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Rare Germline Variants in ATM Predispose to Prostate Cancer: A PRACTICAL Consortium Study

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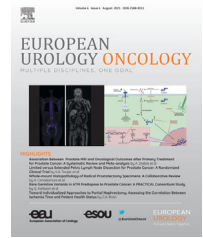
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Priority Article

Rare Germline Variants in ATM Predispose to Prostate Cancer: A PRACTICAL Consortium Study

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Abstract

Background: Germline *ATM* mutations are suggested to contribute to predisposition to prostate cancer (PrCa). Previous studies have had inadequate power to estimate variant effect sizes.

Objective: To precisely estimate the contribution of germline *ATM* mutations to PrCa risk.

Design, setting, and participants: We analysed next-generation sequencing data from 13 PRACTICAL study groups comprising 5560 cases and 3353 controls of European ancestry.

Outcome measurements and statistical analysis: Variant Call Format files were harmonised, annotated for rare *ATM* variants, and classified as tier 1 (likely pathogenic) or tier 2 (potentially deleterious). Associations with overall PrCa risk and clinical subtypes were estimated.

Results and limitations: PrCa risk was higher in carriers of a tier 1 germline *ATM* variant, with an overall odds ratio (OR) of 4.4 (95% confidence interval [CI]: 2.0–9.5). There was also evidence that PrCa cases with younger age at diagnosis (<65 yr) had elevated tier 1 variant frequencies ($p_{\text{difference}} = 0.04$). Tier 2 variants were also associated with PrCa risk, with an OR of 1.4 (95% CI: 1.1–1.7).

Conclusions: Carriers of pathogenic *ATM* variants have an elevated risk of developing PrCa and are at an increased risk for earlier-onset disease presentation. These results provide information for counselling of men and their families.

Patient summary: In this study, we estimated that men who inherit a likely pathogenic mutation in the *ATM* gene had an approximately a fourfold risk of developing prostate cancer. In addition, they are likely to develop the disease earlier.

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Introduction

In 2018, prostate cancer (PrCa) was the second most common cancer diagnosed in men worldwide, with over 1.2 million new cases [1]. The disease has high heritability [2]; family history is a well-known risk factor and genome-wide association studies (GWASs) have identified nearly 200 common germline risk variants [3–5]. Several genes have also been proposed to harbour rare moderate penetrance variants that may contribute to an elevated risk of PrCa. There is convincing evidence that rare loss-of-function variants in *BRCA2* contribute to the development of PrCa [6] and additionally to an aggressive phenotype [7]. Rare variants in several other genes, primarily *ATM*, *BRCA1*, *CHEK2*, *NBN*, *PALB2*, and the mismatch repair genes, have also been proposed to increase PrCa risk [8–17].

Most prior germline sequencing studies reporting *ATM* mutation data have been relatively small (up to a few hundred PrCa cases), lacked control cohorts, or were conducted in non-European ancestral populations for whom the frequency of pathogenic *ATM* mutations may differ from those of Europeans [9,11–14,16,18,19]. Precise estimates of risk for *ATM* mutation carriers have not been established. In a few small clinical studies, *ATM* has also

been shown to be linked with a more aggressive subtype of PrCa. In The Cancer Genome Atlas, about 7% of PrCa primary tumour samples had either somatic or germline alterations in *ATM* [18], and it has also been shown that germline *ATM* variant carriers have reduced survival [13].

In this study, we collected, harmonised, and analysed available *ATM* sequencing data from 14 study groups within The PRACTICAL Consortium and report on the overall association of rare germline *ATM* variants with PrCa from over 8000 European samples.

Participants and methods

Study groups

We collected individual-level data for 10 404 participants from 14 PRACTICAL Consortium study groups across North America (five study groups), Europe (six study groups), Asia (one study group), and Australia (two study groups). We excluded 459 samples of non-European or unknown ethnicity and an additional 1032 samples due to interstudy duplicates, relatedness, or unavailability of phenotype data, leaving 8913 participants from 13 study groups available for analysis (Supplementary Table 1).

Table 1 – Numbers contributed, by study

Study	Total participants	Cancers			Noncancers		
		Noncarriers (N)	Carriers (N)	Prevalence (%)	Noncarriers (N)	Carriers (N)	Prevalence (%)
Tier 1							
CAPS	267	168	5	2.89	94	0	0.00
CeRePP	347	295	2	0.67	49	1	2.00
FHCRC	370	259	5	1.89	105	1	0.94
Finland	291	212	3	1.40	76	0	0.00
Germany	318	188	3	1.57	127	0	0.00
ICR	3350	1990	22	1.09	1336	2	0.15
JHU	186	98	1	1.01	87	0	0.00
MAYO	971	386	5	1.28	577	3	0.52
MCCS	1313	1258	16	1.26	39	0	0.00
MD_Anderson	449	–	–	–	448	1	0.22
Porto	479	476	3	0.63	–	–	–
TASPRAC	26	18	0	0.00	8	0	0.00
UTAH	546	147	0	0.00	399	0	0.00
All	8913	5495	65	1.17	3345	8	0.24
Tier 2							
CAPS	267	166	7	4.05	86	8	8.51
CeRePP	347	272	25	8.42	48	2	4.00
FHCRC	370	243	21	7.95	96	10	9.43
Finland	291	206	9	4.19	76	0	0.00
Germany	318	174	17	8.90	117	10	7.87
ICR	3350	1896	116	5.77	1278	60	4.48
JHU	186	85	14	14.14	83	4	4.60
MAYO	971	368	23	5.88	556	24	4.14
MCCS	1313	1199	75	5.89	38	1	2.56
MD_Anderson	449	–	–	–	438	11	2.45
Porto	479	407	72	15.03	–	–	–
TASPRAC	26	14	4	22.22	7	1	12.50
UTAH	546	143	4	2.72	395	4	1.00
All	8913	5173	387	6.96	3218	135	4.03
Tier 1 + 2							
CAPS	267	161	12	6.94	86	8	8.51
CeRePP	347	270	27	9.09	47	3	6.00
FHCRC	370	238	26	9.85	95	11	10.38
Finland	291	203	12	5.58	76	0	0.00
Germany	318	171	20	10.47	117	10	7.87
ICR	3350	1875	137	6.81	1276	62	4.63
JHU	186	84	15	15.15	83	4	4.60
MAYO	971	363	28	7.16	553	27	4.66
MCCS	1313	1185	89	6.99	38	1	2.56
MD_Anderson	449	–	–	–	437	12	2.67
Porto	479	405	74	15.45	–	–	–
TASPRAC	26	14	4	22.22	7	1	12.50
UTAH	546	143	4	2.72	395	4	1.00
All	8913	5112	448	8.06	3210	143	4.26

Full details of each study group, including recruitment criteria, data collection, and sequencing methods, are given in Supplementary Tables 2 and 3, and the Supplementary material.

Quality control and processing of sequence data

Variant Call Format (VCF) files of the *ATM* gene region (chr11:108093211–108239829 GRCh37/hg19) were standardised to allow consistent variant- and sample-level quality control and variant annotation. VCF files aligned to GRCh38 were converted to GRCh37 using LiftoverVcf. BCFtools [20] norm was utilised to split multiallelic sites to multiple rows, left align variants, and normalise to the reference. Variants with low coverage (depth <10), with low quality (GQ <20 or equivalent), situated within repeat

regions, with an allelic ratio <30% or >70%, or which were monomorphic were excluded. Variant annotation was performed on multisample VCF files using variant effect predictors (VEP; ClinVar classification, ExAC MAF, CADD scores, Impact, and REVEL scores).

Variant categorisation

Only rare variants (defined as ExAC non-Finnish European MAF <0.01) were included in downstream analyses. Rare variants were categorised into two classes. Tier 1 variants were defined as variants with either a pathogenic or likely pathogenic ClinVar <https://www.ncbi.nlm.nih.gov/clinvar/> [21] classification or a “high” VEP [22] impact score; these included transcript ablation, splice acceptor/donor, stop gained/lost, frameshift, and some missense

Table 2 – Numbers contributed to each subtype analysis, by study

Noncancers										Cancers																																																																																														
All										All																																																																																														
Family history					Metastatic					Gleason					Aggressive					Age at diagnosis					Death																																																																															
FH+					FH−					U					M1					M0					U					>7					7					<7					U					Agg.					Int.					Non.					U					<65					≥65					U					PrCa																			
Tier 1 status																																																																																																								
+ve					8					65					26					27					12					8					43					14					18					14					21					12					35					11					15					4					50					14					1					21				
−ve					3345					5495					2053					2557					885					3885					1114					1283					1350					2102					760					2202					1178					1652					463					3660					1714					121					1182									
+ve Prev (%)					(0.24)					(1.17)					(1.25)					(1.04)					(1.09)					(1.59)					(1.09)					(1.38)					(1.03)					(0.99)					(1.56)					(0.93)					(0.90)					(1.35)					(0.81)					(1.75)																								
Total					3353					5560					2079					2584					897					3928					1128					1301					1364					2123					772					2237					1189					1667					467					3710					1728					122					1203									
Tier 2 status																																																																																																								
+ve					135					387					153					169					65					35					272					80					81					106					153					47					143					99					120					25					265					117					5					69				
−ve					3218					5173					1926					2415					832					3656					1048					1220					1258					1970					725					2094					1090					1547					442					3445					1611					117					1134									
+ve Prev (%)					(4.03)					(6.96)					(7.36)					(6.54)					(6.94)					(6.92)					(6.23)					(7.77)					(7.21)					(6.39)					(8.33)					(7.20)					(7.14)					(6.77)					(5.74)																													
Total					3353					5560					2079					2584					897					3928					1128					1301					1364					2123					772					2237					1189					1667					467					3710					1728					122					1203									
Tier 1+2 status																																																																																																								
+ve					143					448					178					193					77					43					312					93					99					120					171					58					176					109					134					29					312					130					6					88				
−ve					3210					5112					1901					2391					820					3616					1035					1202					1244					1952					714					2061					1080					1533					438					3398					1598					116					1115									
+ve Prev (%)					(4.26)					(8.06)					(8.56)					(7.47)					(8.53)					(7.94)					(7.61)					(8.80)					(8.05)					(7.87)					(9.17)					(8.04)					(8.41)					(7.52)					(7.32)																													
Total					3353					5560					2079					2584					897					3928					1128					1301					1364					2123					772					2237					1189					1667					467					3710					1728					122					1203									
Agg. = aggressive; FH = family history; Int. = intermediate aggressive; Non. = nonaggressive; PrCa = prostate cancer; Prev = prevalence; U = unknown.																																																																																																								

Agg. = aggressive; FH = family history; Int. = intermediate aggressive; Non. = nonaggressive; PrCa = prostate cancer; Prev = prevalence; U = unknown.

variants. Tier 2 included variants that had a “moderate” VEP impact score (in-frame insertion/deletion [indels], missense, and protein-altering variants) and were also predicted to be potentially deleterious by at least one of the following two algorithms: combined annotation dependent depletion (CADD [23]; Phred-scaled score >20) or rare exome variant ensemble learner (REVEL [24]; score >0.60).

Statistical analysis

We calculated the prevalence of variants in PrCa cases and controls. Owing to the rarity of individual variants (Table 1 and Supplementary Table 4), mutation status was defined as a binary variable, indicating the presence of at least one variant in the *ATM* gene. Analyses were conducted for tier 1 and 2 variants independently and for both combined.

Odds ratios (ORs) were estimated for the association between mutation status and PrCa diagnosis, and also after stratifying cases by first-degree family history of PrCa, metastatic PrCa, Gleason score (≥ 8 , 7, and ≤ 6), PrCa aggressiveness (aggressive, intermediate, and nonaggressive), age at diagnosis (< 65 and ≥ 65 yr), and death from PrCa (death from PrCa and non-PrCa death/alive). Cases were defined as “aggressive” if they had at least one of stage T4, N1, Gleason score ≥ 8 , metastatic PrCa, or death from PrCa; as “nonaggressive” if they had stage T1–T2 and Gleason score ≤ 6 disease plus, if deceased, death was not due to PrCa; and finally as “intermediate” aggressive if they failed to fulfil either other criteria (ie, had stage T3 and/or Gleason score 7 disease).

To account for possible heterogeneity between study groups in recruitment and sequencing procedures, we generated study-specific ORs and obtained a pooled estimate using a two-stage model [25]. First, we meta-analysed study-specific estimates using the fixed-effect Mantel-Haenszel method with continuity correction [26]. This method has been shown to perform better than inverse variance methods when events are rare [27]. Our analyses were restricted to those of European ancestry and assumed a common effect across study groups. If no appreciable between-study heterogeneity was detected using the I^2 statistic [28], we analysed the data in a pooled data set using Firth logistic regression [29], controlling for study. Prior to each stratified analysis, we removed studies that did not vary in outcome or variant status (ie, contained only cases or only controls, or individuals with no variants). The number of studies excluded varied, depending on the particular analysis (Supplementary Table 5). Owing to the rarity of mutation carriers, we mainly conducted univariate analyses controlling for study, but we also investigated the effect of controlling for age at diagnosis/interview on our results.

We also calculated hazard ratios (HRs) for the association between mutation status and risk of death from PrCa in cases. HRs were estimated from Cox proportional hazard regression models, with time since diagnosis as the underlying timescale. Cases became at risk at their age at PrCa diagnosis and came under observation at their age at

Table 3 – Primary results, tier 1

	Studies (N)	Cancers (N)	Ref. group ^a (N)	OR	95% CI	p value
<i>Tier 1</i>						
Overall	9	4916	2497	4.4	(2.0, 9.5)	2.3×10^{-4}
Subtypes						
Family history						
FH+ cancers vs noncancers	7	1708	2283	5.6	(2.3, 13.9)	2.0×10^{-4}
FH- cancers vs noncancers	6	2289	2207	3.3	(1.4, 7.9)	0.008
FH+ vs FH- cancers	8	1955	2543	1.3	(0.8, 2.3)	0.305
Metastatic						
M1 cancers vs noncancers	4	378	2074	6.4	(2.0, 20.6)	0.002
M0 cancers vs noncancers	8	3491	2410	3.8	(1.7, 8.5)	0.001
M1 vs M0 cancers	9	504	3910	1.8	(0.8, 4.0)	0.146
Gleason						
Gleason ≥ 8 vs noncancers	6	1153	2207	5.5	(2.2, 13.8)	2.3×10^{-4}
Gleason 7 vs noncancers	7	1064	2316	3.9	(1.5, 10.4)	0.006
Gleason ≤ 6 vs noncancers	5	1743	2113	3.1	(1.2, 8.1)	0.018
Gleason ≥ 8 vs Gleason ≤ 6	7	1220	1952	1.3	(0.7, 2.5)	0.431
Aggressive						
Agg. vs noncancers	8	2108	2410	5.4	(2.4, 12.5)	7.4×10^{-5}
Non-Agg. vs noncancers	5	1412	2113	3.2	(1.1, 9.2)	0.028
Agg. vs non-Agg. Cancers	9	2184	1613	1.6	(0.9, 3.0)	0.135
Age at diagnosis						
<65 cancers vs noncancers	8	3095	2410	4.9	(2.2, 11.1)	1.3×10^{-4}
≥ 65 cancers vs noncancers	8	1652	2421	3.8	(1.4, 10.4)	0.010
<65 cancers vs ≥ 65 cancers	10	3623	1650	2.0	(1.0, 3.7)	0.037
Agg. = aggressive; CI = confidence interval; FH = family history; OR = odds ratio; Ref. = reference.						
^a Controls for case/control analyses. Lower-risk subcategory for case-only analyses.						

Table 4 – Primary results, tier 2

	Studies (N)	Cancers (N)	Ref. group ^a (N)	OR	95% CI	p value
<i>Tier 2</i>						
Overall	11	5081	2904	1.4	(1.1, 1.7)	0.008
Subtypes						
Family history						
FH+ cancers vs noncancers	9	1832	2690	1.6	(1.2, 2.1)	0.002
FH- cancers vs noncancers	9	2352	2690	1.2	(0.9, 1.6)	0.206
FH+ vs FH- cancers	10	2079	2584	1.2	(0.9, 1.5)	0.242
Metastatic						
M1 cancers vs noncancers	8	497	2410	1.5	(1.0, 2.3)	0.065
M0 cancers vs noncancers	9	3509	2809	1.3	(1.0, 1.7)	0.047
M1 vs M0 cancers	9	504	3910	1.2	(0.8, 1.7)	0.422
Gleason						
Gleason ≥ 8 vs noncancers	11	1234	2904	1.3	(0.9, 1.8)	0.135
Gleason 7 vs noncancers	10	1148	2896	1.5	(1.1, 2.1)	0.008
Gleason ≤ 6 vs noncancers	11	1937	2904	1.3	(1.0, 1.8)	0.052
Gleason ≥ 8 vs Gleason ≤ 6	11	1296	2114	0.9	(0.7, 1.2)	0.384
Aggressive						
Agg. vs noncancers	11	2161	2904	1.3	(1.0, 1.8)	0.053
Non Agg. vs noncancers	9	1487	2820	1.4	(1.0, 1.9)	0.058
Agg. vs non-Agg. Cancers	11	2231	1667	0.9	(0.7, 1.2)	0.674
Age at diagnosis						
<65 cancers vs noncancers	11	3272	2904	1.3	(1.1, 1.7)	0.018
≥ 65 cancers vs noncancers	12	1809	2904	1.4	(1.0, 1.9)	0.054
<65 cancers vs ≥ 65 cancers	12	3710	1728	0.9	(0.7, 1.2)	0.370
Agg. = aggressive; CI = confidence interval; FH = family history; OR = odds ratio; Ref. = reference.						
^a Controls for case/control analyses. Lower-risk subcategory for case-only analyses.						

consent or first interview. The time to event was calculated from age at diagnosis to death from PrCa. Cases that did not die from PrCa were censored at the age of death from other causes or age of last follow-up, whichever was earliest. For these analyses, we included

studies with available information on follow-up, and restricted the analysis to those studies that had more than five deaths due to PrCa in variant positive and negative strata. Models were adjusted for age at diagnosis and study.

Table 5 – Primary results, tier 1 + tier 2

	Studies (N)	Cancers (N)	Ref. group ^a (N)	OR	95% CI	p value
<i>Tier 1 + 2</i>						
Overall	11	5081	2904	1.5	(1.2, 1.9)	9.3×10^{-5}
<i>Subtypes</i>						
<i>Family history</i>						
FH+ cancers vs noncancers	9	1832	2690	1.8	(1.4, 2.4)	1.4×10^{-5}
FH- cancers vs noncancers	9	2352	2690	1.3	(1.0, 1.8)	0.039
FH+ vs FH- cancers	10	2079	2584	1.2	(1.0, 1.5)	0.120
<i>Metastatic</i>						
M1 cancers vs noncancers	8	497	2410	1.8	(1.2, 2.7)	0.005
M0 cancers vs noncancers	9	3509	2809	1.5	(1.1, 1.8)	0.002
M1 vs M0 cancers	9	504	3910	1.3	(0.9, 1.8)	0.197
<i>Gleason</i>						
Gleason ≥ 8 vs noncancers	11	1234	2904	1.6	(1.1, 2.2)	0.005
Gleason 7 vs noncancers	10	1148	2896	1.7	(1.2, 2.2)	0.001
Gleason ≤ 6 vs noncancers	11	1937	2904	1.5	(1.1, 2.0)	0.009
Gleason ≥ 8 vs Gleason ≤ 6	11	1296	2114	1.0	(0.7, 1.2)	0.715
<i>Aggressive</i>						
Agg. vs noncancers	11	2161	2904	1.6	(1.2, 2.1)	7.8×10^{-4}
Non-Agg. vs noncancers	9	1487	2820	1.5	(1.1, 2.1)	0.013
Agg. vs non-Agg. Cancers	11	2231	1667	1.0	(0.8, 1.3)	0.850
<i>Age at diagnosis</i>						
<65 cancers vs noncancers	11	3272	2904	1.6	(1.2, 2.0)	2.0×10^{-4}
≥ 65 cancers vs noncancers	11	1809	2904	1.5	(1.1, 2.1)	0.008
<65 cancers vs ≥ 65 cancers	12	3710	1728	1.0	(0.8, 1.3)	0.995

Agg. = aggressive; CI = confidence interval; FH = family history; OR = odds ratio; Ref. = reference.

^a Controls for case/control analyses. Lower-risk subcategory for case-only analyses.

All analyses were performed with Stata 16.0 (StataCorp LLC, College Station, TX, USA).

Results

The analyses included 8913 individuals of European ancestry; among them, 65 (1.2%) of 5560 PrCa cases carried a tier 1 *ATM* variant, compared with eight (0.24%) of 3353 controls. For tier 2 variants, 387 (7.0%) cases were carriers compared with 135 (4.0%) controls. For tiers 1 and 2 combined, 448 (8.1%) cases and 143 (4.3%) controls were variant carriers (Table 1). The prevalence of tier 1 variants in individual studies ranged from 0.6% to 2.9% in cases and from 0% to 2.0% for controls. For tier 2 variants, prevalence ranged from 2.7% to 22.2% for cases and from 0% to 12.5% for controls. For tiers 1 and 2 combined, the interstudy range was 2.7–22.2% for cancer cases and 0–12.5% for controls (Table 1).

No sample had more than one tier 1 *ATM* variant. Four cases and no controls had tier 2 variants in addition to a tier 1 variant. Twenty-three cases and two controls had more than one tier 2 variant. Tier 1 variants consisted of frameshift indels ($n=19$), stop-gain mutations ($n=16$), splice site variants ($n=6$), missense variants ($n=8$), one in-frame deletion, and one start lost variant (Fig. 1 and Supplementary Table 4). All missense variants were listed as pathogenic or likely pathogenic in ClinVar, and five of these (observed in seven cases) were in 3' end functional domains. Fourteen variants were observed in more than one sample, of which 12 were identified in multiple studies. Three stop-gain mutations, V1268*, E1978*, and W2769*, were each observed in four samples.

Of 5560 cases, information on family history of PrCa was available for 4663 (83.9%), metastatic disease for 4432 (79.7%), Gleason score for 4788 (86.1%), and aggressiveness for 5093 (91.6%) cases (Table 2 and Supplementary Table 5). Of the 5560 cancer cases, 1203 were listed to have lethal PrCa, 603 died of non-PrCa-related causes, and 69 deaths had an unknown relationship between PrCa and cause of death (Supplementary Table 6). Two study groups (MCCS and ICR) contributed to the time-to-event analysis for risk of PrCa death. Information on age at diagnosis/interview was available for 7474 of 8913 participants. (Supplementary Table 7). The median age at diagnosis was 60 yr (interquartile range [IQR]: 56–67). For controls, the median age at interview was 60 yr (IQR: 55–73). The interstudy range for age at diagnosis was 54–67 yr, whilst for age at interview this was 46–75 yr.

The likelihood of carrying a tier 1 *ATM* variant was greater in PrCa cases than in controls (OR=4.4, 95% confidence interval [CI]: 2.0–9.5, $p=2.3 \times 10^{-4}$; Table 3). Comparing subtypes, ORs were higher in all clinically significant disease subgroups (positive family history, metastatic disease, Gleason score ≥ 8 , and aggressive disease); however, we could not conclude that any differences within the stratified subtype analyses were significant, except for age at diagnosis ($p=0.037$). Cases diagnosed before age 65 yr were more likely to carry a tier 1 variant (OR = 4.9, 95% CI: 2.2–11.1, $p=1.3 \times 10^{-4}$) than those diagnosed after age 65 yr (OR=3.8, 95% CI: 1.4–10.4, $p=0.010$). Finally, we found no appreciable heterogeneity in the various associations when looking at individual study estimates (Supplementary Fig. 1A–C and 2A–C). There were also no appreciable differences in results when tier 1 results

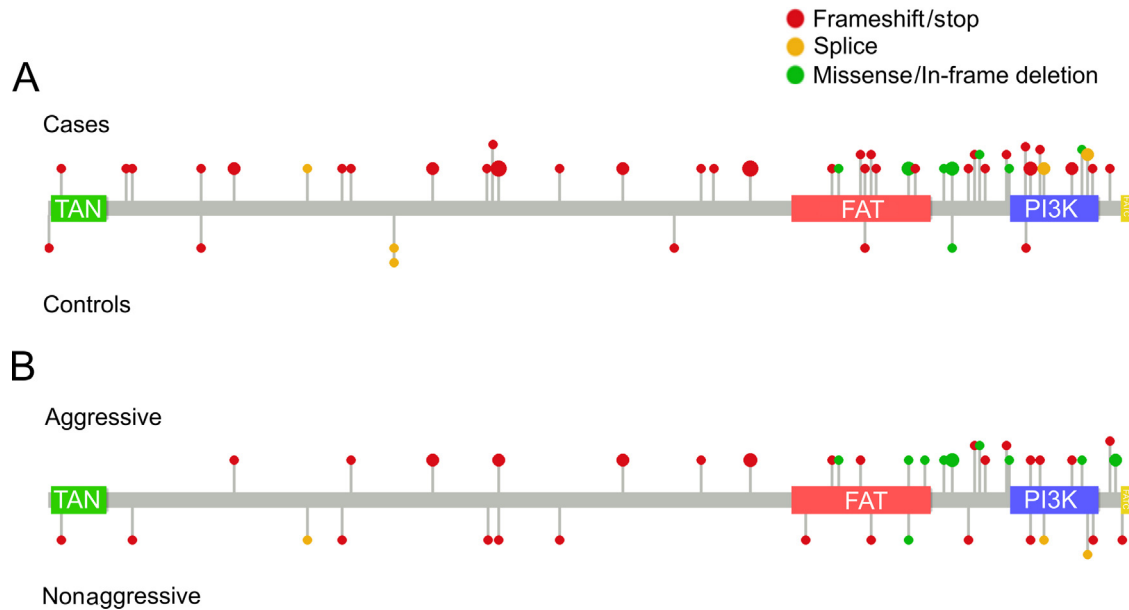


Fig. 1 – Tier 1 mutations identified within the *ATM* gene. Position of tier 1 *ATM* mutations in (A) case and control samples and (B) aggressive and nonaggressive cancer cases. Lollipop size is relative to the number of samples.

were adjusted for age at diagnosis/interview (Supplementary Table 10) or if Finnish populations were excluded (Supplementary Table 13).

Analysis of tier 2 *ATM* variants also revealed a positive association with PrCa risk, albeit smaller than that observed for tier 1 (OR=1.4, 95% CI: 1.1–1.7, $p=0.008$; Table 4). In subgroup analyses, ORs were elevated for cases with a first-degree family history of PrCa (OR=1.6, 95% CI: 1.2–2.1) and cases with metastatic disease (OR=1.5, 95% CI: 1.0–2.3); however, we again could not conclude that there were appreciable differences within a subgroup. When we combined tier 1 and 2 variants, a positive association between PrCa risk and carrier status was observed once more (OR=1.5, 95% CI: 1.2–1.9, $p=9.3 \times 10^{-5}$; Table 5). Subtype analyses revealed trends broadly similar to those seen for tier 1 variants alone, with none of these differences being statistically significant. We also investigated the effect of classifying tier 1 variants as protein truncating variants (PTVs) or non-PTVs, and found that the association with PTVs for overall PrCa risk was stronger (OR=5.7, 95% CI: 2.1–15.3; Supplementary Table 9).

Lastly, we investigated the relationship between *ATM* variants and PrCa-specific death in more detail. Compared with a prevalence of 1.1% in overall PrCa, tier 1 variants were slightly enriched in lethal PrCa cases at 1.7% (95% CI: 1.1–2.7). The prevalence in lethal PrCa cases by categories of age at death was 2.3% (95% CI: 1.2–3.9), 2.0% (95% CI: 0.7–4.2), and 0.4% (95% CI: 0.0–2.0) for those who died at ages <65, 65–74, and ≥ 75 yr. For tier 2 variants, the prevalence for the age categories was 6.3% (95% CI: 4.4–8.6), 4.9% (95% CI: 2.8–8.0), and 5.7% (95% CI: 3.3–9.1), respectively. For tier 1 and 2 variants combined, the overall prevalence was 7.3% (95% CI: 5.9–8.9), and prevalence by the categories of age at death was 8.4% (95% CI: 6.2–11.0), 6.6% (95% CI: 4.1–10.0), and 6.0%

(95% CI: 3.6–9.5), respectively (Supplementary Table 8). In the time-to-event case-only analysis, which was restricted to the MCCS and ICR cohorts, the risk of dying from PrCa for tier 1 variant carriers compared with that for noncarriers was as follows: HR: 1.3 (95% CI: 0.8–2.3, $p=0.3$). For tier 2, the HR was 1.0 (95% CI: 0.7–1.3, $p=0.8$), and for tiers 1 and 2 combined, HR was 1.0 (95% CI: 0.8–1.3, $p=0.9$; Supplementary Table 11).

Discussion

Although GWASs have identified many common, low penetrance PrCa susceptibility loci, no genes have consistently been demonstrated to either have a large effect on risk or contribute to aggressive disease presentation aside from *BRCA2* and *HOXB13*. In the large germline sequencing study presented here, our aim was to determine the contribution of rare *ATM* variants to PrCa predisposition and risk of aggressive disease. We focused primarily on tier 1 variants, which included all rare predicted loss-of-function variants and any nontruncating variants listed as pathogenic or likely pathogenic in ClinVar, and demonstrated their substantial contribution to PrCa susceptibility. We further demonstrated that tier 2 *ATM* variants (rare nontruncating variants predicted to be deleterious by CADD or REVEL) also showed a lower magnitude of association with PrCa risk, suggesting that a subset of rare tier 2 variants of uncertain significance also contributes to PrCa predisposition.

To date, *BRCA2* is the only gene in which tier 1 variants have consistently been linked to aggressive PrCa. We also attempted to establish whether *ATM* carrier status is associated with family history, age of onset, or other clinical

features of disease, as previously suggested in smaller studies [13]. We observed a higher tier 1 mutation prevalence in cases diagnosed at <65 yr of age, and this finding would support that screening should be started at an earlier age for men carrying a mutation. However, we could not conclude that *ATM* mutations, either tier 1 or tier 2, predispose specifically to, or are sufficient to distinguish, more aggressive phenotypes.

Our analysis included only samples of European ancestry, as data from other ethnicities were available only in limited numbers. Whilst differences in mutation prevalence were observed between study groups, overall, *ATM* carrier frequencies appear to be higher in Europeans than in other ancestral populations. A recent PrCa sequencing study in Japanese men [12] reported a significant association between rare pathogenic *ATM* variants and PrCa risk despite much lower frequencies in both cases and controls (0.5% vs 0.2%; OR: ~3), whilst a significant association was also reported for African ancestry cases and controls (0.48% vs 0.3%; OR: ~2) [30].

The importance of identifying DNA repair gene mutation carriers is becoming increasingly evident in the era of precision medicine and targeted therapies [31]. Currently, germline testing of PrCa patients is recommended only for metastatic disease or a family history suggestive of hereditary PrCa, with *BRCA2* considered a priority gene to screen for in all settings. *ATM* sequencing is considered for informing clinical trial eligibility or active surveillance decisions, and for screening of healthy men in high-risk PrCa families [32]. *BRCA1/2* mutation carriers with breast, ovarian, and other cancer types have been shown to benefit from PARP inhibitor treatment in clinical trial studies [33,34], whilst initial studies in metastatic castrate-resistant PrCa patients, which included *ATM* mutation carriers (some with missense variants), have demonstrated evidence that a significant proportion of these patients also responded favourably to this treatment [19,35]. A recent report has also found that for men with localised PrCa, rates of germline pathogenic *ATM* mutations were significantly enriched in cases with Gleason score >7 tumours compared with the rates in cases with Gleason score 6 tumours [36]. In conjunction with our findings that men with PrCa are at substantially higher risk of harbouring germline *ATM* mutations and that these men are possibly also at increased risk of younger-onset and more aggressive clinical presentation, this suggests that larger clinical trials may be warranted to further clarify which patients would benefit from targeted screening and personalised treatments, in addition to whether *ATM* mutation carriers with localised or locally advanced PrCa may also benefit from earlier treatment with PARP inhibitors, prior to progression to incurable metastatic castrate-resistant disease spread. Opposing evidence has also been reported with respect to the effectiveness and toxicity of radiotherapy in individuals with *ATM* sequence variants. In PrCa patients, *ATM* sequence variants have previously been implicated in a greater likelihood of adverse responses to radiotherapy [37–39], although an enhanced response to radiotherapy with no apparent increase in toxicity has also been reported for patients with pathogenic *ATM* mutations [40]. In the context

of breast cancer, there is also conflicting evidence around the role of pathogenic *ATM* variants on the effectiveness of radiation therapy [41]. The implications regarding the use of radiotherapy in PrCa patients who are carriers of germline *ATM* mutations would therefore warrant further investigation.

To our knowledge, this analysis represents the largest *ATM* sequencing study to estimate PrCa risk in men of European ancestry to date. Despite our large sample size, *ATM* carrier numbers remained relatively modest, especially within individual study groups. As the frequency of each single variant was low, we could not make direct conclusions in relation to the specific effect of individual variants on overall PrCa risk or clinical subtypes of the disease. It is also important to note that each study group recruited men according to different criteria, some enriching for aggressive or younger age at diagnosis disease, in addition to using different sequencing technologies and analysis pipelines. For this reason, whilst analyses showed that, in aggregate, *ATM* tier 1 variants, and to a lesser extent tier 2 variants, have a relatively large and significant association with PrCa predisposition, our overall estimates of association could potentially be inflated. In an attempt to discern and control for heterogeneity that may have been introduced by these differences, we performed a two-stage analysis, but due to small sample sizes within individual studies these analyses may still have been underpowered. We were also limited in our ability to detect differences in mutation prevalence between samples or study sites.

Conclusions

Our study provides strong support for *ATM* as a moderate penetrance PrCa risk gene for men of European ancestry. Men who had developed any form of PrCa had an approximately fourfold risk of carrying a protein truncating or likely pathogenic nontruncating germline *ATM* variant. There was evidence that men who carry a tier 1 mutation had a higher risk for early-onset disease. This result provides more robust OR estimates for use in genetic counselling of male carriers, and targeted screening studies will be needed to determine whether genetic-based PrCa screening identifies a higher number of younger patients. These results also provide further information for the selection of relevant therapeutic options for PrCa patients and the management of high-risk disease [32].

Author contributions: Zsafia Kote-Jarai 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.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.euo.2020.12.001>.

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