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Lack of association between common single nucleotide polymorphisms in the *TERT-CLPTM1L* locus and breast cancer in women of African ancestry

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Abstract

As one of the most common cancers worldwide, breast cancer places an extraordinary burden on the populations of African ancestry. Common SNPs in the *TERT-CLPTM1L* locus have been reported to be associated with several types of cancer, including breast cancer. We sought to investigate whether the previously reported common single nucleotide polymorphisms (SNPs) in the *TERT-CLPTM1L* locus could also contribute to the breast cancer risk in women of African ancestry. We genotyped eleven SNPs in 2,892 women of African descent but were unable to detect any significant association between *TERT-CLPTM1L* SNPs and their predispositions for breast cancer risk. Given the differences in linkage disequilibrium patterns across populations, our

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Conflicts Of Interest

The authors declare no conflict of interest.

findings suggest that larger independent studies from diverse populations are expected to evaluate the importance of the *TERT-CLPTMIL* locus in breast cancer.

Keywords

TERT-CLPTMIL; single nucleotide polymorphism; association; breast cancer; African ancestry

Introduction

Breast cancer is one of the most common epithelial cancers and causes an excessive disease mortality in populations of African ancestry. Recent genome wide association studies (GWAS) provided evidence that common low-penetrance single nucleotide polymorphisms (SNPs) contribute to breast cancer development. Common SNPs in the *TERT* (*telomerase reverse transcriptase*)-*CLPTMIL* (*cleft lip and palate transmembrane 1 like*) locus have been reported to be associated with several types of cancer, such as lung cancer/adenocarcinoma, glioma, bladder cancer, prostate cancer, and pancreatic cancer [1–7]. Researchers also hypothesized that common SNPs in the *TERT* gene could play a role in breast cancer susceptibility. However, findings are inconsistent, and most studies included Caucasians only [8–11]. In the present study, we sought to investigate whether common genetic variants in the *TERT-CLPTMIL* locus could contribute to breast cancer susceptibility in women of African ancestry.

Material and methods

Study populations

A total 2,892 women of African ancestry were participated in the present study, consisting of 1,509 breast cancer cases and 1,383 controls. The average age (mean $\pm$ standard deviation (SD)) was 48.0 ± 12.0 years in 1,509 cases and 47.2 ± 17.2 years in 1,383 controls. DNA samples were collected from the Nigerian Breast Cancer Study (681 cases and 282 controls), the Baltimore Breast Cancer Study (117 cases and 111 controls), the Barbados National Cancer Study (93 cases and 244 controls), the Northern California site of the Breast Cancer Family Registry (199 cases and 213 controls), the Racial Variability in Genotypic Determinants of Breast Cancer Risk Study (151 cases and 272 controls), and the Chicago Cancer Prone Study (268 cases and 261 controls). All study subjects were of self-reported African ancestry. This case-control study was approved by the Institutional Review Boards of each participating study and written informed consent was obtained from all study participants.

SNPs and genotyping

Eleven SNPs in the *TERT-CLPTMIL* locus that were previously shown to be associated with cancers were selected: six SNPs (rs2736100, rs2853676, rs4975616, rs402710, rs401681, and rs31489) from GWAS (as of May 2010) for lung cancer/adenocarcinoma, glioma, idiopathic pulmonary fibrosis, and pancreatic cancer [1–6,12]; rs2736098 from a candidate gene study of many cancer types [7], including breast cancer [9]; rs2736109 from a gene-based association study [8]; and three SNPs (rs11133719, rs7726159, and rs3816659) from an association study of ovarian cancer [13].

Genetic association analyses

These eleven SNPs, along with 30 ancestry informative markers (AIMs), were genotyped using the Illumina GoldenGate Genotyping platform (Illumina Inc., San Diego, CA, USA). These AIMs were chosen from a set of 1,373 AIMs with maximum allele frequency

differences between European and African descendants, and these AIMs turned out to have a high correlation of estimates ($r=0.89$) with the entire set [14]. The overall sample success rate of genotyping was 99.4%, and the reproducibility rate was 99.99%. Tests for deviation from Hardy-Weinberg equilibrium (HWE) were carried out using PLINK v1.07 (<http://pengu.mgh.harvard.edu/~purcell/plink/>). Genetic ancestry was estimated from AIMs using STRUCTURE (<http://pritch.bsd.uchicago.edu/structure.html>).

Statistical comparisons between breast cancer cases and controls were conducted using PLINK v1.07. We performed unconditional multiple logistic regression to estimate the association between the *TERT-CLPTMIL* genetic variants and breast cancer risk, adjusting for age, study site, and estimated genetic ancestry. Three genetic models, including additive, dominant, and recessive models, were employed. Haploview v4.2 (<http://www.broad.mit.edu/mpg/haploview/>) was used to explore the linkage disequilibrium (LD) between the studied SNPs. A five-SNP LD block, rs4975616-rs3816659-rs402710-rs401681-rs31489, showed $D'' > 0.9$ and $r^2 > 0.3$ between SNPs. We therefore conducted haplotype analysis based on these five SNPs in PLINK. For all the tests at allelic, genotypic and haplotypic levels, P values were corrected by 10,000-times permutation test.

Results

Test for HWE suggested that the genotypes for all the SNPs were in Hardy-Weinberg proportions and there was no deviation from HWE ($P > 0.001$). All tested SNPs were common genetic variants with minor allele frequencies (MAFs) > 0.05 . One of the AIMs was ruled out of the analysis due to its failure in genotyping. The African ancestral proportions in cases and controls (mean $\pm$ SD) were 98.0 ± 1.2 and 98.1 ± 1.0 in Nigerians, 85.6 ± 10.4 and 85.7 ± 9.8 in Barbadians, whereas 77.6 ± 13.5 and 78.7 ± 12.0 in African Americans, respectively.

Overall we did not observe any P value < 0.05 after permutation in the analyses of allelic and genotypic models (Table 1). For the six aforementioned GWAS index SNPs related to different cancers, there was no evidence of association with breast cancer risk in the present study. All P values after permutation were > 0.05 . Moreover, the five-SNP LD block covers most of the *CLPTMIL* gene, and haplotype analysis suggested that neither the global nor individual haplotypes (with frequency > 0.01) were positively associated with breast cancer risk in women of African ancestry (Table 2).

Discussion

At the chromosomal termini, end-to-end fusion and degradation are inhibited by telomeres which consist of long TTAGGG nucleotide repeats. As a catalytic subunit of the telomerase enzyme, TERT is crucial for the maintenance of telomere DNA length, chromosomal stability, and cellular unlimited proliferation [15]. Thus, *TERT* locus appears to be a promising candidate for the breast cancer susceptibility.

Using 1,509 breast cancer cases and 1,383 controls of African ancestry, we had adequate statistical power of 81.1% and 89.7% to detect a per-allele odds ratio (OR) of 1.20 for SNPs with MAFs of 0.20 and 0.30, respectively. The estimated African ancestry proportions by 29 AIMs showed an expected incremental decrease from Nigeria to Barbados and then to the United States, which is in line with the theory of African Diaspora.

In the present study, testing the pleiotropic effects of three SNPs (rs11133719, rs7726159, and rs3816659) associated with ovarian cancer risk failed to show any evidence of association with breast cancer risk in women of African ancestry. In one GWAS follow-up study [7], rs2736098, rs401681, and rs31489 were positively associated with a risk of basal

cell carcinoma, and the first two SNPs were further found to confer increased risk to other cancers such as lung, bladder, and prostate cancers. rs2736098 has also been found to be associated with a family history of breast cancer ($P = 0.004$, OR = 0.57, 95% confidence interval (CI) = 0.39–0.84) [9]. However, this polymorphism is unlikely to be associated with familial or sporadic breast cancer risk, given the negative finding for rs2853669 which is in LD with rs2736098 [10]. In the present study, we obtained a weak signal at rs2736098 in an unadjusted allelic test ($P = 0.04$, OR = 0.84, 95% CI = 0.71–0.99), but no statistical significance remained after permutation. Another study found an association between rs2736109 and breast cancer risk under a dominant model ($P = 0.0004$, OR = 1.56, 95% CI = 1.22–1.99), and this SNP was the only one that retained significance after adjustment for multiple testing adjustment.[8] Additionally, rs2736109 has recently been reported to be associated with decreased breast cancer risk, and it reduces *TERT* promoter activity together with rs2736108 [16]. However, our data do not support their observations (Table 1).

In conclusion, we were unable to detect any positive association between *TERT-CLPTMIL* SNPs and predisposition to breast cancer risk. Our findings do not support an effect of the tested genetic variants in the *TERT-CLPTMIL* locus on breast cancer susceptibility in women of African ancestry. However, it is worth noting that our current study did not apply a fine-mapping strategy; other genetic variants in LD with previously reported cancer susceptibility polymorphisms might be *bona fide* causal variants contributing to the risk of breast cancer. Larger independent studies from diverse populations are expected to evaluate the importance of the *TERT-CLPTMIL* locus in breast cancer.

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Table 2

Haplotype analysis of 5-SNP LD block (rs4975616-rs3816659-rs402710-rs401681-rs31489) with frequency >0.01.

5-SNP haplotypes	Frequency	OR ^a	P value (covariate-adjusted)	P value (covariate-adjusted+permuted)
Omnibus/global	-	-	0.62	0.62
CTTAT	0.4560	0.944	0.28	0.83
CTCAT	0.0266	0.923	0.64	1.00
TCCGG	0.2560	1.050	0.44	0.95
CCCGG	0.1470	1.090	0.26	0.79
CCTAG	0.0149	0.775	0.26	0.80
CCCAG	0.0862	0.987	0.89	1.00

^aOdds ratio (OR).