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No Association between Variant DNA Repair Genes and Prostate Cancer Risk among Men of African descent

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Abstract

Recent reports hypothesize that multiple variant DNA repair gene interactions influence cancer susceptibility. However, studies identifying high-risk cancer-related genes use single gene approaches that lack the statistical rigor to model higher-order interactions. To address this issue, we systematically evaluated individual and joint modifying effects of commonly studied polymorphic base and nucleotide excision repair genes relative to prostate cancer (PCA) risk using conventional logistic regression models and multifactor dimensionality reduction (MDR). We hypothesized that inheriting two or more compromised DNA repair loci may increase PCA risk due to altered gene product function. Six genetic alterations were evaluated using germ-line DNA samples from 208 PCA cases and 665 disease-free controls via TaqMan Polymerase Chain Reaction. With the exception of *XPD* 312, no association existed between individual DNA repair single nucleotide polymorphisms (SNPs) and PCA. Individuals with the *XPD* 312 Asn/Asn genotype had an 8.6-fold increase in risk (OR = 8.59; 95% CI = 1.81–40.66). We did not observe any significant single gene or gene-gene interactions based on MDR modeling. Our findings emphasize the importance of utilizing a combination of traditional and advanced statistical tools to identify and validate single gene and multi-locus interactions in relation to cancer susceptibility.

Keywords

Base Excision Repair; Nucleotide Excision Repair; Gene-Gene Interactions; Prostate Cancer; Logistic Regression Analysis; Multifactor Dimensionality Reduction

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Introduction

Humans are exposed to a variety of environmental carcinogens and endogenous/exogenous sources of reactive oxygen species, which may lead to DNA damage and ultimately increased susceptibility to prostate cancer (PCA) in men [1,2]. Complex DNA repair systems have evolved to safeguard against the detrimental consequences of environmentally induced DNA damage [3]. There are a number of DNA repair pathways and each is responsible for repairing a specific type of damage.

Two repair pathways primarily responsible for removing major lesions and simple base modifications are nucleotide excision repair (NER) and base excision repair (BER), respectively. NER is essential for removing bulky DNA adducts induced by genotoxic agents. This multi-step process is propelled by interactions among 20–30 proteins, including xeroderma pigmentosum complementation A (*XPA*) and *XPB*. The NER process initiates with damage recognition and is followed by local unwinding of the DNA helix, lesion demarcation, incision of approximately 24–32 nucleotides containing the lesion by endonuclease activity, filling the resulting gap by DNA polymerase, and rejoining of the DNA by DNA ligase [3–7]. The BER mechanism removes various forms of base damage, including single-strand breaks, oxidative DNA damage, alkylation, and nonbulky adducts [8,9]. BER also utilizes coordinated sequential reactions to recognize and correct such damage.

There are a few reports that implicate sequence variants within the DNA repair pathway may partially explain increased risk of developing breast, lung and prostate cancer among men of African descent [10–12]. However, there are limited published reports on whether genetic alterations linked with compromised DNA repair function (i.e., carriers of *OGG1* 326 Cys, *XPA* -4 A, *XPB* 312 Asn, *XPB* 751 Gln, *XRCC1* 399 Gln, and *APEX1* 148 Glu) are involved in prostate tumorigenesis among high-risk subgroups, particularly African-American men. In particular, out of ten studies on the relationship between the aforementioned commonly studied BER/NER repair genes and prostate cancer, one report focused on African-Americans [13], despite the fact that these men suffer the highest prostate cancer incidence and mortality rates [14]. The *XRCC1* Arg 399 Gln SNP may increase PCA susceptibility in Han Chinese but not in Caucasians or Japanese [15–17]. When the *APEX1* 148 Glu allele was considered in combination with the *XRCC1* 399 Gln allele (linked with reduced DNA repair capacity) in Caucasians (258 cases and 215 controls), Chen and co-workers (2006) observed a 2- to 3-fold increase in the risk of developing PCA relative to those with the referent genotype [13]. Inheritance of at least one *XPA* -4 G allele was linked to a 25–27% reduction in lung cancer risk in a meta-analysis involving five studies and seven populations [10,18–22]. To our knowledge, only 3 observational studies have reported on the relationship between these two *XPB* polymorphisms and PCA risk [23–25]. Notably, the *XPB* 312 Asn/Asn alone (OR = 1.81; 95%CI = 1.21–2.69) or combined with 751 Gln/Gln (OR = 1.63; 95%CI = 0.97–2.75) genotypes are associated with a 1.6–1.8-fold increase in PCA risk among Taiwanese and Caucasians, respectively [24,25]. Inheritance of *XPB* 312 combined with 751 variant alleles may jointly influence mutagen sensitivity to hazardous agents and alter cancer susceptibility [21,26,27]. Additionally, a few studies suggest that inheritance of two or more high-risk NER alleles (e.g., *XPA* -4 A, *XPB* 312 Asn, and *XPB* 751 Gln) may be linked to breast, and lung cancer [20,21,27,28]. However, the precise role of these markers in PCA risk among men of African Descent remains largely unknown.

To clarify the role of DNA repair genes in PCA risk within a high-risk sub-group, we evaluated the individual and joint modifying effects of six sequence variants in BER and NER pathways in a case-control study of men of African Descent (208 cases and 665

disease-free controls). We also we evaluated main and SNP combination using an available non-parametric statistical model, namely multifactor dimensionality reduction (MDR). This advanced statistical tool readily overcomes sample size limitations often encountered by parametric statistical methods [e.g., logistic regression (LR) analysis]. MDR has 80% or more statistical power and rigor to evaluate gene-gene interactions, even in the presence of small sample sizes (i.e., at least 200 cases and 200 controls). The goal was to evaluate the genetic contribution to the development of prostate cancer among men of African descent.

Materials and Methods

Study Population

Unrelated male residents (n = 1016) of Washington D.C. and Columbia SC, were considered for eligibility in the current PCA case control study. Study participants (n = 132) were not considered in the current study if they met one or more of the following exclusion criteria: (1) they were diagnosed with benign prostatic hyperplasia (n = 64); (2) had an abnormal PSA and DRE (n = 11); and (3) had European ancestry based on a Global Ancestry score of < 25% (n = 70) [29]. Eligible men of African descent (i.e., self-identified African-Americans, East Africans, West Africans, and Afro-Caribbeans), including 208 patients (ages 41–91) and 665 healthy volunteers (ages 26–89), were recruited from the Howard University Hospital (HUH) Division of Urology PCA patient population, the HUH PCA screening program, and the South Carolina PCA screening program (Table 1). The PCA patients and controls were recruited between 2001 and 2005. Incident PCA cases in the current study were identified by an HUH urologist based on abnormal prostate-specific antigen (PSA) and/or digital rectal examination (DRE) as well as histological findings following a radical prostatectomy. Inclusion criteria of controls were men with PSA levels less than 4.0 ng/ml and/or normal DREs/biopsies. Tumor grade, ranging from 4–10, was collected for 62.0% of the cases (n = 129). Cases (n = 24) were classified with aggressive disease if they had a Gleason score ≥ 7 . All study participants had available DNA extracted from whole blood and provided written informed consent for participation in genetic analysis studies under a protocol approved by the Howard University Institutional Review Board as well as from the HUH Division of Urology.

TaqMan allelic discrimination

Polymorphisms in six DNA repair genes were ascertained via TaqMan-Polymerase Chain Reaction (PCR) allelic discrimination assays using the ABI 7900 sequence detection system and SDS 2.2.1 software (Applied Biosystems, Foster City, CA). To minimize misclassification bias, laboratory technicians were blinded to the case status of study participants as well as quality control samples. Based on 24 non-DNA template controls per batch analysis, the percent cross-contamination during sample handling was minimal (<4.0%). Duplicate genotyping was performed for 72 randomly selected samples for quality control purposes, resulting in concordance rates >98%. The genotype call rates ranged between 89.6–96.2% across the six SNPs.

Ancestry markers

One hundred ancestry previously validate autosomal markers were included to account for potential population stratification among our admixed population of self-reported African-Americans, West African, East African, Afro-Caribbean, as previously described [30]. Study participants were grouped from lowest to highest genetic West African Ancestry, with scores ranging from 0–100%. These 100 markers were assembled using DNA from self-identified African-Americans (Coriell Institute for Medical Research, n = 96), Yoruban West Africans (HapMap, n = 60), West Africans (Bantu and Nilo Saharan speakers, n = 72), Europeans (New York City, n = 24), and CEPH Europeans (HapMap Panel, n = 60), as

previously reported [30]. Individuals (n = 873) with a high degree of West African Ancestry greater than or equal to 75% were considered in the final analysis.

Single and Multiple Gene Effects

To assess whether individuals possessing at least one variant DNA repair allele have an elevated risk of developing PCA, we tested for significant differences in the distribution of DNA repair genotypes using the chi-square test of homogeneity. Associations between PCA risk and candidate polymorphic genes, expressed as odds ratios (ORs) and corresponding 95% confidence intervals (CIs), were estimated using unconditional multivariate LR models adjusted for potential confounders [age (yrs), PSA (ng/ml), and West African Ancestry (continuous)]. All of our cases and controls were also genotyped with a set of 100 genome-wide ancestry informative markers to correct for individual ancestry, as detailed previously [29,30]. Test for trend included genotypes as ordinal variables. Statistical significance was assessed using a P-value < 0.05. All chi-square test and LR analyses were conducted using SAS 9.1.3.

To complement LR analyses, MDR was used to evaluate single gene and gene-gene interactions associated with PCA risk. The details of MDR are detailed and reviewed elsewhere [31–35]. Briefly, it is a “model free” method (it does not assume a specified genetic model) and “nonparametric” (it does not estimate parameters) for detecting and characterizing high-order interactions in observational studies. This data-mining platform readily overcomes sample size limitations often encountered by parametric statistical methods (e.g., LR analysis) by collapsing high-dimensional genetic data into a single dimension. MDR is used to model higher order gene-gene interactions and remains effective with relatively small sample sizes (i.e., at least 200 cases and 200 controls). Statistically significant single and multi-locus models may be adjusted for potential confounders by placing the MDR output variables into a logistic regression model. Validation of multilocus models as effective predictors of PCA susceptibility was derived empirically from 1,000 permutations. This approach accounted for multiple testing issues as long as the entire model fitting procedure was repeated for each randomized dataset, which provided an opportunity to identify false-positives. These MDR permutation results were considered statistically significant at the 0.05 level.

Results

The patient and tumor characteristics in the current study are summarized in Table 1. Cases were significantly older than controls and had higher PSA levels. Although there was a small portion of controls (5.6%) who had PSA levels that exceeded 4.0 ng/ml, these individuals did not have an abnormal DRE or irregular biopsy. There was a significant difference in median West African genetic ancestry estimates comparing cases and controls (P = 0.02).

Within our study set, inheritance of at least one variant *OGGI* 326 Cys (32.0%), *APEX1* 148 Glu (56.6%), *XRCC1* 399 Gln (25.7%), *XPA* -4 A (35.5%), *XPD* 312 Asn (19.2%), and *XPD* 751 Gln (38.7%) (linked with low DNA repair) was fairly common among controls, as delineated in Table 2. The genotype frequencies among controls did not deviate from expected distributions based on the Hardy-Weinberg equilibrium (P ≥ 0.138). These findings were comparable to those observed in other men of African descent sub-groups [27,36–38].

We evaluated whether inheriting at least one variant DNA repair allele was associated with increased PCA risk in men (Table 2). All risk estimates were adjusted for age, PSA, and WAA estimates. In particular, individuals possessing at least one *XPD* 312 Asn allele had a

1.3- to 8.6-fold higher PCA risk when compared to those with the 312 Asp/Asp genotype. However, the risk estimate was only statistically significant among carriers of two 312 Asn alleles (OR = 8.59; 95% CI = 1.81–40.66; P-trend = 0.110). Unfortunately, we were unable to confirm *XPD* 312 as a significant predictor of PCA risk as derived from MDR models. When the DNA repair SNPs were examined one at a time using a chi-square test for homogeneity, there were no significant differences in the allele frequencies between cases and controls for the *OGG1* 326 (P = 0.518), *APEX1* 148 (P = 0.138), *XRCC1* 399 (P = 0.833), *XPA* -4 (P = 0.909), *XPD* 312 (P = 0.095), and *XPD* 751 (P = 0.922) SNPs. After evaluating all possible 2- and 3-way interactions using MDR, we did not observe any significant gene-gene interactions (data not shown).

Discussion

NER and BER pathways are the predominant means for repair of environmental- and oxidative stress-induced DNA damage. As such, we evaluated the impact of individual polymorphisms in selected NER and BER genes on PCA susceptibility among men of African descent. Emphasis was placed on targets commonly published in the literature to determine whether we could confirm previous findings [24,25]. Comparable to the current study, two independent studies demonstrated a 1.6- to 1.8-fold increase in the risk of developing PCA among Caucasians (OR = 1.59; 95% CI = 1.01–2.51) and Taiwanese (OR = 1.75; 95% CI = 1.01–3.05) with the *XPD* 312 Asn/Asn genotype [15,24]. Although we observed a 8.6-fold increase in risk (OR = 8.59; 95% CI = 1.81–40.66) among carriers of two *XPD* 312 Asn alleles using LR analysis, this main effect was not validated by MDR. Unlike LR, MDR can evaluate the predictive nature of an individual locus in the presence of extremely wide 95% CIs, which are typically indicative of low cell counts. In terms of BER genes, five of nine observational studies demonstrated a 2- to 3-fold increase in the risk of developing PCA among *OGG1* Cys/Cys or *XRCC1* Gln/Gln carriers [13,15–17,23,24,38–40]. Based on the current study and a published report, *OGG1*, *XRCC1*, and *APEX1* alone do not appear to play significant roles in PCA susceptibility among men of African descent [13].

Some investigators evaluated whether interactions between NER and BER pathways influence cancer susceptibility with significant findings in three independent studies [21,24,26,41]. Two of these studies used a single gene approach (i.e., LR analysis) to model gene interactions [21,24]. Of these, one study was unable to substantiate the joint modifying effects of NER and BER SNPs in relation to bladder cancer risk [26]. However, Rybicki and co-workers (2004) reported a potential interaction between *XPD* 312 Asn and *XRCC1* 399 Gln variant alleles in relation to PCA among Caucasian study participants [24]. Individuals who were homozygous variant at both loci experienced a 4.8-fold elevation in their risk of developing PCA. In a post hoc analysis (data not shown), we observed a 8-fold increase in PCA risk among our study participants possessing three or more variant *XPD* 312 Asn and *XRCC1* 399 Gln alleles (OR = 8.12; 95% CI = 1.83–36.03; P-value for interaction = 0.241). The wide 95% CI intervals in both aforementioned studies are indicative of low cell counts, which generally result in inaccurate risk estimates. LR analysis simply lacks the statistical rigor to adequately model gene-gene interaction studies. To address this shortcoming, we evaluated the interaction of *XPD* 312 and *XRCC1* 399 using MDR. Unlike Rybicki, we were unable to confirm the joint modifying effects of *XPD***XRCC1* in relation to PCA. These findings reinforce the need to use rigorous statistical tools such as MDR to validate gene-combination effects analyzed using conventional methods.

We evaluated 56 gene interaction MDR models in relation to PCA risk and assessed study strengths and limitations for their implications on the interpretation of findings. The current study adjusted single loci models for genetic heterogeneity (i.e., population admixture). This

is particularly a problem for genetic epidemiology studies involving study participants of African descent on their unique population history of gene flow from divergent populations [42,43]. In addition, it helps to circumvent misclassification of study participants related due to self-identified race/ethnicity (SIRE). However, our findings suggest that inclusion of WAA does not significantly change the risk estimates relative to unadjusted models; if anything it makes them more precise to the nearest tenth. We found that when using traditional statistical methods, multiple comparisons may lead to spurious risk estimates. However, MDR controls for this issue by using a cross validation and permutation testing scheme as a built-in feature. Unfortunately, we were unable to confirm previous individual and gene-gene interactions in relation to PCA among our study participants. This may be partially attributed to failing to consider the genetic heterogeneity of selected targets. Pooled genetic analyses involving >5000 cases and >5000 disease-free men of African descent will permit the identification, evaluation and validation of more than NER and BER sequence variations and their individual and joint modifying effects in relation to PCA susceptibility using various *in silico* databases and advanced statistical tools.

In summary, we did not observe significant individual or joint modifying effects of commonly studied variant DNA repair genes (i.e., *OGGI*, *XRCCI*, *APEXI*, *XPA*, *XPB*) among men of African descent on PCA risk. Given the limited data in the literature, the potential role of combined effects of two or more variant DNA repair genes in relation to PCA susceptibility is inconclusive. In collaboration with a cancer consortium, our laboratory will pool available genotype data to consider a plethora (n = 64) of DNA repair biomarkers as effective predictors of PCA detection and disease prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient and Tumor Characteristics

Characteristics	Cases	Controls	P-value ^a
No. of Participants, n	208	665	---
Age (yrs)			
Median (range)	65 (41–91)	52 (26–89)	0.0001
PSA in ng/ml			
< 4	43 (22.0)	609 (94.4)	< 0.0001
≥4 ng/ml	152 (78.0)	36 (5.6)	
Gleason Score n (%)			
4	17 (13.2)		
5	15 (11.6)		
6	33 (25.6)		
7	40 (31.0)		
8	6 (4.6)		
9	14 (10.9)		
10	4 (3.10)		
Global West African Ancestry Median (SD)	0.791 (0.253–0.947)	0.718 (0.255–0.946)	0.020

Abbreviations: PSA, prostate specific antigen

^aDifferences in frequencies were tested by a Chi-square test of heterogeneity (i.e., PSA ng/ml); Differences in age and Global West African Ancestry between cases and controls were tested using the Wilcoxon sum Rank test.

Table 2

Association between Prostate Cancer and DNA Repair Genes

Gene	Amino Acid Change	Case n (%)	Control n (%)	Risk Estimate [†] OR (95% CI)	Risk Estimate ^{††} Adj OR (95% CI)	P-Value ^{†††}	P-Value for Trend [‡]
BER^{††}		N = 208	N = 665				
<i>OGGI</i> (Ser ³²⁶ Cys)	Ser/Ser	132 (68.0)	452 (70.0)	1.00		0.518	0.864
	Ser/Cys	58 (30.0)	173 (26.8)	1.15 (0.80–1.64)	1.13 (0.71–1.80)		
	Cys/Cys	4 (2.0)	21 (3.2)	0.65 (0.22–1.94)	0.87 (0.22–3.43)		
	≥ 1 Cys	62 (32.0)	194 (30.0)	1.09 (0.78–1.55)	1.11 (0.70–1.74)		
	missing	14 (6.7)	19 (2.9)				
<i>APEXI</i> (Asp ¹⁴⁸ Glu)	Asp/Asp	82 (44.1)	274 (43.4)	1.00		0.138	0.873
	Asp/Glu	88 (47.3)	269 (42.6)	1.09 (0.77–1.54)	1.04 (0.65–1.65)		
	Glu/Glu	16 (8.6)	88 (14.0)	0.61 (0.34–1.09)	0.92 (0.44–1.91)		
	≥ 1 Glu	104 (55.9)	357 (56.6)	0.97 (0.70–1.35)	1.01 (0.65–1.57)		
	missing	22 (10.6)	34 (5.1)				
<i>XRCC1</i> (Arg ³⁹⁹ Gln)	Arg/Arg	137 (72.5)	475 (74.3)	1.00		0.833	0.696
	Arg/Gln	48 (25.4)	149 (23.3)	1.04 (0.72–1.51)	1.21 (0.74–1.99)		
	Gln/Gln	4 (2.1)	15 (2.4)	0.86 (0.28–2.64)	1.54 (0.44–5.35)		
	≥ 1 Gln	52 (27.5)	164 (25.7)	1.10 (0.76–1.58)	1.29 (0.80–2.08)		
	missing	19 (9.1)	26 (3.9)				
NER^{†††}							
<i>XPA</i> G ⁻⁴ A	G/G	127 (66.2)	403 (64.5)	1.00		0.909	0.663
	G/A	56 (29.2)	190 (30.4)	0.94 (0.65–1.34)	0.90 (0.54–1.50)		
	A/A	9 (4.7)	32 (5.1)	0.89 (0.42–1.92)	1.10 (0.39–3.10)		
	≥ 1 A	65 (33.8)	222 (35.5)	0.93 (0.66–1.31)	0.93 (0.57–1.50)		
	missing	16 (7.7)	40 (6.0)				
<i>XPB</i> (Asp ³¹² Asn)	Asp/Asp	146 (76.8)	510 (80.8)	1.00		0.095	0.110
	Asp/Asn	39 (20.5)	116 (18.4)	1.17 (0.78–1.76)	1.28 (0.75–2.17)		
	Asn/Asn	5 (2.6)	5 (0.8)	3.49 (1.00–12.23)	8.59 (1.81–40.66)		
	≥ 1 Asn	44 (23.2)	121 (19.2)	1.27 (0.86–1.88)	1.47 (0.88–2.44)		
	missing	18 (8.6)	34 (5.1)				
<i>XPB</i> (Lys ⁷⁵¹ Gln)	Lys/Lys	110 (60.1)	367 (61.3)	1.00		0.922	0.712

Gene	Amino Acid Change	Case n (%)	Control n (%)	Risk Estimate [†]	OR (95% CI)	Risk Estimate ^{††}	Adj OR (95% CI)	P-Value ^{†††}	P-Value for Trend [‡]
	Lys/Gln	60 (32.8)	194 (32.4)	1.03 (0.72–1.48)		0.92 (0.57–1.48)			
	Gln/Gln	13 (7.1)	38 (6.3)	1.14 (0.59–2.22)		1.18 (0.47–3.00)			
	≥ 1 Gln	73 (40.0)	232 (38.7)	1.05 (0.75–1.47)		0.96 (0.61–1.50)			

[†]Associations were determined using multivariate LR models to estimate the risk of developing PCA using *OGGI* 326 Ser/Ser, *APEX1* 148 Asp/Asp, *XRCC1* 399 Arg/Arg, *XPA* –4 Gln/Gln, *XPD* 312 Asp/Asp, and *XPD* 751 Lys/Lys as the reference genotypes.

^{††}Risk estimates adjusted for age (continuous variable), prostate specific antigen (continuous variable), and admixture (continuous variable).

^{†††}Differences in the frequency of high-risk and low-risk genotypes between cases and controls were determined using the chi-square test of association with a significance level of 0.05.

[‡]P-value for trend adjusted for age, PSA, and admixture.

^{##}BER, base excision repair genes.

^{###}NER, nucleotide excision repair genes.