Admixture Mapping Links RACGAP1 Regulation to Prostate Cancer in African Americans

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Abstract. Background/Aim: Prostate cancer is the most common malignancy in US males. African American men have higher incidence and mortality rates than European Americans. Five single nucleotide polymorphisms are associated with PCa. We hypothesized haplotypes inferred from these SNPs are also associated with PCa. Patients and Methods: We genotyped SNPs in a case-control admixture mapping study. SNP haplotypes inferred for 157 PCa cases and 150 controls were used in the regression analysis. Results: We found an association between “GTCCC”, “ATTCT”, and “ACCCC” haplotypes and PCa after ancestry adjustment (OR=3.62, 95%CI=1.42-9.21, p=0.0070; OR=7.89, 95%CI=2.36-26.31, p=0.0008; OR=4.34, 95%CI=1.75-10.78, p=0.0016). The rs615382 variant disrupts the recombination signal binding protein with immunoglobulin kappa J binding site in Rac GTPase activating protein 1 (RACGAP1). Conclusion: Disruption of notch 1 mediated-repression of RACGAP1 may contribute to PCa in African Americans.

Prostate cancer (PCa) is the third most prevalent cancer in the world after breast and colorectal cancers, and the most common cancer affecting men in the US (1-9). PCa incidence and mortality rates are disproportionately higher among African American (AA) men compared to their European American counterparts (2-9). This disparity is greatest in the nation’s capital, Washington D.C., which has the highest incidence and mortality rates in the country (10). It is unclear what factors account for the observed disparities. Risk factors for PCa include age, race/ethnicity, family history and environmental factors; however, a strong genetic association has yet to be identified (11-13). The observed disparities warrant the use of an approach that leverages allele frequency differences to identify loci contributing to disease pathology.

The approaches and methods used to identify genes that are causal or predispose an individual to PCa have evolved over time. Early efforts studied the disease in familial clusters and twin cohorts (13-24). Study designs then shifted to case-control and candidate gene studies. This shift was facilitated by the completion of the working draft of the genome map, a deliverable of the Human Genome Project. Advances in genotyping technology and the availability of the genome map facilitated the use of single nucleotide polymorphisms (SNPs) in association studies. The International HapMap project leveraged the information provided in the patterns of linkage disequilibrium (LD) to enhance SNP association studies. The differences observed in SNP allele frequencies between populations were later used as a tool in admixture mapping (24-29). Genome-wide association studies (GWAS) have become the standard for SNP association (30-34). Additionally, PCa GWAS results have been pooled in meta-analyses, reanalyzed using new statistical tools and re-sequenced in attempts to replicate findings (35-39).

To date over 70 variant loci have been implicated in PCa etiology via admixture mapping and GWAS (24-39). However, the identified loci do not appear to account for a majority of genetic susceptibility to PCa. In addition, these findings have not been reported with a high degree of consistency. A screening of 21 AIMs (Ancestry Informative Markers) on chromosome 12 identified a cancer susceptibility locus for PCa in African American men (29). A larger follow-
up study was conducted to explore the findings of the screening and the results were published by Ricks-Santi et al. (40) The data from the follow-up study were re-examined to investigate the biological nature of the statistical association. Local and regional patterns of LD, evidence of selective pressure, and disruption of regulatory sequence motifs were among the local sequence features interrogated in this study.

Patients and Methods

Study population. We selected 157 AA men who were older than 40 years of age from the Washington, DC area with histologically diagnosed adenocarcinoma of the prostate, prostate specific antigen (PSA) of >4.0 ng/ml, and a positive digital rectal examination (DRE). We then identified 150 ethnicities matched (AA) controls who were regularly screened with PSA levels <0.0 ng/ml, normal DRE and with no history of PCa among first-degree relatives. PSA values and blood samples were obtained at the time of diagnosis for case subjects and at the time of study enrollment for control subjects. Participants were recruited for a Howard University Institutional Review Board (IRB) approved study through the Division of Urology at the Howard University Hospital (HUH) and from the free prostate cancer screening program at the Howard University Cancer Center (HUCC) from 2000 to 2004.

AIMs selection and genotyping. We selected a total of 21 AIMs on 12p12–q14 to cover an average of 25 Mb upstream and/or downstream of VDR (vitamin D receptor). Allele frequency differences between putative parental populations for African Americans (West African and European) parental populations for all AIMs was >0.30 (based on HapMap data). Genomic DNA extraction was performed on whole blood using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer’s instructions. DNA from 157 PCs and 150 control subjects was genotyped to study the association of 21 AIMs with PCa risk. Polymerase chain reaction (PCR) and pyrosequencing primers were designed using PyroMark Assay Design software ver. 20.0 (Qiagen, Hilden, Germany). DNA samples were polymerase chain reaction (PCR)-amplified using whole-genome amplified DNA, forward and reverse primers, MgCl2, deoxy-nucleotide triphosphates and platinum Taq DNA polymerase (Invitrogen, Grand Island, NY, USA). Results were analyzed with the PyroMark Q24 software (Qiagen, Hilden, Germany). Duplicate test samples and negative controls were included in each 96-well plate.

Association analysis. The association of disease status with AIM genotype and haplotype was analyzed by binary logistic regression using the R statistical software (version 2.9.0) (Vienna, Austria) and SAS/STAT® version 9.1 (SAS Institute, Cary, NC, USA) software packages. Fisher’s exact test and χ2 analysis were used to test the alleles for Hardy-Weinberg equilibrium in controls when appropriate. For this study, the major allele found in people of African descent was considered the reference allele. For each SNP genotype the dominant, co-dominant, recessive and log-additive genetic models were conducted. Confidence intervals (CIs) of 95% were set on the odds ratios (ORs) calculated after adjusting for age and ancestry. Two sided p-values of ≤0.05 were considered to be statistically significant. The adjustment for multiple comparisons was made using the Bonferroni test.

| Characteristic                      | Cases  | Controls | p-Value |
|------------------------------------|--------|----------|---------|
| Number of participants             | 157    | 150      | -       |
| Mean Age (±SD)                     | 65.6±9.1 | 56.0±14.6 | <0.001  |
| Mean PSA level (±SD)               | 51.8±180.9 | 3.5±13.8  | <0.001  |
| Mean % West African ancestry       | 73.0   | 67.0     | 0.047   |

Results

The demographic, clinical, and ancestry data of the human subjects are shown in Table I. The student’s t-test reveals significant differences in age between the PCa and control subjects (p<0.001). The mean age of patients with PCa (65.6±9.1) was significantly older than the controls (56.0±14.6). The mean PSA levels were significantly higher in PCa patients (51.8±180.9) than the controls (3.5±13.8) (p<0.001). The percentage of West African Ancestry was significantly different between PCa (73.0) cases and controls (67.0) (p<0.047).

Association between AIMs and PCa risk. The studied AIMs were in Hardy-Weinberg equilibrium (p<0.05). The allele frequencies in PCa patients were similar to the controls (Table II). Five (rs1993973, rs1561131, rs1843321, rs1963562, and rs615382) of the twenty-one AIMs studied were found to be associated with PCa using the four genetic models (p<0.05) (Table III). AIM rs1993973 was found to be associated with PCa risk under the five genetic models; AIM rs1561131 under the co-dominant and recessive models; AIM rs1843321 only under the log-additive model; AIM rs1963562 under the dominant model only; and AIM...
rs615382 under the co-dominant, recessive and log-additive models. Only AIM rs615382 is located within a genic region and lies within intron two of the RACGAP1 gene. **Haplotype analyses.** The haplotypes were constructed using fastPHASE v2.1 and are shown in Table IV. Three haplotypes 5 “GTCCC”, 9 “ATTCT”, and 11 “ACCCC” showed an
Five AIMs were associated with PCa after the application of different genetic models as well as haplotypes constructed using them. The “ACCCC” haplotype showed a statistically significant association with PCa after adjusting for age and ancestry. Only one AIM in the haplotype is located within a genomic region. SNP rs615382 is located in an intron of the proto-oncogene RACGAP1. RACGAP1, Rac GTPase activating protein (GAP) 1, is under regulation of the Notch signaling pathway. SNP rs615382 disrupts the binding site for recombination signal binding protein for immunoglobulin kappa J (RBP-Jkappa) (44). RBP-Jkappa acts as a transcriptional repressor or activator when bound or unbound to Notch proteins respectively. Loss of the RBP-Jkappa binding site eliminates the ability of RBP-Jkappa to repress RACGAP1 transcription. GAPs bind activated forms of Rho GTPases and stimulate GTP hydrolysis. GAPs negatively regulate Rho-mediated signals and are involved in downstream signaling of Ras-like GTPases.

Discussion

Five AIMs were associated with PCa after the application of different genetic models as well as haplotypes constructed using them. The “ACCCC” haplotype showed a statistically significant association with PCa after adjusting for age and ancestry. Only one AIM in the haplotype is located within a genomic region. SNP rs615382 is located in an intron of the proto-oncogene RACGAP1. RACGAP1, Rac GTPase activating protein (GAP) 1, is under regulation of the Notch signaling pathway. SNP rs615382 disrupts the binding site for recombination signal binding protein for immunoglobulin kappa J (RBP-Jkappa) (44). RBP-Jkappa acts as a transcriptional repressor or activator when bound or unbound to Notch proteins respectively. Loss of the RBP-Jkappa binding site eliminates the ability of RBP-Jkappa to repress RACGAP1 transcription. GAPs bind activated forms of Rho GTPases and stimulate GTP hydrolysis. GAPs negatively regulate Rho-mediated signals and are involved in downstream signaling of Ras-like GTPases.

association of haplotypes with risk for PCa (OR=3.1; 95%CI=1.4-6.7; \textit{p}=0.01, OR=5.9; 95%CI=2.2-15.6; \textit{p}=0.0002 and OR=2.4; 95%CI=1.1-5.2; \textit{p}=0.03; respectively). After adjusting for age and ancestry, these three haplotypes remained significantly associated with PCa risk (Table V).

The search for alteration of regulatory mechanisms using Alibaba and HaploReg yielded the modification of a number of regulatory binding sites. The most notable being the disruption of a binding site for the notch signaling pathway regulated transcriptional modulator RBP-Jkappa in intron 2 of the RACGAP1 gene (Figure 1).

Discussion

Five AIMs were associated with PCa after the application of different genetic models as well as haplotypes constructed using them. The “ACCCC” haplotype showed a statistically significant association with PCa after adjusting for age and ancestry. Only one AIM in the haplotype is located within a genomic region. SNP rs615382 is located in an intron of the proto-oncogene RACGAP1. RACGAP1, Rac GTPase activating protein (GAP) 1, is under regulation of the Notch signaling pathway. SNP rs615382 disrupts the binding site for recombination signal binding protein for immunoglobulin kappa J (RBP-Jkappa) (44). RBP-Jkappa acts as a transcriptional repressor or activator when bound or unbound to Notch proteins respectively. Loss of the RBP-Jkappa binding site eliminates the ability of RBP-Jkappa to repress RACGAP1 transcription. GAPs bind activated forms of Rho GTPases and stimulate GTP hydrolysis. GAPs negatively regulate Rho-mediated signals and are involved in downstream signaling of Ras-like GTPases.

Table IV. \textit{fastPHASE} haplotype unadjusted association with PCa risk.

| Haplotype | Controls | % | Cases | % | OR (95% CI) | \textit{p}-Value |
|-----------|----------|---|-------|---|-------------|----------------|
| GCCCT     | 57       | 19.0% | 42    | 13.4% | -           | -              |
| GCCCC     | 44       | 14.7% | 46    | 14.6% | 1.4 (0.8-2.5) | 0.25 |
| ACCCT     | 29       | 9.7%  | 13    | 4.1%  | 0.6 (0.3-1.3) | 0.26 |
| GTCCCT    | 25       | 8.3%  | 23    | 7.3%  | 1.2 (0.6-2.5) | 0.60 |
| GTCC     | 12       | 4.0%  | 27    | 8.6%  | 3.1 (1.4-6.7) | 0.01 |
| ATTCC     | 14       | 4.7%  | 9     | 2.9%  | 0.9 (0.3-2.2) | 0.82 |
| ATCTC     | 24       | 8.0%  | 27    | 8.6%  | 1.5 (0.8-3.0) | 0.23 |
| ATCCCT    | 17       | 5.7%  | 14    | 4.5%  | 1.1 (0.5-2.5) | 0.84 |
| ATCTCT    | 6        | 2.0%  | 26    | 8.3%  | 5.9 (2.2-15.6) | 0.0002 |
| GTTCT     | 9        | 3.0%  | 9     | 2.9%  | 1.4 (0.5-3.4) | 0.61 |
| ACCCC     | 14       | 4.7%  | 25    | 8.0%  | 2.4 (1.1-5.2) | 0.03 |
| Other     | 49       | 16.3% | 53    | 16.9% | 1.5 (0.8-2.6) | 0.20 |

*Other refers to haplotypes inferred with a frequency of less than 1%.

Table V. \textit{fastPHASE} haplotype association with PCa adjusted for age and ancestry.

| Haplotype | OR (95% CI) | \textit{p}-Value | OR (95% CI) | \textit{p}-Value |
|-----------|-------------|-----------------|-------------|-----------------|
| GCCCT     | 1.98 (0.96-4.07) | 0.0636 | 1.75 (0.84-3.64) | 0.1361 |
| GCCCC     | 0.81 (0.33-1.98) | 0.634 | 0.8 (0.32-1.98) | 0.6298 |
| ACCCT     | 1.74 (0.74-4.07) | 0.2016 | 1.75 (0.74-4.15) | 0.2012 |
| GTCCCT    | 3.97 (1.57-10.05) | 0.0037 | 3.62 (1.42-9.21) | 0.0070* |
| ATCCCT    | 0.69 (0.17-2.82) | 0.6071 | 0.61 (0.15-2.50) | 0.4907 |
| ATCTC     | 2.23 (0.96-5.16) | 0.0620 | 2.36 (1.0-5.54) | 0.05 |
| ATCT     | 1.69 (0.61-4.67) | 0.31 | 1.68 (0.61-4.66) | 0.3176 |
| GTTCT     | 8.30 (2.51-27.45) | 0.0005 | 7.89 (2.37-26.31) | 0.0008* |
| ACCCC     | 4.62 (1.03-4.33) | 0.0009 | 4.34 (1.75-10.78) | 0.0016* |
| Other     | 2.11 (1.05-0.09) | 0.0408 | 1.9 (0.92-3.95) | 0.0845 |

*Other refers to haplotypes inferred with a frequency of less than 1%.
RACGAP1 has been implicated in multiple malignancies including breast, gastric, hepatocellular, and non-small-cell lung carcinoma (45-47). Up-regulation of RACGAP1 has been associated with early recurrence of hepatocellular carcinoma and is overexpressed in non-small-cell lung and luminal breast cancer. RACGAP1 expression was also correlated with tumor progression and poor prognosis in gastric cancer. To date, there have been no reports of RACGAP association with PCa.

We understand that cancer results from an accumulation of genetic mutations. We also understand that although many cancers share common mutations, they are discrete entities that are capable of evolving over time. Loss of RACGAP1 regulation may be one of the mutations acquired in the development of PCa. A larger study of African American tumor samples would reveal whether RACGAP1 overexpression is a common feature of PCa.

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