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Common genetic variation in adiponectin, leptin, and leptin receptor and association with breast cancer subtypes

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Abstract

Adipocytokines are produced by visceral fat, and levels may be associated with breast cancer risk. We investigated whether single nucleotide polymorphisms (SNPs) in adipocytokine genes adiponectin (*ADIPOQ*), leptin (*LEP*), and the leptin receptor (*LEPR*) were associated with basal-like or luminal A breast cancer subtypes. 104 candidate and tag SNPs were genotyped in 1776 of

2022 controls and 1972 (200 basal-like, 679 luminal A) of 2311 cases from the Carolina Breast Cancer Study (CBCS), a population-based case-control study of whites and African Americans. Breast cancer molecular subtypes were determined by immunohistochemistry. Genotype odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression. Haplotype ORs and 95% CIs were estimated using Hapstat. Interactions with waist-hip ratio were evaluated using a multiplicative interaction term. Ancestry was estimated from 144 ancestry informative markers (AIMs), and included in models to control for population stratification. Candidate SNPs *LEPR* K109R (rs1137100) and *LEPR* Q223R (rs1137101) were positively associated with luminal A breast cancer, whereas *ADIPOQ*+45 T/G (rs2241766), *ADIPOQ*+276 G/T (rs1501299), and *LEPR* K656N (rs8129183) were not associated with either subtype. Few patterns were observed among tag SNPs, with the exception of 3 *LEPR* SNPs (rs17412175, rs9436746, and rs9436748) that were in moderate LD and inversely associated with basal-like breast cancer. However, no SNP associations were statistically significant after adjustment for multiple comparisons. Haplotypes in *LEP* and *LEPR* were associated with both basal-like and luminal A subtypes. There was no evidence of interaction with waist-hip ratio. Data suggest associations between *LEPR* candidate SNPs and luminal A breast cancer in the CBCS and *LEPR* intron 2 tag SNPs and basal-like breast cancer. Replication in additional studies where breast cancer subtypes have been defined is necessary to confirm these potential associations.

Keywords

Adiponectin; Leptin; Leptin receptor; Breast cancer; Subtypes; Single nucleotide polymorphism

Introduction

Much of the interest in the basal-like subtype of breast cancer is due to its association with tumor characteristics associated with poor prognosis, higher prevalence in younger and African American women, higher prevalence among BRCA1 carriers, and poorer survival when compared with breast cancers expressing the estrogen receptor (ER) [1–9]; however, the etiology of this tumor subtype remains largely unknown. The Carolina Breast Cancer Study (CBCS) previously reported that basal-like breast cancer was associated with elevated waist-hip ratio (WHR) [10]. One potential mechanism that may explain this association is the induction of pro-tumor pathways by adipocytokines [11, 12]. Adipocytokines are hormones produced in visceral adipose tissue, and circulating levels are correlated with obesity [11–13]. Adipocytokines are also expressed in breast tissue, and have been shown to affect cell proliferation, migration, and invasion [11, 12, 14]. Lower circulating levels of one particular adipocytokine, adiponectin, have been associated with breast cancer in some studies [15–19], though others have reported no association [20]. Case-control studies of the association between circulating levels of another adipocytokine, leptin, and breast cancer have been inconclusive, whereas a prospective study of leptin and breast cancer risk was null [17, 21–24].

Studies of the association between single nucleotide polymorphisms (SNPs) in the adiponectin (*ADIPOQ*), leptin (*LEP*), and leptin receptor (*LEPR*) genes and breast cancer risk have shown little consistency [21, 25–30]. For example, *LEPR* Q223R is the most commonly studied SNP in these genes, and has been reported as positively, inversely, and not associated with breast cancer [21, 25, 27–30]. It is possible that some of the variation in reported *ADIPOQ*, *LEP*, and *LEPR* SNP associations is due to tumor heterogeneity, and that stratification by tumor subtype will reveal subtype-specific associations, as has been demonstrated by others [10, 31–34].

Therefore, we investigated the association between SNPs in *ADIPOQ*, *LEP*, and *LEPR* and basal-like breast cancer, luminal A breast cancer, and breast cancer overall (all cases compared to controls). The relationship between adipocytokines and visceral fat led us to also evaluate interaction between SNPs and WHR, a proxy for central obesity. This analysis focused on basal-like breast cancer due to the specific nature of our hypothesis that basal-like breast cancer risk may be influenced by adipocytokines. Luminal A breast cancer was the most common breast cancer subtype in the CBCS and shows traditional associations with breast cancer risk factors [5, 10]; it is included in this analysis as a point of reference.

Materials and methods

Study population

The CBCS is a population-based case–control study of breast cancer in North Carolina, and has been described previously [10, 35, 36]. Eligible cases were women aged 20–74, diagnosed with primary invasive breast cancer from 1993 to 2001, and living within the study area. Randomized recruitment was used to oversample African American cases and cases younger than 50-years old [37]. Eligible women diagnosed with breast carcinoma in situ were also enrolled from 1996 to 2001. Women aged 20 to 74 years, residing within the study area, and without a history of breast cancer were eligible controls, and were frequency-matched to cases by race and age.

Participants provided informed consent and completed an in-home interview about social and demographic characteristics, medical history, and potential breast cancer risk factors. Height, weight, waist circumference, and hip circumference were measured by a trained nurse. Participants were also asked to provide a blood sample. DNA was extracted from blood and stored at -80°C . A total of 2311 cases and 2022 controls were enrolled. 2045 (88%) cases and 1818 (90%) controls provided a blood sample, and 2039 (88%) cases and 1818 (90%) controls had DNA available for genotyping.

Cases provided written consent for access to medical records and formalin-fixed paraffin-embedded tumor tissue blocks. Immunohistochemistry staining and scoring procedures for the ER, progesterone receptor (PR), human epidermal growth factor receptors 1 and 2 (EGFR and HER2), and cytokeratin (CK) 5/6 have been described in detail by others [5, 10, 38, 39]. Tumor tissue was available for 1845 of 2311 (80%) cases, and immunohistochemistry was completed for 1424 of 2311 (62%) cases. Tumors were classified as follows: 225 basal-like (ER $-$, PR $-$, HER2 $-$, CK 5/6+ and/or EGFR+), 796 luminal A (ER+ and/or PR+, HER2 $-$), 137 luminal B (ER+ and/or PR+, HER2+), 116 HER2+/ER $-$ (ER $-$, PR $-$, HER2+), and 150 unclassified (ER $-$, PR $-$, HER2 $-$, CK 5/6 $-$, and EGFR $-$) [5, 39, 40]. Cases with missing subtype data were more likely to be non-African American and to have an earlier stage at diagnosis [10].

SNP selection

SNPs were selected using pairwise tagging in Tagger ($r^2 \geq 0.80$) [41, 42]. The majority of CBCS participants were white or African American, so SNPs were selected from the International HapMap Project CEU and YRI populations; ASW genotypes were unavailable at the time of SNP selection [43]. Tag selection was performed separately in CEU and YRI data for SNPs with a minimum minor allele frequency (MAF) of 0.10, combined into a single list, and genotyped in all participants. Pairwise tagging for *LEPR* required more than 90 SNPs; tagging was repeated using aggressive tagging, which reduced the number of SNPs by 15 [41]. The list of tag SNPs was supplemented by “candidate” SNPs—SNPs with a reported in vitro functional effect or that had been investigated for an association with breast cancer risk (MAF ≥ 0.05).

158 ancestry informative markers (AIMs) were also genotyped to estimate African and European ancestry [44]. AIMs were selected from a panel that has been used previously by others to estimate ancestry in African Americans, and maximized Fisher's information content and the difference in allele frequencies between ancestral populations [45, 46].

Genotyping results and quality control

SNPs were genotyped as part of a larger set of 1536 SNPs by the UNC Mammalian Genotyping Core using the Illumina GoldenGate assay (Illumina, Inc, San Diego, CA). Assay intensity data and genotype cluster images for all SNPs were reviewed individually. 163 SNPs were excluded due to low signal intensity or inability to distinguish between genotype clusters. Blind duplicates of 169 samples were genotyped to verify the reproducibility of genotype calls. Concordance between duplicates was greater than 99.8% for all pairs.

Exact tests of Hardy–Weinberg equilibrium (HWE) were conducted in controls stratified by self-identified race using Plink v1.05 [47]. In order to confirm that deviations from HWE were not due to erroneous genotype calls, genotyping cluster images were re-reviewed for SNPs with HWE P -values less than 0.01. SNPs reviewed during this process had acceptable signal intensity and cluster definitions, and none were excluded. Overall, 1373 of 1536 (89%) SNPs passed quality control, including 104 of 127 (82%) in *ADIPOQ*, *LEP*, and *LEPR* and 144 of 158 (91%) AIMs.

Subject data were excluded because of genotype calls for less than 95% of SNPs ($N = 103$), gender mismatch ($N = 5$), and suspected contamination ($N = 1$), yielding data for 1776 of 2022 (88%) controls and 1972 of 2311 (85%) cases (Table 1). Participants without genotype data were more likely to be cases, recruited in the second half of the study, and African American. 1220 of 2311 (53%) cases had both genotyping and tumor subtype data; missing genotype data were not associated with tumor subtype.

Variables

Age was defined as age at breast cancer diagnosis for cases or age at study sampling for controls, and was included in models as a continuous variable. Self-identified race was white for 2293 participants, African American for 1400, and missing for 2. Less than 2% of participants reported that they were of another race, and were grouped with white women as non-African American.

Maximum likelihood methods were used to estimate individual proportions of African and European ancestry from 144 AIMs [48]. The median proportion of African ancestry was 81% among self-reported African Americans and 6% among self-reported non-African Americans. African ancestry was used in regression models as a proportion ranging from 0 to 0.96 (the maximum proportion African ancestry).

Body size was measured using standardized equipment [49]. WHR was the ratio of waist circumference to hip circumference, and was categorized based on the tertile distribution in controls. WHR associations with basal-like and luminal A breast cancer were similar for tertiles 2 and 3 (vs. tertile 1) [10], so those two categories were combined. Body mass index (BMI, weight in kg/height in m^2), a potential confounder of WHR associations with breast cancer [50, 51], was included in regression models as a continuous variable. WHR and/or BMI information were missing for 50 cases and 40 controls.

Self-reported family history of breast cancer in a first degree relative was used as a binary variable (yes/no).

Statistical analysis

Allele frequencies were adjusted for the sampling probabilities used to sample participants (online resource 1). R^2 was calculated in Haploview v3 [52]. Both were stratified by case status and self-identified race.

Odds ratios (ORs) and 95% confidence intervals (CIs) for genotype associations with breast cancer overall were estimated using unconditional binary logistic regression using SAS v9.1.3 (SAS, Cary, NC). Associations with basal-like and luminal A breast cancers were estimated using unconditional polytomous logistic regression and statistics testing the equality of parameter estimates for basal-like and luminal A subtypes were calculated based on the asymptotic chi-square distribution of the Wald statistic. Confidence limit ratios (CLRs, upper confidence limit divided by lower confidence limit) were calculated as a measure of relative precision [53]. As mentioned above, this analysis focused on basal-like and luminal A breast cancer; associations for other subtypes were not evaluated.

Genotype associations were modeled using the codominant model, as this does not assume a specific model form for the genotype effects and has greater power than other incorrectly specified model forms when the true underlying mode of inheritance is unknown [54]. If homozygote counts were less than 5 cases, less than 5 controls, or less than 10 cases and 10 controls, rare homozygote and heterozygote categories were combined. If results using the co-dominant model indicated that the underlying model may be recessive or dominant additional analyses specific to that model were conducted. Estimates for associations with basal-like breast cancer were expected to be less precise than associations for luminal A breast cancer due to the smaller number of basal-like cases. Therefore, the results presented were chosen based on both the strength of the OR and precision to avoid bias in reporting results by subtype. Associations with a relatively strong OR (OR ≥ 1.5 or OR ≤ 0.67) or a P -value < 0.05 and a precise CI (CLR ≥ 5) are reported in the results; sample size by genotype for these SNPs is given in online resource 2.

Models were adjusted initially for age and self-identified race, and an offset term was included in models to account for randomized recruitment sampling [37]. Confounding due to ancestry was assessed using the change-in-estimate approach, where a log OR change of 0.10 or more in either direction was considered a meaningful difference. Adjustment for ancestry changed log ORs by more than 0.10 for the association between a subset of SNPs and luminal A breast cancer, and so models were also adjusted for ancestry. Residual confounding by family history of breast cancer was assessed using the same approach. Additional adjustment for family history of breast cancer only affected the results for two SNPs (rs6413506 and rs4655555), and so family history was added to the final regression models for these SNPs only.

Log-additive model ORs and P -values were also calculated for SNP associations. Monte Carlo methods were used to approximate the joint distribution of test statistics and evaluate the family wise error rate to control for multiple comparisons [55]. Estimation of the joint distribution of test statistics before adjusting the alpha level insures that correlation among SNPs does not result in an overly conservative correction. The nominal alpha level for genotype associations was 0.05, and the Monte Carlo-adjusted alpha level was 0.001. All statistical tests were 2-sided.

To determine whether SNPs associated with breast cancer were associated with WHR, ORs for the association between breast cancer-associated SNPs and WHR were estimated using logistic regression in control subjects only, adjusting for BMI and the offset term.

Haplotype analyses were performed using Hapstat [56, 57], which simultaneously estimates the OR parameters and haplotype distribution for a given group of SNPs using maximum likelihood estimation and the EM algorithm. This approach yields unbiased estimates of ORs with appropriate variance estimates when haplotype phase is unknown. Modifications to Hapstat allowed for inclusion of an offset term and relaxation of the assumption of independence between genotypes and environmental variables [58].

For each gene, a 3-SNP sliding window was used to estimate a global P -value for the association between case status and all possible haplotypes in the window. Estimation of individual haplotype effects was pursued for haplotypes with a frequency ≥ 0.05 in controls (online resource 3) that were present in windows with the strongest global associations ($P < 0.01$); an a priori cut-point was not used. Regions were also selected by reviewing genotype ORs for consecutive strings of breast cancer-associated SNPs. Haplotype ORs and 95% CIs were estimated using the codominant model, and adjusted for age, self-identified race, ancestry, and the offset term. Haplotypes with a relatively strong OR (≥ 1.5 or ≤ 0.67) or a $P < 0.05$ and a precise CI (CLR ≥ 5) are reported in the results. Haplotype analyses were exploratory and predicated on SNP associations, and therefore were not adjusted for multiple comparisons.

Multiplicative genotype- and haplotype-WHR interaction was tested by evaluating the statistical significance of a multiplicative genotype- or haplotype-WHR interaction term. Literature reviews have shown that associations between WHR and premenopausal breast cancer were biased towards the null in studies that did not adjust for BMI [50, 51], and a similar pattern was observed in the CBCS for the association between WHR and breast cancer overall (data not shown). Therefore, BMI was included as a confounder in models evaluating WHR interaction. Directed acyclic graph analysis suggested that menopausal status, parity, and lactation were also potential confounders, but inclusion of these covariates did not change the WHR-breast cancer subtype log ORs by ≥ 0.10 , and they were not included in final models. Genotype-WHR interaction was evaluated for all SNPs, and P -values were adjusted for multiple comparisons using Monte Carlo methods, described above. The nominal alpha level for interaction analyses was 0.10, and the Monte Carlo-adjusted alpha level was 0.002. Haplotype-WHR interaction was evaluated using an alpha level of 0.10.

Results

Genotype associations

SNP associations with breast cancer overall were modest, with many effect estimates near the null (Table 2). When stratified by subtype, some ORs were suggestive of specific patterns: a group of 3 SNPs (rs17412175, rs9436746, and rs9436748) spanning 6786 base pairs in *LEPR* intron 2 were inversely associated with basal-like breast cancer, with ORs ranging from 0.48 to 0.57 (Table 2). The SNPs showed varying levels of moderate to low LD in controls (online resource 4). Subtype-specific associations were less consistent for *ADIPOQ* SNPs, some of which were inversely associated with the luminal A (rs16861194) and basal-like (rs16861205) subtypes, and for *LEP* SNPs, some of which were positively associated with luminal A (rs6976701, rs17151922) and basal-like (rs10954174) subtypes (Table 2).

Candidate SNPs *LEPR* K109R (rs1137100) and Q223R (rs1137101) were positively associated with luminal A breast cancer but not basal-like breast cancer, though associations were not statistically different between the two subtypes (Table 2). In addition, K109R and *LEPR* K656N (rs8179183) were associated with breast cancer overall (Table 2). *ADIPOQ*

SNPs +45 T/G (rs2241766) and +276 G/T (rs1501299) were not associated with breast cancer overall or by subtype (online resource 5).

Of the SNPs in Table 2, *ADIPOQ* rs16861194 and *LEPR* rs12042877 were associated with WHR, though neither was in the direction expected based on the breast cancer risk allele (online resource 6). No tag or candidate SNP associations with breast cancer were statistically significant after accounting for multiple comparisons.

Haplotype associations

Haplotypes in *LEP* (haplotypes 1, 2a, 2b, 3) and *LEPR* (haplotype 6b) were strongly associated with breast cancer overall or luminal A breast cancer, with ORs of 2 or greater (Table 3). *LEP* haplotype 3 and *LEPR* haplotype 4a were associated with basal-like breast cancer with moderate precision (Table 3); haplotype 4a includes rs17412175, rs9436746, and rs9436748, which were each individually associated with basal-like breast cancer.

Overall, haplotype associations were stronger than individual SNP associations: the strongest haplotype association was between haplotype 3 and luminal A breast cancer (OR = 3.21, Table 3), whereas the strongest SNP association was an OR of 0.48 (rs9436748 and basal-like breast cancer, Table 2).

Interaction with WHR

Tests of multiplicative interaction between SNPs and WHR were not significant after adjustment for multiple comparisons. In addition, there was no evidence of haplotype interaction with WHR.

Discussion

We estimated associations between tag and candidate SNPs in *ADIPOQ*, *LEP*, and *LEPR* and basal-like breast cancer, luminal A breast cancer, and breast cancer overall in a population-based study of white and African American women. With respect to tag SNPs, our main finding was that three *LEPR* SNPs (rs17412175, rs9436746, rs9436748) in close proximity were inversely associated with basal-like breast cancer; associations between these SNPs and luminal A breast cancer were weak. The SNPs are in moderate to weak LD in cases and controls, and may be markers of a single genetic factor. Other SNP associations showed few discernible patterns: SNPs in a particular gene were not associated only with the basal-like subtype or only with the luminal A subtype. It is likely that many of these associations represent false-positive results. As such, replication in an independent dataset is necessary before further conclusions can be made.

Candidate SNPs in *LEPR*, but not *ADIPOQ*, were associated with luminal A breast cancer and/or breast cancer overall (Table 2). *LEPR* Q223R (rs1137101) was positively associated with luminal A breast cancer in the CBCS; however, the association was not as strong as that reported by Snoussi et al. [27] (online resource 5). Q223R associations with breast cancer have been inconsistent, and reported as both inverse [21, 28] and null [25, 29]; another study suggested that there was a positive association with breast cancer limited to premenopausal women [30]. Quinton et al. [59] reported that the 223R variant was associated with increased serum leptin levels, which is consistent with the hypothesis that altered serum adipocytokine levels are part of the mechanism linking genetic variation to breast cancer risk. Given that Q223R was associated only with luminal A breast cancer and not breast cancer overall in our study, it is possible that some of the variation in results seen in other studies is due to tumor heterogeneity and, more specifically, the relative proportion of luminal A breast cancers in each population.

LEPR K109R (rs1137100) was positively associated with breast cancer overall and the luminal A subtype in the CBCS, in contrast to two previously reported null associations [28, 29]. Reports vary on the biological effect of *LEPR* K109R on serum leptin levels in women. Two studies reported that healthy women with codon 109 RR variants had higher serum leptin levels compared to women with 109 QR variants [28, 60]. In contrast, another study reported that leptin levels were lower among postmenopausal women with at least one copy of the 109R variant, and that there was no association among premenopausal women [61], and two other studies reported no association [62, 63]. A limitation of our study was that adipocytokine levels were not measured. Thus, although we observed associations between Q223R, K109R, and K656N and breast cancer, we were unable to determine whether these SNPs were also associated with changes in adipocytokine levels in our population. Analysis of such intermediate markers can provide support for a hypothesized mechanism, and may provide biological evidence to support genotype associations in future studies.

The molecular mechanisms by which K109R, K656N, or Q223R might affect the leptin receptor have not been identified. A series of experiments showed that the Q223R polymorphism did not affect transcription in mouse models or leptin receptor activity in vitro [64], which conflicts with previously reported associations between Q223R and circulating leptin levels [59, 65, 66]. Further research is necessary to confirm whether these candidate SNPs have functional effects or are markers for other causal genetic variants.

Previously investigated candidate SNPs were not associated with basal-like breast cancer in the CBCS. This may be due to greater imprecision for basal-like estimates because of the smaller number of cases. Another potential explanation is that the candidate SNPs examined in previous studies were examined in all breast cancer cases grouped together, the majority of which are likely to be luminal A breast cancers. It is possible that different functional variants are associated with basal-like tumors. Low penetrance variants specific to the basal-like subtype are unlikely to be detected if basal-like cases constitute a minority of the overall case group.

We used both agnostic (sliding window) and informed (based on SNP ORs) approaches to identify haplotype effects, and found the two approaches to be complementary. Haplotype associations were generally in the same direction as genotype associations for the involved SNPs, and in many cases, the magnitude of the haplotype OR exceeded that of any single SNP within the haplotype. Notably, in the case of *LEP* haplotype 1 the individual genotypes showed no association with breast cancer overall or by subtype (online resource 7), but the haplotype analysis revealed a strong association when the alleles were evaluated jointly. Conversely, many of the breast cancer-associated haplotypes identified by evaluating SNPs with strong genotype associations were not identified by the sliding window analysis. This is likely because the sliding window analysis estimated a global test statistic for all possible haplotypes within the SNP window. Such an analysis may have low power if the majority of haplotypes are not associated with the outcome.

There was potential for selection bias to influence study results, since genotyping data were more likely to be missing for cases and African Americans. Adjustment for self-identified race and age should control for this possible selection bias, assuming that there was no additional bias within case, race, and age strata [67]. Selection bias may have also occurred when determining the breast cancer subtype, as sufficient immunohistochemistry was not available for 47% of enrolled cases. However, genotype distributions between cases with and without subtype information were similar, as was the molecular subtype distribution comparing cases with and without genotyping data (data not shown). This suggests that the genotype distribution in the subset of cases with tumor subtype information was likely representative of the genotype distribution in all cases.

Strengths of this study include analysis of a comprehensive set of tag SNPs enriched with candidate SNPs to increase the chances of detecting a genomic region associated with breast cancer. Tag SNPs were chosen from European and African populations to account for different LD patterns among participants of African or European ancestry, and all associations were adjusted for individual proportions of African ancestry, minimizing residual confounding due to population stratification within self-identified race groups. Although estimates for the basal-like subtype were less precise compared to the luminal A estimates due to smaller sample size, the results presented were chosen based on both OR magnitude and precision to avoid reporting bias that would have resulted from using statistical significance as the sole criteria for evaluating results by subtype.

In summary, the consistency of the strength and direction of association with basal-like breast cancer points toward the 3-SNP region in *LEPR* intron 2 as a promising candidate for an association with basal-like breast cancer risk. Furthermore, *LEPR* candidate SNPs K109R and Q223R were associated with luminal A breast cancer and breast cancer overall. These results suggest that genetic variation in *LEPR* may be associated with breast cancer risk, but that specific regions may have subtype-specific effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of CBCS participants with genotyping data

	Controls	All cases	Luminal A	Basal-like
<i>N</i>	1776	1972	679	200
Median age in years (range)	51 (21–74)	50 (23–74)	52 (23–74)	46 (25–74)
Self-identified race				
African American	658	742	233	108
Non-African American	1117	1229	446	92
Unknown	1	1		
Menopausal status				
Premenopausal	761	879	277	111
Postmenopausal	1015	1093	402	89
Waist-hip ratio				
<0.77	596	610	194	43
0.77–0.83	478	549	204	60
0.84	681	784	274	92
Missing	21	29	7	5
BMI (kg/m ²)				
<25	545	712	243	57
25 to <30	543	551	177	56
30 to <35	338	349	132	39
35	313	319	112	43
Missing	37	41	15	5
Stage				
CIS ^a		838	151	18
1		615	224	43
2		635	237	108
3		146	41	19
4		43	8	6
Missing ^b		1471	18	6

^a CIS carcinoma in situ^b Invasive breast cancer cases

Table 2

Association between selected SNPs^a in *ADIPOQ*, *LEP*, and *LEPR* and breast cancer in the CBCS

	All cases		Luminal A		Basal-like		Luminal A versus basal-like ^d	
	OR (95% CI) ^b	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c
<i>ADIPOQ</i>								
rs16861194								
GG	0.70 (0.47, 1.04)	0.079	0.56 (0.30, 1.03)	0.063	0.74 (0.34, 1.64)	0.457	0.538	0.538
AG	1.00 (0.85, 1.19)	0.971	0.98 (0.77, 1.23)	0.833	0.78 (0.53, 1.14)	0.195	0.275	0.275
AA	Referent		Referent		Referent			
G versus A	0.93 (0.81, 1.07)	0.318	0.88 (0.73, 1.07)	0.209	0.82 (0.60, 1.10)	0.186	0.629	0.629
rs16861205								
AA + AG	0.98 (0.83, 1.16)	0.818	1.02 (0.81, 1.29)	0.856	0.66 (0.45, 0.97)	0.035	0.037	0.037
GG	Referent		Referent		Referent			
A versus G	0.97 (0.84, 1.13)	0.726	0.98 (0.80, 1.20)	0.843	0.68 (0.48, 0.96)	0.029	0.052	0.052
<i>LEP</i>								
rs6976701								
AA + AG	1.16 (0.91, 1.50)	0.237	1.42 (1.01, 1.99)	0.042	0.99 (0.60, 1.64)	0.975	0.192	0.192
GG	Referent		Referent		Referent			
A versus G	1.12 (0.88, 1.41)	0.365	1.37 (1.00, 1.87)	0.051	0.91 (0.57, 1.47)	0.706	0.417	0.417
rs3793162								
AA + AG	0.75 (0.59, 0.95)	0.017	0.82 (0.58, 1.14)	0.239	0.79 (0.50, 1.26)	0.317	0.895	0.895
GG	Referent		Referent		Referent			
A versus G	0.78 (0.64, 0.96)	0.021	0.84 (0.63, 1.14)	0.263	0.82 (0.55, 1.23)	0.339	0.902	0.902
rs17151922								
TT	1.17 (0.75, 1.83)	0.492	0.89 (0.44, 1.77)	0.732	0.98 (0.41, 2.34)	0.970	0.837	0.837
GT	1.30 (1.05, 1.62)	0.017	1.41 (1.04, 1.92)	0.025	1.01 (0.65, 1.55)	0.981	0.157	0.157
GG	Referent		Referent		Referent			
T versus G	1.19 (1.00, 1.42)	0.044	1.18 (0.92, 1.50)	0.190	1.00 (0.71, 1.41)	0.991	0.403	0.403
rs10954174								
AA + AG	1.13 (0.84, 1.50)	0.421	1.01 (0.66, 1.54)	0.958	1.66 (0.99, 2.78)	0.052	0.098	0.098
GG	Referent		Referent		Referent			

	All cases		Luminal A		Basal-like		Luminal A versus basal-like ^d
	OR (95% CI) ^b	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c	
A versus G	1.07 (0.82, 1.39)	0.629	0.93 (0.63, 1.38)	0.722	1.49 (0.94, 2.38)	0.090	0.087
<i>LEPR</i>							
rs9436299							
CC	1.30 (1.00, 1.69)	0.050	1.46 (1.04, 2.05)	0.027	0.91 (0.46, 1.82)	0.788	0.191
AC	0.97 (0.84, 1.12)	0.682	0.95 (0.78, 1.16)	0.611	1.25 (0.91, 1.71)	0.167	0.112
AA	Referent	Referent	Referent	Referent	Referent	Referent	Referent
C versus A	1.06 (0.95, 1.18)	0.264	1.10 (0.95, 1.27)	0.212	1.10 (0.86, 1.40)	0.445	0.991
rs17412175							
AA	0.87 (0.70, 1.06)	0.168	0.85 (0.64, 1.12)	0.258	0.56 (0.31, 1.01)	0.053	0.177
AT + TT	Referent	Referent	Referent	Referent	Referent	Referent	Referent
A versus T	0.94 (0.84, 1.06)	0.320	0.93 (0.80, 1.08)	0.358	0.87 (0.66, 1.14)	0.313	0.638
rs9436746							
CC	0.88 (0.75, 1.02)	0.095	0.87 (0.70, 1.07)	0.178	0.57 (0.39, 0.85)	0.005	0.047
AA + AC	Referent	Referent	Referent	Referent	Referent	Referent	Referent
C versus A	0.93 (0.84, 1.02)	0.126	0.89 (0.78, 1.02)	0.082	0.79 (0.64, 0.99)	0.039	0.183
rs9436748							
TT	0.81 (0.66, 0.99)	0.043	0.82 (0.62, 1.08)	0.153	0.48 (0.27, 0.87)	0.015	0.131
GG + GT	Referent	Referent	Referent	Referent	Referent	Referent	Referent
T versus G	0.93 (0.84, 1.04)	0.202	0.94 (0.81, 1.08)	0.367	0.78 (0.61, 1.00)	0.051	0.177
rs6657868							
AA	1.07 (0.88, 1.31)	0.480	1.18 (0.91, 1.55)	0.218	1.16 (0.74, 1.84)	0.518	0.945
AG	0.99 (0.85, 1.15)	0.854	0.99 (0.80, 1.21)	0.900	1.45 (1.02, 2.06)	0.038	0.043
GG	Referent	Referent	Referent	Referent	Referent	Referent	Referent
A versus G	1.03 (0.93, 1.13)	0.574	1.07 (0.94, 1.22)	0.305	1.11 (0.90, 1.37)	0.336	0.993
rs17127655							
TT + CT	0.78 (0.62, 0.98)	0.030	0.76 (0.54, 1.06)	0.105	0.65 (0.41, 1.04)	0.073	0.566
CC	Referent	Referent	Referent	Referent	Referent	Referent	Referent
T versus C	0.83 (0.68, 1.00)	0.048	0.83 (0.63, 1.09)	0.185	0.67 (0.44, 1.00)	0.052	0.955
rs6588147							
GG	1.21 (0.93, 1.58)	0.154	1.36 (0.96, 1.91)	0.081	0.74 (0.35, 1.59)	0.441	0.130

	All cases		Luminal A		Basal-like		Luminal A versus basal-like ^d
	OR (95% CI) ^b	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c	
AG	1.02 (0.88, 1.18)	0.838	1.04 (0.85, 1.27)	0.722	1.39 (1.01, 1.91)	0.042	0.091
AA	Referent		Referent		Referent		
G versus A	1.06 (0.95, 1.19)	0.272	1.11 (0.96, 1.29)	0.156	1.12 (0.87, 1.43)	0.379	0.977
rs6704167							
TT	0.86 (0.69, 1.08)	0.193	0.87 (0.65, 1.17)	0.366	0.67 (0.37, 1.19)	0.174	0.392
AT	1.02 (0.88, 1.19)	0.787	0.97 (0.79, 1.19)	0.799	1.18 (0.85, 1.63)	0.329	0.288
AA	Referent		Referent		Referent		
T versus A	0.95 (0.86, 1.06)	0.356	0.94 (0.82, 1.09)	0.418	0.93 (0.74, 1.18)	0.572	0.276
rs7529650							
AA	0.97 (0.79, 1.18)	0.740	0.90 (0.69, 1.17)	0.421	0.89 (0.55, 1.43)	0.629	0.978
AG	0.89 (0.75, 1.06)	0.184	0.78 (0.62, 0.98)	0.036	1.21 (0.84, 1.76)	0.307	0.029
GG	Referent		Referent		Referent		
A versus G	0.99 (0.89, 1.09)	0.792	0.95 (0.83, 1.09)	0.495	0.96 (0.77, 1.20)	0.727	0.955
rs2025804							
CC	1.31 (1.02, 1.69)	0.037	1.51 (1.08, 2.09)	0.015	1.11 (0.59, 2.06)	0.751	0.346
CT	0.96 (0.83, 1.11)	0.575	1.02 (0.84, 1.24)	0.837	1.20 (0.88, 1.65)	0.253	0.343
TT	Referent		Referent		Referent		
C versus T	1.06 (0.96, 1.18)	0.252	1.14 (0.99, 1.32)	0.070	1.12 (0.88, 1.42)	0.346	0.886
rs11808888							
AA	0.99 (0.77, 1.27)	0.916	0.97 (0.68, 1.39)	0.878	0.60 (0.34, 1.06)	0.079	0.124
AG	1.05 (0.89, 1.23)	0.584	0.95 (0.76, 1.18)	0.642	0.98 (0.69, 1.39)	0.909	0.869
GG	Referent		Referent		Referent		
A versus G	1.01 (0.90, 1.13)	0.875	0.97 (0.82, 1.14)	0.708	0.83 (0.65, 1.07)	0.155	0.274
rs11208654							
CC	1.29 (0.99, 1.66)	0.055	1.43 (1.03, 2.00)	0.035	1.03 (0.54, 1.96)	0.920	0.334
CT	1.00 (0.86, 1.15)	0.949	1.08 (0.89, 1.31)	0.448	1.25 (0.92, 1.71)	0.157	0.381
TT	Referent		Referent		Referent		
C versus T	1.07 (0.96, 1.19)	0.194	1.15 (0.99, 1.33)	0.059	1.13 (0.89, 1.43)	0.328	0.703
rs10889556							
GG	1.19 (0.94, 1.51)	0.140	1.40 (1.02, 1.92)	0.037	1.24 (0.74, 2.07)	0.416	0.656

	All cases		Luminal A		Basal-like		Luminal A versus basal-like ^d
	OR (95% CI) ^b	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c	
AG	0.95 (0.82, 1.10)	0.501	1.03 (0.85, 1.26)	0.738	1.21 (0.87, 1.67)	0.253	0.379
AA	Referent		Referent		Referent		
G versus A	1.04 (0.94, 1.15)	0.450	1.13 (0.98, 1.30)	0.093	1.14 (0.91, 1.43)	0.270	0.975
rs7526141							
TT	0.83 (0.66, 1.05)	0.129	0.95 (0.69, 1.29)	0.738	0.66 (0.36, 1.21)	0.177	0.258
CT	0.96 (0.81, 1.14)	0.638	1.04 (0.83, 1.32)	0.712	0.98 (0.67, 1.44)	0.909	0.750
CC	Referent		Referent		Referent		
T versus C	0.92 (0.82, 1.03)	0.156	0.98 (0.85, 1.15)	0.841	0.85 (0.65, 1.12)	0.252	0.324
rs1751492							
CC	1.30 (1.01, 1.67)	0.043	1.33 (0.94, 1.87)	0.106	1.19 (0.68, 2.09)	0.533	0.751
CT	1.06 (0.92, 1.22)	0.444	1.13 (0.93, 1.37)	0.217	1.09 (0.80, 1.49)	0.588	0.861
TT	Referent		Referent		Referent		
C versus T	1.10 (0.99, 1.23)	0.066	1.14 (0.99, 1.32)	0.070	1.09 (0.86, 1.38)	0.463	0.750
rs1171267							
TT	1.25 (1.01, 1.54)	0.040	1.29 (0.97, 1.71)	0.080	1.21 (0.77, 1.92)	0.408	0.912
GG + GT	Referent		Referent		Referent		
T versus G	1.08 (0.98, 1.20)	0.121	1.11 (0.97, 1.27)	0.140	1.11 (0.89, 1.39)	0.340	0.437
rs1782763							
CC	1.36 (1.09, 1.71)	0.007	1.38 (1.03, 1.87)	0.033	1.29 (0.79, 2.12)	0.309	0.796
TT + CT	Referent		Referent		Referent		
C versus T	1.07 (0.96, 1.18)	0.215	1.11 (0.97, 1.28)	0.135	1.07 (0.86, 1.35)	0.543	0.979
rs1409802							
AA	1.50 (1.10, 2.06)	0.011	1.64 (1.09, 2.48)	0.018	1.08 (0.50, 2.33)	0.850	0.296
AG	1.02 (0.88, 1.17)	0.823	1.13 (0.93, 1.37)	0.231	1.05 (0.76, 1.44)	0.769	0.676
GG	Referent		Referent		Referent		
A versus G	1.11 (0.99, 1.24)	0.084	1.19 (1.02, 1.39)	0.024	1.05 (0.81, 1.35)	0.731	0.3438
rs1137100 (K109R)							
GG	1.45 (1.06, 1.97)	0.020	1.64 (1.10, 2.45)	0.016	1.02 (0.48, 2.21)	0.951	0.242
AG	1.00 (0.87, 1.16)	0.963	1.10 (0.91, 1.34)	0.328	1.04 (0.75, 1.42)	0.832	0.714
AA	Referent		Referent		Referent		

	All cases			Luminal A			Basal-like			Luminal A versus basal-like ^d
	OR (95% CI) ^b	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c		
G versus A rs1343982	1.09 (0.97, 1.22)	0.137	1.18 (1.01, 1.38)	0.032	1.03 (0.79, 1.33)	0.832			0.316	
AA	1.43 (1.11, 1.83)	0.005	1.47 (1.05, 2.04)	0.023	1.37 (0.81, 2.30)	0.238			0.799	
GG + AG	Referent		Referent		Referent					
A versus G rs10889563	1.13 (1.01, 1.25)	0.028	1.17 (1.02, 1.35)	0.028	1.08 (0.86, 1.36)	0.508			0.515	
AA	0.91 (0.75, 1.10)	0.344	0.75 (0.58, 0.97)	0.030	0.81 (0.52, 1.26)	0.352			0.735	
AG	0.80 (0.68, 0.95)	0.009	0.71 (0.57, 0.89)	0.003	0.84 (0.59, 1.21)	0.347			0.398	
GG	Referent		Referent		Referent					
A versus G rs12042877	0.95 (0.87, 1.05)	0.339	0.86 (0.76, 0.98)	0.023	1.01 (0.93, 1.09)	0.832			0.032	
TT	1.43 (1.11, 1.84)	0.006	1.49 (1.06, 2.09)	0.020	1.55 (0.93, 2.58)	0.093			0.889	
CC + CT	Referent		Referent		Referent					
T versus C rs10749754	1.13 (1.02, 1.26)	0.024	1.19 (1.03, 1.37)	0.019	1.17 (0.93, 1.47)	0.190			0.883	
AA	1.11 (0.91, 1.34)	0.299	1.35 (1.04, 1.74)	0.024	1.21 (0.78, 1.87)	0.402			0.644	
AG	0.92 (0.79, 1.08)	0.318	0.97 (0.78, 1.21)	0.772	1.15 (0.79, 1.67)	0.458			0.390	
GG	Referent		Referent		Referent					
A versus G rs1137101 (Q223R)	1.05 (0.95, 1.15)	0.362	1.16 (1.01, 1.32)	0.030	1.09 (0.88, 1.36)	0.412			0.6365	
GG	0.91 (0.75, 1.10)	0.311	1.35 (1.04, 1.75)	0.025	1.10 (0.72, 1.69)	0.665			0.383	
AG	0.89 (0.75, 1.06)	0.187	1.07 (0.86, 1.35)	0.538	1.01 (0.70, 1.47)	0.944			0.776	
AA	Referent		Referent		Referent					
G versus A rs4655537	1.05 (0.95, 1.16)	0.325	1.16 (1.02, 1.32)	0.026	1.05 (0.85, 1.30)	0.669			0.936	
AA	0.99 (0.81, 1.23)	0.961	0.72 (0.54, 0.98)	0.034	0.92 (0.57, 1.47)	0.715			0.362	
AG	0.96 (0.83, 1.11)	0.588	0.87 (0.71, 1.06)	0.168	0.92 (0.67, 1.28)	0.634			0.732	
GG	Referent		Referent		Referent					
A versus G rs3828034	0.99 (0.90, 1.09)	0.811	0.86 (0.75, 0.98)	0.027	0.95 (0.76, 1.18)	0.637			0.401	

	All cases			Luminal A			Basal-like			Luminal A versus basal-like ^d
	OR (95% CI) ^b	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c		
CC	0.96 (0.60, 1.54)	0.874	0.92 (0.48, 1.76)	0.806	1.52 (0.57, 4.08)	0.404	1.52 (0.57, 4.08)	0.404	0.316	
CT	0.83 (0.69, 0.98)	0.032	0.96 (0.76, 1.21)	0.750	0.70 (0.45, 1.09)	0.113	0.70 (0.45, 1.09)	0.113	0.182	
TT	Referent		Referent		Referent		Referent			
C versus T	0.88 (0.76, 1.02)	0.079	0.96 (0.79, 1.17)	0.704	0.85 (0.59, 1.23)	0.401	0.85 (0.59, 1.23)	0.401	0.578	
rs12405556										
TT	1.35 (1.00, 1.83)	0.053	1.58 (1.06, 2.33)	0.023	1.02 (0.49, 2.12)	0.959	1.02 (0.49, 2.12)	0.959	0.257	
GT	1.00 (0.86, 1.15)	0.958	1.06 (0.87, 1.30)	0.542	0.97 (0.70, 1.35)	0.876	0.97 (0.70, 1.35)	0.876	0.621	
GG	Referent		Referent		Referent		Referent			
T versus G	1.07 (0.96, 1.20)	0.228	1.16 (0.99, 1.35)	0.065	0.99 (0.76, 1.29)	0.943	0.99 (0.76, 1.29)	0.943	0.274	
rs3762274										
GG	1.09 (0.89, 1.33)	0.395	1.40 (1.07, 1.82)	0.013	1.08 (0.71, 1.67)	0.710	1.08 (0.71, 1.67)	0.710	0.275	
AG	0.90 (0.77, 1.05)	0.191	0.96 (0.77, 1.20)	0.733	0.87 (0.61, 1.25)	0.455	0.87 (0.61, 1.25)	0.455	0.613	
AA	Referent		Referent		Referent		Referent			
G versus A	1.03 (0.93, 1.14)	0.564	1.17 (1.02, 1.33)	0.026	1.03 (0.83, 1.28)	0.788	1.03 (0.83, 1.28)	0.788	0.269	
rs11801408										
TT	0.84 (0.66, 1.08)	0.168	0.77 (0.54, 1.09)	0.142	0.65 (0.37, 1.14)	0.135	0.65 (0.37, 1.14)	0.135	0.611	
CC + CT	Referent		Referent		Referent		Referent			
T versus C	0.90 (0.80, 1.00)	0.053	0.93 (0.80, 1.09)	0.382	0.88 (0.69, 1.12)	0.287	0.88 (0.69, 1.12)	0.287	0.632	
rs8179183 (K656N)										
CC	0.70 (0.48, 1.03)	0.068	0.70 (0.41, 1.20)	0.195	0.78 (0.34, 1.77)	0.551	0.78 (0.34, 1.77)	0.551	0.814	
CG	0.90 (0.77, 1.04)	0.145	1.05 (0.86, 1.28)	0.648	0.84 (0.60, 1.18)	0.323	0.84 (0.60, 1.18)	0.323	0.236	
GG	Referent		Referent		Referent		Referent			
C versus G	0.87 (0.77, 0.99)	0.032	0.97 (0.82, 1.14)	0.697	0.86 (0.65, 1.13)	0.282	0.86 (0.65, 1.13)	0.282	0.429	
rs4655555 ^e										
AA	1.13 (0.76, 1.69)	0.536	1.43 (0.86, 2.38)	0.165	0.75 (0.26, 2.14)	0.593	0.75 (0.26, 2.14)	0.593	0.242	
AT	0.99 (0.85, 1.16)	0.937	1.07 (0.87, 1.32)	0.535	0.94 (0.67, 1.33)	0.740	0.94 (0.67, 1.33)	0.740	0.504	
TT	Referent		Referent		Referent		Referent			
A versus T	1.02 (0.90, 1.16)	0.774	1.12 (0.95, 1.32)	0.185	0.92 (0.67, 1.24)	0.586	0.92 (0.67, 1.24)	0.586	0.217	
rs17127826										
GG	0.70 (0.43, 1.14)	0.150	0.50 (0.23, 1.10)	0.086	0.78 (0.32, 1.93)	0.597	0.78 (0.32, 1.93)	0.597	0.417	

	All cases		Luminal A		Basal-like		Luminal A versus basal-like ^d
	OR (95% CI) ^b	P-value ^c	OR (95% CI)	P-value ^c	OR (95% CI)	P-value ^c	
AA + AG	Referent		Referent		Referent		
G versus A	1.01 (0.86, 1.20)	0.888	0.94 (0.74, 1.19)	0.598	1.01 (0.73, 1.40)	0.941	0.679
rs6413506 ^e							
AG + GG	1.42 (0.96, 2.08)	0.076	1.56 (0.94, 2.58)	0.087	1.23 (0.61, 2.49)	0.557	0.544
AA	Referent		Referent		Referent		
G versus A	1.38 (0.95, 2.01)	0.092	1.55 (0.95, 2.53)	0.079	1.20 (0.60, 2.38)	0.612	0.483

^a SNPs displayed in table have a P-value < 0.05, OR 0.67 or OR 1.5 for breast cancer overall, luminal A subtype, and/or basal-like subtype

^b Odds ratio and 95% confidence interval, adjusted for age, self-identified race, African ancestry, and offset term

^c P-value is unadjusted for multiple comparisons

^d H₀: β (luminal A) = β (basal-like)

^e Additionally adjusted for family history of breast cancer

Table 3

Association between selected haplotypes and breast cancer in the CBCS

Haplotype	Copies	All cases			Luminal A			Basal-like		
		OR (95% CI) ^a	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	
<i>LEP</i>										
1: rs12706832, rs10244329, rs11763517, rs7795794										
A-T-T-G										
	2	2.14 (1.57, 2.93)	<0.001	2.27 (1.32, 3.89)	0.003	1.14 (0.43, 2.99)	0.791	1.14 (0.43, 2.99)	0.791	0.791
	1	0.82 (0.71, 0.95)	0.009	1.31 (1.00, 1.73)	0.051	0.89 (0.64, 1.26)	0.518	0.89 (0.64, 1.26)	0.518	0.518
	0	Referent		Referent		Referent		Referent		Referent
2: rs11760956, rs10954173, rs3793162, rs3828942, rs17151922										
2a: G-G-A-G-G										
	2	2.69 (1.62, 4.46)	<0.001	1.78 (0.75, 4.25)	0.194	2.51 (0.78, 8.06)	0.123	2.51 (0.78, 8.06)	0.123	0.123
	1	0.79 (0.64, 0.96)	0.020	0.79 (0.57, 1.09)	0.150	0.65 (0.40, 1.07)	0.091	0.65 (0.40, 1.07)	0.091	0.091
	0	Referent		Referent		Referent		Referent		Referent
2b: G-G-G-G-T										
	2	2.32 (1.62, 3.33)	<0.001	2.09 (1.09, 4.02)	0.027	1.11 (0.34, 3.58)	0.867	1.11 (0.34, 3.58)	0.867	0.867
	1	0.90 (0.77, 1.05)	0.167	1.27 (0.95, 1.68)	0.101	0.94 (0.66, 1.33)	0.722	0.94 (0.66, 1.33)	0.722	0.722
	0	Referent		Referent		Referent		Referent		Referent
3: rs17151922, rs10954174, rs11761556										
T-G-C										
	2	2.00 (1.26, 3.17)	0.003	3.21 (1.49, 6.90)	0.003	<i>b</i>		<i>b</i>		
	1	0.92 (0.77, 1.11)	0.388	1.22 (0.92, 1.63)	0.169	0.63 (0.39, 1.00)	0.050	0.63 (0.39, 1.00)	0.050	0.050
	0	Referent		Referent		Referent		Referent		Referent
<i>LEPR</i>										
4: rs17412175, rs9436746, rs9436748										
4a: A-C-T										
	2	0.97 (0.78, 1.22)	0.821	0.93 (0.68, 1.27)	0.646	0.61 (0.32, 1.19)	0.151	0.61 (0.32, 1.19)	0.151	0.151
	1	0.79 (0.69, 0.91)	0.001	0.79 (0.65, 0.97)	0.026	0.83 (0.58, 1.20)	0.318	0.83 (0.58, 1.20)	0.318	0.318
	0	Referent		Referent		Referent		Referent		Referent
4b: T-A-G										

Haplotype	Copies	All cases			Luminal A			Basal-like		
		OR (95% CI) ^a	P-value	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
5: rs10749754, rs12042877, rs12564626										
5a: A-T-A										
	2	1.15 (0.95, 1.39)	0.139	1.24 (0.96, 1.61)	0.095	1.63 (1.03, 2.58)	0.035			
	1	0.99 (0.87, 1.12)	0.825	0.95 (0.78, 1.15)	0.611	1.52 (1.03, 2.23)	0.034			
	0	Referent	Referent	Referent	Referent	Referent	Referent			
5b: G-C-G										
	2	1.37 (1.06, 1.76)	0.016	1.52 (1.07, 2.16)	0.020	1.15 (0.57, 2.33)	0.697			
	1	1.03 (0.90, 1.17)	0.694	1.11 (0.92, 1.34)	0.276	1.04 (0.75, 1.43)	0.825			
	0	Referent	Referent	Referent	Referent	Referent	Referent			
6: rs12405556, rs3762274										
6a: G-A										
	2	0.88 (0.73, 1.06)	0.165	0.71 (0.55, 0.92)	0.009	0.87 (0.56, 1.35)	0.536			
	1	0.84 (0.74, 0.96)	0.013	0.74 (0.61, 0.91)	0.005	0.92 (0.65, 1.31)	0.644			
	0	Referent	Referent	Referent	Referent	Referent	Referent			
6b: T-A										
	2	2.59 (1.31, 5.11)	0.006	2.39 (0.83, 6.85)	0.105	_b				
	1	1.24 (0.96, 1.59)	0.094	1.19 (0.85, 1.66)	0.309	_b				
	0	Referent	Referent	Referent	Referent	Referent	Referent			
6c: T-G										
	2	1.32 (0.96, 1.80)	0.083	1.60 (1.05, 2.46)	0.030	0.96 (0.38, 2.41)	0.934			
	1	0.96 (0.83, 1.11)	0.553	1.05 (0.86, 1.28)	0.648	0.86 (0.60, 1.23)	0.414			
	0	Referent	Referent	Referent	Referent	Referent	Referent			
7: rs2025804, rs7518849, rs10158579										
7a: T-C-T										
	2	1.43 (0.83, 2.20)	0.101	1.57 (0.83, 3.00)	0.168	1.99 (0.78, 5.04)	0.149			
	1	0.90 (0.76, 1.06)	0.216	0.74 (0.58, 0.95)	0.017	1.25 (0.88, 1.78)	0.215			
	0	Referent	Referent	Referent	Referent	Referent	Referent			

Haplotype	Copies	All cases		Luminal A		Basal-like	
		OR (95% CI) ^a	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
7b: T-T-T							
	2	0.91 (0.75, 1.11)	0.363	1.00 (0.77, 1.29)	0.975	0.65 (0.40, 1.07)	0.093
	1	0.91 (0.81, 1.03)	0.133	0.82 (0.68, 0.99)	0.035	0.79 (0.58, 1.08)	0.144
	0	Referent		Referent		Referent	

^aOdds ratio, 95% confidence interval, adjusted for age, self-identified race, African ancestry, and offset term

^bParameters not estimated due to small sample size