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The Prevalence of the *HOXB13* G84E Prostate Cancer Risk Allele in Men Treated with Radical Prostatectomy

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Abstract

Objectives—

- To determine the prevalence and clinical correlates of the G84E mutation in the homeobox transcription factor (or *HOXB13*) gene using DNA samples from 9,559 men with prostate cancer undergoing radical prostatectomy.

Patients and Methods—

- DNA samples from men treated with radical prostatectomy at the University of Michigan and John Hopkins University were genotyped for G84E and confirmed by Sanger sequencing.
- The frequency and distribution of this allele was determined according to specific patient characteristics (family history, age at diagnosis, pathologic Gleason grade and stage).

Results—

- 128 of 9,559 patients were heterozygous carriers of G84E (1.3%).
- Patients who possessed the variant were more likely to have a family history of prostate cancer (46.0% vs. 35.4% p=0.006).
- G84E carriers were also more likely diagnosed at a younger age compared to non-carriers (55.2 years vs. 58.1 years; p<0.0001).

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Conflicts of Interest
None disclosed

- No difference in the proportion of patients diagnosed with high-grade or advanced stage tumors by carrier status was observed.

Conclusion—

- In our study, carriers of the rare G84E variant in *HOXB13* were both younger at the time of diagnosis and more likely to have a family history of prostate cancer compared to homozygotes for the wild-type allele.
- No significant differences in allele frequency were detected according to select clinical characteristics of prostate cancer.
- Further investigation is required to evaluate the role of *HOXB13* in prostate carcinogenesis.

Keywords

HOXB13; prostate cancer; family history; genetic epidemiology

Introduction

The findings from epidemiologic studies signal a familial component to prostate cancer. Family history, particularly among first-degree relatives, is a strong risk factor for prostate cancer with an approximate 2- to 2.5-fold increase in risk associated with a positive history of disease. Risk has been shown to increase with the number of affected relatives and is inversely related to the age at diagnosis among those relatives.(1) However, the specific genes which explain the observed associations have largely eluded researchers for decades. Recently, we discovered a rare, recurrent mutation in the *HOXB13* gene (G84E) which was associated with a significant increase (~10- to 20-fold) in the risk of prostate cancer. The frequency of the variant was 1.4% in all men with prostate cancer in the study and increased to 3.1% among men diagnosed with early-onset and familial prostate cancer.(2)

The homeobox transcription factor gene *HOXB13*, located on the long arm of chromosome 17 (17q21), belongs to a super family of genes considered critical to animal embryonic development and characterized by a highly-conserved DNA-binding domain. *HOXB13* is thought to play a role in development of the prostate gland; however the expression of its protein remains elevated into adulthood. The mechanism whereby *HOXB13* influences prostate carcinogenesis is currently unknown, but it is certain to be an area of intense investigation.

A number of studies have subsequently confirmed the presence of the G84E mutation and its association with familial and hereditary prostate cancer.(3–8) In the current investigation, we set out to determine the prevalence of G84E in a large case series of men with prostate cancer undergoing radical prostatectomy at one of two institutions representing a population of men with both sporadic and familial disease. Because of the relative rarity of the mutation, this large sample of patients enables us to examine clinical characteristics that impact survival by carrier status which may provide valuable clues as to the function of the gene in prostate cancer.

Patients and Methods

Study Subjects

Eligible patients were diagnosed at any age with primary prostate cancer, histologically confirmed, and treated with radical prostatectomy at either the University of Michigan Medical Center (UM) (N=1,511) between 1999 and 2012 or Johns Hopkins University

(JHU) Hospital (N=8,048) between 1993 and 2012. Note that a proportion (39%) of these patients was included in our initial report describing the *HOXB13* G84E mutation in men with prostate cancer.(2) Demographic and clinical information collected on each patient included date and age at diagnosis (UM), date of and age at radical prostatectomy (UM and JHU), race, family history of prostate cancer, pathologic Gleason grade, pathologic (TNM) stage, and surgical margin status. Patients were followed passively for disease recurrence, additional treatment(s), and vital status through 2012. The protocol and consent documents were approved by the institutional review boards at each institution.

Genotyping Methods

DNA was extracted from whole blood using standard methods. Samples were genotyped using the Mass ARRAY system (Sequenom) or Taqman assay (rs138213197) (Applied Biosystems, Foster City, CA). All G84E mutation carriers identified on either platform as well as a randomly-selected subset of samples (~10%) were subjected to duplicate genotyping using Sanger sequencing in a blinded fashion with 100% concordance among duplicate samples.

Statistical Analysis

All analyses were conducted using Statistical Analysis Systems software (SAS Inc. v.9.2, Cary, NC). The genotype frequencies for G84E were tested for and consistent with Hardy-Weinberg equilibrium ($p>0.05$). We calculated the distribution of categorical parameters among all subjects and the median and range for all continuously-measured parameters of interest. As there were no homozygotes for the variant allele, the frequency of carriers was determined among all subjects. Simple chi-square tests were used to compare the frequencies for select characteristics between carriers and non-carriers of G84E. Breslow-Day chi-square tests were used to evaluate the potential for effect modification by age at diagnosis on the association between genotype and both family history and Gleason sum. P-values less than 0.05 were considered statistically significant.

Results

Select characteristics and the genotype frequencies for G84E of the 9,559 prostate cancer patients included in our investigation are summarized in Table 1. Age at diagnosis was available for 98% of UM patients, with a median of 59 years, with a range of 38 to 77 years. For the remaining 2% of patients with missing information, we used age at surgery to approximate age at diagnosis as there was a mean difference of just 4 months between age at diagnosis and age at surgery in the UM series. Age of surgery was available for JHU patients with a similar distribution to UM (median age = 58 years; range 33 to 77 years). Approximately 85% of UM patients and 88% of JHU patients were white. Further, approximately 36% of patients at each institution had a documented family history of prostate cancer in a first or second degree relative. A greater proportion of UM patients exhibited high (4+3 and higher) Gleason grade tumors, and elevated pre-treatment PSA (10 ng/mL and higher) compared to JHU patients. Alternatively, a greater proportion of JHU patients were diagnosed with non-organ confined disease (T3a and higher) compared to UM patients. The G84E carrier rate was 1.3% among all patients with no appreciable difference in the proportion of patients possessing the risk allele between JHU (1.4%) and UM patients (1.1%). No homozygous carriers were detected. Since mutation carriers were almost exclusively white (2 patients of unknown race were carriers), the remaining analysis was restricted to the 8,341 white patients in the study.

Table 2 summarizes the associations between G84E genotype and select clinical characteristics at time of diagnosis. G84E carriers in this study were more likely diagnosed

at a younger age compared to non-carriers (55.2 years vs. 58.1 years, p<0.0001). Patients who possessed the variant were also more likely to have a family history of prostate cancer (46.0% vs. 35.4% p=0.006). In a regression model mutually adjusting for both G84E genotype and family history on the probability of being diagnosed with early-onset prostate cancer (≤ 60 years) we observed a nearly two-fold increase in the odds of early-onset disease associated with the mutation (OR=1.90; 95% CI =1.23-2.94), which was slightly higher than the odds ratio detected for family history (OR=1.45; 95% 1.32-1.59). There was no difference observed in the proportion of patients with high-grade tumors by carrier status (16.7% of carriers vs. 17.5% of non-carriers had tumors with Gleason sum ≥ 4+3 p=0.95). Likewise, there was no difference in the proportion of patients diagnosed with advanced stage (≥ pT3a) tumors by carrier status (24.6% vs. 27.5% p=0.52). Finally, our analysis of the various relationships between carrier status and clinical measures of interest did not provide evidence for effect modification between G84E and family history of disease on age at diagnosis, tumor stage, or Gleason sum.

Discussion

Findings from the current investigation confirm the presence of the prostate cancer susceptibility allele *HOXB13* G84E variant in a subset of men with prostate cancer. The observed prevalence of the risk allele (1.3%) among all patients was consistent with previous estimates,(4;6) including our own.(2) Additionally G84E carriers were more likely diagnosed at a younger age and have a positive family history of prostate cancer compared to non-carriers. However, we did not observe any difference in the distribution of Gleason grade or tumor stage between carriers and non-carriers of the G84E mutation.

Our research team was the first to report the association between *HOXB13* and prostate cancer(2) with the initial discovery of the G84E variant as a result of targeted sequencing of 202 genes in a 15.5 Mb candidate region on 17q21-22. This region was identified in a linkage analysis of pedigree data from 175 families with hereditary prostate cancer participating in the University of Michigan Prostate Cancer Genetics Project (PCPG).(9) The probands (the youngest case with DNA) from 4 families (3 from PCGP and 1 from JHU) with the strongest evidence for linkage in this region were all observed to harbor a substitution G→A in the second position of codon 84 resulting in the replacement of glycine by glutamic acid. Subsequent genotyping of family members observed complete co-segregation of the mutation with disease among affected relatives with just one unaffected carrier of G84E. Finally, an OR of 20.1 ($p=8.5\times10^{-7}$),and a carrier frequency of 1.4% among cases, was reported in a case-control study of 5,011 cases and 1,401 controls also from UM and JHU.(2) In our initial report examining clinical characteristics and their relationship to G84E carrier status, we included all cases available to us including a large number of cases from the hereditary prostate cancer studies at each of our institutions. In this present report, we have included men presenting for radical prostatectomy, not specifically selected for early-onset and/or family history of disease.

The International Consortium for Prostate Cancer Genetics (ICPCG) confirmed the presence of G84E in 112 (4.6%) of the 2,443 families (all of European descent) participating in the consortium. After exclusion of PCGP and JHU participants, an OR for prostate cancer of 4.3 (95% CI=2.32, 7.96) was reported among G84E carriers in remaining ICPCG families.(5) Several studies have reported associations with prostate cancer with G84E ranging from 3.3 to 8.8(3;4;6–8;10;11) and with one exception(4) stronger estimates among men with early-onset, familial and hereditary prostate cancer. Stott-Miller et al., observed a 4-fold increase in the likelihood of diagnosis associated with G84E among men with no family history of prostate cancer, but only 1.5-fold increase among men with a positive family history in a first-degree relative. The same investigation suggested the risk allele was also associated

with higher grade and advanced stage disease, a finding not replicated by others including the current study.(10;12) A recently published meta-analysis of G84E and prostate cancer risk in European Americans (including 24,213 cases and 73,631 controls) reported a pooled odds ratio of 4.07 (95% CI=3.05-5.45) with an overall carrier rate of 0.7%.(12) Akbari et al. observed a significant difference in the frequency of G84E between prostate cancer cases and controls in a large Canadian study, the prevalence was < 1% in both groups (0.7% and 0.1% respectively).(7) Work from the ICPCG identified a common haplotype occurring in 95% of G84E carriers.(5) The frequency of the haplotype is significantly higher in Nordic countries suggesting a founder allele arising in this region of the world. In a phylogenetic analysis of 40 haplotypes among 3,239 Caucasian participants of the REDUCE trial, Chen et al. suggests that the G84E mutation is a relatively recent event occurring approximately 220 years ago in Northern Europe. (11) The variation of the frequency of the G84E allele reported in North American populations may therefore be influenced by population substructure.

An Australian study of early-onset (< 60 years at diagnosis) prostate cancer cases unselected for family history (with a carrier frequency of 1.4%) generated estimates of the cumulative risk (to age 80 years) of prostate cancer associated with the G84E mutation. Age-specific estimates of prostate cancer penetrance varied from 4.6% by age 60 years to 45.7% by age 80 years for a G84E carrier born in 1920; this compared to a carrier born in 1950 where the cumulative risk varied from 19.2% by age 60 years to 60.0% by age 80 years.(13) Our prior investigation of G84E in a prostate biopsy series at UM, the carrier rate was lower than expected, just 4 of 948 men (0.42%). Despite the fact that 3 of 4 men were subsequently diagnosed with prostate cancer (positive predictive value of 0.75); we suggested there would be limited utility in testing for G84E, because of its rarity in the general population.(14)

Studies have also examined association between the G84E mutation and risk of breast and colon cancer with some inconsistency in their findings. While Akbari et al.(15) observed no association between the variant and breast cancer in a large case-control study, two other reports suggest a 3- to 6-fold increase in the odds of breast cancer associated with the mutation among women with familial breast cancer (non-Ashkenazi *BRCA1/2* negative). (8;16) Laitinen et al. reported no statistical difference in the frequency of the mutation between colon cancer cases (1.6%) and controls (0.9%).(8)

In addition to G84E, additional rare *HOXB13* mutations have been detected by our group(2) and others.(7) Recently, a novel rare mutation in *HOXB13* (G135E) was reported to be associated with prostate cancer among Chinese men.(17) In this case-series (n=96), the entire coding region of the gene was sequenced and a single patient was observed to have the mutation. A subsequent case-control study of 671 cases and 1,536 controls identified 2 additional carriers of G135E, both cases. The variant, observed in the second of two highly-conserved MEIS (myeloid ecotropic viral integration site) binding domains on exon 1 of the gene (G84E is located in the first), was predicted to have a deleterious effect on *HOXB13* protein function using the PolyPhen software program.(17)

HOXB genes are thought to regulate a number of processes which influence cancer initiation and progression, and it appears that there is some organ specificity in the function of different genes within this family in tumorigenesis.(18) *HOXB13* was first identified in 1996,(19) and is involved early embryonic development of the gland and prostate cell differentiation.(20) *HOXB13* has been shown previously to regulate transcriptional activity of the androgen receptor (AR)(21) critical to prostate tumor growth. Furthermore, Norris et al. suggests a more complicated interaction between *HOXB13* and AR, whereby *HOXB13* can either act directly on AR to regulate the activity of some genes or as a coregulator with AR on others.(22)

There are limitations to the current investigation which require some consideration in the interpretation of its findings. Despite the fact that we were able to assemble a large case-series for this investigation, the low-frequency of the mutation in the population limited our ability to generate precise estimates of the association between G84E and the characteristics under investigation while also controlling for important covariates. However, our analysis stratifying associations of interest by age at diagnosis (≤ 60 years vs. > 60 years) suggests that family history of prostate cancer was more common among those with the mutation, and more so among those diagnosed at an earlier age. G84E carriers diagnosed at an earlier age were also slightly more likely to have high-grade disease (16.3%) than non-carriers (14.0%), with the reverse relationship observed among carriers diagnosed after age 60 where they were less likely to be diagnosed with high-grade disease (17.9%) than non-carriers (23.7%). However, these differences were not deemed statistically significant.

And despite the compatibility of our prevalence estimates with prior reports, our findings may not be generalized to all men diagnosed with prostate cancer. The fact that these men were appropriate candidates for surgery would necessarily exclude men known to have advanced disease at time of diagnosis. However, the demographic (age at diagnosis and race) and clinical (Gleason grade and pathologic tumor stage) characteristics of the cases participating in this investigation are similar to other large, prostate cancer cohorts of men treated with radical prostatectomy (23–25). The relatively high proportion of the patient population with a family history of prostate cancer (~36%), may reflect the referral patterns in the regions the academic institutions serve as well as the educational level of the patient population. Furthermore, it is likely that men with a family history of disease are screened more frequently and therefore may be more likely to be diagnosed with less advanced stage disease. Our data indicate approximately 25% of patients with a positive family history were diagnosed with advanced (≥ pT3a) stage disease as opposed to 28% of patients without a family history ($p=0.001$). Likewise, 15% of patients with a positive family history were diagnosed with high (≥ 4+3) grade disease as opposed to 19.5% of patients without a family history ($p<0.0001$). Therefore, the fact that this mutation was associated with family history may potentially have biased the findings related to stage toward the null and may explain the absence of any association between G84E with either grade or stage. However, our analyses stratified on family history do not support this notion. The mutation frequency among men with both high grade disease and a positive family history was 1.3% compared to 1.4% among men with high grade disease without a family history ($p_{\chi 2 Breslow\text{-}Day}=0.19$). Similar results were observed with respect to tumor stage (data not shown).

In conclusion, the results of this study confirm the presence of the G84E mutation in the *HOXB13* gene in prostate cancer and estimate its prevalence to be just less than 2% of prostate cancer patients. While no significant association was observed between G84E and tumor pathologic features, the increase in the frequency of this mutation in patients with a positive family history and earlier onset disease reinforce the importance of uncommon, but highly-penetrant genes in the genetic epidemiology of prostate cancer. Further investigation is clearly warranted to reveal the underlying biologic mechanism to explain this relationship.

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Table 1

Demographic and tumor characteristics of the prostate cancer patients

	University of Michigan (UM)		Johns Hopkins (JH)	
Characteristic	**N**	**%**	**N**	**%**
Total cases	1511		8048	
Age at diagnosis / surgery*				
≤ 60 years	873	57.8	5119	63.6
> 60 years	638	42.2	2929	36.4
Race				
White	1289	85.3	7052	87.6
Black	98	6.5	622	7.7
Other/unknown	124	8.2	374	4.6
Family History				
Yes	540	35.7	2862	35.6
No	893	59.1	4567	56.7
Unknown	78	5.2	619	7.7
Year of Surgery				
1990–1999	55	3.6	592	7.4
2000–2009	1135	75.1	6533	81.2
2010–2012	321	21.2	923	11.5
Pre-op PSA (in ng/mL)				
< 2.5	112	7.4	1568	19.5
2.5 - < 4.0	181	12.0	1309	16.3
4.0 - < 10.0	933	61.7	4463	55.5
≥ 10.0	247	16.3	686	8.5
Unknown	38	2.5	22	0.3
Pathologic Gleason Score				
< 7	378	25.0	4563	56.7
7 (3+4)	735	48.6	2107	26.2
7 (4+3)	260	17.2	810	10.1
> 7	87	5.8	533	6.6
Unknown	51	3.4	35	0.4
Pathologic T-Stage				
pT2	1260	83.4	5650	70.2
pT3a	186	12.3	1954	24.1
pT3b	48	3.2	402	5.1
pT3x	0	0.0	2	0.0
pT4	10	0.7	0	0.0
Unknown/pTx	7	0.5	40	0.5
Pathologic N-Stage				
N1	14	0.9	164	2.0
N0/N2/Nx	1497	99.1	7884	98.0

	University of Michigan (UM)		Johns Hopkins (JH)	
Characteristic	**N**	**%**	**N**	**%**
PSA recurrence				
Yes	101	6.7	655	8.1
No	1383	91.5	7230	89.8
Unknown	27	1.8	163	2.0
Surgical margins				
Yes	217	14.4	1122	13.9
No	1269	84.0	6880	85.5
Unknown	25	1.7	46	0.6
Seminal vesicle invasion				
Yes	53	3.5	365	4.5
No	1440	95.3	7681	95.4
Unknown	18	1.2	2	0.0
Genotype at rs138213197				
GG	1494	98.9	7937	98.6
GA	17	1.1	111	1.4

Table 2

Comparing *HoxB13* gene carriers to non-carriers according to select prostate cancer characteristics

	University of Michigan (UM)					Johns Hopkins (JH)					All				
	GG		GA			GG		GA			GG		GA		
Characteristic	**N**	**%**	**N**	**%**	**p-value***	**N**	**percent**	**N**	**percent**	**p-value***	**N**	**percent**	**N**	**percent**	**p-value***
Total	1274		15			6941		111			8215		126		
Age at diagnosis / surgery					0.43					0.0004					0.0003
≤ 60	721	56.6	10	66.7		4371	63.0	88	79.3		5092	62.0	98	77.8	
> 60	553	43.4	5	33.3		2569	37.0	23	20.7		3122	38.0	28	22.2	
Family History					0.28					0.01					0.006
No	767	60.2	7	46.7		3948	56.9	49	44.1		4715	57.4	56	44.4	
Yes	465	36.5	8	53.3		2447	35.3	50	45.0		2912	35.4	58	46.0	
Unknown	42	3.3	0	0.0		546	7.9	12	10.8		588	7.2	12	9.5	
Pathologic Gleason Score					0.56					0.95					0.95
< 7	324	25.4	2	13.3		4008	57.7	65	58.6		4332	52.7	67	53.2	
7 (3+4)	610	47.9	9	60.0		1767	25.5	29	26.1		2377	28.9	38	30.2	
≥ 7 (4+3)	298	23.4	4	26.7		1137	16.4	17	15.3		1435	17.5	21	16.7	
Unknown	42	3.3	0	0.0		29	0.4	0	0.0		71	0.9	0	0.0	
Pathologic Tumor Stage					1.0					0.51					0.52
≤ T2 /N0	1051	82.5	13	86.7		4870	70.2	80	72.1		5921	72.1	93	73.8	
≥T3 or any T/ N1	218	17.1	2	13.3		2040	29.4	29	26.1		2258	27.5	31	24.6	
Unknown	5	0.4	0	0.0		31	0.4	2	1.8		36	0.4	2	1.6	

* Chi-square test or Fisher's exact test for comparisons with small cells (excludes missing data).