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Candidate Gene Association Study of BMI-Related Loci, Weight, and Adiposity in Old Age

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Most genome-wide association studies are confined to middle-aged populations. It is unclear whether associations between single nucleotide polymorphisms (SNPs) and obesity persist in old age. We aimed to relate 10 body mass index (BMI)–associated SNPs to weight, BMI, % fat, visceral and subcutaneous adipose tissue in Health ABC and AGES-Reykjavik comprising 4,846 individuals of European Ancestry, and 1,139 African Americans over age 65. SNPs were scaled using effect estimates from candidate SNPs. In Health ABC, a SNP near GNPDA2 was modestly associated with weight and SAT area ($p = .008$, $p = .001$). Risk score (sum of scaled SNPs) was associated with weight, BMI, and SAT area ($p < .0001$ for all), but neither GNPDA2 nor risk score was associated with weight, BMI, visceral adippose tissue, subcutaneous adipose tissue, or % fat in AGES-Reykjavik. In African Americans, a SNP near SEC16B was weakly associated with weight ($p = .04$). In this sample of older adults, no BMI-associated SNPs were associated with weight or adiposity.

Key Words: Obesity—Aging—Genetics—SNPs.

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OVER the past 20 years, the prevalence of obesity, defined as body mass index (BMI) greater than 30 kg/m^2, has risen dramatically. This is a worldwide trend, affecting men and women of all ages and racial backgrounds. In the United States, nearly one third of adults are obese (1). In European countries like Iceland, obesity rates are over 20% (2), comparable to rates observed in the United States in the 1990s.

Twin and adoption studies have shown that genetic factors play a role in the development of obesity (3). Genome-wide association studies have identified common variants at numerous loci that associate with fat mass, weight, and obesity (4–6). However, these studies have largely been confined to middle-aged European ancestry (EA) populations, and it is unclear whether these relationships persist in old age or in African Americans (AA). With the increasing prevalence of obesity and population aging, it is important to understand factors associated with obesity in old age. The purpose of this study is to conduct a candidate gene analysis of associations between BMI-related loci, weight, and detailed adiposity measures in older adults.

Methods

Study Design and Participants

The Health, Aging and Body Composition Study (Health ABC) is a prospective study of 3,075 community-dwelling, initially well-functioning, AA and EA men and women aged 70–79 years at baseline. Participants were recruited from a random sample of white Medicare beneficiaries and all black Medicare-eligible residents in the Memphis, Tennessee, and Pittsburgh, Pennsylvania areas. A subsample of participants were genotyped, 1,139 AAs and 1,663 EAs. Replication was performed in 3,219 Icelandic men and women who participated in the Age Gene/Environment Susceptibility-Reykjavik study (AGES-Reykjavik). AGES-Reykjavik is a single center population study of 5,764

individuals aged 76–95 nested within the Reykjavik Study. All participants signed informed consent forms approved by institutional review boards. Detailed recruitment and study design of both studies have been published (7,8).

Anthropometric Measurements

Baseline weight was measured using a digital scale (AGES-Reykjavik) or balance beam scale (Health ABC), and height was measured using a stadiometer. BMI was calculated in kilogram per meter square. Participants in Health ABC were asked to recall their usual body weight at age 50. Midlife weight was measured in AGES-Reykjavik as part of the Reykjavik Study.

Computed tomography imaging of the abdomen at the level of the L4/L5 vertebrae was performed in both studies. Visceral adipose tissue and subcutaneous adipose tissue were estimated from a single 10-mm thick transaxial section. Adipose areas (in centimeter square) were calculated by multiplying the number of pixels of a given tissue by the pixel area. Visceral adipose tissue was manually distinguished from subcutaneous adipose tissue by tracing along the facial plane defining the internal abdominal wall. Percent body fat was measured with dual-energy x-ray absorptiometry (Hologic QDR4500A, Waltham, NY) in Health ABC and was calculated from bioelectric impedance (Xitron Hydra ECF/ICF Bio-Impedance Spectrum Analyzer) in AGES-Reykjavik.

Genetic Analysis

In Health ABC, participants were genotyped by the Center for Inherited Disease Research (CIDR) using a Illumina Human1M-Duo BeadChip array. Genomic data were extracted from buffy coat using PUREGENE DNA Purification Kit. Genotyping was successful on 1,151,215 single nucleotide polymorphisms (SNPs). Both cohorts used MACH software (version 1.0.16) to impute autosomes and criteria of minor allele frequency ≥1%, call rate ≥97%, and Hardy weinberg equilibrium (HWE) $p \leq 10–6$ for SNPs used in imputation. AGES-Reykjavik genotyping was conducted on a subsample of 3,219 participants with the Illumina 370CNV BeadChip array. In Health ABC, six SNPs were imputed in EAs, rs15558902, rs571312, rs10938397, rs10767664, rs12444979, and rs543874, and six SNPs were imputed in AAs, rs1558902, rs2867125, rs571312, rs10938397, rs10767664, and rs543874. The quality of imputation was greater than 0.9750 for all SNPs in EAs and AAs. In AGES-Reykjavik, seven SNPs were imputed, rs1558902, rs571312, rs10938397, rs10767664, rs7359397, rs12444979, and rs543874. The quality of imputation was similar to Health ABC and ranged from 0.925 to 0.9998. Additional genotyping and imputation details have been published for Health ABC (9,10) and AGES-Reykjavik (11,12).

Candidate SNPs associated with obesity were identified from literature on BMI-related loci that met the following criteria: (a) sample size of both discovery and replication greater than 5,000; (b) no missing effect estimates (odds ratios, β, or confidence intervals); (c) minor allele frequency of at least 1% and 4%) $p < 1 \times 10^{-8}$ for both discovery and replication phases. If SNPs were in linkage disequilibrium ($r^2 > .30$), the SNP most strongly related to BMI based on effect estimates was included (13). Reference frequencies of candidate SNPs were compared with dbSNP build 36 of the public human genome reference to determine alleles corresponding to the forward strand. In the case of reversed allele frequency, the direction of the effect estimate was flipped. Allele counts were scaled by the effect estimates (per allele change in BMI) of candidate SNPs (effect estimate multiplied by allele frequency), which were applied to genotype data to create scaled doses for each SNP. This allows for incorporation of effects of different magnitude as the effect size for each SNP varies (14). A multilocus genetic risk score for each individual was constructed by summing the number of risk alleles for each scaled SNP.

Data Analysis

Associations were determined using linear regression, assuming additive effects of allele dosage. Midlife weight, weight in old age, BMI, percent body fat, and visceral and subcutaneous adipose tissue were analyzed as continuous dependent variables, sex, age, and study site within Health ABC as covariates, and each SNP and risk score as the predictor variable. The number of participants varies between anthropometric measurements due to missing data. All analyses were performed separately according to race. To account for the genetic substructure in the AAs, principal component analysis with 10 components was used. Use of principal component analysis to correct for population stratification is detailed by Price and coworkers (15) and has been utilized in previous genome-wide association studies, which included AAs from Health ABC (16,17). Significance was set at $p < .0005$ using the Bonferroni correction method based on the number of SNPs tested per phenotype per cohort to account for multiple testing burden. Analyses were conducted with R version 2.14.0 and SPSS version 19.0.

Results

From our literature search, we identified 10 candidate SNPs from study by Speliotes and coworkers (4) that met our inclusion criteria. The effect size of each SNP from Speliotes and coworkers (4) is shown in Table 1 along with the position, nearest gene, and minor allele frequencies in Health ABC and AGES-Reykjavik.

A total of 6,018 participants had weight and genotype data. Baseline characteristics of participants in Health ABC and AGES-Reykjavik with measured weight are shown in Table 2. On average, participants had heavy body weights. In Health ABC, 68.2% of participants were overweight or obese, and 67.5% of participants in AGES-Reykjavik were overweight or obese. Participants in both studies averaged weight gain from midlife (6.08% and 4.12%, respectively).

Table 1. Candidate SNPs Associated With BMI

SNP	Position (bp)	Nearest Gene	Health ABC Al 1	Health ABC Al 2	β*	Health ABC MAF	Health ABC R^2	AGES-Reykjavik MAF	AGES-Reykjavik R^2
European ancestry									
rs1558902	52,361,075	FTO	A	T	0.39	0.4268	0.9990	0.4069	0.9103
rs2867125	604,210	TMEM18	C	T	0.31	0.1795	0.9999	0.1613	0.9997
rs571312	55,980,115	MC4R	A	C	0.23	0.2282	0.9997	0.2578	0.9644
rs10938397	44,877,284	GNPDA2	A	G	–0.18	0.4387	0.9959	0.4008	0.871
rs10767664	27,682,562	BDNF	A	T	0.19	0.2147	0.9983	0.1842	0.9993
rs2815752	72,585,028	NEGR1	A	G	0.13	0.3575	1.0000	0.4185	1.0000
rs7359397	28,790,742	SH2B1	C	T	–0.15	0.3722	1.0000	0.4299	0.9996
rs12444979	19,841,101	GPRC5B	C	T	0.17	0.1504	0.9947	0.104	0.9975
rs2241423	65,873,892	MAP2K5	A	G	–0.13	0.2477	1.0000	0.204	0.9988
rs543874	176,156,103	SEC16B	A	G	–0.22	0.1643	0.9995	0.2083	0.9897
African American									
rs1558902	52,361,075	FTO	T	A	–0.39	0.102	0.8767		
rs2867125	604,210	TMEM18	T	C	–0.31	0.1165	0.9972		
rs571312	55,980,115	MC4R	A	C	0.23	0.3546	0.9980		
rs10938397	44,877,284	GNPDA2	G	A	0.18	0.2318	0.9940		
rs10767664	27,682,562	BDNF	A	T	0.19	0.0716	0.9996		
rs2815752	72,585,028	NEGR1	A	G	0.13	0.4381	1.0000		
rs543874	176,156,103	SEC16B	A	G	–0.22	0.249	0.9995		

Note. MAF, minor allele frequency; R^2, imputation quality from MACH.
*Per allele change in kilogram per meter squared from Speliotes and coworkers (4).

Table 2. Characteristics of Participants With Baseline Weight in Health ABC and AGES-Reykjavik

	Health ABC	AGES-Reykjavik
No. of participants	2,802	3,216
Women, *n* (%)	1,435 (51.2)	1,865 (58.0)
African American, *n* (%)	1,139 (40.7)	—
Age, mean (*SD*)	73.6 (2.87)	76.4 (5.45)
Weight in kg, mean (*SD*)	75.9 (14.9)	75.8 (14.7)
Body mass index in kg/m^2, mean (*SD*)	27.4 (4.77)	27.1 (4.44)
<25, *n* (%)	891 (31.8)	1,042 (32.4)
25.0–29.9, *n*(5)	1,196 (42.7)	1,465 (45.5)
≥30.0, *n* (%)	715 (25.5)	709 (22.0)
% Weight change from midlife, mean (*SD*)	+6.08 (14.0)	+4.12 (13.0)
Smoking status, *n* (%)*		
Never	1,206 (43.0)	1,351 (42.0)
Former	1,299 (46.4)	1,456 (45.3)
Current	293 (10.5)	409 (12.7)

*Data missing for four participants. Cohort characteristics are shown for reference and were not statistically compared.

Table 3 shows associations between SNPs, weight in midlife and old age, and adiposity measures in EAs. In Health ABC, a SNP at rs10938397, near GNPDA2, associated with midlife weight, weight in old age (p = .008), and subcutaneous adipose tissue (p = .001), but it did not meet the statistical threshold and was not associated with any measure of weight or adiposity in AGES-Reykjavik. The overall risk score from the 10 SNPs was associated with midlife weight, weight in old age, BMI, and subcutaneous adipose tissue (p < .0001 for all) in Health ABC but not AGES-Reykjavik. There were weak trends (p < .05) between four SNPs and midlife weight in Health ABC and between one SNP and midlife weight in AGES-Reykjavik. Of these five SNPs, none of the associations carried over to old age. In AAs, a SNP at rs543874, near SEC16B, was associated with weight in midlife (p = .004) and old age (p = .05, Table 4), but the signal did not meet the statistical threshold. Risk score was also modestly associated with midlife weight (p = .02). No other associations with risk score or SNPs were observed.

Discussion

In this analysis, we investigated the association between BMI-related SNPs, weight, and fat mass in older EA and AAs. Our findings suggest that genes related to BMI in midlife do not track into old age. Although we found modest associations between loci and anthropometric measurements within Health ABC, there were no SNPs that replicated in AGES-Reykjavik. Within Health ABC participants, the SNPs associated with weight appear to differ between EA and AAs, which is in accordance with other studies that show inconsistent replication of obesity variants between EAs and AAs (18,19).

SNPs that were modestly associated with midlife weight did not show the same association with weight or adiposity in old age, suggesting the absence of a carryover effect of BMI-related SNPs into old age. Early lifetime environmental effects may also help to explain the discordance between BMI-related SNPs in midlife and old age. The participants in Health ABC and AGES-Reykjavik were born earlier than some of the participants in the Speliotes study (4) from which the candidate SNPs were identified, and thus environmental factors may have differed. Similarly, discordance between Health ABC and AGEs-Reykjavik may be related to differences in environmental factors as industrialization in Iceland occurred later than in the United States.

Table 3. Association of BMI-Related SNPs and Anthropometric Traits in European Ancestry Participants

		Health ABC									AGES-Reykjavik								
		Midlife weight, kg			Weight, kg			BMI, kg/m^2			Midlife weight, kg			Weight, kg			BMI, kg/m^2		
	Nearest	Allele Effect			Allele Effect			Allele Effect			Allele Effect			Allele Effect			Allele Effect		
SNP	Gene	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*
rs1558902	FTO	1,630	0.03	.44	1,663	0.03	.30	1,662	0.06	.03	3,207	0.02	.26	3,216	0.03	.22	3,216	0.03	.09
rs2867125	TMEM18	1,630	0.05	.11	1,663	0.03	.25	1,662	0.04	.09	3,207	−0.02	.47	3,216	−0.01	.68	3,216	−0.01	.69
rs571312	MC4R	1,630	0.06	.08	1,663	0.02	.45	1,662	0.03	.22	3,207	0.05	.01	3,216	0.03	.13	3,216	0.03	.12
rs10938397	GNPDA2	1,630	0.11	.001	1,663	0.08	.008	1,662	0.05	.03	3,207	−0.01	.64	3,216	−0.01	.74	3,216	−0.01	.49
rs10767664	BDNF	1,630	0.06	.06	1,663	0.03	.26	1,662	0.02	.51	3,207	0.04	.09	3,216	0.05	.01	3,216	0.04	.01
rs2815752	NEGR1	1,630	0.07	.03	1,663	0.03	.35	1,662	0.02	.38	3,207	0.03	.10	3,216	0.02	.40	3,216	0.02	.34
rs7359397	SH2B1	1,630	0.09	.005	1,663	0.04	.23	1,662	0.01	.82	3,207	0.04	.07	3,216	0.02	.23	3,216	0.02	.31
rs12444979	GPRC5B	1,630	0.02	.46	1,663	0.06	.03	1,662	0.06	.01	3,207	0.02	.32	3,216	0.00	.90	3,216	0.01	.51
rs2241423	MAP2K5	1,630	0.08	.01	1,663	0.04	.21	1,662	0.00	.99	3,207	−0.01	.87	3,216	−0.02	.23	3,216	−0.02	.21
rs543874	SEC16B	1,630	0.08	.02	1,663	0.05	.08	1,662	0.04	.09	3,207	−0.01	.74	3,216	−0.01	.55	3,216	−0.01	.46
Score		1,630	0.18	<.0001	1,663	0.12	<.0001	1,662	0.11	<.0001	3,207	−0.02	.40	3,216	−0.01	.77	3,216	0.00	.80
		% Body Fat			Visceral Adipose Tissue, cm^2			Subcutaneous Adipose Tissue, cm^2			% Body Fat			Visceral Adipose Tissue, cm^2			Subcutaneous Adipose Tissue, cm^2		
rs1558902	FTO	1,600	0.03	.44	1,604	0.01	.63	1,574	0.05	.06	2,418	0.02	.45	3,172	0.01	.79	3,172	0.01	.15
rs2867125	TMEM18	1,600	0.03	.35	1,604	0.01	.80	1,574	0.04	.15	2,418	−0.04	.20	3,172	−0.01	.75	3,172	−0.01	.76
rs571312	MC4R	1,600	0.04	.27	1,604	−0.03	.34	1,574	0.04	.19	2,418	0.03	.35	3,172	0.01	.67	3,172	0.01	.23
rs10938397	GNPDA2	1,600	0.09	.01	1,604	0.01	.61	1,574	0.09	.001	2,418	−0.01	.65	3,172	0.00	.97	3,172	0.00	.05
rs10767664	BDNF	1,600	−0.02	.61	1,604	−0.02	.41	1,574	0.03	.22	2,418	0.01	.65	3,172	0.02	.32	3,172	0.02	.01
rs2815752	NEGR1	1,600	0.00	.93	1,604	−0.01	.65	1,574	0.01	.70	2,418	0.04	.21	3,172	0.01	.61	3,172	0.01	.05
rs7359397	SH2B1	1,600	−0.02	.63	1,604	−0.01	.77	1,574	0.01	.79	2,418	0.00	.91	3,172	0.00	.96	3,172	0.00	.007
rs12444979	GPRC5B	1,600	0.07	.05	1,604	0.03	.25	1,574	0.03	.30	2,418	0.01	.84	3,172	−0.01	.59	3,172	−0.01	.58
rs2241423	MAP2K5	1,600	0.00	.92	1,604	0.01	.63	1,574	0.01	.63	2,418	0.02	.59	3,172	0.02	.35	3,172	0.02	.36
rs543874	SEC16B	1,600	0.03	.40	1,604	0.00	.92	1,574	0.05	.08	2,418	−0.04	.22	3,172	−0.02	.38	3,172	−0.02	.74
Score		1,600	0.08	.02	1,604	0.01	.82	1,574	0.12	<.0001	2,418	0.00	.94	3,172	0.00	.96	3,172	0.00	.59

Note. Linear regression, values adjusted for age, sex, and study site (site adjustment only in Health ABC).

Table 4. Association of BMI-Related SNPs and Anthropometric Traits in African Americans

		Health ABC														
		Midlife Weight, kg			Weight, kg			BMI, kg/m^2			% Body Fat			Visceral Adipose Tissue, cm^2			Subcutaneous Adipose Tissue, cm^2		
	Nearest	Allele Effect			Allele Effect			Allele Effect			Allele Effect			Allele Effect			Allele Effect		
SNP	Gene	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*	*N*	Size (β)	*p*
rs1558902	FTO	1,080	0.02	.54	1,139	−0.02	.48	1,139	−0.05	.11	1,099	−0.11	.84	1,096	0.03	.32	1,055	−0.02	.53
rs2867125	TMEM18	1,080	0.02	.58	1,139	−0.02	.49	1,139	−0.02	.61	1,099	−0.02	.71	1,096	−0.07	.02	1,055	−0.02	.59
rs571312	MC4R	1,080	0.01	.75	1,139	0.02	.45	1,139	0.03	.29	1,099	0.08	.08	1,096	0.03	.32	1,055	0.04	.32
rs10938397	GNPDA2	1,080	0.05	.16	1,139	0.02	.61	1,139	0.02	.52	1,099	0.00	.95	1,096	−0.01	.67	1,055	0.02	.62
rs10767664	BDNF	1,080	0.04	.18	1,139	0.00	.99	1,139	0.00	.95	1,099	−0.04	.41	1,096	−0.05	.10	1,055	0.00	.98
rs2815752	NEGR1	1,080	−0.01	.69	1,139	−0.03	.35	1,139	−0.02	.54	1,099	−0.03	.57	1,096	−0.03	.35	1,055	−0.01	.71
rs543874	SEC16B	1,080	0.09	.004	1,139	0.06	.05	1,139	0.04	.15	1,099	0.03	.53	1,096	0.02	.55	1,055	0.03	.36
Score		1,080	0.08	.02	1,139	0.01	.67	1,139	0.01	.88	1,099	0.02	.65	1,096	−0.02	.59	1,055	0.01	0.72

Note. Linear regression, values adjusted for age, sex, and study site (site adjustment only in Health ABC).

Previous studies have also reported discordance between SNPs in midlife and old age. Qi and coworkers (20) found decreased associations between an FTO variant and BMI in individuals older than 65 years compared with younger age groups. Kilpeläinen and coworkers (21) reported age-dependent effects of an obesity-related variant in PCSK1 such that the contribution to obesity in individuals older than 59 years was insignificant. A weakening association between candidate genes and obesity with age may also explain why associations in Health ABC were not replicated in AGES-Reykjavik participants who were on average older (66–95 years vs. 70–79 years) but otherwise had similar demographic characteristics as Health ABC participants.

Age-related changes in weight that result in individuals transitioning away from their midlife phenotype may underlie the diminishing associations between SNPs, weight, and BMI. In Health ABC and AGES-Reykjavik, weight fluctuation from midlife to old age was common and only one third of the participants maintained their weight within 5%. Likewise, age-related body composition changes may account for the null associations between BMI-related SNPs, visceral adipose tissue area, subcutaneous adipose tissue area, and % body fat we observed. Even in the absence of BMI changes, fat accumulates with age (22,23). Fat distribution also changes with age; in a comparison of older and middle-age men, older men had significantly higher amounts of abdominal adipose tissue despite having lower BMI (24).

A limitation of this study was the application of candidate SNPs from a genome-wide association study that was predominately EA compared with our study population that included AAs as there were no genome-wide association studies of obesity-related traits in AAs that met our selection criteria for SNPs. We also lacked access to a second cohort of AAs for replication. Additionally, the AGES-Reykjavik cohort was included in the replication stage of Speliotes and coworkers (4) from which we identified candidate genes although they comprised only 1.3% of the population (3,219 of 249,796 participants). An important limitation in this analysis is our sample size. Although we had a group of thousands of persons, it is a relatively small sample size for testing associations with candidate genes. It is possible that we had inadequate power to detect associations given the small effect size of some of the SNPs. Our analysis may have benefited from additional participants; however, cohorts of older adults with genetic data and detailed adipose measures are limited, and previous studies with smaller sample sizes than ours have identified significant associations between loci and BMI (25,26). Strengths of this study include the use of two large well-characterized population cohorts with data in midlife and old age and the use of adiposity measures from computed tomography imaging, dual-energy x-ray absorptiometry, and bioelectric impedance.

In conclusion, SNPs previously associated with BMI in middle-aged populations were not associated with weight or adiposity in older EAs and AAs. This suggests that genetic factors related to obesity may vary with age.

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