

Short Communication

Common Genetic Variation at *PTEN* and Risk of Sporadic Breast and Prostate Cancer

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Abstract

PTEN frequently shows loss of heterozygosity in breast and prostate cancers, and mutations in this gene are responsible for Cowden disease, a rare Mendelian syndrome that includes breast cancer as part of its phenotype. Thus, *PTEN* serves as a candidate susceptibility gene for both breast and prostate cancer risk. Whether common inherited variation (either coding or noncoding) at the *PTEN* locus contribute to nonfamilial, sporadic breast and prostate cancer risk is not known. In this study, we employed a linkage disequilibrium–based approach to test for association between common genetic variation at the *PTEN* locus and breast and prostate cancer risk in African-American, Native Hawaiian, Japanese, Latina, and White men and women in the Multiethnic Cohort Study. We genotyped 17 common single nucleotide polymorphisms (SNP; $\geq 5\%$ frequency in at least one ethnic group) spanning the *PTEN* gene to define the common alleles in these populations.

These SNPs were in strong linkage disequilibrium, indicating that our survey captured most of the common sequence variation across this locus. Eight tagging SNPs were selected to predict the common *PTEN* haplotypes (≥ 0.05 frequency) in these populations (two additional tagging SNPs were required for African Americans). These SNPs were evaluated in a breast cancer case-control study (cases, $n = 1,615$; controls, $n = 1,962$) and prostate cancer case-control study (cases, $n = 2,320$; controls, $n = 2,290$) nested within the Multiethnic Cohort Study. Multiple testing was explicitly accounted for by applying a permutation-based framework. We found no strong association with any common haplotype in relation to breast or prostate cancer risk. In summary, our results show that common variants in *PTEN* do not substantially influence risk of these two common cancers. (Cancer Epidemiol Biomarkers Prev 2006;15(5):1021–5)

Introduction

PTEN (phosphatase and tensin homologue) encodes a dual-specificity protein phosphatase that negatively regulates phosphatidylinositol 3-kinase/AKT signaling, a pathway with an established role in promoting cell cycle progression and survival (1). Loss of *PTEN* protein expression in breast carcinomas has been associated with histologic features related to poor prognosis (2, 3). A large fraction of advanced prostate cancers also show loss of heterozygosity and reduced *PTEN* expression (4, 5).

Rare, germ line mutations in *PTEN* have been identified and result in Cowden disease, which is characterized by benign hamartomatous lesions and a 25% to 50% lifetime risk of developing breast cancer. Patients are also at risk for thyroid (and perhaps other) cancers (6). Twenty to 40% of Cowden's disease families with linkage to the region containing *PTEN* at 10q23 do not have an identifiable mutation in *PTEN* (7),

suggesting that variants in the promoter or other noncoding regions of *PTEN* may be biologically relevant (8).

In the broader context of the nonfamilial (sporadic) form of breast and prostate cancers, the relevance of common variants (both coding and noncoding) in *PTEN* to cancer risk is largely unknown (9–11). In the present study, we defined and tested the ancestral haplotype patterns at the *PTEN* locus in large multiethnic case-control studies of breast and prostate cancer to comprehensively assess the role of common genetic variation in this gene in relation to risk of these common cancers.

Materials and Methods

The Multiethnic Cohort. The Multiethnic Cohort Study (MEC) consists of >215,000 men and women in Hawaii and Los Angeles (with additional African Americans from elsewhere in California) and has been described in detail elsewhere (12). In brief, the cohort comprised a general population sample of African Americans, Native Hawaiians, Japanese, Latinos, and Whites who entered the MEC between 1993 and 1996, by completing a 26-page self-administered questionnaire that asked detailed information about dietary habits, demographic factors, personal behaviors, history of prior medical conditions, family history of common cancers, and for women, reproductive history and exogenous hormone use. The participants were between the ages 45 and 75 years at enrollment.

Incident cancers in the MEC are identified by cohort linkage to population-based cancer Surveillance, Epidemiology, and

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Table 1. Associations between *PTEN* haplotypes and breast cancer risk

SNP no.	rs1234212	rs11202586*	rs1234221*	rs1903860*	rs1234220*	rs1234219*	rs1903858	rs2299939*	rs1234224*	rs1234223	rs1234213	rs2673832*
	1	2	3	4	5	6	7	8	9	10	11	12
Haplotypes												
1	C	T	A	T	A	A	A	A	A	G	G	G
2	C	T	C	T	A	A	A	C	A	G	G	G
3	C	T	A	T	A	A	A	C	A	G	G	G
4	C	T	A	T	A	A	A	C	A	G	G	G
5	C	T	A	T	A	A	G	C	A	G	G	C
6	T	C	A	C	A	A	G	C	G	G	A	C
7	T	C	A	T	A	A	G	C	G	G	A	C
8	T	T	A	T	G	G	G	C	G	C	A	C
9	T	T	A	T	A	A	G	C	G	G	A	C

Abbreviations: AA, African Americans; NH, Native Hawaiians; JA, Japanese; LA, Latinas; WH, Whites.

*Tagging SNPs.

†Haplotypes frequencies estimated among cases and controls using tagging SNPs.

‡ORs estimated using unconditional logistic regression adjusted for age and ethnicity. Noncarriers of each haplotype constitute the reference group.

§OR estimated among African Americans.

End Results registries covering Hawaii and Los Angeles County and to the California State cancer registry covering all of California. Information on stage and grade of disease at the time of diagnosis is also collected from the cancer registries. Women diagnosed with regional or metastatic disease were classified as having advanced breast cancer. For prostate cancer, advanced disease was defined as regional or metastatic disease or localized disease with a Gleason score of >7.

Beginning in 1994, blood samples were collected from incident breast and prostate cancer cases and a random sample of MEC participants to serve as a control pool for genetic analyses in the cohort. The participation rates for providing a blood sample were 74% and 66% for cases and controls, respectively. Eligible cases in these nested case-control studies consisted of women with incident breast cancer or men with incident prostate cancer diagnosed after enrollment in the MEC through May 31, 2002. Controls were participants without breast or prostate cancer, respectively, before entry into the cohort and without a diagnosis up to May 31, 2002. The breast cancer case-control study consists of 1,615 invasive breast cancer cases and 1,962 controls, whereas the prostate cancer case-control study consists of 2,320 invasive prostate cancer cases and 2,290 controls. This study was approved by the Institutional Review Boards at the University of Southern California and at the University of Hawaii.

Characterizing Linkage Disequilibrium and Haplotype Patterns. In this study, we implemented a haplotype-based approach to comprehensively examine common genetic

variation throughout the *PTEN* gene as described in detail previously (13, 14). We initially surveyed common genetic variation across 146.5 kb of the *PTEN* gene, using markers from the public single nucleotide polymorphism (SNP) map. Our goals were to capture the common haplotypes patterns across the *PTEN* locus. To do this, we genotyped 17 common SNPs across the locus (frequency of $\geq 5\%$ in at least one ethnic group) selected from the National Center of Biotechnology Information SNP database (<http://www.ncbi.nlm.nih.gov/SNP/>). SNPs were genotyped in a multiethnic panel of 349 women in the MEC without a history of cancer ($n = 69-70$ per ethnic group). This sample size guaranteed that any haplotype with a frequency of $\geq 5\%$ will be represented at least once among the 140 chromosomes with a probability of >99%.

The $|D'|$ and r^2 statistics were used to assess pairwise linkage disequilibrium between SNPs as described (14). Linkage disequilibrium block structure was examined using the 90% confidence bounds of D' to define sites of historical recombination between SNPs with minor allele frequencies of $\geq 10\%$ (15).

Haplotype Construction and Tagging SNP Selection. Haplotype frequency estimates were constructed from the genotype data in the multiethnic panel (one ethnicity at a time) within linkage disequilibrium blocks using the expectation-maximization algorithm of Excoffier and Slatkin (16). The squared correlation (R_i^2) between the true haplotypes (h) and their estimates were then calculated as described (17). Haplotype-tagging SNPs for the case-control study were then

Table 2. Associations between *PTEN* haplotypes and prostate cancer risk

SNP no.	rs1234212	rs11202586*	rs1234221*	rs1903860*	rs1234220*	rs1234219*	rs1903858	rs2299939*	rs1234224*	rs1234223	rs1234213	rs2735343*
	1	2	3	4	5	6	7	8	9	10	11	12
Haplotypes												
1	C	T	A	T	A	A	A	A	A	G	G	G
2	C	T	C	T	A	A	A	C	A	G	G	G
3	C	T	A	T	A	A	A	C	A	G	G	G
4	C	T	A	T	A	A	A	C	A	G	G	G
5	C	T	A	T	A	A	G	C	A	G	G	C
6	T	C	A	C	A	A	G	C	G	G	A	C
7	T	C	A	T	A	A	G	C	G	G	A	C
8	T	T	A	T	G	G	G	C	G	C	A	C
9	T	T	A	T	A	A	G	C	G	G	A	C

Abbreviations: AA, African Americans; NH, Native Hawaiians; JA, Japanese; LA, Latinas; WH, Whites.

*Tagging SNPs.

†Haplotypes frequencies estimated among cases and controls using tagging SNPs.

‡ORs estimated using unconditional logistic regression adjusted for age and ethnicity. Noncarriers of each haplotype constitute the reference group.

§OR estimated among African Americans.

Table 1. Associations between *PTEN* haplotypes and breast cancer risk (Cont'd)

rs2735343*	rs926091	rs532678	rs701848*	rs478839	Haplotype frequencies [†] (cases/controls)					OR (95% CI) [‡] , heterozygous vs homozygous	OR (95% CI) [‡] , rare homozygous vs homozygous
13	14	15	16	17	AA (n = 345/426)	NH (n = 109/290)	JA (n = 425/420)	LA (n = 335/386)	WH (n = 401/440)		
A	C	C	C	G	0.05/0.05	0.13/0.12	0.18/0.20	0.20/0.24	0.19/0.20	0.88 (0.75-1.03)	0.96 (0.65-1.43)
A	C	C	C	G	0.04/0.05	0.39/0.43	0.24/0.23	0.17/0.12	0.18/0.22	0.97 (0.83-1.13)	1.08 (0.77-1.51)
A	C	C	T	A	0.34/0.34	0.08/0.06	0.05/0.05	0.10/0.09	0.16/0.14	1.10 (0.93-1.31)	1.04 (0.70-1.55)
G	C	C	T	A				0.06/0.08	0.09/0.10	0.79 (0.61-1.02)	1.08 (0.22-5.39)
A	C	T	T	A	0.05/0.05					1.05 (0.65-1.71) [§]	
A	T	T	T	A	0.08/0.08	0.22/0.21	0.34/0.34	0.19/0.19	0.14/0.13	1.04 (0.90-1.22)	0.98 (0.69-1.40)
A	C	T	T	A	0.07/0.05				0.06/0.06	1.12 (0.86-1.47)	0.84 (0.12-5.95)
A	C	T	T	A		0.07/0.07	0.09/0.09	0.14/0.16	0.07/0.05	0.87 (0.71-1.05)	2.82 (1.26-6.33)
A	C	T	T	A	0.20/0.22			0.05/0.05	0.05/0.06	0.98 (0.79-1.23)	0.65 (0.35-1.23)

chosen by finding the minimum set of SNPs, which would have $R_i^2 \geq 0.7$ for all haplotypes with an estimated frequency of $\geq 5\%$. Pairwise r^2 measures were calculated to assess how well the chosen tagging SNPs were correlated with the variants that were not genotyped in the cases and controls.

Comparison of Tagging SNP and Haplotype Frequencies between Cases and Controls. Haplotype frequencies among cases and controls were estimated using the tag SNPs selected to distinguish the common haplotypes ($\geq 5\%$ frequency) for each ethnic group. We first did a global likelihood ratio test to test whether the frequency distributions of the common haplotypes differed between cases and controls. We used the methods described by Zaykin et al. to perform global tests of no association between haplotypes and cancer risk and estimate haplotype-specific odds ratios (OR; refs. 14, 18). ORs and 95% confidence intervals (95% CI) were estimated for each haplotype using unconditional logistic regression. Associations with both the tagging SNPs and common haplotypes were examined in ethnic-stratified analyses, and summary ORs are presented adjusted for ethnicity and age. For haplotypes found to be nominally associated with risk, a test for heterogeneity was done to examine whether the effects varied by age or ethnicity. Multiple testing was explicitly accounted for by applying a permutation-based framework. Permutation testing revealed that $P = 0.003$ for breast and prostate cancer should define results as statistically significant (equivalent to $P = 0.05$ for the locus accounting for the number of tests done). We used the Statistical Analysis System, version 8.2 for all analyses (SAS Institute, Inc., Cary, NC).

Genotyping. Genotyping for linkage disequilibrium and haplotype discovery was done by time-of-flight mass spectrometry using the Sequenom platform at the Broad Institute. Genotyping of the tag SNPs was done by the 5' nuclease Taqman allelic discrimination assay using the ABI 7900 (Applied Biosystems, Foster City, CA) in the University of

Southern California Genomics Center. Replicate blinded quality control samples were included to assess reproducibility of the genotyping procedure; concordance was $>99\%$ in the multiethnic panel and in the case-control studies. All tag SNPs were in Hardy-Weinberg equilibrium among controls in at least four of the five ethnic groups ($P > 0.05$).

Results

Characterization of Linkage Disequilibrium and Common Haplotype Patterns. Our goal was to genotype at least six high-frequency markers ($\geq 10\%$) in regions of strong linkage disequilibrium to maximize the likelihood of capturing the common genetic diversity (see Materials and Methods and ref. 15). The 17 SNPs genotyped were in strong linkage disequilibrium (Table 1) and spanned from 14.3 kb upstream through 5.7 kb downstream of the *PTEN* gene (total distance = 123.0 kb; average spacing of one common SNP every ~ 7.2 kb). The frequency of these markers in each population and the linkage disequilibrium plot are provided in Supplementary Table S1 and in Supplementary Fig. S1, respectively.

In this region of strong linkage disequilibrium, we observed a total of nine common haplotypes (frequency of $\geq 5\%$) among the populations in the multiethnic panel. These haplotypes accounted for at least 87% of all chromosomes in each ethnic group except African Americans (72%); the remaining chromosomes were comprised of haplotypes with frequencies of $<5\%$ in all populations. Only one haplotype was present in one ethnic group (haplotype 5 among African Americans) at an appreciable frequency.

We selected 10 markers as tagging SNPs that strongly predicted these common haplotypes (Table 1); SNPs rs1234221 and rs1234224 were only required for African Americans. The average R_i^2 in predicting the common haplotypes across all ethnic groups was 0.91, and we observed only minor

Table 2. Associations between *PTEN* haplotypes and prostate cancer risk (Cont'd)

rs2673832*	rs926091	rs532678	rs701848*	rs478839	Haplotype frequencies [†] (cases/controls)					OR (95% CI) [‡] , heterozygous vs homozygous	OR (95% CI) [‡] , rare homozygous vs homozygous
13	14	15	16	17	AA (n = 683/650)	NH (n = 71/68)	JA (n = 462/471)	LA (n = 647/649)	WH (n = 457/452)		
A	C	C	C	G	0.04/0.05	0.12/0.13	0.18/0.20	0.23/0.23	0.16/0.18	0.89 (0.77-1.02)	0.84 (0.60-1.17)
A	C	C	C	G	0.05/0.05	0.37/0.38	0.25/0.24	0.14/0.13	0.22/0.20	1.10 (0.96-1.27)	1.08 (0.76-1.53)
A	C	C	T	A	0.33/0.34	0.06/0.02	0.06/0.06	0.10/0.11	0.15/0.16	1.08 (0.94-1.25)	0.74 (0.55-1.00)
G	C	C	T	A		0.06/0.05		0.08/0.07	0.11/0.11	0.94 (0.77-1.16)	2.70 (1.13-6.47)
A	C	T	T	A	0.05/0.06					0.83 (0.58-1.19) [§]	
A	T	T	T	A	0.08/0.08	0.25/0.26	0.35/0.32	0.16/0.17	0.15/0.13	1.05 (0.91-1.20)	1.11 (0.82-1.50)
A	C	T	T	A	0.06/0.05				0.05/0.06	0.96 (0.76-1.21)	0.60 (0.15-2.52)
A	C	T	T	A		0.07/0.09	0.08/0.08	0.17/0.15	0.07/0.07	1.06 (0.89-1.26)	1.08 (0.64-1.84)
A	C	T	T	A	0.22/0.20			0.05/0.04		1.09 (0.91-1.30)	1.16 (0.69-1.97)

differences in haplotype frequencies predicted solely by the tagging set of SNPs versus haplotype frequencies as defined by all of the SNPs (Table 1). To assess how well the 10 tagging SNPs captured the unmeasured SNPs (the remaining seven SNPs in the linkage disequilibrium block), we computed the pairwise r^2 values (correlations) of the tag SNPs to each unmeasured variant. All r^2 values were >0.82 (average r^2 across populations for the unmeasured SNPs = 0.97); thus, we believe that the chosen tagging SNPs (and the haplotypes they define) provide a thorough representation of common variation at this locus.

Associations of Tagging SNPs and Common Haplotypes and Breast Cancer Risk. The distribution of baseline characteristics in breast cancer cases and controls for each ethnic group is provided in Supplementary Table S2. In the haplotype analysis, the overall distribution of haplotypes between breast cancer cases and controls was not statistically significant ($P = 0.27$). Because this test examines the global distribution of the haplotypes, it could potentially miss risk effects of individual haplotypes. Therefore, we also evaluated the effects of individual haplotypes on cancer risk. We observed homozygous carriers of haplotype 8 (OR, 2.82; 95% CI, 1.26-6.33; $P_{\text{nominal}} = 0.01$) to have a modest increase in risk compared with noncarriers, although this did not reach statistical significance based on our previously defined threshold (see Materials and Methods). The heterozygous status was not associated with increased risk ($P = 0.15$; Table 2). Testing of individual SNPs 4 and 5, which were highly correlated with haplotype 8 (and each other), was similarly associated with increased risk [SNP4, rs1234220 (intron 1): GG versus AA genotypes, OR, 2.09; 95% CI, 1.20-3.63; $P = 0.009$; SNP5, rs1234219 (intron 1): GG versus AA genotypes, OR, 2.77; 95% CI, 1.25-6.14; $P = 0.01$]. We found no evidence that these effects varied significantly across ethnic groups or by age (data not shown). These modest effects were attenuated when limiting the analysis to women with advanced disease (cases, $n = 447$), and no significant associations were noted between any of the remaining tag SNPs or common haplotypes and breast cancer risk (data not shown).

Associations of Tagging SNPs and Common Haplotypes and Prostate Cancer Risk. The distribution of baseline characteristics in prostate cancer cases and controls for each ethnic group is provided in Supplementary Table S3. In an identical analysis of the common haplotypes (and tagging SNPs) in *PTEN*, we observed no strong haplotype or SNP effects in relation to prostate cancer risk. The global test of haplotype effects was not significant ($P = 0.33$). We observed a modest positive association limited to men homozygous for haplotype 4 (versus noncarriers: OR, 2.70; 95% CI, 1.13-6.47; $P = 0.03$) and SNP 9 (rs2673832, intron 6), which predicts this haplotype ($P_{\text{nominal}} = 0.03$). The heterozygous state was not associated with increased risk ($P = 0.54$). We found no evidence that these effects varied significantly across ethnic groups or by age (data not shown). None of the other tagging SNPs tested individually revealed significant associations, and significant effects were not observed among men with advanced disease (cases, $n = 762$; data not shown).

Discussion

Application of linkage analysis in hereditary cancer syndromes has successfully identified numerous loci, thereby offering tremendous insight into the genetic causes of cancer predisposition. These syndromes are typically caused by a single locus and only account for a small fraction of all cancer cases. The bulk of cancers that are diagnosed and treated in clinics, however, do not follow clear cut Mendelian modes of transmission and arise from the contribution of low penetrant alleles at multiple loci as well as the environment. Recent

large-scale efforts to determine the structure and content of common genetic variation in the human genome now permit us to thoroughly test the contributions of common inherited variation to sporadic cancer.

Due to its role in Cowden syndrome and its frequent loss of expression in advanced prostate cancers, the *PTEN* gene is a particularly strong candidate in which to assess the effect of common variation on breast and prostate cancer risk. Previous studies investigating the role of germ line polymorphisms in the *PTEN* gene have focused on a very small number of candidate noncoding variants because no common amino acid altering variants have been identified (<http://www.genome.utah.edu/genesnps>; refs. 9, 19). No associations with breast or prostate cancer risk have been reported; however, these studies have not been comprehensive with respect to surveying common genetic variation. Our results lend conclusive support to previous studies showing no strong associations between common inherited variation in *PTEN* and sporadic breast or prostate cancer risk. Conditioning on the α levels defined by the permutation test as the criteria for a significant association ($P = 0.003$), we calculated that in this study, we had 90% power to detect relative risks of 1.44 (breast) and 1.38 (prostate) for a dominant allele with a frequency of 10% (assuming an R_{hi}^2 of 0.9) and 90% power to detect relative risks of 3.10 (breast) and 2.82 (prostate) for a recessive allele with a frequency of 10%. Although some alleles showed nominally significant associations ($P = 0.01$ for haplotype 8 for breast cancer and $P = 0.03$ for haplotype 4 for prostate cancer), the magnitude of these P s would not be unexpected given the number of tests that we did, and based on our permutation testing, we did not consider these findings statistically significant.

We acknowledge that this locus may still prove to be involved in breast and prostate cancer risk. Specifically, many rare (<5%) variants (that our sample size is not adequately powered to test) may contribute to disease. To address this hypothesis, however, large-scale resequencing efforts (to discover the rare variants) and testing of these variants in even larger studies, such as the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium (<http://epi.grants.cancer.gov/BPC3/>), will be required. In summary, our data do not support a significant contribution of inherited variation in *PTEN* to the risk of sporadic breast or prostate cancer.

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