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Cancer Epidemiology, Biomarkers & Prevention

Research Article

HOXB13 Mutation and Prostate Cancer: Studies of Siblings and Aggressive Disease

John S. Witte[1], Joel Mefford[1], Sarah J. Plummer[2], Jinghua Liu[1], Iona Cheng[3], Eric A. Klein[4], Benjamin A. Rybicki[5], and Graham Casey[2]

Abstract

Background: Recent work detected for the first time a high-risk prostate cancer mutation, in homeobox B13 (*HOXB13*) among European-Americans.

Methods: We further evaluated this G84E missense mutation (rs138213197) in two genetic association studies of prostate cancer: a family-based study of brothers and a case–control study of more aggressive disease (N = 2,665 total). We then calculated overall impact of this mutation by pooling all published studies of European-Americans.

Results: In our studies, the mutation was found exclusively among men with prostate cancer (carrier frequency = 1.48%) or unaffected brothers of cases carrying the mutation (frequency = 0.34%), and carrying the mutation gave an OR for disease = 4.79 ($P = 0.01$). The G84E mutation was more common among men with an earlier age of onset (≤55 years) or a family history of prostate cancer. We also observed for the first time an African-American case carrying the G84E mutation, although at *HOXB13* both of his chromosomes were of European-American ancestry. The pooled analysis also indicated that carrying the G84E mutation results in an almost five-fold increase in risk of prostate cancer ($P = 3.5 \times 10^{-17}$), and this risk is even higher among cases with an early age of prostate cancer onset (≤55 years) or a family history of disease: a test of heterogeneity across these strata gives $P < 1 \times 10^{-5}$.

Conclusions: The *HOXB13* mutation substantially increases risk of early onset, familial prostate cancer in European-American men.

Impact: Testing for the G84E mutation in men with a positive family history may help distinguish those who merit more regular screening for prostate cancer. *Cancer Epidemiol Biomarkers Prev; 22(4); 675–80.*

Introduction

Prostate cancer is a complex disease with high morbidity and mortality, and the highest heritability of common cancers (1). Genome-wide association studies have successfully detected well more than 50 common low-risk single-nucleotide polymorphisms for prostate cancer, and taken together, these variants explain an increasing proportion of heritability although much remains unexplained (2). In contrast, linkage studies searching for high-penetrance prostate cancer genes have had limited success: while numerous chromosomal regions potentially containing prostate cancer genes have been localized, until recently, no high-penetrance genes within these regions have been convincingly identified (3). This contrasts with the situation for other common cancers such as breast and ovarian cancers, where numerous high-risk genes have been detected (e.g., BRCA1/2).

Now a high-penetrance gene for prostate cancer has been detected, *HOXB13*, which encodes the transcription factor homeobox B13. The gene was detected by sequencing 94 unrelated men from heavily loaded prostate cancer families exhibiting linkage to a previously reported region on chromosome 17q21-22 (4–6). In 4 families of European-American ancestry, a rare nonsynonymous mutation—substitution of glutamic acid for glycine—was detected in *HOXB13* (G84E, rs138213197; ref. 7). This mutation was then genotyped in a large number of additional samples and was seen in 72 of 5083 cases (carrier frequency = 1.44%) but only 1 of 1,401 controls (frequency = 0.07%). The G84E mutation frequency was increased to 2.2% when restricting to men with an early age of disease onset (≤ 55 years) or a positive family history of prostate cancer

Authors' Affiliations: [1]Departments of Epidemiology & Biostatistics and Urology, Institute for Human Genetics, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco; [2]Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles; [3]Cancer Prevention Institute of California, Fremont, California; [4]Glickman Urological and Kidney Institute and Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio; and [5]Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan

Corresponding Author: John S. Witte, Departments of Epidemiology & Biostatistics and Urology, University of California San Francisco, San Francisco, CA 94158. Phone: 415-505-3066; E-mail: jwitte@ucsf.edu

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(7). Other studies have confirmed this finding in men with European ancestry (8–10), and different *HOXB13* mutations have been detected in prostate cancer cases of African and Asian ancestry (7, 9, 11).

To further investigate the potential role of the high-penetrance *HOXB13* mutation in prostate cancer, we tested the G84E missense mutation in 2 studies with different designs than previously undertaken: a family-based study of brothers concordant and discordant for disease and a case–control study of more aggressive disease at diagnosis. In addition to helping characterize this mutation in a broader set of samples, these studies allow us to investigate the carrier status among unaffected first-degree relatives of cases, whether the mutation is more common among men with aggressive prostate cancer and whether it occurs among African-American men. We also calculated the overall impact of *HOXB13* G84E on prostate cancer with a pooled analysis of all results in European-American men published to date.

Materials and Methods

Study subjects

The subjects in both studies were recruited from the major medical institutions in the greater Cleveland, OH area and from the Henry Ford Health System, Detroit, MI. The family-based study has been previously described (12). Briefly, it included sets of siblings where one brother had prostate cancer diagnosed at age 73 years or younger and at least one brother with or without prostate cancer ($N = 1{,}124$; 647 cases, 477 controls). The sibling sets included 423 pairs (341 case–control, 82 case–case); 60 trios (39 with 1 case and 2 controls; 13 with 2 cases and 7 control, and 8 with 3 cases); and 16 quartets or larger. All controls were no more than 8 years younger than their brother's age at diagnosis. These age restrictions were used in an attempt to increase the potential for genetic factors affecting disease and to reduce the probability that the controls were not unaffected due simply to being of a younger age. The second population included aggressive incident prostate cancer cases and controls from the same medical institutions ($N = 1{,}540$, 998 cases and 542 controls). This has also been previously described (13). These cases were newly diagnosed with histologically confirmed disease, with any one of the following: Gleason score ≥ 7; tumor stage $\geq$ T2c; or a prostate-specific antigen (PSA) level greater than 10 ng/mL at diagnosis.

For both populations, case diagnoses were verified from medical record review and Gleason scores were based on pathology reports from radical prostatectomy specimens when available and otherwise from biopsy specimens. Controls had no diagnosis of prostate cancer or any other non-skin cancer. At the study entry, controls underwent prostate cancer screening with serum PSA testing and follow-up if their PSA was elevated (93% and 100% of the controls had their PSA tested in the family-based and case–control studies, respectively). If a value of 4.0 ng/mL or greater was attained, then a formal evaluation for prostate cancer by a urologist was undertaken. Depending on the evaluation, a biopsy of the prostate for histologic diagnosis was conducted. They were retained in the study as controls unless a subsequent diagnosis of prostate cancer was made—at which time they were reclassified as cases.

Ethics approval for these studies was obtained from the Institutional Review Board human subjects research committees at all institutions/hospitals from which participants were recruited (the Cleveland Clinic Foundation, University Hospitals of Cleveland/Case Western Reserve University, and the Henry Ford Health Systems), and at the University of Southern California (Los Angeles, CA) and University of California, San Francisco (San Francisco, CA). All men in these studies provided written informed consent.

Genotyping and sequencing

Standard venipuncture was used to collect blood samples from all study participants in tubes with EDTA as an anticoagulant. gDNA was extracted from buffy coats using the QIAmp DNA Blood Kit or the EZ1 DNA Blood Kit (QIAGEN, Inc.). A custom TaqMan SNP genotyping assay (Life Technologies) was used for detection of the *HOXB13* G84E mutation. The TaqMan assay used the Type-it Fast SNP PCR Master Mix (Qiagen) and was read on a 7900HT Real-Time PCR System (Life Technologies). To ensure quality control, 2% of samples were randomly selected and regenotyped. All observed mutations were PCR-amplified and sequenced (Genewiz). Both the replicate samples and the sequenced samples were 100% concordant with the observed genotypes.

Statistical analyses

Case and control carrier frequencies of the *HOXB13* G84E were calculated overall, and among cases within strata defined by age of onset (i.e., $\leq$55 years) and family history of prostate cancer (defined as having at least one first- or second-degree relative with prostate cancer). To formally evaluate the case–control differences in mutation frequencies within both of our study populations, we estimated ORs and *P* values from a mixed-effects logistic regression model. This allows for correlated nonindependent outcomes among family members due to family structure or shared environment via a random-effects intercept and adjusts for potential confounders (i.e., age, race/ethnicity, and medical institution). We also undertook a pooled analysis of the *HOXB13* G84E results published to date in European-Americans. The counts of carriers and noncarriers by disease status were used to calculate summary frequencies, as well as ORs, 95% confidence intervals (CI), and *P* values for association, again overall and within strata defined by age of onset and family history. Across these strata, we tested for heterogeneity in the mutation—prostate cancer associations. All *P* values are from 2-sided tests, and all analyses were undertaken with R.

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Results

Demographic and clinical details for the 1,645 cases and 1,019 controls from the 2 study populations are given in Table 1. The stage and grade are lower in the family-based than aggressiveness study, reflecting the inclusion criteria for the latter.

The *HOBX13* G84E mutation (rs138213197) was detected exclusively among men with prostate cancer or unaffected brothers of cases carrying the mutation (Table 2). In particular, within the family-based study, 12 cases (carrier frequency = 12/635 = 1.89%) and 3 controls (frequency = 3/474 = 0.63%) carried the mutation. When only considering families where the control brothers were at least as old as the cases, we observed a very similar carrier frequency (2/284 = 0.70%). Six of the 12 cases came from 3 families—that is there were 3 sets of concordantly affected mutation carriers. Another 3 of the 12 had unaffected siblings who also carried the mutation. Thus, in total 12 of the 15 men (80%) with the mutation were from 6 families with multiple carriers (9 cases, 3 controls). The percentage of families segregating the *HOBX13* G84E mutation was 9/526 = 1.71%. In the study of more aggressive disease, 8 cases carried the *HOXB13* G84E mutation (frequency = 0.81%), but none of the controls were carriers (Table 2). Combining the data from both of our studies in the mixed-effects model, carrying the mutation increased risk of prostate cancer almost five fold (adjusted OR = 4.79, $P = 0.01$).

The frequency of carrying the *HOXB13* G84E mutation was higher among cases with an earlier age at disease onset: for age ≤ 55 years, the carrier frequency = 2.64%, whereas for age > 55 years, the frequency = 0.96% (Table 2). A smaller difference in the mutation frequency was observed among cases with and without a family history of prostate cancer: 1.46% versus 1.10%, respectively (Table 2). When looking at each study alone, even this small difference was no longer evident—possibly reflecting the limited number of observations. Specifically, the mutation frequency among cases with and without a family history of prostate cancer was 1.77% versus 1.99% for the family-based study and 0.77% versus 0.71% for the aggressiveness study. There was no noteworthy association between the mutation and tumor stage or grade ($P = 0.36$) or recurrence/biochemical failure following treatment ($P = 0.75$).

One of the carriers in the aggressive disease study was African-American, the first time this has been reported among prostate cancer cases. To further investigate this, we estimated his local ancestry at *HOXB13*. First, we genotyped his germline DNA with the Illumina 1M array

Table 1. Characteristics of family-based and aggressive disease prostate cancer study populations from Cleveland, OH and Detroit, MI.

	Family-based study		Aggressiveness study[a]	
	Cases	**Controls**	**Cases**	**Controls**
n (%)	647 (58%)	477 (42%)	998 (65%)	542 (35%)
Age, mean (±SD)	61.9 (±6.8)	62.7 (±9.1)	64.1 (±7.9)	65.8 (±8.6)
>55 y	520 (80%)	367 (77%)	853 (86%)	470 (87%)
≤55 y	127 (20%)	110 (23%)	145 (14%)	72 (13%)
Family history of prostate cancer				
Negative	351 (55%)	393 (83%)	847 (87%)	530 (98%)
Positive	287 (45%)	81 (17%)	130 (13%)	10 (2%)
Race/ethnicity, *n* (%)				
White	584 (90%)	438 (92%)	698 (70%)	432 (80%)
African-American	63 (10%)	39 (8%)	300 (30%)	110 (20%)
Gleason score, *n* (%)				
≤6	339 (55%)	NA	218 (24%)	NA
7	204 (33%)	NA	508 (56%)	NA
≥8	73 (12%)	NA	184 (20%)	NA
Tumor stage, *n* (%)				
T1	302 (50%)	NA	404 (39%)	NA
T2a–T2b	214 (36%)	NA	183 (19%)	NA
T2c	37 (6%)	NA	291 (31%)	NA
≥T3	44 (7%)	NA	97 (11%)	NA
PSA; ng/mL, median (I–III quartile)[b]	7.0 (5.0–11.0)	1.5 (0.8–2.6)	6.6 (4.8–11.4)	1.2 (0.7–2.2)

[a]Aggressive disease defined as having any of the following: Gleason score ≥ 7; tumor stage ≥ T2c; or PSA level greater than 10 ng/mL at diagnosis

[b]At diagnosis for cases; at recruitment into study for controls.

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Table 2. *HOXB13* G84E mutations (rs138213197) detected in family-based and aggressive prostate cancer studies.

Study	G84E carriers (*n*)	G84E noncarriers (*n*)	Carrier frequency, %
Family-based			
Controls	3	474	0.63%
Cases	12	635	1.89%
Aggressive disease			
Controls	0	542	0%
Cases	8	990	0.81%
Both studies			
Controls	3	1016	0.29%
Cases	20	1625	1.22%
Both cases only			
Age at prostate cancer diagnosis			
>55 y	13	1360	0.96%
≤55 y	7	265	2.64%
Family history of prostate cancer			
Negative	13	1185	1.10%
Positive	6	411	1.46%

and selected his resulting single-nucleotide polymorphism data spanning chromosome 17. Then we used the program HAPMIX to phase his chromosome 17 genotypes and estimate his ancestry (14). As a reference population, we used the phased haplotypes of the African (YRI) and European (CEU) populations from the HapMap Project (15). We found that across a large region of chromosome 17 (~23 Mb) that includes *HOXB13*, both of the African-American carrier's chromosomes are of European ancestry, indicating that this appears to be a European founder mutation. In fact, within the 1000 Genomes Project data (ref. 16; accessed 9/12), the *HOXB13* G84E mutation has only been observed twice, both times in Northern Europeans: once in a British sample and once in Finnish sample (carrier frequency in Europeans = 2/758 = 0.2%).

Table 3 presents the *HOXB13* G84E mutation results to date from prostate cancer studies of European-Americans, the 1000 Genomes Project, and the Exome Sequencing Project (accessed 9/12). The overall mutation carrier frequency in European-American prostate cancer cases = 1.34% and in controls = 0.28%. Comparing the *HOXB13* G84E mutation carriers versus noncarriers gives an overall OR for prostate cancer = 4.86 (95% CI, 3.18–7.69; $P = 3.5 \times 10^{-17}$). Restricting the cases to men diagnosed at 55 years or younger, the carrier frequency increased to 2.30% and the prostate cancer OR = 8.41 (95% CI, 5.27–13.76; $P = 2.7 \times 10^{-22}$). Looking at cases only, men with an earlier age of disease onset were over twice as likely to carry the mutation: OR = 2.60 (95% CI, 1.77–3.83), and a test for heterogeneity across the age strata was highly statistically significant ($P_{\text{heterogeneity}} = 5.2 \times 10^{-7}$). Among men with a positive family history of prostate cancer, the carrier frequency and OR were 1.97% and 7.19, respectively (95% CI, 4.55–11.67; $P = 9.3 \times 10^{-21}$). For cases, those with a positive family history carried the mutation over twice as often as cases without a family history (OR, 2.33; 95% CI, 1.56–3.52; $P_{\text{heterogeneity}} = 1.2 \times 10^{-5}$). Across all studies, the *HOXB13* G84E mutation frequency did not differ among men with more or less aggressive disease (not shown).

Discussion

In our 2 studies and pooled analysis, we have confirmed and further characterized a high-risk prostate cancer mutation in *HOXB13* that is more common among men with an early age of disease onset or a positive family history but not aggressive disease. The mutation is rare and observed primarily among prostate cancer cases of European ancestry (or in our study their unaffected brothers). While uncommon, the mutation results in a substantial increase in risk of disease, which is over 8-fold higher among men with an age of onset ≤ 55 years.

Nevertheless, the mutation is not segregating entirely with prostate cancer—as unaffected brothers and other controls carry mutations as well. Of course, these men may have undetected cancer or may be diagnosed in the future. The segregation pattern indicates that the *HOXB13* G84E mutation explains at least some of the prostate cancer linkage to the surrounding chromosome 17 region (4). However, not all families linked to the region segregate the mutation, suggesting that there are additional high-risk mutations at this locus (17). In fact, different rare *HOXB13* mutations have been observed among prostate cancer cases of African (7, 9) and Asian ancestry (11).

The current analysis did not include 2 Swedish studies that detected the G84E mutation at substantially higher frequencies: 4.51% among prostate cancer cases and 1.33%

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Table 3. Summary and pooled analysis of HOXB13 mutations in European ancestry populations by prostate cancer status, stratified by age of onset and family history

Subjects	Study	Carriers (*n*)	Noncarriers (*n*)	Carrier frequency	OR (95% CI)[a]	*P*
Controls						
	Ewing and colleagues (7)	1	1400	0.07%		
	Breyer and colleagues (8)	2	823	0.24%		
	Akbari and colleagues (9)	2	1757	0.11%		
	Witte and colleagues (this manuscript)	3	867	0.34%		
	1,000 Genomes Project[b]	2	532	0.37%		
	Exome Sequencing Project[b]	17	4272	0.40%		
	All controls	27	9651	0.28%		
Cases						
	Ewing and colleagues (7)	72	5011	1.42%		
	Breyer and colleagues (8)	20	1106	1.78%		
	Akbari and colleagues (9)	10	1515	0.66%		
	Witte and colleagues (this manuscript)	19	1263	1.48%		
	All cases	121	8895	1.34%	4.86 (3.18–7.69)	3.48×10^{-17}
Age at diagnosis > 55y						
	Ewing and colleagues (7)	22	2681	0.81%		
	Breyer and colleagues (8)	13	755	1.69%		
	Akbari and colleagues (9)	7	1472	0.47%		
	Witte and colleagues (this manuscript)	12	1064	1.11%		
	All cases	54	5972	0.90%	3.23 (2.00–5.34)	4.08×10^{-7}
Age at diagnosis $\leq$ 55y						
	Ewing and colleagues (7)	46	2084	2.16%		
	Breyer and colleagues (8)	7	351	1.96%		
	Akbari and colleagues (9)[c]	3	43	6.52%		
	Witte and colleagues (this manuscript)	7	199	3.40%		
	All cases	63	2677	2.30%	8.41 (5.27–13.76)	2.72×10^{-22}
Negative family history						
	Ewing and colleagues (7)	19	2391	0.79%		
	Breyer and colleagues (8)	4	264	1.49%		
	Akbari and colleagues (9)	6	1170	0.51%		
	Witte and colleagues (this manuscript)	12	922	1.28%		
	All cases	41	4805	0.86%	3.09 (1.83–5.23)	6.26×10^{-6}
Positive family history[d]						
	Ewing and colleagues (7)	45	2019	2.18%		
	Breyer and colleagues (8)	16	842	1.86%		
	Akbari and colleagues (9)	4	345	1.15%		
	Witte and colleagues (this manuscript)	6	325	1.81%		
	All cases	71	3531	1.97%	7.19 (4.55–11.67)	9.27×10^{-21}

[a]Unadjusted ORs comparing cases with controls.
[b]European ancestry.
[c]From screening population of men older than 50 years.
[d]Case had at least one first- or second-degree relative with prostate cancer.

among controls (10), which may reflect a founder mutation and the potentially low genetic drift among some parts of Sweden—although it is unclear whether the carriers are more commonly observed among individuals from particular ancestral subregions of the country (e.g., northern; ref. 18). An evaluation of 767 Chinese cases and

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1,536 controls did not detect any carriers of the G84E mutation (11). As for other cancers, the G84E mutation has been observed at an increased frequency (0.7%) among women with normal BRCA1/2, familial breast cancer who were not of Ashkenazi Jewish ancestry (19).

The G84E mutation is in a highly conserved functional domain of *HOXB13* and is predicted by the Sorting Intolerant from Tolerant (SIFT) and PolyPhen algorithms to damage function. This domain mediates binding of HOXB13 to members of the MEIS homeobox protein family that function as HOX cofactors (7). HOX expression is crucial to development, and the HOX paralogue group 13 is involved with urogenital system development (20, 21). HOXB13 is highly expressed in normal adult prostate, underexpressed in prostate tumors that are still androgen-dependent but may be overexpressed again in late-stage castrate-resistant tumors (22). Moreover, HOXB13 appears to interact with and suppress androgen receptor–mediated transcriptional activation (23–26).

These findings confirm that *HOXB13* G84E is a high-penetrance mutation for prostate cancer in men of European ancestry that substantially increases risk of early-onset hereditary prostate cancer. The G84E mutation does not appear to affect disease aggressiveness. These observations suggest that carriers may merit closer screening than the general population but should not be subject to more aggressive therapy if diagnosed with prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.S. Witte, G. Casey
Development of methodology: J.S. Witte, S.J. Plummer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.S. Witte, S.J. Plummer, E.A. Klein, B.A. Rybicki, G. Casey
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S. Witte, J. Mefford, J. Liu, I. Cheng
Writing, review, and/or revision of the manuscript: J.S. Witte, J. Mefford, S.J. Plummer, J. Liu, I. Cheng, E.A. Klein, B.A. Rybicki, G. Casey
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.S. Witte, J. Mefford, S.J. Plummer
Study supervision: J.S. Witte, G. Casey

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