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ORIGINAL REPORT

Germline *BRCA* Mutations Are Associated With Higher Risk of Nodal Involvement, Distant Metastasis, and Poor Survival Outcomes in Prostate Cancer

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ABSTRACT

Purpose
To analyze the baseline clinicopathologic characteristics of prostate tumors with germline *BRCA1* and *BRCA2* (*BRCA1/2*) mutations and the prognostic value of those mutations on prostate cancer (PCa) outcomes.

Patients and Methods
This study analyzed the tumor features and outcomes of 2,019 patients with PCa (18 *BRCA1* carriers, 61 *BRCA2* carriers, and 1,940 noncarriers). The Kaplan-Meier method and Cox regression analysis were used to evaluate the associations between *BRCA1/2* status and other PCa prognostic factors with overall survival (OS), cause-specific OS (CSS), CSS in localized PCa (CSS_M_0), metastasis-free survival (MFS), and CSS from metastasis (CSS_M_1).

Results
PCa with germline *BRCA1/2* mutations were more frequently associated with Gleason $\geq$ 8 ($P = .00003$), T3/T4 stage ($P = .003$), nodal involvement ($P = .00005$), and metastases at diagnosis ($P = .005$) than PCa in noncarriers. CSS was significantly longer in noncarriers than in carriers (15.7 *v* 8.6 years, multivariable analyses [MVA] $P = .015$; hazard ratio [HR] = 1.8). For localized PCa, 5-year CSS and MFS were significantly higher in noncarriers (96% *v* 82%; MVA $P = .01$; HR = 2.6%; and 93% *v* 77%; MVA $P = .009$; HR = 2.7, respectively). Subgroup analyses confirmed the poor outcomes in *BRCA2* patients, whereas the role of *BRCA1* was not well defined due to the limited size and follow-up in this subgroup.

Conclusion
Our results confirm that *BRCA1*/2 mutations confer a more aggressive PCa phenotype with a higher probability of nodal involvement and distant metastasis. *BRCA* mutations are associated with poor survival outcomes and this should be considered for tailoring clinical management of these patients.

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INTRODUCTION

More than 900,000 new cases of prostate cancer (PCa) are diagnosed worldwide every year.[1,2] Although the majority of patients with PCa are cured with radical primary treatment or may only need active surveillance, others will eventually succumb to advanced disease. In fact, PCa accounts for the second commonest cause of male cancer-related deaths in the United States[2] and the sixth worldwide, with more than 250,000 deaths a year.[1] Thus it is essential to identify up front those patients with a lethal form of PCa.

PCa is rarely diagnosed in men younger than 50 years, but its incidence rises rapidly thereafter. Excluding advanced age, the strongest risk factor for the disease is a family history of PCa,[3-5] suggesting the importance of genetic factors in disease development.[6] Genome-wide association studies have identified more than 70 susceptibility loci associated with modest relative risks of PCa, which, taken together, explain approximately 30% of the familial PCa risk.[7] Rarer genetic variants conferring higher PCa risks have also been identified. Germline *BRCA2* mutations are the genetic events that confer the highest risk of PCa known to date (8.6-fold in men $\leq$ 65

years),[8-10] whereas the effect of *BRCA1* is more modest (3.4-fold).[11] Germline *BRCA2* and *BRCA1* mutations are present in 1.2% and 0.44% of PCa cases, respectively.[10,11]

Previous studies have suggested an association of *BRCA2* mutations with aggressive tumor phenotype and/or poor overall survival (OS).[12-17] The Icelandic *BRCA2 999del5* and the Ashkenazi *BRCA1 185delAG* and *BRCA2 6174delT* founder mutations have also been associated with poor PCa cause-specific survival (CSS), which is considered a more robust end point than OS.[12,15] In general, these series were limited to small number of *BRCA1/2* carriers or had little clinical information, and comprehensive multivariable analyses (MVA) were not possible. Thus the real prognostic contribution of *BRCA*1/2 mutations compared with other classical prognostic factors for PCa outcome remains unresolved.

In the present study, we aimed to analyze the prognostic value of *BRCA1* and *BRCA2* germline mutations for PCa outcomes in a large series of patients with comprehensive clinicopathologic, therapeutic, and survival data.

PATIENTS AND METHODS

Study Design

This was a retrospective analysis of PCa outcomes in patients with germline *BRCA1* or *BRCA2* (*BRCA1/2*) mutations and noncarriers. Patients with PCa and *BRCA1/2* mutations were identified from two ongoing prospective cohort studies: United Kingdom Genetic Prostate Cancer study (UKGPCS; NIHR869)[18] and Epidemiological Study of *BRCA1/2* Mutation Carriers (EMBRACE; NIHR1358).[19] A total of 2,181 patients with PCa, of 3,818 enrolled in UKGPCS, who were ≤ 65 years at diagnosis and/or had a family history of PCa were screened for *BRCA1/2* mutations. Those who did not carry *BRCA1/2* mutations have been included as noncarriers. The carriers' group was enriched with those carriers participating in EMBRACE who had developed PCa. In addition, all patients included in this analysis met the following criteria: (1) histologic confirmation of PCa, and (2) availability of clinical and follow-up data. Patients without clinical data or who could not be traced were excluded (Fig 1).

UKGPCS and EMBRACE are observational studies and did not interfere with PCa management. Patients were treated and followed up according to departmental protocols, standardized in 1999 by the National Institute for Clinical Excellence.[20]

The primary aim of this study was to evaluate the evidence for the independent prognostic value of *BRCA1/2* mutation status on PCa cause-specific survival (CSS). Secondary aims included the analysis of the impact of *BRCA1/2* mutations as a whole and separately (*BRCA1* and *BRCA2*) on PCa baseline characteristics and outcomes, including CSS, overall survival (OS), CSS in localized PCa (CSS_M_0), metastatic disease-free survival (MFS), and CSS from metastatic disease (CSS_M_1). This study was approved by the local institutional review boards.

BRCA *Mutation Analysis in the UKGPCS Study*

Germline DNA was extracted from peripheral-blood samples. The coding region of the *BRCA1* and *BRCA2* genes were screened using multiplex fluorescent heteroduplex detection, Sanger sequencing,[9,10] and multiplex ligation-dependent probe amplification.[11]

Data Collection

Data from patients enrolled in UKGPCS and EMBRACE were collected at study entry and updated annually. Data sources used in these studies included medical records, pathology reports, and trial standardized questionnaires. Baseline variables collected at diagnosis included date at PCa diagnosis, method of PCa diagnosis, age, TNM stage, Gleason score, and prostate-specific antigen (PSA) level. Other variables related to patients' management and outcomes were PSA doubling-time (PSADT), administered treatments for PCa, date of progression/metastasis, and date/cause of death. Time to biochemical relapse was not analyzed because PSA values were not consistently monitored in a significant proportion of patients.

Statistical Methods

The associations between PCa baseline clinicopathologic data and *BRCA* carrier status were analyzed using χ^2 test, Mantel-Haenszel linear-trend test, or the Mann-Whitney *U* test, as appropriate. On the basis of previous literature, Gleason scores were categorized into a total score of ≤ 6, 7, and ≥ 8, according to the grade of anaplasia.[21] OS time was calculated from the date of PCa diagnosis until date of death from any cause or censored at the last follow-up. CSS was calculated similarly to OS, but if cause of death was different from PCa, CSS time was censored at the time of death. CSS_M_0 was only considered for patients without metastatic disease at diagnosis, and CSS_M_1 was analyzed in all patients with metastatic disease at presentation, or those who developed

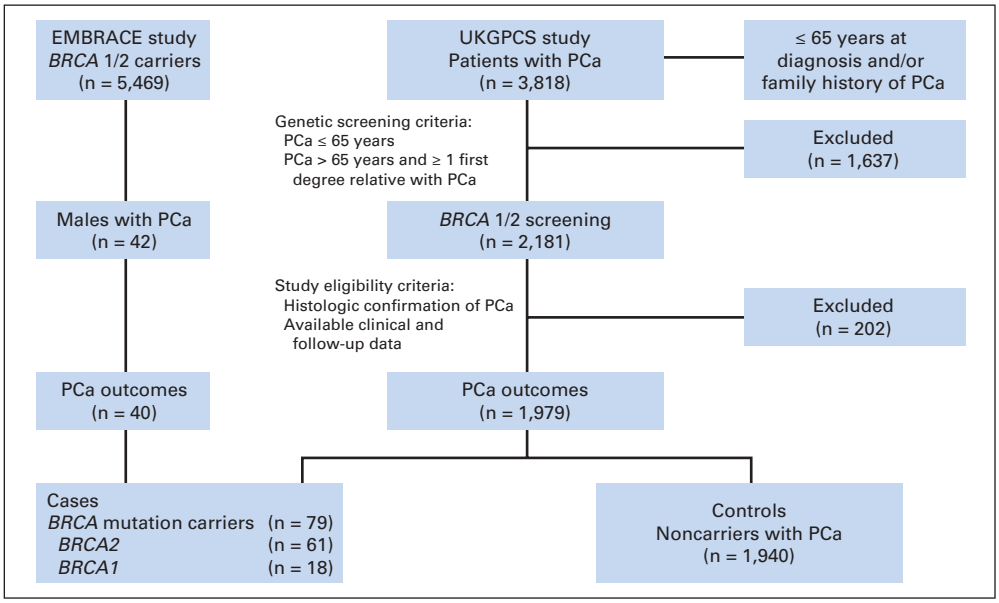

Fig 1. CONSORT diagram. EMBRACE, Epidemiological Study of *BRCA1* and *BRCA2* Mutation Carriers; PCa, prostate cancer; UKGCPS, United Kingdom Genetic Prostate Cancer Study.

metastasis during follow-up. In patients with early disease (M0), MFS was estimated from the date of diagnosis until the date of metastatic disease. Median survival and 5-year survival rates were estimated using the Kaplan-Meier method, and survival curves generated for each group (*BRCA*1, *BRCA2*, and noncarriers) were compared using the log-rank test.

To identify the independent prognostic value of *BRCA* mutations, an MVA model for each survival outcome was created using a Cox regression model to control the effect of other prognostic variables potentially acting as confounding factors. Numeric variables were categorized based on the median distribution value for the pertinent variable or a previously described relevant cutoff. All variables with a *P* value less than .05 in the univariable analysis (UVA) were included in the MVA.

To analyze the benefit of adding *BRCA* status to the Kattan nomogram,[22] one of the most commonly used predictive tools in patients with local disease, we derived the different logistic regression models and their areas under the receiver operating characteristic curve (AUCs) at 5-, 8-, and 10-year OS, CSS_M_0, and MFS.

All *P* values were two-sided. The SPSS program (version 19.0, SPSS, Chicago, IL) was used for statistical analysis. Data collection cutoff for this analysis was October 31, 2011, when the median follow-up was 50 months (range, 3.5 to 245 months).

RESULTS

Patient Characteristics

A total of 2,019 patients with PCa were eligible, of whom 79 were *BRCA* carriers (18 *BRCA1* and 61 *BRCA2*) and 1,940 were noncarriers. Mutations in both genes were varied (13 types in *BRCA1* and 40 in *BRCA2*) and not clustered in a single region of either gene (Appendix Table A1, online only). Sixteen percent of patients were ≤ 65 years at diagnosis, and 34% had familial history of PCa.

In our series, PCa was mainly diagnosed as a result of clinical symptoms. However, the proportion of *BRCA* carriers diagnosed through PSA screening was significantly higher compared with noncarriers (22% *v* 10%; $P = .001$), with more *BRCA2* than *BRCA1* carriers (25% *v* 11%; $P = .021$) diagnosed in this way. Median age at diagnosis was similar in both carriers and noncarriers (58 years [range, 42 to 88 years] in carriers *v* 57 years [range, 32 to 89 years] in noncarriers; $P = .14$), and no differences were seen in presenting PSA (11.5 *v* 11.3 ng/mL; $P = .93$).

Poorly differentiated PCa (Gleason score ≥ 8) was twice as common in *BRCA1/2* carriers as in noncarriers (35% *v* 15%; $P = .00003$). Advanced stage (T3-T4) was more frequent in *BRCA1/2* carriers than in noncarriers (37% *v* 28%; $P = .003$) as well as nodal involvement (N1: 15% *v* 5%; $P = .0005$) and metastatic spread (M1: 18% *v* 9%; $P = .005$). When patients with local disease (N0M0 patients) were stratified according to their risk of relapse,[21] no differences were seen between carriers and noncarriers ($P = .22$; Table 1).

Median PSA at diagnosis was higher in *BRCA2* than in *BRCA1* carriers (15.1 *v* 8.6 ng/mL; $P = .63$) who also had a higher frequency of poorly differentiated tumors (38% *v* 28%), but these differences were not statistically significant. T stage, frequency of nodal involvement, and metastasis at diagnosis were similar in both groups (Table 1).

Treatment

BRCA mutation carriers and noncarriers received similar treatments (Table 2); 79% of noncarriers and 72% of *BRCA* carriers underwent radical treatment with either surgery or radiotherapy ($P = .20$), and 36% and 37%, respectively, also received adjuvant androgen-deprivation therapy ($P = 0.6$). All patients who developed metastasis (n = 330) received palliative hormone treatment; 54% of them had not received any hormone treatment before the diagnosis of metastatic disease. In addition, 17% of noncarriers and 34% of carriers ($P = .018$) were treated with chemotherapy.

CSS From PCa

Two hundred twenty deaths that occurred during follow-up were attributed to PCa (three in *BRCA1* carriers, 21 in *BRCA2* carriers, and 196 in noncarriers). Median CSS in carriers and noncarriers was 8.6 years and 15.7 years, respectively ($P = 7 \times 10^{-8}$). A trend toward improved CSS was observed for *BRCA1* carriers compared with *BRCA2* carriers, but this was not significant (median CSS, 10.5 and 8.6 years, $P = 0.37$; Table 3 and Fig 2C). Cox regression analysis confirmed the independent prognostic value of *BRCA1/2* mutations for CSS ($P = .015$; HR = 1.8; 95% CI, 1.1 to 3.6). Within the carrier group, *BRCA2* mutations contributed the most to this risk ($P = .007$; HR = 1.9; 95% CI, 1.1 to 3.4). Other prognostic factors included age more than 65 years, PSA more than 10 ng/mL, Gleason score, tumor size, and metastasis at diagnosis (Fig 2D).

OS

After 9,553 person-years of follow-up for the entire cohort, 358 deaths occurred (four in *BRCA1* carriers, 29 in *BRCA2* carriers, and 325 in noncarriers). Median OS in noncarriers was superior to that in carriers (12.9 *v* 8.1 years; $P = 1 \times 10^{-7}$). There was also a nonsignificant trend toward improved OS for *BRCA1* compared with *BRCA2* carriers (10.5 *v* 6.5 years; $P = 0.25$; Table 3; Fig 2A). MVA confirmed the independent prognostic value of *BRCA1/2* status in PCa for OS ($P = .012$; HR = 1.9; 95% CI, 1.1 to 3.3); similarly to CSS, *BRCA2* mutations contributed the most ($P = .004$; HR = 1.9; 95% CI, 1.1 to 3.1), but did not confirm any prognostic value for *BRCA1* mutations. Other significant risk factors for OS in the Cox regression analysis included age more than 60 years and PSA more than 10 ng/mL at diagnosis, Gleason score, tumor size, and metastasis (Fig 2B).

CSS in Localized PCa

When considering only nonmetastatic patients (M_0) at diagnosis, 5-year CSS_M_0 in noncarriers was significantly improved compared with carriers (96% *v* 82%; $P = 9 \times 10^{-8}$), but there was no significant difference between *BRCA1* and *BRCA2* carriers (89% *v* 82%; $P = 0.29$) The independent prognostic value of *BRCA1/2* status in CSS_M0 was again confirmed ($P = .011$; HR = 2.6; 95% CI, 1.2 to 5.3); *BRCA2* mutations were once more the main contributor to this risk (Table 3; Fig 1E). Independent prognostic factors for CSS_M_0 also included tumor size and Gleason score (Fig 1F).

MFS

During follow-up, 132 noncarriers, 1 *BRCA1* carrier, and 17 *BRCA2* carriers with localized PCa at diagnosis developed metastasis. Five-year MFS in noncarriers was significantly higher than in *BRCA* carriers (93% *v* 77%; $P = .0001$), but there was no difference between *BRCA1* and *BRCA2* carriers (91% *v* 73%; $P = .28$; Table 3; Fig 2I). MVA confirmed the independent prognostic value of *BRCA* mutations for MFS ($P = .009$; HR = 2.7; 95% CI, 1.3 to 5.7; Fig 2J).

CSS From Metastasis

Longer median CSS_M1 was observed in noncarriers compared with carriers (3.4 *v* 2.3 years) but the difference was not significant

Table 1. Prostate Cancer Characteristics in *BRCA* Mutation Carriers and in Noncarriers

Patient Characteristic	*BRCA* Mutation Carriers						Noncarriers (n = 1,940)		*P* (carriers *v* noncarriers)
	Total (n = 79)		*BRCA1* (n = 18)		*BRCA2* (n = 61)				
	No.	%	No.	%	No.	%	No.	%	
Age, years									
Median	58.3		60.8		57.6		57.2		.142
Range	41.7-88		48.3-73.5		41.7-88		32.3-88.9		
Histologic grade/Gleason score									
Gleason ≤ 6/grade 1	20	25.3	6	33.3	14	23.0	733	37.8	< .001
Gleason 7/grade 2	19	24.1	4	22.2	15	24.6	511	26.3	
Gleason ≥ 8/grade 3	28	35.4	5	27.8	23	37.7	299	15.4	
Unknown	12	15.2	3	16.7	9	14.8	397	20.5	
Tumor stage, T									
T1, not clinically apparent	8	10.1	1	5.6	7	11.5	439	22.6	.003
T2, confined to prostate	25	31.6	6	33.3	19	31.1	550	28.4	
T3, palpable, beyond capsule	22	27.8	4	22.2	18	29.5	474	24.4	
T4, fixed or invading locally	7	8.9	2	11.1	5	8.2	71	3.7	
Tx, cannot be assessed	17	21.5	5	27.8	12	19.7	406	20.9	
Nodal stage, N									
N0, no nodal metastasis	42	53.2	8	44.4	34	55.7	986	50.8	< .001
N1, nodal metastasis	12	15.2	2	11.1	10	16.4	89	4.6	
Nx, cannot be assessed	25	31.6	8	44.4	17	27.9	865	44.6	
Metastasis, M									
M0, no distant metastasis	65	82.3	15	83.3	50	82	1,774	91.4	.005
M1, distant metastasis	14	17.7	3	16.7	11	18	166	8.6	
PSA at diagnosis, ng/mL									
Median	11.5		8.9		15.1		11.3		.926
Range	0.5-3,000		0.7-3,000		0.5-761		0.2-7,800		
Anatomic stage/prognostic group									
Stage I	8	10.1	2	11.1	6	9.8	373	19.2	.001
Stage IIA	9	11.40	1	5.6	8	13.1	325	16.8	
Stage IIB	13	16.5	3	16.7	10	16.4	213	11.0	
Stage III	12	16.5	4	22.2	11	18.1	367	18.9	
Stage IV	22	27.8	3	16.7	19	31.1	249	12.8	
Cannot be assessed	14	17.7	5	27.8	7	11.5	413	21.3	
Risk stratification for localized PCa									
Low risk	8	17.8	2	20	6	17.1	373	28.6	.224
Intermediate risk	22	48.9	4	40	18	51.4	538	41.3	
High risk	15	33.3	4	40	11	31.4	392	30.1	

Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen.

(Table 3; Fig 2G). In MVA, patients who presented with metastasis at diagnosis were likely to have longer survival than those who developed metastasis after radical treatment. A Gleason score ≥ 8 was also an independent predictor of poor outcome (Fig 2H).

DISCUSSION

To our knowledge, this is the largest study to date that has investigated the clinical characteristics and outcome of patients with PCa with and without germline *BRCA* mutations. The study included 1,940 noncarriers and 79 *BRCA* carriers (61 *BRCA2* and 18 *BRCA1*). The carrier group, with 13 *BRCA1* and 40 *BRCA2* different mutations, comprises the widest spectrum of mutations in these genes compared with previous studies. Our analyses provide more precise estimates of the prognostic implications of *BRCA1/2* mutations in PCa.

We have demonstrated that node involvement and distant metastasis are more common in patients with PCa who have *BRCA1/2* mutations than in noncarriers, but also that those carriers with local disease develop metastasis earlier. *BRCA1/2* carriers with PCa are currently treated following the same protocols used for noncarriers, as the most appropriate management for this group of patients has not been investigated. Although clinical trials are still needed, radical treatment with either surgery or radiotherapy seems to be preferable to active surveillance for these patients, even for cases classified as low risk.[21,23]

Our series is the first to report on survival in metastatic patients. Although median CSS_M_1 was 2.3 and 3.4 years for carriers and noncarriers, respectively, the difference was not significant, and MVA did not show any statistical trend to shorter CSS_M_1 in the *BRCA1/2* patients. Interestingly, *BRCA1/2* carriers more frequently had castration-resistant disease at metastatic progression and thus received chemotherapy more often. The lack of difference observed in CSS_M_1 could be explained if *BRCA1/2* carriers responded to chemotherapy similarly to noncarriers, as has recently been suggested by

Table 2. Prostate Cancer Treatments Administered

Treatment	Noncarriers			*BRCA* Carriers			
	No. of Patients	Total No.	%	No. of Patients	Total No.	%	*P*
Primary radical treatment in nonmetastatic disease							
External-beam radiotherapy	794	1,774	44.8	23	65	35.4	.135
Radical prostatectomy	539	1,774	30.3	22	65	33.8	.551
Brachytherapy	67	1,774	3.8	2	65	3.1	1
Any local radical treatment	1,400	1,774	78.9	47	65	72.3	.201
Primary hormone treatment indication							
Early disease							.599
Neoadjuvant-adjuvant	636	1,774	35.9	24	65	36.9	
Single therapy	112	1,774	6.3	6	65	9.2	
Advanced disease							.210
Palliative	165	298	55.4	14	32	43.8	
Other treatments for metastatic disease							
Chemotherapy	51	298	17.1	11	32	34.4	.018

Gallagher et al,[24] although a larger study is needed to confirm this. However, based on the current knowledge of *BRCA1/2*-related breast and ovarian cancers,[25-29] studies evaluating the benefit of platinum-based chemotherapy and poly adenosine diphosphate ribose polymerase inhibitors in these patients are warranted.

The implementation of early diagnosis in these patients may also be crucial, and currently the IMPACT (Identification of Men With a Genetic Predisposition to Prostate Cancer: Targeted Screening in Men at Higher Genetic Risk and Controls) study is evaluating the utility of PSA-based PCa screening in asymptomatic *BRCA1/2* carriers.[30] In the general population, PSA screening remains controversial,[31-35] and a national screening program for PCa has never been implemented in the United Kingdom, where it is estimated that only 6% of men aged 45 to 89 years have routine PSA testing.[36] Consequently, PCa in the

Table 3. Outcome of Patients With Prostate Cancer by *BRCA* Mutation Status

Group	5-Year Rate	95% CI	Median (years)	95% CI	Log-Rank *P*
Overall survival					
Controls	86.4	84.4 to 88.4	12.9	11.8 to 14	< .001*
BRCA mutation carriers	62.0	49.1 to 74.9	8.1	5 to 11.1	
BRCA1 mutation carriers	82.5	60.4 to 100	10.5	6.7 to 14.5	.338†
BRCA2 mutation carriers	57.9	43.4 to 72.4	6.5	3.4 to 9.6	< .001‡
Cause-specific survival					
Controls	90.6	88.8 to 92.4	15.7	—	< .001*
BRCA mutation carriers	70.1	57.2 to 83	8.6	6.4 to 10.7	
BRCA1 mutation carriers	80.8	56.9 to 100	10.5	—	.200†
BRCA2 mutation carriers	67.9	53.4 to 82.4	8.6	7.7 to 9.5	< .001‡
Cause-specific survival in M0 patients					
Controls	96.2	95 to 97.4	—§	—	< .001*
BRCA mutation carriers	81.5	69 to 94	11.3	7.1 to 15.4	
BRCA1 mutation carriers	88.9	68.3 to 100	—§	—	.576†
BRCA2 mutation carriers	80.2	65.9 to 94.5	8.8	6.2 to 11.5	< .001‡
Metastasis-free survival in M0 patients					
Controls	93.4	91.6 to 95.2	—‖	—	< .001*
BRCA mutation carriers	77.0	62.7 to 91.3	—‖	—	
BRCA1 mutation carriers	90.9	73.8 to 100	—‖	—	.801†
BRCA2 mutation carriers	73.1	55.9 to 90.3	10.6	3.6 to 17.6	< .001‡
Cause-specific survival from prostate cancer metastasis					
Controls	35.2	28.5 to 41.9	3.4	2.8 to 4.0	.623*
BRCA mutation carriers	22.4	5.2 to 39.6	2.3	2 to 2.5	
BRCA1 mutation carriers	37.5	0 to 93.6	2.3	0 to 4.9	.767†
BRCA2 mutation carriers	20.6	2.8 to 38.4	2.3	1.5 to 3.1	.460‡

*Univariable *P* value (log-rank test) for all *BRCA* carriers versus noncarriers.
†Univariable *P* value (log-rank test) for *BRCA1* carriers versus noncarriers.
‡Univariable *P* value (log-rank test) for *BRCA2* carriers versus noncarriers.
§After a median follow-up of 50 months, median CSS_M_0 was not reached.
‖After a median follow-up of 50 months, median MFS was not reached.

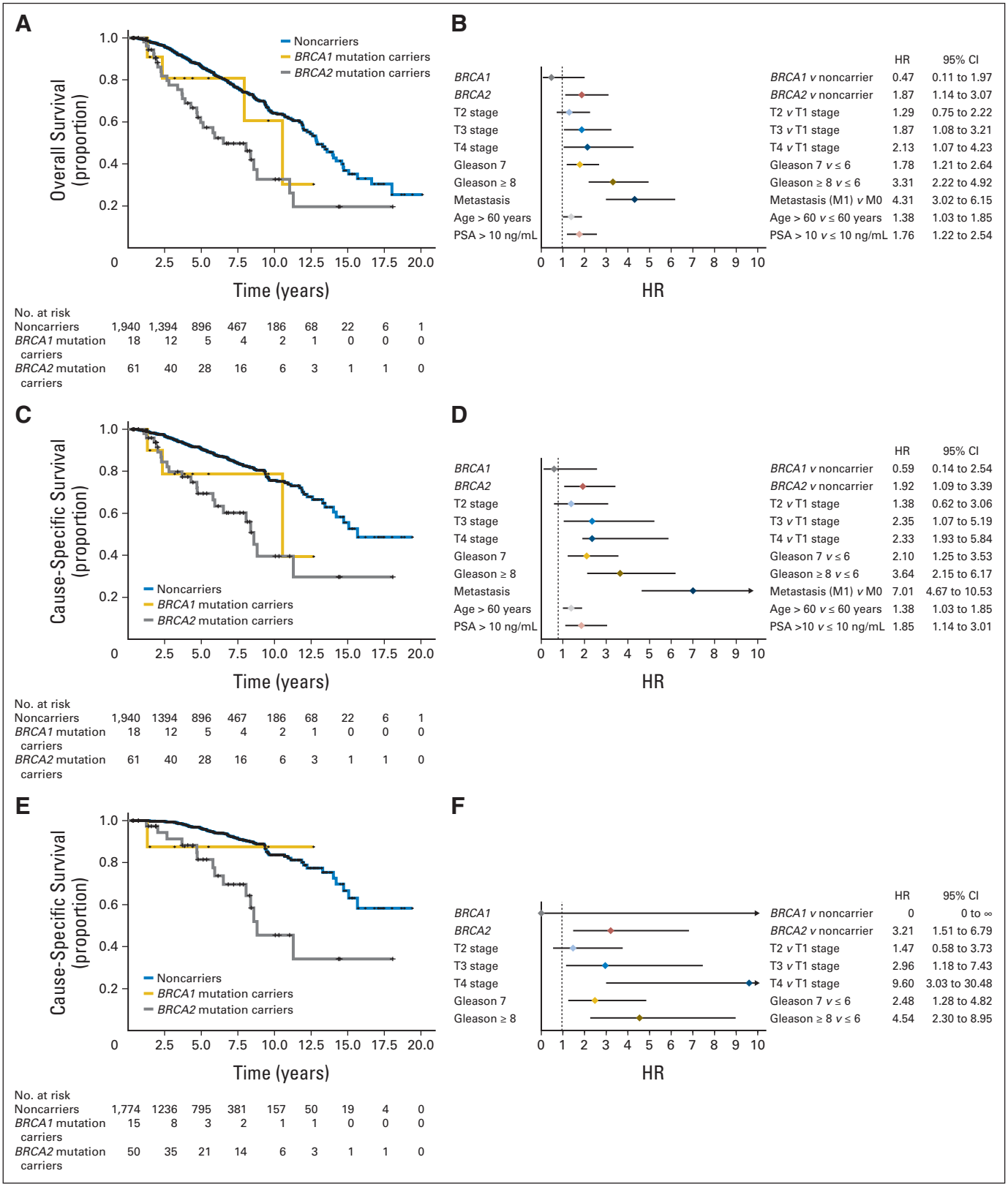

Fig 2. Kaplan-Meier survival curves: (A) overall survival (OS); (C) cause-specific survival (CSS); (E) CSS in early prostate cancer (PCa; CSS_M0); (G) CSS from metastatic disease; and (I) metastasis-free survival (MFS) in early PCa. Survival curves for noncarrier patients are represented in blue; *BRCA1* and *BRCA2* mutation carriers are illustrated in gold and gray, respectively. Diagrams illustrating the relative strength (hazard ratio [HR]) of each prognostic factor in the multivariate Cox regression: (B) OS; (D) CSS; (F) CSS_M0; (H) CSS from metastatic disease; and (J) MFS. The colored diamonds and the horizontal lines represent the estimated HR and their respective 95% CIs. The vertical discontinuous line represents no effect. If a CI overlaps this line, the effect of this factor did not significantly differ from no effect. PSA, prostate-specific antigen.

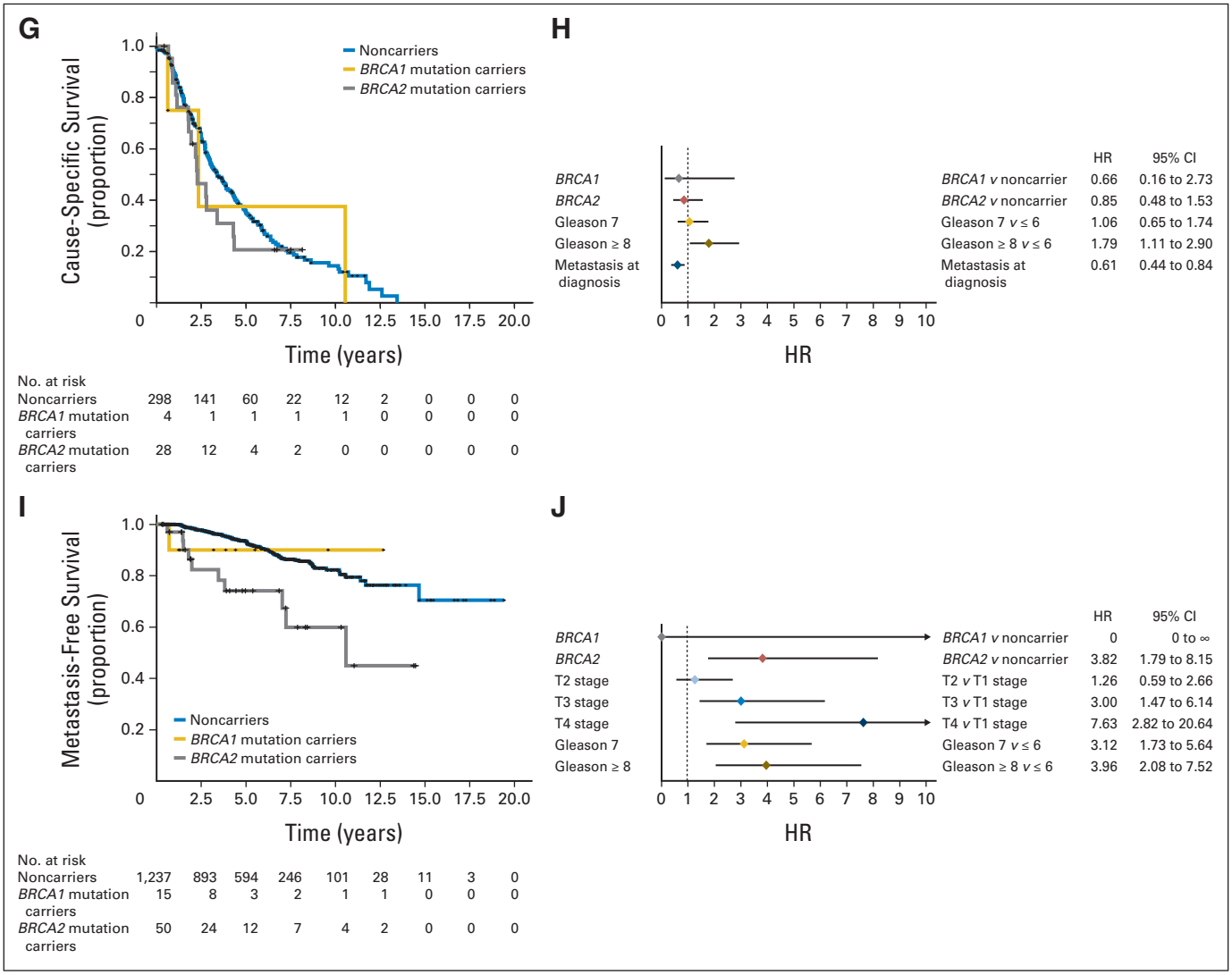

Fig 2. Continued.

majority of patients in our series was clinically detected. The aggressive characteristics and worse PCa outcomes observed in *BRCA2* carriers could not be attributed to a greater delay in diagnosis compared with the other two groups, as *BRCA2* carriers were more frequently diagnosed by PSA screening.

Our study was consistent with others[13,15,17,37] that have not observed differences in age at diagnosis between carriers and noncarriers. However, we could not rule out that some specific mutations, such as the Icelandic founder mutation (*BRCA2 999del5*), could be associated with PCa at a younger age.[12]

We confirmed that patients with PCa with germline *BRCA* mutations have poorer OS and CSS compared with noncarriers. Subgroup analyses and MVA suggest that the association with poor outcome was mostly dependent on *BRCA2*, whereas the contribution of *BRCA1* mutations remains unclear, as the number of *BRCA1* patients and events were still small to draw any definitive conclusions.

Previously, other series have failed to clarify the clinical value of *BRCA1* in PCa due to even smaller number of cases than our series[13,15] and the lack of clinicopathologic features[14] In our study, we observed that although *BRCA1* carriers presented with similar baseline risk characteristics as *BRCA2* carriers, their survival parameters (OS, CSS, CSS_M_0, and MFS) were more similar to those noncarrier patients. These nonsignficant differences between *BRCA1* and *BRCA2* carriers should be interpreted cautiously and as hypothesis-generating data rather than conclusive results.

Other studies have reported shorter survival and greater HR associated with *BRCA2* mutations.[12,15-17] Tryggovadotir et al[12] reported a median CSS for *BRCA2* of 2.1 years with an MVA HR of 2.4, whereas in our study, median CSS for these patients was 8.6 years with an MVA HR of 1.9. This difference could be mostly attributed to the greater frequency of N1 and/or M1 stage in patients with the Icelandic mutation. Thorne et al[17] analyzed a group of 40 patients with 26 different *BRCA2* mutations whose baseline characteristics were similar or even less advanced/aggressive than the patients in our series. They reported a remarkably shorter CSS (3.5 years) and a greater HR (4.97) for the *BRCA2* carriers compared with our study. Although we cannot explain the differences in survival, the excess of HR in their series could be explained by the small number of variables tested in the MVA.

Table 4. Comparative Kattan Nomogram Versus Kattan Plus *BRCA* Status

Model and End Point	5 Year		8 Year		10 Year	
	AUC (%)	Likelihood Ratio Test *P**	AUC (%)	Likelihood Ratio Test *P**	AUC (%)	Likelihood Ratio Test *P**
All patients with local (N0 and M0) disease						
Evaluable patients, n†		927		521		267
Metastasis-free survival						
Kattan model	81.1	—	76.2	—	76.6	—
Kattan + *BRCA*	82.5	.048	76.6	.128	77.8	.143
Cause-specific survival						
Kattan model	79.9	—	77.6	—	76.1	—
Kattan + *BRCA*	80.5	.102	78.9	.083	77.0	.076
Overall survival						
Kattan model	79.6	—	78.1	—	76.2	—
Kattan + *BRCA*	81.5	.071	79.8	.002	77.3	.096
Patients treated with prostatectomy for N0 and M0 disease						
Evaluable patients, n†		397		188		79
Metastasis-free survival						
Kattan model	82.4	—	81.0	—	81.4	—
Kattan + *BRCA*	91.0	.122	88.7	.158	87.0	.007
Cause specific survival						
Kattan model	76.7	—	75.0	—	72.1	—
Kattan + *BRCA*	80.9	.148	81.7	.081	82.0	.002
Overall survival						
Kattan model	88.7	—	81.5	—	76.0	—
Kattan + *BRCA*	91.1	.277	84.5	.020	80.0	.005

Abbreviation: AUC, area under the receiver operating characteristic curve.
*Comparison of the logistic regression model for original Kattan nomogram alone (baseline prostate-specific antigen, Gleason score, and clinical tumor [T] stage) score versus the addition of *BRCA* carrier status using the likelihood ratio test.
†All these survival analyses were handled as a simple binary variable for the logistic regression analyses. The number of patients for the different time points differs from the total of patients because those lost to follow-up before the end of the fixed time point were considered not to be evaluable for the analysis.

In a series with 832 patients with localized PCa, including six with the *BRCA1 185delAG* and 20 with *BRCA2 6174delT* Ashkenazi mutations, Gallagher et al[15] reported a better median CSS in their *BRCA2* carriers compared with our series (13.8 *v* 8.8 years).

The reported HR for *BRCA2* status in their study was greater than in ours (5.48 *v* 3.21), despite the CSS in noncarriers being similar in both series (5-year OS > 95%). MFS in their study was also longer compared with ours. These findings suggest that *BRCA2 6174delT* may be associated with better outcomes than other *BRCA2* mutations.

The addition of *BRCA* carrier status improved the predictive ability of the commonly used Kattan nomogram[22] for MFS and CSS_M_0, as shown in Table 4. For some scenarios this was statistically significant; however, this nomogram was originally derived for the prediction of time to treatment failure based on PSA and/or clinical recurrence, an end point that has not been analyzed in our study.

A potential limitation of our study is the selection of patients with familial PCa; nevertheless numerous reports have shown that a family history of PCa does not affect PCa outcome.[38-40] However, our patients were randomly selected with respect to known prognostic factors for PCa. The differences between univariate and multivariate associations in our series suggested that some of these prognostic variables acted as confounding factors.

In conclusion, our results show that a wide spectrum of pathogenic mutations in the *BRCA1* and *BRCA2* genes confers a more aggressive PCa phenotype with a higher probability of locally advanced and metastatic disease and that the presence of a germline *BRCA2* mutation is a prognostic marker associated with poorer survival. Trials analyzing the response of these patients to different treatment modalities and molecular studies to identify the key drivers and therapeutic targets of this PCa subgroup are urgently needed, as this would enable tailored management for these patients.

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Appendix

Epidemiological Study of BRCA1 *&* BRCA2 *Mutation Carriers (EMBRACE).* Douglas F. Easton is the principal investigator of the study. EMBRACE Collaborating Centres are as follows: Coordinating Centre, Cambridge: Susan Peock, Debra Frost, Steve D. Ellis, Elena Fineberg, Radka Platte. North of Scotland Regional Genetics Service, Aberdeen: Zosia Miedzybrodzka, Helen Gregory. Northern Ireland Regional Genetics Service, Belfast: Patrick Morrison, Lisa Jeffers. West Midlands Regional Clinical Genetics Service, Birmingham: Trevor Cole, Kai-ren Ong, Jonathan Hoffman. South West Regional Genetics Service, Bristol: Alan Donaldson, Margaret James. East Anglian Regional Genetics Service, Cambridge: Marc Tischkowitz, Joan Paterson, Sarah Downing, Amy Taylor. Medical Genetics Services for Wales, Cardiff: Alexandra Murray, Mark T. Rogers, Emma McCann. St James's Hospital, Dublin & National Centre for Medical Genetics, Dublin: M. John Kennedy, David Barton. South East of Scotland Regional Genetics Service, Edinburgh: Mary Porteous, Sarah Drummond. Peninsula Clinical Genetics Service, Exeter: Carole Brewer, Emma Kivuva, Anne Searle, Selina Goodman, Kathryn Hill. West of Scotland Regional Genetics Service, Glasgow: Rosemarie Davidson, Victoria Murday, Nicola Bradshaw, Lesley Snadden, Mark Longmuir, Catherine Watt, Sarah Gibson, Eshika Haque, Ed Tobias, Alexis Duncan. South East Thames Regional Genetics Service, Guy's Hospital London: Louise Izatt, Chris Jacobs, Caroline Langman. North West Thames Regional Genetics Service, Harrow: Huw Dorkins. Leicestershire Clinical Genetics Service, Leicester: Julian Barwell. Yorkshire Regional Genetics Service, Leeds: Julian Adlard, Gemma Serra-Feliu. Cheshire & Merseyside Clinical Genetics Service, Liverpool: Ian Ellis, Catherine Houghton. Manchester Regional Genetics Service, Manchester: D Gareth Evans, Fiona Lalloo, Jane Taylor. North East Thames Regional Genetics Service, NE Thames, London: Lucy Side, Alison Male, Cheryl Berlin. Nottingham Centre for Medical Genetics, Nottingham: Jacqueline Eason, Rebecca Collier. Northern Clinical Genetics Service, Newcastle: Fiona Douglas, Oonagh Claber, Irene Jobson. Oxford Regional Genetics Service, Oxford: Lisa Walker, Diane McLeod, Dorothy Halliday, Sarah Durell, Barbara Stayner. The Institute of Cancer Research and Royal Marsden NHS Foundation Trust: Ros Eeles, Susan Shanley, Nazneen Rahman, Richard Houlston, Elizabeth Bancroft, Elizabeth Page, Audrey Ardern-Jones, Kelly Kohut, Jennifer Wiggins Elena Castro, Emma Killick, Sue Martin, Gillian Rea, Anjana Kulkarni. North Trent Clinical Genetics Service, Sheffield: Jackie Cook, Oliver Quarrell, Cathryn Bardsley. South West Thames Regional Genetics Service, London: Shirley Hodgson, Sheila Goff, Glen Brice, Lizzie Winchester, Charlotte Eddy, Vishakha Tripathi, Virginia Attard. Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton: Diana Eccles, Anneke Lucassen, Gillian Crawford, Donna McBride, Sarah Smalley.

United Kingdom Genetic Prostate Cancer study (UKGPCS). Rosalind Eeles is the principal investigator of the UKGPCS study. A complete list with all collaborators can be find at www.icr.ac.uk/ukgpcs.

Table A1. List of *BRCA1* and *BRCA2* Mutations Carried by the Patients Included in the Study

Mutation ID	Mutation Type	Patients
BRCA1 mutations		
c.1-1447insA	Frameshift	1
c.68_69delAG (185delAG)	Frameshift	4
c.212 + 1G> (IVS 5 + 1)	Frameshift	1
c.1175_1214del40	Frameshift	1
c.1961dupA	Frameshift	1
c.2071delA	Frameshift	1
c.2073dupA	Frameshift	1
c.2594delC	Frameshift	1
c.3756_3759delGTCT	Frameshift	1
c.4065_4068delTCAA	Frameshift	3
c.4327C>T	Nonsense	1
c.4945delA	Frameshift	1
c.5503C>T	Nonsense	1
BRCA2 mutations		
c.755_758delACAG	Frameshift	1
c.1231delA	Frameshift	1
c.1265delA	Frameshift	1
c.1787delATGAAACATCTTAA	Frameshift	1
c.1813insA	Frameshift	1
c.1929delG	Frameshift	1
c.2558insA	Frameshift	1
c.2807delAACA	Frameshift	1
c.2836delGA	Frameshift	1
c.3158T>G	Nonsense	1
c.3405C>A	Nonsense	1
c.3847delGT	Frameshift	1
c.4478delAAAG	Frameshift	2
c.4877delAA	Frameshift	2
c.4889C>G	Nonsense	1
c.4965C>G	Nonsense	1
c.4981delT	Frameshift	2
c.5303delTT	Frameshift	1
c.5350_5351delAA	Frameshift	1
c.5645C>CA	Nonsense	1
c.5682C>G	Frameshift	3
c.5946delT (6174delT)	Frameshift	2
c.6155C>G	Missense	1
c.6275_6276delTT	Frameshift	4
c.6405delCTTAA	Frameshift	2
c.6591_6592delTG	Frameshift	1
c.6486_6489delACAA	Frameshift	1
c.7008-?_7805+?del	Large deletion	1
c.7084delAAAAG	Frameshift	1
c.7543dupA	Frameshift	2
c.7757G>A	Nonsense	1
c.7771insA	Nonsense	2
c.7966C>T	Nonsense	1
c.7977-1G>C (IVS 17 G>C)	Splice site	3
c.8167G>C	Missense	1
c.8297delC	Frameshift	2
c.8904delC	Frameshift	2
c.9097dupA	Frameshift	1
c.9253insA	Frameshift	2
c.9294C>G	Nonsense	1
c.9382C>T	Nonsense	3
Del exon 14-16	Large deletion	1