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# Genetic variations in the Hippo signaling pathway and breast cancer risk in African American women in the AMBER Consortium

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## Abstract

The Hippo signaling pathway regulates cellular proliferation and survival, thus exerting profound effects on normal cell fate and tumorigenesis. Dysfunction of the Hippo pathway components has been linked with breast cancer stem cell regulation, as well as breast tumor progression and metastasis. TAZ, a key component of the Hippo pathway, is highly expressed in triple negative breast cancer; however, the associations of genetic variations in this important pathway with breast cancer risk remain largely unexplored. Here, we analyzed 8309 germline variants in 15 genes from the Hippo pathway with a total of 3663 cases and 4687 controls from the African American Breast Cancer Epidemiology and Risk Consortium. Odds ratios (ORs) were estimated using logistic regression for overall breast cancer, by estrogen receptor (ER) status (1983 ER positive and 1098 ER negative), and for case-only analyses by ER status. The Hippo signaling pathway was significantly associated with ER-negative breast cancer (pathway level $P = 0.02$). Gene-based analyses revealed that *CDH1* was responsible for the pathway association ($P < 0.01$), with rs4783673 in *CDH1* statistically significant after gene-level adjustment for multiple comparisons ($P = 9.2 \times 10^{-5}$, corrected $P = 0.02$). rs142697907 in *PTPN14* was associated with ER-positive breast cancer and rs2456773 in *CDK1* with ER-negativity in case-only analysis after gene-level correction for multiple comparisons (corrected $P < 0.05$). In conclusion, common genetic variations in the Hippo signaling pathway may contribute to both ER-negative and ER+ breast cancer risk in AA women.

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**Abbreviations**

| | |
|---|---|
| AA | African-American |
| ER | estrogen receptor |

## Introduction

Functional screens in *Drosophila* identified the Hippo signaling pathway, which regulates organ size by modulating cell growth, proliferation and apoptosis (1–3). The majority of the Hippo pathway components are highly conserved from *Drosophila* to mammalian species, and dysregulation of this pathway is widely observed in cancer (4–6). The core of this pathway in mammals is composed of a kinase cascade wherein the STE20-like kinase 1/2 (MST1/2), in complex with its regulatory protein salvador 1 (SAV1), phosphorylates and activates large tumor suppressor kinase 1/2 (LATS1/2) in complex with its regulatory protein MOB kinase activator 1A (MOB1A). This in turn phosphorylates and inactivates the transcriptional co-activators, yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ). When YAP/TAZ translocate to the nucleus, they induce expression of cell-proliferative and anti-apoptotic genes, mainly through interactions with transcription factors, such as: TEA domain family members (TEADs) (3). In recent years, knowledge of the complexity of YAP/TAZ regulation has expanded considerably. The G protein-coupled receptors (GPCRs) and the cytokine receptor leukemia inhibitory factor receptor (LIFR) are associated with the activation of LATS kinases (7,8). In addition, YAP/TAZ are also directly regulated by the extracellular matrix (9), mechanotransduction (10,11), actin cytoskeleton and Rho GTPases (11,12).

We and others have previous shown that TAZ is overexpressed in breast cancers, especially in triple negative breast cancer (13–15). The expression levels and activity of TAZ are frequently upregulated in high-grade metastatic breast cancer (16–18). Activation of YAP induces epithelial to mesenchymal transition and promotes breast tumor metastasis (19,20). Both YAP and TAZ have been shown to be involved in breast cancer stem cell regulation (16,17,21,22) and mediated drug resistance in breast cancer (19,23). In addition, it has been demonstrated that hypermethylation of the promoter regions of LATS1/2 occurred in breast cancers and the decreased expression of LATS1/2 was significantly associated with large tumor size and high lymph node metastasis (24).

Epidemiological studies indicate that African-American (AA) women are more likely to be diagnosed with more aggressive breast cancer, including estrogen receptor (ER)-negative and TN breast cancer, and have higher cancer mortality than European American (EA) women (25–27). Although the mechanisms underlying these disparities are largely unknown, emerging evidence supports that cancer biology may be different across patients of different ancestral background (25,28). Considering the critical role of Hippo signaling pathway played in triple-negative breast cancer, we hypothesize that this pathway may contribute in part to the biological difference in breast cancer between AA and EA women. The *African American Breast Cancer Epidemiology and Risk* (AMBER) Consortium was established to investigate potential genetic and non-genetic risk factors for aggressive breast cancer in AA women. Here, we comprehensively examined genetic variations in Hippo signaling pathway with breast cancer risk in this large AA breast cancer consortium.

## Study population and methods

The AMBER consortium is a large collaborative effort to aggregate an adequate sample size to study epidemiology of breast cancer subtypes in AA women. Established in 2011, the consortium consists of two case-control studies, the Women's Circle of Health Study (WCHS) and the Carolina Breast Cancer Study (CBCS), and two prospective cohort studies, the Black Women's Health Study (BWHS) and the Multiethnic Cohort (MEC). A detailed description of the consortium and the four contributing studies can be found elsewhere (29–34).

The WCHS is a case-control study enrolling women aged 25–75 with invasive breast cancer and ductal carcinoma *in situ* (DCIS), initially in New York City (NYC) and New Jersey (NJ), and later exclusively in NJ (31,32). Cases were ascertained in NYC hospitals with large referral patterns of AAs and through the NJ State Cancer Registry. Controls frequency matched on state, race and age were identified through random digital dialing and community events. The CBCS is a population-based case–control study in North Carolina beginning in 1993 (30). Breast cancer patients aged 20–74 were identified through the NC State Cancer Registry, and controls were enrolled through Division of Motor Vehicle lists and Health Care Finance Administration lists.

The BWHS is a prospective study of 59 000 AA women across the USA who were 21–69 years of age at the study entry in 1995 and have been followed by biennial questionnaire since that time (33). Women diagnosed with breast cancer are identified by self-report in follow-up questionnaires, and confirmed by medical records, state cancer registries, and the National Death Index. The MEC is a multiethnic prospective cohort in Hawaii and southern California with follow-up of 215 000 men and women aged 45–75 at the time of study entry (1993–1996) (34). Breast cancer diagnoses identified through linkage to state cancer registries. Controls for the BWHS and MEC were AA participants who had not been diagnosed with breast cancer.

All study participants provided informed consent, and the study was approved by Institutional Review Boards at participating institutions. Estrogen receptor (ER) status information was obtained from pathology reports and/or Cancer Registry Data. The study population included in the genotype study has been previously described in detail (35). A brief summary of the number of cases and controls from each contributing study included in this analysis, with index age and ER status (for cases) is provided in Supplementary Table 1, available at *Carcinogenesis* Online.

### Genetic marker selection, genotyping, quality control and imputation

Genes from select candidate pathways of interest were identified by querying the Molecular Signature Database (MSigDB) (36) and tagSNPs from each gene were chosen using criteria of $r^2 \geq 0.8$ and minor allele frequency ≥ 10% in the Yoruban (YRI) population from the 1000 Genome Project (37). These SNPs were added as part of the custom content to the Illumina Human Exome Beadchip v1.1 and samples from BWHS, CBCS and WCHS were genotyped by the Center for Inherited Disease Research (CIDR), followed by stringent sample and marker QC steps (38). Imputation to the 1000 Genomes data using the IMPUTE2 program (39) was performed by the University of Washington (UW). MEC samples had been genotyped previously using the Illumina 1M-Duo chip and also imputed to the 1000 Genomes data. The imputed MEC data were pooled with those from the BWHS, CBCS and WCHS to create a final analytical dataset. Markers with mismatching alleles or allele frequencies that were different by > 0.15 between MEC and the other three studies, and markers with MAF < 0.6% or imputation info score < 0.5 in either study were excluded. For the present analysis of the Hippo signaling pathway, a total of 7017 variants in 14 genes belonging to this pathway were included (Table 2).

### Statistical analysis

To control for potential admixture bias, principal component analysis was conducted using the *smartpca* program in the EIGENSOFT package (40) to infer population structure. Paired sample relatedness was assessed by PLINK (41). As a result, 35 individual outliers in principal component analysis and 162 first-degree relatives identified were flagged for sensitivity analysis. No substantial changes in risk estimates were found after excluding these individuals and they were thus kept in the analysis. Ten PCs were tested for association with case–control status while controlling for covariates, including index age, study, geographic region and DNA source. Although none was significantly associated with breast cancer risk, to be conservative, three PCs with a $P < 0.10$ were included in the logistic regression models.

In addition to analyzing overall breast cancer risk, stratified analyses were conducted by ER status compared to controls, as well as case-only analyses comparing ER– to ER+ cases. Three levels of analyses of genetic variations were performed: pathway level, gene level and single marker level, under the hypothesis that aggregating the effects of multiple markers within a gene or a biological pathway might be more statistically powerful and less prone to multiple testing bias than single marker analysis. Pathway- and gene-level analyses were performed first, using the adaptive rank truncated product (ARTP) statistic (42), which can optimize the number of single marker *P* values combined in each gene-level and pathway-level test. For pathway-level analysis, the PIGE software implementation of the ARTP method takes gene-level information into consideration when combining markers in a pathway (https://cran.r-project.org/web/packages/PIGE/index.html). To avoid redundancy of markers in high LD ($r^2 \geq 0.8$), the ARTP gene-level tests combined the optimal number of most significant SNP *P* values from among the top 10 pruned-in SNPs for each gene. This number was deliberately chosen to ensure adequate representation of genetic variations in each gene, while not to include too many null variants to dilute the effects of truly causal markers. The ARTP pathway tests combined the optimal percentage (in 5% increments) of the most significant gene *P* values in each pathway, without exceeding 50%. This approach was chosen to ensure excellent representation of associated genetic variants, while not diluting any effects from truly causal markers by including too many null markers in the analysis. Following gene-level testing, single marker-level analyses were pursued using PLINK with dosage data and controlling for age, study, geographic region, DNA source and three top PCs. We corrected for multiple testing within these genes with a Bonferroni correction for the effective number of independent markers tested within a gene using Gao's SimpleM approach (43), and called this the 'gene-wide' significance. Single marker associations for top genes were plotted with linkage disequilibrium data using the LocusZoom program (44).

## Results

As shown in Table 1, the Hippo pathway was significantly associated with ER-negative breast cancer risk (pathway level $P = 0.02$), likely attributable to *CDH1* (gene level $P = 0.004$). When CDH1 gene was removed from the analysis, the pathway-level significance become non-significant ($P = 0.63$). The pathway was not associated with risk of overall cancer or ER-positive cancer, or with ER status in case-only analyses (pathway level $P > 0.05$). In analysis of genes and breast cancer risk, *CDH1* was nominally associated with overall breast cancer risk ($P = 0.02$); and *CDK1* was nominally associated with ER negative disease in case-only analysis ($P = 0.01$).

Figure 1 displays the single variant associations of *CDH1* with ER-negative breast cancer risk. The best signal locus was an intronic SNP, rs4783673. The T allele was associated with 19% reduced risk of ER-negative breast cancer (OR = 0.81, 95% CI 0.73, 0.90, $P = 9.2E{-}5$), which remained significant after correction for multiple testing at the gene level (corrected $P = 0.02$) (Table 2). When this SNP was removed, *CDH1* remained significant at the gene level ($P = 0.005$) but the Hippo pathway was no longer significant ($P = 0.13$). Although *CDH1* was also associated with overall breast cancer risk at the gene level, no individual variants in the gene were significantly associated with overall breast cancer after correction for multiple testing (data not shown). The most significant SNP in *CDH1* for overall breast cancer was rs4783673, the T allele of which was associated with a 12% reduced risk at a borderline significance level (OR = 0.88, 95% CI, 0.82, 0.94, $P = 2E{-}4$, corrected $P = 0.06$). This was the same variant identified above with ER-negative breast cancer, and thus the association with overall breast cancer risk was likely driven by this subtype.

No gene in the Hippo pathway was associated with ER-positive breast cancer at the gene level (Table 1). However, an intronic SNP rs142697907 in *PTPN14* was significant at the single marker-level after within gene adjustment for multiple testing. The A allele was associated with a 75% increased risk of

**Table 1.** *P* values of pathway- and gene-level test with breast cancer risk (*P* values lower than 0.05 is in bold)

| Gene | # Total marker | # Effective marker | Overall | ER+ | ER– | ER– versus ER+ |
|---|---|---|---|---|---|---|
| Hippo pathway | 7017 | 2244 | 0.36 | 0.83 | **0.02** | 0.24 |
| *AREG* | 666 | 186 | 0.45 | 0.89 | 0.29 | 0.41 |
| *CDH1* | 666 | 269 | **0.02** | 0.08 | **0.004** | 0.50 |
| *CDK1* | 195 | 74 | 0.73 | 0.65 | 0.09 | **0.01** |
| *CTGF* | 26 | 12 | 0.76 | 0.58 | 0.91 | 0.80 |
| *CTNNA1* | 939 | 149 | 0.72 | 0.99 | 0.97 | 0.96 |
| *CTNNB1* | 138 | 56 | 0.32 | 0.69 | 0.59 | 0.53 |
| *DLG5* | 714 | 166 | 0.63 | 0.64 | 0.64 | 0.75 |
| *FAT1* | 976 | 455 | 0.83 | 0.35 | 0.97 | 0.48 |
| *PTPN14* | 1151 | 384 | 0.29 | 0.21 | 0.09 | 0.20 |
| *RASSF1* | 53 | 32 | 0.76 | 0.57 | 0.99 | 0.41 |
| *SIAH1* | 10 | 7 | 0.35 | 0.22 | 0.14 | 0.21 |
| *STK4* | 586 | 113 | 0.96 | 0.96 | 0.79 | 0.22 |
| *TEAD4* | 430 | 188 | 0.27 | 0.52 | 0.41 | 0.69 |
| *WWTR1* | 467 | 153 | 0.73 | 0.33 | 0.54 | 0.07 |

ER-positive cancer (OR = 1.75, 95% CI 1.33, 2.30, *P* = 7.4E–5, corrected *P* = 0.03).

A 3′ UTR SNP, rs2456773 in *CDK1* was likely the variant driving the association of CDK with ER status in case-only analysis. The C allele was associated with 25% increased odds of ER-negative versus ER-positive cancer (OR = 1.25, 95% CI 1.11, 1.42, *P* = 3.2E–4, corrected *P* = 0.02) (Table 2). A second nearby 3′ UTR SNP, rs10711 in perfect LD with rs2456773 ($r^2$ = 1.0), was also associated with ER status. In case-control analyses performed separately by ER status, rs2456773 was only associated with ER-negative cancer (OR = 1.20, 95% CI 1.06, 1.34, *P* = 0.003), but not with ER-positive cancer (OR = 0.96, 95% CI 0.88, 1.06, *P* = 0.42).

## Discussion

Here, we report findings of a comprehensive analysis of germline variations in the Hippo signaling pathway with breast cancer risk and by tumor ER status. The unique strengths of the study include a large population of AA women with breast cancer and controls and a systematic interrogation of common genetic variations in all available genes in this pathway. We found evidence of the overall Hippo pathway being associated with ER-negative breast cancer risk, which may be attributed to *CDH1*. Our finding corroborates that from laboratory studies linking the Hippo pathway with ER-negative and triple-negative breast cancer.

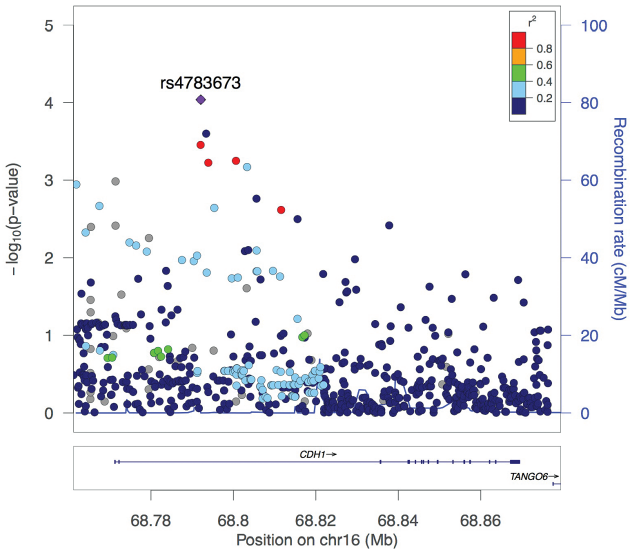


**Figure 1.** The single variant associations of *CDH1* with ER-negative breast cancer risk. Plots of log-transformed *P* values from single marker analysis for top genes in each subgroup test were generated using the LocusZoom program. The labeled marker in the plots were the most significant SNP (index SNP) in each gene, and the LD between the each of other markers in the gene and the index SNP was color coded, with red color indicating strong LD ($r^2$ > 0.8) and blue color indicating weak LD ($r^2$ < 0.2). Genotyped SNPs were indicated by closed dots and imputed SNPs were indicated by closed squares.

*CDH1* encodes a classical member of the cadherin family, which plays an important role in maintaining the epithelial integrity. Down regulation of CDH1 has been considered as one of the main molecular alterations for tumor invasion and metastasis (45). Complete E-cadherin loss has been reported in 86% to 100% of invasive lobular breast cancer (46). Interestingly, E-cadherin reduction has been found in triple negative breast cancer patients with lymph node metastasis (47,48). Given the well established role of somatic changes in CDH1 in cancer invasion and metastasis, a number of studies have investigated the associations of *CDH1* germline variants with risk of various human cancers. A meta-analysis concluded that one SNP in the promoter region, rs16260 (-160 C>A), was associated with increased risk of all cancers, but not with breast cancer in stratified analyses by cancer type (49). In our AA population, we did not find any association of rs16260 with breast cancer risk.

We also found a low frequency variant in *PTPN14* associated with 75% increased risk of ER-positive breast cancer risk. *PTPN14* encodes a member of the protein tyrosine phosphatase, which has been shown to mediate the dephosphorylation of tyrosine residues in some adherens junction proteins such as β-catenin (50). In addition, it was reported that PTPN14 suppressed metastasis by reducing the intracellular protein trafficking through the secretory pathway (51). We and other have previously demonstrated that PTPN14 negatively regulated YAP oncogenic function through direct interaction with YAP (52) and activation of LATS1/2 proteins (53). Interestingly, PTPN14 loss-of-function and deleterious missense mutations were found in skin cancer (54). To our knowledge, there is no published study of germline variants in *PTPN14* with cancer risk. It should be noted, however, that the variant we identified with ER-positive breast cancer had a low frequency of 0.02 and was imputed with a moderate info score of 0.83. Thus, the result should be interpreted with caution because of possible imputation inaccuracy. Nevertheless, given the growing research interest in PTPN14 in cancer, our data may provide support for further study of variants in this gene in breast cancer.

To explore whether the significant gene we identified in AA women were also associated with breast cancer in EA women, we queried all available variants in *CDH1* using publicly available data from the GAME-ON GWAS look up tool. The T allele of rs4783673 in *CDH1* was associated with slightly decreased risk of ER-negative breast cancer in an EA population (*P* = 0.07), which is consistent with our finding of this SNP in AA women. However, none of the variants in this gene was associated with overall or ER-negative breast cancer risk after correcting for multiple comparisons. The low replication rate of significant genetic variants from EA to AA populations and vice versa is not unexpected, as observed in previous studies from us and others (35,55,56). This low replication rate may be due to distinct differences in genetic architecture between the two populations.

Several limitations should be noted in our study. Although we included a large number of genes and variants in the analysis,

**Table 2.** Top variants associated with breast cancer risk after gene-wide correction for multiple test (*P* ≤ 0.05)

| SNP | Gene | A1/A2 | Function | A1 frequency | Info score | OR (95% CI) | P | Corrected P |
|---|---|---|---|---|---|---|---|---|
| ER-positive breast cancer | | | | | | | | |
| rs142697907 | *PTPN14* | A/G | Intronic | 0.02 | 0.83 | 1.75 (1.33–2.30) | 7.42E–05 | 0.03 |
| ER-negative breast cancer | | | | | | | | |
| rs4783673 | *CDH1* | T/C | Intronic | 0.65 | 0.99 | 0.81 (0.73–0.90) | 9.21E–05 | 0.02 |
| ER-negative versus ER-positive breast cancer | | | | | | | | |
| rs2456773 | *CDK1* | C/G | 3′ UTR | 0.25 | 0.98 | 1.25 (1.11–1.42) | 3.22E–04 | 0.02 |

several genes in the core Hippo signaling pathway, such as LAST1/2 and YAP1, were not included as candidates for tagSNP selection in development of the chip. Although SNPs in exonic regions of these genes were typed as the standard content in the exome chip array, variants in other regions of these genes were not typed. As a result, the marker density of these genes was much lower and was biased to exons, making imputed data from non-exonic regions more error-prone compared to genes selected as candidates in the genotyping process. Thus, we did not included Hippo pathway genes with only exonic SNPs typed in the analysis, and future studies with better coverage of the pathway are warranted. Another limitation of our study came from the lack of complete information on all immunohistochemical markers needed to classify triple-negative or basal-like breast cancer subtype. Given the emerging evidence from laboratory studies linking the Hippo pathway with triple negative breast cancer, it would be interesting to analyze genetic variants in this pathway with this subtype. In the AMBER consortium, central staining and defining of breast cancer subtypes is ongoing, and follow up analysis will be conducted when such data become available. Lastly, the lack of functionality of the identified SNPs is a typical limitation of SNP association studies, including ours. However, the identified associations provide clues for future experimental studies to characterize the functional impact of those genetic variations.

To conclude, in the first large study of common genetic variants in the Hippo signaling pathway with breast cancer risk in AA women, we found that this pathway was specifically associated with ER-negative breast cancer risk. Considering that AA women are at higher risk of ER-negative cancer than European American women, further studies are needed to assess whether the Hippo pathway may be a part of the biological differences underlying breast cancer disparities.

## Supplementary material

Supplementary Table 1 can be found at http://carcin.oxfordjournals.org/

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