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Associations of the Melanocortin 3 Receptor C17A + G241A haplotype with body composition and inflammation in African American adults

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Summary:

Background: The *MC3R* haplotype C17A+G241A, which encodes a partially-inactivated receptor, has high prevalence in Individuals of predominately African ancestry. In pediatric cohorts, homozygosity for this common variant has been associated with obesity, reduced lean mass, and greater fasting insulin. However, metabolic and body composition measures have not been well studied in adults with this haplotype.

Methods: A convenience sample of 237 healthy African American adult volunteers was studied. Taqman assays were used to genotype *MC3R* variants. Labs were drawn in the morning in the fasted state. Body composition data was obtained via dual-energy X-ray absorptiometry. An analysis of covariance was used to examine the associations of genotype with metabolic and body composition measures controlling for age and sex.

Results: Individuals homozygous for the *MC3R* C17A+G241A haplotype had significantly greater body mass index, fat mass, fat mass percentage, and C-Reactive Protein, with reduced lean mass percentage as compared to heterozygous and wild-type participants (all p's<0.05); fasting insulin was marginally non-significant between groups (p=0.053). After adjusting for fat mass, laboratory differences no longer remained significant.

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conclusions: Homozygosity for *MC3R* C17A+G241A is associated with increased adiposity in African American adults. Further studies are needed to elucidate the mechanisms behind these associations.

Keywords

melanocortin 3 receptor; missense variants; obesity; Body Mass Index; fat mass; lean mass; inflammation; Genetic Variation; Genotype; Homozygote

Introduction

Recent studies examining the genetic underpinnings of obesity have suggested that the melanocortin 3 receptor (MC3R) plays a role in body composition and nutrient partitioning (Chen *et al.*, 2000, Demidowich *et al.*, 2017). In mice, inactivating *Mc3r* causes increased feeding efficiency leading to obesity with increased fat mass, but with reduced lean mass (Chen *et al.*, 2000, Kumar *et al.*, 2009, Butler *et al.*, 2017, Renquist *et al.*, 2011).

The common minor human *MC3R* C17A+G241A haplotype, which leads to 2 amino acid substitutions Thr6Lys and Val81Ile in the protein translated from the first start site of the human gene, leads to a partially inactive protein transcript (Feng *et al.*, 2005). In a large pediatric cohort, individuals homozygous for the *MC3R* C17A+G241A haplotype were reported to have greater BMI, body fat, plasma leptin, and insulin concentrations, with reduced lean mass when compared to those who were heterozygous (Het) for the C17A + G241A haplotype and homozygous for the wild-type *MC3R* gene (WT) (Feng *et al.*, 2005). The greater adiposity and reduced signal transduction associated with homozygosity for the C17A+G241A haplotype has since been replicated in other pediatric cohorts (Savastano *et al.*, 2009, Lee *et al.*, 2007, Aris *et al.*, 2015). Supportive data for the effects of this haplotype have also been reported in mice. When the murine *Mc3r* was replaced with the human *MC3R* C17A+G241A haplotype, homozygous knockin mice also displayed increased feeding efficiency, greater adiposity, and reduced lean mass (Lee *et al.*, 2016). Among adult human cohorts, however, the *MC3R* C17A+G241A haplotype has not been associated with greater BMI (Li *et al.*, 2000, Hani *et al.*, 2001, Wong *et al.*, 2002, Rutanen *et al.*, 2007, Calton *et al.*, 2009, Matsuoka *et al.*, 2007) and scant data exist for its effects on other anthropometric or metabolic parameters (Hani *et al.*, 2001, Rutanen *et al.*, 2007). A major limitation of most of these prior studies is the low number of *homozygous* participants (Calton *et al.*, 2009, Li *et al.*, 2000, Hani *et al.*, 2001, Wong *et al.*, 2002, Rutanen *et al.*, 2007); consequently, many prior conclusions were based largely on the assumption that heterozygotes and homozygotes are phenotypically identical or there would be additive effects from each minor allele/haplotype.

Although labelled as a common variant, the *MC3R* C17A+G241A haplotype is relatively rare in most races and ethnicities, with an estimated prevalence of homozygous individuals between 0.4–3.5% (Obregon *et al.*, 2010, Lee *et al.*, 2007, Rutanen *et al.*, 2007, Hani *et al.*, 2001). Individuals of predominately African ancestry are the exception, as over half carry at least one copy of the haplotype, and 12–16% are homozygous for C17A+G241A (Li *et al.*, 2000, Feng *et al.*, 2005, Savastano *et al.*, 2009). As such individuals have been

underrepresented in most adult cohort studies examining *MC3R* polymorphisms, it remains unclear if homozygous individuals have a different anthropometric and metabolic phenotype than Het or WT adults.

To our knowledge, this is the first study of a large cohort of adults that has assessed the association of the *MC3R* C17A+G241A haplotype with body composition data such as fat mass and lean mass. Our primary hypothesis was that homozygosity for the *MC3R* C17A +G241A haplotype would be associated with greater BMI and fat mass in African American adults. We additionally hypothesized that this increase in adiposity would be associated with greater insulin resistance and inflammation in homozygous individuals as compared to Het and WT.

Materials and Methods

A convenience sample of 237 healthy adult African Americans, age greater than 16 years, was accrued from participants in several ongoing and completed clinical trials (, , ,) performed at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. All studies were approved by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development institutional review board, and the study conforms to the recognized standards of the US Federal Policy for the Protection of Human Subjects. All participants signed informed consent prior to participation in any of the protocols. For the purposes of this study, only self-identified non-Hispanic African American individuals were included in the analysis. This sample was enriched for obesity because of the nature of these clinical trials.

Blood samples were collected in the morning after a ten hour fast. Fat mass, fat mass percentage, lean mass, and lean mass percentage were assessed by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR-4500A or Discovery instrument (Bedford, MA) before any interventions were carried out. Genotype analyses for the *MC3R* allelic variants C17A (rs3746619) + G241A (rs3827103) were performed using Taqman assays (ThermoFisher Scientific, Waltham, MA). Because C17A is in linkage disequilibrium with G241A 91–97% of the time (Savastano *et al.*, 2009), participants were coded as homozygous if all four alleles were the less common nucleotides (AA+AA), heterozygous if there were one, two, or three less-common alleles present, and WT if all four alleles were the common nucleotides (CC+GG). As no significant differences were seen between Het and WT in any parameters (Table 1 **and** Table 2), they were combined as has been done previously (Feng *et al.*, 2005, Savastano *et al.*, 2009) into the same group for all analyses. Due to the varying nature of the protocols, not all measures were obtained for every individual.

Our primary outcome measures were BMI and fat mass, with secondary measures consisting of other anthropometric, metabolic, and inflammatory measures. Primary analyses to examine the effect of genotype on these measures were performed as ANCOVAs using SPSS version 25.0 (SPSS, Inc., Chicago, IL). All continuous variables were logarithmically or arcsin square root transformed as appropriate to maintain assumptions of normality as per the Kolmogorov-Smirnov normality test, and the Normal Q-Q Plot of the resultant data were visually inspected. All measures were controlled for age and sex. All overall corrected

ANCOVA models were significant, except for log(insulin) and log(HOMA-IR). The overall model still remained nonsignificant for these two variables, even when re-analyzed without age and sex as covariates. In secondary ANCOVA analyses, measures were further controlled for fat mass (kg) as indicated in the text to determine if metabolic changes related to haplotype were independent of adiposity. Chi-square tests were used to evaluate if haplotypes were in Hardy-Weinberg equilibrium.

Results

The baseline characteristics of the 237 African American adult participants for whom data were available are shown in Table 1. The distribution of *MC3R* genotypes were consistent with Hardy-Weinberg equilibrium (p=0.16). No significant differences in age or sex were found between groups.

BMI was significantly greater in homozygous individuals as compared to heterozygous and WT individuals (37.6±8.8 vs. 35.2±8.0 kg/m^2; p=0.039; Table 2). Moreover, homozygous participants demonstrated significantly greater fat mass (45.0±18.8 vs. 39.7±15.5 kg; p=0.031) and fat mass percentage (41.9±9.4 vs. 39.5±9.3%; p=0.021), with decreased lean mass percentage (56.7±9.5 vs. 59.3±9.1%; p=0.012). Weight, height, and lean mass were not different between genotypes (ps>0.05).

Regarding metabolic parameters, homozygous participants had marginally non-significant greater fasting insulin (136.1±118.1 vs. 114.6±82.6 pmol/L; p=0.053; Table 3) and a significantly greater level of inflammation, as measured by hsCRP (69.3±115.7 vs. 39.8±75.8 nmol/L; p<0.05), as compared to heterozygous and WT participants. However, once fat mass (kg) was added to the ANCOVA model, the associations with haplotype were no longer significant. Triglycerides trended towards significance once fat mass was added to the model (actual values: 0.9±0.6 vs. 0.9±0.4 mmol/L; adjusted values: 0.73±0.08 vs 0.83±0.16; p=0.066). Other measures of metabolic health were not significant between groups.

Discussion

In this cohort, homozygosity for the *MC3R* C17A+G241A haplotype was associated with a metabolically unhealthy phenotype, including increased BMI, fat mass, fat mass percentage, and systemic inflammation. These body composition findings are consistent with previous data in children and mouse models (Savastano *et al.*, 2009, Lee *et al.*, 2016, Lee *et al.*, 2007, Aris *et al.*, 2015), but have not been observed in previous adult studies (Li *et al.*, 2000, Hani *et al.*, 2001, Schalin-Jantti *et al.*, 2003, Rutanen *et al.*, 2007, Calton *et al.*, 2009, Obregon *et al.*, 2010, Santos *et al.*, 2011, Matsuoka *et al.*, 2007, Wong *et al.*, 2002).

Most *MC3R* adult cohorts to date have been from European backgrounds, where homozygosity for *MC3R* C17A+G241A is rare (Alsmadi *et al.*, 2014, Zegers *et al.*, 2010, Li *et al.*, 2000, Hani *et al.*, 2001, Boucher *et al.*, 2002, Schalin-Jantti *et al.*, 2003, Yiannakouris *et al.*, 2004). Indeed, homozygous participants made up less than 4% of these cohorts, and therefore were often grouped with heterozygous individuals for the purposes of analyses. However, our data suggest that heterozygous individuals are more phenotypically similar to

WT, not homozygous individuals, in line with previous mouse studies (Lee *et al.*, 2016). Thus, it may be necessary to combine heterozygotes with WT rather than with homozygotes to observe differences between genotypes for *MC3R* C17A+G241A.

Compared with Caucasian Americans, the minor (C17A+G241A) haplotype is much more common among in African American individuals, with two-thirds carrying at least one copy of the partially inactive haplotype, and over 15% carrying two copies (Feng *et al.*, 2005). Our study and others have shown that homozygosity for the minor haplotype among African American individuals is associated with greater BMI and adiposity (Feng *et al.*, 2005, Savastano *et al.*, 2009), which in turn is most likely responsible for the greater insulin and inflammatory levels seen in these individuals. Interestingly, despite the greater adiposity, no differences were seen in measures of the metabolic syndrome such as fasting glucose, HDL, or triglycerides.

In contrast to individuals with obesity due inactivating *MC4R* mutations (Forbes & Welle, 1983, Farooqi *et al.*, 2003), individuals homozygous for the *MC3R* C17A+G241A haplotype had significantly increased fat mass *without* a coincident increase in lean mass. Rather, the lean mass percentage was decreased in homozygous individuals, which may explain in part the marginal differences in BMI between genotypes. Indeed, the *MC3R* C17A+G241A haplotype likely has greater consequences on adiposity, than obesity *per se*. Further work is needed to elucidate whether this increased adiposity primarily represents expansion of benign (e.g. subcutaneous) or pathologic (e.g. hepatic or visceral) adipose depots.

To our knowledge, inflammation has not been previously investigated with respect to the *MC3R* C17A+G241A haplotype in humans. Our study suggests that the increased inflammation seen in homozygous individuals is secondary to their increased adiposity, a known driver of inflammation, rather than an intrinsic effect of the mutated protein. However, MC3R is well-known to have immunomodulatory properties (Gonzalez-Rey *et al.*, 2007, Patel *et al.*, 2010, Henagan *et al.*, 2011), and our study examined only one marker of inflammation, hsCRP. Although knockin mouse models for the human *MC3R* C17A +G241A did not demonstrate any differences in inflammatory markers despite their increased adiposity (Lee *et al.*, 2016), the haplotype's immune effects in humans warrants further investigation.

A strength of our study is the composition of our cohort, which contained a large sample of homozygous Black adults. Additionally, the use of DXA allowed for fat mass to be employed as an important covariate in our analyses. Furthermore, statistical analyses were rigorously performed, ensuring that data was normally distributed prior to analysis, and included multiple covariates into the model. Limitations include that the cohort studied was enriched for individuals with obesity, potentially introducing selection bias, and that not all variables were available for all participants. Additionally, our study did not include more rigorous testing of glucose homeostasis, such as hyperinsulinemic euglycemic clamps. Our study also primarily consisted of younger adults (e.g. less than 50 years old); further studies are necessary to investigate whether the differences found between groups persist later in life. Finally, we did not have participant permission to perform studies to determine if degree of racial admixture affected the results.

In summary, in a large cohort of African American adults, homozygosity for the *MC3R* C17A+G241A haplotype was associated with increased BMI and adiposity, and, likely as a result of greater adiposity, with higher inflammation and with a trend towards greater fasting insulin. Further studies are needed to better understand pathways involved and to determine whether these phenotypic findings have significant clinical consequences.

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Table 1.

Participant Baseline Characteristics According to Genotype

	HOM	Het	WT	p
N (%)	51 (21.5%)	106 (44.7%)	80 (33.8%)	
Age (y)	30.1±12.7	28.9±14.1	30.6±14.3	0.710
Sex (% Female)	72.5%	84.9%	73.8%	0.095

Age is represented as mean ± SD. HOM: Homozygous for the less common, partially-inactive *MC3R* C17A+G241A haplotype; Het: heterozygous at one or both loci; WT: Homozygous for the more common or "wild type" *MC3R* C17+G241 haplotype.

Table 2.

Anthropometric Measures Among Participants According to Genotype

	HOM	Het	WT	Het+WT	p-value Het vs. WT	p-value HOM vs. Het+WT
Weight (kg)	105.5±24.7	98.4±21.3	98.6±22.8	98.5±21.9	0.693	0.079
Height (cm)	167.6±9.2	167.1±8.0	168.0±9.5	167.5±8.6	0.676	0.497
BMI (kg/m^2)	37.6±8.8	35.2±7.2	35.2±9.1	35.2±8.0	0.830	0.039 *
Fat mass (kg)	45.0±18.8	39.4±14.4	40.0±17.0	39.7±15.5	0.984	0.031 *
Fat mass (%)	41.9±9.4	39.4±8.5	39.6±10.4	39.5±9.3	0.351	0.021 *
Lean mass (kg)	57.0±11.3	56.1±10.4	55.9±9.8	56.0±10.1	0.226	0.884
Lean mass (%)	56.7±9.5	59.2±8.4	59.4±10.0	59.3±9.1	0.579	0.012 *

Data are represented as mean±SD. HOM: Homozygous for the less common, partially inactive *MC3R* rs3746619 *A* + rs3827103 *A* haplotype; Het: heterozygous at one or both loci; WT: Homozygous for the more common *MC3R* rs3746619 *C* + rs3827103 *G* haplotype. Data were analyzed as ANCOVA comparing Het vs. WT or HOM vs. Het+WT, adjusting for age and sex. Complete data were not available for 7 HOM participants for Fat mass, Fat mass %, Lean mass, or Lean mass %.

* p <0.05

Table 3.

Laboratory Measures Among Participants According to Genotype

	HOM	Het	WT	Het+WT	p-value, Het vs. WT; model adjusted for age and sex	p-value, HOM vs. Het+WT; model adjusted for age and sex	p-value, HOM vs. Het+WT; model adjusted for age, sex, and fat mass
Insulin (pmol/L)	136.1±118.1	113.9±78.5	116.0±88.2	114.6±82.6	0.937	0.053	0.312
Glucose (mmol/L)	5.0±1.0	4.9±0.6	5.1±1.7	5.0±1.2	0.754	0.783	0.924
HOMA-IR	4.52±3.97	3.72±3.05	3.97±3.76	3.83±3.37	0.896	0.067	0.369
Total Cholesterol (mmol/L)	4.4±0.9	4.2±0.9	4.2±0.9	4.2±0.9	0.793	0.264	0.761
HDL-Cholesterol (mmol/L)	1.3±0.3	1.3±0.3	1.3±0.3	1.3±0.3	0.677	0.399	0.415
LDL-Cholesterol (mmol/L)	2.6±0.8	2.5±0.8	2.5±0.7	2.5±0.8	0.753	0.492	0.927
Triglycerides (mmol/L)	0.9±0.6	0.9±0.4	0.9±0.4	0.9±0.4	0.675	0.274	0.066
hsCRP (nmol/L)	69.3±115.7	41.3±58.8	38.0±91.2	39.8±75.8	0.993	0.028 *	0.629

Data are represented as mean ± SD. HOM: Homozygous for the less common, partially inactive *MC3R* rs3746619 *A* + rs3827103 *A* haplotype; Het: heterozygous at one or both loci; WT: Homozygous for the more common *MC3R* rs3746619 *C* + rs3827103 *G* haplotype. Data were analyzed as ANCOVA comparing Het vs. WT and HOM vs. Het+WT. Complete subject data were not available for Total, HDL- and LDL-Cholesterol (2 Het participants), triglycerides (1 Het participant), and hsCRP (7 HOM, 38 Het, and 17 WT participants).

* p <0.05