

The Frequency of Germ-line Mutations in the Breast Cancer Predisposition Genes *BRCA1* AND *BRCA2* in Familial Prostate Cancer¹

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ABSTRACT

Predisposition to prostate cancer has a genetic component, and there are reports of familial clustering of breast and prostate cancer. Two highly penetrant genes that predispose individuals to breast cancer (*BRCA1* and *BRCA2*) are known to confer an increased risk of prostate cancer of about 3-fold and 7-fold, respectively, in breast cancer families. Blood DNA from affected individuals in 38 prostate cancer clusters was analyzed for germ-line mutations in *BRCA1* and *BRCA2* to assess the contribution of each of these genes to familial prostate cancer. Seventeen DNA samples were each from an affected individual in families with three or more cases of prostate cancer at any age; 20 samples were from one of affected sibling pairs where one was ≤ 67 years at diagnosis. No germ-line mutations were found in *BRCA1*. Two germ-line mutations in *BRCA2* were found, and both were seen in individuals whose age at diagnosis was very young (≤ 56 years) and who were members of an affected sibling pair. One is a 4-bp deletion at base 6710 (exon 11) in a man who had prostate cancer at 54 years, and the other is a 2-bp deletion at base 5531 (exon 11) in a man who had prostate cancer at 56 years. In both cases, the wild-type allele was lost in the patient's prostate tumor at the *BRCA2* locus. However, intriguingly, in neither case did the affected brother also carry the mutation. Germ-line mutations in *BRCA2* may therefore account for about 5% of prostate cancer in familial clusters.

INTRODUCTION

Prostate cancer is the second most common cause of cancer mortality in men in the United Kingdom. Approximately 14,000 cases/year and 8,742 deaths/year are reported in England and Wales (1, 2). Its incidence is increasing by 10% every 5 years (3), even when the effect of screening is taken into account, and 13% of cases occur in men in their preretirement years. One percent of cases occur in men < 55 years of age in the United Kingdom. There is increasing evidence that there is an inherited component to many of the common cancers (4), and prostate cancer is no exception. Familial clustering of prostate cancer has been observed, the most dramatic of which is the large prostate cancer kindreds described in Utah, United States (5);

furthermore, case-control studies (6) show that relatives of cases have an increased relative risk of developing the disease, and this has been confirmed in two cohort studies (7, 8). This relative risk increases markedly when the age of the index case decreases or the number of affected individuals in a cluster increases, which is evidence that this increased risk has a genetic component. One segregation analysis has led to the proposed model of at least one highly penetrant gene (88% of gene carriers would develop prostate cancer by age 85) that accounts for 43% of cases diagnosed at < 55 years (9); two others support this model, but with a higher gene frequency of about 1% and a penetrance of 63% (10, 11). Other reports have suggested a recessive or X-linked model (12, 13). Recently, a highly penetrant prostate cancer susceptibility locus *HPC1* was mapped to 1q, but this only accounts for up to 34% of families with four or more cases in one study of 91 families (14) or, at most, 20% of such large clusters in another study of 35 families (15). In the latter study, 1q linkage analysis in 101 clusters with ≤ 3 cases showed no evidence of linkage to 1q. Recent studies have suggested that other loci exist: (a) one at 1q42 (16) that has not yet been confirmed; (b) one at Xq27-28 (17) that accounts for 16% of families; and (c) one at 1p36 (18). Preliminary evidence from analysis of 187 prostate cancer clusters in our laboratory indicates that these loci do not account for all of familial prostate cancer. Other genes therefore remain to be located.

There is an association between breast and prostate cancer in families; a higher incidence of prostate cancer among male relatives of breast cancer patients has been reported previously (19-21). Anderson and Badzioch (22) report a doubling of familial breast cancer risk when prostate cancer is present in the family history. *BRCA1* and *BRCA2* are located on chromosomes 17q12-21 and 13q12-13, respectively. LOH⁴ studies in prostate cancer have shown that 52% of tumors have LOH at 17q; in one study, 44% of tumors had LOH with a marker intragenic in the breast cancer predisposition gene *BRCA1* (23). *BRCA1* carriers also have a 3-fold increased risk of mortality from prostate cancer (24). We have demonstrated a 25% incidence of LOH at the *BRCA2* locus in familial and sporadic prostate cancer (25). Tonin *et al.* (26) calculated that there was a relative risk of 7.2 of prostate cancer in *BRCA2* carriers but did not mention an age-at-onset effect.

One family with four prostate cancer cases but no breast cancer has been reported to have a germ-line *BRCA1* mutation (27) that is 185delAG, a common *BRCA1* mutation in Ashkenazi Jewish families with breast cancer (28). This family was indeed of this ethnic origin. Workers from Iceland (29) have reported a common *BRCA2* mutation (999del5) in nine Icelandic cancer families with multiple cases of

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⁴ The abbreviations used are: LOH, loss of heterozygosity; PTT, protein truncation

breast cancer. Some of these families also had multiple cases of prostate cancer. Icelandic studies have shown 2.7% of prostate cancer cases in Iceland carry this mutation (30). Four studies (31–34) have reported that there is no increased frequency of the founder Ashkenazi *BRCA1* and *BRCA2* mutations over that expected in this population when germ-line DNA from prostate cancer cases with and without a family history are analyzed.

The Cancer Research Campaign/British Prostate Group United Kingdom Familial Prostate Cancer Study aims to investigate the role of genetic susceptibility to prostate cancer. As part of the study of high penetrance genes, prostate cancer cases with an increased chance of harboring a prostate cancer susceptibility gene are being collected. Those clusters with a relative risk of developing prostate cancer of ≥ 4 are targeted for collection (35); these are clusters of ≥ 3 prostate cancers at any age or in sibling pairs, preferably where one is < 65 years at diagnosis. The first 38 of these clusters were analyzed in this study; *BRCA1* and *BRCA2* were analyzed from germ-line DNA to assess the contribution of *BRCA1* and *BRCA2* germ-line mutations to familial prostate cancer. This is the first study to analyze the entire coding region of *BRCA1* and *BRCA2* in a non-Ashkenazi series of prostate cancer clusters.

MATERIALS AND METHODS

Patient Material. Peripheral blood DNA from 38 affected individuals who were members of prostate cancer clusters was studied. The composition of the clusters is shown in Table 1. Wherever possible, DNA from the youngest available member of each cluster was studied. Tumor DNA was prepared after

microdissection of tumor tissue from paraffin sections. Microdissected tissue was removed into 200 μ l of extraction buffer [$1 \times$ RedHot polymerase buffer (Applied Biosystems), 1.5 M $MgCl_2$, 0.45% NP40, 0.45% Tween 20, and 200 μ g/ml proteinase K] and incubated at 55°C for 12 h. After incubation, proteinase K was deactivated by heating to 99°C for 10 min.

Mutation Analysis. *BRCA1* and *BRCA2* were both screened for germ-line mutations using a combination of the PTT and a nonradioactive HA to identify variants in the sample set. PTT is an efficient technique for screening large DNA fragments (≥ 1 kb) for truncating mutations and was used to analyze exon 11 of *BRCA1* (which represents approximately 60% of the coding sequence) and exons 10 and 11 of *BRCA2* (60% of the coding region). The remaining exons and splice boundaries of both genes were screened using HA. The majority of germ-line mutations reported in *BRCA1* and *BRCA2* result in truncation of the predicted protein as a result of frameshift, nonsense, or splice site alterations; therefore, the combination of PTT and HA was considered a sensitive and efficient method of analysis. Direct sequence analysis was used to confirm the precise nucleotide alteration associated with PTT and/or HA variants. The primer sequences for *BRCA2* and their respective product sizes and amplification conditions have been described previously (36).

PTT was performed for the largest two exons of *BRCA2* and for the largest exon only for *BRCA1*. Primers were designed to PCR amplify exons 10 and 11 of *BRCA2* and exon 11 of *BRCA1* from genomic DNA in overlapping fragments ranging in size from 1.0–1.3 kb. PTT was performed as described previously (36).

Coding exons 2, 3, 5–10, and 12–24 of *BRCA1* and 2–9 and 12–27 of *BRCA2* were amplified from genomic DNA. The 5' and 3' splice boundaries for exon 11 of *BRCA1* and exons 10 and 11 of *BRCA2* were also amplified from genomic DNA. SSCA/HA was performed in $1 \times$ mutation detection enhancement polyacrylamide gels as described previously (36). Syder Green

Table 1 Composition of prostate cancer clusters

Identifier no. (individual tested)	Age at diagnosis of prostate cancer in individual analyzed (yrs)	No. of individuals affected with prostate cancer in family	Age at prostate cancer diagnosis of other relative(s) in family (yrs)	Other cancers in cluster Site (age at onset; yrs)
PR3380.201	49	5	73, 70, uk ^a , 73	Pe(uk), Br(40, 44, uk), Bl(uk), NHL(34)
PRS2036.201	65	5	69, 63, 56, 74	
PR3658.201	43	4	87, 37, 72	Br(70), Ov(70), Bas(25)
PRS2015.205	65	4	70, 65, 67	
PRS2018.201	67	4	69, 70, 67	Co(78)
PRS2051.201	72	4	60, 75, 77	Lu(57, uk), uk(uk)
PR3106.201	67	3	74, 81	Th/B(40), Te(uk), Ey(uk)
PR3382.201	71	3	87, 62	Co(72)
PRS2016.201	64	3	73, 60	Re(51), Co(54)
PRS2024.201	56	3	41, 87	Br(76)
PRS2025.202	71	3	75, 65	
PRS2031.202	59	3	67, 80	Lu(68), Co(85), SSC Sc(60), uk(uk)
PRS2039.201	66	3	uk, uk	
PRS2045.201	71	3	86, 67	NHL(<8), Lu(64), Ov/Ut(uk)
PRS2053.201	71	3	72, 77	
PRS2059.201	76	3	71, 81	Bon(uk), Li(58), Lu(76)
PRY1061.201	49	3	58, 61	
PRY1081.201	46	3	58, 77	uk(51)
PR3173.201	63	2	64	
PR3222.201	58	2	82	Br(59), St(73)
PR3378.201	59	2	71	Th(70, uk), Br(uk), Bon(64)
PR3498.201	61	2	64	Co(uk)
PR3569.201	54	2	72	St(53), Lu(uk, uk)
PRS2001.201	62	2	64	
PRS2003.201	62	2	64	
PRS2005.202	63	2	66	Sp(uk)
PRS2010.201	60	2	63	Lu(66)
PRS2012.201	62	2	62	
PRS2017.202	60	2	66	Co(47, 63, uk), St/Bo(uk), Lu(uk), Ki(uk), uk(uk)
PRS2047.201	64	2	64	St(59)
PRS2052.201	57	2	66	
PRS2058.201	67	2	72	Ut/Ov(55)
PRY1010.201	49	2	66	Br(uk, uk, uk), Lu(uk), Co(uk)
PRY1026.201	52	2	65	
PRY1042.201	54	2	48	Pa(55)
PRY1052.201	54	2	78	Ov(58)
PRY1056.201	53	2	uk	
PRY1064.201	49	2	69	Ki(51)

^a uk, unknown; B, brain; Bas, basaloid anal cancer; Bl, bladder; Bon, bone; Br, breast; Co, colon; Ey, eye; Ki, kidney; Li, liver; Lu, lung; NHL, Non-Hodgkin's lymphoma; Ov,

staining was used for DNA detection. Sequence analysis of variant PTT and SSCA/HA samples was performed using the ABI 373A DNA sequencer by dye terminator cycle sequencing with AmpliTaq DNA polymerase FS (Perkin-Elmer).

Haplotype Analysis. Peripheral blood DNA and tumor DNA from paraffin-embedded tumor tissue was PCR amplified with three polymorphic microsatellite markers, D13S260, D13S263, and D13S267, which flank the *BRCA2* gene on chromosome 13q12. PCR products were electrophoresed at 250 V on 8–12% polyacrylamide gels for 14–16 h at a constant temperature of 18°C. Gels were visualized after silver staining as described previously (36).

Immunohistochemical Staining for BRCA2 Protein. Sections (4 μ m) were cut from blocks of prostate cancer tissue, picked up on adhesive-coated slides (Vector Laboratories, Burlingame, CA), and baked overnight at 56°C before staining. The BRCA2 antigen was unmasked by placing the sections in a pressure cooker containing boiling 0.01 M citrate buffer (pH 6.0) and boiling under pressure for 2 min. Sections were cooled in running tap water and rinsed in Tris-buffered saline before the application of the rabbit polyclonal BRCA2 antibody (courtesy of N. Spurr and D. M. Barnes, Imperial Cancer Research Fund) for 1 h. Antibody binding was detected using a conventional peroxidase-conjugated streptavidin biotin complex method (Dako Ltd., High Wycombe, United Kingdom). Sites of peroxidase activity were detected using diaminobenzidine as the chromogen. A breast carcinoma known to express BRCA2 was used as a positive control. A negative control in which the primary antibody was replaced with Tris-buffered saline was included for each case. The presence of any nuclear staining was recorded as positive.

The BRCA2 antibody used was raised against a COOH terminus peptide synthesized using the sequence published by Wooster *et al.* (37). The peptide, which contained residues 2301–2320 (DGKGKEEFYRALCDVKAT) with a peak corresponding to a calculated M_r of 2101, was prepared using the fastmoc HBTU method to a standard purity (25).

RESULTS

Mutation analysis of *BRCA1* revealed no variants that appeared to be related to the disease phenotype in any of the 38 prostate cancer

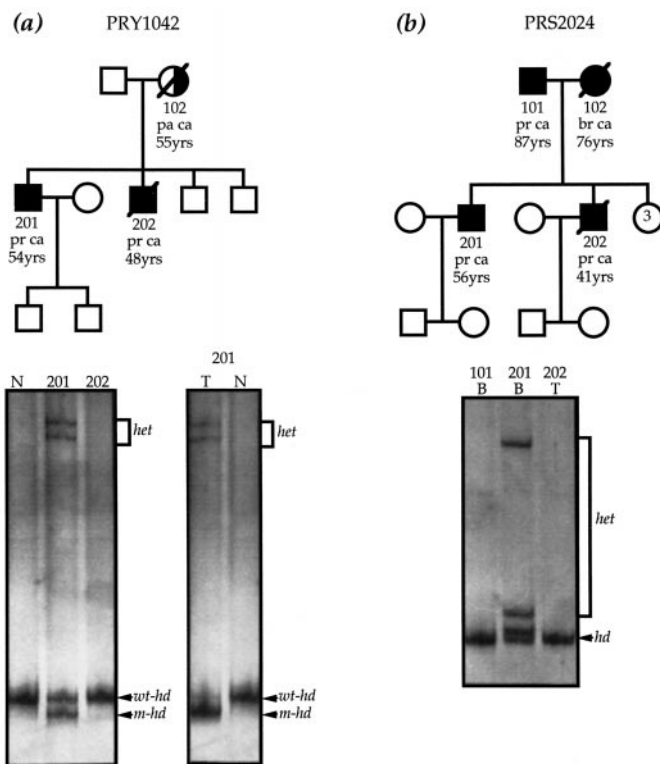


Fig. 2. *a*, the pedigree of family PRY1042. The mutation in this family, 6710delACAA, is detected as a heteroduplex variant (*het*) in index case 201. This variant is not present in the affected brother (202) or in a normal sample (*N*). *pa ca*, pancreatic cancer; *pr ca*, prostate cancer. Analysis of tumor DNA from individual 201 shows loss of the wild-type homoduplex DNA band (*wt-hd*) and retention of the shorter, mutant homoduplex band (*m-hd*). This is compared with wild-type homoduplex DNA seen in a normal sample (*N*). *b*, the mutation in family PRS2024, 5531delTT, was detected as a heteroduplex variant (*het*) and a homoduplex conformer (*hd*) in blood DNA from index case 201. This variant is not present in blood DNA from the affected father (101) or in tumor DNA (*T*) from the affected brother (202). *br ca*, breast cancer.

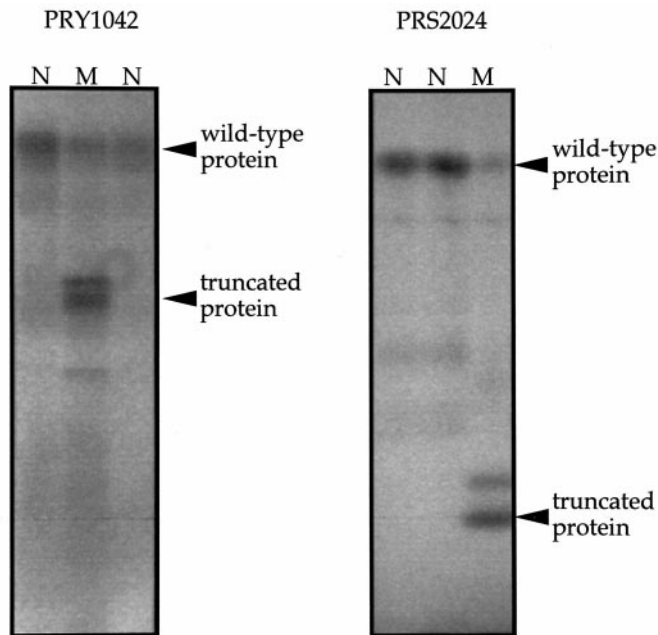


Fig. 1. The protein truncation test performed for BRCA2. *a*, analysis of PTT fragment 4 in affected individual 201 from family PRY1042 shows a truncated mutant protein (*M*) compared with only wild-type protein detected in two normal samples (*N*). *b*, analysis of affected individual 201 from family PRS2024 shows a truncated mutant protein (*M*) compared with only wild-type protein detected in two normal

families. Several frequently observed variants were detected using HA, but sequencing revealed these to be either coding or noncoding polymorphisms that have been reported previously.⁵

Analysis of *BRCA2* revealed three variants that were not detected in any other individuals from the sample set. Two of these variants were detected as truncated proteins by PTT; the third was detected as a heteroduplex variant in exon 22. In family PRY1042, from individual 201, a PTT variant in exon 11 (Fig. 1) was characterized as a 4-bp deletion beginning at nucleotide 6710 (6710delACAA) that is predicted to cause a frameshift and premature truncation of the predicted protein at codon 2166. This mutation has not been reported previously. HA using primers designed to amplify the region flanking this mutation confirmed the presence of this alteration in the index case and also showed loss of the wild-type allele in DNA from tumor tissue from the same individual. However, HA of DNA prepared from tumor tissue from the affected sibling, who was diagnosed with prostate cancer at 48 years, indicated that this individual did not carry the *BRCA2* mutation (Fig. 2*a*). Haplotype analysis using three polymorphic microsatellite markers flanking the *BRCA2* gene at chromosome 13q12–13 was performed on DNA from the two affected brothers from family PRY1042. Although it was not possible to phase the haplotypes, the allele sizes of each marker indicate that both copies of chromosome 13 differ between the two brothers (data not

shown). This is consistent with the observation of a germ-line *BRCA2* mutation in one affected brother but not in the other.

A PTT variant in exon 11 in a prostate cancer case diagnosed at 56 years from family PRS2024 (Fig. 1) was characterized as a 2-bp deletion beginning at nucleotide 5531 (5531delTT). This is a novel mutation and is predicted to result in frameshift and truncation at codon 1772. The family history of PRS2024 with respect to the index case consists of the father diagnosed with prostate cancer at 87 years, the mother diagnosed with breast cancer at 76 years, and a brother diagnosed with prostate cancer at 41 years. HA confirmed the presence of the mutation in the index case but indicates that the same alteration is not present in the father's constitutional DNA or in tumor DNA from the affected brother (Fig. 2*b*). No DNA was available from the proband's mother. Neither deletion was found in over 100 normal individuals tested.

A heteroduplex variant was detected in exon 22 in a prostate cancer case diagnosed at 46 years, from family PRS1081. This variant was characterized as a single-base substitution (G to T at nucleotide 9078) that is predicted to convert a lysine amino acid residue to an asparagine residue (K2950N) and has not been reported previously. DNA was not available from a second affected individual from the family to confirm segregation of this alteration with the disease. To examine whether this alteration is a putative missense mutation or merely a rare variant without disease association, DNA was analyzed from a series of normal individuals for the presence of the sequence change. The identification of the K2950N alteration in 2 of 340 (0.59%) normal chromosomes suggests that this change is a rare polymorphism that is not associated with the disease. Several other heteroduplex variants were observed throughout *BRCA2* in the sample set. However,

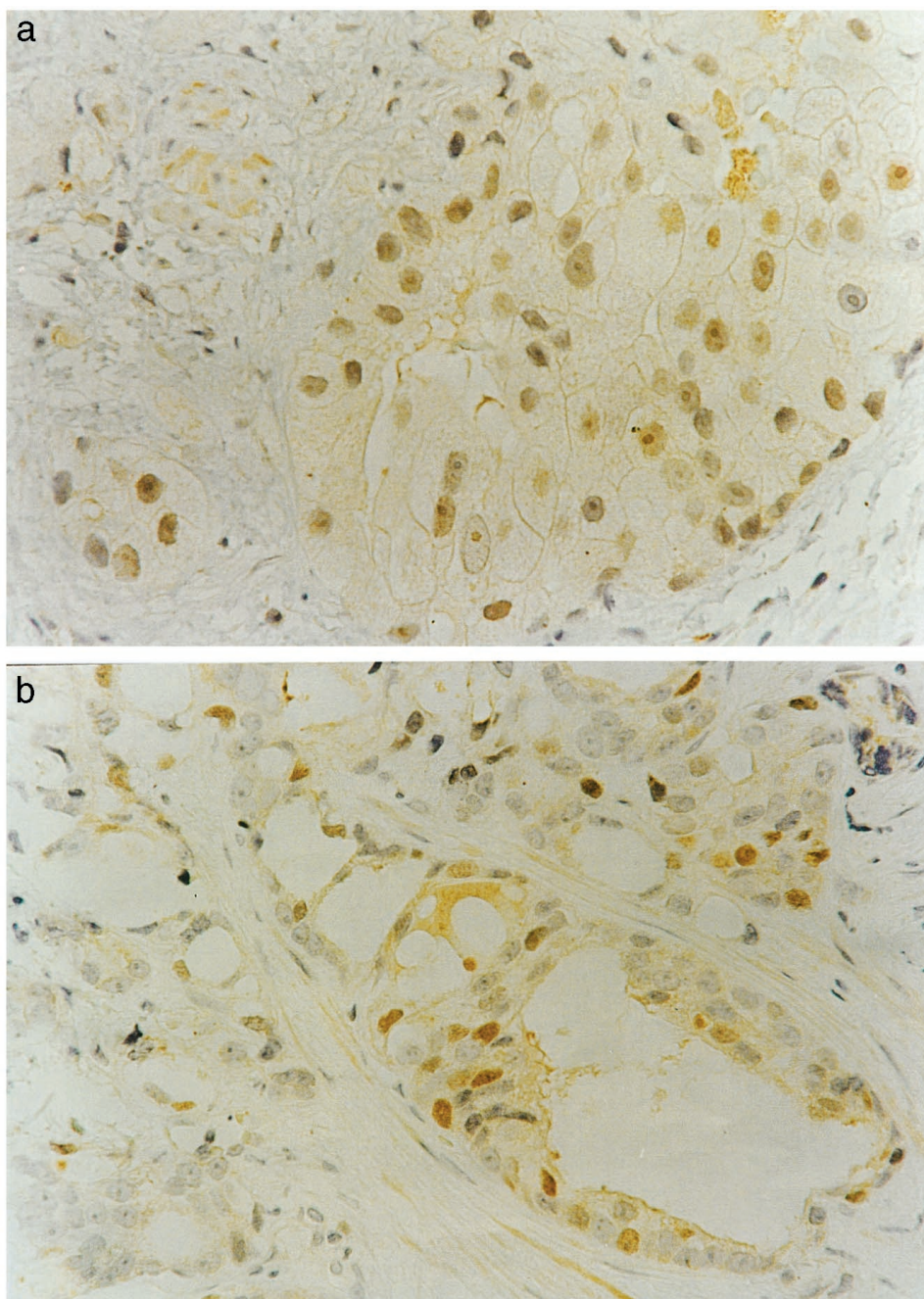


Fig. 3. *a*, prostate cancer cells from the brother (PRY1042.202) of the individual (PRY1042.201) who has a germ-line deletion (6710delACAA). This shows weakly positive staining with antibody to *BRCA2* protein in individual 1042.202, who does not carry the mutation. ($\times 400$). *b*, multifocal areas of intense staining for antibody to *BRCA2* protein in prostate cancer cells from the patient who has a polymorphism in *BRCA2* (K2950N variant; $\times 400$).

these all occurred relatively frequently and were characterized as either previously reported coding or intronic polymorphisms that are not considered to be disease related.

The *BRCA2* antibody stains 25% (25) of sporadic prostate cancer samples. We found that the two individuals with deletions in *BRCA2* did not exhibit any staining in their prostate tumors, but their siblings without mutation and the individual with the K2950N variant did so. In the latter case, multifocal areas of intense nuclear staining were observed within tumor areas (Fig. 3, *a* and *b*).

DISCUSSION

The data we have reported suggest that approximately 5% (2 of 38) of families identified with a history of prostate cancer, based on either affected sibling pairs or three or more affected individuals in the family, may contain an individual with a germ-line mutation in the *BRCA2* gene. These data also indicate that *BRCA1* does not contribute significantly to familial prostate cancer. The actual proportions of germ-line *BRCA2* and *BRCA1* mutations in such families may be greater; it is possible that mutations may have been missed using the combination of the PTT and HA, and we would not have detected missense mutations in the regions screened by PTT. It is surprising that the two disease-associated *BRCA2* mutations that were detected were not present in the affected sibling in each of the families. In family PRY1042, the germ-line mutation 6710delACAA and loss of the wild-type allele in tumor tissue detected in the index case suggest that the mutation in *BRCA2* is cancer-causing and acting as a tumor suppressor gene. This is consistent with previous reports that suggest that sporadic ovarian cancers with germ-line *BRCA2* mutations and breast tumors from a *BRCA2* linked family show nonrandom loss of the wild-type allele (38, 39). The germ-line mutation in family PRS2024 was detected in the index case diagnosed with prostate cancer but not in his father (who was diagnosed at 87 years), suggesting that the father may be a sporadic case, nor was it present in tumor DNA from the affected brother. The mother was diagnosed with breast cancer at 76 years of age, and it is probable that she is also a germ-line carrier of the mutation, although no DNA was available to test this hypothesis.

The fact that several reports have now shown that germ-line mutations in the *BRCA2* gene are associated with an increased risk of prostate cancer (29, 40, 41) makes *BRCA2* a putative candidate gene for familial prostate cancer in general. Our data using linkage analysis at the *BRCA2* locus in 100 affected sibling pairs with prostate cancer has estimated that up to 30% of such pairs (95% confidence interval, 0–70%) may be due to the *BRCA2* gene (42). Although the Cancer Research Campaign/British Prostate Cancer United Kingdom Familial Prostate Cancer Study ascertained sibling pairs with at least one of the affected siblings at age <67 years at diagnosis, the two mutations described here have occurred in prostate cancer cases occurring at ≤56 years, and *BRCA2* germ-line mutations may therefore contribute to a significant proportion of young cases within these pairs. We were surprised to find that in both of the sibling pairs, the *BRCA2* mutation was not present in the affected brother. This was unexpected because both brothers affected who did not carry the mutation were younger than those who did. There are two possible explanations for this. The first is that the *BRCA2* mutation is not cancer causing. This is unlikely because both mutations are deletions and would be expected to have a major effect on the function of the protein. Furthermore, the wild-type allele was lost in the subsequent prostate tumor in PRY1042, individual 201. It is interesting that *BRCA2* antibody

mutations but positive in their brothers who did not have a truncating mutation and also in the individual with the K2950N variant. The overall frequency of positive *BRCA2* staining in sporadic prostate cancer is 25% (25). The second possible explanation is that there is another gene segregating in the prostate cancer clusters PRY1042 and PRS2024 and that the *BRCA2* mutation is acting as a modifier. There is some evidence for this in Icelandic families with *BRCA2* mutations, in which prostate cancer incidence is inversely proportional to male breast cancer incidence in branches of the same family with the same germ-line mutation (29). Both families with *BRCA2* mutations contained an individual with a cancer at another site. PRY1042 contained a case of pancreatic cancer, and PRS2024 contained a case of breast cancer. In PRS2024, the father of the prostate cancer case with the germ-line *BRCA2* mutation did not have the mutation, despite being affected with the disease. If it had been inherited and was not a novel mutation, then this is presumed to have been inherited from the case's mother. This raises the possibility that *BRCA2* germ-line mutations are only seen in the context of prostate cancer families with associated cancers known to occur in *BRCA2* families [namely breast, pancreatic, ovarian, and gall bladder cancer (41)]. Of the 38 families, 25 (66%) had prostate cancer and other cancers. Table 1 lists the other cancers. Of 25 prostate cancer families with prostate and other cancers, two had germ-line mutations in *BRCA2* (8%). None of the 13 families with prostate cancer alone had *BRCA2* mutations. Our data suggest that a proportion of prostate cancer families may harbor germ-line mutations in the *BRCA2* gene. Because the clusters we analyzed were small, it is possible that we have underestimated the contribution of germ-line mutations in *BRCA2* to prostate cancer overall. Additional studies are warranted in larger series of both prostate cancer clusters and isolated cases at varying ages to determine the size of this proportion in different prostate cancer populations.

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