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Prevalence of *HOXB13* mutation in a population of Ashkenazi Jewish men treated for prostate cancer

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Abstract

OBJECTIVE—To determine the prevalence of *HOXB13* G84E mutation in a population of prostate cancer patients of Ashkenazi Jewish heritage, an ethnic group common to the New York City area.

MATERIALS AND METHODS—A retrospective analysis of germline DNA samples from Ashkenazi Jewish men and a comparison group of non-Ashkenazi men treated for prostate cancer at our institution. Patients were genotyped for G84E using a TaqMan assay (Applied Biosystems). Positive cases were confirmed using Sanger sequencing.

RESULTS—Median age at prostate cancer diagnosis was 68 years for 889 Ashkenazi Jewish patients, 64 years for 920 non-Ashkenazi Jewish patients. The median follow up was 9 years for Ashkenazi Jewish patients and 8.8 years for non-Ashkenazi Jewish patients. Only 4 patients were found to be heterozygous carriers of G84E. They were all of non-Ashkenazi Jewish ancestry and were diagnosed at 70, 66, 78, and 49 years of age. Two of them presented with high-risk prostate cancer. The prevalence of G84E in the non-Ashkenazi sample was 0.4%.

CONCLUSIONS—*HOXB13* G84E mutation was not observed in prostate cancer patients of Ashkenazi Jewish ancestry treated at our institution. Screening for G84E, therefore, may be unnecessary in Ashkenazi Jewish men if these results are validated by other studies.

Keywords

Prostatic neoplasms; germline mutation; risk

Introduction

Prostate cancer has a proven hereditary basis; almost one-quarter of prostate cancer cases occur in familial clusters, and 9% can be attributed to cancer traits that segregate in an autosomal dominant Mendelian inheritance pattern (1, 2). Men with first-degree relatives

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with prostate cancer have a 2–4 times higher risk of developing prostate cancer over the course of their lives.(3) Furthermore, African Americans are at an increased risk of developing prostate cancer independent of socioeconomic factors, indicating that genetic variants may determine the risk of prostate cancer in this group (4).

In a recent study, Ewing et al, sequenced 202 genes in the 17q21–22 region, which has been implicated in prostate cancer susceptibility, in germline DNA of 94 unrelated familial prostate cancer patients selected for linkage to the candidate region (5). Probands from four families were heterozygous for a rare missense mutation (G84E) in *HOXB13*. The mutation was also found in all 18 men in these four families who had prostate cancer and had DNA available for analysis. Overall, the mutation was found in 72 (1.4%) of the 5,083 men with prostate cancer but only 1 (0.1%) of the 1,401 control subjects (0.1%) ($P = 8.5\times10^{-7}$). Furthermore, the mutation was significantly more prevalent in men with early-onset, familial prostate cancer (3.1%) than in those with late–onset disease and no family history of prostate cancer (0.6%). Subsequent studies by other groups have also reported the prevalence of G84E mutation in familial prostate cancer patients. In a study cohort consisting of 928 familial prostate cancer patients and 930 controls, Breyer et al. found the G84E mutation in 1.9% of probands, with a 2.7% occurrence in patients with more than 3 affected family members (6). Akbari et al. performed a case-control study, sequencing germline DNA from peripheral leukocytes of 1,843 men diagnosed with prostate cancer and 2,225 controls to identify possible mutations in *HOXB13*. The mutation was more prevalent in Caucasian men than in ethnically matched controls (0.7% vs. 0.1%, P = 0.01) (7). Finally, Karlsson et al. genotyped samples from two population-based, Swedish, case-control studies and found the prevalence of the G84E mutation to be more than 1% in the general Swedish population, which is higher than we and others have reported for controls (around 0.1%) (8).

The aim of this study is to determine the prevalence of *HOXB13* G84E mutation in men of Ashkenazi Jewish heritage treated for prostate cancer at Memorial Sloan-Kettering Cancer Center.

Materials and Methods

Germline DNA was extracted from blood samples of 889 Ashkenazi Jewish and a comparison group of 920 non-Ashkenazi Jewish men treated for prostate cancer at Memorial Sloan-Kettering Cancer Center between 1990 and 2006. Ancestry was self-reported. DNA was collected through IRB-approved protocol. A TaqMan assay (Applied Biosystems) specific to G84E was designed, and the genotyping was performed by real-time PCR according to the manufacturer's instructions. Detection was performed on the ABI Prism 7900 using the Sequence Detection Software (Applied Biosystems). Suspected carriers of the SNP were verified through Sanger sequencing (Figure 1). Primer3 software v 0.4.0 (available at http://frodo.wi.mit.edu/) was used to design PCR primers for Sanger validation of samples with the variant, as indicated by the TaqMan assay. PCR was performed using Platinum Taq DNA Polymerase (Invitrogen), and PCR products were cleaned-up using Exo/Sap IT (USB) and sequenced at the MSKCC Genomics Core Laboratory. Sequencher v. 4.8 (Gene Codes) was used for assembling and aligning the reads to the reference sequence (Human genome build 19) obtained from Ensembl (http://www.ensembl.org).

Results

The median age at diagnosis of prostate cancer was 68 and 64 years for Ashkenazi Jewish and non-Ashkenazi Jewish patients, respectively. Of a total of 1,809 prostate cancer patients included in the study, 4 patients were found to be heterozygous for the G84E mutation. None of the patients carrying the mutation were of Ashkenazi Jewish descent, and none had family history of the disease. Those patients were white males 70, 66, 78, and 49 years old at diagnosis. Two presented with high-risk prostate cancer and both died, with one having prostate cancer documented as the cause of death (Table 2). Thus, the prevalence of this mutation is 0% in the Ashkenazi Jewish prostate cancer patients and 0.4% in the non-Ashkenazi Jewish prostate cancer patients in our study.

Discussion

Prostate cancer has well known hereditary components; however, no high-penetrance susceptibility gene conferring increased risk for this disease has been reported until a rare SNP, G84E in *HOXB13*, was found to be associated with a 20-fold increase in the risk of prostate cancer among over 5,000 men of European descent.(5) This finding has been validated in several studies.(6)

The Ashkenazi Jewish population, compromising about 80% of Jews worldwide, is known to be a relatively homogeneous genetic group with well-known ancestry-associated mutations. For example, 2.3 percent (120 out of 5,318) of Ashkenazi Jewish individuals were found to carry one of three founder mutations in *BRCA1* and *BRCA2* (9), five times higher than of the general population (10). Ashkenazi Jews are present in high numbers in the New York City area (about 12% of the population) and well represented in our DNA repository. The availability of samples from this unique population, and the possibility of G84E being a founder mutation in Ashkenazi Jewish men, stimulated this effort to genotype HOXB13 G84E variant in DNA to determine this variant's prevalence in Ashkenazi Jewish men with prostate cancer. None of the patients genotyped, however, tested positive for G84E.

Previously published results suggest a potential role for genetic testing for G84E in individuals with early-onset prostate cancer or a family history of the disease. It is notable that a single mutation was found, simplifying the development and deployment of a clinical test. However, before testing for G84E is offered outside research studies, critical questions remain to be answered, including: What is the actual risk associated with this mutation? What screening would be recommended and how will it impact clinical care of men with prostate cancer? If these questions are answered, and if it was determined that testing for G84E could change disease management, then Ashkenazi Jewish patients could be saved the anxiety and the expense of testing if our findings are validated by other studies in the same population.

The statistical power to find differences in prevalence is always an issue in small studies like ours. However, considering an approximate prevalence of G84E of 0.6% in prostate cancer patients and 0.1% in controls, we would have had more than 90% power to find carriers of

G84E in our study cohort. Another limitation of this study is that genotyped individuals were all from a single referral center in New York City and may not be representative of the population of affected individuals in general. Therefore, further studies will be needed to validate these findings.

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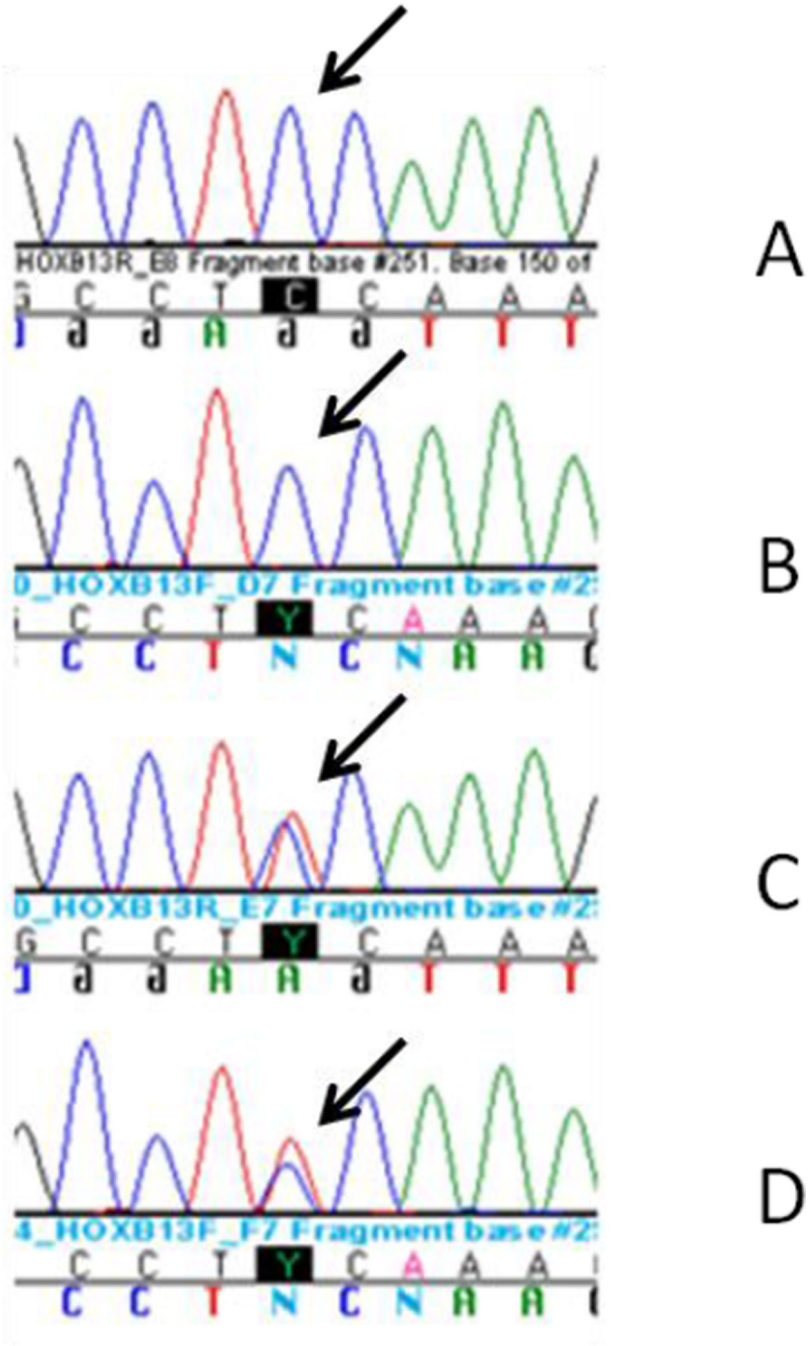

Figure 1.

DNA Sequence Chromatogram Obtained from Germline DNA of Men with Prostate Cancer Carrying Wild Type (A: forward stand, B: reverse strand) or Mutated *HOXB13* (C: forward stand, D: reverse strand)

Table 1

Patient and tumor characteristics of 889 Ashkenazi Jewish and 920 non-Ashkenazi sporadic prostate cancer patients treated at Memorial Sloan Kettering-Cancer Center

Variable	Non-Ashkenazi (%)	Ashkenazi (%)
Median age on diagnosis	64	68
Race		
White	93.7	-
Asian	2.8	-
Black	1.0	-
Other	2.5	-
PSA		
<10	63.9	69.1
10–20	19.0	18.6
>20	17.1	12.3
Gleason Score		
<=6	35.3	38.4
7	42.1	38.7
8–10	22.6	22.9
T stage		
T1	44.4	45.7
T2	38.4	38.0
T3	17.2	16.3
Median follow up (Months)	105	108
Death due to prostate cancer	10.3	13.5

Table 2

Patient and tumor characteristics of *HOXB13* mutation (rs138213197) heterozygous carriers in 920 non-Ashkenazi sporadic prostate cancer patients treated at Memorial Sloan Kettering-Cancer Center

Age at diagnosis	PSA at diagnosis	Gleason score	TNM stage	Metastasis	Death from Prostate Cancer
70	< 10	4+5	T3cN0MX	Yes	Unknown
66	< 10	3+3	T1c	Unknown	Unknown
78	Unknown	5+5	T3aN1M1b	Yes	Yes
49	>10	3+4	T3aN1M0	No	No

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