Published OnlineFirst June 19, 2012; DOI: 10.1158/1055-9965.EPI-12-0495

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Confirmation of the *HOXB13* G84E Germline Mutation in Familial Prostate Cancer

Joan P. Breyer[1], T. Grant Avritt[1], Kate M. McReynolds[1], William D. Dupont[2], and Jeffrey R. Smith[1,3]

Abstract

Background: A recent study of familial and early onset prostate cancer reported a recurrent rare germline mutation of *HOXB13* among men of European descent. The gene resides within the 17q21 hereditary prostate cancer linkage interval.

Methods: We evaluated the G84E germline mutation (rs138213197) of *HOXB13* in a case–control study of familial prostate cancer at Vanderbilt University (Nashville, TN) to independently evaluate the association of the mutation with familial prostate cancer. We genotyped 928 familial prostate cancer probands and 930 control probands without a personal or family history of prostate cancer.

Results: Our study confirmed the association between the G84E mutation of *HOXB13* and risk of prostate cancer among subjects of European descent. We observed the mutation in 16 familial cases and in two controls, each as heterozygotes. The odds ratio (OR) for prostate cancer was 7.9 [95% confidence interval, (CI) 1.8–34.5, $P = 0.0062$] among carriers of the mutation. The carrier rate was 1.9% among all familial case probands and 2.7% among probands of pedigrees with $\geq$3 affected. In a separate case series of 268 probands of European descent with no additional family history of prostate cancer, the carrier rate was 1.5%.

Conclusions: The germline mutation G84E of *HOXB13* is a rare but recurrent mutation associated with elevated risk of prostate cancer in men of European descent, with an effect size that is greater than observed for previously validated risk variants of genome wide association studies.

Impact: This study independently confirms the association of a germline *HOXB13* mutation with familial prostate cancer. *Cancer Epidemiol Biomarkers Prev; 21(8); 1348–53. ©2012 AACR.*

Introduction

Prostate cancer is estimated to have the largest heritable risk component of all common cancers, roughly twice that of breast cancer (1, 2). Family history remains the best clinical predictor of risk. Segregation analyses have been most consistent with a rare genetic component of age-dependent penetrance. The collective results of linkage studies of familial prostate cancer suggest complex heritability: incomplete penetrance (mutations associated with more modest effect sizes than typical of simple Mendelian disease), polygenic inheritance (multiple loci acting jointly to cause disease), and genetic heterogeneity (underlying causal mutations in many genes, each infrequent). These obstacles have posed a marked challenge for the discovery of gene mutations underlying familial prostate cancer. Genome-wide association studies (GWAS) of prostate cancer have detected validated risk variants, but these have been of low effect size (ORs, 1.1–2.0) and collectively have accounted for approximately 25% of observed heritable risk (3–19). These do not explain the observed inheritance patterns of hereditary prostate cancer pedigrees (20). The power of a GWAS to detect uncommon genetic variants of large effect might be anticipated to be low, given that only 3% to 5% of prevalent cases meet criterion for hereditary prostate cancer and given that commercial chips used were designed to detect common disease variants.

With this background in mind, the recently described germline mutation G84E of *HOXB13* among familial prostate cancer cases is a noteworthy discovery (21). This mutation resides within a replicated linkage interval (22–25) on 17q21-22 and was detected by sequencing genes of this interval among probands of linked hereditary prostate cancer pedigrees. The germline mutation was observed in 4 of 85 (4.7%) linked pedigrees of European descent and cosegregated with disease. The 85 linked pedigrees were a subset of those used for genetic mapping, most without evidence of linkage to the region. Within a case–control series of that study, the mutation was detected in 45 of 2,064 (2.2%) familial cases, in 19 of 2,410 (0.8%) sporadic cases, and in one of 1,401 (0.07%) controls. Our study sought independent confirmation of the association of the *HOXB13* germline mutation with

Authors' Affiliations: Departments of [1]Medicine and [2]Biostatistics, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine; and [3]Medical Research Service, Veteran's Affairs Tennessee Valley Healthcare System, Nashville, Tennessee

Corresponding Author: Jeffrey R. Smith, Department of Medicine, Vanderbilt University School of Medicine, 529 Light Hall, 2215 Garland Avenue, Nashville, TN 37232. Phone: 615-936-2171; Fax: 615-936-2661; E-mail: jeffrey.smith@vanderbilt.edu

doi: 10.1158/1055-9965.EPI-12-0495

Published OnlineFirst June 19, 2012; DOI: 10.1158/1055-9965.EPI-12-0495

prostate cancer in familial prostate cancer case probands and controls with no personal or family history of prostate cancer.

Materials and Methods

Study population

We initiated the Familial Prostate Cancer Study (FPCS) as an observational hospital-based study of familial prostate cancer at Vanderbilt University (Nashville, TN) in 2003. The FPCS is among the largest case–control studies of familial prostate cancer (Table 1). We recruited incident familial prostate cancer case probands (≥2 affected first- or second-degree relatives in the pedigree) at the time of treatment for the principal diagnosis of prostate cancer (confirmed by review of pathology), and control probands at the time of routine preventative screening for prostate cancer. Controls had no personal or family history of prostate cancer (first- and second-degree relatives), no known prostate-specific antigen (PSA) > 4 ng/dL or abnormal digital rectal exam, and no history of prostate biopsy. This familial study design provides improved power to detect genetic risk variants (26). Approximately 95% of eligible subjects agreed to participate, with written informed consent under Institutional Review Board (IRB) governance. We matched cases to controls in a 1:1 ratio by race and age, within 2.5 years of age at diagnosis or screen. A small excess of familial cases remained unmatched to controls in the ongoing study. All subjects completed a structured questionnaire of family cancer history, demographics, and grandparental ancestry. The date, age, and PSA level at diagnosis of adenocarcinoma or at screen was recorded for each subject. The initial clinical staging (clinical tumor–node–metastasis, TNM), biopsy Gleason score, treatment modality, and date(s) were recorded. More than 97% of case subjects underwent radical prostatectomy, providing definitive histopathologic diagnoses. For these, surgical pathology staging (pathologic TNM), seminal vesicle invasion, margin status, left and right lobe Gleason scores and sum, and capsular penetration were recorded. Among familial cases of European descent with available pathologic staging, 175 of 844 (21%) were of pT3, pT4, N1, or M1 stage. Pathologic staging was not available from prostatectomy for the remaining 21 (2%) of the 865 familial cases of European descent.

In addition, a series of independent singleton cases, without a family history of prostate cancer among first- or second-degree relatives, was also accrued. This included 271 cases of European descent (mean age of diagnosis 58.4) and 104 of African descent (mean age of diagnosis 61.1); 44% and 27% were diagnosed ≤age 55, respectively. Among the singleton cases of European descent, 68 of 256 (27%) were of pT3, pT4, N1, or M1 stage. Pathologic staging was not available from prostatectomy for the remaining 15 of the 271 total singleton cases.

Table 1. Familial Prostate Cancer Study

		Controls	Cases
Total, no.		930	928
Caucasian, no.		830	865
African-American, no.		100	63
Mean age[a], y		60.1	60.1
Mean no. of brothers		1.8	1.7
Median PSA[a]		0.9	5.5
Age diagnosis ≤ 60, no.		—	470
Age diagnosis ≥ 61, no.		—	458
Gleason sum ≤ 6, no.		—	469
Gleason sum ≥ 7, no.		—	427
Affected in pedigree, no.[b]	0	930	—
	2	—	575
	≥3	—	353

[a]At diagnosis for cases, at screen for controls.
[b]Proband plus first- and second-degree affected relatives.

Genotyping

DNA was extracted from whole blood on an Autopure LS robot using the Puregene DNA Purification System Standard Protocol (Qiagen). DNA was quantified using the PicoGreen dsDNA Quantitation Kit (Invitrogen), imaged with a Molecular Devices/LJL Analyst HT (Molecular Devices). Single-nucleotide polymorphism (SNP) genotyping for rs138213197 was conducted using the TaqMan platform (Applied Biosystems). Mutations were confirmed by Sanger sequencing of identified carriers. Genotypes were successfully obtained for 99.2% of subjects. Genotype data were in Hardy–Weinberg equilibrium among controls, familial cases, and singleton cases of European descent. The SNP was monomorphic without mutation carriers among African-Americans.

Statistical analyses

Unconditional logistic regression analysis was used to estimate prostate cancer OR, adjusted for age. Analyses were restricted to subjects of European descent. ORs, 95% CI, and *P* values were derived under a dominant model. Hardy–Weinberg equilibrium analysis was conducted using Haploview. An association between genotype and prostate cancer was considered nominally significant if the associated 2-sided *P* value was less than 0.05. The study sought to replicate a previously observed association. Comparisons of carriers and noncarriers of the A rs138213197 variant were made with respect to age at diagnosis, Gleason score, and advanced stage (tumor stage ≥3, or positive lymph nodes, or metastatic disease). These analyses were conducted using the Wilcoxon rank-sum test for age, the score test for trend for Gleason score, and Fisher exact test for advanced stage.

Results

The G84E germline mutation of *HOXB13* (allele A on coding strand, encoding glutamate) was observed in 2 study controls and in 20 cases, each in the heterozygous

Published OnlineFirst June 19, 2012; DOI: 10.1158/1055-9965.EPI-12-0495

Table 2. Characteristics of *HOXB13* G84E (glutamate) carriers of European descent

Subject	Status	Age diagnosis/ screen	PSA[a]	Pedigree type[b]	Stage			Gleason	# Cases in pedigree[c]	Other reported cancers in pedigree[c]
1	Case	49	4.6	MM	pT2c	pN0	pMX	5	4	Five additonal third-degree relatives with prostate cancer
2	Case	69	4.8	MM	pT2c	pN0	pMX	7	4	Lung, female breast, hepatocellular, colon
3	Case	48	4.1	MM	pT2c	pN0	pMX	6	3	Stomach
4	Case	58	4.0	MM	pT2c	pN0	pMX	6	3	Lung, ovary, female breast
5	Case	65	6.8	MM	pT2c	pN0	pMX	6	3	Lung, head and neck
6	Case	59	10.8	Bilineal	pT2c	pN1	pMX	7	3	None
7	Case	64	6.2	MM	pT2c	pN0	pMX	7	3	Female breast, additional unknown type
8	Case	55	3.9	Bilineal	pT3a	pN0	pMX	5	3	Leukemia, melanoma, pancreas, ovary, multiple myeloma
9	Case	66	4.2	MM	pT3a	pN0	pMX	7	3	Lung, ovary
10	Case	66	6.3	MM	pT2a	pN0	pMX	7	2	Head and neck, eye
11	Case	56	3.9	MM	pT2c	pN0	pMX	6	2	Melanoma, colon, glioma, Hodgkin's lymphoma, lung
12	Case	54	4.1	MM	pT2c	pN0	pMX	7	2	Unknown type
13	Case	67	3.4	MM	pT2c	pNX	pMX	7	2	Melanoma, leukemia
14	Case	61	5.2	NMM	pT2c	pN0	pMX	6	2	Uterine
15	Case	64	>50	NMM	T2c	NX	MX	8	2	None
16	Case	59	15	NMM	pT3b	pNX	pMX	9	2	Lymphoma
17	Case	41	10.3	Singleton	pT2c	pNX	pMX	7	1	Ovary, lung
18	Case	68	8.5	Singleton	pT2c	pN0	pM0	5	1	None
19	Case	50	8.1	Singleton	pT2c	pN0	pMX	7	1	Unknown type
20	Case	48	4.5	Singleton	pT2c	pN0	pMX	7	1	None
21	Control	80	1.64	—	—	—	—	—	0	None
22	Control	56	0.78	—	—	—	—	—	0	Cervical, lung

[a]PSA at diagnosis for case, at screen for control.

[b]MM designates apparent male-to-male transmission (autosomal dominant), whereas NMM indicates no apparent male-to-male transmission (X-linked or sibship).

[c]Among first- and second-degree relatives.

state. All carriers were of European descent. One control carrier was age 80, with 2 unaffected male siblings and a screening PSA of 1.64. The other control carrier was age 56 with 3 unaffected male siblings and screening PSA level of 0.78. Both men had PSA levels near or below the median level for Caucasians of the respective age groups (27, 28). A low rate of misclassification of controls is expected, because a given control may later develop the disease, and because not all prostate cancer is accompanied by an elevated PSA level.

Characteristics of individual mutation carriers are given in Table 2, and Table 3 presents the OR and significance of prostate cancer association with the G84E germline mutation. Cancers other than of the prostate were common in the pedigrees of these probands, of unknown significance. We compared the familial case study population to controls, and the singleton study population to the same controls. We also evaluated strata of familial cases defined by the number affected in the pedigree, by age of diagnosis, by Gleason score, and by extraprostatic disease at diagnosis (Table 4).

The point estimate of the OR, adjusted for age, was 7.9 ($P = 6.2 \times 10^{-3}$; 95% CI, 1.8–34.5) in a comparison of familial cases and controls. The estimate was greater among cases with a family history of three or more affected (OR = 11.8), relative to a family history of only 2 affected (OR = 5.8). The estimate for cases with no additional family history (OR = 5.6) was similar to the latter but insignificant. Effect size was not further increased among cases with a family history of 4 or more affected (OR = 7.0). Given the rarity of the mutation, the CIs of the OR estimates were broad.

The association appeared similar in familial cases above and below the mean age of diagnosis; there was no significant difference in age of diagnosis between mutation carriers and noncarriers. The point estimates of the OR were higher among familial cases with less differentiated or with extra-prostatic disease at diagnosis.

Published OnlineFirst June 19, 2012; DOI: 10.1158/1055-9965.EPI-12-0495

Table 3. Association of prostate cancer with *HOXB13* G84E (rs138213197) on chromosome 17q21.32

Affected in pedigree[a]	Carrier rate (%)	OR (95% CI)	*P*
0	2 of 825 (0.002)		
1	4 of 268 (0.015)	5.6 (0.9–33.9)	0.061
≥1	20 of 1,126 (0.018)	7.2 (1.7–31.2)	8.1×10^{-3}
2	7 of 529 (0.013)	5.8 (1.2–28.2)	0.030
≥2	16 of 858 (0.019)	7.9 (1.8–34.5)	6.2×10^{-3}
≥3	9 of 329 (0.027)	11.8 (2.5–55.3)	1.8×10^{-3}
≥4	2 of 125 (0.016)	7.0 (1.0–51.4)	0.055

[a]First- and second-degree relatives (0, controls; 1, case probands with no others in pedigree affected; 2, case probands with one additional in pedigree affected, etc.).

However, there was no significant difference between mutation carriers and noncarriers with respect to either index of aggressive disease.

Discussion

Our study confirms the recently described association of the germline G84E mutation with familial prostate cancer. The association was most evident in pedigrees with 3 or more affected men. OR estimates for the mutation were generally lower in our study than originally estimated. Nonetheless, the effect size appears to be much greater than for other validated associations detected in GWAS investigations.

Given the rarity of the mutation, power was limited to assess the relative impact of the mutation upon age of diagnosis or upon disease aggressiveness. Ewing and colleagues observed a mean age at diagnosis of 52.9 for carriers, and 57.1 for noncarriers, a significant difference in their study. The average age of diagnosis of carriers in our familial prostate cancer study was 58.4; this age was nominally but not significantly different than the 60.2 mean age of diagnosis of noncarriers. Ewing and colleagues found no evidence to support a difference between Gleason grade between G84E carriers and noncarriers and did not investigate an effect on advanced stage prostate cancer. Our analysis observed a nominally higher carrier frequency among cases with higher Gleason score and among cases with extra-prostatic disease at diagnosis, but these differences were not statistically significant.

In Cancer Genome Anatomy Project SAGE data, *HOXB13* is expressed in human stomach, colon, and particularly prostate, and expression is reduced in cancers of these sites. The homeodomain protein suppresses both TCF4- (Wnt pathway) and androgen receptor–mediated transcriptional activation to inhibit cell proliferation (29–32). A *HOXB13* loss-of-function mutation that leads to an increased risk of prostate cancer is consistent with known prostate cancer biology. However, *HOXB13* expression is increased in late stage, hormone-refractory prostate

Table 4. Association of prostate cancer with *HOXB13* G84E in strata of age of diagnosis and disease aggressiveness

Affected in pedigree[a]	Stratum	Carrier rate (%)	OR (95% CI)	*P*
≥2	≤60[b]	8 of 435 (0.018)	9.9 (1.4–68.6)	0.020
≥2	≥61	8 of 423 (0.019)	7.7 (1.6–37.0)	0.011
≥2	Gleason ≤ 6	7 of 433 (0.016)	6.4 (1.3–32.1)	0.023
≥2	Gleason ≥ 7	9 of 400 (0.023)	9.9 (2.1–46.0)	3.5×10^{-3}
≥2	≥pT3, N1, or M1	4 of 175 (0.023)	9.7 (1.8–53.5)	9.2×10^{-3}
≥3	≤60	5 of 177 (0.028)	13.9 (1.8–105.5)	0.011
≥3	≥61	4 of 152 (0.026)	10.2 (1.8–57.8)	8.9×10^{-3}
≥3	Gleason ≤ 6	5 of 180 (0.028)	11.3 (2.0–62.4)	5.5×10^{-3}
≥3	Gleason ≥ 7	4 of 135 (0.030)	13.1 (2.4–72.4)	3.2×10^{-3}
≥3	≥pT3, N1, or M1	3 of 57 (0.053)	23.3 (3.8–143.0)	6.8×10^{-4}

[a]First- and second-degree relatives (0, controls; 1, case probands with no others in pedigree affected; 2, case probands with one additional in pedigree affected).
[b]Proband age of diagnosis.

Published OnlineFirst June 19, 2012; DOI: 10.1158/1055-9965.EPI-12-0495

cancer and may also participate in progression to androgen-independent cell proliferation (33). An intriguing correlative question is whether mutation carriers may be predisposed to develop prostate cancer but not to progress to androgen independence. Furthermore, *HOXB13* expression is regulated by *FOXA1*, a gene identified as recurrently somatically mutated in prostate cancer through recent exome sequencing efforts (34, 35). Additional studies of this mutation in familial prostate cancer are warranted to clarify its role.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.P. Breyer, J.R. Smith
Development of methodology: J.P. Breyer, J.R. Smith
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.P. Breyer, T.G. Avritt, K.M. McReynolds, J.R. Smith
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.P. Breyer, T.G. Avritt, W.D. Dupont, J.R. Smith
Writing, review, and/or revision of the manuscript: J.P. Breyer, W.D. Dupont, J.R. Smith
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.M. McReynolds, J.R. Smith
Study supervision: J.R. Smith

Acknowledgments

The authors thank the study participants and Drs. Sam Chang, Peter Clark, Michael Cookson, Rodney Davis, S. Duke Herrell, Richard Hock, William Maynard, Douglas Milam, Jason Pereira, and Joseph Smith.

Grant Support

This study was supported by a MERIT grant from the U.S. Department of Veteran's Affairs and by an award from the V Foundation.

Received April 23, 2012; revised June 12, 2012; accepted June 12, 2012; published OnlineFirst June 19, 2012.

References

1. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78–85.
2. Page WF, Braun MM, Partin AW, Caporaso N, Walsh P. Heredity and prostate cancer: a study of World War II veteran twins. Prostate 1997;33:240–5.
3. Yeager M, Chatterjee N, Ciampa J, Jacobs KB, Gonzalez-Bosquet J, Hayes RB, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. Nat Genet 2009;41:1055–7.
4. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, et al. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 2008;40:316–21.
5. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, et al. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 2008;40:310–5.
6. Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, et al. A common variant associated with prostate cancer in European and African populations. Nat Genet 2006;38:652–8.
7. Gudmundsson J, Sulem P, Gudbjartsson DF, Blondal T, Gylfason A, Agnarsson BA, et al. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nat Genet 2009;41:1122–6.
8. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nat Genet 2008;40:281–3.
9. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007;39:977–83.
10. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet 2007;39:631–7.
11. Wang L, McDonnell SK, Slusser JP, Hebbring SJ, Cunningham JM, Jacobsen SJ, et al. Two common chromosome 8q24 variants are associated with increased risk for prostate cancer. Cancer Res 2007;67:2944–50.
12. Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G, et al. Cumulative association of five genetic variants with prostate cancer. N Engl J Med 2008;358:910–9.
13. AlOlama AA, Kote-Jarai Z, Giles GG, Guy M, Morrison J, Severi G, et al. Multiple loci on 8q24 associated with prostate cancer susceptibility. Nat Genet 2009;41:1058–60.
14. Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M, Severi G, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. Nat Genet 2009;41:1116–21.
15. Sun J, Zheng SL, Wiklund F, Isaacs SD, Purcell LD, Gao Z, et al. Evidence for two independent prostate cancer risk-associated loci in the HNF1B gene at 17q12. Nat Genet 2008;40:1153–5.
16. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007;39:645–9.
17. Duggan D, Zheng SL, Knowlton M, Benitez D, Dimitrov L, Wiklund F, et al. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. J Natl Cancer Inst 2007;99:1836–44.
18. Kim ST, Cheng Y, Hsu FC, Jin T, Kader AK, Zheng SL, et al. Prostate cancer risk-associated variants reported from genome-wide association studies: meta-analysis and their contribution to genetic variation. Prostate 2010;70:1729–38.
19. Kote-Jarai Z, Olama AA, Giles GG, Severi G, Schleutker J, Weischer M, et al. Seven prostate cancer susceptibility loci identified by a multistage genome-wide association study. Nat Genet 2011;43:785–91.
20. Hemminki K, Forsti A, Bermejo JL. Estimating risks of common complex diseases: familial and population risks. J Med Genet 2008;45:126–7.
21. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 2012;366:141–9.
22. Lange EM, Gillanders EM, Davis CC, Brown WM, Campbell JK, Jones M, et al. Genome-wide scan for prostate cancer susceptibility genes using families from the University of Michigan prostate cancer genetics project finds evidence for linkage on chromosome 17 near BRCA1. Prostate 2003;57:326–34.
23. Lange EM, Robbins CM, Gillanders EM, Zheng SL, Xu J, Wang Y, et al. Fine-mapping the putative chromosome 17q21-22 prostate cancer susceptibility gene to a 10 cM region based on linkage analysis. Hum Genet 2007;121:49–55.
24. Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR, Meyers DA, et al. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. Am J Hum Genet 2005;77:219–29.
25. Cropp CD, Simpson CL, Wahlfors T, Ha N, George A, Jones MS, et al. Genome-wide linkage scan for prostate cancer susceptibility in Finland: evidence for a novel locus on 2q37.3 and confirmation of signal on 17q21-q22. Int J Cancer 2011;129:2400–7.

Published OnlineFirst June 19, 2012; DOI: 10.1158/1055-9965.EPI-12-0495

26. Peng B, Li B, Han Y, Amos CI. Power analysis for case-control association studies of samples with known family histories. Hum Genet 2010;127:699–704.

27. Kalish LA, McKinlay JB. Serum prostate-specific antigen levels (PSA) in men without clinical evidence of prostate cancer: age-specific reference ranges for total PSA, free PSA, and percent free PSA. Urology 1999;54:1022–7.

28. Chun FK, Perrotte P, Briganti A, Benayoun S, Lebeau T, Ramirez A, et al. Prostate specific-antigen distribution in asymptomatic Canadian men with no clinical evidence of prostate cancer. BJU Int 2006;98: 50–3.

29. Kim SD, Park RY, Kim YR, Kim IJ, Kang TW, Nam KI, et al. HOXB13 is co-localized with androgen receptor to suppress androgen-stimulated prostate-specific antigen expression. Anat Cell Biol 2010;43:284–93.

30. Jung C, Kim RS, Zhang H, Lee SJ, Sheng H, Loehrer PJ, et al. HOXB13 is downregulated in colorectal cancer to confer TCF4-mediated transactivation. Br J Cancer 2005;92:2233–9.

31. Jung C, Kim RS, Zhang HJ, Lee SJ, Jeng MH. HOXB13 induces growth suppression of prostate cancer cells as a repressor of hormone-activated androgen receptor signaling. Cancer Res 2004;64: 9185–92.

32. Jung C, Kim RS, Lee SJ, Wang C, Jeng MH. HOXB13 homeodomain protein suppresses the growth of prostate cancer cells by the negative regulation of T-cell factor 4. Cancer Res 2004;64:3046–51.

33. Kim YR, Oh KJ, Park RY, Xuan NT, Kang TW, Kwon DD, et al. HOXB13 promotes androgen independent growth of LNCaP prostate cancer cells by the activation of E2F signaling. Mol Cancer 2010;9:124.

34. McMullin RP, Dobi A, Mutton LN, Orosz A, Maheshwari S, Shashikant CS, et al. A FOXA1-binding enhancer regulates Hoxb13 expression in the prostate gland. Proc Natl Acad Sci U S A 2010;107:98–103.

35. Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat JP, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet 2012;44:685–9.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Confirmation of the *HOXB13* G84E Germline Mutation in Familial Prostate Cancer

Joan P. Breyer, T. Grant Avritt, Kate M. McReynolds, et al.

Cancer Epidemiol Biomarkers Prev 2012;21:1348-1353. Published OnlineFirst June 19, 2012.