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A common variant at the *TERT-CLPTM1L* locus is associated with estrogen receptor–negative breast cancer

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The authors declare no competing financial interests.

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Abstract

Estrogen receptor (ER)-negative breast cancer shows a higher incidence in women of African ancestry compared to women of European ancestry. In search of common risk alleles for ER-negative breast cancer, we combined genome-wide association study (GWAS) data from women of African ancestry (1,004 ER-negative cases and 2,745 controls) and European ancestry (1,718 ER-negative cases and 3,670 controls), with replication testing conducted in an additional 2,292 ER-negative cases and 16,901 controls of European ancestry. We identified a common risk variant for ER-negative breast cancer at the *TERT-CLPTM1L* locus on chromosome 5p15 (rs10069690: per-allele odds ratio (OR) = 1.18 per allele, $P = 1.0 \times 10^{-10}$). The variant was also significantly associated with triple-negative (ER-negative, progesterone receptor (PR)-negative and human epidermal growth factor-2 (HER2)-negative) breast cancer (OR = 1.25, $P = 1.1 \times 10^{-9}$), particularly in younger women (<50 years of age) (OR = 1.48, $P = 1.9 \times 10^{-9}$). Our results identify a genetic locus associated with estrogen receptor negative breast cancer subtypes in multiple populations.

Compared to women of European ancestry, women of African descent are more likely to be diagnosed with ER-negative breast cancer[1]. ER-negative tumors and triple-negative tumors are observed at even higher rates among African women currently residing in Africa[2], suggesting a genetic component to the high risk of ER-negative phenotypes in women of African descent. Similarly, ER-negative breast cancers and triple-negative breast cancers are also the predominant histological subtypes in women with germline mutations in *BRCA1* (ref. 3). The enrichment for ER-negative disease in this genetically predisposed population also suggests the existence of additional genetic factors that contribute to the risk of ER-negative disease. Support for the presence of these factors was recently provided by a GWAS of breast cancer in *BRCA1* mutation carriers, in which a common risk variant for ER-negative breast cancer on chromosome 19p13 was identified that also was significantly associated with ER-negative and triple-negative disease in the general population[4].

To search for genetic risk factors for ER-negative breast cancer phenotypes, we combined results from a GWAS of breast cancer in African-American women (African American Breast Cancer Consortium (AABC): 3,016 cases (1,004 with ER-negative disease) and 2,745 controls) with results from a GWAS of triple-negative breast cancer in women of European ancestry (Triple-Negative Breast Cancer Consortium (TNBCC): 1,718 cases and 3,670 controls). Genotyping in AABC was conducted with the Illumina Infinium 1M Duo. In TNBCC, cases were genotyped with the Illumina 660W array, a subset of cases from the Mammary Carcinoma Risk Factor Investigation (MARIE) component were genotyped using the Illumina CNV370 SNP array, and cases and controls from the Helsinki Breast Cancer Study (HEBCS) component were genotyped using the Illumina 550-Duo SNP array. Genotypes of TNBCC cases were compared with GWAS data for publicly available controls (Online Methods). Both studies imputed genotypes for common SNPs in phase 2 HapMap populations (release 21) (Supplementary Table 1 and Online Methods). A total of 3,154,485 SNPs, genotyped and imputed, were analyzed in stage 1 of the meta-analysis.

We observed little evidence of inflation in the test statistics in AABC ($\lambda = 1.01$) or TNBCC ($\lambda = 1.04$) or in the meta-analysis of the two GWAS ($\lambda = 1.02$; Supplementary Fig. 1). In the combined results, only SNP rs10069690 (NCBI36/hg18, chr5:1,332,790) located in intron 4 of the *TERT* gene (encoding telomerase reverse transcriptase) at chromosome 5p15 showed a genome-wide significant association with ER-negative breast cancer (AABC: OR per allele = 1.32, $P = 1.3 \times 10^{-6}$; TNBCC: OR = 1.25, $P = 1.2 \times 10^{-3}$; combined OR = 1.29, $P = 1.0 \times 10^{-8}$). Whereas SNP rs10069690 was genotyped in AABC, it was imputed in TNBCC ($R^2 = 0.55$). To verify the imputed genotypes and the significance of the association in TNBCC, we re-genotyped rs10069690 in available DNA samples from 2,963 TNBCC cases and 1,632 study-specific TNBCC controls (Online Methods). Although the

overlapping samples between the TNBCC GWAS and the re-genotyping study showed that the quality of imputation for rs10069690 in the GWAS was poor (Online Methods), the association with ER-negative breast cancer for rs10069690 remained statistically significant in the larger re-genotyped TNBCC sample (OR = 1.18, $P = 1.0 \times 10^{-3}$; Table 1 and Fig. 1) and in the new combined results for AABC and the re-genotyped TNBCC sample (OR = 1.24, $P = 1.6 \times 10^{-8}$).

To further confirm the association at 5p15, we genotyped SNP rs10069690 in women of European ancestry, which included 8,365 cases (1,359 ER negative) and 10,935 controls from the US National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3) and 6,182 cases (933 ER negative) and 5,966 controls from Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH). Evidence for replication was observed for rs10069690 and ER-negative breast cancer in both studies (BPC3: OR = 1.09, $P = 0.077$; SEARCH: OR = 1.21, $P = 6.9 \times 10^{-4}$; Table 1).

In combining the results across all studies (6,009 ER-negative cases and 20,708 controls with genotype data), rs10069690 was significantly associated with an increased risk of ER-negative breast cancer (OR = 1.18, 95% confidence interval (CI), 1.13–1.25; $P = 1.0 \times 10^{-10}$; Table 1). The risk for heterozygote and homozygote carriers was 1.15 (95% CI, 1.06–1.23) and 1.46 (95% CI, 1.29–1.64), respectively. We observed little evidence of heterogeneity for the reported association for this variant by study or country in AABC (test for heterogeneity, $p_{het} = 0.86$), TNBCC ($p_{het} = 0.85$) or BPC3 ($p_{het} = 0.37$; Supplementary Table 2).

In an analysis of ER-positive cases, rs10069690 was only weakly associated with risk in African Americans (AABC: 1,558 ER-positive cases and 2,743 controls with genotype data, OR = 1.08, $P = 0.10$) and in women of European ancestry (BPC3: 4,890 ER-positive cases and 10,397 controls, OR = 1.03, $P = 0.31$; SEARCH: 3,534 ER positive cases and 5,966 controls, OR = 1.03, $P = 0.37$; combined for all populations: OR = 1.04, $P = 0.06$, $p_{het} = 0.64$). The statistical power to detect an OR of 1.18 (observed for ER-negative disease) for ER-positive disease was >99% in the combined sample (9,982 cases and 19,106 controls), assuming the risk allele frequency of 0.26 in people of European decent. This result suggests that the association with breast cancer might be specific for ER-negative subtypes (P value for case-only test of ER negative versus ER positive = 1.7×10^{-4}).

We further stratified the cases by HER2 status to assess whether this region may be a risk locus for triple-negative disease. In AABC, BPC3 and SEARCH the association with rs10069690 was greater for triple-negative tumors than for ER-negative, PR-negative, HER2-positive tumors (Table 2), and, in combining all studies, including TNBCC, the association with rs10069690 was significantly greater for triple-negative disease (3,707 triple-negative cases and 19,728 controls with genotype data, OR = 1.25, $P = 1.1 \times 10^{-9}$; 376 ER-negative, PR-negative, HER2-positive cases and 18,126 controls, OR = 1.03, $P = 0.71$; P value for case-only test = 0.010). The association with rs10069690 was also observed to be significantly greater for ER-negative and triple-negative disease at younger ages (<50 years: ER negative, OR = 1.32, $P = 1.4 \times 10^{-8}$; triple negative, OR = 1.48, $P = 1.9 \times 10^{-9}$; P for interaction with age = 0.035 and 3.2×10^{-3}, respectively; Supplementary Table 3). We found no significant association with rs1006960 among ER- and PR-positive cases when stratified by HER2 status (513 triple-positive cases and 18,126 controls, OR = 1.09, $P = 0.21$; 2,808 ER-positive, PR-positive, HER2-negative cases and 18,126 controls, OR = 1.04, $P = 0.29$), which suggests the association may be limited to triple-negative disease and not all HER2-negative tumors.

Similar to 8q24 (refs. 5–7) and 11q13 (refs. 8–10), the *TERT-CLPTM1L* locus harbors multiple risk variants for different cancers (reviewed in ref. 11). SNP rs10069690 is modestly correlated (r^2 = 0.13–0.43 in 1000 Genomes Project populations of European and African ancestry, Supplementary Fig. 2) with variants found for serous ovarian cancer (rs7726159), glioma (rs2736100) and lung cancer (rs2736100, rs2735940)[12–14]. Aside from risk variant rs2853676 found for glioma[14], which we found to be associated with risk in TNBCC (P = 0.014, r^2 = 0.05 with rs10069690), none of the known risk variants identified for other cancers in the *TERT-CLPTM1L* region was significantly associated with breast cancer risk in TNBCC or AABC. Although rs7726159 was not tested in AABC or TNBCC (as it is not on the Illumina arrays or in HapMap), it is noteworthy that the first common risk variant identified for ER-negative breast cancer, at chromosome 19p13, is also associated with risk for serous ovarian cancer[15]. The *TERT* gene encodes the catalytic subunit of telomerase, which controls telomere length, a process linked with genomic instability and implicated in tumorigenesis. Sequencing of the coding exons of *TERT* in 96 African-American women (Online Methods) did not reveal a coding variant strongly correlated with rs10069690. The *TERT* locus may highlight another biological process common to the pathogenesis of ER-negative breast cancer subtypes and serous ovarian cancer that is also shared with other cancers.

Identification of the variant directly responsible for the association will be required to fully address the extent to which this locus contributes to the greater incidence of ER-negative and triple-negative tumors in women of African ancestry. However, it is notable that the risk allele frequency of rs10069690 is greater in African American women (frequency, 0.57) than in women of European ancestry (frequency, 0.26). If this variant is an equally good surrogate for the biologically functional allele in each population, then this locus may be responsible for a 15% (95% CI, 10–20%) higher incidence rate of ER-negative or triple-negative breast cancer in women of African compared to European ancestry (Online Methods). Larger studies with well-characterized tumor pathology information will be needed to determine whether the association we observed applies to all ER-negative disease or just the triple-negative subtype. Our findings provide further support for the presence of genetic susceptibility to ER-negative breast cancer subtypes and demonstrate the importance of discovery efforts in multiple populations.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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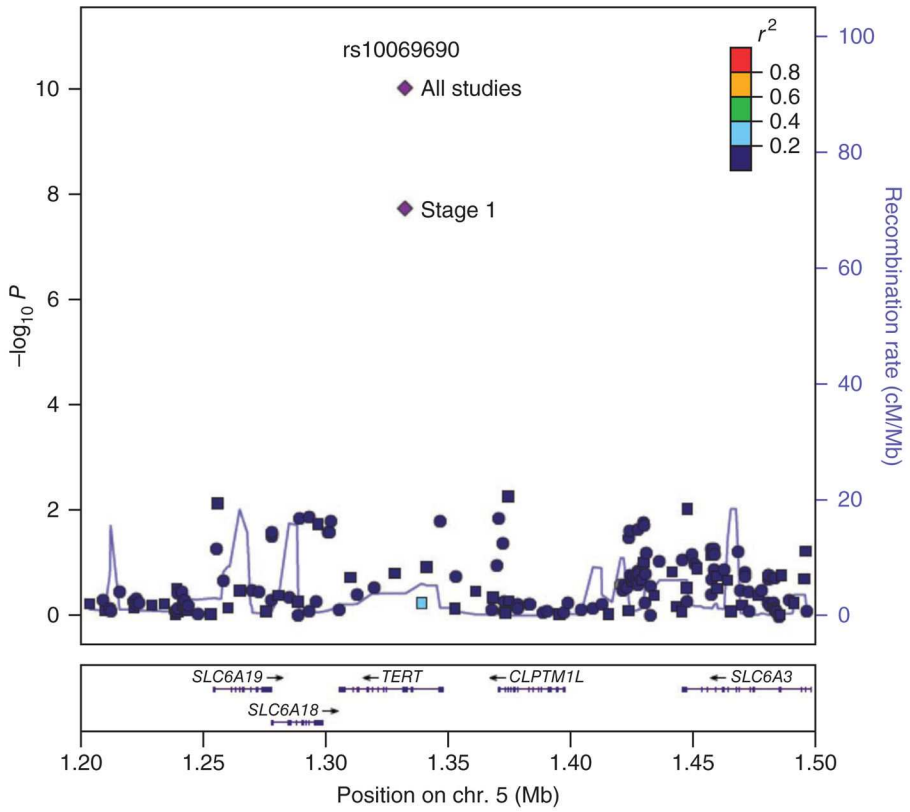

Figure 1.

A regional plot of the $-\log_{10} P$ values for SNPs at the chromosome 5p15 risk locus from the meta-analysis of the AABC and TNBCC stage 1 studies. SNP rs10069690 is designated with the purple diamonds. The colors depict the strength of the correlation (r^2) between SNP rs10069690 and the SNPs tested in the region. The correlation is estimated using 1000 Genomes Project (1KGP) data for the HapMap CEU population (June 2010). Squares are SNPs that were genotyped in AABC and TNBCC. Circles are SNPs that were genotyped in one study and imputed in the other or imputed in both studies. The blue line indicates the recombination rates in centimorgans (cM) per megabase (Mb). Also shown are the SNP Build 36 coordinates and genes in the region.

Table 1

Association of rs10069690 at 5p15 and ER-negative breast cancer risk

Stage	Consortium or study	Cases/controls[a]	RAF[b] T allele	Heterozygotes OR (95% CI)[c]	Homozygotes OR (95% CI)[c]	Per-allele OR (95% CI)[c]	*P* value (1-d.f.)[d]
1	AABC	1,002/2,743	0.57	1.32 (1.05–1.67)	1.74 (1.37–2.21)	1.32 (1.18–1.48)	1.3×10^{-6}
1	TNBCC	2,785/1,602	0.27	1.10 (0.97–1.26)	1.53 (1.21–1.95)	1.18 (1.07–1.30)	1.0×10^{-3}
2	BPC3	1,289/10,397	0.26	1.08 (0.96–1.22)	1.19 (0.95–1.49)	1.09 (0.99–1.19)	0.077
2	SEARCH	933/5,966	0.26	1.23 (1.06–1.43)	1.44 (1.10–1.89)	1.21 (1.09–1.36)	6.9×10^{-4}
Combined		6,009/20,708		1.15 (1.06–1.23)	1.46 (1.29–1.64)	1.18 (1.13–1.25)	1.0×10^{-10}

[a] Number of cases and controls with genotype data for rs10069690. All subjects were directly genotyped.

[b] Risk allele frequency (RAF) in controls.

[c] Adjusted for age, study and principal components in AABC. Adjusted for age and country in TNBCC. Adjusted for age, study and country (European Prospective Investigation into Cancer and Nutrition (EPIC) only) in BPC3. Adjusted for age in SEARCH. Combined results are from the meta-analysis.

[d] *P* for trend (one degree of freedom (1-d.f.)).

Table 2

Association of rs10069690 at 5p15 stratified by Her2 status

Consortium or study	Subtype	Cases/controls[a]	Heterozygotes OR (95% CI)[b]	Homozygotes OR (95% CI)[b]	Per-allele OR (95% CI)[b]	*P* value (1-d.f.)[c]	Case-only *P*
AABC[d]	$ER^-PR^-HER2^-$	440/2,407	1.35 (0.97–1.89)	1.78 (1.27–2.49)	1.33 (1.14–1.55)	3.0×10^{-4}	0.19
	$ER^-PR^-HER2^+$	115/2,407	1.83 (0.99–3.40)	1.59 (0.82–3.05)	1.15 (0.86–1.52)	0.34	
TNBCC	$ER^-PR^-HER2^-$	2,785/1,602	1.10 (0.97–1.26)	1.53 (1.21–1.95)	1.18 (1.07–1.30)	1.0×10^{-3}	–
BPC3[e]	$ER^-PR^-HER2^-$	300/9,753	1.19 (0.93–1.52)	1.64 (1.10–2.46)	1.25 (1.04–1.49)	0.015	0.13
	$ER^-PR^-HER2^+$	198/9,753	0.99 (0.73–1.33)	0.95 (0.53–1.70)	0.98 (0.78–1.23)	0.87	
SEARCH	$ER^-PR^-HER2^-$	182/5,966	1.42 (1.03–1.95)	2.41 (1.47–3.95)	1.51 (1.20–1.89)	4.2×10^{-4}	0.058
	$ER^-PR^-HER2^+$	63/5,966	1.31 (0.79–2.16)	0.27 (0.04–1.95)	0.97 (0.64–1.46)	0.88	
Combined	$ER^-PR^-HER2^-$	3,707/19,728[f]	1.17 (1.06–1.30)	1.69 (1.43–1.99)	1.25 (1.16–1.34)	1.1×10^{-9}	0.010
	$ER^-PR^-HER2^+$	376/18,126	1.15 (0.91–1.46)	1.11 (0.73–1.70)	1.03 (0.88–1.21)	0.71	

[a] Number of cases and controls with genotype data for rs10069690. All subjects were directly genotyped.

[b] Adjusted for age, study and principal components in AABC. Adjusted for age and country in TNBCC. Adjusted for age, study and country (EPIC only) in BPC3. Adjusted for age in SEARCH. Combined results are from the meta-analysis.

[c] P for trend (1-d.f.).

[d] Excludes San Francisco Bay Area Breast Cancer Study (SFBCS) and Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), as HER2 data were not available.

[e] Excludes WHS, as HER2 data were not available.

[f] Includes TNBCC. Without TNBCC: 922 $ER^-PR^-HER2^-$ cases and 18,126 controls; OR per allele = 1.33 (1.20–1.48), $P = 6.3 \times 10^{-8}$; heterozygotes: OR = 1.29 (1.09–1.53); homozygotes: OR = 1.85 (1.47–2.33).