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Germline *BLM* mutations and metastatic prostate cancer

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Abstract

Background: Biallelic loss-of-function *BLM* mutations result in Bloom syndrome: a genetic disorder characterized by growth deficiencies, photosensitivity, and multiple cancer susceptibilities. There are conflicting reports about whether or not heterozygous *BLM* carriers are at a higher risk of various cancers. Without *BLM* protein functionality, there is evidence of increased sister chromatid exchange and chromosomal instability.

Methods: Metastatic prostate cancer patients (N = 796) underwent germline genetic testing as part of routine care at three academic centers. Patients with heterozygous *BLM* mutations were identified. Tumor tissue was analyzed for somatic alterations in those patients who had a germline pathogenic mutation. Control data using a population sample were extracted from the Genome Aggregation Database.

Results: Heterozygous *BLM* germline mutations in 5 of 796 patients (prevalence, 0.63%). All mutations were loss-of-function truncating alterations. None of the mutations were BLM^{Ash}. The control population (gnomAD) frequency of pathogenic or likely pathogenic *BLM* mutations was 0.18% (212 of 116 653). The relative risk (RR) of *BLM* mutations in metastatic prostate cancer patients was 3.4 (95% CI, 1.42-8.33; $P < .0062$) compared to gnomAD controls. Tumor DNA sequencing in the *BLM* carriers showed no evidence of somatic *BLM* mutations. Interestingly, 3 of 5 *BLM* germline carriers had bi-allelic *BRCA2* inactivation evident on tumor sequencing. One patient had both germline and somatic mutations in *BRCA2*. Excluding the patient with the germline *BRCA2* mutation (*BLM* prevalence, 4 of 796: 0.50%) still yielded a statistically significant finding vs the gnomAD controls (RR, 2.8; 95% CI, 1.02-7.39; $P < .04$).

Conclusion: Truncating *BLM* germline mutations occur at a higher frequency in patients with advanced prostate cancer as compared to control populations. Though no biallelic loss of *BLM* was no noted in cancers, a surprising number of the *BLM* germline heterozygotes had pathogenic *BRCA2* mutations in their tumor.

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Keywords

BLM; BRCA2; DNA-repair; germline testing; metastatic prostate cancer

1 | INTRODUCTION

The *BLM* gene encodes a RecQ DNA helicase involved in maintenance of genomic integrity and regulation of homologous recombination. In particular, this helicase participates in the unwinding of DNA in 3′-to-5′ direction and is involved with 5′ resection during DNA double-strand break repair. Without *BLM* protein functionality, there is an increase in sister chromatid exchange resulting in greater chromosomal instability.

Biallelic loss-of-function *BLM* mutations result in Bloom syndrome: a genetic disorder characterized by growth deficiencies, photosensitivity, and multiple cancer susceptibilities often developing at an early age.[1] The most frequent *BLM* mutation (c. 2281delATCTGAinsTAGATTC), also known as BLM^{Ash}, is a relatively common founder mutation found in the Ashkenazi Jewish population. There are conflicting reports about whether or not heterozygous *BLM* carriers are at a higher risk of various cancers, with most studies examining colorectal carcinoma risk.[2] Previous case-control studies have not found an association between *BLM* carrier status and prostate or ovarian cancer.[3] However, in prostate cancer, both a genome-wide haplotype association study in the Chinese population and a study of familial prostate cancer have preliminarily identified certain risk variants associated with the *BLM* gene.[4,5] Germline mutations in DNA-repair genes occur at higher incidence in metastatic prostate cancer patients[6]; however, the potential role of *BLM* in prostate cancer remains unknown. Herein we examined the potential significance of germline pathogenic *BLM* mutations in prostate cancer patients.

2 | MATERIALS AND METHODS

A total of 796 metastatic prostate cancer patients underwent germline genetic testing as part of routine clinical care at 3 academic centers. Patients with heterozygous *BLM* mutations were identified from Tulane Cancer Center (TCC), Johns Hopkins (JH), and University of Washington (UW). The clinical testing was performed through commercial germline testing (Invitae), the UW-BROCA panel, or whole-exome sequencing. Tumor tissue was also analyzed for somatic alterations in those patients who had a germline pathogenic mutation. Control data using a population sample were extracted from the Genome Aggregation Database (gnomad.broadinstitute.org).

3 | RESULTS

Of the 796 prostate cancer patients interrogated, 5 heterozygous *BLM* germline mutations (prevalence, 0.63%) were identified; 2 of 295 TCC patients, 2 of 172 JH patients, and 1 of 302 UW patients (see Table 1). All mutations were loss-of-function truncating alterations (see Table 2). None of the mutations were BLM^{Ash}. The control population (gnomAD) frequency of pathogenic or likely pathogenic *BLM* mutations was much lower at 0.18% (212 of 116 653). The relative risk (RR) of *BLM* mutations in metastatic prostate cancer

patients was 3.4 (95% CI, 1.42-8.33; $P < .0062$) compared to gnomAD controls. Tumor DNA sequencing in all 5 *BLM* carriers showed no evidence of "second hit" somatic *BLM* mutations. Interestingly, 3 of 5 *BLM* carriers on tumor sequencing had bi-allelic *BRCA2* inactivation; one of these patients had both germline and somatic mutations in *BRCA2*. Excluding the patient with the germline *BRCA2* mutation (*BLM* prevalence, 4 of 796: 0.50%) still yielded a statistically significant finding when comparing prostate cancer patients with *BLM* mutations vs the gnomAD controls (RR, 2.8; 95% CI, 1.02-7.39; $P < 0.04$).

4 | DISCUSSION

In conclusion, pathogenic germline *BLM* mutations may influence risk of developing metastatic prostate cancer as evidenced by the increased frequency of *BLM* pathogenic mutations in these analyses. Though these findings are intriguing, the frequency of germline *BLM* alterations in prostate cancer patients should be validated and assessed in a larger study population. The concurrent somatic *BRCA2* inactivation found in a subset of prostatic tumors is notable, and may suggest a cancer-specific interaction between these two genes known to be involved in homologous recombination.

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TABLE 1

BLM mutation carriers

Patient	Site	Age at diagnosis	Race	Gleason score	Time between diagnosis and metastatic disease	Family history
1	JH	59	Caucasian	5 + 4	5 mo	Mother with breast cancer, and brother with Hodgkin lymphoma
2	JH	68	Caucasian	4 + 4	At diagnosis	Father with colorectal cancer
3	TCC	62	Caucasian	4 + 3	Undetermined	Mother with breast and skin cancer, and brother with skin cancer
4	TCC	63	Caucasian	4 + 3	At diagnosis	Father with prostate and lung cancer, and grandfather with prostate cancer
5	UW	63	Caucasian	4 + 4	11 y	Mother and grandmother with colon cancer

Note: Clinical characteristics and family history for *BLM* mutation carriers.

Abbreviations: JH, Johns Hopkins; TCC, Tulane Cancer Center; UW, University of Washington.

TABLE 2

BLM alterations detected in five prostate cancer patients

Patient	Site	Position	Reference allele	Variant allele	Gene	Protein change	Annotation	Concurrent *BRCA2* (somatic)
1	JH	chr15:91290721	G	A	*BLM*	splicing	NM_000057, c.98 + 1 G > A	Yes[a]
2	JH	chr15:91337589	-	T	*BLM*	splicing	NM_000057.3, c.3210 + 2delT	Yes
3	TCC	chr15:91310196	-	AAAT	*BLM*	p.L751Kfs*25	NM_000057, c.2250_2251insAAAT	No
4	TCC	chr15:91337405	G	-	*BLM*	p.D1010Mfs*24	NM_000057, c.3028del	No
5	UW	chr15:91310151	ATCTGA	TAGATTC	*BLM*	p.Y736Lfs*5	NM_000057.2, c.2207_2212delATCTGAinsTAGATTC	Yes

Abbreviations: JH, Johns Hopkins; TCC, Tulane Cancer Center; UW, University of Washington.

[a]Patient 1 has both germline and somatic BRCA2 variants.