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Energy homeostasis genes and breast cancer risk: The influence of ancestry, body size, and menopausal status, the breast cancer health disparities study

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Abstract

Background—Obesity and breast cancer risk is multifaceted and genes associated with energy homeostasis may modify this relationship.

Methods—We evaluated 10 genes that have been associated with obesity and energy homeostasis to determine their association with breast cancer risk in Hispanic/Native American (2111 cases, 2597 controls) and non-Hispanic white (1481 cases, 1585 controls) women.

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Author contribution

Martha Slattery: write grant, obtained funding, oversaw study design and conduct, oversaw analysis, wrote manuscript.
Abbie Lundgreen: performed statistical analysis and approved final manuscript.
Lisa Hines: contributed data, edited and approved final manuscript.
Roger Wolff: selected genes and oversaw lab work and approved final manuscript.
Gabriella Torres-Meija: contributed data, edited, read and approved final manuscript.
Kathy Baumgartner: contributed data, edited, read, and approved final manuscript.
Esther John: contributed data, edited, read, and approved final manuscript.

Conflict of interest

The authors have no conflict of interest to report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2015.08.012.

Results—Cholecystokinin (*CCK*) rs747455 and proopiomelanocortin (*POMC*) rs6713532 and rs7565877 (for low Indigenous American (IA) ancestry); *CCK* rs8192472 and neuropeptide Y (*NYP*) rs16141 and rs14129 (intermediate IA ancestry); and leptin receptor (*LEPR*) rs11585329 (high IA ancestry) were strongly associated with multiple indicators of body size. There were no significant associations with breast cancer risk between genes and SNPs overall. However, *LEPR* was significantly associated with breast cancer risk among women with low IA ancestry (P_{ARTP} = 0.024); *POMC* was significantly associated with breast cancer risk among women with intermediate (P_{ARTP} = 0.015) and high (P_{ARTP} = 0.012) IA ancestry. The overall pathway was statistically significant for pre-menopausal women with low IA ancestry (P_{ARTP} = 0.05), as was cocaine and amphetamine regulated transcript protein (*CARTPT*) (P_{ARTP} = 0.014) and ghrelin (*GHRL*) (P_{ARTP} = 0.007). P*OMC* was significantly associated with breast cancer risk among post-menopausal women with higher IA ancestry (P_{ARTP} = 0.005). Three SNPs in *LEPR* (rs6704167, rs17412175, and rs7626141), and adiponectin (*ADIPOQ*); rs822391) showed significant 4-way interactions (GxExMenopausexAncestry) for multiple indicators of body size among pre-menopausal women.

Conclusions—Energy homeostasis genes were associated with breast cancer risk; menopausal status, body size, and genetic ancestry influenced this relationship.

Keywords

Breast cancer; Disparities; Energy homeostasis

1. Introduction

The association between obesity and risk of breast cancer is complex, with differences in associations being reported by menopausal status, hormone receptor status of tumor, and ethnicity [1–4]. Studies that have included Hispanic women suggest significant inverse associations with BMI among pre-menopausal women, and either no association or an inverse association between BMI and breast cancer risk among post-menopausal women, but a positive association with weight gain, particularly among those who were lean in young adulthood. These findings suggest that the associations between obesity and breast cancer risk are multifaceted and may be influenced by genetic makeup. Considerable evidence from both human and animal studies suggests that genes play an important role in regulating obesity and energy homeostasis [5,6].

We hypothesize that genetic variation in genes that are associated with obesity, energy homeostasis, and satiety may help explain differences observed for breast cancer associations between pre- and post-menopause and indicators of body size. Additionally, genetic variation in energy homeostasis genes may help explain the influence of race and ethnicity on breast cancer risk. We examine 10 genes, including adiponectin (*ADIPOQ*), cocaine and amphet-amine regulated transcript protein (*CARTPT*), cholecystokinin (*CCK*), ghrelin/obestatin prepropeptide (*GHRL*), leptin (*LEP*), leptin receptor (*LEPR*), Membrane bound *O*-acyltransferase domain containing 4 (*MBOAT4*), melanocortin 4 receptor (*MC4R*), neuropeptide Y (*NPY*), and proopiomelanocortin (*POMC*), and evaluate their associations with body size measures and with breast cancer risk. Both adiponectin and leptin are

adipokines that are secreted by adipocytes [7]. Leptin has been directly associated with obesity, while adiponectin has been inversely associated with obesity and visceral fat accumulation [8]. Among these genes, *LEP* and *LEPR* have been studied the most with breast cancer and have been associated with obesity [9]. Several studies have evaluated polymorphisms in these genes with breast cancer, with conflicting results [10–16]. However, consideration of level of obesity as a component of risk has generally not been done, although the study by Llanos suggested that BMI level may influence risk associated with both leptin and adiponectin [9]. Several of our target genes including, *CARTPT*, *CCK*, *MC4R*, *NPY*, and *POMC*, are neuropeptides involved in the regulation of appetite and satiety. *GHRL* is involved in energy homeostasis and regulation of body weight through its influence on satiety. Polymorphisms in *GHRL* have been linked to breast cancer risk as well as to obesity and insulin levels [17]. *MBOAT4* codes the ghrelin *O*-acyltransferase (GOAT) enzyme that acrylates ghrelin to enable its endocrine actions [18].

In this study, we focus on energy homeostasis genes to evaluate associated breast cancer risk in an ethnically diverse population. In this hypothesis-driven study, we evaluate pre- and post-meno-pausal breast cancer risk separately given differences in reported association with BMI for these groups. Additionally we consider Indigenous American (IA) ancestry to better understand the contribution of the underlying genetic ancestry in this ethnically diverse population that may be modifying breast cancer risk associated with these energy homeostasis genes. Our hypothesis is that the energy homeostasis pathway will be associated with breast cancer risk and associations will vary by IA ancestry as well as by menopausal status.

2. Methods

Data from the Breast Cancer Health Disparities Study that includes participants from three population-based case-control studies [19], the 4-Corners Breast Cancer Study (4-CBCS) [1], the Mexico Breast Cancer Study (MBCS), and the San Francisco Bay Area Breast Cancer Study (SFBCS) [2,20,21] who completed an in-person interview and who had a blood or mouthwash sample available for DNA extraction were used. In the 4-CBCS, participants were between 25 and 79 years; participants from the MBCS were between 28 and 74 years; the SFBCS included women aged 35–79 years. The 4-CBCS consisted of population-based breast cancer cases and controls from Arizona, Colorado, New Mexico and Utah who were diagnosed between October 1999 and May 2004. Of cases contacted, 852 Hispanic, 22 American Indian, and 1683 NHW women participated. Of controls contacted, 913 Hispanic, 23 American Indian, and 1669 NHW women participated. Blood was collected and DNA extracted for 76% of participants in Arizona, 71% of participants in Colorado, 75% of participants in New Mexico, and 94% of participants in Utah. Of participants contacted, 63% of Hispanic and 71% of NHW cases participated; for controls these numbers were 36% and 47% respectively. For the MBCS, cases were diagnosed between January 2004 and December 2007. A total of 1000 cases and 1074 controls were recruited, and blood was collected and DNA extracted from 85% and 96% of women, respectively. The SFBCS included breast cancer cases diagnosed between April 1997 and April 2002. DNA was available for 93% of cases and 92% of controls interviewed, including 1105 cases (793 Hispanics, 312 NHW) and 1318 controls (998 Hispanics, 320

NHW). Participation was 89% for cases and 92% for controls contacted. All participants signed informed written consent prior to participation and the Institutional Review Board for Human Subjects approved the study at each institution.

3. Data harmonization

Data were harmonized across all study centers and questionnaires as previously described [19]. In the United States, women were ask to self-report their race/ethnicity and were classified as non-Hispanic white (NHW) if they reported no Hispanic or Native American (NA) ancestry. Women who reported any Hispanic or NA ancestry were classified accordingly. Women also were classified as either pre-menopausal or post-menopausal based on responses to questions on menstrual history. Women who reported still having periods during the referent year (defined as the year before diagnosis for cases or before selection into the study for controls) were classified as pre-menopausal. Women were classified as post-menopausal if they reported either a natural or surgically-induced menopause or if they reported taking hormone therapy (HT) and were still having periods or were at or above the 95th percentile of age for those who reported having a natural menopause (i.e., ≥12 months since their last period). Women were categorized as having a positive family history of breast cancer if they reported having a first-degree relative with breast cancer.

Body size indicators used were body mass index (BMI) of weight (kg)/height $(m)^2$, weight gain since young adult, waist circumference (an indicator of central obesity), hip circumference, waist-to-hip ratio (WHR) as a measure of body fat distribution, and waist-to-height ratio (WHtR) as an indicator of visceral adiposity independent of height. These indicators were chosen given previous associations with breast cancer [4]. Weight was based on self-reported weight during the reference year or weight measured at interview if weight during the reference year was not available. Height was based on measured height at interview or self-reported height if the measurement was declined. Categories of BMI were normal BMI (<25.0 kg/m^2), overweight (25.0–29.9 kg/ m^2), or obese (30 kg/m^2). In the SFBCS, young-adult BMI was based on self-reported weight at age 25–30 years for cases diagnosed from 1995 to 1998 and their matched controls, or on self-reported weight at age 20–29 years for cases diagnosed from 1998 to 2002 and their matched controls. In the 4-CBCS and MCBCS, young-adult BMI was based on the average weight reported at ages 15 years and 30 years. Weight gain (in kg) was calculated as the difference between self-reported young-adult weight and self-reported weight in the reference year (or measured weight at interview if self-reported weight was not available). Women who lost weight were excluded from weight gain analyses. Current BMI was categorized as underweight to normal weight (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2). All other body size variables were categorized according to the tertile distribution among controls.

4. Genetic data

DNA was extracted from either whole blood (n = 7287) or mouthwash (n = 634) samples. Whole genome amplification (WGA) was applied to the mouthwash-derived DNA samples prior to genotyping. A tag SNP approach was used to characterize variation across candidate

genes. Tag SNPs were selected using the following parameters: linkage disequilibrium (LD) blocks were defined using a Caucasian LD map of validated SNPS and an $r^2 = 0.8$; minor allele frequency (MAF) > 0.1; range = −1500 bps from the initiation codon to +1500 bps from the termination codon; and 1 SNP/LD bin. Additionally, 104 ancestry informative markers (AIMs) were used to distinguish European and IA ancestry in the study population [19]. All markers were genotyped using a multiplexed bead array assay format based on Golden Gate chemistry (Illumina, San Diego, California). A genotyping call rate of 99.93% was attained (99.65% for WGA samples). We included 132-blinded internal replicates representing 1.6% of the sample set. The duplicate concordance rate was 99.996% as determined by 193,297 matching genotypes among sample pairs. In the current analysis we evaluated tag SNPs for *ADIPOQ* (12 SNPs), *CARTPT* (5 SNPs), *CCK* (4 SNPs), *GHRL* (8 SNPs), *LEP* (9 SNPs), *LEPR* (27 SNPs), *MBOAT4* (1 SNP), *MC4R* (3 SNPs), *NPY* (4 SNPs), and *POMC* (5 SNPs). These genes and SNPs are described in online Supplement Table 1. As shown in Supplemental Table 1, 57 of the SNPs evaluated had a significant difference in MAF between NHW and Hispanic/NA women, while 25 SNPs were not significantly different in MAF between these two groups.

5. Statistical methods

5.1. Genetic ancestry estimation

The program STRUCTURE was used to compute individual ancestry for each study participant assuming two founding populations [22,23]. A three-founding population model was assessed but did not fit the population structure. Participants were classified by percent IA ancestry. Assessment across categories of ancestry was done using cut-points, 0–28%, 29–70%, and 71–100%, based on the distribution of genetic ancestry in the control population with the goal of creating distinct ancestry groups with sufficient power to assess breast cancer risk. Previous analysis with these ancestry categories has shown that they relate significantly to breast cancer risk [19]. In assessing interaction with body size factors, the two upper IA groups were combined to provide more power.

5.2. Robust regression

Robust regression was used to estimate associations between candidate genes/SNPs and body size variables of BMI, weight gain, waist circumference, hip circumference, WHR, and WHtR by ancestry among controls. Body size variables were transformed prior to assessment to meet the normalization requirement. Beta coefficients and *p* values for linear trend are provided for the three ancestry groups.

5.3. SNP associations

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Conditional logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for breast cancer risk associated with SNPs, adjusting for study as a categorical variable and age, genetic ancestry, body mass index (BMI, kg/m^2) in the referent year, vigorous physical activity level during the referent year, alcohol consumption, and parity all as continuous variables Total energy intake was not included as a covariate in the final models because adjustment for total energy intake altered risk estimates by less

than 0.01. Since we observed no differences in association by in situ and invasive for the 4-CBCS, we included all women in the analysis of breast cancer risk. Associations with SNPs were assessed assuming a co-dominant model. Based on the initial assessment, SNPs that appeared to have a dominant or recessive mode of inheritance, were subsequently evaluated with those inheritance models. Genes and SNPs were assessed for their association with breast cancer risk by strata of genetic ancestry and menopausal status.

5.4. ARTP analysis

We used the adaptive rank truncated product (ARTP) method that utilizes a highly efficient permutation algorithm to determine the significance of association of each gene and of all genes combined with breast cancer risk overall, by menopausal status, and by genetic ancestry strata. The gene *p* values were generated using the ARTP package in R, permuting outcome status 10,000 times while using same adjustments as in the original analysis [26,27]. ARTP analysis adjust for number of genes being assessed within the pathway (energy homeostasis pathway) to determine the overall pathway significance and the number of SNPs within a gene to determine the gene significance. We report those genes and related SNPs that contributed to the gene significance in the tables. We presented raw and adjusted SNP *p* values; adjustments for multiple comparisons for SNPs within the gene used the step-down Bonferroni correction, taking into account the correlated nature of the data using the SNP spectral decomposition method proposed by Nyholt [24] and modified by Li et al. [25].

Tests for interaction across menopausal and genetic ancestry groups were calculated using a Wald one degree of freedom (1-df) test. To look at interactions that took into account ancestry, menopausal status, anthropometric measure, and SNP we utilized the step-down Bonferroni correction to adjust for multiple comparisons. We report those results that had a three-way interaction of SNP, body size indicator, and ancestry where the *p* value was <0.15.

6. Results

The mean age was 56.6 and 56.0 year for NHW controls and cases respectively; and 52.3 years and 52.7 years for U.S. Hispanic/NA/Mexican controls and cases (Table 1). The majority of women were post-menopausal. Virtually all women who self-reported being NHW had low IA ancestry, while the majority of those who self-reported being Hispanic/NA or were from Mexico had intermediate (64.9% of controls and 66% of cases) or high (24.4% of controls and 21.0% of cases) IA ancestry.

Several genes were associated with body size variables, although the associations with specific genes and SNPs varied by IA ancestry (Table 2). Among women with low IA ancestry (<28%) *LEPR* (1 SNP) was associated with BMI. *POMC* rs1866146 and rs6713532 were associated with waist and hip circumference and WHtR, *POMC* rs7565877 was associated with WHR, and *POMC* rs934778 was associated with WHtR. Among women with high IA ancestry (>70%), SNPs in *ADIPOQ* was associated with WHR (2 SNPs) and weight gain (1 SNP); *LEP* (1 SNP) was associated with hip circumference; *GHRL* rs26802 was associated with weight gain while *GHRL* rs3755777 was associated with hip circumference. *LEPR* was associated with weight gain (1 SNP), waist circumference (1

SNP), hip circumference (1 SNP), WHR (2 SNPs) and WHtR (1 SNP). Several markers were associated with two or more anthropometric measures among the intermediate IA ancestry group, including SNPs in *LEPR, CCK, NPY, and POMC*.

There were no significant associations with breast cancer risk between genes and SNPs overall; however, associations were observed within specific IA ancestry strata (Table 3). *LEPR* was significantly associated with breast cancer risk among women with low IA ancestry (P_{ARTP} = 0.024) and was marginally associated among women with the highest IA ancestry (P_{ARTP} = 0.075). Four SNPs (rs1171271, rs4370791, rs1938484, and rs6588147) in *LEPR* were significantly associated with reduced breast cancer risk for the homozygote rare genotype among women with low IA ancestry. Among women with high IA ancestry, three *LEPR* SNPS (rs12145690, rs1180445, and rs1475397) were associated with reduced breast cancer risk for the homozygote rare genotype, while rs4655802 was associated with increased risk for the rare homozygote genotype. Five of these SNPs were significantly different by ancestry group, while the others were of marginally significant by ancestry group (*p* range 0.07–0.08). *POMC* was significantly associated with breast cancer risk among women with intermediate (P_{ARTP} = 0.015) and high IA ancestry (P_{ARTP} = 0.012). Three *POMC* SNPS, rs1866146, rs6713532, and rs934778 contributed to the reduced risk in these groups.

Assessment of breast cancer risk by menopausal status showed that among pre-menopausal women, the overall pathway was statistically significant for pre-menopausal women with low IA ancestry (P_{ARTP} = 0.05). *CARTPT* was significantly associated with risk of pre-menopausal breast cancer among all women (P_{ARTP} = 0.014) and those with low IA ancestry (P_{ARTP} = 0.015) (Table 4). *GHRL* also was associated with breast cancer risk among pre-menopausal women with low IA ancestry (P_{ARTP} = 0.007). *POMC* was significantly associated with breast cancer risk among post-menopausal women with high IA ancestry (P_{ARTP} = 0.005). The association with *LEPR* was of borderline significance for post-menopausal women with low IA ancestry (P_{ARTP} = 0.06) and for women with intermediate IA ancestry (P_{ARTP} = 0.08) (data not shown in table).

We assessed interaction between energy homeostasis genes and anthropometric variables by genetic ancestry in combination with menopausal status. Associations for the most part were limited to pre-menopausal women (Tables 5; numbers associated with Table 5 are provided in online Supplement Table 2). Five SNPs in *LEPR* (rs6704167, rs17412175, rs10749754, and rs7526141), and *ADIPOQ* rs822391 showed significant 3- and 4-way interactions (gene × body size × menopausal status × ancestry) for multiple indicators of body size. *LEPR* rs17412175 and rs6704167 and *ADIPOQ* rs17300539 interacted with BMI, while *ADIPOQ* rs822391 interacted with WHR and WHtR (Table 5). Additionally several *LEPR* SNPs interacted with weight gain, WHR, and hip circumference among pre-menopausal women with significantly stronger associations in women with lower IA ancestry. There were few associations among post-menopausal women (data not shown in table). Among women with a BMI ≥ 30 kg/m^2 reduced risks were found among those with $LEPR_{AA}$ rs6704167 (OR 0.65, 95% CI 0.46– 0.92; *p* interaction *G* × BMI 0.024) or $LEPR_{TT}$ rs17412175 (OR 0.68, 95% CI 0.47–0.97; *p* interaction G × BMI 0.027).

7. Discussion

In this study, we found that genetic variation among genes that regulate energy homeostasis were associated with body size as well as with breast cancer risk. Among certain subgroups of the population, *LEPR*, *ADIPOQ*, *POMC*, *GHRL* appeared to have the greatest influence on body size measures and breast cancer risk. These genes (*LEPR, GHRL, ADIPOQ*) are involved in hormonal signaling from distant peripheral tissues that communicate the state of energy homeostasis within the body. *POMC* functions in the arcuate nucleus of the hypothalamus as a transducer of peripheral signals in regard to energy stress and modulation of satiety [28]. Breast cancer risk was influenced both by menopausal status and IA ancestry; body size further modulated risk indicating the multifaceted nature of the disease.

The observed associations with genes were not consistent across body size indicators or ancestry groups. Focusing on the strongest associations ($p < 0.01$) was most insightful. SNPs in that category were *CCK* rs747455 and *POMC* rs6713532 and rs7565877 for those with the least IA ancestry; *CCK* rs8192472 and *NYP* rs16141 and rs14129 for those with intermediate IA ancestry; and *LEPR* rs11585329 for those with the most IA ancestry. The importance of these SNPs is further supported by the observation that they were associated with multiple indicators of body size; the associations with *CCK* rs8192472 and *NPY* rs16141 and rs16129 were highly significant with almost all indicators of body size. CCK is a satiety hormone and has been associated with obesity. *CCK* rs8192472 specifically has been reported as being associated with obesity and was identified as a predictor of obesity in GWAS [29]. We found that *CCK* rs8192472 was marginally associated with breast cancer risk among women with high IA ancestry after adjustment for multiple comparisons (data not shown, OR = 0.55, 95% CI 0.33–0.91; $p = 0.02$ and p_{adj} 0.059). Two of the four SNPs analyzed for *NPY* were associated with all but one of the body size indicators. *NPY* is a neuropeptide, operating within the arcuate nucleas, a major integrator of appetite control in the hypothalamus and is associated with satiety. A functional polymorphism of *NYP* (rs16147) has been associated with leptin levels and WHR among women [30]; rs16147 is in high LD with rs16129 ($R^2 > 0.9$). *NPY* rs16131 has been associated with obesity and metabolic syndrome in young children [31]. Our findings support the hypothesis that genetic variation in *NPY* is associated with body size among women with low IA ancestry. *LEPR* has been associated repeatedly with obesity and body size, although we did not find reports specifically for rs11585329, the SNP for which we observed the strongest association.

Associations with breast cancer risk became evident when considering IA ancestry and menopausal status.*LEPR* and *POMC* were associated with breast cancer risk when stratified by IA ancestry, with *LEPR* having stronger associations among women with low IA ancestry and *POMC* having stronger associations among women with high IA ancestry. *CARTPT* and *GHRL* were associated with breast cancer risk mainly among pre-menopausal women with low IA ancestry, while *POMC* was associated with breast cancer risk among post-menopausal women with high IA ancestry. We could not find reports of previous associations between *CARTPT* and breast cancer; however, mutations in *CARTPT* have been associated with reduced metabolic rate, obesity, and diabetes [32]. *GHRL*, a mediator of growth hormone release [33], has been examined more extensively with breast cancer risk, with several studies showing no association [34,35], although a modest association with

rs171407 has been observed [17]. *GHRL* rs35683 and rs35682 from our platform were in high LD with rs171407 ($R^2 > 0.80$); we saw a significant inverse association with breast cancer risk for both of these SNPs among pre-menopausal women with low IA ancestry. Although no reported associations between *POMC* and breast cancer were identified in the literature, there is biological plausibility for associations to exist, given the role of *POMC* in appetite control and obesity, including early onset obesity [36,37]. It is possible that women with greater IA ancestry may be susceptible to variation in this gene given, a higher prevalence of diabetes and early onset obesity. This could be from obesity itself or from intake of specific foods that may further influence breast cancer risk.

The leptin-signaling pathway is positively associated with obesity and has been shown to stimulate the growth of human breast cancer cells. Furthermore, leptin may induce aromatase activity increasing the amount of estrogen in adipose tissue [12]. Leptin can activate *POMC* and inhibit *NPY* [38] and is involved in inflammatory response and regulation of insulin sensitivity. While we did not observe associations between *LEP* SNPs and breast cancer risk, similar to reports by others [8,10,39], we did observe several associations between *LEPR* and breast cancer risk. The biological effects of LEP are exerted through binding to the leptin receptor. This receptor is expressed in a variety of immune cells and has been shown in breast cancer cell lines to have direct communication with estrogen receptor alpha [40]. Others have reported associations between *LEPR* and risk of breast cancer [15]; rs1137101 has been most commonly studied [11,34]. Of the 27 SNPs we examined in *LEPR*, 15, including rs1137101, were associated with breast cancer risk. The majority of associations we observed were among women with low IA ancestry. Although few studies have evaluated associations by IA ancestry, differences in association by African ancestry with *LEPR* variants have been reported. In our study, we observed that the prevalence of genotypes differed by ancestry, with lower MAF frequency among women with higher IA ancestry, making associations less precise and more difficult to detect in this group. Body size in conjunction with menopausal status and IA ancestry further influenced the observed risk between SNPs and breast cancer risk. Significant interactions were generally observed for pre-menopausal women and low IA ancestry. Significant interactions have been reported between various *LEPR* SNPS and several indicators of body size which we evaluated in relation to breast cancer risk, including BMI, weight gain, hip circumference, waist circumference, WHR, and WHtR. Some studies have shown stronger associations with *LEPR* among obese individuals, while others have not [11,39]. The functionality of the SNPs is unclear; however, it is likely that they are correlated with disruption or enhancement of the leptin-signaling pathway. Leptin levels have been correlated with estrogen levels [40], therefore the observation of a stronger effect among pre- menopausal women is plausible. It is possible that in the presence of estrogen, genetic variation in the *LEPR* has a greater influence on the biological properties of leptin

Adiponectin, like leptin, is an adipokine. Variation in *ADIPOQ* has been linked to breast cancer risk in some studies [41]. Similar to *LEPR*, associations in our study were observed only among pre- menopausal women and were influenced by BMI and WHR. Others have shown a correlation between *ADIPOQ* rs17366568 and serum levels of adiponectin among white women, but not among African American women [42]. However, we did not observe

that SNP as being associated with breast cancer risk in any ancestry group. Likewise, *ADIPOQ* rs1501299 was associated with breast cancer risk among African Americans in the Women's Health Initiative but not among Hispanic women [43]; we did not observe a significant association between that SNP and breast cancer risk. Adiponectin can regulate the secretion of estrogens, TNF, and IGF; circulating levels of adiponectin are decreased in obese and diabetic subjects [41,44]. It also has been hypothesized that adiponection may have anti-carcinogenic effects based on its ability to decrease the production of reactive oxygen species [45]. Obesity likewise can lead to both insulin and leptin resistance resulting in what has been labeled as "dysfunctional adipose tissue" [46,47]. As adipose tissue expands the composition of adipose tissue changes, adipokines such as leptin and inflammatory cytokines increase while adiponectin decreases. This dysfunction from increased adipose tissue plays a critical role in insulin resistance, inflammation, and level of endogenous sex steroids [47]. Thus, the interaction between indicators of obesity and *ADIPOQ* SNPs, like those with *LEPR*, could impact breast cancer risk via multiple mechanisms [7]. If these SNPs alter the level of adiponectin, the effect on breast cancer risk could jointly depend on level of obesity and related adiponectin levels. For instance, if a person with a BMI > 30 kg/m^2 had a genotype that increased adiponectin levels, their resulting adiponectin level could be comparabletoan individual with a different genotype who was of normal weight; conversely the level of estrogen, TNF, or IGF could be influenced by SNPs that influence adiponectin levels.

The study has limitations and several strengths. Perhaps the greatest weakness is interpreting the findings given that the functionality of most of the SNPs is unknown. We used a tagSNP approach to gather information on the genetic variation across the gene. However, other important SNPs may be outside of the range we used for tagSNP selection and may importantly influence our candidate genes in terms of breast cancer risk. Our tagSNP approach was implemented on a customized Illumina platform and included SNPs that were validated and considered to have a high probability of yielding results. We were able to simultaneously evaluate SNPs, body size measurements, menopausal status and IA ancestry, although we do not know how estrogen, insulin, and actual levels of leptin and adiponectin are expressed in these subgroups; estrogen receptor and progesterone receptor status are not available for the entire population. Given the study design we were unable to assess levels of leptin or adiponectin. Our sample was large and we were able to examine associations simultaneously by level of IA ancestry and menopausal status, which we believe is a strength. However, statistical power is always an issue when examining subgroups, and it is also a consideration for this study. Given the much lower MAF for many SNPs in categories of higher IA ancestry, study power is further compromised and lack of associations in those groups could be influenced by sample size. Because of power issues when evaluating interactions we combined the upper two ancestry groups given similar associations with breast cancer risk in the majority of the previous analysis. However, meaningful interactions could have been missed given the broader classification and the sample size needed to detect interactions. Other factors that influence energy homeostasis, such as total energy intake and food composition were not included given the complicated nature of these analyses that would involve looking at similar interactions as those presented here and is beyond the scope of this manuscript.

Our findings support the hypothesis that genetic variation in genes involved in energy homeostasis is associated with breast cancer risk. Associations were generally stronger for pre-menopausal women, although *POMC* was associated with risk among post-menopausal women with high IA ancestry. *LEPR*, *CCK*, *GHRL*, and *ADIPOQ* were associated with breast cancer risk; however, factors such as level of IA ancestry and body size further modified risk. These findings provide insight into the complexity of factors that impact breast cancer risk and should be replicated in other large admixed populations. To better understand breast cancer risk associated with genetic ancestry, it is necessary to consider the complex relationship between genes, anthropometric, and meno-pausal status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Slattery ML, et al. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. Breast Cancer Res. Treat. 2007; 102:85–101. [PubMed: 17080310]
2. John EM, et al. Lifetime physical activity and breast cancer risk in a multiethnic population: the San Francisco Bay area breast cancer study. Cancer Epidemiol. Biomarkers Prev. 2003; 12:1143–1152. [PubMed: 14652273]
3. John EM, et al. Overall and abdominal adiposity and premenopausal breast cancer risk among hispanic women: the breast cancer health disparities study. Cancer Epidemiol. Biomarkers Prev. 2015; 24:138–147. [PubMed: 25352526]
4. John EM, et al. Body size throughout adult life influences postmenopausal breast cancer risk among hispanic women: the breast cancer health disparities study. Cancer Epidemiol. Biomarkers Prev. 2015; 24:128–137. [PubMed: 25352523]

5. Schleinitz D, et al. The genetics of fat distribution. Diabetologia. 2014; 57:1276–1286. [PubMed: 24632736]
6. Joost HG, et al. The genetic basis of obesity-associated type 2 diabetes (diabesity) in polygenic mouse models. Mamm. Genome. 2014; 25:401–412. [PubMed: 24752583]
7. Grossmann ME, et al. The balance between leptin and adiponectin in the control of carcinogenesis —focus on mammary tumorigenesis. Biochimie. 2012; 94:2164–2171. [PubMed: 22728769]
8. Brooks JD, et al. Variation in genes related to obesity, weight, and weight change and risk of contralateral breast cancer in the WECARE Study population. Cancer Epidemiol. Biomarkers Prev. 2012; 21:2261–2267. [PubMed: 23033454]
9. Llanos AA, et al. Adipokines in plasma and breast tissues: associations with breast cancer risk factors. Cancer Epidemiol. Biomarkers Prev. 2012; 21:1745–1755. [PubMed: 22892282]
10. He BS, et al. Effect of LEPR Gln223Arg polymorphism on breast cancer risk in different ethnic populations: a meta-analysis. Mol. Biol. Rep. 2012; 39:3117–3122. [PubMed: 21698367]
11. Gu F, et al. Leptin and leptin receptor genes in relation to premenopausal breast cancer incidence and grade in Caucasian women. Breast Cancer Res. Treat. 2012; 131:17–25. [PubMed: 21947707]
12. Cleveland RJ, et al. Common genetic variations in the LEP and LEPR genes, obesity and breast cancer incidence and survival. Breast Cancer Res. Treat. 2010; 120:745–752. [PubMed: 19697123]
13. Gallicchio L, et al. Body mass, polymorphisms in obesity-related genes, and the risk of developing breast cancer among women with benign breast disease. Cancer Detect. Prev. 2007; 31:95–101. [PubMed: 17428620]
14. Liu C, et al. Polymorphisms in three obesity-related genes (LEP, LEPR, and PON1) and breast cancer risk: a meta-analysis. Tumour Biol. 2011; 32:1233–1240. [PubMed: 21887553]
15. Snoussi K, et al. Leptin and leptin receptor polymorphisms are associated with increased risk and poor prognosis of breast carcinoma. BMC Cancer. 2006; 6:38. [PubMed: 16504019]
16. Teras LR, et al. No association between polymorphisms in LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 and postmenopausal breast cancer risk. Cancer Epidemiol. Biomarkers Prev. 2009; 18:2553–2557. [PubMed: 19723917]
17. Dossus L, et al. Polymorphisms of genes coding for ghrelin and its receptor in relation to anthropometry, circulating levels of IGF-I and IGFBP-3, and breast cancer risk: a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). Carcinogenesis. 2008; 29:1360–1366. [PubMed: 18375957]
18. Lim CT, et al. The expression of ghrelin *O*-acyltransferase (GOAT) in human tissues. Endocr. J. 2011; 58:707–710. [PubMed: 21646729]
19. Slattery ML, et al. Genetic variation in genes involved in hormones, inflammation and energetic factors and breast cancer risk in an admixed population. Carcinogenesis. 2012; 33:1512–1521. [PubMed: 22562547]
20. John EM, et al. Migration history, acculturation, and breast cancer risk in Hispanic women. Cancer Epidemiol. Biomarkers Prev. 2005; 14:2905–2913. [PubMed: 16365008]
21. Torres-Mejia G, et al. Moderate-intensity physical activity ameliorates the breast cancer risk in diabetic women. Diabetes Care. 2012; 35:2500–2502. [PubMed: 23033240]
22. Falush D, et al. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics. 2003; 164:1567–1587. [PubMed: 12930761]
23. Pritchard JK, et al. Inference of population structure using multilocus genotype data. Genetics. 2000; 155:945–959. [PubMed: 10835412]
24. Nyholt DR. A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. Am. J. Hum. Genet. 2004; 74:765–769. [PubMed: 14997420]
25. Li J, et al. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. Heredity. 2005; 95:221–227. [PubMed: 16077740]
26. Yu K, et al. Pathway analysis by adaptive combination of *P*-values. Genet. Epidemiol. 2009; 33:700–709. [PubMed: 19333968]

27. Yu, Kai; William Wheeler, OL. ARTP Gene and Pathway p-values computed using the Adaptive Rank Truncated Product. pp. R package. 2011
28. Woods SC, et al. Signals that regulate food intake and energy homeostasis. Science. 1998; 280:1378–1383. [PubMed: 9603721]
29. Namjou B, et al. EMR-linked GWAS study. investigation of variation landscape of loci for body mass index in children. Front. Genet. 2013; 4:268. [PubMed: 24348519]
30. Mutschler J, et al. Functional polymorphism in the neuropeptide Y gene promoter (rs16147) is associated with serum leptin levels and waist-hip ratio in women. Ann. Nutr. Metab. 2013; 62:271–276. [PubMed: 23652383]
31. Olza J, et al. Influence of variants in the NPY gene on obesity and metabolic syndrome features in Spanish children. Peptides. 2013; 45:22–27. [PubMed: 23624317]
32. Banke E, et al. Cocaine- and amphetamine-regulated transcript is expressed in adipocytes and regulate lipid- and glucose homeostasis. Regul. Pept. 2013; 182:35–40. [PubMed: 23318496]
33. Wu JT, et al. Ghrelin: integrative neuroendocrine peptide in health and disease. Ann. Surg. 2004; 239:464–474. [PubMed: 15024307]
34. Feigelson HS, et al. Genetic variation in candidate obesity genes ADRB2, ADRB3, GHRL, HSD11B1, IRS1, IRS2, and SHC1 and risk for breast cancer in the Cancer Prevention Study II. Breast Cancer Res. 2008; 10:R57. [PubMed: 18611262]
35. Wagner K, et al. Polymorphisms in genes involved in GH1 release and their association with breast cancer risk. Carcinogenesis. 2006; 27:1867–1875. [PubMed: 16606630]
36. Speliotes EK, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat. Genet. 2010; 42:937–948. [PubMed: 20935630]
37. Jackson RS, et al. Proopiomelanocortin products and human early-onset obesity. J. Clin. Endocrinol. Metab. 1999; 84:819–820. [PubMed: 10022461]
38. Gao Q, et al. Cross-talk between estrogen and leptin signaling in the hypothalamus. Am. J. Physiol. Endocrinol. Metab. 2008; 294:E817–E826. [PubMed: 18334610]
39. Nyante SJ, et al. Common genetic variation in adiponectin, leptin, and leptin receptor and association with breast cancer subtypes. Breast Cancer Res. Treat. 2011; 129:593–606. [PubMed: 21516303]
40. Fusco R, et al. Cellular and molecular crosstalk between leptin receptor and estrogen receptor-{alpha} in breast cancer: molecular basis for a novel therapeutic setting. Endocr. Relat. Cancer. 2010; 17:373–382. [PubMed: 20410173]
41. Kaklamani VG, et al. Variants of the adiponectin and adiponectin receptor 1 genes and breast cancer risk. Cancer Res. 2008; 68:3178–3184. [PubMed: 18451143]
42. Cohen SS, et al. ADIPOQ, ADIPOR1, and ADIPOR2 polymorphisms in relation to serum adiponectin levels and BMI in black and white women. Obesity (Silver Spring). 2011; 19:2053–2062. [PubMed: 21273992]
43. Kaklamani VG, et al. Adiponectin pathway polymorphisms and risk of breast cancer in African Americans and Hispanics in the Women's Health Initiative. Breast Cancer Res. Treat. 2013; 139:461–468. [PubMed: 23624817]
44. Dalamaga M, et al. The role of adiponectin in cancer: a review of current evidence. Endocr. Rev. 2012; 33:547–594. [PubMed: 22547160]
45. Schaffler A, et al. Mechanisms of disease: adipokines and breast cancer— endocrine and paracrine mechanisms that connect adiposity and breast cancer. Nat. Clin. Pract. Endocrinol. Metab. 2007; 3:345–354. [PubMed: 17377617]
46. Prieto-Hontoria PL, et al. Role of obesity-associated dysfunctional adipose tissue in cancer: a molecular nutrition approach. Biochim. Biophys. Acta. 2011; 1807:664–678. [PubMed: 21111705]
47. van Kruijsdijk RC, et al. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol. Biomarkers Prev. 2009; 18:2569–2578. [PubMed: 19755644]

Table 1

Description of study population by estimated IA ancestry.

	Low (0–28%) IA ancestry					**Intermediate (29–70%) IA ancestry**					**High (71–100%) IA ancestry**				
	Controls		**Cases**		***P* Value[a]**	**Controls**		**Cases**		***P* value**	**Controls**		**Cases**		***P* value**
	N	**%**	***N***	**%**		***N***	**%**	***N***	**%**		***N***	**%**	***N***	**%**	
Total	1855	44.4	1747	48.6	NA	1693	40.5	1400	39.0	NA	634	15.2	445	12.4	NA
Study site															
4 Corners Breast Cancer Study	1446	78.0	1318	75.4	NA	574	33.9	474	33.9	NA	24	3.8	32	7.2	NA
Mexico City Breast Cancer Study	11	0.6	26	1.5		470	27.8	426	30.4		513	80.9	364	81.8	
San Francisco Breast Cancer Study	398	21.5	403	23.1		649	38.3	500	35.7		97	15.3	49	11.0	
Age (years)															
<40	148	8.0	111	6.4	NA	200	11.8	124	8.9	NA	79	12.5	54	12.1	NA
40–	484	26.1	491	28.1		519	30.7	468	33.4		236	37.2	163	36.6	
50–	491	26.5	493	28.2		498	29.4	406	29.0		176	27.8	131	29.4	
60–	398	21.5	419	24.0		345	20.4	297	21.2		132	20.8	75	16.9	
>70	334	18.0	233	13.3		131	7.7	105	7.5		11	1.7	22	4.9	
Mean	56.2		55.6			52.7		53.1			50.7		51.0		
Menopausal status															
Pre-menopausal	589	32.3	584	34.2	NA	658	40.1	541	39.7	NA	274	43.5	200	45.8	NA
Post-menopausal	1236	67.7	1122	65.8		982	59.9	821	60.3		356	56.5	237	54.2	
Estimated Native American Ancestry															
U.S. NHW	1577	85.0	1472	84.3	NA	7	0.4	7	0.5	NA	1	0.2	2	0.4	NA
U. S. Hispanic or Mexican	278	15.0	275	15.7		1686	99.6	1393	99.5		633	99.8	443	99.6	
	Median	<(IQR)[b]	Median	(IQR)		Median	(IQR)	Median	(IQR)		Median	(IQR)	Median	(IQR)	
BMI (kg/m^2)	25.95	(22.89, 30.79)	25.95	(22.85, 30.51)	0.61	29.59	(26.27, 33.89)	28.55	(25.30, 32.51)	<.01	29.56	(26.86, 32.86)	28.60	(25.66, 32.63)	0.01
Weight gain	12.93	(6.80, 22.34)	13.61	(6.80, 22.51)	0.69	15.77	(9.07, 23.81)	14.00	(8.00, 22.40)	<.01	15.36	(8.97, 21.26)	13.20	(7.70, 21.20)	0.09

	Low (0–28%) IA ancestry					Intermediate (29–70%) IA ancestry					High (71–100%) IA ancestry				
	Controls		Cases		*P* Value[a]	Controls		Cases		*P* value	Controls		Cases		*P* value
	N	%	*N*	%		*N*	%	*N*	%		*N*	%	*N*	%	
Waist	33.23	(29.75, 38.00)	33.63	(30.00, 38.00)	0.45	36.50	(33.25, 40.50)	36.22	(33.00, 39.69)	0.01	37.91	(35.11, 41.32)	37.36	(34.49, 40.16)	0.02
Hip	41.50	(39.00, 45.09)	42.00	(39.00, 45.50)	0.46	42.36	(39.83, 46.00)	41.75	(39.37, 45.25)	<.01	41.73	(39.25, 44.61)	41.65	(38.94, 44.50)	0.28
Waist/hip ratio	0.80	(0.75, 0.85)	0.80	(0.76, 0.85)	0.40	0.85	(0.81, 0.90)	0.86	(0.81, 0.90)	0.61	0.90	(0.86, 0.95)	0.90	(0.85, 0.94)	0.09
Waist/height ratio	0.52	(0.46, 0.59)	0.53	(0.47, 0.60)	0.65	0.60	(0.54, 0.66)	0.59	(0.54, 0.65)	<.01	0.64	(0.59, 0.70)	0.63	(0.57, 0.68)	<.01

[a] Wilcoxon rank-sum *p* value.

[b] Interquartile range (IQR).

Table 2

Associations between energy homeostasis genes and body size by ancestry among controls.

	Base	BMI[a]		Weight gain[a]		Waist[a]		Hip[a]		Waist-to-hip Ratio[a]		Waist-to-height ratio[a]	
Marker	**Change**	**β[b]**	***P* value**	**β**	***P* value**	**β**	***P* value**	**β**	***P* value**	**β**	***P* value**	**β**	***P* value**
<28% IA ancestry													
rs747455 (*CCK*)	G > A	0.157	0.39	0.051	0.57	0.503	**0.02**	0.17	0.22	0.009	<.01	0.008	**0.01**
rs35683 (*GHRL*)	C > A	0.057	0.73	0.007	0.92	0.333	0.1	0.368	**0.03**	0.002	0.53	0.006	0.07
rs35682 (*GHRL*)	A > G	0.073	0.67	−0.096	0.86	0.291	0.16	0.357	**0.03**	0.001	0.73	0.005	0.12
rs26802 (*GHRL*)	T > G	−0.093	0.50	−0.131	0.75	−0.267	0.24	−0.388	**0.02**	0.001	0.83	−0.003	0.34
rs27647 (*GHRL*)	T > C	0.249	0.20	0.702	0.09	0.215	0.3	0.373	**0.02**	−0.001	0.6	0.004	0.19
rs9436739 (*LEPR*)	T > A	0.566	**0.04**	1.048	0.11	0.34	0.21	0.115	0.53	0.005	0.14	0.004	0.31
rs16129 (*NPY*)	G > T	−0.298	0.09	−0.916	**0.02**	−0.221	0.24	−0.196	0.17	−0.001	0.63	−0.003	0.30
rs1866146 (*POMC*)	T > C	−0.426	0.05	−0.669	0.18	−0.438	**0.03**	−0.394	**0.03**	−0.003	0.18	−0.007	**0.03**
rs6713532 (*POMC*)	T > C	−0.412	0.08	−0.872	0.15	−0.498	**0.03**	−0.526	**<.01**	−0.002	0.45	−0.007	**0.04**
rs7565877 (*POMC*)	A > G	0.051	0.88	0.568	0.39	0.502	0.12	−0.06	0.85	0.011	**<.01**	0.008	0.10
rs934778 (*POMC*)	T > C	0.212	0.28	0.638	0.19	0.435	0.05	0.255	0.17	0.004	0.11	0.007	**0.04**
28–70% IA ancestry													
rs17300539 (*ADIPOQ*)	G > A	0.717	0.1	1.736	0.08	0.899	**0.03**	0.617	0.18	0.007	0.17	0.015	**0.03**
rs17366568 (*ADIPOQ*)	G > A	−0.027	0.79	0.77	0.24	0.522	0.14	−0.005	0.82	0.01	**0.02**	0.009	0.11
rs3846659 (*CARTPT*)	G > C	0.323	0.19	0.743	0.20	0.561	**0.03**	0.421	**0.04**	0.003	0.47	0.008	0.06
rs16871468 (*CARTPT*)	T > G	0.073	0.76	−0.668	0.26	0.136	0.43	0.036	0.89	0.005	**0.03**	0.002	0.44
rs17358300 (*CARTPT*)	T > C	0.218	0.24	−0.163	0.99	0.323	0.05	0.188	0.20	0.005	**0.01**	0.005	0.08
rs8192472 (*CCK*)	G > A	−0.568	**<.01**	−1.011	**<.01**	−0.548	**<.01**	−0.485	**<.01**	−0.002	0.45	−0.009	**<.01**
rs11571842 (*CCK*)	G > A	−0.353	0.06	−0.66	0.05	−0.203	0.21	−0.199	0.18	−0.001	0.81	−0.003	0.22
rs35683 (*GHRL*)	C > A	0.432	**0.03**	0.224	0.39	0.316	0.11	0.241	0.16	0.002	0.36	0.005	0.16
rs26802 (*GHRL*)	T > G	−0.374	0.07	−0.296	0.42	−0.463	**0.03**	−0.18	0.30	−0.005	0.05	−0.008	**0.02**
rs7526141 (*LEPR*)	C > T	−0.495	0.03	−0.643	0.11	−0.176	0.44	−0.294	0.11	0.000	0.82	−0.003	0.47
rs9436740 (*LEPR*)	A > T	0.191	0.28	0.909	**0.02**	0.061	0.76	0.056	0.88	−0.001	0.71	0.000	0.96
rs17412175 (*LEPR*)	T > A	−0.512	**0.01**	−0.684	0.08	−0.197	0.33	−0.328	0.06	0.001	0.73	−0.003	0.38
rs970468 (*LEPR*)	T > G	0.375	0.05	0.717	0.06	0.30	0.10	0.29	0.07	0.002	0.35	0.005	0.13
rs6704167 (*LEPR*)	A > T	−0.451	**0.03**	−0.887	**0.04**	−0.144	0.48	−0.236	0.20	0.000	0.99	−0.007	0.09

	Base	BMI[a]		Weight gain[a]		Waist[a]		Hip[a]		Waist-to-hip Ratio[a]		Waist-to-height ratio[a]	
Marker	**Change**	**β[b]**	***P* value**	**β**	***P* value**	**β**	***P* value**	**β**	***P* value**	**β**	***P* value**	**β**	***P* value**
rs3790429 (*LEPR*)	A > T	−0.543	**0.01**	−0.665	0.08	−0.148	0.48	−0.156	0.37	−0.001	0.87	−0.002	0.64
rs1180445 (*LEPR*)	T > C	0.30	0.18	−0.15	0.79	−0.143	0.52	0.105	0.56	−0.005	0.05	−0.002	0.53
rs16141 (*NPY*)	C > A	0.575	<.01	0.979	**0.01**	0.538	<**.01**	0.434	**0.02**	0.004	0.1	0.009	<**.01**
rs16129 (*NPY*)	G > T	0.66	<.01	0.892	**0.04**	0.555	<**.01**	0.48	<**.01**	0.003	0.14	0.009	<**.01**
rs2023890 (*NPY*)	T > C	0.62	**0.04**	0.451	0.26	0.351	0.13	0.295	0.14	0.002	0.47	0.007	0.10
rs6713532 (*POMC*)	T > C	−0.315	0.09	−0.569	0.22	−0.254	0.13	−0.335	0.05	−0.001	0.69	−0.004	0.15
rs7565427 (*POMC*)	G > A	0.529	0.20	1.124	0.14	0.712	0.06	0.466	0.19	0.009	0.04	0.011	0.08
>70% IA ancestry													
rs17300539 (*ADIPOQ*)	G > A	−0.12	0.87	0.914	0.82	1.002	0.24	−0.113	0.71	0.026	**0.01**	0.012	0.38
rs16861210 (*ADIPOQ*)	G > A	−0.066	0.95	0.142	0.93	1.132	0.13	0.013	0.91	0.02	**0.03**	0.016	0.19
rs17366568 (*ADIPOQ*)	G > A	−1.328	0.07	−3.902	**0.01**	−0.321	0.61	0.015	1.00	−0.008	0.35	−0.01	0.43
rs17358300 (*CARTPT*)	T > C	−0.275	0.24	−1.232	0.05	−0.222	0.29	−0.15	0.29	−0.003	0.31	−0.005	0.22
rs4684677 (*GHRL*)	T > A	−0.242	0.44	−0.415	0.60	−0.428	0.10	−0.503	**0.04**	−0.002	0.61	−0.007	0.15
rs26802 (*GHRL*)	T > G	0.24	0.53	1.626	**0.03**	0.159	0.58	0.36	0.24	−0.003	0.53	0.004	0.46
rs3755777 (*GHRL*)	G > C	−0.394	0.26	−0.758	0.29	−0.573	0.05	−0.647	**0.02**	−0.002	0.71	−0.009	0.07
rs2071045 (*LEP*)	T > C	0.357	0.20	1.245	0.13	0.279	0.38	0.568	**0.03**	−0.005	0.21	0.004	0.45
rs1171265 (*LEPR*)	G > A	0.457	0.12	0.962	0.19	0.424	0.13	0.515	0.05	−0.003	0.36	0.007	0.14
rs6673324 (*LEPR*)	G > A	0.444	0.11	0.813	0.23	0.408	0.14	0.557	**0.03**	−0.004	0.22	0.007	0.13
rs10749754 (*LEPR*)	G > A	0.108	0.64	0.514	0.23	0.044	0.93	0.283	0.28	−0.006	0.05	0.000	0.97
rs1137101 (*LEPR*)	A > G	0.082	0.70	0.683	0.17	0.026	0.99	0.274	0.31	−0.006	**0.04**	0.000	0.98
rs4655537 (*LEPR*)	G > A	0.066	0.97	−1.026	0.05	−0.063	0.80	−0.169	0.45	0.004	0.24	−0.001	0.82
rs11585329 (*LEPR*)	G > T	−0.707	0.14	−1.798	0.07	−1.069	0.01	−0.69	0.06	−0.008	0.16	−0.021	<**.01**
rs1938484 (*LEPR*)	C > A	0.036	0.97	0.84	0.16	−0.054	0.74	0.272	0.42	−0.007	**0.03**	−0.002	0.69
rs1805096 (*LEPR*)	C > T	−0.002	0.88	1.118	**0.04**	0.113	0.64	0.221	0.31	−0.003	0.41	0.001	0.77

[a] Models adjusted for age, genetic ancestry, height, study, and physical activity.

Bold text indicates $p < 0.05$.

[b] β is for one unit of change for each anthropometric variable.

Table 3

Associations between energy homeostasis genes, SNPs, and breast cancer risk by genetic ancestry.

	0–28% IA ancestry					29–70% IA ancestry					71–100% IA ancestry					
	Controls	Cases				Controls	Cases				Controls	Cases				Interaction
	N	*N*	OR[a]	(95% CI)	Gene P_{ARTP}[b]	*N*	*N*	OR	(95% CI)	Gene P_{ARTP}	*N*	*N*	OR	(95% CI)	Gene P_{ARTP}	*P*-value
					0.024					0.639					0.075	
LEPR (rs12145690)																
AA	537	504	1.00			433	356	1.00			126	111	1.00			0.131
AC	887	883	1.05	(0.90,1.23)		808	683	1.02	(0.86,1.22)		308	218	0.84	(0.60,1.16)		
CC	394	345	0.93	(0.77,1.12)		419	329	0.98	(0.80,1.20)		188	102	0.67	(0.46,0.97)		
P raw; adjusted			0.535; 1.000					0.838; 1.000					0.032; 0.352			
LEPR (rs4655802)																
AA	637	610	1.00			569	447	1.00			215	117	1.00			0.028
AG	872	845	1.01	(0.87,1.16)		780	683	1.11	(0.94,1.31)		301	217	1.30	(0.96,1.75)		
GG	309	278	0.94	(0.77,1.15)		311	240	0.99	(0.80,1.22)		106	97	1.63	(1.12,2.37)		
P raw; adjusted			0.617; 1.000					0.857; 1.000					0.010; 0.155			
LEPR (rs1180445)																
TT/TC	1747	1665	1.00			1558	1280	1.00			559	406	1.00			0.069
CC	72	69	1.00	(0.71,1.40)		102	90	1.10	(0.81, 1.48)		63	25	0.54	(0.33,0.90)		
P raw; adjusted			0.977; 1.000					0.547; 1.000					0.018; 0.241			
LEPR (rs1475397)																
CC/CT	1683	1608	1.00			1454	1200	1			527	390	1.00			0.081
TT	136	125	0.95	(0.73,1.22)		207	170	1.04	(0.83,1.29)		95	41	0.60	(0.40,0.90)		
P raw; adjusted			667; 1.000					0.754; 1.000					0.014; 0.203			
LEPR (rs1171271)																
TT/TC	1667	1630	1.00			1510	1236	1.00			557	376	1.00			
CC	152	104	0.69	(0.53,0.89)		151	134	1.13	(0.88,1.44)		65	55	1.28	(0.86,1.93)		0.005
P raw; adjusted			0.005; 0.0780					355; 1.000					0.227; 0.743			
LEPR (rs4370791)																
AA/AG	1650	1619	1.00			1476	1210	1.00			542	366	1.00			0.005

	0–28% IA ancestry					29–70% IA ancestry					71–100% IA ancestry					Interaction
	Controls	Cases				Controls	Cases				Controls	Cases				
	N	*N*	OR[a]	(95% CI)	Gene P_{ARTP}[b]	*N*	*N*	OR	(95% CI)	Gene P_{ARTP}	*N*	*N*	OR	(95% CI)	Gene P_{ARTP}	*P*-value
GG	168	114	0.68	(0.53,0.88)		184	159	1.10	(0.87,1.38)		79	65	1.29	(0.89,1.88)		
P raw; adjusted			0.003; 0.046					0.426; 1.000					0.181; 0.743			
LEPR (rs1938484)																
CC/CA	1741	1692	1.00			1511	1245	1.00			531	357	1.00			0.009
AA	78	42	0.55	(0.37,0.80)		150	125	1.08	(0.84,1.40)		91	74	1.32	(0.92,1.89)		
P raw; adjusted			0.002; 0.036					0.537; 1.000					0.126; 0.743			
LEPR (rs6588147)																
AA/AG	1587	1556	1.00			1398	1134	1.00			496	326	1.00			0.007
GG	228	173	0.77	(0.62,0.95)		261	232	1.13	(0.93,1.37)		125	105	1.28	(0.94,1.74)		
P raw; adjusted			0.016; 0.229					0.234; 1.000					0.122; 0.743			
					0.646					0.015					0.012	
POMC (rs1866146)																
TT	770	740	1.00			376	367	1.00			87	52	1.00			0.968
TC	812	791	1.02	(0.89,1.18)		857	668	0.8	(0.66,0.95)		292	198	1.20	(0.80,1.81)		
CC	234	203	0.89	(0.72,1.10)		428	333	0.79	(0.64,0.97)		243	181	1.40	(0.92,2.13)		
P raw; adjusted			0.500; 1.000					0.028; 0.084					0.097; 0.193			
POMC (rs6713532)																
TT	1049	1000	1.00			387	384	1.00			91	54	1.00			0.399
TC	658	623	0.99	(0.86,1.14)		867	684	0.8	(0.67,0.95)		301	209	1.22	(0.82,1.83)		
CC	112	110	1.02	(0.77,1.34)		406	301	0.74	(0.60,0.91)		230	168	1.4	(0.92,2.12)		
P raw; adjusted			0.999; 1.000					0.005; 0.018					0.110; 0.193			
POMC (rs934778)																
TT	886	827	1.00			967	755	1.00			354	286	1.00			0.064
TC/CC	933	906	1.05	(0.92,1.20)		694	615	1.15	(0.99,1.34)		268	145	0.65	(0.49,0.85)		
P raw; adjusted			0.489; 1.000					0.061; 0.122					0.002; 0.005			

[a] Adjusted for age, study, genetic admixture, reference year BMI, reference year vigorous activity, parity, and alcohol consumption.

Table 4

Associations between energy homeostasis genes by menopausal status.

		Controls	Cases	All Women			0–28% IA ancestry			29–70% IA ancestry			>70% IA Ancestry			
		N	*N*	OR[a]	(95% CI)	Gene P_{ARTP}[b]	OR	(95% CI)	GeneP_{ARTP}	OR	(95% CI)	Gene P_{ARTP}	OR	(95% CI)	Gene P_{ARTP}	Interaction *p* value
		Pre-menopausal														
CARTPT						0.014			0.015			0.63			0.5	
rs2239670	GG/GA	1440	1283	1.00			1.00			1.00			1.00			0.313
	AA	39	19	0.55	(0.32, 0.97)		0.78	(0.33, 1.82)		0.45	(0.17, 1.19)		0.35	(0.09, 1.39)		
	P-value: raw; adjusted			0.039; 0.117			0.560; 1.000			0.107; 0.430			0.137; 0.513			
rs17358300	TT/TC	1198	1117	1.00			1.00			1.00			1.00			0.749
	CC	281	185	0.73	(0.60, 0.90)		0.66	(0.46, 0.94)		0.84	(0.61, 1.14)		0.69	(0.42, 1.11)		
	P-value: raw; adjusted			0.003; 0.013			0.020; 0.061			0.254; 0.763			0.128; 0.513			
rs3846659	GG	1118	1010	1.00			1.00			1.00			1.00			0.139
	GC/CC	358	292	0.86	(0.72, 1.03)		0.7	(0.53, 0.91)		1.15	(0.86, 1.52)		0.78	(0.43, 1.41)		
	P-value: raw; adjusted			0.098; 0.196			0.007; 0.028			0.346; 0.763			0.416; 0.832			
GHRL							0.251		0.007			0.38			0.26	
rs35683	CC	660	558	1.00			1.00			1.00			1.00			0.003
	CA	624	594	1.01	(0.85, 1.19)		0.84	(0.64, 1.11)		1.10	(0.86, 1.41)		1.20	(0.76, 1.89)		
	AA	195	150	0.79	(0.61, 1.02)		0.58	(0.41, 0.82)		1.15	(0.74, 1.78)		1.29	(0.40, 4.14)		
	P-value: raw; adjusted			0.172; 0.554			0.003; 0.013			0.398; 1.000			0.398; 1.000			
rs35682	AA	643	545	1.00			1.00			1.00			1.00			0.002
	AG	626	595	1.00	(0.84, 1.18)		0.82	(0.61, 1.08)		1.11	(0.86, 1.42)		1.26	(0.80, 1.98)		
	GG	210	161	0.79	(0.61, 1.01)		0.57	(0.40, 0.80)		1.11	(0.73, 1.70)		1.31	(0.41, 4.21)		
	P-value: raw; adjusted			0.139; 0.554			0.001; 0.009			0.447; 1.000			0.305; 1.000			
rs27647	TT	787	706	1.00			1.00			1.00			1.00			0.02
	TC/CC	689	595	0.86	(0.73, 1.01)		0.8	(0.62, 1.02)		0.79	(0.62, 1.01)		1.65	(1.01, 2.69)		
	P-value: raw; adjusted			0.063; 0.363			0.071; 0.285			0.058; 0.347			0.045; 0.272			
		Post-Menopausal Women														
POMC						0.871			0.769			0.11			0.005	
rs934778	TT	1368	1142	1.00			1.00			1.00			1.00			0.248

	Controls	Cases	All Women			0–28% IA ancestry			29–70% IA ancestry			>70% IA Ancestry			
	N	*N*	OR[a]	(95% CI)	Gene P_{ARTP}[b]	OR	(95% CI)	GeneP_{ARTP}	OR	(95% CI)	Gene P_{ARTP}	OR	(95% CI)	Gene P_{ARTP}	Interaction *p* value
TC/CC	1170	1003	1.00	(0.89, 1.12)		0.98	(0.83, 1.16)		1.20	(0.99, 1.46)		0.52	(0.36, 0.76)		
P-value: raw; adjusted			0.996; 1.000			0.848; 1.000			0.062; 0.187			<.001; 0.002			

[a] Odds Ratios and 95% confidence Intervals (CI) adjusted for age, study, genetic admixture, reference year BMI, reference year vigorous activity, parity, and alcohol consumption.

[b] Pathway PARTP values for pre-menopausal women: all women = 0.22; 0–28% IA = 0.05, 29–70% IA = 0.58; >70% IA = 0.55; for Post-menopausal women: all women = 0.71, 0–28% IA = 0.61, 29–70% IA = 0.27, and >70% IA = 0.09.

Table 5

Interactions between body size variables and feeding behavior genes by IA ancestry among pre-menopausal women.

	<28% IA ancestry							>28% IA ancestry							
						Interaction P								Interaction P[b]	
	OR[a]	(95% CI)	OR	(95% CI)	OR	(95% CI)	2-way	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	2-way	3-way	4-way
	BMI <25		BMI 25–29		BMI >30			BMI <25		BMI 25–29		BMI>30				
LEPR (rs6704167)																
AA	1.00		0.96	(0.60, 1.54)	1.11	(0.67, 1.84)	0.10	1.00		0.50	(0.33, 0.76)	0.41	(0.27, 0.62)	0.002	0.0011	**0.0003**
AT	1.30	(0.91, 1.86)	1.15	(0.73, 1.79)	1.27	(0.80, 2.00)		0.50	(0.32, 0.81)	0.44	(0.29, 0.67)	0.42	(0.27, 0.65)			
TT	1.75	(1.05, 2.93)	0.72	(0.37, 1.41)	0.95	(0.48, 1.89)		0.32	(0.14, 0.69)	0.33	(0.17, 0.66)	0.47	(0.25, 0.86)			
LEPR (rs17412175)																
TT	1.00		0.93	(0.56, 1.54)	0.98	(0.58, 1.66)	0.59	1.00		0.54	(0.36, 0.83)	0.44	(0.28, 0.67)	0.004	0.0188	0.0059
TA	1.18	(0.82, 1.70)	0.94	(0.61, 1.46)	1.12	(0.71, 1.76)		0.53	(0.33, 0.85)	0.45	(0.29, 0.68)	0.39	(0.25, 0.60)			
AA	1.36	(0.84, 2.19)	0.83	(0.44, 1.56)	1.11	(0.56, 2.21)		0.36	(0.17, 0.77)	0.3	(0.15, 0.60)	0.60	(0.33, 1.09)			
ADIPOQ (rs17300539)																
GG	1.00		0.78	(0.56, 1.07)	1.02	(0.73, 1.43)	0.24	1.00		0.68	(0.51, 0.91)	0.59	(0.44, 0.80)	0.04	0.015	0.029
GA/AA	1.21	(0.79, 1.85)	1.20	(0.62, 2.31)	0.66	(0.33, 1.33)		0.62	(0.28, 1.35)	0.68	(0.39, 1.18)	0.96	(0.55, 1.68)			
	Weight gain low		Weight gain middle		Weight gain high			Weight gain low		Weight gain middle		Weight gain high				
LEPR (rs4655537)																
GG	1.00		1.48	(0.95, 2.31)	1.14	(0.70, 1.85)	0.03	1.00		0.52	(0.36, 0.77)	0.47	(0.31, 0.71)	0.098	0.0073	0.074
GA	0.88	(0.60, 1.30)	1.05	(0.68, 1.63)	0.78	(0.48, 1.27)		0.65	(0.45, 0.96)	0.50	(0.34, 0.73)	0.50	(0.33, 0.77)			
AA	1.2	(0.68, 2.11)	1.05	(0.52, 2.11)	0.32	(0.12, 0.86)		0.65	(0.34, 1.24)	0.39	(0.20, 0.74)	0.52	(0.26, 1.05)			
LEPR (rs10749754)																
GG	1.00		0.91	(0.54, 1.53)	0.43	(0.22, 0.82)	0.01	1.00		0.73	(0.44, 1.21)	1.11	(0.65, 1.89)	0.012	**0.0007**	0.0254
GA/AA	0.75	(0.50, 1.10)	1.08	(0.71, 1.65)	0.83	(0.53, 1.31)		1.73	(1.15, 2.59)	0.99	(0.66, 1.48)	0.83	(0.55, 1.28)			
LEPR (rs1137101)																
AA	1.00		0.88	(0.52, 1.47)	0.47	(0.25, 0.89)	0.02	1.00		0.68	(0.41, 1.13)	1.00	(0.58, 1.71)	0.044	0.0034	0.0574
AG/GG	0.78	(0.53, 1.16)	1.14	(0.74, 1.75)	0.85	(0.54, 1.34)		1.52	(1.01, 2.27)	0.90	(0.60, 1.35)	0.77	(0.50, 1.18)			
	Waist low		Waist middle		Waist high			Waist low		Waist middle		Waist high				
LEPR (rs6704167)																

			<28% IA ancestry					>28% IA ancestry							
						Interaction P							Interaction P[b]		
	OR[a]	(95% CI)	OR	(95% CI)	OR	(95% CI)	2-way	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	2-way	3-way	4-way
AA	1.00		1.30	(0.80, 2.12)	1.38	(0.81, 2.36)	0.02	1.00		0.89	(0.61, 1.30)	0.59	(0.40, 0.88)	0.002	0.0002	**0.0001**
AT	1.43	(1.02, 2.02)	1.46	(0.93, 2.29)	1.49	(0.92, 2.41)		0.69	(0.45, 1.05)	0.65	(0.44, 0.97)	0.69	(0.46, 1.05)			
TT	1.75	(1.08, 2.83)	1.32	(0.65, 2.70)	0.68	(0.30, 1.50)		0.29	(0.13, 0.66)	0.69	(0.37, 1.28)	0.75	(0.40, 1.40)			
LEPR (rs17412175)																
TT	1.00		1.45	(0.86, 2.45)	1.18	(0.67, 2.06)	0.18	1.00		0.85	(0.58, 1.26)	0.59	(0.39, 0.89)	0.002	0.0026	**0.003**
TA	1.3	(0.92, 1.84)	1.21	(0.77, 1.90)	1.34	(0.83, 2.15)		0.63	(0.41, 0.97)	0.64	(0.43, 0.95)	0.59	(0.39, 0.89)			
AA	1.47	(0.93, 2.33)	1.33	(0.69, 2.57)	0.96	(0.45, 2.03)		0.34	(0.16, 0.69)	0.64	(0.34, 1.22)	0.88	(0.48, 1.62)			
LEPR (rs7526141)																
CC	1.00		1.28	(0.75, 2.17)	1.33	(0.74, 2.40)	0.02	1.00		0.94	(0.64, 1.38)	0.62	(0.42, 0.93)	0.017	0.0012	**0.0005**
CT	1.3	(0.91, 1.85)	1.50	(0.95, 2.36)	1.48	(0.91, 2.41)		0.75	(0.49, 1.14)	0.69	(0.46, 1.02)	0.79	(0.53, 1.19)			
TT	1.52	(0.97, 2.37)	0.98	(0.50, 1.92)	0.73	(0.36, 1.45)		0.42	(0.20, 0.89)	0.95	(0.51, 1.77)	0.68	(0.37, 1.28)			
	WHR low		WHR middle		WHR high			WHR low		WHR middle		WHR high				
ADIPOQ (822391)																
TT	1.00		0.67	(0.47,0.95)	0.71	(0.42,1.21)	0.05	1.00		1.16	(0.81,1.64)	1.18	(0.83,1.68)	0.024	0.0054	0.0063
TC/CC	0.97	(0.71,1.31)	1.41	(0.92,2.17)	0.94	(0.45,1.96)		1.67	(1.00,2.77)	1.27	(0.84,1.92)	0.97	(0.64,1.48)			
	WHtR Low		WHtR Middle		WHtR High			WHtR low		WHtR middle		WHtR high				
LEPR (rs6704167)														0.008	0.0012	**0.0014**
AA	1.00		1.23	(0.77, 1.96)	1.07	(0.57, 2.02)	0.04	1.00		0.87	(0.59, 1.30)	0.55	(0.36, 0.83)			
AT	1.35	(0.97, 1.88)	1.34	(0.87, 2.08)	1.49	(0.87, 2.55)		0.72	(0.46, 1.14)	0.63	(0.42, 0.95)	0.62	(0.40, 0.95)			
TT	1.59	(1.00, 2.52)	1.47	(0.73, 2.97)	0.29	(0.09, 0.90)		0.42	(0.18, 0.95)	0.50	(0.27, 0.93)	0.74	(0.40, 1.40)			
LEPR (rs7526141)																
CC	1.00		1.26	(0.75, 2.11)	1.04	(0.52, 2.08)	0.05	1.00		0.87	(0.58, 1.31)	0.58	(0.38, 0.88)	0.039	0.005	0.0084
CT	1.29	(0.92, 1.83)	1.26	(0.82, 1.93)	1.62	(0.93, 2.85)		0.75	(0.48, 1.19)	0.68	(0.45, 1.02)	0.66	(0.43, 1.01)			
TT	1.35	(0.88, 2.06)	1.43	(0.72, 2.83)	0.40	(0.17, 0.94)		0.57	(0.26, 1.24)	0.62	(0.33, 1.13)	0.73	(0.39, 1.37)			
ADIPOQ (rs822391)																
TT	1.00		0.89	(0.61, 1.27)	0.71	(0.44, 1.16)	0.02	1.00		1.18	(0.84, 1.64)	0.87	(0.62, 1.24)	0.137	0.0095	0.0132
TC	1.1	(0.80, 1.52)	1.35	(0.83, 2.18)	1.17	(0.64, 2.16)		1.62	(0.99, 2.64)	0.86	(0.58, 1.30)	0.91	(0.59, 1.40)			
CC	0.6	(0.28, 1.28)	2.84	(0.88, 9.20)	2.11	(0.37, 11.95)		4.96	(0.99, 24.81)	1.48	(0.57, 3.78)	1.08	(0.35, 3.32)			

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[a] Odds ratios (OR) and 95% confidence Intervals adjusted for age, genetic ancestry, study, reference year vigorous activity, age at first birth, parity, and alcohol consumption.

[b] Interactions are: 2 way = SNP by body size within broader strata; 3 way = SNP by body size by IA ancestry; 4 way = SNP by body size by IA ancestry by menopausal status; adjusted *p* values are <0.15 for the three-way interaction for inclusion in the table.