated single nucleotide polymorphisms (SNPs) in intron 1 of fat mass and obesity-associated (*FTO*). Red SNPs are associated with obesity in African Americans (AAs) only. Blue SNPs are associated with obesity in Europeans only. Black SNPs are associated with obesity in both European and African Ancestry populations. Red linkage disequilibrium (r^2) values pertain to AAs from the 1000 Genomes African Southwest (ASW) population.

ing at rs1421085 (CC to TT) in preadipocytes homozygous for the obesity risk alleles at rs1421085 (C), rs9930506 (A), and rs1558902 (A) restored the transcriptional repressor ARID5B's binding motif in an enhancer spanning rs1421085. ARID5B binding inhibited *IRX3* and *IRX5* expression, resulting in the differentiation of preadipocytes into more energy-consuming beige adipocytes rather than white adipocytes. Interestingly, others have found that *IRX3* has the opposite effect, and its presence induces thermogenesis in vitro and in vivo (58).

The majority (but not all, for example rs1558902 and rs9930506) of the obesity-associated *FTO* SNPs in Europeans and African Americans (AAs) are therefore mutually exclusive based on LD patterns in AAs (26, 27). While the European- and African-specific groups of SNPs are indistinguishable among Europeans due to LD, in AAs each group of SNPs belongs to an independent LD cluster of correlated SNPs, despite being physically intercalated (Fig. 1, Table 1) (27).

European- and African-ancestry groups' distinct population genetic histories account for their disparate LD patterns. AAs represent an admixture of Africans and Europeans, and the former are the oldest of modern human populations in evolutionary terms. Compared with other ancestral groups Africans have experienced more generations for LD to decay via recombination and mutation (49, 50).

As a consequence of reduced LD, fewer SNPs from GWAS of AAs may tag physiologically relevant loci, and disease-associated SNPs may reside closer to disease-causing alleles, compared with GWAS of evolutionarily younger populations such as Europeans and Asians (31). We therefore sought to fine-map the obesity-associated *FTO* locus by leveraging the increased haplotype

Table 1. *Linkage disequilibrium (r^2) between obesity-associated FTO SNPs in the 1000 Genomes ASW population*

	AA SNP		Eur SNP	AA SNP	Eur SNP	AA SNP	Eur and AA SNP (IRX3 eQTL)
	rs1421085	rs1558902	rs8050136	rs3751812	rs9939609	rs17817964	rs9930506
AA SNP							
rs1421085	-						
Eur and AA SNP							
rs1558902	**0.972**	-					
Eur SNP							
rs8050136	0.138	0.136	-				
AA SNP							
rs3751812	**0.966**	**0.939**	0.147	-			
Eur SNP							
rs9939609	0.117	0.116	**0.841**	0.125	-		
AA SNP							
rs17817964	**0.908**	**0.883**	0.151	**0.934**	0.127	-	
Eur and AA SNP (IRX3 eQTL)							
rs9930506	0.420	0.400	0.090	0.430	0.070	0.460	-

ASW, African Southwest; eQTL, expression quantitative trait locus; FTO, fat mass and obesity-associated; SNP, single nucleotide polymorphism.

diversity and reduced LD in AAs, as well as functional genomic annotations from the Encyclopedia of DNA Elements (ENCODE) (10) and Roadmap Epigenomics (37) Projects.

SUBJECTS AND METHODS

Individual-level Data

The Population Architecture using Genomics and Epidemiology (PAGE) study comprises large, ethnically diverse, and well-characterized extant population studies, with subjects ranging from age 20 to 85 yr (29). Through the Database of Genotypes and Phenotypes (dbGaP phs000223.v5.p1), we obtained access to Illumina Metabochip SNP data from 3335 self-reported African Americans from the Atherosclerosis Risk in Communities (ARIC) cohort who were genotyped as part of the PAGE Metabochip Pilot Study (Table 2).

Summary Statistics

We performed statistical fine-mapping of the *FTO* locus by analyzing summary association statistics [Z-scores computed from estimated effect sizes on ln(BMI) and the corresponding standard errors for each analyzed SNP] from the largest study of *FTO* and adiposity in AAs to date (34). This study involved a meta-analysis of data from over 20,000 AAs genotyped on the Metabochip by the PAGE consortium (Supplemental Table S1; see https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738). Further details regarding each source population and genotyping are in Supplemental Text 1 and 2 (https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738), as well as the reports by Peters et al. (34) and Gong et al. (13). This SNP array was designed to reliably capture common and rare variation at metabolic trait-associated loci from GWAS, including the *FTO* locus, for signal fine-mapping (3, 8, 13).

Summary association data are available for a total of 51 *FTO* SNPs: all seven SNPs previously reported in studies of obesity in Europeans and AAs; the four SNPs most significantly associated with obesity in the PAGE meta-analysis of adiposity GWAS among AAs (rs56137030, rs62033400, rs7188250, and rs62033413); three other *FTO* SNPs that were associated with obesity in previous GWAS of Europeans (rs1121980, rs6499640, and rs9941349), 30 rs56137030 tag SNPs at the *FTO* locus (21 with $r^2 > 0.5$ and 9 with $r^2 > 0.2$ to < 0.5 in AAs); and seven SNPs highlighted in previous studies of AAs (Supplemental Table S2; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738). We matched the summary statistics' reference and alternate alleles' designations to those in the 1000 Genomes Project's African Southwest (ASW) population.

Outcome Definition

BMI, the primary outcome, was log-transformed to normalize the distribution and to reduce the influence of outliers on the analyses.

Confounding by Ancestry

In our analyses of individual-level ARIC data, we adjusted for population stratification as a covariate using principal components analysis (PCA). To account for possible heterogeneity arising from differential admixture in AAs, we used the ADMIXTURE program (1) to generate ancestry proportions in a supervised analysis, using 90 HapMap YRI and 165 CEU subjects as proxies for ancestral African and European populations, and examined whether the phasing and allelic association analysis results differed between AAs who shared relatively more (i.e., ≥60%) or less (<60%) markers with the YRI trios. This cutoff was based on the observation that over 90% of the ARIC cohort shared ≥60% markers with YRI trios (Supplemental Fig. S1; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738).

Functional SNP Annotations

The ENCODE project has annotated more than 80% of the human genome with functional elements including sites of deoxyribonuclease I (DNase I) hypersensitivity (DHS), transcription factor binding, and histone modification (10). In addition, the National Institutes of Health Roadmap Epigenomics Consortium has generated reference epigenomic maps for "normal" human cells and tissues, using RNA-Seq, DHS, DNA methylation, and histone modification data (37) (Supplemental Text S4; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738). The Roadmap reference epigenomes' full names and additional information are given in Supplemental Table S2; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738.

Analytic Approaches

We used the statistical fine-mapping program PAINTOR (21) to prioritize *FTO* SNPs associated with BMI in AAs, while incorporating pairwise LD as well as functional annotations. As additional input, PAINTOR required specification of the number of SNPs that were truly "causal" (driving the association signal at the *FTO* locus); we therefore first performed haplotype analyses on individual-level data to determine the number of unique signals influencing BMI in AAs.

Haplotype analyses of individual-level ARIC data. Using PLINK 1.90 (5), we inferred orthogonal principal components (PCs) of ancestry representing the top eigenvectors of the standardized similarity matrix between samples. The genomic control variance inflation factor (λ_{GC}) was used to show whether population stratification was inflating the genotype-disease test statistic. A postadjustment λ_{GC} value near unity (<1.05) (35) and significant *P* values for previously established obesity-SNP relationships confirmed that the PCs adequately accounted for population stratification.

We phased haplotypes composed of the *FTO*-associated SNPs rs1421085, rs1558902, rs8050136, rs3751812, rs9939609, rs17817964, and rs9930506 using PLINK 1.07 (36) and estimated haplotype frequencies, with the minimum frequency set to 1%. Next, while adjusting for age, sex, and ancestry, we tested for haplotype associations with ln(BMI) using a χ^2 test with n-1 degrees of freedom, where n was the number of haplotypes identified in the prior phasing step. Since we expected risk alleles at *FTO* SNPs with prior obesity associations in AAs (rs1421085, rs1558902, rs3751812, and rs17817964) to drive any haplotypic association(s) between *FTO* and adiposity in AAs, we tested whether the haplotype(s) containing their alternate alleles (all in perfect LD) were associated with adiposity while designating the other haplotypes to the reference haplogroup. Statistical significance was set at $\alpha = 0.05$, and there was no need to correct for multiple comparisons, as these analyses were restricted to a small number of haplotypes, with all but one set to the reference haplogroup.

We also separately phased *FTO* SNPs associated with obesity in African populations (rs1421085, rs1558902, rs3751812, and

Table 2. *Descriptive statistics for AAs in the ARIC study with individual-level SNP data available*

Study Duration	*n*	Mean Age ± SD (Range)	*n* (%) Women	Mean BMI ± SD	*n* (%) with BMI ≥30 kg/m^2
1987–present	3,335	53.5 ± 5.8 (45–64)	2,090 (62.7%)	29.7 ± 6.3	1,365 (66.3%)

AA, African American; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index.

rs17817964) and in Europeans (rs8050136 and rs9939609) using PHASE 2.1 (41, 42) and examined average BMI values for each haplotype as well as all combinations of "African" and "European" haplotypes. Since the *IRX3* expression quantitative trait locus (eQTL) rs9930506 is not in strong LD with the other *FTO* SNPs in AAs ($r^2 = 0.35–0.39$), we separately considered this SNP in additional analyses of both AA and European haplotypes.

Statistical fine-mapping of summary association statistics from PAGE Meta-GWAS. PAINTOR takes as input *1*) the Z-score or Wald statistic $\left(\frac{\hat{\beta}}{SE(\hat{\beta})}\right)$ from regressing ln(BMI) on each SNP, *2*) an LD matrix representing pairwise Pearson correlation coefficients between each SNP, and *3*) an annotation matrix with rows corresponding to SNPs and columns representing unique annotations (i.e., SNP i is a member of annotation K if entry $[i,k] = 1$). We created an LD matrix using data from the 1000 Genomes ASW population and generated a 51×1145 annotation matrix for all 51 *FTO* SNPs for which summary statistics and LD data were available (Supplemental Table S9; https://figshare.com/articles/FTO_Table_S9_xlsx/9971447). Functional annotations included DHS data from Maurano et al. (30) and Thurman et al. (48) as well as chromatin states from Hoffman et al. (19) and the Roadmap Epigenomics Consortium (37).

The prior probability of association for each SNP was governed by whether its coordinate coincided with those of tissue-specific functional annotations. To determine which annotations were directly relevant to the truly causal subset of adiposity-associated SNPs, we used an empirical Bayes approach (21). We fit a PAINTOR model for each annotation independently to generate annotation-specific marginal log likelihoods and then divided these values by the marginal likelihood for the null model (no annotations) to compute likelihood ratio test statistics ($\sim\chi^2$ with 1 d.f.). We included the most statistically significant ($P < 0.10$) annotations in a final PAINTOR model to calculate each SNP's posterior probability of association with adiposity.

Ethics Statement

This study was approved by the Institutional Review Board of Columbia University (IRB-AAAN4760).

RESULTS

Data sets

We first analyzed haplotypes in individual-level data from 3,335 persons with African ancestry (Table 2) to determine the number of putative causal SNPs for the BMI association signal at the *FTO* locus. Next, we statistically fine-mapped the *FTO*-adiposity association with PAINTOR by analyzing summary statistics from 20,488 AAs, incorporating pairwise LD between SNPs (Supplemental Tables S1 and S2; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738), as well as functional annotations based on epigenetic data. The Metabochip was the primary genotyping platform.

Principal Components Analysis

We adjusted for confounding by population stratification in the individual-level data using all autosomal Metabochip SNPs outside of the 2.5 kb flanking the *FTO* and *RPGRIP1L* genes, to avoid controlling for the effect of interest. After we pruned the marker list to exclude SNPs in strong pairwise LD ($r^2>0.3$) as well as common variants (minor allele frequency >0.05), 69,209 markers remained, well above the ~10,000 SNPs needed to accurately infer population structure (47). Without any adjustment for population stratification, the variance inflation (λ_{GC}) was 1.19, and the association between the previously identified obesity-associated *FTO* SNP rs1421085 and lnBMI in ARIC was not significant ($P = 0.80$). After adjustment for the top three PCs, the λ_{GC} was negligible (1.04), while the rs1421085-lnBMI relationship was nominally significant ($P = 0.06$).

Haplotype Phasing, Association Testing, and Stratified Analyses

We used individual-level genotype and phenotype data to perform phasing and to identify the risk-associated multimarker haplotype(s) and then determined the minimum number of unique signals that may underlie their relationship with adiposity. Phasing the *FTO* SNPs rs1421085, rs1558902, rs8050136, rs9939609, rs3751812, rs17817964, and rs9930506 yielded six haplotypes (Supplemental Table S4; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738). CAATTTG was the multimarker haplotype containing the risk alleles for SNPs associated with obesity in studies of AAs (rs1421085, rs1558902, rs3751812, and rs17817964) and was designated as the risk haplotype. Mean BMI was slightly elevated for CAATTTG carriers compared with noncarriers (Supplemental Table S5; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738).

The CAATTTG multimarker risk haplotype was nominally associated with ln(BMI) in the full ARIC cohort ($F = 3.68$; $P = 0.055$), and the association became significant ($F = 4.65$; $P = 0.031$) after restricting to ARIC subjects who share over 60% of their markers with the YRI trios from the HapMap Project (Supplemental Table S6; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738). The association weakened when the threshold was increased to include those sharing >70% or >80% of their markers with the Yorubans ($P = 0.083$; $P = 0.097$, respectively), but the sample size diminished with further restriction to increase homogeneity. All analyses were adjusted for age, sex, as well as the top three PCs of ancestry.

Given the tight LD we observed between the SNPs exclusively associated with disease in African-ancestry populations, we separately phased the *FTO* SNPs associated with obesity in AAs only, along with rs1558902 (rs1421085, rs1558902, rs3751812, and rs17817964), and Europeans only (rs8050136 and rs9939609). We considered rs9930506 separately (below), since it was not in strong LD with either SNP cluster. BMI was elevated among carriers of both the African multimarker risk haplotype (CATT), and the European risk haplotype (AT) (Table 3).

We further considered how BMI varied with respect to combinations of European- and African-ancestry *FTO* multimarker haplotypes, as well as rs9930506 genotype (Table 3). The European risk haplotype (AT) did not appear to increase mean BMI beyond levels attributable to the risk alleles of SNPs significant in studies of AAs. However, the rs9930506 risk allele (A) [**A**/CATT (mean BMI 31.7 ± 6.1) versus **G**/CATT (mean BMI 29.8 ± 6.4)] appeared to increase BMI beyond the level attributable to the African risk haplotype CATT alone. Therefore, there may be at least two distinct signals, from the African risk haplotype (CATT) and the rs9930506 risk (A) allele, underlying the relationship between *FTO* and obesity in AAs. We were unable to test whether these

Table 3. *BMI among ARIC subjects with haplotypes derived from European and African obesity-associated SNPs*

rs1421085	rs1558902	rs8050136	rs3751812	rs9939609	rs17817964	rs9930506	Multimarker Haplotype Count (Frequency)	Mean BMI ± SD
African Obesity-associated SNPs								
T	T	-	G	-	C	-	5,888 (0.883)	29.7 ± 6.2
C	**A**	-	**T**	-	**T**	-	700 (0.105)	29.8 ± 6.3
European Obesity-associated SNPs								
-	-	C	-	A	-	-	3,462 (0.519)	29.6 ± 6.3
-	-	C	-	**T**	-	-	285 (0.043)	30.0 ± 6.1
-	-	**A**	-	A	-	-	4 (0.001)	28.7 ± 8.3
-	-	**A**	-	**T**	-	-	2,919 (0.438)	29.8 ± 6.2
European SNP Haplotypes versus the African TTGC Haplotype								
T	T	C	G	A	C	-	3,442 (0.516)	29.6 ± 6.3
T	T	C	G	**T**	C	-	281 (0.042)	29.9 ± 6.1
T	T	**A**	G	A	C	-	4 (0.001)	28.7 ± 8.3
T	T	**A**	G	**T**	C	-	2,161 (0.324)	29.7 ± 6.1
European SNP Haplotypes versus the African CATT Haplotype								
C	**A**	C	**T**	A	**T**	-	-	-
C	**A**	C	**T**	**T**	**T**	-	-	-
C	**A**	**A**	**T**	A	**T**	-	-	-
C	**A**	**A**	**T**	**T**	**T**	-	700 (0.105)	29.8 ± 6.4
rs9930506 Alleles versus the African TTGC Haplotype								
T	T	-	G	-	C	G	660 (0.010)	29.4 ± 5.8
T	T	-	G	-	C	**A**	5,228 (0.784)	29.7 ± 6.3
rs9930506 Alleles versus the African CATT Haplotype								
C	**A**	-	**T**	-	**T**	G	698 (0.105)	29.8 ± 6.4
C	**A**	-	**T**	-	**T**	**A**	2 (0.0003)	31.7 ± 6.1
European SNP Haplotypes and rs9930506 Alleles versus the African TTGC Haplotype								
T	T	C	G	A	C	G	261 (0.039)	29.4 ± 5.5
T	T	C	G	**T**	C	G	-	-
T	T	**A**	G	A	C	G	-	-
T	T	**A**	G	**T**	C	G	401 (0.060)	29.5 ± 5.9
T	T	C	G	A	C	**A**	3,181 (0.477)	29.7 ± 6.4
T	T	C	G	**T**	C	**A**	281 (0.042)	29.9 ± 6.1
T	T	**A**	G	A	C	**A**	3 (0.0004)	28.7 ± 8.3
T	T	**A**	G	**T**	C	**A**	1,760 (0.264)	29.8 ± 6.1
European SNP Haplotypes and rs9930506 Alleles versus the African CATT Haplotype								
C	**A**	C	**T**	A	**T**	G	-	-
C	**A**	C	**T**	**T**	**T**	G	-	-
C	**A**	**A**	**T**	A	**T**	G	-	-
C	**A**	**A**	**T**	**T**	**T**	G	698 (0.105)	29.8 ± 6.4
C	**A**	C	**T**	A	**T**	**A**	-	-
C	**A**	C	**T**	**T**	**T**	**A**	-	-
C	**A**	**A**	**T**	A	**T**	**A**	-	-
C	**A**	**A**	**T**	**T**	**T**	**A**	2 (0.0003)	31.7 ± 6.1

Risk alleles are in boldface.

patterns were statistically significant because of small sample sizes. Similar trends were apparent in analyses restricted to ARIC subjects with >60% marker sharing with YRI individuals.

Statistical Fine-Mapping of the FTO Locus for Mechanistic Inferences

To further analyze the *FTO* locus we carried out statistical fine-mapping assuming two putative causal SNPs [the risk alleles at rs1421085, rs1558902, rs3751812, and rs17817964 (CATT) and the rs9930506 risk allele (A) driving increased mean BMI], utilizing summary statistics for 51 *FTO* SNPs (Supplemental Table S2; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738) from a previous study of the *FTO* locus and obesity (34) as well as 1,145 functional annotations from ENCODE and Roadmap, while accounting for LD.

First, we identified the tissue-specific functional annotations that were potentially significant ($P < 0.10$) in a PAINTOR model assuming two causal SNPs underlie the BMI association signal at the *FTO* locus (Supplemental Table S7; https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738). The SNPs located in the annotated sites are presented in Supplemental Table S8 (https://figshare.com/articles/FTO_Suppl_physiologicalgenomics_docx/8309738). The significant annotations included 1) possible enhancers containing H3K27ac marks (EnhAc) and 2) regions positionally biased toward the 5′ end of actively transcribed genes (Tx5′) in fat (E023), brain [substantia nigra (E074)], cartilage (E049), and liver (E066).

Using these annotations, we then generated a PAINTOR model of the posterior probability of association (PPA) for each SNP. The results are summarized in Table 4, which also shows the potentially significant annotations in regions containing the highest-ranking SNPs. rs9927317 and rs62033405 had the highest PPA (Fig. 2). rs9927317 overlapped with significant Tx5′ annotations in mesenchymal stem cell-derived adipocytes (E023), mesenchymal stem cell-derived chondrocytes (E049), and substantia nigra (E074), while rs62033405 overlapped with EnhAc sites in adipocytes (E023) and chon-

Table 4. *FTO SNPs' summary association statistics and posterior probability of association with adiposity in AAs in PAINTOR models assuming two causal SNPs underlie the FTO-obesity relationship*

rsID	Chr. 16 Pos.	Alt. Allele	Ref. Allele	MAF	Beta	Z Score	*P* Value	PPA	Overlapping Significant Annotations
rs6499640	53769677	**G**	A	0.35	−0.05	−0.25	8.10E-01	0.00	
rs72803664	53784911	**A**	G	0.11	−0.13	−0.36	7.10E-01	0.00	
rs1108102	53789508	**A**	T	0.14	−0.09	−0.32	7.40E-01	0.00	
rs1421085	53800954	**C**	T	0.12	1.11	3.54	3.00E-04	0.00	
rs11642015	53802494	**T**	C	0.11	1.09	3.47	4.90E-04	0.00	
rs62048402	53803223	**A**	G	0.12	1.13	3.60	2.40E-04	0.00	
rs1558902	53803574	**A**	T	0.12	1.13	3.28	1.00E-03	0.00	
rs56094641	53806453	**G**	A	0.12	1.12	3.57	2.80E-04	0.00	
rs55872725	53809123	**T**	C	0.11	1.09	3.47	5.30E-04	0.00	
rs1121980	53809247	**A**	G	0.47	0.35	1.83	7.20E-02	0.00	
rs62033400	53811788	**G**	A	0.12	1.35	4.41	1.10E-05	0.00	
rs16945088	53812524	**G**	A	0.29	−0.16	−0.76	4.50E-01	0.00	
rs8057044	53812614	**G**	A	0.29	−0.27	−1.29	2.10E-01	0.00	
rs17817449	53813367	**G**	T	0.39	0.37	1.84	5.90E-02	0.00	
rs17817497	53815435	**C**	T	0.11	0.99	3.16	1.80E-03	0.00	
rs8050136	53816275	**A**	C	0.44	0.42	2.08	3.20E-02	0.00	
rs113191842	53817318	**A**	G	0.06	1.23	2.77	5.70E-03	0.00	
rs3751812	53818460	**T**	G	0.11	1.02	3.25	1.20E-03	0.00	
rs9939609	53820527	**T**	A	0.48	0.04	0.21	8.20E-01	0.00	
rs9927317	53820996	**G**	C	0.26	0.85	3.83	1.50E-04	0.94	E023 Tx5′, E049 Tx5′, E074 Tx5′
rs17817712	53821125	**G**	A	0.11	1.03	3.28	1.10E-03	0.00	
rs62033405	53822387	**T**	C	0.12	1.35	4.30	1.40E-05	0.99	E023 EnhAc, E049 EnhAc
rs79994966	53823727	**C**	T	0.11	1.34	4.27	1.80E-05	0.00	
rs28432761	53823878	**C**	T	0.19	0.83	3.29	9.70E-04	0.00	
rs11647020	53823990	**T**	C	0.2	0.73	2.89	3.50E-03	0.00	
rs11646715	53824007	**A**	G	0.19	0.84	3.20	1.10E-03	0.00	
rs62033406	53824226	**G**	A	0.14	0.85	3.00	2.50E-03	0.00	
rs9941349	53825488	**T**	C	0.19	0.69	2.73	5.40E-03	0.00	
rs56137030	53825905	**A**	G	0.12	1.35	4.41	8.30E-06	0.00	
rs28567725	53826028	**C**	T	0.22	0.87	3.59	2.40E-04	0.00	
rs9931494	53827179	**G**	C	0.19	0.94	3.72	1.60E-04	0.00	
rs10468280	53827479	**G**	A	0.11	1.01	3.22	1.40E-03	0.00	
rs62033408	53827962	**G**	A	0.11	1.03	3.28	1.10E-03	0.00	
rs17817964	53828066	**T**	C	0.12	1.02	3.36	8.60E-04	0.00	
rs62033413	53830055	**G**	C	0.12	1.33	4.34	1.40E-05	0.00	
rs9930506	53830465	G	**A**	0.22	0.66	2.72	5.50E-03	0.00	
rs9933040	53830867	**A**	T	0.22	0.65	2.68	6.00E-03	0.00	
rs9922708	53831146	**T**	C	0.21	0.64	2.44	1.60E-02	0.00	
rs72805611	53831354	**T**	C	0.12	0.97	3.20	1.30E-03	0.00	
rs9922619	53831771	**T**	G	0.19	0.69	2.73	5.70E-03	0.00	
rs7204609	53833605	**C**	T	0.34	−0.16	−0.76	4.30E-01	0.00	
rs7188250	53834607	**C**	T	0.12	1.34	4.38	1.30E-05	0.01	
rs72805612	53834608	**A**	G	0.12	1.36	4.33	1.40E-05	0.01	
rs11075993	53837144	**T**	G	0.12	0.98	3.12	5.00E-01	0.00	
rs72805613	53837342	**G**	A	0.12	0.89	2.93	3.30E-03	0.00	
rs8044769	53839135	**T**	C	0.25	−0.33	−1.50	1.30E-01	0.00	
rs12149832	53842908	**A**	G	0.12	0.92	2.93	2.50E-03	0.00	
rs11649091	53845169	**G**	T	0.16	1.1	3.88	9.10E-05	0.00	
rs11642841	53845487	**A**	C	0.11	0.88	2.72	5.70E-03	0.00	
rs7191513	53990523	**G**	A	0.46	−0.03	−0.15	8.70E-01	0.00	
rs9932411	54005163	**T**	C	0.33	0.12	0.57	5.50E-01	0.00	

Risk alleles are in boldface. Betas for ln(BMI) represent the % change in BMI conferred per copy of the risk allele. Significant functional annotations overlapping with the two highest-PPA SNPs are indicated in the last column. MAF, minor allele frequency; PPA, posterior probability of association; Tx5′, transcribed – 5′ preferential; EnhAc, primary H3K27ac possible enhancer.

drocytes (E049). To predict the target genes of these SNP-spanning putative regulatory elements, we examined GTEx data but found that rs9927317 and rs62033405 do not tag eQTLs in fat, brain or cartilage tissues or cells assayed by GTEx.

DISCUSSION

FTO has the strongest statistical association with BMI in GWAS, but the molecular basis for the association of the intron 1 SNPs driving this signal remains unclear. And, while *FTO* variants have modest effect sizes (risk alleles at this locus increase BMI by 0.39 kg/m^2), they are enriched for regulatory elements (30, 37) that likely modulate the expression of genes involved in adiposity-related physiology. It is possible that multiple mechanisms in several cell types are responsible (26). In this study, we sought to identify the specific alleles and tissues responsible for the relationship between *FTO* and adiposity by capitalizing on the Metabochip's locally high SNP density, AAs' low LD and high haplotype diversity, and leveraging functional annotations in non-coding DNA.

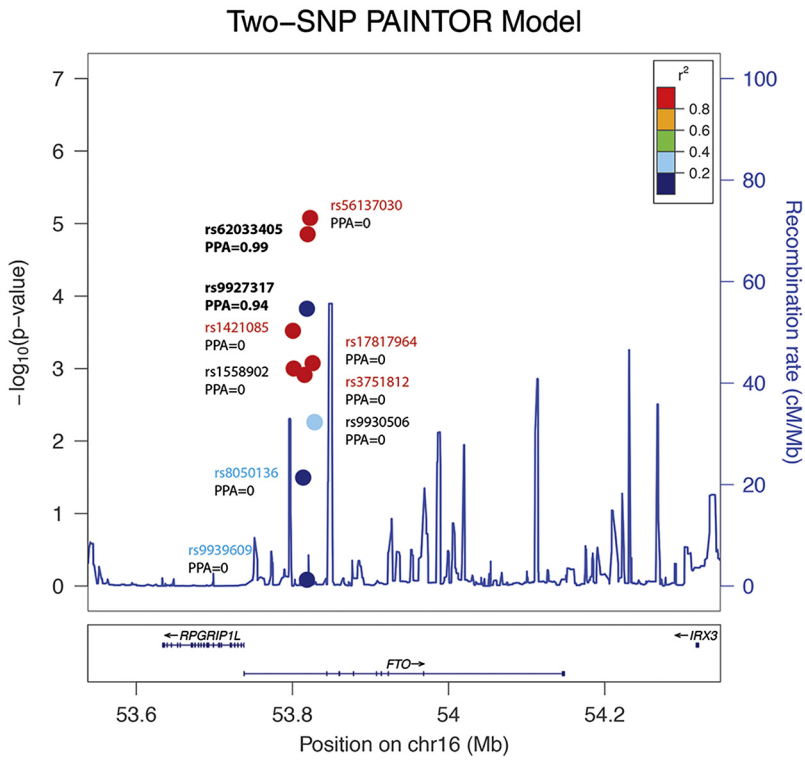

Fig. 2. *FTO* SNPs with the highest posterior probability of association (PPA) with obesity in AAs based on a PAINTOR model assuming two causal SNPs. SNPs with blue labels are associated with obesity in Europeans. SNPs with red labels are associated with obesity in African Americans (AAs). SNPs with black labels are associated with obesity in both European and African Ancestry populations. SNPs are positioned with respect to the statistical significance of their association with lnBMI in AAs from the association study by Peters et al (34). Dot colors indicate SNPs' linkage disequilibrium (r^2) with the cluster of obesity-associated SNPs in AAs.

Haplotype association analyses confirmed a significant relationship between the *FTO* multimarker haplotype (CAATTTG), containing previously established obesity risk alleles at rs1421085, rs1558902, rs8050136, rs9939609, rs3751812, and rs17817964, plus the reference allele (G) at rs9930506, and ln(BMI) in subjects from the ARIC study ($P = 0.031$). Our analyses showed that: *1*) the CATT haplotype containing African risk alleles and *2*) the risk (A) allele at rs9930506 both contributed to increased mean BMI in AA adults.

We next performed statistical fine-mapping using PAINTOR to distinguish *FTO* SNPs in LD by ranking them by their PPA with adiposity; we also sought to identify the tissues or cellular contexts in which these markers might contribute to differences in adiposity. We utilized summary association statistics from a study of *FTO*-adiposity associations in 20,000 AAs, currently the best-powered high-resolution analysis of *FTO* available for this population (34). In the model assuming two causal SNPs, rs9927317 and rs62033405, had the highest PPA. PAINTOR did not probabilistically implicate any of the SNPs previously identified in major obesity GWAS as causal, although this is not unexpected since SNPs selected for genotyping arrays employed in GWAS are usually chosen based on the efficiency with which they tag variation genome-wide (9).

The cluster of SNPs previously associated with obesity in AAs was indirectly represented in the PAINTOR results, as the cluster is in LD with rs62033405 ($r^2 > 0.8$) (Fig. 2, Table 4). In contrast, rs9927317, the other SNP implicated by PAINTOR, is not strongly correlated with any other SNPs in summary statistics made available by the authors. As expected, rs9939609 and rs8050136 had PPAs of 0 since they are not associated with obesity in AAs.

rs9930506, the second signal identified in the haplotype association analyses, is an *IRX3* eQTL but was not represented among the high-PPA SNPs, as rs9927317 and rs62033405 were only weak proxies ($r^2 \sim 0.25$). The relationship between rs9930506 and adiposity in AAs was nominally significant ($P = 3.9 \times 10^{-5}$) when analyses were restricted to candidate genes ($P = 5.8 \times 10^{-5}$ significance threshold), but not significant Metabochip-wide following correction for multiple testing ($P = 2.5 \times 10^{-7}$ significance threshold) (13), suggesting that greater statistical power may be needed to detect its possible effect in this population.

"EnhAc" denotes a possible enhancer site due to the presence of H3K27ac marks associated with the activation of enhancer regions. rs62033405 was enriched for EnhAc chromatin states in white adipocytes (E023) and cartilage (E049), while rs9927317 was significantly enriched for Tx5′ chromatin states in E023, E049, as well as the substantia nigra (E074). Follow-up experiments are needed to identify the target gene(s). "Tx5′" indicates that the annotated region is preferentially associated with the start (5′) end of actively transcribed genes, in this case *FTO*, and is enriched for H3K79me2, H4K20me1, and H3K36me3 marks that are associated with transcriptional regulation and maintenance of genomic integrity (11, 20, 22).

The substantia nigra is part of a dopamine signaling circuit that also includes the ventral tegmental area, caudate putamen, and nucleus accumbens. *Fto*-deficient mice display impaired dopamine type 2 and type 3 receptor (D2/3R)-dependent neuronal activation and behavioral responses (18) related to reward sensitivity and addiction. We identified EnhAc and Tx5′ annotations overlapping intronic *FTO* SNPs in white adipocytes (E023), while Claussnitzer et al. (7) showed that perturbation of an rs1421085-spanning enhancer in preadipocytes (E025) resulted in their preferential differentiation into beige adipocytes versus white adipocytes. In line with both of

these findings, our group has shown that *Fto* influences biological processes at multiple points in the adipocyte lineage, promoting adipogenesis in preadipocytes as well as maintaining lipid content in mature white adipocytes (28). Overall, our findings are consistent with previous work implicating *FTO* SNPs in obesity pathogenesis in distinct tissues such as the brain and adipose tissue (4, 7, 39, 43, 45, 53).

We identified tissues with biologically plausible roles in obesity pathophysiology, particularly the substantia nigra and adipocytes. Our haplotype analyses identified two independent BMI-elevating signals important for characterizing the contribution of the *FTO* locus to adiposity in AAs (the CATT multimarker haplotype and the rs9930506-A allele), which are distinguishable in African- but not European-ancestry populations due to LD. Our PAINTOR analysis assigned the highest posterior probability of association with BMI in AAs to rs62033405, which is in strong LD with the SNPs contributing to the multimarker CATT signals from the rs1421085, rs1558902, rs3751812, and rs17819964 risk alleles, providing an additional line of evidence that these SNPs reliably represent an *FTO* adiposity risk signal in AAs. Larger and higher-resolution studies in this population are needed to understand whether the same can be said for the signals we identified at rs9930506 and rs9927317. Due to extensive and high LD in European-ancestry groups, the aforementioned SNPs are indistinguishable from variants such as rs9939609 and rs8050136, although the latter two SNPs and their proxies in AAs better represent *FTO* associations with adiposity in Europeans since they are not associated with BMI in AAs. Thus, based upon the analyses reported here, and by others (27), in studies of *FTO* contributions to phenotypes related to adiposity (BMI) in diverse populations, AAs should be scored using SNPs rs1421085, rs3751812, and rs17817964 and Europeans using SNPs rs8050136 and rs9939609; the first SNPs in each set are likely the most representative given previous demonstration of their effects on CUX1 binding and gene regulation (7, 44–46). The single SNP rs1558902 could be used to score both AAs and Caucasians, but with reduced specificity. The use of diverse populations is advantageous for gene discovery related to complex traits (57).

While we performed statistical fine-mapping on a reasonably large number of *FTO* SNPs, the actual disease-relevant markers may not have been identified in this study and may only be implicated through analyses of higher-resolution genetic data from AAs. Using the same summary statistics, we attempted to impute the association information for additional SNPs at the *FTO* locus, but the available markers were not sufficiently dense. We also considered summary information from other studies of obesity in African-ancestry populations, but none had as many *FTO* SNPs for fine-mapping as well as a larger sample size. Lastly, the present study lacked adjustment for unmeasured lifestyle and environmental factors such as diet and exercise, which may modify the penetrance of *FTO* genotypes on adiposity (52). As additional association data and functional annotations from larger samples as well chromatin looping data from disease-relevant contexts (23) become available, analyses similar to those we report here have potential to further refine *FTO* locus association signals for obesity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.G. conceived and designed research; R.G. performed experiments; R.G. analyzed data; R.G., G.S., J.H.L., and R.L.L. interpreted results of experiments; R.G. prepared figures; R.G. drafted manuscript; R.G., J.H.L., and R.L.L. edited and revised manuscript; R.G., G.S., J.H.L., and R.L.L. approved final version of manuscript.

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