The *ADPRT V762A* Genetic Variant Contributes to Prostate Cancer Susceptibility and Deficient Enzyme Function

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ABSTRACT

The *ADP-ribosyltransferase* (*ADPRT*) gene encodes a zinc-finger DNA-binding protein, poly(ADP-ribose) polymerase-1 (PARP-1), that modifies various nuclear proteins by poly(ADP-ribosyl)ation and functions as a key enzyme in the base excision repair pathway. We have conducted two studies to test whether an amino acid substitution variant, *ADPRT V762A* (*T2444C*), is associated with prostate cancer (CaP) risk and decreased enzyme function. The first study used genomic DNA samples from an ongoing, clinic-based case-control study (488 cases and 524 controls) to show that a higher percentage of the CaP cases carried the *ADPRT 762 AA* genotype than controls (4% *versus* 2%). In Caucasians, the *AA* genotype was significantly associated with increased CaP risk [odds ratio (OR), 2.65; 95% confidence interval (CI), 1.08–6.49], and the *VA* genotype was associated with a slight but not significantly increased CaP risk (OR, 1.18; 95% CI, 0.85–1.64) using *VV* as the referent group after adjustment for age, benign prostatic hyperplasia, and family history. Furthermore, this association was stronger in younger (<65) men (OR, 4.77; 95% CI, 1.01–22.44) than older (≥65) men (OR, 1.78; 95% CI, 0.55–5.82). The second study used freshly isolated peripheral lymphocytes from 354 cancer-free subjects to demonstrate that the *ADPRT 762 A* allele contributed to significantly lower adenosine diphosphate ribosyl transferase (ADPRT)/PARP-1 activities in response to H_2O_2 in a gene dosage-dependent manner ($P < 0.0001$, test for linear trend). The PARP-1 activities (mean ± SD $dpm/10^6$ cells) were $18,554 \pm 9,070$ ($n = 257$), $14,847 \pm 7,082$ ($n = 86$), and $12,155 \pm 6,334$ ($n = 11$) for *VV*, *VA*, and *AA* genotypes, respectively. This study is the first to provide evidence that the *ADPRT V762A*-genetic variant contributes to CaP susceptibility and altered ADPRT/PARP-1 enzyme function in response to oxidative damage.

INTRODUCTION

Prostate cancer (CaP) is the most common cancer in American men (1). Despite rapid advances in human genetic research, critical questions about genetic susceptibility to CaP remain to be elucidated. Ethnicity/race and family history (FH) are associated with CaP risk, and incidence increases with age; >70% of all cases are diagnosed in men over 65 (1). An accumulation of genetic abnormalities and a decline in DNA repair during aging may lead to CaP. Germline mutations or polymorphisms in DNA-repair genes *BRCA1/2*, *CHEK2*, *XRCC1*, and *OGG1* are associated with CaP risk (2–5).

Two previous studies revealed that age-related structural changes in the DNA from CaP tissue are likely a result of oxidative damage inflicted by hydroxyl radicals (6, 7). The results from these studies suggest that base excision repair (BER) is involved in CaP suscepti-

bility (3, 4, 6, 7). Because adenosine diphosphate ribosyl transferase/poly(ADP-ribose) polymerase-1 (ADPRT/PARP-1) plays a critical role in both BER and maintaining the genomic stability of cells exposed to genotoxic stress and because previous studies associated higher ADPRT/PARP-1 enzyme activation with lower human cancer risk (8, 9), we hypothesize that genetic polymorphisms of *ADPRT* may contribute to lower enzyme activity and CaP risk.

The human *ADPRT* gene encodes the 113k Da ADPRT/PARP-1 enzyme (EC 2.4.2.30). It plays critical roles in DNA-damage signaling, BER, recombination, genomic stability, and the transcriptional regulation of tumor suppressor genes, such as p53 (10, 11). ADPRT/PARP-1 is constitutively expressed at a basal level, and its catalytic activity is strongly stimulated in response to single- or double-strand breaks (12). ADPRT/PARP-1 consists of three domains: (*a*) a DNA-binding domain, (*b*) an automodification domain, and (*c*) a catalytic domain at the COOH terminus (13). It specifically recognizes and binds DNA single-strand breaks, recruits other DNA-repair proteins to the site of damage, and serves as an energy source for ligation (14–16).

Two small studies reported that a sequence polymorphism in the *ADPRT* pseudogene on chromosome 13q34 is associated with colon cancer and CaP in African Americans (17, 18). More recently, several nucleotide variants in the *ADPRT* gene have been identified (13, 19). However, most of those SNPs are very rare in the general population (variant allele <1%), except the codon 762 variant (exon 17, 2444 *T* to *C*, *V* to *A*), which is present in about 5 to 33% of the general population and located in the most conserved region coding for the COOH-terminal catalytic domain (13, 19).[7] The loss of a methyl group from *V* to *A* moves the 762 residue further away from the *888G* residue, which is a part of the active site and totally conserved during evolution (13). On the basis of the current understanding of *ADPRT* gene function in the DNA-repair pathway and the structural data, we conducted two studies to test whether the *ADPRT V762A* variant may affect CaP risk and enzyme catalytic activity.

MATERIALS AND METHODS

CaP Case-Control Study Population. Cases and controls were recruited from the Departments of Urology and Internal Medicine of the Wake Forest University School of Medicine using sequential patient populations as described previously (20). All subjects received a detailed description of the study protocol and signed their informed consent, as approved by the medical center's Institutional Review Board. Then blood samples were collected from all subjects. The general eligibility criteria were (*a*) able to comprehend informed consent and (*b*) without previously diagnosed cancer. The exclusion criteria were (*a*) clinical diagnosis of autoimmune diseases, (*b*) chronic inflammatory conditions, and (*c*) infections within the past 6 weeks.

Two groups of cases were recruited from the Urology Clinic: (*a*) incident, newly diagnosed, untreated cases, and (*b*) prevalent, cases diagnosed with CaP within 5 years and free of cancer/treatments for at least 6 months before study entry. Controls were frequency-matched to cases by age. Two groups of controls were recruited from the Urology and Internal Medicine Clinics: (*a*) men with normal prostate-specific antigen levels and normal digital rectal

[7] http://www.ncbi.nlm.nih.gov.

exam and (*b*) men with abnormal prostate-specific antigen or digital rectal exam but negative biopsy results for CaP. Case status was confirmed by pathology reports. A self-administered questionnaire collected information on (*a*) demographic factors, such as age, race, weight, and height; (*b*) medical history and medication use; (*c*) smoking history; and (*d*) FH of cancer. Men with at least one first-degree relative with CaP were considered to have a positive FH. The response rate for cases and controls was 94% and 83%, respectively.

Population for the Genotype-Enzyme Activity Association Study. Cancer-free subjects were recruited from New York University Tisch Hospital. All subjects received a detailed description of the study protocol and signed their informed consent, as approved by the Institutional Review Board at New York University. The general eligibility criteria were as follows: (*a*) able to comprehend informed consent and (*b*) without previously diagnosed cancer. A self-administered questionnaire collected information on (*a*) demographic factors, such as age and race; (*b*) smoking history; and (*c*) FH of cancer.

Single-Nucleotide Polymorphism Genotyping Analysis. Blood samples (20 ml) were collected from each study subject and processed within 2 hours after phlebotomy. Genomic DNA was extracted from 200 μl of frozen whole blood using the QIAamp DNA Blood Mini kit (Qiagen, Inc., Valencia, CA). The MassARRAY system (Sequenom, Inc., San Diego, CA) was used for SNP genotyping. The primers used were as follows: 5′-ACGTTGGATGCACCAT-GATACCTAAGTCGG-3′ (forward) and 5′-ACGTTGGATGATGTCCAG-CAGGTTGTCAAG-3′ (reverse) for the PCR reactions and 5′-CAGGTTGT-CAAGCTTCC-3′ for extension. As part of quality control efforts, we first determined genotypes of a panel of 90 DNA samples from Coriell Institute for Medical Research (Camden, NJ) and compared them with the published individual genotype data at two websites.[8] Other quality control checks were in place at every step; the same controls (*n* = 4) were routinely genotyped in each plate of 96 DNA samples. Cases and controls were grouped together in each plate to avoid any systematic biases between plates. The Hardy-Weinberg equilibrium test was performed as another critical quality control check.

ADPRT/PARP-1 Enzyme Activity. Blood samples (30 ml) were collected in a nonfasting state and processed within 2 hours for peripheral mononuclear leukocytes isolation using the Lymphocyte Separation Medium (Organon Teknika Co., Durham, NC). The freshly isolated leukocytes were used for ADPRT/PARP-1 enzyme activity assays as determined by the rate of incorporation of [^{3}H]adenine-NAD$^+$ into cells as described previously (8). Data were recorded as dpm trichloroacetic acid (*TCA*)-precipitable [^{3}H]adenine labeled NAD$^{+/}$ 10^6 cells induced by H_2O_2 (100 μmol/L).

Statistical Analyses. Student's *t* test, χ^2 test, and Fisher's exact test were used to compare the distribution of demographic characteristics and allelic frequencies between cases and controls. Fisher's exact tests were used to test whether genotype data were in Hardy-Weinberg equilibrium. Logistic regression was used to calculate crude and adjusted ORs and 95% CIs to evaluate the association between genotype and cancer risk. ANOVA was used to evaluate age of disease diagnosis by genotype and ADPRT/PARP-1 enzyme activity results by genotype. All of the statistical analyses were carried out using the Statistical Analysis System for personal computers (SAS Institute, Cary, NC) and the S-Plus Statistical Package (Insightful Corp., Seattle, WA).

RESULTS

To validate the genotyping method for the *ADPRT V762A* variant, we first compared the genotypes of a panel of 90 samples with the published data, and the correct calling rate was 100%. As shown in Table 1, *ADPRT* genotype data were available for 488 CaP cases and 524 controls, and we had complete demographic information on 89% of cases and 92% of controls. Cases and controls were similar with respect to mean age (*P* = 0.51). However, the distributions of age, benign prostatic hyperplasia (BPH), and FH differed significantly between cases and controls. We over-sampled African-American controls to evaluate racial/ethnic difference in genotype distribution. There was no significant difference in smoking history (*P* = 0.94) between cases and controls. A higher percentage of controls had a

Table 1 *Characteristics of study subjects*

Characteristics and category	Controls; *n* = 524 (%)	Cancer cases; *n* = 488 (%)	*P* value *
Age			
Mean ± SD	64.56 ± 8.69	64.91 ± 8.33	0.51
Age			
≤50	13 (3)	17 (4)	0.02
51–60	180 (34)	134 (27)	
61–70	183 (35)	211 (43)	
≥71	148 (28)	126 (26)	
Race			
African American	97 (19)	50 (10)	<0.01
Caucasian	427 (81)	438 (90)	
Smoking history †			
No	176 (34)	161 (34)	0.94
Yes	339 (66)	316 (66)	
Missing	9	11	
BPH history ‡			
No	212 (41)	255 (54)	<0.01
Yes	309 (59)	215 (46)	
Missing	3	18	
FH §			
No	395 (82)	315 (73)	<0.01
Yes	86 (18)	117 (27)	
Missing	43	56	

* *P* values from Student's *t* test, Fisher's exact test, or χ^2 test.
† Smoking history, ever smoked at least 100 cigarettes.
‡ BPH history.
§ FH, first-degree relatives with CaP (father or brother).

history of clinically significant BPH than cases (*P* < 0.01). More cases had a first-degree relative with CaP than controls (*P* < 0.01).

The distributions of the *ADPRT* genotypes in two groups of controls were in Hardy-Weinberg equilibrium (*P* = 0.98 and 0.33). In combined analysis, the distributions of the *ADPRT* genotypes for both Caucasian and African-American controls were in Hardy-Weinberg equilibrium (*P* = 0.53 and 0.63, respectively). As shown in Table 2, the *ADPRT V762A* genotype distributions differed significantly between African Americans and Caucasians in both case (*P* < 0.01) and control groups (*P* < 0.01). None of the African-American subjects carried the *AA* genotype. The *ADPRT* genotype distribution did not differ in two groups of controls (*P* = 0.55). Therefore, the combined data were used for subsequent analyses. The genotype distribution did not differ between incident and prevalent cases (*P* = 0.53). Therefore, the combined data were used for subsequent analyses. Among Caucasian cases, the difference in the genotype distribution of men <65 years of age as compared with men ≥65 years approached but did not achieve statistical significance (*P* = 0.07). There was no difference in genotype distribution by FH and BPH status in either Caucasian cases or controls.

As shown in Table 3, in Caucasians, the *AA* genotype was significantly associated with increased CaP risk (OR, 2.65; 95% CI, 1.08–6.49), and the *VA* genotype was associated with a slight but not significantly increased CaP risk (OR, 1.18; 95% CI, 0.85–1.64) using *VV* as the referent group after adjustment for age, BPH, and FH. The *ADPRT* genotype did not have significant effects on tumor grade; the mean ± SE of Gleason score was 6.38 ± 0.06 (*n* = 277) for *VV*, 6.17 ± 0.10 (*n* = 105) for *VA*, and 6.24 ± 0.26 (*n* = 17) for *AA* genotype, respectively (*P* = 0.1, ANOVA). In Caucasian subjects <65 years of age, *AA* genotype showed a stronger association with CaP risk compared with that in Caucasian subjects ≥65 years of age. Furthermore, cancer cases with the *AA* genotype had a significantly younger age of diagnosis (mean ± SD; 61.23 ± 7.47; *P* < 0.05) compared with those with the *VV* (63.78 ± 8.29) or *VA* (65.41 ± 7.54) genotype, respectively. In African Americans, 9% controls (9 of 97) and 10% cases (5 of 50) carried the *VA* genotype, and there was no case-control difference in genotype distribution either in the total population or subpopulations stratified by age.

Using freshly isolated lymphocytes from 354 cancer-free subjects

Table 2   *Distribution of ADPRT genotype by race, age, FH, and BPH*

Characteristic	Cases (%)				Controls (%)			
	VV	VA	AA	P value*	VV	VA	AA	P value*
Race								
African American	45 (90)	5 (10)	0 (0)		88 (91)	9 (9)	0 (0)	
Caucasian	306 (70)	113 (26)	19 (4)	<0.01	313 (73)	107 (25)	7 (2)	<0.01
Subgroup (Caucasians)								
1	230 (73)	74 (23)	12 (4)		208 (75)	65 (23)	5 (2)	
2	76 (62)	39 (32)	7 (6)	0.53	105 (70)	42 (28)	2 (1)	0.55
Age (Caucasians)								
<65	158 (72)	48 (22)	13 (6)		160 (74)	53 (25)	3 (1)	
≥65	148 (68)	65 (29)	6 (3)	0.07	153 (73)	54 (25)	4 (2)	0.64
FH (Caucasians)								
No	187 (66)	84 (30)	11 (4)		234 (74)	77 (24)	6 (2)	
Yes	79 (72)	24 (22)	6 (6)	0.25	58 (73)	20 (25)	1 (2)	0.96
BPH (Caucasians)								
No	159 (69)	63 (27)	10 (4)		113 (72)	43 (27)	2 (1)	
Yes	142 (71)	49 (25)	9 (4)	0.82	200 (74)	63 (24)	5 (2)	0.67

* P values from Fisher's exact test or χ^2 test, comparing characteristics, adjusted for case/control status.

in a different population, we evaluated whether the *ADPRT V762A* genotype influenced ADPRT/PARP-1 enzyme activity in response to H_2O_2. The enzyme activity was not influenced by age ($P = 0.43$), gender ($P = 0.15$), race/ethnicity ($P = 0.19$), or smoking status ($P = 0.46$). Subjects with a FH of any cancer had a slightly lower ADPRT/PARP-1 enzyme activity, with a P value that approached but did not achieve statistical significance ($P = 0.07$). The *ADPRT 762 A* allele contributed to significantly lower PARP-1 activities in response to H_2O_2 in an allele dosage-dependent manner ($P < 0.0001$, test for linear trend). The PARP-1 activities (mean ± SD $dpm/10^6$ cells) were $18,554 \pm 9,070$ ($n = 257$), $14,847 \pm 7,082$ ($n = 86$), and $12,155 \pm 6,334$ ($n = 11$) for *VV*, *VA*, and *AA* genotypes, respectively. To demonstrate the distribution of enzyme activity by genotype, Fig. 1 shows the box plots of ADPRT/PARP-1 activity in subjects with the *VV*, *VA*, and *AA* genotype, respectively.

DISCUSSION

Although it has been well established that DNA repair plays critical roles in human carcinogenesis, limited data are available on the association between DNA repair and CaP risk. In this study, we provide direct evidence that an amino acid substitution variant in the *ADPRT* gene may contribute to decreased cellular repair function and

be able to serve as a marker for CaP susceptibility. Intriguingly, both associations follow an allele dosage-dependent manner, the *AA* genotype is associated with a significantly higher CaP risk and lower enzyme activity, and the *VA* genotype carriers have a slight but not significantly increased CaP risk and decreased enzyme activity. Because this variant allele is relatively common in the general population (5–33%), our findings have biological and public health significance.

The genotype distribution of our Caucasian control population was comparable with that seen in a previous study of Caucasians (13). In this study, the *ADPRT 762 AA* genotype was seen only in Caucasians and not in African Americans (Table 2). Therefore, future, larger studies should test whether this genotype also plays a role in CaP risk in African Americans. Although the significantly increased frequency of the *AA* genotype in CaP cases compared with controls might be attributable to a random genotype error, this factor is unlikely to affect our results, because the genotyping data in our quality control samples had a 100% correct calling rate. Furthermore, the genotyping laboratory implemented rigorous quality control by including both case and control samples in the same 384-well plates, incorporating multiple controls in each plate, using robots in each step, and determining allele by a computer program. Therefore, any genotyping error that exists after these steps should be random in both cases and controls.

Table 3   *Association between ADPRT genotype and CaP risk*

Subjects	Genotype				VA versus VV		AA versus VV	
	VV	VA	AA	P value*	Crude OR (95%CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Caucasians								
Total controls	313	107	7		1.00(Ref.)‡	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)
Total cases	306	113	19	0.02	1.08(0.59–1.96)	1.18(0.85–1.64)	2.78(0.68–11.41)	2.65(1.08–6.49)
<65 years								
Controls	151	48	2		1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)
Cases	144	41	11	0.03	0.90(0.36–2.23)	1.11(0.67–1.83)	5.77(0.58–57.51)§	4.77(1.01–22.44) ‡
≥65 years								
Controls	162	59	5		1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)
Cases	162	72	8	0.49	1.22(0.55–2.70)	1.21(0.78–1.87)	1.60(0.24–10.46)	1.78(0.55–5.82)
African Americans								
Total controls	88	9	0		1.00(Ref.)	1.00(Ref.)		
Total cases	45	5	0	0.88	1.09(0.14–8.28)	0.98(0.24–3.99)	NA‖	NA
<65 years								
Controls	63	5	0					
Cases	30	3	0	0.93	NA	NA	NA	NA
≥65 years								
Controls	25	4	0					
Cases	15	2	0	0.80	NA	NA	NA	NA

* P value, Fisher's exact or χ^2 test.
† OR adjusted for age, BPH, and FH.
‡ Referent.
§ An expected cell value is less than five; Fisher's exact or χ^2 test results should be considered.
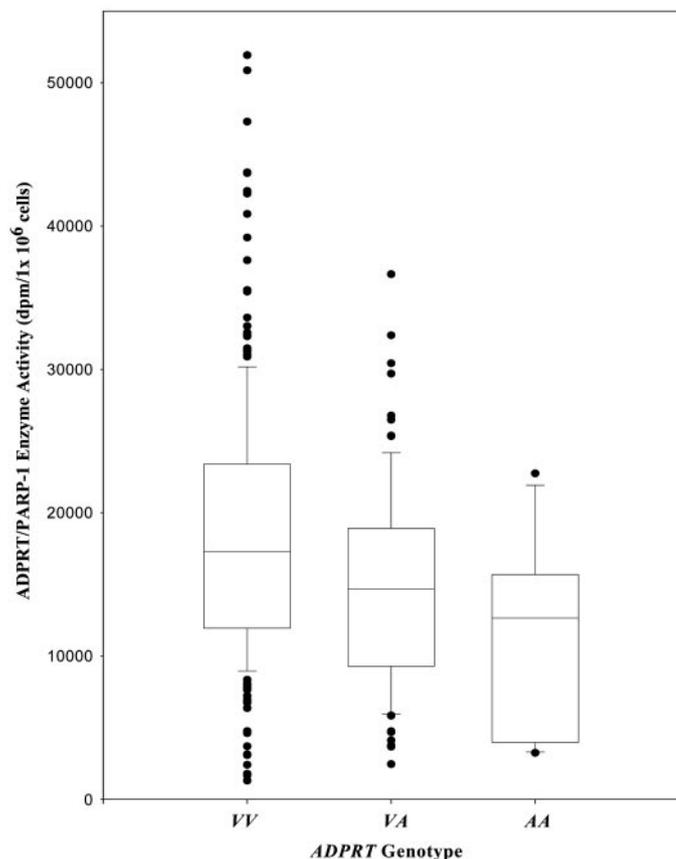‖ Not applicable.

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Fig. 1. *Box plots* of ADPRT/PARP-1 enzyme activity in subjects with *762 VV*, *VA*, and *AA* genotype, respectively. The *boundary of the box closest to zero* indicates the 25th percentile; a *line within the box* marks the median; and the *boundary of the box farthest from zero* indicates the 75th percentile. *Whiskers* above and below the box indicate the 90th and 10th percentiles. The *black dots* represent outliers falling outside the 5th and 95th percentiles.

Previous studies reported a lower poly(ADP-ribosyl)ation activity in breast and laryngeal cancer patients (8, 9) and a higher activity associated with longevity (21). However, the association between ADPRT/PARP-1 activity and cancer risk/longevity is inconclusive because of their small sample size. The sequence variant *ADPRT V762A* has been studied in centenarian and lung cancer populations (13, 22). No association was observed between lung cancer risk and *ADPRT* haplotypes of SNPs in codons 81, 284, and 762 (22). It is not clear whether the *ADPRT 762 AA* genotype plays a unique role in prostate carcinogenesis.

In contrast to our current positive findings, a previous study did not observe an association between the *AA* genotype and ADPRT/PARP-1 enzyme activity (13). The current study's larger sample size ($n = 354$ *versus* $n = 95$ in the previous study) and statistical power may contribute to the different results. In addition, the previous study used EBV-immortalized lymphoblastoid cells from centenarians for the genotype-function study, and the current study used freshly isolated lymphocytes. It is not clear whether aging and/or the EBV immortalization process may have also influenced results.

BER is one of the most critical cellular defense systems. It corrects both endogenous and exogenous mutagen-induced lesions involved in human carcinogenesis. The human genome is exposed to as many as 10,000 oxidative insults every day, most of which are removed by BER. Therefore, efficient BER is critical in maintaining genome integrity. It has been suggested that chronic oxidative stresses and oxidative genomic damage may contribute to prostate carcinogenesis

(23, 24). This concept is further supported by the observation that poly(ADP-ribose) and a BER enzyme, apurinic/apyrimidinic endonuclease-1/ref-1, were significantly higher in prostate tumor cells compared with normal prostate cells (25, 26). Our current data also support the results from previous studies associating CaP risk with oxidative DNA damage and the BER pathway (3–6). To fully assess the role of BER in addition to *ADPRT* in CaP susceptibility, we are currently evaluating other BER SNPs and a plasmid-based BER-functional assay.

We considered several limitations of this study. First, we need to study other sequence variants of *ADPRT* and haplotype in the future. Second, we have not yet evaluated whether genetic variations of *ADPRT* may lead to deficient enzyme activity in CaP risk. Third, because the *ADPRT* gene plays a critical role in BER, we must also evaluate how ADPRT/PARP-1 enzyme function affects overall BER activity in the future. In summary, this study provides the first direct evidence associating the *ADPRT 762 AA* genotype with CaP risk and decreased cellular repair response to oxidative damage. However, our current findings must be validated in larger studies before we can conclude that the *ADPRT V762A* variant can serve as a predisposition marker for CaP.

ACKNOWLEDGMENTS

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AACR American Association for Cancer Research

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