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Genetic Variation in Cell Cycle Regulatory Gene *AURKA* and Association With Intrinsic Breast Cancer Subtype

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Abstract

AURKA is a putative low-penetrance tumor susceptibility gene due to its prominent role in cell cycle regulation and centrosomal function. Germline variation in *AURKA* was evaluated for association with breast cancer and intrinsic breast cancer subtypes in the Carolina Breast Cancer Study (CBCS), a population-based case-control study of African Americans (AA) and Caucasians (Cau). Tag and candidate single nucleotide polymorphisms (SNPs) on *AURKA* were genotyped in 1946 cases and 1747 controls. In race-stratified analyses adjusted for age and African ancestry, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate SNP associations with breast cancer. In a race-combined analysis with similar adjustment, these associations were also examined by intrinsic breast cancer subtype. Using dominant models, most *AURKA* SNPs demonstrated no association with breast cancer in the race-stratified analyses. Among AA, rs6092309 showed an inverse association with breast cancer (OR = 0.69, 95% CI = 0.53–0.90). In the race-combined analyses, rs6099128 had reduced ORs for luminal A (OR = 0.76, 95% CI = 0.60–0.95) and basal-like breast cancer (OR = 0.54, 95% CI = 0.37–0.80). Rs6092309 showed a similar pattern of association with each subtype. Three SNPs (rs6014711, rs911162, rs1047972) had positive associations with basal-like breast cancer, and ORs reduced or close to 1.00 for other subtypes. Our results suggest inverse associations between some *AURKA* SNPs and overall breast cancer in AA. We found differential associations by specific subtypes and by race. Replication of these findings in larger AA populations would allow more powerful race-stratified subtype analyses.

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Ethical Standards: All experiments comply with the current laws of the United States of America, where they were performed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Keywords

AURKA; breast; cancer; subtypes; SNP

INTRODUCTION

Previous research has established at least five distinct breast cancer subtypes that vary in their gene expression profiles and in their responsiveness to endocrine therapies [1–4]. Furthermore, risk factors for breast cancer have been shown to differ by intrinsic subtype [5], suggesting distinct etiologic and molecular pathways of carcinogenesis. Common low-penetrant susceptibility single nucleotide polymorphisms (SNPs) may play an important role in the etiology of breast cancer, individually conferring small increases in risk [6–10]. In aggregate, these increases in risk may become substantial [6–10]. *AURKA*, encoding a serine/threonine kinase (Aurora-A), is a putative oncogene that plays a role in cell cycle regulation [11]. Overexpression of *AURKA* has been associated with centrosomal duplication abnormalities, chromosomal instability, and aneuploidy in mammalian cells, common characteristics of cancer cells [12,13]. *AURKA* overexpression has been demonstrated in several types of cancer and has been correlated with poor prognosis [14–16]. Previous studies of genetic variation in *AURKA* and risk of breast cancer have been largely limited to investigations of a single polymorphism (rs2273535) in Asian and Caucasian (Cau) populations, and none have focused on African Americans (AA). Some effect estimates among Asian and Cau populations were increased [17–21], some decreased [22], and some suggested no association [23,24]. These inconsistent results could be due to tumor heterogeneity and/or differences in population substructure. Importantly, these associations have not been previously investigated by breast cancer subtype, and this approach could elucidate important subtype-specific associations, as has been shown in previous studies of other breast cancer risk factors [5,25–27].

We evaluated SNPs on *AURKA* in association with breast cancer rate in the Carolina Breast Cancer Study (CBCS), a large population-based case-control study of breast cancer in AA and Cau women in North Carolina. The CBCS allowed us to examine genetic risk factors given the increased incidence of breast cancer in younger AA women [28], as well as increased mortality and a preponderance of the basal-like subtype among AA women [25,29]. Capitalizing on the CBCS study design, which oversampled African American women, we examined main effects of *AURKA* SNPs on breast cancer rate stratified by race. We also utilized the carefully characterized intrinsic subtype information in this study to evaluate *AURKA* genetic variation in association with specific intrinsic subtypes. This subtype-specific analysis is important because *AURKA* overexpression has been associated with aneuploidy and basal-like tumors have been shown to demonstrate a high degree of aneuploidy [30,31].

METHODS

Study Population

The CBCS is a population-based, case-control study of genetic and environmental risk factors for breast cancer among AA and Cau women residing in North Carolina [32]. CBCS study design and methods have been previously described by Newman et al. [32]. Study participants were recruited and selected from 24 contiguous counties in central and eastern North Carolina [32]. CBCS recruitment was conducted in two phases—from 1993 through 1995 (Phase 1) and from 1996 through 2001 (Phase 2). Women living in the study area between the ages of 20 and 74 and diagnosed with invasive breast cancer for the first time were eligible cases in Phase 1. CBCS Phase 2 included women diagnosed with in situ breast cancer (CIS) as well as those diagnosed with invasive breast cancer. Cases were identified using a rapid case ascertainment system via the North Carolina Central Cancer Registry (NCCCR). After eligibility criteria were met, randomized recruitment case sampling was undertaken to ensure adequate representation of AA and younger women [33]. Phase 2 CIS cases did not undergo random recruitment sampling; all eligible CIS cases were enrolled.

Controls were selected from two sources: women younger than 65 were selected from a list maintained by the North Carolina Division of Motor Vehicles; women between the ages of 65 and 74 were selected from Health Care Financing Administration records. Controls were sampled from these lists using modified randomized recruitment, and sampling fractions were designed to ensure frequency-matching of cases to controls by race and 5-year age interval [34,33].

Potential cases and controls were contacted first by letter and then by telephone, if available. Women agreeing to participate were scheduled for an in-home visit by a registered nurse interviewer. The nurse interviewer collected anthropometric measurements, questionnaires, permission/consent to obtain tumor tissue, and a 30cc blood sample. Germline DNA was extracted from peripheral blood lymphocytes and stored at −80°C for future analysis [32]. The CBCS pathologist performed a standardized review of all breast tissue received to confirm the diagnosis of breast cancer and to characterize histology [32]. Slides were cut from paraffin blocks for molecular and immunohistochemical (IHC) assays, procedures for which have been described previously [29,35,36]. The study procedures for recruitment and enrollment into the CBCS were approved by the Institutional Review Board of the University of North Carolina (UNC), and all study participants gave written informed consent.

Subtyping of Cases by Immunohistochemistry (IHC)

For invasive cases, estrogen receptor (ER), and progesterone receptor (PR) status were primarily obtained from medical records (80%). Clinical laboratories determined ER/PR results on these cases. Approximately half of the clinical laboratories used IHC on paraffin-embedded tissue, and employed cutoffs for receptor positivity from more than 0% to more than 20%. The other half performed biochemical assays on frozen tissue with cut-offs for receptor positivity of 10–15 fmol/mg [36]. For approximately 11% of invasive cases, ER/PR status was not available in the medical record; however, paraffin-embedded tissue was

available and ER/PR status was ascertained by the UNC IHC Core laboratory. For these cases, IHC scoring was based on UNC Hospitals Department of Pathology standards, using a cut-off of 5% positive nuclei staining in invasive breast cancer cells [29]. A random sample of ER+ and ER− cases based on medical record abstraction was drawn to compare with IHC performed by the UNC IHC Core laboratory. A kappa statistic of 0.62 and concordance of 81% resulted from the comparison, indicating good agreement [37]. Nine percent of invasive cases had missing data for ER/PR status [29].

CBCS intrinsic breast cancer subtypes were based on expression of ER, PR, human epidermal growth factor receptor 2 (HER2), cytokines (CK) 5/6, and human epidermal growth factor receptor 1 (HER1) according to previously published definitions [29]. Tumors that were negative for expression of all five markers were unclassified. Negative staining for all markers is not necessarily indicative of receptor negativity in the tumor, and can result from poor tumor block quality or inadequate tissue present in the tumor block [29]. Tissue subtype analysis was performed in the following manner: HER2 status in invasive cases was determined using the CB11 monoclonal antibody as previously described [35]. HER2 positivity was defined by weak to strong staining of membrane or membrane plus cytoplasm in at least 10% of tumor cells [29]. Interscorer agreement of the HER2 IHC assay was evaluated on a subset of cases (n = 184), yielding overall concordance of 82% [29]. HER1 and cytokeratin (CK) 5/6 characterization have been previously described [38,39], and invasive cases demonstrating any staining were classified as positive [29]. All assays were performed by the UNC IHC Core laboratory. ER, HER2, CK5/6, and HER1 classification and determination for CIS cases were described in detail previously [40]. All assays were performed by the UNC IHC Core laboratory (IC). PR status was not determined for CIS cases due to its high correlation with ER expression and to preserve tissue [25].

SNP Selection

SNPs in this study were genotyped as part of a larger panel of 1536 SNPs by the UNC Mammalian Genotyping Core using the Illumina Golden Gate Assay (Illumina, San Diego, CA). Detailed genotyping procedures and quality control measures for the entire 1536 SNP panel were described previously [41,42]. Assay intensity data and genotype cluster images for all SNPs were reviewed individually. To ensure quality control of genetic data, SNPs with low signal intensity or SNPs that were unable to be distinguished by genotype cluster were excluded. For each SNP, Hardy–Weinberg equilibrium (HWE) was evaluated in SAS v9.3 (SAS, Cary, NC) using a one-degree-of-freedom chi square exact test among race-stratified controls to determine if genotype frequencies were distributed as expected given the allele frequencies. Specifically for the evaluation of *AURKA*, a combination of tag and candidate SNPs were selected for genotyping. Tag SNPs were identified for Cau and AA from Utah residents with ancestry from northern and western Europe (CEU) and individuals of Yoruban descent from Idaban, Nigeria (YRI) HapMap populations respectively [43], and selected using the Tagger program developed by de Bakker et al. [44]. Tag SNPs were selected based on a linkage disequilibrium (LD) $r^2 \geq 0.80$ and a minor allele frequency (MAF) of ≥0.10 in either CEU or YRI populations. Tag SNPs in each population were then combined and CBCS participants were genotyped for the pooled list. Candidate SNPs were chosen for replication of previous GWAS hits [41]. Five SNPs in *AURKA* were excluded

from the overall analysis due to HWE *P*-values <0.05 in either AA or Cau (*N* = 3) or because they were not polymorphic in the CBCS population (*N* = 2); one SNP was excluded from the combined race subtype analysis because it was not polymorphic in Cau (rs34987347). Detailed genotyping procedures and quality control measures were described previously [41,42]. The software package *Structure* and a set of 144 ancestry informative markers (AIMs) were used to determine the proportion of African and European ancestry for each participant [45,41].

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, as estimates of the rate ratios [46], for genotype associations with breast cancer overall and by immunohistochemical (IHC) subtype using unconditional binary logistic regression in SAS v9.3 (SAS). All SNP's were coded using a dominant model, with the most common allele in Cau as the referent allele in both race groups to facilitate race comparisons. All genotype associations were adjusted for age, potential population stratification using the AIMs variable, and an offset term (defined as the natural log of recruitment probability of cases/ recruitment probability of controls) to adjust for differing randomized recruitment sampling probabilities between phases of CBCS [41,47]. Subtype-specific analyses were performed in the combined race group rather than by race due to small sample numbers within strata of subtype, and were adjusted for self-identified race, age, the AIMs variable, and the offset term.

To address multiple comparisons, the false discovery rate (FDR) was employed to adjust *P*-values in SAS v9.3 (SAS) [48]. Control of the FDR, as opposed to more stringent control of the family wise error rate (FWER, e.g., Bonferroni correction), models the number of errant null hypotheses rejected in addition to whether an errant rejection was made.

RESULTS

Participant Characteristics

Among self-reported AA, the median proportion of African ancestry was 81%. The median proportion of African ancestry among self-reported Cau was 6%. Immunohistochemical subtype data was available for 1412 of 2277 (62%) cases, and successful genotyping data was collected for 1946 of 2277 (85%) cases. Of the 2277 cases, 1210 (53%) were successfully genotyped and subtyped (742 AA/1204 Cau) (Table 1). The distribution of tumor subtype in cases with genotype data was as follows: 199 basal-like, 674 luminal A, 114 luminal B, 94 HER2+/ER−, and 129 unclassified (Table 1). Cases with missing subtype data were more likely to be Cau and have an earlier stage at diagnosis [25]. Of 1985 controls, 1747 (88%) were successfully genotyped (658 AA/1089 Cau) (Table 1). Participants were excluded from analysis because of genotype calls for <95% of SNPs (*N* = 569), gender mismatch (*N* = 5), and suspected contamination of DNA specimen (*N* = 1) [41]. Participants missing genotype data were more likely to be AA cases.

Genotype Associations

Here, we focus on patterns to identify those SNPs for which the effect estimates were pronounced; and, we focus on estimates that were least influenced by chance (i.e., those estimates with the lowest confidence limit ratios (CLRs); the ratio of the upper to lower 95% confidence limits-a measure of precision [49]). Odds ratios for *AURKA* SNPs in the race-stratified analysis with breast cancer, not divided by subtype, were all close to 1.00 (Table 2). Among AA, rs6092309 showed a decreased odds ratio (OR = 0.69, 95% CI: 0.53–0.90) and rs911162 had a slightly elevated odds ratio with breast cancer (OR = 1.23, 95% CI: 0.82–1.84). Table 3 presents the subtype-specific (race-combined) results. Rs6092309 had decreased ORs for the luminal A (OR = 0.61, 95% CI: 0.41–0.92), HER2 (OR = 0.69, 95% CI: 0.29–1.61) and basal-like (OR = 0.75, 95% CI: 0.44–1.25) subtypes. Rs6099128 showed a similar pattern of associations among luminal A (OR = 0.76, 95% CI: 0.60–0.95), HER2 (OR = 0.86, 95% CI: 0.52–1.41) and basal-like (OR = 0.54, 95% CI: 0.37–0.80) subtypes. Three *AURKA* SNPs had elevated ORs for basal-like breast cancer (rs6014711; OR = 1.33, 95% CI: 0.97–1.84), (rs911162; OR = 1.32, 95% CI: 0.70, 2.51), (rs1047972; OR = 1.34, 95% CI: 0.97, 1.85) and ORs reduced or close to 1.00 for all other subtypes. One SNP showed a twofold elevated odds ratio for HER2+/ER− breast cancer (rs16979826; OR = 2.14, 95% CI: 1.06, 4.29). None of the effect measure estimates were statistically significant at $P < 0.05$ after FDR correction.

DISCUSSION

Compared to previous studies, this study represents a more comprehensive investigation of *AURKA* related to breast cancer in a population of AA and Cau women. Previous studies of *AURKA* have focused largely on a few functional SNPs (rs2273535—Phe31Ile, rs1047972—Val57Ile) in Cau and Asian populations and have not investigated the influence of subtype. Our main finding was a decreased association between rs6092309 and breast cancer among AA women. Among Cau women this SNP led to an elevated but imprecise odds ratio estimate because of a MAF of less than 1% in both Cau cases and controls. In the combined race group subtype-specific analysis, rs6092309 showed odds ratios less than one across all subtypes. These results suggest that the association of *AURKA* genetic variation with subtype-specific breast cancer may differ by race. Rs6092309 is located within an intronic region of *AURKA*, is not predicted to be deleterious by SIFT or PolyPhen, and has not been previously studied with respect to breast cancer. Rs6092309 is in weak LD with other SNPs on *AURKA* in the HapMap YRI population (Release #27), demonstrates weak residual LD among SNPs genotyped in CBCS AA controls, and may be a marker for an ungenotyped genetic factor.

The importance of population stratification and race also emerged in subtype specific analyses, where there was evidence of heterogeneity in the relationships between *AURKA* SNPs and luminal A and basal-like breast cancer. Intronic SNPs rs2298016 and rs6099128 both demonstrated decreased odds ratios for basal-like breast cancer (Table 3). A population-based case-control study of breast cancer in Han Chinese women found rs2298016 to be inversely associated with breast cancer (OR = 0.52, 95% CI = 0.32–0.87, $P = 0.01$) [50]. However, the minor/test allele in the Han Chinese population was opposite that

in the CBCS population and subtype-specific results were not reported in that study. Furthermore, rs2298016 was positively associated with both HER2+/ER− and unclassified breast cancer subtypes in CBCS cases. The instability of ORs for these SNPs across populations suggests significant differences in LD structure and/or different subtype distributions among the study populations. Allele and genotype frequencies for rs2298016 among AA cases and controls were comparable to those in Cau (Online Resource 1), however LD structure was considerably different between races. This study was not powered to examine associations by race and breast cancer subtype, but exploratory subtype analysis of rs2298016 showed a decreased association between rs2298016 and basal-like breast cancer in AA (OR = 0.55, 95% CI = 0.35–0.88), with weaker effects among Cau (OR = 0.81, 95% CI = 0.51–1.28). Allele and genotype frequencies for rs6099128 among AA cases and controls were also similar to those in Cau (Online Resource 1), and LD structure was similar between races. Exploratory subtype analysis by race showed an odds ratio less than one for the association between rs6099128 and basal-like breast cancer among AA (OR = 0.45, 95% CI = 0.27–0.75), with weaker effects in Cau (OR = 0.71, 95% CI = 0.39–1.28). Rs6099128 was negatively associated with luminal A breast cancer; upon exploratory race-specific subtype analysis, a stronger negative association (OR = 0.68, 95% CI = 0.49–0.93) among Cau women compared to AA (OR = 0.86, 95% CI = 0.61–1.20). These results should be considered in the context of small sample sizes and imprecise effect estimates, but may suggest race-specific differences by breast cancer subtype.

Our study found no association between rs2273535 and breast cancer overall in Cau or AA women. We also found no association for rs2273535 among luminal A cases, and a slightly negative association with basal-like breast cancer. Several published studies have investigated the effects of missense SNP rs2273535 (Phe31Ile) and rs1047972 (Val57Ile) in association with breast cancer overall. Sun et al. [17] found increased risk for breast carcinoma associated with the Ile/Ile genotype of rs2273535 (OR = 1.66, 95% CI = 1.29–2.12) in a case-control study of unrelated Han Chinese women. Additional studies of rs2273535 in both Chinese [18,23] and Cau [20] populations failed to replicate the finding. A 2011 meta-analysis of rs2273535, which included 11 case-control studies, reported a slight inverse association between the Ile/Ile genotype and risk of breast cancer (OR = 0.86, 95% CI = 0.74–0.99), but only in Asian populations [51]. The coding region polymorphism rs1047972 on *AURKA* resulting in a valine to isoleucine substitution has also been heavily investigated for association with risk of breast cancer. Egan et al. [20] reported no association with breast cancer risk among Cau women with the Ile/Ile genotype (OR = 0.92, 95% CI = 0.50–1.71) in a population-based case-control study. Our study found no association between rs1047972 and breast cancer overall or luminal A breast cancer. However, an elevated odds ratio for rs1047972 and basal-like breast cancer was found (OR = 1.34, 95% CI = 0.97–1.85).

Limitations of this study include diminished statistical power to detect subtype-specific effects of *AURKA* due to small numbers of cases within strata of breast cancer subtype. Furthermore, whereas this study employed IHC to classify breast cancer subtypes, gene expression profiling using mRNA-based assays containing thousands of genes was originally used to characterize intrinsic breast cancer subtypes [2,3]. IHC assays do not

provide as much information about tumor biology as mRNA-based expression assays do, and could result in misclassification of subtype [29]. However, IHC-based subtyping has been shown to identify common tumor subtypes with similar biologic characteristics, does not require fresh tissue, and has been widely used in population-based studies as a surrogate for gene expression profiling methods [29,52]. Although our study population was large, the effect sizes of *AURKA* SNP associations with breast cancer risk are likely small and thus more subtle main or subtype effects will require a much larger study sample to determine more accurate estimates. Additionally, sample sizes were not sufficient to reliably conduct subtype-specific race stratified analyses of *AURKA*. A third phase of the CBCS is underway to augment the number of AA cases with characterized tumor subtype, which will allow for further genetic evaluation to address this limitation. There was potential for selection bias to influence study results since 38% of cases were unable to be subtyped. However, genotyping distributions were similar between cases with and without subtype data (data not shown). Likewise, subtype distributions were similar between cases with and without genotyping data (Online Resource 2). This suggests that the genotype distribution in cases with subtype data is likely representative of the genotype distribution in all cases. Similarly, the subtype distribution in cases with genotype data is likely representative of the subtype distribution in all cases.

This study applied a candidate gene approach that was based on a plausible biological mechanism involving the cell-cycle regulatory gene *AURKA*, which is implicated in oncogensis [12,13,53]. Strengths of this study include: (1) the availability of a comprehensive set of tag and candidate SNPs in *AURKA*, which improves our survey and coverage of this important oncogene; (2) inclusion of a relatively large number of AA women, in whom variation at *AURKA* has not been evaluated; (3) inclusion of 5-marker intrinsic subtype data based on the most current understanding of breast tumor heterogeneity; and (4) use of AIMS to adjust for population stratification, a factor which has been shown to impact effect estimates significantly if not controlled for [41]. Furthermore, we report associations regardless of statistical significance for two reasons. First, to acknowledge that inherited variation at *AURKA* has not been well studied in African Americans, nor has it been investigated by molecular subtype; thus our results provide an important foundation for future replication and follow-up. Second, our reporting of results was deliberately tempered to avoid publication bias and the so-called “winner’s curse”—a phenomenon whereby statistically significant estimates, and therefore literatures in which such estimates are preferentially published, are exaggerated or biased away from the null [54].

In summary, these results represent the first comprehensive examination of *AURKA* SNPs in a population-based study with a large group of African American participants. Odds ratios for associations between *AURKA* SNPs and breast cancer overall were modest and consistent by race. Associations by intrinsic breast cancer subtype were relatively imprecise compared to overall estimates, but results were suggestive of decreased associations between a few *AURKA* SNPs and breast cancer subtype. Exploratory results also suggested race-specific effects within subtype. Given the likelihood of small effect sizes of *AURKA* SNPs on rate of breast cancer, evaluating subtype-specific effects in larger groups of AA

and Cau women may better estimate the effect of *AURKA* on the rate of distinct breast cancer subtypes.

Supplementary Material

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Abbreviations

AA	African American
AIM	ancestry informative marker
CBCS	Carolina Breast Cancer Study
CI	confidence interval
CIS	breast carcinoma in situ
ER	estrogen receptor
FDR	false discovery rate
HER1	human epidermal growth factor receptor 1
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
LD	linkage disequilibrium
OR	odds ratio
PR	progesterone receptor
SNP	single nucleotide polymorphism

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Table 1

Characteristics of CBCS Participants With Genotype Data

	Cases (%)	Controls (%)
N	1946 *(100)*	1747 *(100)*
Self-identified race		
African American	742 *(38.1)*	658 *(37.7)*
Caucasian	1204 *(61.9)*	1089 *(62.3)*
Age		
20–24	6 *(0.3)*	1 *(0.0)*
25–29	21 *(1.1)*	10 *(0.6)*
30–34	85 *(4.4)*	60 *(3.4)*
35–39	172 *(8.8)*	133 *(7.6)*
40–44	276 *(14.2)*	242 *(13.9)*
45–49	387 *(19.9)*	359 *(20.5)*
50–54	208 *(10.7)*	237 *(13.6)*
55–59	216 *(11.1)*	191 *(10.9)*
60–64	201 *(10.3)*	166 *(9.5)*
65–69	200 *(10.3)*	185 *(10.6)*
70–74	174 *(8.9)*	163 *(9.3)*
Menopausal status		
Premenopausal	864 *(44.4)*	746 *(42.7)*
Postmenopausal	1082 *(55.6)*	1001 *(57.3)*
Stage		
1	609 *(31.3)*	
2	627 *(32.3)*	
3	144 *(7.4)*	
4	42 *(2.2)*	
CIS	437 *(22.5)*	
Missing[a]	87 *(4.5)*	
Tumor size[b]		
≤2 cm	769 *(51.0)*	
>2–5 cm	502 *(33.3)*	
>5 cm	146 *(9.7)*	
Missing	92 *(6.1)*	
Subtype		
Luminal A	674 *(34.6)*	
Luminal B	114 *(5.9)*	
HER2+/ER−	94 *(4.8)*	
Basal-like	199 *(10.2)*	
Unclassified	129 *(6.6)*	
Missing	736 *(37.8)*	

[a] Invasive breast cancer cases.

[b] Not available for CIS (carcinoma in situ) cases.

Table 2

Odds ratios (ORs) and 95% Confidence Intervals (CIs) for the Association Between Single Nucleotide Polymorphisms (SNPs) on *AURKA* and All Incident Cases of Breast Cancer by Race

	Caucasian cases and controls		African American cases and controls	
SNP	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**
rs1047972				
AG + AA	1.05 (0.87, 1.27)	0.99	0.97 (0.76, 1.24)	0.92
GG	Referent		Referent	
rs34987347[c]				
TC + TT			1.04 (0.34, 1.27)	0.99
CC	Referent		Referent	
rs1468056				
CG + CC	1.09 (0.91, 1.30)	0.99	1.05 (0.75, 1.47)	0.92
GG	Referent		Referent	
rs16979826[d]				
CT + CC			0.96 (0.73, 1.27)	0.92
TT			Referent	
rs16979829				
GT + GG	1.10 (0.77, 1.58)	0.99	0.97 (0.77, 1.23)	0.92
TT	Referent		Referent	
rs16979865				
CA + CC	1.07 (0.84, 1.38)	0.99	0.85 (0.64, 1.13)	0.92
AA	Referent		Referent	
rs2180691				
AG + AA	0.99 (0.84, 1.18)	0.99	0.90 (0.56, 1.45)	0.92
GG	Referent		Referent	
rs2273535				
TA + TT	1.00 (0.84, 1.20)	0.99	1.07 (0.84, 1.36)	0.92
AA	Referent		Referent	
rs2298016				
CG + CC	1.01 (0.85, 1.21)	0.99	0.97 (0.78, 1.21)	0.92
GG	Referent		Referent	
rs6014711				
AG + AA	1.04 (0.86, 1.25)	0.99	0.97 (0.76, 1.23)	0.92
GG	Referent		Referent	
rs6024840				
GA + GG	1.02 (0.86, 1.25)	0.99	0.80 (0.62, 1.04)	0.70
AA	Referent		Referent	
rs6092309				
AG + AA	2.13 (0.47, 9.65)	0.99	0.69 (0.53, 0.90)	0.14
GG	Referent		Referent	

	Caucasian cases and controls		African American cases and controls	
SNP	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**
rs6099122				
GT + GG	1.20 (0.79, 1.81)	0.99	0.86 (0.69, 1.07)	0.92
TT	Referent		Referent	
rs6099126				
TC + TT	1.10 (0.74, 1.63)	0.99	0.89 (0.71, 1.12)	0.92
CC	Referent		Referent	
rs6099128				
GT + GG	0.85 (0.98, 1.06)	0.99	0.81 (0.64, 1.02)	0.70
TT	Referent		Referent	
rs1468055				
AC + AA	1.06 (0.88, 1.26)	0.99	0.95 (0.63, 1.41)	0.92
CC	Referent		Referent	
rs6024836				
AG + AA	1.02 (0.86, 1.22)	0.99	0.95 (0.67, 1.35)	0.92
GG	Referent		Referent	
rs2064863				
AC + AA	1.00 (0.83, 1.20)	0.99	0.91 (0.50, 1.64)	0.92
CC	Referent		Referent	
rs6099119				
GA + GG	2.08 (0.21, 20.73)	0.99	1.11 (0.77, 1.62)	0.92
AA	Referent		Referent	
rs911162				
AG + AA	0.82 (0.41, 1.67)	0.99	1.23 (0.82, 1.84)	0.92
GG	Referent		Referent	

[a] Case-control odds ratio and 95% confidence interval adjusted for age, African ancestry and offset term.

[b] False discovery rate (FDR) adjusted *P*-values.

[c] Too few heterozygotes and homozygotes for the minor allele in Caucasian.

[d] Tag SNP only in African Americans.

Table 3

Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the Association Between Single Nucleotide Polymorphisms (SNPs) on *AURKA* and Subtype of Breast Cancer

	Luminal A (N_{cases} = 674)		Luminal B (N_{cases} = 114)		HER2+/ER− (N_{cases} = 94)		Basal-like (N_{cases} = 199)		Unclassified (N_{cases} = 129)	
SNP	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**
rs1047972										
AG + AA	0.96 (0.78, 1.18)	0.90	0.75 (0.48, 1.18)	0.87	0.84 (0.52, 1.36)	0.90	1.34 (0.97, 1.85)	0.76	0.93 (0.62, 1.40)	0.90
GG	Referent		Referent		Referent		Referent		Referent	
rs1468056										
CG + CC	1.28 (1.03, 1.59)	0.38	1.06 (0.68, 1.64)	0.95	1.04 (0.64, 1.70)	0.96	1.13 (0.78, 1.63)	0.90	0.90 (0.58, 4.41)	0.90
GG	Referent		Referent		Referent		Referent		Referent	
rs16979826										
CT + CC	0.81 (0.54, 1.21)	0.90	0.69 (0.28, 1.72)	0.90	2.14 (1.06, 4.29)	0.41	0.88 (0.51, 1.50)	0.90	1.18 (0.65, 2.15)	0.90
TT	Referent		Referent		Referent		Referent		Referent	
rs16979829										
GT + GG	0.92 (0.69, 1.23)	0.90	0.97 (0.54, 1.77)	0.96	1.05 (0.57, 1.92)	0.96	1.22 (0.82, 1.82)	0.90	1.03 (0.63, 1.69)	0.96
TT	Referent		Referent		Referent		Referent		Referent	
rs16979865										
CA + CC	1.20 (0.93, 1.55)	0.79	0.71 (0.39, 1.31)	0.90	1.01 (0.56, 1.82)	0.98	0.91 (0.59, 1.41)	0.90	1.05 (0.64, 1.73)	0.96
AA	Referent		Referent		Referent		Referent		Referent	
rs2180691										
AG + AA	0.96 (0.77, 1.20)	0.90	1.02 (0.65, 1.61)	0.96	1.25 (0.74, 2.11)	0.90	0.96 (0.64, 1.43)	0.96	1.01 (0.62, 1.65)	0.98
GG	Referent		Referent		Referent		Referent		Referent	
rs2273535										
TA + TT	0.96 (0.78, 1.17)	0.90	1.30 (0.87, 1.94)	0.87	1.11 (0.71, 1.74)	0.90	0.81 (0.58, 1.13)	0.87	1.36 (0.92, 2.00)	0.79
AA	Referent		Referent		Referent		Referent		Referent	
rs2298016										
CG + CC	0.96 (0.79, 1.16)	0.90	1.14 (0.77, 1.70)	0.90	1.38 (0.90, 2.11)	0.79	0.67 (0.48, 0.93)	0.38	1.34 (0.93, 1.95)	0.79
GG	Referent		Referent		Referent		Referent		Referent	
rs6014711										
AG + AA	0.95 (0.77, 1.17)	0.90	0.74 (0.47, 1.17)	0.87	0.79 (0.48, 1.29)	0.90	1.33 (0.97, 1.84)	0.76	0.93 (0.61, 1.40)	0.90

	Luminal A (N_{cases} = 674)		Luminal B (N_{cases} = 114)		HER2+/ER− (N_{cases} = 94)		Basal-like (N_{cases} = 199)		Unclassified (N_{cases} = 129)	
SNP	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**
GG	Referent		Referent		Referent		Referent		Referent	
rs6024840										
GA + GG	0.95 (0.78, 1.16)	0.90	1.21 (0.80, 1.84)	0.90	1.28 (0.80, 2.05)	0.90	0.76 (0.54, 1.06)	0.79	1.00 (0.66, 1.50)	0.99
AA	Referent		Referent		Referent		Referent		Referent	
rs6092309										
AG + AA	0.61 (0.41, 0.92)	0.38	0.95 (0.43, 2.09)	0.96	0.69 (0.29, 1.61)	0.90	0.75 (0.44, 1.25)	0.90	0.62 (0.32, 1.20)	0.79
GG	Referent		Referent		Referent		Referent		Referent	
rs6099122										
GT + GG	1.08 (0.81, 1.42)	0.90	1.06 (0.58, 1.92)	0.96	1.56 (0.86, 2.83)	0.79	1.15 (0.77, 1.71)	0.90	0.71 (0.44, 1.17)	0.87
TT	Referent		Referent		Referent		Referent		Referent	
rs6099126										
TC + TT	1.05 (0.79, 1.39)	0.90	0.83 (0.45, 1.52)	0.90	1.35 (0.73, 2.49)	0.90	1.10 (0.73, 1.66)	0.90	0.86 (0.53, 1.41)	0.90
CC	Referent		Referent		Referent		Referent		Referent	
rs6099128										
GT + GG	0.76 (0.60, 0.95)	0.38	1.09 (0.70, 1.69)	0.90	0.86 (0.52, 1.41)	0.90	0.54 (0.37, 0.80)	0.19	0.61 (0.38, 0.97)	0.41
TT	Referent		Referent		Referent		Referent		Referent	
rs1468055										
AC + AA	1.01 (0.81, 1.27)	0.96	1.28 (0.82, 2.00)	0.90	0.80 (0.46, 1.37)	0.90	1.10 (0.75, 1.63)	0.90	0.79 (0.48, 1.30)	0.90
CC	Referent		Referent		Referent		Referent		Referent	
rs6024836										
AG + AA	1.02 (0.82, 1.27)	0.96	0.90 (0.58, 1.39)	0.90	0.85 (0.52, 1.39)	0.90	0.85 (0.59, 1.24)	0.90	0.63 (0.41, 0.98)	0.48
GG	Referent		Referent		Referent		Referent		Referent	
rs2064863										
AC + AA	0.87 (0.69, 1.11)	0.90	1.25 (0.76, 2.06)	0.90	1.12 (0.64, 1.97)	0.90	0.93 (0.61, 1.43)	0.90	0.94 (0.56, 1.58)	0.95
CC	Referent		Referent		Referent		Referent		Referent	
rs6099119										
GA + GG	1.15 (0.68, 1.93)	0.90	0.28 (0.04, 2.11)	0.87	0.58 (0.13, 2.49)	0.90	1.61 (0.85, 3.06)	0.90	1.37 (0.62, 3.05)	0.90
AA	Referent		Referent		Referent		Referent		Referent	
rs911162										
AG + AA	0.83 (0.50, 1.40)	0.90	0.85 (0.29, 2.47)	0.93	0.87 (0.30, 2.55)	0.95	1.32 (0.70, 2.51)	0.90	0.68 (0.26, 1.79)	0.90

	Luminal A (N_{cases} = 674)		Luminal B (N_{cases} = 114)		HER2+/ER− (N_{cases} = 94)		Basal-like (N_{cases} = 199)		Unclassified (N_{cases} = 129)	
SNP	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**	**OR[a] (95% CI)**	**P_{adj} [b]**
GG	Referent		Referent		Referent		Referent		Referent	

[a] Case-control odds ratio and 95% confidence interval adjusted for age, self-identified race, African ancestry and offset term.

[b] False discovery rate (FDR) adjusted *P*-values.