FTO Genetic Variation and Association With Obesity in West Africans and African Americans

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OBJECTIVE—The *FTO* gene is one of the most consistently replicated loci for obesity. However, data from populations of African ancestry are limited. We evaluated genetic variation in the *FTO* gene and investigated associations with obesity in West Africans and African Americans.

RESEARCH DESIGN AND METHODS—The study samples comprised 968 African Americans (59% female, mean age 49 years, mean BMI 30.8 kg/m^2) and 517 West Africans (58% female, mean age 54 years, mean BMI 25.5 kg/m^2). *FTO* genetic variation was evaluated by genotyping 262 tag single nucleotide polymorphisms (SNPs) across the entire gene. Association of each SNP with BMI, waist circumference, and percent fat mass was investigated under an additive model.

RESULTS—As expected, both African-ancestry samples showed weaker linkage disequilibrium (LD) patterns compared with other continental (e.g., European) populations. Several intron 8 SNPs, in addition to intron 1 SNPs, showed significant associations in both study samples. The combined effect size for BMI for the top SNPs from meta-analysis was 0.77 kg/m^2 (P = 0.009, rs9932411) and 0.70 kg/m^2 (P = 0.006, rs7191513). Two previously reported associations with intron 1 SNPs (rs1121980 and rs7204609, r^2 = 0.001) were replicated among the West Africans.

CONCLUSIONS—The *FTO* gene shows significant differences in allele frequency and LD patterns in populations of African ancestry compared with other continental populations. Despite these differences, we observed evidence of associations with obesity in African Americans and West Africans, as well as evidence of heterogeneity in association. More studies of *FTO* in multiple ethnic groups are needed. ***Diabetes*** **59:1549–1554, 2010**

The fat mass and obesity associated gene (*FTO*) (GeneID: 79068) is currently the most consistently replicated gene for obesity in humans. The first studies establishing this association were published in 2007 (1–3); since then, multiple studies have been done to confirm the epidemiological association and elucidate the physiological role played by the protein product of the gene (4). While the epidemiological evidence for the association of *FTO* with obesity is quite strong, it has not been consistently replicated in all populations studied, and there remain multiple populations for which data are scarce or absent.

Data on *FTO* genetic variation and association with obesity in African ancestry populations are quite scarce. Populations with a majority of African ancestry are interesting with respect to obesity because they show wide variation in the prevalence of obesity across levels of industrialization (for example, across West Africa, the Caribbean, and the U.S.) (5,6). At the same time, they often exhibit significant disparities compared with other ethnic groups within the same country, for example, African Americans when compared with other ethnic groups in the U.S. (7). Given the greater genetic diversity and different linkage disequilibrium (LD) structure exhibited by African-ancestry populations, understanding genetic variation in the *FTO* gene in African populations promises to provide novel insights into its association with obesity.

We have evaluated *FTO* genetic variation in two populations of African ancestry, African Americans and West Africans, and tested the association of *FTO* variants with obesity (as measured by BMI, waist circumference [WC], and percent fat mass [PFM]) in an effort to replicate previous findings and to search for novel associations of *FTO* variants with obesity in populations of African ancestry.

RESEARCH DESIGN AND METHODS

The study included two sets of participants: *1*) 968 unrelated African Americans (estimated African ancestry 0.78 ± 0.11) enrolled from the Washington, D.C., metropolitan area in the U.S. as part of the Howard University Family Study, and *2*) 517 unrelated West Africans enrolled as control subjects as part of the Africa-America Diabetes Mellitus (AADM) Study. After obtaining written informed consent, participants underwent an interview followed by a physical examination during which weight, height, and WC were measured using standard methods. BMI was computed as weight (measured in kilograms) divided by the square of the height (measured in meters). Body composition was estimated using bioelectric impedance analysis with validated population-specific equations as previously described (8). PFM was calculated as (fat mass/weight)*100. DNA was extracted from buffy coats using PureGene kits (Gentra).

Based on the International HapMap Project (HapMap) YRI data, tag single nucleotide polymorphisms (SNPs) at a pairwise r^2 >0.8 and with a minor allele frequency (MAF) ≥0.02 were selected for genotyping. The resulting 273 SNPs were genotyped as part of a custom Illumina panel using the Illumina GoldenGate Assay. Of the 273 SNPs, 264 were successfully genotyped, giving a locus success rate of 96.7%. The genotype call rate was 99.32%. The concordance rate for blind duplicates was 99.98%. Two SNPs deviated significantly ($P < 0.001$) from Hardy-Weinberg equilibrium and were excluded from further analysis, leaving 262 SNPs.

MAFs were computed and LD visualized using Haploview (9). Association with obesity traits was tested under an additive model with adjustment for age and sex using PLINK version 1.06. Potential population stratification was accounted for in each sample by adjusting for the first principal component derived from a set of 142 ancestry-informative SNPs genotyped in the African American subjects and by adjusting for ethnic group among the West African subjects. Each sample was analyzed separately. Then, combined analysis was done using a meta-analysis technique that computes weighted statistics for

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TABLE 1
Characteristics of the 968 African American and 517 West African study participants

	African Americans		West Africans	
	Men	Women	Men	Women
n	401	567	219	298
Age (years)	49.0 ± 10.8	49.4 ± 12.5	56.1 ± 12.8	52.0 ± 12.9
Weight (kg)	88.9 ± 24.1	85.8 ± 24.0	69.4 ± 15.2	68.8 ± 16.3
Height (cm)	175.6 ± 7.5	163.1 ± 7.2	170.0 ± 6.8	160.7 ± 6.6
BMI (kg/m^2)	28.8 ± 7.5	32.3 ± 8.8	23.9 ± 4.8	26.6 ± 6.1
WC (cm)	96.3 ± 17.1	97.7 ± 17.1	87.3 ± 12.1	89.2 ± 12.9
PFM	28.7 ± 9.7	41.4 ± 8.5	18.5 ± 10.3	32.8 ± 12.0

Data are mean ± SD.

association and tests for heterogeneity, implemented in METAL (Meta Analysis Helper, available through the University of Michigan). Previous European studies have estimated that the *FTO* variant explains ~1% of the phenotypic variance in BMI (1–3). The present study has ~88% power (for the African American sample) and ~63% power (for West African sample) to explain ~1% of the variance in BMI for a SNP with an MAF of at least 0.05 at a two-tailed α level of 0.05.

Given the strong prior information about the role of *FTO* variation in obesity, we considered our evaluation of the association between intron 1 SNPs and obesity a replication study; thus, nominal *P* values ≤0.05 were considered significant. For SNPs in the rest of the gene, tests of associations could be considered discovery rather than replication for which a Bonferroni-corrected *P* value threshold of 0.0002 (0.05/209 SNPs) would be significant.

RESULTS

The characteristics of the study subjects are shown in Table 1. The African Americans weighed significantly more and had higher BMI, WC, and PFM than the West Africans. MAFs were generally similar between the two samples (supplementary Table 1, available in an online appendix at http://care.diabetesjournals.org.cgi/content/full/db09-1252/DC1). However, seven (2.7%) SNPs showed a difference (δ) in allele frequencies ≥0.1, and 88 (33.6%) SNPs showed a $\delta \geq 0.05$ (supplementary Fig. 1).

The LD structure across the gene in both study samples is shown in Fig. 1. Using the CI method of Gabriel et al. (10) to construct haplotype blocks, the African American sample had 59 haplotype blocks with 138 SNPs outside blocks while the West African sample had 58 blocks with 142 SNPs outside blocks. The LD structure in the two study samples is more fragmented than European or Asian continental populations (represented by the HapMap CEU and JPT/CHB samples, respectively) (Fig. 1 and supplementary Fig. 2). This pattern of low LD was also observed for the intron 1 region surrounding rs9939609, the most consistently reported obesity-associated *FTO* SNP (supplementary Fig. 3). Using a common set of polymorphic SNPs, the proportion of SNPs exceeding specific r^2 thresholds of 0.2, 0.4, 0.6, and 0.8, respectively, in the HapMap CEU, CHB, and JPT samples were approximately threefold higher than those in the present study and the HapMap YRI sample ($P < 0.0001$, supplementary Fig. 2, and supplementary Table 2). In contrast, there were no significant differences in these proportions between the West African and African American samples in the present study or between these and the HapMap YRI sample.

Table 2 shows the SNPs displaying $P \leq 0.01$ in either study population or in the meta-analysis. The top scoring SNPs for BMI were in intron 8 (Fig 2). For WC and PFM, the most significantly associated SNPs were in intron 8 or intron 1 (Table 2, Fig 2). The effect sizes for BMI were 0.9–1.7 kg/m^2 in West Africans, ~1–1.6 kg/m^2 in African Americans, and ~0.8 kg/m^2 in the meta-analysis for the two significant SNPs showing consistent direction of effect. The effect sizes for WC and PFM are shown in Table 2. Some SNPs (one for BMI, one for WC, and three for PFM) showed significant heterogeneity of association between the two study samples (Table 2). Haplotype analysis around these top-scoring SNPs showed that none of the haplotypes had a stronger association with any of the traits than the single SNPs they contained (data not shown). The only nonsynonymous coding SNP, rs16952624 (A405V), in this study (MAF 0.041 in West Africans, 0.024 in African Americans) showed no association with any of the obesity phenotypes in the West African (*P* 0.52–0.70) or African American sample (*P* 0.18–0.67). We note that none of the discovery SNPs in intron 8 reached statistical significance at a *P* value threshold of 0.0002 after correcting for multiple comparisons using the conservative Bonferroni-correction method.

We tested SNPs in the *FTO* gene previously reported to be associated with obesity in populations of European ancestry, including rs9939609, rs1121980, rs17817449, and rs7204609. The minor allele frequencies in our samples and the *P* values for association are shown in Table 2. We replicated the association with obesity for both rs1121980 and rs7204609 at $P \leq 0.05$ in the West African sample but not in the African American sample. Similarly, we looked for association in the set of 16 SNPs tested in the only published African sample to date (11) and found that rs7204609, rs17817288 and rs12447107 showed significant association with PFM in our West African sample (supplementary Table 4). As in the Gambian study (11), these SNPs did not show association with BMI in this study.

One of the potential advantages of studying an African population is the opportunity to fine-map loci that have been identified in populations with stronger LD. We therefore looked for evidence of association of SNPs with an $r^2 > 0.2$ with the strongest reported *FTO* variant (rs9939609) in the HapMap CEU. Only one of 13 such SNPs (rs8055197, $r^2 = 0.58$ in HapMap CEU) showed a small *P* value in the present study ($P = 0.012$ for BMI and $P = 0.015$ for WC, both in African Americans). Conversely, none of the SNPs in Table 1 showed strong LD with rs9939609 in the present study (maximum $r^2 = 0.337$ among West Africans, 0.223 among African Americans, (supplementary Table 5).

DISCUSSION

The *FTO* gene is one of the few genes to show consistent association with human obesity, particularly in populations of European ancestry (1,12–16), with few exceptions (17). In contrast, evidence from studies of other continental populations has been less consistent. Some studies of multiple Asian populations did not confirm this association (18–20) while other studies did (21,22). There are few studies from populations of African origin, and the data from such studies have been largely negative. In the first study that included African Americans, Scuteri et al. (1) did not replicate the *FTO* association with obesity in a sample of 1,100 African Americans, neither did two other studies (11,23). The first study that found association between *FTO* variants and obesity in an African-ancestry population was a study of childhood obesity (24). More recently, Wing et al. (25) showed that rs8050136 and rs9939609 were associated with BMI and WC among African Americans in the Insulin Resistance Atherosclero-

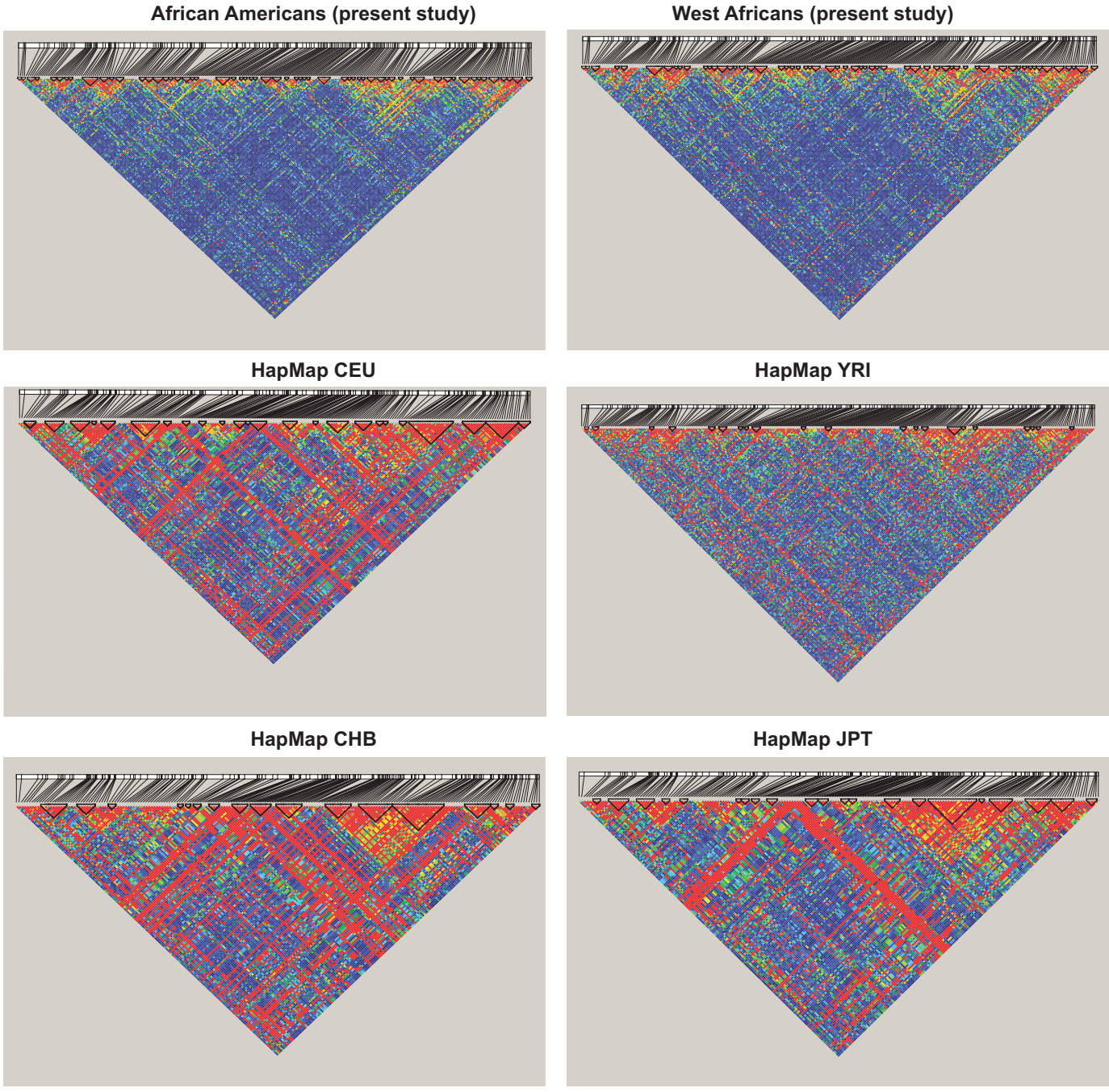

FIG. 1. LD patterns across the *FTO* gene in the two study samples (African Americans and West Africans) and in four HapMap population samples (European, CEU; East Asian, CHB and JPT; and African, YRI). (A high-quality digital representation of this figure is available in the online issue.)

sis Study (IRAS) Family Study. The only study so far of a sub-Saharan African population (11) was negative. Potential explanations for these differences between populations include differences in sample size, allele frequency differences, different LD patterns, and heterogeneity (as demonstrated for a few variants in this study).

In the present study, we tagged the entire span of the *FTO* gene (not just previously associated intron 1 SNPs) in two populations of African ancestry (African Americans and West Africans) to investigate association with obesity in these populations. To our knowledge, the set of 262 tag SNPs we studied is the largest set of SNPs to be directly genotyped in the *FTO* gene in any single study to date. Multiple SNPs in intron 8 (in addition to intron 1 SNPs) showed significant nominal association with the obesity phenotypes in the present study. This finding is significant because, to date, the focus on *FTO* variants associated with obesity has been, for the most part, on the specific SNPs or other intron 1 SNPs reported in the initial genome-wide association study. When significant associations are found within a gene, replication studies in other populations (especially those of a different continental ancestry) that scan the entire gene (rather than just one or a few SNPs) may lead to the discovery of other important genetic variants. Consistent with expectations, we found that both the West African and African American study samples showed weaker LD patterns across the gene when compared with other continental (e.g., European and

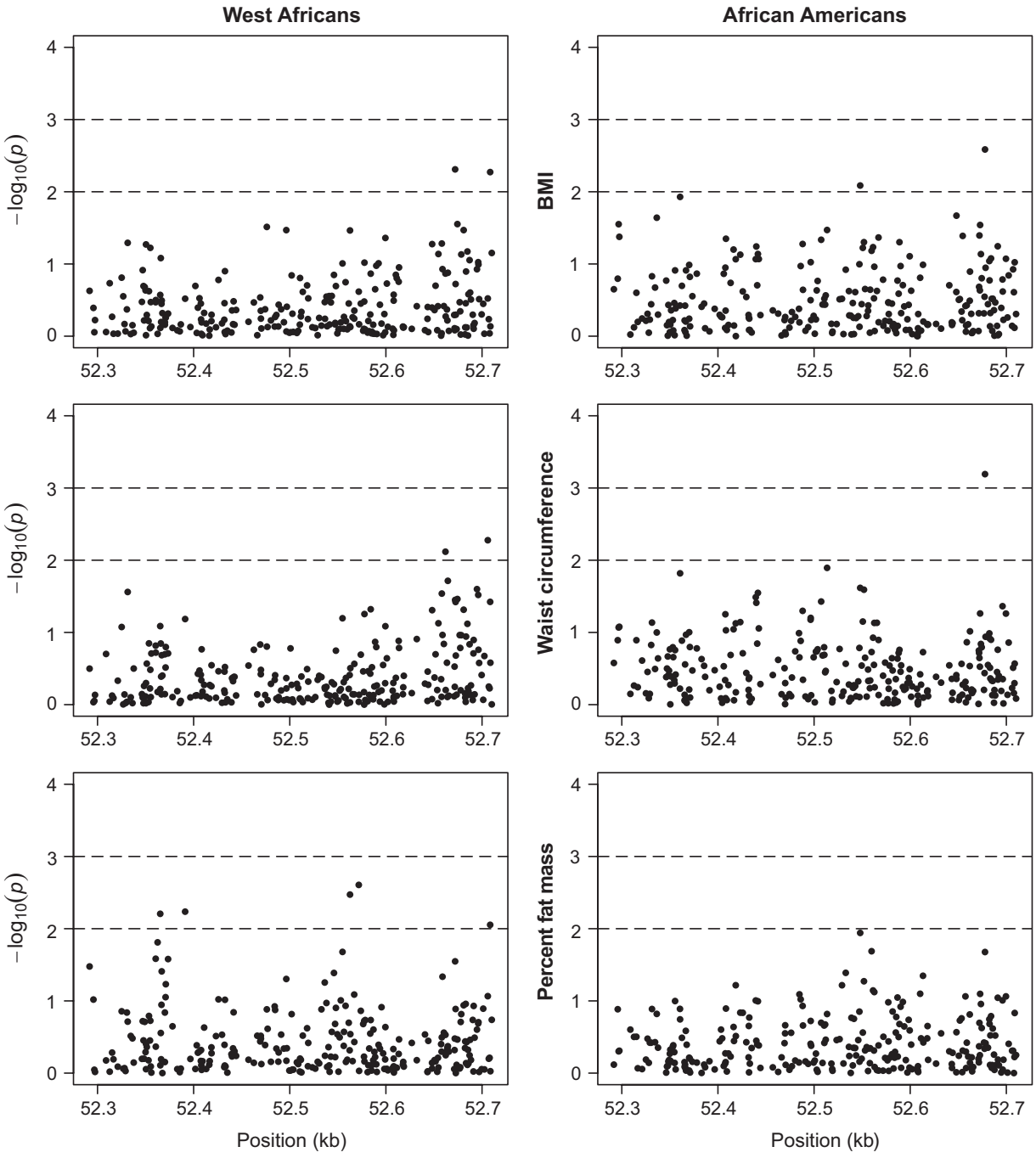

FIG. 2. Association analysis plots for BMI, waist circumference and percent fat mass in the two study samples of African Americans and West Africans.

Asian) populations. Studying populations of different ancestries (especially those with smaller LD) could help fine-map disease or trait loci. However, since the rs9939609 association in intron 1 of *FTO* reported in Europeans did not replicate in this study (as well as several other studies of African ancestry populations), African populations may not be the optimum choice to fine-map this locus.

The overall evidence from this study of populations with a majority of African ancestry adds to the growing body of knowledge supporting the role of *FTO* variants in obesity across multiple human populations. The location of most of these significant SNPs in intron 8 and the downstream region (rather than intron 1) suggests that there may be more than one genetic variant within *FTO* influencing obesity in humans. Further studies are needed to confirm, refine, and extend these findings.

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TABLE 2
Best evidence* for association of *FTO* variants with the obesity-related traits among West Africans and African Americans and on meta-analysis

			West Africans					African Americans					Meta-Analysis				
SNP	Location	A1	*P*	β	L95 β	U95 β	MAF	*P*	β	L95 β	U95 β	MAF	*P*	β	SE (β)	Dir	*P* (Het)
BMI (kg/m^2)																	
rs708262	INTRON 8	T	0.005	0.99	0.30	1.67	0.40	0.040	−0.84	−1.65	−0.04	0.38	0.412	0.22	0.27	+−	0.001
rs11076022	3′_UTR	G	0.005	−1.66	−2.82	−0.50	0.09	0.765	−0.17	−1.26	0.93	0.15	0.033	−0.87	0.41	−−	0.067
rs9932411	INTRON 8	T	0.034	0.90	0.07	1.72	0.21	0.109	0.66	−0.15	1.46	0.31	0.009	0.77	0.29	++	0.687
rs7191513	INTRON 8	G	0.202	0.45	−0.24	1.13	0.42	0.008	0.97	0.25	1.69	0.48	0.006	0.70	0.25	++	0.300
rs11076017	INTRON 8	T	0.950	0.03	−1.04	1.11	0.12	0.003	1.55	0.54	2.55	0.20	0.024	0.84	0.37	++	0.044
WC (cm)																	
rs16953075	3′_UTR	T	0.005	2.57	0.77	4.38	0.23	0.587	0.58	−1.51	2.67	0.15	0.013	1.72	0.70	++	0.157
rs16952987	INTRON 8	A	0.008	−2.48	−4.29	−0.66	0.21	0.292	−0.99	−2.82	0.85	0.23	0.008	−1.74	0.66	−−	0.257
rs9933611	INTRON 1	G	0.028	−3.18	−5.99	−0.36	0.08	0.073	−2.87	−5.99	0.26	0.06	0.004	−3.04	1.07	−−	0.885
rs2689269	INTRON 8	A	0.030	−1.71	−3.26	−0.17	0.46	0.043	−1.60	−3.14	−0.05	0.49	0.003	−1.65	0.56	−−	0.918
rs8055197	INTRON 1	G	0.190	−1.27	−3.17	0.63	0.20	0.015	−2.25	−4.06	−0.44	0.28	0.008	−1.78	0.67	−−	0.465
rs11076017	INTRON 8	T	0.631	−0.58	−2.93	1.77	0.12	0.001	3.60	1.54	5.66	0.20	0.024	1.78	0.79	−+	0.009
PFM (%)																	
rs16952725	INTRON 8	C	0.002	−4.01	−6.59	−1.42	0.05	0.925	0.09	−1.86	2.05	0.04	0.078	−1.40	0.80	−+	0.013
rs9932411	INTRON 8	T	0.003	2.05	0.69	3.41	0.21	0.075	0.78	−0.08	1.65	0.31	0.002	1.15	0.37	++	0.125
rs7204609	INTRON 1	C	0.006	−1.59	−2.71	−0.46	0.44	0.683	0.18	−0.68	1.03	0.36	0.176	−0.47	0.35	−+	0.014
rs17817288	INTRON 1	G	0.006	1.61	0.46	2.75	0.40	0.704	0.16	−0.66	0.97	0.40	0.057	0.64	0.34	++	0.043
rs11076022	3′_UTR	G	0.009	−2.56	−4.47	−0.65	0.09	0.598	0.32	−0.86	1.49	0.15	0.355	−0.47	0.51	−+	0.012
rs16952520	INTRON 1	G	0.026	1.36	0.17	2.56	0.32	0.129	0.74	−0.21	1.69	0.26	0.010	0.98	0.38	++	0.425
rs7191513	INTRON 8	G	0.125	0.89	−0.24	2.02	0.42	0.011	1.00	0.23	1.77	0.48	0.003	0.96	0.33	++	0.879

*All SNPs with association *P* values <0.01 using an additive model in either sample or the meta-analysis.

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