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Familial prostate cancer: the damage done and lessons learnt

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Abstract

Background—A 51-year-old French Canadian man commenced screening for prostate cancer at the request of his family physician given his extensive family history of prostate cancer in five brothers, his father and two paternal uncles. His prostate specific antigen (PSA) level was 4.9ng/ml and a subsequent six-core biopsy revealed the presence of a prostate adenocarcinoma with a Gleason score of 7 (3+4). He was treated with a radical prostatectomy. Repeat PSA tests revealed a gradual rise in PSA levels despite androgen deprivation therapy with bicalutamide and goserelin over the course of 3 years. Genetic evaluation was undertaken in view of his personal and family history. The proband died a year later of widespread metastasis, at the age of 58.

Investigations—Doppler ultrasound for the proband's leg, abdominal and pelvic computed tomography (CT) scan with intravenous (IV) and oral contrast as well as chest CT with IV contrast for the assessment of metastatic prostate cancer; genetic counselling and mutation analysis for French Canadian founder mutations in the *BRCA1* and *BRCA2* genes; mutations specific analysis of the mother's formalin-fixed, paraffin-embedded (FFPE) breast tissue blocks; examination of loss of heterozygosity at the *BRCA2* gene locus; immunohistochemistry to determine the expression of the ERG nuclear oncoprotein in prostate tumours; genotyping with eight selected risk-associated single nucleotide polymorphisms (SNPs); genetic testing for the G84E variant in the *HOXB13* gene

Diagnosis—Early-onset and aggressive prostate cancer associated with a missense French Canadian *BRCA2* founder mutation, c.5857G>T (p.Glu1953*).

Management—Radical prostatectomy, hormone therapy with bicalutamide and goserelin, palliative chemotherapy initially with docetaxel plus prednisone then with mitoxantrone plus prednisone, as well as genetic counselling and testing for the proband and his family members.

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Competing interests

The authors declare no competing interests

Author contributions

N. Taherian researched data for this article. N. Taherian wrote the article. All authors made a substantial contribution to discussion of content and review of the manuscript before submission.

THE CASE

A 51-year-old French Canadian man with a strong family history of prostate cancer presented to his family physician's office because he was concerned about his family history of prostate cancer. Given that his brother and father died of prostate cancer, and they were both diagnosed in their 50's, his physician ordered a PSA test followed by a six-core prostate biopsy. His PSA level was 4.9ng/ml and all prostatic biopsy tissues were positive for adenocarcinoma with a Gleason score of 7 (3+4). Within a year of his diagnosis, the proband had a radical prostatectomy, which revealed a prostate adenocarcinoma with Gleason 7 (3+4) and extensive perineural invasion very close to the resection margins. The seminal vesicles were free of tumour and there was no vascular invasion present. His PSA level was 0.38ng/ml one month after his prostatectomy. Later that year, hormone therapy (bicalutamide) was administered for three months and the PSA level decreased to 0.02ng/ml. However, his PSA started to rise over the next 18–24 months and attempts to stabilise it using goserelin were unsuccessful.

A Doppler ultrasound examination of the proband's right leg, performed 6 years after his prostatectomy, showed evidence of an enlarged right inguinal lymph node (measuring 1.8cm). He also had an abdominal and pelvic computed tomography (CT) scan with intravenous (IV) and oral contrast that revealed: extension of the prostate carcinoma to the right side of his pelvis, extensive lymphadenopathy and compression of the inferior vena cava, as well as lung metastasis, and possible metastatic lesions in the liver. Metastatic lymphadenopathy and lung nodules were diagnosed on a chest CT scan with IV contrast.

One month later, the proband's PSA level was 69.36ng/ml. He was given zoledronic acid (Zometa, 3.5mg) and prednisone (20 mg daily) and commenced treatment for metastatic prostate cancer. The first line of treatment consisted of chemotherapy with 10 cycles of Docetaxel (Taxotere 75mg/m², 130mg, every 3 weeks) and prednisone (20mg daily) over the course of 6 months. The dose of zoledronic acid varied according to the proband's creatinine clearance rate. At the third cycle, his PSA level fell to 45.06 and continued to decrease. The PSA level reached its nadir (33.78ng/ml) by the 5th cycle and increased steadily thereafter. By the 8th cycle, his PSA was 61.64ng/ml and he complained of unilateral left knee and hip pain. He was referred for palliative radiotherapy due to a left femoral metastasis. His PSA level remained high (90.83ng/ml) until the last cycle of chemotherapy. After one month, he started on his second line of treatment with 7 cycles of mitoxantrone (12mg/m², 20 mg, every 3 weeks) and prednisone (cycle 1: 8mg po bid; cycle 2–5: 5mg po bid for a total of 12 weeks, cycle 6–7: 10mg daily and two units of probiotics). Dexamethasone was administered at the 2nd cycle (8mg po bid x1) and at the 3rd cycle (8mg po bid x2). Zoledronic acid was also given (dose adjusted according to creatinine clearance rate).

Owing to the early age of diagnosis and aggressive nature of his prostate adenocarcinoma, the proband was referred for genetic counselling and testing. His family history (Figure 1) was remarkable for early-onset prostate cancer in three brothers and his father (individuals III-2, III-4, III-6, and II-7 in Figure 1) and late-onset prostate cancer in two brothers and two paternal uncles (individuals III-3, III-5, II-1 and II-3 in Figure 1). Pathology reports were obtained for the majority of affected relatives, except for one paternal uncle (II-1) and one brother (III-2), who reportedly complained of kidney and back pain 5 years prior to his diagnosis of metastatic prostate cancer. Prostate tumour tissue samples from the proband's father (II-7) and paternal uncle (II-3) were unavailable. Local review of the available prostate formalin-fixed paraffin-embedded (FFPE) tumour tissue from the proband and four of his affected brothers (III-3, III-4, III-5 and III-6) was conducted to obtain the TNM stage and uniform Gleason score (Table 1).

Other notable medical histories on pedigree analysis included a paternal aunt with early-onset breast cancer (diagnosed at age 40 years) who died aged 76 years (II-4), the proband's mother who developed a late-onset infiltrating ductal carcinoma of the breast and died at age 89 years (II-8), and two maternal cousins who were diagnosed with prostate cancer (III-17 and III-18), one of which was early-onset (age 54 years).

Given this remarkable family history, genetic testing was performed. The first line of testing consisted of genetic analysis of founder mutations in the *BRCA1* and *BRCA2* genes that are commonly identified in families of French Canadian descent with a family history of breast and ovarian cancer.^{1, 2} Using a PCR-based assay followed by restriction digestion with KpnI (*kelpsiella pneumonia*, New England Biolabs, Ipswich, MA, USA), a deleterious missense mutation, c.5857G>T (p.Glu1953*), was detected in the *BRCA2* gene of the proband.

Two months later, genetic testing was offered to the proband's living siblings (III-3 to III-10), nephews (IV-1 to IV-3) and cousins (III-12 and III-18 on Figure 1). The same *BRCA2* mutation was identified in three of the proband's brothers (III-2, III-4 and III-6) with early-onset prostate cancer, and three of his sisters (III-8, III-9 and III-10). Individual III-2 was no longer alive at the time of genetic testing, but the presence of the *BRCA2* mutation in two of his sons (IV-1 and IV-2) confirmed that he was also a carrier of this mutation. Two of the proband's brothers with late-onset prostate cancer (III-3 and III-5) did not carry the familial mutation. The *BRCA2* mutation was also not detected in FFPE tissue from the patient's mother's breast biopsy, indicating that the mutation was paternally inherited.

Examination of loss of heterozygosity (LOH) at the *BRCA2* locus was conducted to study the relevant significance of the *BRCA2* mutation and the diagnosis of prostate cancer in this family. LOH was examined in available FFPE prostate cancer tissue obtained from both the proband and one of his affected brothers who carries the mutation (III-6) using a sequencing-based approach described previously.³ The proband's tumour showed loss of the wild type *BRCA2* allele, but his brother's tumour showed no evidence of LOH.

To determine if the prostate cancer diagnosed in carriers in this family was characterised by genetic factors other than *BRCA2*, we studied ERG nuclear oncoprotein overexpression in prostate tumours from the proband and four of his brothers (III-3 -III-6 on Table 1). Sections (4 µm thick) isolated from FFPE tissue blocks were stained with a Ventana autostainer. Prior to staining, heat induced antigen retrieval was carried out by vegetable steamer in sodium citrate antigen retrieval buffer (10 mM pH 6.0) for 40 min, and then cooling down to room temperature for about 20 minutes. The slides were incubated for 60 minutes at 37 °C with ERG rabbit monoclonal antibody (Epitomics, clone EPR 3864) at 1:50 dilution. A Ventana iView DAB detection kit (Ventana Tucson, Arizona, USA) was used for horseradish peroxidase detection and counter stain. The ERG nuclear oncoprotein was found to be overexpressed in prostate tumours from three brothers (III-3, III-5 and III-6, only one of whom carried the *BRCA2* mutation. Figure 2 shows nuclear staining for ERG in a prostate specimen from individual III-6.

We wondered if this family would have been identified as a *BRCA2*-linked family if we were unaware of the familial mutation. To study this, we ran LINKAGE⁴ under the assumption of: (a) a 5% phenocopy rate and (b) a uniform sevenfold increased risk for *BRCA2*-related prostate cancer.⁵ The men tested for *BRCA2* mutations were classified into different liability classes based on their affected status and age at diagnosis (see Supplementary Table 1). We assumed a 30-fold increased risk for early-onset *BRCA2*-related prostate cancer (diagnosis at <60 years of age).⁶ Under these conditions, we obtained a logarithmic of the odds (LOD) score of +0.36, which although positive represents a ratio of only 2.3 to 1 in favour of the causative gene being *BRCA2*. For any genetic marker, a

LOD score of 3.0 (1000: 1 in favour of that location) is traditionally required to demonstrate linkage in gene mapping studies. In our analysis, the maximum possible LOD score with complete penetrance was found to be +0.67, or 4.7:1 in favour of *BRCA2*. The observed LOD score is less than the maximal LOD score mainly because of the presence of the two brothers who have prostate cancer but did not carry the mutation.

This led us to wonder if the presence of prostate cancer in the noncarriers (III-3 and III-5) could be explained in part by the presence of low-penetrance single nucleotide polymorphisms (SNPs) that are associated with prostate cancer risk. Genotyping was performed with eight SNPs known to be associated with prostate cancer risk (Table 2). We selected these SNPs on the basis of the effect size and the published *P* value^{7–10}. Two different scores were calculated for each individual genotype (see Supplementary Table S2); the first score was a simple count of the number of risk alleles carried by each individual and the second was a score weighted by the LOD ratio for each SNP. No difference was observed in the scores for each SNP between affected and unaffected men, indicating that the clustering of prostate cancer in this family is not likely to be attributed to variation at these susceptibility loci.

The proband died two months after his second line of palliative treatment for metastatic prostate cancer. He experienced pain in his back and left leg while he was undergoing this treatment. His PSA level had increased exponentially after the 5th cycle of mitoxantrone and prednisone, and was 146.34ng/ml by the 7th cycle.

We recently analysed the DNA samples from all the men (III-1, III-3-III-7, III-12, III-18, and IV-1-IV-3) who were tested for *BRCA1/2* gene mutations, for a novel variant (G84E) in the *HOXB13* gene.¹¹ None of these men carried the G84E variant.

DIAGNOSIS

Prostate cancer is the most common cancer diagnosed in men in Canada with a lifetime prevalence of 1 in 7 of the general Canadian population.¹² The majority of men are diagnosed after the age of 70 years; however, with the availability and widespread use of PSA screening for early detection of prostate cancer, the incidence of this disease has risen in younger men (< 55 years old).¹³ Men who develop high-grade or advanced prostate cancer at or below the age of 55 years tend to have a worse clinical prognosis with a greater risk of cancer-specific mortality at 10 years than older men with aggressive disease.¹⁴ Some data suggest that an early age at diagnosis in families with several affected relatives is suggestive of hereditary or familial susceptibility to prostate cancer.^{15, 16} Understanding the aetiology of prostate cancer and identifying genetic factors that predispose to aggressive disease in a subgroup of younger men with familial prostate cancer would allow for targeted screening and treatment, and therefore improved cancer-related survival in these men.

Segregation analyses of the clustering of prostate cancer in families provide evidence for a hereditary form of prostate cancer caused by a rare susceptibility allele with a dominant mode of inheritance and a moderate-to-high lifetime penetrance.^{17–19} Data from linkage analyses suggest that several chromosomal loci are associated with prostate cancer risk in hereditary prostate cancer families,^{20–23} meaning that the identification of a particular prostate-cancer-causing gene is complicated by the genetic heterogeneity of this disease and the presence of different incompletely penetrant loci in different families.²⁴

Genome-wide association studies have identified various chromosomal regions that harbour prostate cancer susceptibility alleles, or SNPs, which individually confer a small increased risk for disease, but when present in high numbers and in combination with a known disease marker (such as increased PSA level) can provide a useful tool for the identification of men

at high risk of developing early-onset and aggressive prostate cancer.²⁵ One particular region, 17q21-22, contains the *HOXB13* gene encoding the homeobox transcription factor B13, which is involved in prostate development. A novel variant (G84E) of the *HOXB13* gene has recently been shown to be associated with hereditary prostate cancer in families selected for linkage to 17q21-22.¹¹ The G84E variant was found in four index patients and all of their affected relatives, and was more common in patients with early-onset and familial disease than in those with late-onset and nonfamilial prostate cancer (3.1% versus 0.6%, $P = 2.0 \times 10^{-6}$).¹¹ Notably, this *HOXB13* mutation is not associated with the 17q risk alleles previously identified in genome-wide associated studies.¹¹

BRCA2 is another gene with an important role in the development of early-onset and aggressive prostate cancer. The Breast Cancer Linkage Consortium reported a significantly increased risk of prostate cancer in the families of patients with breast or ovarian cancer that carries a *BRCA2* mutation, where the relative risk (RR) for prostate cancer was estimated to be 4.65 (95% CI 3.48–6.22).⁵ In addition, the risk was higher in men younger than 65 years (RR = 7.33; 95% CI 4.66–11.52) than in older men (RR = 3.39; 95% CI 2.34–4.92; $P = 0.01$).⁵ Protein-truncating *BRCA2* mutations have also been associated with a 23-fold risk for prostate cancer to age 56 in a cohort of men unselected for family history.⁶

Men who carry *BRCA2* mutations are more likely to develop early-onset prostate cancer^{26, 27} and have a shorter survival time than *BRCA1* mutation carriers and men in the general population.^{28, 29} This decreased survival might be explained by the finding of an aggressive phenotype (Gleason score ≥ 8 and high T stage, pT3) in the majority of tumours in the *BRCA2* carriers who die from prostate cancer.³⁰ A poor prognosis for prostate cancer has also been reported in carriers of founder *BRCA2* mutations in the Icelandic population.^{31, 32} The Ashkenazi Jewish *BRCA2* founder mutation, c.5946delT (p.Ser1982fs), confers a threefold increased risk for prostate cancer, and carriers are more likely to develop high-grade prostate cancer than noncarriers.³³ In the large Swedish family reported by Gronberg *et al.*,³⁴ a truncating *BRCA2* mutation (c.5823delA [p.Val1942fs]) was responsible for hereditary prostate cancer in the father and four of his sons who developed early-onset disease. This mutation was also detected in three daughters diagnosed with breast cancer. All of the affected men with prostate cancer died of metastatic disease.

Here, we describe a French Canadian family with hereditary prostate cancer associated with a founder mutation in *BRCA2*. Among the seven affected first degree relatives (III-1 to III-6, and II-7), three were found to be carriers of the c.5857G>T (p.Glu1953*) mutation, two are obligate carriers, and two do not carry the mutation. Three of the proband's sisters who were tested for the familial *BRCA2* mutation were found to be carriers and did not develop breast or ovarian cancer (III-8-10). With the exception of one reported case of early-onset breast cancer in a paternal aunt (II-4), there is no other significant history of breast cancer in this family.

In this family, age at prostate cancer diagnosis was observed to be lower in carriers of the familial *BRCA2* mutation (≤ 56 years) than in noncarriers (≥ 65 years). The proband's father (II-7), who was an obligate carrier of this mutation, developed early-onset prostate cancer at 54 years of age. Overall, the Gleason score was observed to be higher in carriers than noncarriers and all male carriers except for one brother (III-6) developed aggressive prostate cancer with a Gleason of ≥ 7 (Table 1). Moreover, it might be argued that prostate cancer in the carriers was rapidly progressive as two brothers (III-1 and III-2) and their father (II-7) died from metastatic disease. Brother (III-4) was diagnosed early, owing to his own vigilance. However, it is difficult to draw any conclusions from these results.

Further evidence supporting involvement of the *BRCA2* mutation in the development of prostate cancer is demonstrated by LOH at the *BRCA2* gene, a potentially important marker for cancer prognosis and a hallmark of tumour suppressor genes. In sporadic prostate cancer, LOH is rarely detected at *BRCA2* with only 7% of sporadic tumours demonstrating LOH within the *BRCA2* gene.³⁵ LOH has been observed in breast, ovarian, cervical, colon, ureteral, male breast, and prostate tumours in families at high-risk of breast cancer with evidence of linkage to *BRCA2*.³⁶ In a small sample of men with germline *BRCA1* or *BRCA2* mutations, LOH was found in 10 of 14 tumours from *BRCA2* mutation carriers, and none of four tumours from *BRCA1* carriers.²⁶ LOH was also studied in four prostate tumours and one breast tumour from the previously mentioned Swedish family; two of the prostate tumours demonstrated LOH at *BRCA2*.³⁴ Similarly, in our French Canadian family, LOH was observed in one of two prostate tumours from *BRCA2* carriers.

Another potential indicator of aggressive prostate cancer is overexpression of the *ERG* proto-oncogene, as described by Vanaja and colleagues,³⁷ who demonstrated increased *ERG* expression in 50% of the prostate tumours they analysed. Park *et al.*³⁸ reported that all *ERG* fusion genes, regardless of the fusion partner involved in the rearrangement, lead to *ERG* overexpression in prostate tumours.³⁸ They also reported increased *ERG* expression in tumours with high-grade prostatic intraepithelial neoplasia (HPIN) compared to adjacent benign glands, suggesting that *ERG* overexpression might be a marker of rapidly progressive disease.³⁸ In the present family, *ERG* overexpression was observed in the radical prostatectomy specimens of one carrier (III-6) and two noncarriers (III-5 and III-6). These results indicate that overexpression of the *ERG* nuclear oncoprotein is not associated with *BRCA2*-related prostate cancer. Interestingly, all three tumours that demonstrated *ERG* overexpression demonstrated HPIN.

Evidently, the *BRCA2* mutation is not entirely responsible for the diagnoses of prostate cancer in this family and only very weak evidence of linkage to *BRCA2* was obtained (i.e. the LOD score is positive but very low). However, it is notable that we did not observe a higher number of prostate cancer risk alleles (for the eight selected SNPs) between affected and unaffected men, suggesting that these susceptibility loci do not significantly contribute to prostate cancer risk in this family. Furthermore, the hereditary prostate cancer in this family is not associated with the *HOXB13 G84E* variant.

TREATMENT AND MANAGEMENT

In Canada, annual PSA screening is available to all men over the age of 50 years old.³⁹ A PSA value 4.0 ng/ml is considered to be above the normal range (0–3.9 ng/ml); however, the decision to perform a diagnostic prostate biopsy depends on other factors including age and ethnicity, as well as other parameters of PSA measurements, such as PSA doubling time, density, and percentage of free to total PSA.³⁹ The effectiveness of PSA screening in the general population has been questioned,⁴⁰ but the situation is likely to be different for men at higher risk of developing prostate cancer. According to the preliminary results of the IMPACT study, PSA screening in men who carry *BRCA1* or *BRCA2* mutations can detect clinically significant prostate cancer (defined as an advanced stage on TNM classification).⁴¹ In the family described here, the decision to pursue PSA screening and prostate biopsy among unaffected brothers was influenced by the diagnosis of early-onset prostate cancer in their father and the proband (III-2) before any prior knowledge of their *BRCA2* mutation status.

Palliative chemotherapy with docetaxel and prednisone is recommended for the management of metastatic prostate cancer that fails to respond to treatment with radical prostatectomy and hormone therapy.^{42, 43} Median survival from advanced prostate cancer is

also improved with docetaxel therapy (18.9 months) as compared with chemotherapy using mitoxantrone and prednisone (16.5 months).⁴² However, about 50% of patients are resistant to docetaxel therapy.^{42, 43} Similarly, in a small sample of Ashkenazi Jewish men who had docetaxel therapy for metastatic prostate cancer, a PSA response (defined by at least a 50% decline in PSA level) was observed in half of the *BRCA1/2* founder mutation carriers. Docetaxel therapy did not however improve the overall survival rate in this patient population.⁴⁴

The prostate tumour in the proband metastasised despite treatment with radical prostatectomy and hormone therapy. Although his PSA level initially declined with docetaxel therapy (from 69.36ng/ml pre-treatment to 33.78ng/ml at the 5th cycle), it rose exponentially until the completion of his treatment. Neither docetaxel nor mitoxantrone improved his overall PSA level or pain. Further investigations are required to determine which chemotherapeutic regimen would benefit men with *BRCA1/2*-related prostate cancer, especially in the setting of metastatic disease.

CONCLUSIONS

The case presented here adds to the existing evidence supporting *BRCA2* as a highly penetrant prostate-cancer-causing gene and conveys four valuable lessons concerning familial prostate cancer. Firstly, *BRCA2* mutation carriers are at increased risk of developing clinically advanced prostate cancer, and are at higher risk for metastatic disease than noncarriers. Secondly, breast cancer does not always occur in *BRCA2*-related families, as three carrier women in this family were not diagnosed with breast cancer. The proband's mother had late-onset breast cancer but did not carry the familial mutation. Testing for *BRCA2* should be offered to affected men with a family history of prostate cancer alone.

Thirdly, identifying a gene that might be responsible for familial prostate cancer remains challenging even in a family with six affected brothers. For example, the G84E variant of the *HOXB13* gene, which is present in less than 1 in 1,000 men, causes hereditary prostate cancer and, like *BRCA2* mutations, is more common in early-onset and familial disease. However, this mutation does not explain either the linkage signal on 17q or the elevated odds ratio associated with SNPs on chromosome 17q. Perhaps whole genome approaches will reveal such rare but clinically important mutations.

Finally, although we cannot make specific screening recommendations based on these results, we suggest that men with a family history of early-onset and aggressive prostate cancer should be particularly vigilant regarding prostate cancer, even if they do not carry the known deleterious variant. Those who do carry the disease-causing mutation should be offered regular PSA screening and early consideration of prostate biopsy. Future results of the IMPACT study will indicate if prostate biopsy, irrespective of PSA level, is warranted in certain *BRCA2* mutation carriers, because a diagnostic biopsy will be offered to all men with PSA values in the normal range at the end of the study.⁴¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Pedigree analysis of a family affected by hereditary prostate cancer. The proband (III-1, arrow) presented to his physician owing to concerns regarding his family history. Genetic testing was performed to elucidate carrier status for the *BRCA2* gene founder mutation, c. 5857G>T (pGlu1953*). The carrier status of the individuals who were tested is indicated as +/- and -/-, for carriers and non-carriers (wild type), respectively. Blood and tissue samples were not available for genetic testing in individuals II-7 and III-2; however their carrier status was inferred from the information provided by the pedigree (and indicated as +/-). For the affected individuals, the age at diagnosis is indicated next to the type of cancer. The 'current' age (at the time when this pedigree was obtained in 2009) or the age at death is indicated in parenthesis.

Figure 2. Histology of prostate tissue that harbors the familial *BRCA2* mutation (from individual III-6). (A) Haematoxylin and eosin stain of formalin-fixed paraffin embedded tissue obtained from the proband's radical prostatectomy reveals Gleason score 6 (3+3) characterised by individual small-sized glands infiltrating between benign glands. (B) Avidin-biotin immunoperoxidase staining shows overexpression of the ERG nuclear oncoprotein in nuclei of nearly all tumour cells.

Table 1
Prostate cancer in a French Canadian family with founder mutation (c.5857G>T [pGlu1953*]) in the *BRCA2* gene

Family member [*]	'Current' age or age at death (years)	Age at diagnosis (years)	Preoperative PSA (ng/ml) [‡]	Gleason score [‡]	Reviewed FFPE tissue [§]				ERG nuclear oncogene expression		LOH at <i>BRCA2</i> locus
					Gleason score	TNM	Positive margins?	HPIN [?]	Intensity	Positive <i>tumour cells</i> (%)	
Carriers											
III-1	d.58	51	4.9	7 (3+4)	9 (4+5)	pT2N0	No	No	n/a	nil	Yes
III-4	61	53	7.6	7	8 (4+4)	n/a	ND	No	n/a	nil	ND
III-6	60	54	2.01	6 (3+3)	6 (3+3)	pT2N0	No	Yes	2	70	No
Inferred carriers											
II-7	d.58	54	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
III-2	d.61	56	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Noncarriers											
III-3	74	65	n/a	6 (3+3)	6 (3+3)	pT2N0	No	Yes	3	100	ND
III-5	73	66	8.23	6 (3+3)	7 (3+4)	pT3b	Yes	Yes	3	90	ND

* Corresponds to individual numbers in pedigree shown in Figure 1.

[‡] Obtained from patients' medical records and pathology reports, when available.

[§] Review of available FFPE tumour blocks by collaborating uropathologist, Dr. Louis Bégin, performed one year after we meet with the family. Intensity of ERG nuclear oncoprotein immunohistochemical expression was scored as follows: nil, no staining; 1, mild; 2, moderate; and 3, marked.

Abbreviations: FFPE, formalin-fixed paraffin-embedded; HPIN, high-grade prostatic intraepithelial neoplasia; LOH, loss of heterozygosity; n/a, not applicable; ND, not determined;

Table 2

Eight SNPs and chromosomal loci associated with prostate cancer risk.

SNP	Chromosomal region	Gene	P-value	References
rs1465618	2p21	<i>THADA</i>	1.60×10^{-08}	7
rs10486567	7p15.2	<i>JAZF1</i>	2.14×10^{-26}	8
rs1512268	8p21.2	<i>NKX3.1</i>	3.40×10^{-30}	7
rs6983267	8q24.21		6.20×10^{-23}	9
rs10993994	10q11.23	<i>MSMB</i>	7.31×10^{-13}	8, 10
rs7931342	11q13		1.70×10^{-12}	8, 10
rs2735839	19q13.33	<i>KLK2/KLK3</i>	1.50×10^{-18}	10
rs5759167	22q13.2	<i>BIK</i>	5.90×10^{-29}	7

Abbreviations: *THADA*, thyroid adenoma associated; *JAZF1*, juxtaposed with another zinc finger protein 1; *NKX3.1*, NK3 homeobox 1; *MSMB*, microseminoprotein beta; *KLK2*, kallikrein-related peptidase 2; *KLK3*, kallikrein-related peptidase 3; *BIK*, BCL2 -interacting killer (apoptosis-inducing)