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

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## 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 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 for prostate cancer was 7.9 (95% 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 ≥ 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.

### Keywords

hereditary prostate cancer; polymorphism; association

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## 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 suggests 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 (odds ratios ranging from 1.1 to 2.0) and collectively have accounted for ~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 3–5% of prevalent cases meet criterion for hereditary prostate cancer, and given that commercial chips employed 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 four of 85 (4.7%) linked pedigrees of European descent, and co-segregated with disease. The 85 linked pedigrees were a subset of those employed 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 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 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 1$^{st}$ or 2$^{nd}$ degree relatives in the pedigree) at the time of treatment for the principal diagnosis of prostate cancer (confirmed by review of pathology), and controls probands at the time of routine preventative screening for prostate cancer. Controls had no personal or family history of prostate cancer (1$^{st}$ & 2$^{nd}$ 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 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 TNM), biopsy Gleason score, treatment modality and date(s) were recorded. Over 97% of case subjects

underwent radical prostatectomy, providing definitive histopathologic diagnoses. For these, surgical pathology staging (pathological 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.

### Genotyping

DNA was extracted from whole blood on an Autopure LS robot using the Puregene DNA Purification System Standard Protocol (Qiagen, Valencia, CA). DNA was quantified using the PicoGreen dsDNA Quantitation Kit (Invitrogen, Carlsbad, CA), imaged with a Molecular Devices/LJL Analyst HT (Molecular Devices, Union City, CA). SNP genotyping for rs138213197 was conducted using the TaqMan platform (Applied Biosystems, Foster City, CA). Mutations were confirmed by Sanger sequencing of identified carriers. Genotypes were successfully obtained for 99.2% of subjects. Genotype data was 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 odds ratio, adjusted for age. Analyses were restricted to subjects of European descent. ORs, 95% confidence intervals, and *P* values were derived under a dominant model. Hardy-Weinberg equilibrium analysis was performed employing 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 non-carriers 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 performed using the Wilcoxon rank-sum test for age, the score test for trend for Gleason score, and Fisher's exact test for advanced stage.

## Results

The G84E germline mutation of *HOXB13* (A allele on coding strand, encoding glutamate) was observed in two study controls and in 20 cases, each in the heterozygous state. All carriers were of European descent. One control carrier was age 80, with two unaffected male siblings and a screening PSA of 1.64. The other control carrier was age 56 with three 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 odds ratio 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 extra-prostatic disease at diagnosis (Table 4).

The point estimate of the odds ratio, 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 two 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 four or more affected (OR = 7.0). Given the rarity of the mutation, the confidence intervals of the odds ratio 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 non-carriers. The point estimates of the odds ratio were higher among familial cases with less differentiated or with extra-prostatic disease at diagnosis. However, there was no significant difference between mutation carriers and non-carriers 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 three or more affected men. Odds ratio 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 et al. observed a mean age at diagnosis of 52.9 for carriers, and 57.1 for non-carriers, 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 non-carriers. Ewing et al. found no evidence to support a difference between Gleason grade between G84E carriers and non-carriers, 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 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.

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## 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. 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 1st and 2nd degree affected relatives.

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**Table 2**

Characteristics of *HOXB13* G84E (Glutamate) Carriers of European Descent.

| Subject | Status | Age Dx/Screen | PSA[a] | Ped Type[b] | Stage | | | Gleason | # Cases in Ped[c] | Other Reported Cancers in Ped[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 | MM | pT2c | pN0 | pMX | 6 | 3 | lung, ovary, female breast |
| 5 | Case | 65 | 6.8 | MM | pT2c | pN0 | pMX | 6 | 3 | lung, head & 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), while NMM indicates no apparent male-to-male transmission (X-linked or sibship).

[c]Among 1st and 2nd degree relatives.

## 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 1126 (0.018) | 7.2 (1.7 – 31.2) | $8.1 \times 10^{-3}$ |
| 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) | $6.2 \times 10^{-3}$ |
| ≥ 3 | 9 of 329 (0.027) | 11.8 (2.5 – 55.3) | $1.8 \times 10^{-3}$ |
| ≥ 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).

## 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) | $3.5 \times 10^{-3}$ |
| ≥ 2 | ≥ pT3, N1, or M1 | 4 of 175 (0.023) | 9.7 (1.8 – 53.5) | $9.2 \times 10^{-3}$ |
| ≥ 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) | $8.9 \times 10^{-3}$ |
| ≥ 3 | Gleason ≤ 6 | 5 of 180 (0.028) | 11.3 (2.0 – 62.4) | $5.5 \times 10^{-3}$ |
| ≥ 3 | Gleason ≥ 7 | 4 of 135 (0.030) | 13.1 (2.4 – 72.4) | $3.2 \times 10^{-3}$ |
| ≥ 3 | ≥ pT3, N1, or M1 | 3 of 57 (0.053) | 23.3 (3.8 – 143.0) | $6.8 \times 10^{-4}$ |

[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, etc).

[b] Proband age of diagnosis.