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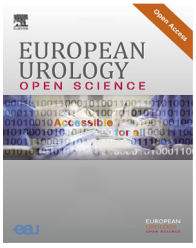

European Association of Urology

Prostate Cancer

# Germline ATM Mutations Detected by Somatic DNA Sequencing in Lethal Prostate Cancer

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**Abstract**

***Background:*** Germline mutations in the ataxia telangiectasia mutated (*ATM*) gene occur in 0.5–1% of the overall population and are associated with tumour predisposition. The clinical and pathological features of *ATM*-mutated prostate cancer (PC) are poorly defined but have been associated with lethal PC.
***Objective:*** To report on the clinical characteristics including family history and clinical outcomes of a cohort of patients with advanced metastatic castration-resistant PC (CRPC) who were found to have germline *ATM* mutations after mutation detection by initial tumour DNA sequencing.
***Design, setting, and participants:*** We acquired germline *ATM* mutation data by saliva next-generation sequencing from patients with *ATM* mutations in PC biopsies sequenced between January 2014 and January 2022. Demographics, family history, and clinical data were collected retrospectively.
***Outcome measurements and statistical analysis:*** Outcome endpoints were based on overall survival (OS) and time from diagnosis to CRPC. Data were analysed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).
***Results and limitations:*** Overall, seven patients ($n$ = 7/1217; 0.6%) had germline *ATM* mutations detected, with five of them having a family history of malignancies, including breast, prostate, pancreas, and gastric cancer; leukaemia; and lymphoma. Two patients had concomitant somatic mutations in tumour biopsies in genes other than *ATM*, while two patients were found to carry more than one *ATM* pathogenic mutation. Five tumours in germline *ATM* variant carriers had loss of ATM by immunohistochemistry. The median OS from diagnosis was 7.1 yr (range 2.9–14 yr) and the median OS from CRPC was 5.3 yr (range 2.2–7.3 yr). When comparing these data with PC patients sequenced by The Cancer Genome Atlas, we found that the spatial localisation of mutations was similar, with distribution of alterations

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occurring on similar positions in the *ATM* gene. Interestingly, these include a mutation within the FRAP-ATM-TRRAP (FAT) domain, suggesting that this represents a mutational hotspot for *ATM*.

***Conclusions:*** Germline *ATM* mutations are rare in patients with lethal PC but occur at mutational hotspots; further research is warranted to better characterise the family histories of these men and PC clinical course.

***Patient summary:*** In this report, we studied the clinical and pathological features of advanced prostate cancers associated with germline mutations in the *ATM* gene. We found that most patients had a strong family history of cancer and that this mutation might predict the course of these prostate cancers, as well as response to specific treatments.



## 1. Introduction

The heritability of prostate cancer (PC) is complex. A small but significant proportion is accounted for by rare, moderate, or highly penetrant pathogenic variants in genes such as *HOXB13*, *BRCA2*, *MSH2*, *ATM*, *BRCA1*, *CHEK2*, *NBN*, and *PALB2*. A greater proportion of PC heritability is attributable to common, low-penetrance single nucleotide polymorphisms occurring at risk loci scattered throughout the genome—an excess of 260 such loci have been identified to date [1–3]. The ataxia telangiectasia mutated (*ATM*) gene (chromosome 11q22–23; 66 exons with a 9168 base pair coding sequence) is one of the largest genes in the genome and is a tumour suppressor gene that encodes a PI3K-related serine/threonine protein kinase that identifies DNA damage and helps maintain genomic integrity [1,2]. Upon DNA double-strand breaks, the primary sensor MRE11-RAD50-NBS1 (MRN) complex recruits and activates ATM, which phosphorylates several downstream effectors involved in cell-cycle checkpoint arrest (eg, Chk2), DNA repair (BRCA1 and RAD51), and apoptosis (p53) [1]. This indirect role of ATM in DNA repair has therefore led to it being grouped together with other genes related to defective DNA repair. ATM is not, however, directly involved in homologous recombination repair (HRR) [1], and cells with inactivated ATM do not accumulate the genomic signature of HRR failure associated with BRCA1 and BRCA2 inactivation despite having impaired DNA damage responses that can partly be compensated by other kinases [3]. The plethora of ATM targets leads to coordination of pathways that are key to DNA repair, with ATM loss of function being synthetic lethal when combined with pharmacological therapeutic strategies including poly(ADP-ribose) polymerase (PARP) and ATR inhibition [4–6].

The general population frequency of heterozygous deleterious germline mutations in *ATM* is approximately 0.5–1%, while truncating pathogenic variants are rarer (~0.29%) [7]. Biallelic pathogenic variants cause the rare autosomal recessive syndrome ataxia telangiectasia, a progressive neurological disorder associated, as the name suggests, with ataxia and conjunctival telangiectasia, as well as immunodeficiency, radiosensitivity, and cancer predisposition. Heterozygous carriers of constitutional pathogenic variants in *ATM* are not at risk of ataxia telangiectasia, but are at an increased risk of certain cancers, including breast, prostate, and pancreatic cancer. The associated disease penetrance is genotype dependent, with the greatest risk associated with truncating variants compared with other variant types, although a recurrent high-risk missense variant (c.7271T>G) has been associated with a particularly high breast (and possibly other) cancer risk owing to a dominant negative effect [8–10]. In PC patients, the percentage with germline mutations in DNA repair genes (including *ATM*) ranges from 4.6% in patients with localised disease to 11.8–16.2% in patients with metastatic disease [11,12]. In The Cancer Genome Atlas (TCGA) data set, about 7% of PC diagnostic tumour samples have either somatic or germline alterations in *ATM* [8]. In multiple clinical studies, *ATM* somatic genomic alterations have been reported in 5–8% of castration-resistant PC (CRPC), appearing to be significantly more frequent in metastatic than in local disease [8]. The clinical and pathological features of germline *ATM* mutation–associated PC remain inadequately described, and precise estimates of the frequency of germline *ATM* mutations in patients with lethal PC still need to be determined. Notwithstanding this, the evidence indicates that these are mostly associated with aggressive disease and poor prognosis [13].

Herein, we report on a tumour-first testing approach in a large series of sequenced metastatic PC patients to identify a cohort of advanced PC patients with germline *ATM* mutations, and report on associated family history and disease course.

## 2. Patients and methods

### 2.1. Patients and samples

Tumour samples were acquired between January 2014 and January 2022 utilising approved protocol for molecular characterisation at the Royal Marsden Hospital (04/Q0801/60), for which all patients provided written informed consent. If more than one biopsy core for diagnosis was available, the highest Gleason score lesion was used. All blocks were reviewed by a pathologist with PC expertise. Demographic and clinical data for each patient were collected retrospectively from the electronic patient record.

### 2.2. Immunohistochemistry

ATM protein expression was determined by immunohistochemistry (IHC) using a rabbit monoclonal anti-ATM antibody, clone Y170 (catalogue no. ab32420; Abcam Plc, Cambridge, UK) [14]. ATM loss was defined as complete loss of ATM by IHC (H score 0) [14,15].

### 2.3. Targeted next-generation sequencing

Genomic DNA was isolated using the QIAmp DNA FFPE Tissue kit (Qiagen) from tumour tissue or from saliva with a QiaAmp DNA mini kit (Qiagen). Targeted sequencing libraries were constructed using a customised panel (Generead DNAseq Mix-n-Match Panel version 2; Qiagen) and sequenced using a MiSeq sequencer (Illumina) [6]. FASTQ files were generated using the Illumina MiSeq Reporter v2.5.1.3. Sequence alignment, and mutation calling were performed using the Qiagen GeneRead Targeted Exon Enrichment Panel Data Analysis Portal (https://ngsdata-analysis.qiagen.com). Mutation calls were reviewed manually in Integrative Genomics Viewer (https://software.broadinstitute.org/software/igv) according to the standard operating procedure for somatic variant refinement of tumour sequencing data, following the principles described previously [16]. Mutation annotation was based on the data from publicly available databases (ClinVar, COSMIC, and Human Genome Mutation Database), published literature, and in silico prediction tools.

*ATM* variants identified in tumour-derived DNA were prioritised for review if these were of the following variant types: frameshift indel, a mutation resulting in a stop gain, splice site mutations, missense mutations in the kinase domain previously described as likely pathogenic, or where presumed biallelic variants and/or loss of heterozygosity (LOH) was noted. Site-specific germline confirmatory testing was completed for those variants deemed pathogenic if the variant allele frequency was at least 50%.

### 2.4. Statistical analysis

Outcome endpoints were based on (1) overall survival from PC diagnosis, (2) overall survival from CRPC, and (3) time from diagnosis to CRPC. For survival analyses, patients were censored at the date of death. For time to CRPC, no censoring was involved as all patients became castration resistant. Data were analysed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

Overall, seven patients ($n$ = 7/1217; 0.6%) were detected as having germline *ATM* mutations in this cohort (Fig. 1). The characteristics of these patients are presented in Table 1. All seven patients had prostatic adenocarcinoma without neuroendocrine features at the time of biopsy (regardless of hormone-sensitive PC [HSPC] or CRPC sample), and the majority had high-risk Gleason scores, in keeping with the cohort studied. Five of these seven patients had family histories of cancer, including four patients with first- and/or second-degree relatives affected by *ATM*-associated cancers. One patient had no reported family history of cancer, while information related to cancer family history was unavailable for one patient. Regarding previous treatments, all patients were exposed to at least one androgen receptor axis–targeted therapy (enzalutamide and/or abiraterone) and to docetaxel chemotherapy (Fig. 2). Three patients received carboplatin, but none of them responded after three cycles and two after a poly(ADP-ribose) polymerase (PARP) inhibitor. Overall five patients received a PARP inhibitor, with two of these patients being on this for over 1 yr.

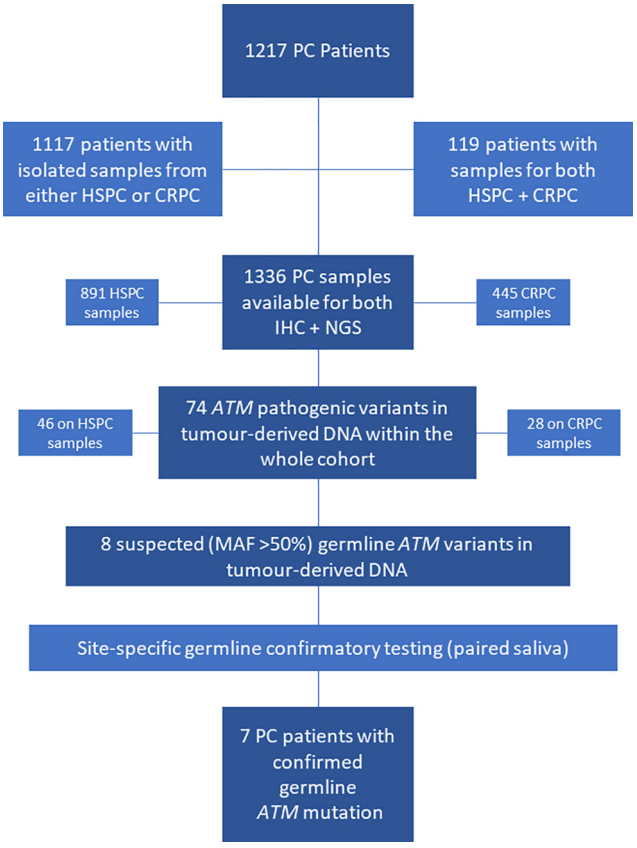


**Fig. 1 – CONSORT diagram representing study population. ATM = ataxia telangiectasia mutated; CRPC = castration-resistant PC; HSPC = hormone-sensitive PC; IHC = immunohistochemistry; MAF = minor allele frequency; NGS = next-generation sequencing; PC = prostate cancer.**

### 3.1. ATM IHC + next-generation sequencing

ATM IHC and targeted somatic next-generation sequencing (NGS) were performed on 1336 samples from 1217 patients; 219 had available biopsies for both HSPC and CRPC (Fig. 1). Of the seven patients with germline *ATM* mutations, two were found to have more than one *ATM* pathogenic mutation (patient #6 carried *ATM* p.E1971Rfs*19 c.5910del and *ATM* p.I2752F [phase unconfirmed], while patient #8 carried *ATM* p.V1528Cfs*15 c.4579del and *ATM* p.Q1098Rfs*11; Table 2). Two patients carried the same pathogenic variant (p.v1268* p.Glu1267_Val1268insTer). Not all the tumours in these seven patients had ATM loss on IHC, suggesting that mutated ATM can be expressed and detected by IHC; interestingly, one of these three men did not demonstrate either ATM loss or LOH. Localisation of the detected *ATM* mutations is presented in Figure 3.

### 3.2. Outcomes

The median overall survival from diagnosis for patients with *ATM* mutations of germline origin was 7.1 yr (range 2.9–14 yr), and the median overall survival from CRPC was 5.3 yr (range 2.7–7.3 yr). The median time from diagnosis to castration resistance was 31 mo (range 6–102 mo).

**Table 1 – Study population characteristics**

| # | Diagnosis | | | | | | | | | Sites of disease | Family history |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Race | Histology | Timing of biopsy | Gleason | PSA (ng/dl) | T | N | M [a] | | |
| 1 | 50 | White | Acinar adenocarcinoma | HSPC | 8 | 109 | 3 | × | 1 | Bone + nodal | Mother: pancreatic cancer (diagnosed at 73 yr of age); son: Hodgkin lymphoma (17 yr old); brother: PC (69 yr old) |
| 2 | 62 | Black | Acinar adenocarcinoma | CRPC | Unknown [b] | 2000 | × | × | 1 | Bone + nodal | No |
| 3 | 71 | White | Acinar adenocarcinoma | HSPC | 7 | 5 | × | 0 | 0 | Bone | Unknown [c] |
| 4 | 53 | White | Acinar adenocarcinoma | HSPC | 9 | 21 | 4 | 1 | 1 | Bone + nodal | Mother: breast cancer (63 yr old); maternal aunt: breast cancer (80 yr old); paternal grandmother: gastric cancer (70 yr old) |
| 5 | 68 | White | Acinar adenocarcinoma | CRPC | 9 | 238 | 3 | 1 | 0 | Bone | Father: leukaemia (61 yr old) |
| 6 | 68 | White | Acinar adenocarcinoma | HSPC | 9 | 766 | × | × | 1 | Bone + nodal + visceral | Mother: ovarian cancer (62 yr old); father: anal cancer (60 yr old); sister: bowel cancer (unknown age of diagnosis) |
| 8 | 65 | White | Acinar adenocarcinoma | CRPC | 9 | 4.6 | 2 | 1 | 1 | Bone + nodal | Sister: breast cancer (40 yr old) |

CRPC = castration-resistant prostate cancer; HSPC = hormone-sensitive prostate cancer; PC = prostate cancer; PSA = prostate-specific antigen.
[a] This refers to presence/absence of metastases at diagnosis, that is, synchronicity of metastatic disease.
[b] Diagnosed and treated upfront as metastatic disease. Biopsy performed later on from bone marrow and, as such, Gleason is unreliable.
[c] Information regarding this patient's family history was unavailable from records.

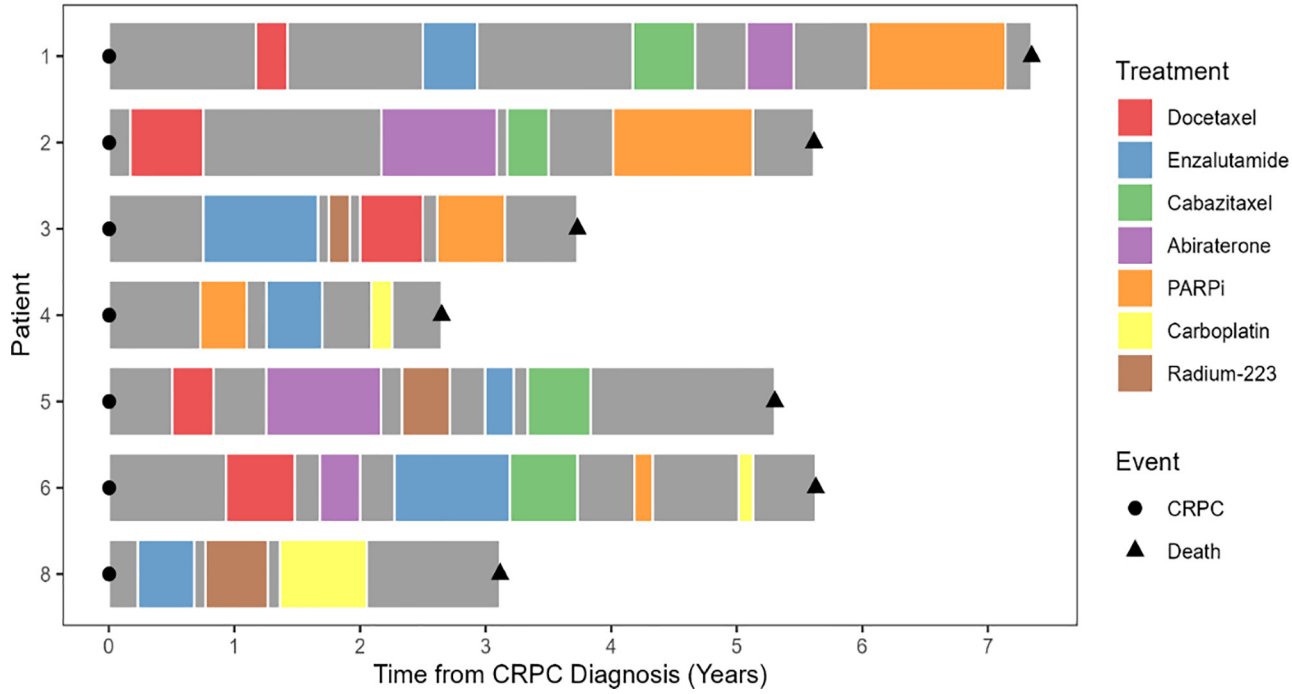


**Fig. 2 – Swimmers' plot representing individual sequence of treatments for prostate cancer and survival outcomes. The anchoring point for the chart is the date of castration resistance, and the final event of the seven patients is death. Treatments are identified by colour (as per label), and grey areas represent time off active treatment (aside from an LHRH agonist, if not surgically castrated). CRPC = castration-resistant prostate cancer; LHRH = luteinising hormone-releasing hormone; PARPi = poly(ADP-ribose) polymerase inhibitor.**

## 4. Discussion

We previously reported on 692 men with metastatic PC, with 82 (11.8%) having at least one presumed pathogenic germline mutation in a gene involved in DNA repair; 11 men (1.6%) were found to carry germline *ATM* mutations in that report, all truncating variants [12]. One patient had mutations in both *ATM* and *CHEK2* [12]. This germline mutation frequency is in keeping with the prevalence observed in the cohort of 498 PC patients sequenced by TCGA (1.4%; $n$ = 7/498) but is higher than the frequency

**Table 2 – NGS and IHC analyses**

| # | Germline ATM mutation | HGVS | Transcripts | dbSNP | ClinVar | Loss of heterozygosity | ATM loss IHC | Concomitant mutations |
|---|---|---|---|---|---|---|---|---|
| 1 | p.V1268* | c.3801delG | NM_000051.3 | rs587779834 | Pathogenic | Yes | Yes | No |
| 2 | p.W2638* | c.7913G>A | NM_000051.3 | rs377349459 | Pathogenic | No | No (HS 50) | No |
| 3 | p.V1268* | c.3801delG | NM_000051.3 | rs587779834 | Pathogenic | Yes | Yes | No |
| 4 | p.Leu263fs | c.788delT | NM_000051.3 | rs587781978 | Pathogenic | Yes | Yes | No |
| 5 | p.E2304Gfs*69 | c.6908dup | NM_000051.3 | rs773570504 | Pathogenic | Yes | Yes | No |
| 6 | p.E1971Rfs*19 | c.5910del | NM_000051.3 | rs587782198 | Pathogenic | Yes | No (HS 110) | ATM p.I2752F |
| 8 | p.V1528Cfs*15 | c.4579del | NM_000051.4 | rs1565461674 | Pathogenic | Yes | No (HS 15) | ATM p.Q1098Rfs*11, AR p.H875Y, TP53 p.T155I |

ATM = ataxia telangiectasia mutated; IHC = immunohistochemistry; NGS = next-generation sequencing.

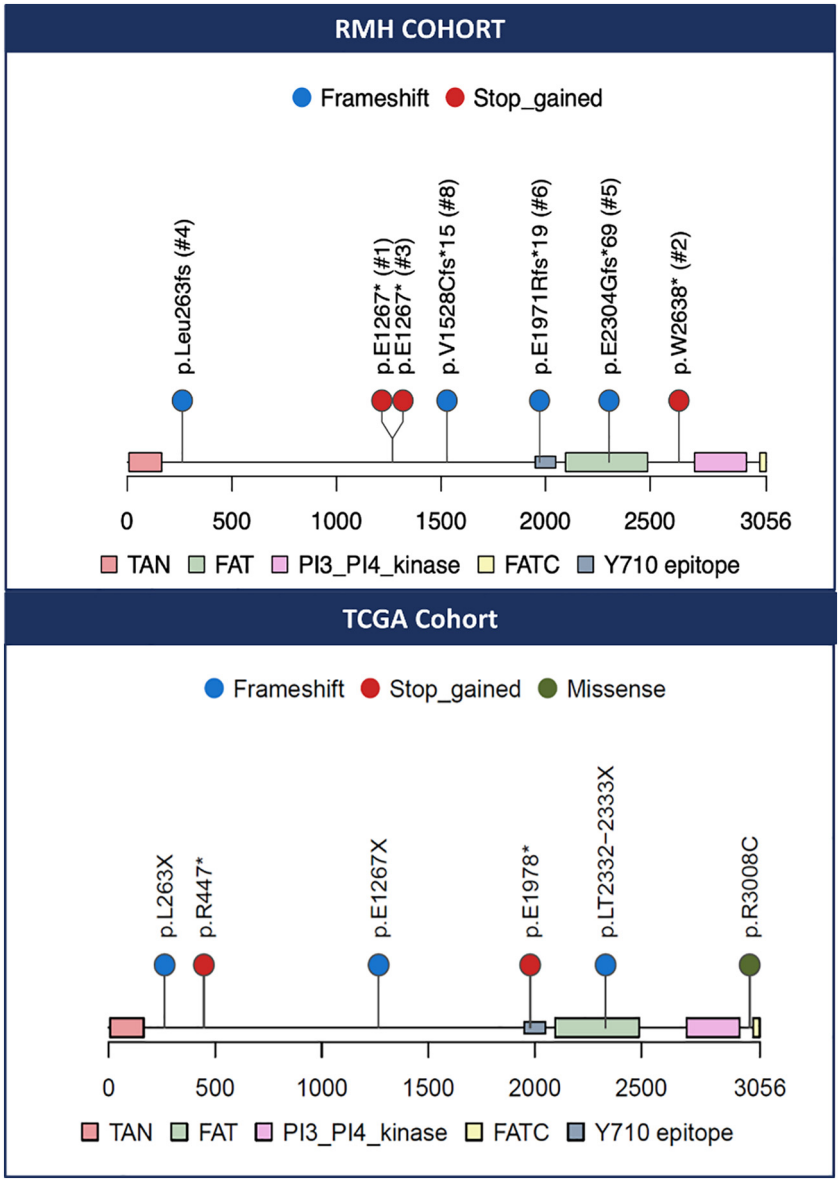


**Fig. 3 – Lollipop plots representing spatial localisation and type of germline mutations found in the ATM gene for (A) our study population (RMH cohort) and (B) The Cancer Genome Atlas (TCGA) cohort of patients with PC. ATM = ataxia telangiectasia mutated; PC = prostate cancer; RMH = Royal Marsden NHS Foundation Trust.**

detected in this report (0.6%), which identified germline mutations from somatic tumour biopsy targeted NGS; this latter approach may have missed *ATM* aberrations such as intronic mutations [17]. Karlsson et al [8] analysed NGS PC patient data generated by 13 study groups comprising 5560 PC cases; overall, 1.2% (65/5560) were reported to

have a pathogenic/likely pathogenic (ClinVar) germline *ATM* variant (19 frameshift indels, 16 stop-gain mutations, six splice site variants, eight missense variants, one in-frame deletion, and one start site loss variant). They also observed, based on controls, a higher mutation prevalence in cases diagnosed at <65 yr of age. However, they were unable to conclude that *ATM* mutations predispose to more aggressive PC phenotypes. Abida et al [18] performed comprehensive genomic and transcriptomic analyses of 429 patients with metastatic CRPC (mCRPC). No association was found between *ATM* gene alterations and time on treatment or overall survival, which is in keeping with the observations from Mateo et al [19]. In contrast, one study of circulating tumour DNA genomics reported poorer outcomes for patients with *ATM* mutations, independently of clinical prognostic factors and circulating tumour DNA abundance [20].

Interestingly, comparing the data herein with the TCGA PC data, we found that the spatial localisation of mutations was overlapping, with mutation distribution occurring in similar positions throughout the *ATM* gene. A number of mutation hotpots have been identified in *ATM*, in particular codons 337 and 3008 [21]. Analyses of *ATM* mutations in cell lines and patient samples across all cancer types from the Broad Institute Cancer Cell Line Encyclopaedia and TCGA have been unable to identify specific genotypes that correlate with disease development or with increased total mutational burden. In a cohort of 48 PC tissues and paired normal samples, Mangolini et al [22] observed recurrent variation within the FRAP-ATM-TRRAP (FAT) domain. However, not all *ATM* aberrations were of germline origin.

Regarding our immunohistochemical findings, six patients with germline *ATM* mutation presented with LOH and four patients with ATM loss on IHC (H score = 0). Preservation of protein expression by IHC, in the setting of biallelic loss, is not uncommon, for example, depending on the assay used, abnormal truncated protein may still be detectable by antibody binding its epitope on expressed nonfunctional protein [23]. As such, these findings suggest that not all *ATM* germline alterations result in loss of protein expression, due to either absence of loss of the second allele or continued protein expression despite the mutation.

Beyond serving as a potential prognostic biomarker in PC, *ATM* loss of function may also be predictive of response to therapy [2]. Responses and survival benefit have been reported for PARP inhibition in patients with mCRPC [24–27]. Two of our five patients with germline *ATM* mutations who received PARP inhibitors derived benefit from therapy for 13 mo. Platinum-based chemotherapy has also been postulated to have antitumor activity against mCRPC with biallelic DNA repair aberrations. In a case series that included 80 patients with germline or somatic alterations in homologous recombination DNA repair genes, prostate-specific antigen and radiological responses were noted for almost 48% of patients [28]. *ATM* mutations were detected in 12 patients (15%), with only three of these being of germline origin. None of our three patients who received carboplatin experienced an antitumor response, although in two of these patients, this was administered after prior PARP inhibitor exposure; it is recognised that PARP inhibitor resistance associates with carboplatin resistance.

We acknowledge that this is a retrospective single-centre analysis, that family history information was not available for all individuals, and that sequencing was performed via a panel-based approach with limited sensitivity to detect complex genomic aberrations. Notwithstanding, our analyses support *ATM* germline testing in addition to tumour profiling for the benefit of wider families as well as of patients. In addition to potential therapeutic implications in the management of PC, knowledge of *ATM* germline status supports advising on other associated cancer risks. Each sibling and each child of an individual who carries a pathogenic germline *ATM* variant have a 50% (one in two) risk of inheriting the same variant and are eligible for genetic testing on a predictive basis. The risk is genotype dependent, with truncating variants conferring more risk than missense variants, apart from the high-risk missense variant c.7271T>G, which confers a particularly high risk due to an intrinsic dominant negative effect. In the UK, women who carry this particular variant are eligible for magnetic resonance imaging and mammographic screening, and carriers of this and other high-risk genotypes may be eligible for risk-reducing breast surgery. Hence, knowledge of the *ATM* status in a male has significant implications for female relatives. Furthermore, preimplantation genetic testing and other reproductive options are available to carriers of high-risk pathogenic variants in cancer predisposition genes, so results have significant implications for carriers of reproductive age. This is particularly relevant if there are consanguineous relationships in a family because of the additional risk of having a child with ataxia telangiectasia.

## 5. Conclusions

Overall, therefore, germline *ATM* mutations may be associated with lethal PC, and their detection has major clinical implications. Efforts are warranted to better characterise their impact on cancer risk and on clinical course and treatment outcome in prostate cancer.

***Author contributions***: Johann De Bono had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: De Bono, Grochot.
*Acquisition of data*: Grochot, Carreira, Miranda, Figueiredo, Bertan, Neeb, Bora Gurel, de la Maza, Guo, Carmichael, Westaby, McVeigh.
*Analysis and interpretation of data*: De Bono, Grochot, Carreira, Miranda, Figueiredo, Bertan, Yuan, Ferreira, Neeb, Gurel, Mateo, Sharp, McVeigh.
*Drafting of the manuscript*: De Bono, Grochot, Carreira, Mateo, Sharp, McVeigh.
*Critical revision of the manuscript for important intellectual content*: De Bono, Grochot, Carreira, Mateo, Sharp, McVeigh.
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