Rare germline mutations in African American men diagnosed with early-onset prostate cancer

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ABSTRACT

Background: African Americans have both a higher incidence of prostate cancer and greater disease-specific mortality compared with non-Hispanic whites. Historically, the investigation of the contribution of rare genetic variants to prostate cancer in African American men has been hampered by low participation in large genetic studies, particularly those focused on early-onset and familial disease.

Methods: We sequenced 160 genes purported to be involved in carcinogenic pathways in germline DNA samples collected from 96 African American men diagnosed with early-onset prostate cancer (≤55 years at diagnosis). REVEL software was used to determine the pathogenic potential of observed missense variants.

Results: We observed 3 protein-truncating mutations, one in *BRCA2* and 2 in *BRIP1* in three African American men diagnosed with early-onset prostate cancer. Furthermore, we observed 5 rare, mostly private, missense variants among 4 genes (*BRCA1*, *BRCA2*, *PMS2* and *ATM*) that were predicted to be deleterious and hence likely pathogenic in our patient sample.

Conclusions: Protein-truncating mutations in *BRCA2* and *BRIP1* were discovered in African American men diagnosed with early-onset prostate cancer. Further study is necessary to determine the role of rare, missense variants to prostate cancer incidence and progression in this group of high-risk men.

BACKGROUND

Prostate cancer is the most common invasive cancer among men in the United States with 161,360 new cases expected to be diagnosed in 2017(1). Advancing age, race and a family history of prostate cancer continue to be the most important predictors of risk. The incidence of prostate cancer is approximately 60% higher among African American men compared to non-Hispanic white men. The death rate among African American men with prostate cancer is more than 2 times that of their non-Hispanic white counterparts. (2;3) A number of driving factors have been investigated in an attempt to explain these disparities including differential access to and use of medical care, particularly screening for early detection and definitive treatment post-diagnosis.(4) The presence of comorbid conditions certainly impacts overall mortality in men with prostate cancer, but there is also evidence to suggest that hypertension, insulin resistance and abdominal obesity increase risk of disease progression after definitive treatment. The prevalence of hypertension and diabetes in particular is higher in African Americans and symptoms are not as well controlled compared to whites.(5;6)

Family history of prostate cancer, particularly among first-degree relatives, is a well-recognized risk factor for the disease pointing to the importance of genetics in prostate cancer risk. It has been estimated that up to 40% of prostate cancers diagnosed may be attributed to one or more gene variants or mutations.(7) However, the field of prostate cancer genetics has been challenged by both the clinical and genetic heterogeneity of the disease as well as the high rate of sporadic cases. Genome-wide association studies (GWAS) have resulted in the discovery of >100 common genetic variants associated with prostate cancer. GWAS single nucleotide polymorphisms (or SNPs) explain some of the familial clustering of disease, but in aggregate these variants only account for ~30% of the familial risk.(8;9) It is unknown how many of these common variants are actually tagging less-common, yet highly-penetrant, coding variants. The declining cost of next-generation sequencing (NGS) over the past few years has made sequencing coding regions of the genome a feasible strategy for the identification of rare mutations.

As with most cancers, an earlier age at onset of prostate cancer, with or without a family history, is also an important indicator of the influence of inherited susceptibility.(10) As proof, men with early-onset prostate cancer have been shown to have a higher likelihood of harboring disease-associated GWAS SNPs (11) and rare mutations such as *HOXB13* G84 E.(12) Despite the fact that only 10% of prostate cancers in the United States are diagnosed at or before age 55 years (herein defined as early-onset prostate cancer), (13) there is evidence indicating that prostate cancer in younger men may be more clinically aggressive. Lin et al observed among men with high grade and locally advanced disease, younger men tended to have a poorer prognosis compared to older men.(14) We recently reported, using data from the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) program, that both 5- and 10-year relative survival rates in men with early-onset prostate cancer were significantly worse compared to men in their 60s and 70s.(13) This is particularly true of African American men with early-onset disease.(15) However, our understanding of the genetic epidemiology of prostate cancer in African American men lags behind that of whites primarily due to low African American participation in large scale genetic studies. Thus, the current investigation focuses on the identification and characterization of rare germline mutations in young African American men diagnosed with clinically significant prostate cancer.

PATIENTS AND METHODS

Eligible patients were diagnosed at 55 years of age or younger with pathologically-confirmed prostate cancer and self-identified as African American. All patients were either subjects in an ongoing prostate cancer cohort at the Karmanos Cancer Institute (KCI) in Detroit, Michigan who donated DNA specimens for genetic investigation or participants of the University of Michigan Prostate Cancer Genetics Project (UM PCGP) in Ann Arbor, Michigan, a study founded to determine the genetic contribution to hereditary and early-onset prostate cancer. Informed consent was obtained from each participant and protocol for each study was approved by the respective Institutional Review Boards. Family history of prostate cancer among first-degree relatives and patient blood specimens were collected during baseline interviews for each study and relevant clinical information and treatment at time of diagnosis was abstracted from medical records.

Laboratory Methods

DNA was extracted from whole blood using standard protocol (Gentra® Puregene®). Targeted enrichment was performed via PCR using overlapping primer sets across the exonic portions of the selected genes with a goal depth-of-coverage of at least 40x. After targeted enrichment, samples were submitted to the University of Michigan DNA Sequencing Core for library preparation and NGS using HiSeq V4 (Illumina, San Diego, CA) technologies. A commercially-available gene panel was used which included 160 genes purported to be involved in carcinogenesis (Supplementary Table 1) (Human Comprehensive Cancer GeneRead DNASeq Targeted Panel V2 (Qiagen, Valencia, CA).

Bioinformatics

Analysis of data was performed using the GeneRead Targeted Exon Enrichment Panel Data Analysis Portal (Qiagen Inc). Each identified variant was assessed based on the variant's putative functional importance [preference given to stop/loss, frame-shifts insertions/deletions, important splice variants (Tier 1) followed by missense variants (Tier 2)], number of subjects carrying the minor allele, and observed frequency of the minor allele in publically available databases (e.g. ESP, dbSNP, and 1000 Genomes Project). To determine the pathogenic potential of missense variants we used REVEL, an ensemble method which incorporates 18 individual prediction scores from 13 tools and has been shown to be particularly useful in the assessment of pathogenicity of rare variants.(16) Pathogenic variants were confirmed through Sanger sequencing. The number of carriers observed in our study population was reported along with the minor allele frequency of variants among African American samples from the Exome Aggregation Consortium (EXAC version 1.0, 02/27/2017).

RESULTS

Of the 96 samples selected for sequencing, 66 were from UM and 30 were from KCI. Clinical characteristics of the cases are summarized in Table 1. The median age of prostate cancer diagnosis of the men was 50 years (range 40 to 55 years). The median pre-diagnosis PSA was 7 ng/ml (range 1.2 to 3686 ng/ml). Half of the men had Gleason 3+4 disease. More than half of men were diagnosed with stage T2 disease and 9 men had either nodal or distant metastasis at diagnosis.

We discovered samples from three African American men possessed a protein truncating mutation, one in the *BRCA2* gene and two in the *BRCA1*-Interacting Protein-1 gene or *BRIP1*. Details related to the mutation, clinical characteristics and cancer family history are provided in Table 2. The only truncating mutation in *BRCA2* was the result of a single point mutation (c.1970T>A; p. L657*) in a patient diagnosed at age 48 with Gleason 7 (3+4) disease, tumor stage unknown, with a positive family history of breast cancer. The two frameshift mutations in *BRIP1* were the result of a deletion of adenine and thymine at codon 3730 (c. 3730_3731del2; p. M1244Vfs*5) (Case B) and an insertion of cytosine at codon 69 (c. 69insC; p.S24Vfs*44) (Case C). These men were diagnosed at age 51 and 54 years, respectively. Case B was diagnosed with Gleason 7 (4+3), stage T2a disease and Case C with Gleason 3+4, stage T3a disease. Neither man had any reported family history of prostate, breast or ovarian cancer.

Table 3 lists rare (minor allele frequencies (MAF) <1% in both African American and European American individuals in ESP), likely deleterious (based on REVEL scores >0.7) missense mutations occurring in a panel of 16 DNA repair genes (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FAM175A*, *GEN1*, *MRE11A*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51C*, and *RAD51D*). Deleterious mutations were previously identified in these 16 genes in a study of germline DNA samples isolated from 692 men with metastatic prostate cancer (5% African American participants) by Pritchard et al.(17) In our cohort, we found 2 mutations in *ATM*, and one each in *BRCA1*, *BRCA2* and *PMS2* that were confirmed with Sanger sequencing.

DISCUSSION

Results from the current investigation indicate the presence of deleterious mutations in both *BRCA2* and *BRIP1* among African American men diagnosed with early-onset prostate cancer. We also found two rare missense mutations, one each in *BRCA1* and *BRCA2,* that were predicted to be pathogenic based on the in silico prediction tool REVEL. *BRCA2* mutations have been associated with a 2- to 6-fold increase in prostate cancer risk.(18-21) Numerous studies have signaled the importance of both hereditary breast and ovarian cancer genes (*BRCA1* and *BRCA2*) with prostate cancer risk predominantly in populations of Ashkenazi Jewish, Norwegian, Dutch and Icelandic descent.(22) . These two tumor suppressor genes are involved in the maintenance of genomic stability through their role in double-strand DNA repair and mutations in DNA repair genes have been linked to both early-onset and hereditary prostate cancer, as well as more aggressive clinical features time of diagnosis, with earlier progression to metastatic disease and higher prostate cancer-specific mortality.(23-28) Moreover, *BRCA1/2* mutations have also been connected to response to therapy in prostate cancer, in particular response to treatment with platinum-based chemotherapy and Poly (ADP-ribose) polymerase (PARP) inhibitors.(29;30) Clinical trial results suggest that *BRCA2* mutation carriers with metastatic castrate resistant prostate cancer treated with olaparib experience high response to treatment.(31) Based on the role of *BRCA1* and *BRCA2* in prostate cancer risk and disease progression, NCCN guidelines recommend prostate cancer screening beginning at age 40 for men known to harbor a mutation in either *BRCA1* or *BRCA2*.(32)

To our knowledge, no other investigation has sought to characterize the role of *BRCA1/2* mutations in African American men with prostate cancer, thus much of our knowledge about the prevalence and spectrum of mutations are derived from studies of African American women with breast cancer. An estimate of the prevalence of *BRCA* mutations in a population of African Ancestry unselected for family history or early-onset cancer has yet to be determined. However, studies of young African American breast cancer patients suggest that the prevalence may be higher than populations of European ancestry, identifying both novel founder mutations as well as an increase in the proportion of mutations that might be characterized as variants of unknown significance (VUS).(33-37) In a recent study of African American women diagnosed with primary invasive breast cancer selected for familial disease or tumor characteristics indicative of increased genetic susceptibility, Churpek identified damaging mutations in 22% of patients, 80% of which were mutations in *BRCA1* or *2*. Mutations were also observed in *PALB2*, *CHEK2*, *BARD1*, *ATM*, *PTEN* and *TP53*.(33)

Far less is known of the role of *BRIP1* and prostate cancer risk specifically, although the gene interacts with *BRCA1* playing a role in DNA damage repair.(38;39) *BRIP1* is implicated in Fanconi anemia, a rare autosomal recessive disorder, associated with an increased risk for acute myeloid leukemia and other solid tumors, including breast and prostate cancer.(40-43) In a recently published series of 692 men with metastatic prostate cancer, one truncating mutation in *BRIP1* was observed.(17) Our own work identified 7 missense variants in *BRIP1* among 94 individuals with hereditary prostate cancer but no protein truncating mutations were observed.(44)

In this study, we also discovered two germline missense variants in *ATM* and one in *PMS2* that are rare and predicted to be pathogenic based on the in silico prediction tool REVEL. The Ataxia Telangiectasia Mutated (*ATM*) is a gene with a pivotal function in cell division and DNA repair and thus an attractive cancer susceptibility candidate. Prior studies have identified mutations in *ATM* in patients with prostate cancer including lethal forms of the disease.(17;45;46) With the exception of *BRCA2*, it is the most commonly mutated DNA repair gene in men with lethal disease.(17;46) The *PMS2* (or post-meiotic segregation 2) gene functions in mismatch repair and is suggested to protect against prostate cancer progression through promotion of apoptosis in cancer cells.(47) It has also been shown that a reduction or loss of the *PMS2* protein is associated with poorer differentiation of prostate tumors.(48)

The current cohort represents one of the largest investigations of early-onset prostate cancer in African American men aimed at identifying uncommon and rare germline variants associated with heightened prostate cancer susceptibility. This valuable patient resource is further enhanced by the enrichment of patients with a positive family history of prostate cancer, careful collection of family histories of prostate and other cancers, and well-characterized clinical information. Enrichment of patient populations with men diagnosed with early-onset and familial disease is a useful tool for discovery of variants. However, the generalizability of these findings to the larger population of African American men with prostate cancer is questionable given the study is clinic- and not population-based. Both KCI and UM are large tertiary referral hospitals, and are therefore likely to see patients with more clinically aggressive disease.

Our results provide evidence that rare mutations in DNA repair genes are important in African American men diagnosed with early-onset disease. Given the potential therapeutic benefit in *BRCA* mutation carriers in particular, screening young African American men with prostate cancer irrespective of their family history of breast and ovarian cancer could have a significant impact on long-term survival. Further investigation in larger, population-based patient populations will be critical in understanding the prevalence and range of mutations in African American men.

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Table 1. Clinical Characteristics of African American Men with Early-Onset Prostate Cancer (n=96)

Variable	Number (%)	[Range]
Median age of diagnosis	50 years	[40-55 years]
Gleason Grade		
6	15 (15.6%)	
3+4=7	48 (50.0%)	
4+3=7	12 (12.5%)	
>7	19 (19.8%)	
Unknown	2 (2.1%)	
Median PSA at diagnosis	7 ng/ml	[1.2 to 3686 ng/ml]
T Stage		
T2	52 (54.2%)	
T3	18 (18.8%)	
T4	1 (1.0%)	
Unknown	25 (26%)	
N0/NX and M0/MX	74 (77.1%)	
M1 or N1	9 (9.4%)	
Missing	13 (13.5%)	

Table 2. Characteristics of African American Prostate Cancer Patients with Germline Protein Truncating Mutations

	Case A	**Case B**	**Case C**
Gene	*BRCA2*	*BRIP1*	*BRIP1*
GRCh37/hg19 Position	13:32910462	17:59760675	17:59938832
Nucleotide Change	c.1970 T>A	c.3730delAT	c.69insC
Protein Effect	Leu657Stop	Met1244ValfsTer5	Ser24ValfsTer44
Characteristics			
Age at diagnosis (years)	48	51	54
Pathologic Gleason Score	3+4=7	4+3=7	3+4=7
Stage	Unknown	T2bN0M0	T3aN0M0
PSA at Diagnosis (ng/ml)	6.1	9.2	3.5
Family History			
Prostate Cancer	No	No	No
Breast Cancer	Yes (first-degree)	No	No
Ovarian Cancer	No	No	No

Table 3. Rare (MAF < 1%) germline missense variants with high predictive pathogenicity (REVEL >0.7) in African American patients with early-onset prostate cancer observed in genes previously implicated in prostate cancer.

Chr	Pos GRCh37	dbSNP ID	Ref	Var	Gene	Codon Change	AA Change	# Carriers	ESP EA MAF (%)	ESP AA MAF (%)	Revel Score
13	32913077	rs28897728	G	A	BRCA2	c.4585G>A	G1529R	1	0.07	0	0.90
17	41249297	rs55688530	G	T	BRCA1	c.557C>A	S186Y	1	0	0.68	0.78
7	6042124	rs116349687	A	G	PMS2	c.497T>C	L166P	1	0	0.32	0.78
11	108160480	rs138327406	T	G	ATM	c.4388T>G	F1463C	1	0.16	0.02	0.76
11	108201014	rs201314561	C	T	ATM	c.7381C>T	R2461C	1	0	0.07	0.71