DNA damage repair gene germline profiling for metastatic prostate cancer patients of different ancestries

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ADDITIONNAL INFORMATION

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Patient consent statement All patients selected for this study were recruited in the PROGENE study (FWA00006032), and provided written informed consent in order to participate in the study. This paper does not contain any individual person's data in any form.

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ABSTRACT

Background: Germline and somatic mutations in DNA damage repair genes (DDRg) are now recognized as new biomarkers for the management of metastatic prostate cancers (mPC). We evaluate the frequency of germline DDRg mutations among French mPC patients of European and African ancestries.

Methods: Targeted next-generation sequencing of 21 DDRg was performed on germline DNA from 557 mPC patients, including 15.1% of cases with an African origin.

Results: Forty-seven germline mutations in 11 DDR genes were identified in 46 patients of the total cohort (8.3%). BRCA2 (4.1%) and ATM (2.0%) were the most frequently mutated genes. There was no difference in DDRg mutation frequency between mPC patients of European ancestry and those of African origin. Germline mutations of BRCA2 were associated with a positive family history of breast cancer (p=0.02). The mean age at metastatic stage (59.7 vs 67.0; p = 0.0003) and the mean age at death (65.2 vs 73.9; p = 0.0003) were significantly earlier for carriers of BRCA2 mutation than for non-carriers. Moreover, Cox model showed that BRCA2 positive status was statistically associated with poorer survival (Hazard ratio: 0.29; 95%Confidence interval 0.18-0.48; p<0.0001).

Conclusion: We showed that, in France, BRCA2 and ATM are the main predisposing DDR genes in mPC patients, with a particular aggressiveness for BRCA2 leading to early metastatic stage and death.

KEYWORDS

DNA damage repair gene; germline; metastatic; mutation; prostate cancer

INTRODUCTION

Prostate cancer (PC) is the most frequent malignancy in men in Northern America and Europe.[1] Recognized risk factors for PC are age, familial history of PC or other cancers, and ethnicity with a higher risk of PC for men of African ancestry compared to European one.[2] Numerous genetic variants have also been associated with PC susceptibility, but only few rare predisposition genes have been identified to date.[2] Among them, inherited mutations of DNA damage repair genes (DDRg) seemed to be the most frequent ones, and have been detected in 4.6 % of localized PC patients.[3] The frequency of these germline mutations was even higher among the patients with an aggressive form of the disease[4], notably in metastatic prostate cancer (mPC) ones. Indeed, Pritchard et al.[3] reported that this frequency reached 11.8% among 692 mPC patients. Since then, numerous studies were performed on mPC and metastatic castration-resistant PC (mCRPC) patients, and showed that germline mutation frequency of these genes ranged from 7.3 to 20.1%.[5-12]

In addition to these germline mutations, somatic DDRg mutations have been identified in tumoral tissues from PC patients, and approximately 20-25% of mPC tumors harbored mutations in DDRg.[13] In mPC patients, the response to treatment has been shown to vary depending on whether or not a DDRg mutation is present.[14] Mutation carriers better responded to treatment with Poly(ADP) ribose polymerase (PARP) inhibitors[15], carboplatin-based chemotherapy[16], first line of next-generation hormonal therapy[7] and radium-223 therapy[17], whereas they showed a lower response rate to taxane[18], compared to non-carriers. Germline and tumoral mutations in DDRg are then recognized as new biomarkers for the management of mPC[19], and germline genetic testing for a panel of DDRg that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH6, MSH2 and PMS2 is now recommended for all men with high-risk or metastatic PC.[20]

In order to better define and personalize this genetic testing, it is needed to define the frequency of these DDRg mutations among mPC patients of different geographic and ethnic origins. For example, in their recent study, Darst et al.[21] reported that BRCA2 and PALB2 had the most statistically significant gene-based associations among 155 DDRg sequenced in germline DNA from 5 545

European-ancestry men (2 775 nonaggressive and 2 770 aggressive PC cases, including 467 mPC patients). However, until now, most of the large studies on DDRg germline mutation were performed on mPC patients from North America[3,6,9,11,12,21], and few included mPC cases from North and South of Europe[3,8,21]. Moreover, only one study including 188 African American patients compared the frequency of DDR gene germline mutations among mPC cases of African and European origins.[12] In order to contribute to the inventory of the DDRg germline mutational profiles, according to the geographic origin and the ancestry, we report results of the germline sequencing of 21 DDRg on a new population of 557 mPC French patients, with a European or an African ancestry.

MATERIALS AND METHODS

The patients selected for this study were recruited in the PROGENE study (FWA00006032), based on mPC disease status. They all provided written informed consent in order to participate in this study that complied with the Declaration of Helsinki and was approved by the CCP Ile de France IV (IRB: 00003835). Family history of prostate or breast cancer was defined as positive if at least one first-degree relative of the patient had this malignancy. Ancestry was based on self-report and on skin phenotype selected by the clinician in the medical questionnaire. Patients of Asian ancestry (N = 7) or from North African origin (N=18), 2 patients born in India and 1 originating from Southern America were classified as “other”, and were excluded from comparison between patients from African and European ancestries.

Germline DNA was extracted from saliva or blood using standard protocol. A custom targeted DNA panel was designed for full exon and splice site coverage of 21 DNA repair genes (List in Table 2). Sequencing libraries were generated from germline DNA using SeqCap EZ Prime kit (Roche Diagnostics) and read using an Illumina NextSeq 500 platform (Illumina, San Diego, CA). The mean coverage was X150 for each sample. Bioinformatical analysis was done using the module SeqNext (Seqpilot). Sequencing files were annotated using ClinVar and VarSome version 11.2 records. Variants reported as pathogenic or likely pathogenic (Classification of variants according to ACMG/AMP

recommendations and/or according to national and international databases) were considered positive.

T-test was used for comparing mean ages at metastatic stage or at death between carriers or non-carriers of germline mutation. We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between carrier status of a germline mutation and family history of cancer (either breast or prostate), adjusting for age at diagnosis and ancestry in the total population, or adjusting for age at diagnosis only when considering patients from a specific ancestry. Logistic regression was also used to analyze association between germline mutation carrier status and hormone sensitive/castration resistance status, with adjustment for ancestry. Adjustment for ancestry was performed by considering 5 classes: European, African, Asian, North African and Others. Comparisons between carriers and non-carriers of a BRCA2 mutation were performed by first considering patients carrying non-BRCA2 DDRg mutation as non-carriers, and a secondly, by excluding these patients with another DDRg mutation. Cox proportional hazards analysis was carried out for survival analyses, using Schoenfeld's global test to verify assumption of proportionality. All tests were two-sided, and $p < 05$ was considered to indicate statistical significance.

RESULTS

The characteristics of the patients are presented in Table 1. The mean age (SD) at the metastatic stage was 66.5 years old (9.3). Ancestry distribution was 79.9% European, 15.1% African, and 5.0% other. Typology of metastases was classified as only in distant lymph nodes (33.9%), bone metastasis (52.8%) and visceral metastasis (13.3%). 270 (48.5%) cancers were castration resistant at the inclusion. 146 (26.2%) patients had a positive family history of PC, and 43 (7.7%) had a personal history of cancer other than prostate.

Forty-seven germline mutations in 11 DDR genes were identified in 46 patients of the total cohort (8.3%). BRCA2 (4.1%) and ATM (2.0%) were the most frequently mutated genes in our series of mPC cases (Table 2, Supplementary table 1). The frequency of identified mutations was less than 1% for

the other 9 genes (BARD1, BRCA1, BRIP1, CHEK2, MRE11A, MSH2, MSH6, NBN and PMS2). All mutations were unique except three ones: one ATM mutation (c.2921+1G>A) that was found in two patients, one of European ancestry and one of African ancestry, and two BRCA2 mutations (c.5946delT and del ex12-ex13) that were observed in two metastatic cases of European ancestry (Supplementary Table 1). The patient who carried a MSH2 germline mutation was diagnosed with thyroid and colon cancers at the same age as prostate cancer.

There was no difference in DDRg mutation frequency between mPC patients of European ancestry and those of African origin (8.3% vs 7.1%; p =0.93). The frequencies of BRCA2 and ATM mutations were thus 3.6% and 1.2%, for patients of African ancestry, and 4.0% and 2.2% for European men (Supplementary Table 2). Similarly, the frequency of mutations was not statistically different between hormone-sensitive and castrate-resistant mPC patients (6.0% vs 10.4%; p = 0.06).

Germline mutations of BRCA2 were associated with a positive family history of breast cancer (10.0% of the BRCA2 mutation carriers had at least one first degree relative with breast cancer vs 3.3% for the non-carriers; p=0.02; Supplementary table 3). This association was restricted to carriers of BRCA2 germline mutations, and wasn't observed when we compared mPC patients with or without DDRg mutations (12.9% of the mutation carriers had at least one first degree relative with breast cancer vs 7.6% for the non-carriers; p=0.17). Similarly, a higher proportion of BRCA2 germline mutation carriers had a positive family history of PC (7.5% vs 2.9% for the non-carriers), but the difference wasn't statistically significant.

The mean age at metastatic stage (62.1 vs 67.0 years old; p = 0.0009) and the mean age at death (68.3 vs 73.9 years old; p = 0.0022) were significantly earlier for carriers of DDRg mutation than for non-carriers (Supplementary table 4). These results were mainly driven by BRCA2 mutation carriers. Indeed, the mean age at metastatic stage (59.7 vs 66.8; p = 0.0004) and the mean age at death (65.2 vs 73.8; p = 0.0003) were even significantly earlier for carriers of BRCA2 mutation than for non-carriers. Similar results were found when we excluded the nonBRCA2 DDRg mutation carriers from the analyses, with mean age at metastatic stage (59.7 vs 67.0; p = 0.0003) and mean age at death

(65.2 vs 73.9; p = 0.0003) for carriers of BRCA2 mutation versus non-carriers. In agreement with those results, when we excluded the BRCA2 mutation carriers, the mean age at metastatic stage (64.5 vs 67.0; p = 0.22) and the mean age at death (72.3 vs 73.9; p = 0.57) didn't remain significantly different between carriers of DDRg mutation and non-carriers. When we stratified the patients by ancestry, the same results were found among patients of European ancestry, but no significant difference in mean age at metastatic stage or death was observed among carriers or not of DDRg mutation from African ancestry (Supplementary table 4). Moreover, Cox model showed that BRCA2 positive status was statistically associated with poorer survival in the total cohort of mPC patients (Hazard ratio: 0.29; 95% Confidence interval: 0.18-0.48; p<0.0001), but that positive status for overall DDRg mutations, with or without BRCA2, was not (p = 0.13 and p = 0.92, respectively).

DISCUSSION

In our study, BRCA2 was the most frequently mutated gene in mPC patients of either European or African origin (4.0% and 3.6%, respectively). Similarly, the frequency of germline BRCA2 mutation was the highest among analysed DDR genes in almost all reported studies on mPC, mCRPC and lethal PC,[3,6,8,9,11,12,22,23] with frequency ranging from 1.9% to 5.4% (Table 2). Accordingly, reviews of the literature concluded that the DDR gene with the highest prevalence of germline mutation was BRCA2 in those patients.[24, 25] Only, Darst et al.[21] reported a frequency of BRCA2 mutation that wasn't the highest one, but this study included Finnish patients who carried no BRCA2 mutation. This is in agreement with previous results from Ikonen et al.[26] who screened 444 unselected PC patients for six BRCA2 recurrent germline mutations in Finland, and found no mutation. They concluded that BRCA2 mutations have no major role in predisposition to prostate cancer in Finland.

ATM was the second most frequently mutated DDR gene (2.0%) in our total cohort of mPC patients. Most of the other large studies on mPC and mCRPC had reported a similar frequency of ATM germline mutation, ranging from 1.6 to 2.1% (Table 2). However, two studies, performed on mPC[11] and mCRPC[6] found a less frequent rate of ATM mutations (0.3%). This could be due to the smaller

size of their cohort, the origin of the patients, or to a difference in interpretation of ATM variants as it has been shown that the classification of its variants might be discordant from one laboratory to another.[27]

Two other genes, CHEK2 and PALB2, had different mutation frequency between studies (Table 2). Concerning CHEK2, it could be explained by the higher or lesser frequency of the c.1100delC Eastern European founder mutation observed according studies. Indeed, in our study and the one by Castro et al.[8], this mutation was rare, whereas it accounted for 50% of CHEK2 mutations in the study by Pritchard et al.[3]. Darst et al.[21] found a higher rate of PALB2 mutations (1.1%), compared to the other large studies (Table 2), but even in this study, its frequency varied according the geographical origin of the populations, ranging from 2.6% in US patients to 0.0% in Australian ones.

We observed no difference in DDRg mutation frequency between patients of African and European origins. The same observation was made by Ledet et al.[12] who didn't find difference in mutation frequency between African and European American patients when they considered all the DDRg they had analysed. Particularly, the frequency of BRCA2 wasn't different between patients of African and European origins in the two studies. To counteract one of the limitations of our study which is the small number of patients of African ancestry, we combined our data with those of Ledet et al.[12] and, again, found comparable BRCA2 mutation frequency between patients of both origins (4.7% and 4.1%, among patients of European and African ancestry, respectively; p=0.75). However, both studies, and even their combination, are underpowered to draw conclusion on population differences, and studies including, in particular, a larger number of metastatic PC patients of African ancestry are needed to address this point. Another limitation of these two studies is that ancestry was self-reported.

Conversely, we found an association between the presence of BRCA2 germline mutation and a family history of breast cancer in this population of metastatic PC patients, which is in agreement with our previous observation of a higher frequency of this mutation among PC patients, both metastatic or not, who have a family history of breast cancer.[28] This association was restricted to BRCA2, and

wasn't observed for all DDR genes. When we stratified the patients according ancestry, the frequency of patients with a positive family history of breast cancer was higher among the BRCA2 mutation carriers (9.2%) than the non-carriers (3.2%) from European ancestry, even if the difference was not statistically significant (p=0.06). This tendency wasn't observed among the patients of African ancestry (Supplementary table 3). In their study, Ledet et al.[12] reported that family history of breast cancer predicted the existence of germline mutations in DDR genes in European but not African-American patients. The absence of association observed among mPC patients of African ancestry could be due to the smaller number of these patients, compared to the European ones, in the two studies or may reflect the specific importance of familial history of cancers among the European patients. However, these associations would need to be validated in larger populations as our results related to familial information self-reported by the patients, that weren't clinically confirmed.

Finally, germline mutations of DDR genes were associated with both an early age at metastatic disease and an early age at death in our study. These associations were mostly driven by BRCA2 and indeed, patients with a germline mutation of BRCA2 had a poorer overall survival. This is in agreement with previous studies performed on BRCA2 which showed that mutation of this DDR gene is associated with a poor outcome[29,30] and worse prognosis.[10] However, this seemed not to be true for all DNA damage repair genes, and studies, including not only BRCA2 but also other DRR genes, didn't find difference in response to treatment or overall survival in patients who carried or not mutations of those genes.[9,31,32] Large studies, with sufficient statistical power, are therefore needed to evaluate the impact of mutations of each DDR gene on the clinical outcomes of mPC patients.

CONCLUSIONS

Our study showed that in Western Europe (France), PALB2 and CHEK2 germline mutations remain rare, while those of BRCA2 and ATM are the main predisposing ones in mPC patients, with a particular aggressiveness for BRCA2 leading to early metastatic stage and death. The small disparities

in the prevalence of BRCA2 mutations between patients of European and African ancestry suggest that this gene remains the most targetable event based on germline analysis in mPC patients from the French population regardless of their ancestry.

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Table 1: Characteristics of the patients

Ancestry **Number (%)**	**All** **557 (100%)**	**European** **445 (79.9%)**	**African** **84 (15.1%)**	**Other** **28 (5.0%)**
Mean age at diagnosis (years) ± SD	64.6 ± 9.0	64.0 ± 8.8	67.1 ± 10.9	67.1 ± 11.0
Mean age at metastatic status (years) ± SD	66.5 ± 9.3	66.2 ± 9.0	68.2 ± 10.7	67.6 ± 10.4
Castration-resistant Number (%) Mean age at CRPC (years) ± SD	 270 (48.9%) 68.2 ± 9.8	 217 (49.2%) 67.7 ± 9.5	 43 (51.8%) 70.7 ± 10.3	 10 (35.7%) 67.4 ± 13.8
Deceased Number (%) Mean age at death (years) ± SD	 351 (63.0%) 73.3 ± 10.3	 296 (66.5%) 73.1 ± 10.0	 46 (54.8%) 75.1 ± 11.7	 9 (32.1%) 71.8 ± 13.4
Deceased due to prostate cancer Number (%) Mean Age at death (years) ± SD	 135 (24.3%) 71.3 ± 10.4	 100 (22.5%) 71.3 ± 10.2	 27 (32.1%) 71.5 ± 10.6	 8 (28.6%) 71.0 ± 14.1
Typology of metastasis Distant lymph nodes Bone metastasis Visceral metastasis	 189 (33.9%) 294 (52.8%) 74 (13.3%)	 153 (34.4%) 236 (53.0%) 56 (12.6%)	 25 (29.8%) 48 (57.1%) 11 (13.1%)	 11 (39.3%) 10 (35.7%) 7 (25.0%)
Positive family history of prostate cancer	146 (26.2%)	138 (31.0%)	5 (6.0%)	3 (10.7%)
Positive family history of breast cancer	70 (12.6%)	65 (14.6%)	2 (2.4%)	3 (10.7%)
Personal history of cancer (other than prostate)	43 (7.7%)	34 (7.6%)	6 (7.1%)	3 (10.7%)

Table 2: Number and frequency of germline mutation carriers in DNA repair genes found among patients with metastatic prostate cancer.

Chr	Gene	This study mPC (N=557)	Darst et al. mPC (N=467)	Pritchard et al. mPC (N=692)	Yadav et al. mPC (N = 704)	Boyle et al. mPC (N = 317)	Ledet et al. mPC (N = 867)	Castro et al. mCRPC (N = 419)	Annala et al. mCRPC (N = 319)
11	***ATM***	11 (2.0%)	10 (2.1%)	11 (1.6%)	13 (1.8%)	1 (0.3%)	9 (1.1%)	8 (1.9%)	1 (0.3%)
2	***BARD1***	1 (0.2%)	-	0	1 (0.1%)	1 (0.3%)	-	0	-
15	***BLM***	0	1 (0.2%)	-	-	2 (0.6%)	2 (0.4%)	-	-
17	***BRCA1***	1 (0.2%)	2 (0.4%)	6 (0.9%)	3 (0.4%)	3 (0.9%)	7 (0.8%)	4 (1.0%)	1 (0.3%)
13	***BRCA2***	23 (4.1%)	9 (1.9%)	37 (5.4%)	14 (2.0%)	6 (1.9%)	42 (4.9%)	14 (3.3%)	16 (5.0%)
17	***BRIP1***	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.4%)	0	-	0	-
16	***CDH1***	0	-	-	-	0	-	-	-
22	***CHEK2***	4 (0.7%)	10 (2.1%)	10 (1.9%)	14 (2.0%)	5 (1.6%)	16 (1.9%)	2 (0.5%)	-
4	***FAM175A***	0	-	1 (0.2%)	-	0	-	0	-
3	***MLH1***	0	6 (1.3%)	0	0	0	-	0	0
11	***MRE11A***	1 (0.2%)	0	1 (0.1%)	0	0	-	2 (0.5%)	-
2	***MSH2***	1 (0.2%)	-	1 (0.1%)	0	0	1 (0.1%)	1 (0.2%)	0
2	***MSH6***	1 (0.2%)	2 (0.4%)	1 (0.1%)	0	0	4 (0.5%)	0	0
8	***NBN***	2 (0.4%)	3 (0.6%)	2 (0.3%)	2 (0.3%)	0	4 (0.5%)	0	-
16	***PALB2***	0	5 (1.1%)	3 (0.4%)	2 (0.3%)	0	4 (0.5%)	0	2 (0.6%)
7	***PMS2***	1 (0.2%)	-	2 (0.3%)	-	1 (0.3%)	3 (0.4%)	0	-
5	***RAD50***	0	11 (2.4%)	-	3 (0.4%)	-	-	0	-
17	***RAD51C***	0	-	1 (0.1%)	0	0	-	0	0
17	***RAD51D***	0	-	3 (0.4%)	0	0	2 (0.2%)	0	0
17	***TP53***	0	1 (0.2%)	-	3 (0.4%)	0	4 (0.5%)	-	1 (0.3%)
7	***XRCC2***	0	-	0	0	0	-	0	-

mPC: metastatic prostate cancer; mCRPC: metastatic castration-resistant prostate cancer