Featured Article

Truncating *BRCA1* Mutations Are Uncommon in a Cohort of Hereditary Prostate Cancer Families with Evidence of Linkage to 17q Markers

Kimberly A. Zuhlke,[1] Jennifer J. Madeoy,[5] Jennifer Beebe-Dimmer,[2] Kirsten A. White,[1] Angela Griffin,[1] Ethan M. Lange,[6] Stephen B. Gruber,[1,3,4] Elaine A. Ostrander,[5] and Kathleen A. Cooney[1,2]

Departments of [1]Internal Medicine, [2]Urology, and [3]Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan; [4]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan; [5]Clinical Research and Human Biology Divisions, Fred Hutchinson Cancer Research Center, Seattle, Washington; and [6]Department of Public Health Sciences, Section on Biostatistics, Wake Forest School of Medicine, Winston-Salem, North Carolina

ABSTRACT

Purpose: **A genome-wide scan of 175 hereditary prostate cancer families from the University of Michigan Prostate Cancer Genetics Project provided evidence of prostate cancer linkage to 17q markers near the *BRCA1* gene. To examine the possibility that germ-line *BRCA1* mutations were associated with hereditary prostate cancer, individuals from 93 families with evidence of linkage to chromosome 17q were screened for germ-line *BRCA1* mutations.**

Experimental Design: **One individual from each of the 93 families, the majority with three or more cases of prostate cancer, were screened for *BRCA1* mutations with denaturing high-performance liquid chromatography (HPLC). Fragments exhibiting denaturing HPLC variant patterns were additionally analyzed by direct sequencing.**

Results: **Sixty-five of the individuals selected for sequencing from 65 unrelated families were determined to have wild-type *BRCA1* sequence by denaturing HPLC. One individual from a family with both prostate and ovarian cancer was found to have a truncating *BRCA1* mutation (3829delT). An additional 27 germ-line variants were identified, including 15 missense variants.**

Conclusions: **These sequencing results suggest that *BRCA1* truncating mutations do not account for the linkage evidence on chromosome 17 observed in University of Michigan Prostate Cancer Genetics Project families. A recently completed combined genome scan has also detected linkage to 17q22, and studies are ongoing to identify the relevant prostate cancer susceptibility gene in this region.**

INTRODUCTION

The search for prostate cancer predisposition genes has been complicated by locus heterogeneity and the high, sporadic rate of disease in the general population. Whole genome approaches have been used to map prostate cancer susceptibility loci, including *HPC1* (1), *HPCX* (2), *PCAP* (3), *CAPB* (4), and *HPC20* (5); however, many of these loci have not been widely confirmed in replication studies (see reviews; ref. 6, 7). Given the complexity of this disease, analysis of additional multiplex prostate cancer families using genome-wide scans will likely point to additional genomic regions that may harbor prostate cancer susceptibility genes or provide confirmation of regions suggested by previously reports published. Consistent with this supposition, we recently conducted a genome-wide scan on 175 pedigrees, the majority containing three or more individuals diagnosed with prostate cancer, and detected suggestive evidence for linkage on chromosome 17q (LOD = 2.36; ref. 8). The strongest evidence was observed in the subset of pedigrees with four or more affected individuals (LOD = 3.28). The closest genome-wide scan marker to this peak, D17S1868, is located within 5 cM of the breast cancer susceptibility gene *BRCA1*.

The evidence of a prostate cancer susceptibility gene at 17q is additionally strengthened by new results from a combined genome-wide linkage scan on 426 prostate cancer pedigrees (9), which included the 175 pedigrees from our initial report (8). In the combined analysis, the LOD score at *D17S1868* was 2.72 when analyzing all of the pedigrees. However, the peak LOD score (LOD = 3.40) was observed at the neighboring genome-wide scan marker *D17S787*, which is ~13 cM distal to *BRCA1*. Although the results at *D17S787* were in large part driven by the 175 pedigrees from Lange *et al.* (8), there also was supportive evidence of linkage in pedigrees from Johns Hopkins University (LOD = 1.38) and Finland (LOD = 0.68) at this peak location. Evidence for linkage was strongest in pedigrees with early age of diagnosis and in pedigrees with four or more confirmed affected men; both of these subsets of pedigrees are plausibly enriched for an inherited form of prostate cancer.

The *BRCA1* gene at 17q21 (OMIM *113705) was identified by Miki *et al.* (10) based on the identification of a number of deleterious mutations in genomic DNA from individuals in families with breast and/or ovarian cancer after mapping of the

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Requests for reprints: Kathleen A. Cooney, 7310 Cancer Center Geriatric Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0946. Phone: (734) 764-2248; Fax: (734) 615-2719; E-mail: kcooney@umich.edu.

locus by Hall *et al.* (11) in 1990. The gene has 24 exons, including a single large exon (exon 11) that includes about 50% of the coding sequence. Overall, the gene encodes a protein product of 1,863 amino acids. Many of the mutations reported in the literature to date describe variants, which result in a truncated protein. Some missense mutations, for example those occurring in the RING-finger domain (amino acids 20 to 68; ref. 12), have also been shown by genetic studies to be pathogenic. Two common *BRCA1* founder mutations in individuals of Ashkenazi Jewish descent have been described, namely the 185delAG in exon 2 and the 5385insC in exon 20. Founder mutations elsewhere in the gene have been reported from studies of other populations (13–15).

BRCA1 has been investigated for its potential role in prostate cancer susceptibility because of the observation that male carriers of *BRCA1* mutations in families with hereditary breast/ovarian cancer have an increased risk of prostate cancer. Specifically, in a large study of families with known *BRCA1* mutations identified from centers across Europe and North America, the risk of prostate cancer was slightly elevated in male mutation carriers under age 65 [relative risk 1.82, 95% confidence interval (CI) 1.01–3.29] but not in those ≥65 years of age (ref. 16; see Discussion). Other investigators have examined men with early onset and/or familial prostate cancer for the presence of *BRCA1* mutations (17–20). Most of these studies have found little evidence for an association between prostate cancer susceptibility and the inheritance of *BRCA1* germ-line mutations. However, these reports have generally been limited in size and scope and often focused on families without younger mean ages at diagnosis. Indeed, most of the families studied have fallen short of the now well-established criteria for hereditary prostate cancer families proposed by Carter et al. (21).

Given the provocative findings of chromosome 17q linkage in our prostate cancer genome-wide scans, we set out to fully scan the entire *BRCA1* coding region together with intron/exon boundaries for germ-line *BRCA1* variants in a cohort of men from families whose disease could be attributed to a locus at 17q. This analysis represents the most comprehensive study of germ-line *BRCA1* variants in hereditary prostate cancer done to date.

MATERIALS AND METHODS

Patient Selection. A genome-wide mode-of-inheritance-free linkage scan, using 405 genetic markers, was conducted on 175 families participating in the University of Michigan Prostate Cancer Genetics Project. One hundred seventy pedigrees had three or more affected individuals diagnosed with prostate cancer, and the remaining five families were selected based on the occurrence of two cases of prostate cancer diagnosed before age 55 years (8). Ninety-five of the 175 University of Michigan Prostate Cancer Genetics Project families genes were determined to have a nonparametric linkage score >0 at 60.1 cM on chromosome 17. This distance was selected because it represents the linkage peak for all of the 175 families analyzed together. Ninety-three of these families are included in this report. DNA was isolated from nucleated blood cells by use of the Puregene Kit (Gentra Systems, Minneapolis, MN). All of the participants provided written informed consent, and all of the research protocols and consent forms were approved by the Institutional Review Board at the University of Michigan.

Mutation Screening Using Transgenomic Denaturing High-Performance Liquid Chromatography (HPLC). Using 25 ng of genomic DNA, we amplified coding regions of *BRCA1* in 35 separate amplicons for denaturing HPLC, as described previously in Wagner *et al.* (22). PCR reactions were carried out in a total of 32.5 μL with 1.35 μmol/L concentration of each primer, 2.5 or 1.5 mmol/L $MgC1_2$, 0.2 mmol/L deoxynucleoside triphosphates, 1× PCR reaction buffer, and 0.5 units Taq DNA Polymerase (Roche Diagnostics, Basel, Switzerland). After PCR amplification, products were heteroduplexed by slow cooling. Heteroduplexed products were then analyzed using denaturing HPLC and WAVEMAKER version 4.1.44 software. Ten microliters of PCR product were used in each analysis. Analysis temperatures (50°C to 62°C) were predicted by the software and selected to allow maximal separation of different species within each analysis. Fragments 2, 11AB, 11S, 11TU, 15, 16, and 21 were each analyzed at two separate temperatures corresponding to the melting of two separate domains within each fragment. Any denaturing HPLC variant pattern that was seen in <5% of the study population was additionally analyzed by direct sequencing (23). Less than 1% of the 3255 amplicons were not assessable because of technical reasons.

Direct Sequence Analysis. PCR was used to amplify 40 ng of genomic DNA with primer sequences from Wagner *et al.* (22), although some modifications were required. PCR primers were purchased from Invitrogen Life Technologies, Inc. (Carlsbad, CA) and are available on request. With the exception of exons 8 and 11K, each reaction contained 4 μL of 10× PCR buffer (Invitrogen Life Technologies, Inc.), 1 μL 50 mmol/L $MgC1_2$, 1 μL 10 mmol/L deoxynucleoside triphosphates, 5 μL each of the two PCR primers at 5 μmol/L concentration, 2.0 μL template DNA at 20 ng/μl, and 0.5 μL of Taq (Platinum Taq Polymerase, Invitrogen) in 30.5 μL of double-distilled H_2O, for a total reaction volume of 50 μL. Details for PCR conditions for exon 8 and 11K are available on request. PCR products were cleaned with Montage PCR Centrifugal Filter Devices (Millipore, Billerica, MA) and sequenced using an ABI Prism 3100 Genetic Analyzer using Big Dye Terminator v1.1 chemistries (Applied Biosystems, Foster City, CA). Forward and reverse strand sequences were obtained for all individuals noted to have a possible germ-line variant denaturing HPLC. Sequences were screened with Mutation Surveyor Software (SoftGenetics, State College, PA). If a missense (or possibly deleterious) variant was identified in one family member, all of the members of that particular family who had donated blood samples to the University of Michigan Prostate Cancer Genetics Project were also sequenced to test for potential cosegregation of the mutation with disease.

Statistical Analysis. Data analysis to describe the demographic and clinical characteristics of the eligible pedigrees was done using SAS v.8.2 (Cary, NC, 2001). Frequency distributions and/or means with SD and ranges were produced depending on the nature of available variables.

Table 1 Demographic and clinical characteristics of 93 University of Michigan Prostate Cancer Genetics Project families used for *BRCA1* mutation screening

	n (%) or mean (range)
Race	
White	82 (88.2)
Black	10 (10.7)
Other	1 (1.1)
Number of prostate cancer cases/family	
Confirmed	4.1 (2 to 14)
Total	4.3 (2 to 14)
Mean age at diagnosis of confirmed prostate cancer cases in pedigree (yrs)	63.7 (37 to 88)
Number of families with breast cancer*	
0	58 (62.4)
1 to 2	30 (32.2)
>2	5 (5.4)
Number of families with ovarian cancer*	
0	85 (91.4)
1 to 2	8 (8.6)
>2	0 (0.0)

* Cases of breast and/or ovarian cancer were counted only if they were in a first and/or second degree relationship to a man with confirmed prostate cancer.

RESULTS

The clinical characteristics of the 93 University of Michigan Prostate Cancer Genetics Project families with a nonparametric linkage score >0 at 60.1 cM on chromosome 17 are presented in Table 1. The majority of families were Caucasian, and the average number of confirmed cases of prostate cancer was 4.1 per family (range 2 to 14). Pedigrees were studied to identify other types of cancers that may be present in chromosome 17-linked prostate cancer families. Only cases of cancer occurring in family members in a first- and/or second-degree relationship to a man with confirmed prostate cancer were considered. Thirty-five of the 93 families (38%) had one or more cases of breast cancer in the pedigree. Eight families (9%) had one or more cases of ovarian cancer, and five families had cases of both breast and ovarian cancer. Other types of cancers were observed in these families, including cases of colon, stomach, lung, and thyroid cancers. Seventeen of the 93 families (18%) had only prostate cancer reported.

One individual was selected for *BRCA1* mutation screening from each of the 93 University of Michigan Prostate Cancer Genetics Project families with evidence of linkage to chromosome 17 using the following approach, which was designed to select the individual in the pedigree that was most likely to harbor a deleterious *BRCA1* mutation. In 85 families, the youngest man with prostate cancer in each pedigree for whom we had a DNA sample was used for mutation screening. In three families, an older family member with prostate cancer was selected for testing. In these families, the older affected man had at least one first- and/or second-degree relative with breast cancer, whereas the youngest affected man in these pedigrees was more distantly related to the woman with breast cancer. In the remaining five families, DNA from a woman with breast cancer was used for *BRCA1* mutation screening. In each case, the woman was in a first-degree relationship (*e.g.*, a sister) to a man with prostate cancer in the pedigree. The average age of prostate cancer diagnosis was 55.7 +/− 7.8 years (range 37 to 74 years) in the men whose DNA was screened for *BRCA1* mutations. Similarly, the average age at diagnosis of breast cancer in the five women whose DNA was screened for *BRCA1* mutations was 58.2 +/− 15.6 years (range 43 to 77 years).

Sixty-five of the family members from 65 unrelated families were determined to have wild-type *BRCA1* sequence by denaturing HPLC. A total of 28 different sequence variants were identified among University of Michigan Prostate Cancer Genetics Project family members (Table 2, Fig. 1); some individuals harbored more than one germ-line variant. Five of the variants identified herein have not been reported previously in the Breast Cancer Information Core Database (http://research.nhgri.nih.gov/projects/bic/): 667–79T→C, H448Y, 5194–53C→T, 5271 + 85delT, and I1858T. If a missense variant or insertion/deletion was identified in one family member, all of the available family members were tested for the same variant. Because we used direct sequencing to confirm the presence of germ-line variants in family members, we had the opportunity to identify additional sequence variants in selected indi-

Table 2 Germ-line *BRCA1* variants identified in hereditary prostate cancer families from the University of Michigan Prostate Cancer Genetics Project

	Exon/ intron	No. of families	Race
Deleterious mutations			
3829delT	Exon 11	1	White
Missense variants			
Q356R	Exon 11	1	White
H448Y*	Exon 11	1	Black
D693N	Exon 11	7	White
N723D	Exon 11	1	Black
M1008V	Exon 11	1	Black
E1038G	Exon 11	3	White
S1040N	Exon 11	3	White
K1183R	Exon 11	1	Black
Q1200H	Exon 11	1	Black
R1203Q	Exon 11	2	1 White/ 1 Black
E1214K	Exon 11	1	White
R1347G	Exon 11	1	White
S1512I	Exon 15	1	White
S1613G	Exon 16	2	White
M1625I	Exon 16	1	White
I1858T*	Exon 24	1	Black
Unclassified variants			
561–34 C→T	Intron 7	4	White
667–79T→C*	Intron 8	1	Black
667–58 delT	Intron 8	4	White
2201C→T	Exon11	10	9 White/ 1 Black
2430T→C	Exon 11	10	9 White/ 1 Black
5194–53C→T*	Intron 17	6	White
5271 + 66G→A	Intron 18	6	White
5271 + 85delT*	Intron 18	1	White
5396 + 60insGTATTCCACTCC	Intron 20	1	White
5526 + 8T→C	Intron 22	1	Black
5711 + 36C→G	Exon 24	1	Black

* Germ-line variants that have not been reported previously.

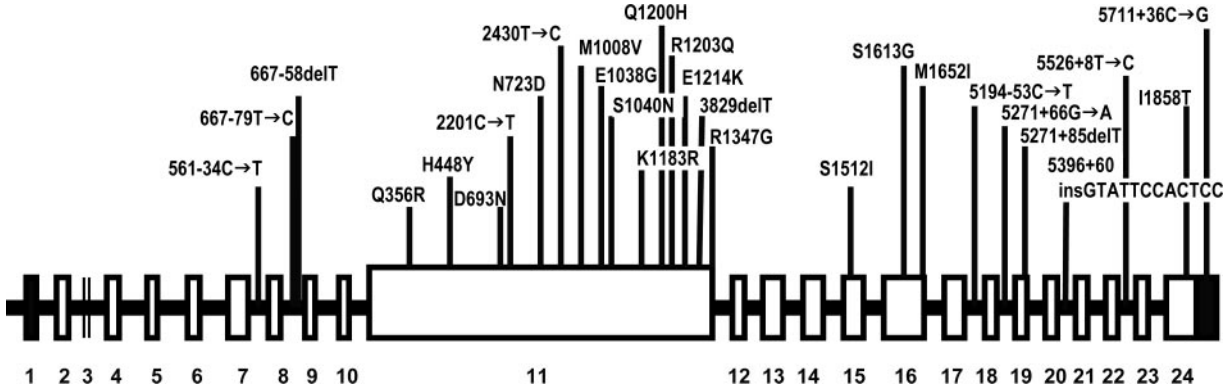

Fig. 1 Schematic drawing of *BRCA1* mutations identified in University of Michigan Prostate Cancer Genetics Project families. The exons are indicated by *boxes* and numbered below the figure; noncoding regions are indicated by *solid black lines*.

viduals who were not initially selected for whole-gene analysis. Three of the reported variants, namely E1038G, K1183R, and E1214K, were present in affected family members but not in the individual selected for denaturing HPLC mutation screening.

The protein truncating mutation 3829delT *BRCA1* mutation was identified in a family that is bilineal with respect to prostate cancer. There is a history of ovarian cancer on the maternal side of the family. The proband and his unaffected maternal uncle were shown to carry the 3829delT mutation.

DISCUSSION

The finding of prostate cancer linkage to chromosome 17q21 markers in University of Michigan Prostate Cancer Genetics Project families led us to consider more fully the possibility that germ-line *BRCA1* mutations may be contributing to hereditary prostate cancer. Because suggestive linkage was observed in our genome-wide scans, we targeted 93 families with individual nonparametric linkage scores >0 and selected the single individual most likely to carry a mutation for denaturing HPLC analysis. By this approach, only 1 of 93 families was discovered to have a deleterious mutation; this pedigree did not have strong evidence for prostate cancer linkage to chromosome 17 markers (nonparametric linkage = 0.22). Although a number of additional germ-line variants, particularly missense changes, were identified in our University of Michigan Prostate Cancer Genetics Project families, we found no evidence to suggest that these variants in *BRCA1* were associated with increased evidence of linkage (data not shown). It is also difficult to draw conclusions about the frequency of missense variants in this study population given the absence of an appropriate control group. To more fully test whether variants in *BRCA1* explain the evidence for prostate cancer linkage at 17q, ideally one would like to have *BRCA1* sequence data from all family members from all prostate cancer pedigrees, regardless of nonparametric linkage score. Given the considerable expense of screening for *BRCA1* mutations, such a test was beyond the scope of this study. Interestingly, *BRCA1* is located near the outer limits of the 1-LOD drop linkage support interval presented in the new combined linkage scan on 17q (9). Taken together with our *BRCA1* mutation results, we conclude that *BRCA1* is unlikely to be the hereditary prostate cancer gene indicated by our combined linkage results on 17q.

The precise role of *BRCA1* mutations in prostate cancer has been a subject of debate over the last decade. The most recent data regarding prostate cancer risk in *BRCA1* mutation carriers comes from the Breast Cancer Linkage Consortium in which a cohort of 11,847 individuals from 699 families harboring *BRCA1* mutations were studied. These investigators observed an increased risk of prostate cancer in male mutation carriers under age 65 (relative risk 1.82, 95% CI 1.01–3.29) but not in men $\geq$65 years of age (relative risk 0.84, 95% CI 0.53–1.22; ref. 16). By comparison, similar data from the Breast Cancer Linkage Consortium showed that the risk of prostate cancer in *BRCA2* (OMIM $*$600185) mutation carriers is higher than for *BRCA1* mutation carriers. The relative risk for prostate cancer in men with *BRCA2* mutations who are less than 65 years of age was 7.3 (95% CI = 4.7–11.5), and the overall relative risk was 4.7 for men of all ages (95% CI = 3.5–6.2). Male *BRCA2* mutation carriers are also at an increased risk for the development of breast cancer (24).

Additional studies have attempted to determine the role of *BRCA1* mutations specifically in hereditary prostate cancer. Langston *et al.* (20) sequenced the entire *BRCA1* gene using genomic DNA from 49 men with early onset prostate cancer diagnosed before age 65 years derived from a population-based, case-control study of middle aged men and prostate cancer. In the Langston *et al.* (20) study, the Ashkenazi 185delAG founder mutation was identified in one subject diagnosed with prostate cancer in his early 60s who reported no female relatives with breast and/or ovarian cancer but several male relatives with prostate cancer. Six additional rare sequence variants were also identified. No germ-line *BRCA1* mutations were identified in affected family members from hereditary prostate cancer families studied by Sinclair *et al.* (17) and Gayther *et al.* (19). The total number of families in these reports was 51, and in contrast to our report, chromosome 17 linkage data were not used to select families for analysis.

Several groups have also examined the frequency of the *BRCA1* founder mutations among Ashkenazi men with prostate cancer. For example, in a study of 83 men with prostate cancer,

Nastiuk *et al.* (25) identified only one individual who was a carrier of the185delAG *BRCA1* mutation. This is not substantially different from the frequency reported in the general Ashkenazi population. However, a recent report provides a more accurate measure of the degree of risk elevation associated with the *BRCA1* Ashkenazi founder mutations. Giusti *et al.* (26) studied 940 Ashkenazi men diagnosed with prostate cancer in Israel and found an increased risk of prostate cancer carriers of the 185delAG mutation compared with Ashkenazi men over 50 years of age with no history of prostate cancer. The controls in this study came from two independent studies of Ashkenazi men in the United States and Israel, and the results were statistically significant (odds ratio 2.5; 95% CI 1.1–6.0). In the Giusti *et al.* (26) study, the percentage of cases with a family history of disease was not reported, but the cases were not specifically enriched for men with hereditary prostate cancer. By comparison, Wilkens *et al.* (18) were unable to detect either *BRCA1* founder mutations in 47 family members from 18 Ashkenazi prostate cancer families from the United States. Thus, whereas the Ashkenazi *BRCA1* founder mutations may increase the risk of prostate cancer, other more penetrant mutations may account for the clustering of prostate cancer within Ashkenazi families.

In our study of hereditary prostate cancer families, we identified one deleterious *BRCA1* mutation in a family with both prostate and ovarian cancer. However, we also identified 16 missense variants whose precise significance is unknown. Some of the missense changes, for example D693N in exon 11, were observed in five unrelated families in our study and have been described as polymorphisms of unknown or unlikely significance in Breast Cancer Information Core Database. Other changes such as H448Y and I1858T have not been reported previously. In our study, the H448Y substitution was identified in a bilineal family in which some unaffected males were determined to carry the variant, and the I1858T substitution was shared among both members of a brother pair with early onset prostate cancer (data not shown). It is also important to note that both families with novel *BRCA1* missense substitutions are African American. Studies of breast and ovarian cancer families have shown that the pattern of genetic variation in the *BRCA1* gene differs between African Americans compared with other racial groups (27). Because relatively few African American families have undergone clinical *BRCA1* testing, the degree of known polymorphic variation in this population is less clear, and our report adds to this developing dataset.

If the *BRCA1* gene is acting as a tumor suppressor gene in prostate cancer, somatic inactivation of one (or both) allele(s) may be observed, particularly in men harboring germ-line mutations. Gao *et al.* (28) observed a high rate of loss of heterozygosity in sporadic prostate cancers using chromosome 17q markers. In the Gao *et al.* (28) report, 11 of 21 informative tumors showed allelic loss at one or more 17q markers, and 8 of 18 (44%) informative cases had loss of heterozygosity using the intragenic *BRCA1* marker *D17S85*. More recent mapping work by Dai *et al.* (29), however, places the common region of 17q deletion in sporadic prostate cancers distal to *BRCA1*. This study used P1 probes and fluorescent *in situ* hybridization to define an 85kB common region of deletion in prostate cancer located 470 kB distal to *BRCA1*. This data suggests that there is a tumor suppressor gene distal to *BRCA1* that may be important in prostate carcinogenesis.

In conclusion, epidemiologic data derived primarily from studies of breast and ovarian cancer families suggest that *BRCA1* mutations result in a small but detectable increase in risk for prostate cancer, especially for early onset disease. Our recent observation of prostate cancer linkage to chromosome 17q marker (8) motivated this comprehensive mutational analysis of *BRCA1* in hereditary prostate cancer families. We were unable to identify deleterious mutations in a sufficient number of University of Michigan Prostate Cancer Genetics Project families to account for our reported linkage evidence. This suggests the existence of a hereditary prostate cancer gene near *BRCA1* on chromosome 17, and efforts are ongoing toward additionally localizing and characterizing this putative locus.

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