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European Association of Urology

Brief Correspondence

Germline DNA Repair Gene Mutation Landscape in Chinese Prostate Cancer Patients

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Article info

Article history:
Accepted June 10, 2019

Associate Editor:
James Catto

Statistical Editor:
Andrew Vickers

Keywords:
Germline mutation
DNA repair genes
Chinese population
Prostate cancer

Abstract

Genetic testing for prostate cancer (PCa) patients is in constant development. Specific genetic alterations indicate personalized managing strategies, requiring clinicians to refer appropriate patients for genetic testing. However, our understanding of genetic epidemiology of PCa is mainly based on data from Caucasian populations. In addition, there is evidence that alterations in DNA repair genes (DRGs) may be ethnic specific in other cancers such as breast cancer. Thus, whether Caucasian-based genetic information can be used to guide clinical practice in Chinese population remains unknown. Aiming to clarify the landscape of germline DRG mutation in Chinese patients with PCa, we sequenced 316 patients for 18 DRGs. Among all cases, 9.8% (31/316, 95% confidence interval [CI]: 6.5–13%) carried pathogenic mutations in 18 PCa-related DRGs: 6.3% in *BRCA2*, 0.63% in *BRCA1*, 0.63% in *ATM*, and 2.5% in 15 other genes. Overall, we observed similar germline DRG mutation frequencies, although there is large disparity in the risk of PCa between China and the West. Our study called for a comprehensive analysis in detailed mutation spectra to refine management strategies further, given the ethnic diversity.

Patient summary: We sequenced germline pathogenic mutations in 18 DNA repair genes in 316 patients and elucidated the mutation landscape of Chinese prostate cancer (PCa) patients. Our study confirmed the necessity of genetic testing in Chinese PCa and called for a comprehensive analysis in detailed mutation spectra to refine management strategies further, given the ethnic diversity.

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Prostate cancer (PCa) is recognized as one of the most heritable cancers [1]. Recently, DNA repair deficiency has emerged as a potential driver of PCa. Compared with the general population, the risk of PCa is estimated to be 1.8–3.75- or 2.5–8.6-fold higher for carriers with germline *BRCA1* or *BRCA2* mutations, respectively [2,3]. Moreover, the frequency of germline mutation (12%) of DNA repair genes (DRGs) in men with metastatic PCa is higher than that in the general population [4]. Owing to the high proportion of germline mutation carriers, a guideline for genetic testing was established. The National Comprehensive Cancer Network (NCCN) Prostate Cancer guideline (version 1.

https://doi.org/10.1016/j.eururo.2019.06.004
0302-2838/

2019) proposed germline genetic testing of DRGs, which include *BRCA2, BRCA1*, *ATM*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, in men with PCa ranging from high-risk to metastatic disease, regardless of family history.

Despite this important advance in patient management, our understanding of PCa genetic epidemiology is mainly based on data from Caucasian population of Europe and North America, with limited data from other ethnicities. Germline DRG mutation data in Chinese PCa patients are sparse. There is large disparity in PCa incidence and mortality between China and Western countries. The estimated incidence and mortality of PCa in China are 9.1 and 4.7 per 100 000, whereas in America the incidence and mortality of PCa are 75.7 and 7.7, respectively, according to data from GLOBOCAN 2018 [5,6]. Differences in genetic background along with environmental factors and clinical practice patterns may play essential roles in such disparity, but the exact extent of the contribution of genetic factors is unknown. Notably, prostate-specific antigen (PSA) screening significantly affects the percentage of metastatic PCa (5.0% in the USA vs 30% in China) at initial diagnosis [7]. Thus, it is plausible that screening may affect the incidence of detection of germline mutation. Of importance, evidence from breast cancer suggests that germline alterations in DRGs can be ethnic specific [8]. Considering the large differences in the disease spectrum between Chinese and Western populations, as well as evidence of ethnic specificity, whether the NCCN guideline for genetic testing also applies to the Chinese population remains unclear. Thus, the germline DRG mutation landscape of Chinese PCa patients needs to be elucidated.

To explore the germline mutation spectrum of DRGs in Chinese PCa cases, we retrospectively analyzed 316 patients undergoing genetic testing for DRGs, including 187 metastatic cases, 30 regional lymph node metastatic cases, 74 high- to very-high-risk cases, and 25 low–intermediate patients. The risk status was categorized according to the NCCN risk criteria. Detailed enrollment criteria are described in the Supplementary material. We performed germline testing, focusing on 18 DRGs related to treatment implications and predisposition to PCa: *ATM, ATR, BRCA1, BRCA2, BRIP1, CHEK2*, *FAM175A, FANCA, GEN1, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C*, and *RAD51D*. We used a refined classification system to filter pathogenic germline mutations according to the American College of Medical Genetics and Genomics (ACMG) guideline [9]. Detailed definition of pathogenicity is summarized in the Supplementary material.

Pathogenic variants were identified in 31 of 316 (9.8%, 95% confidence interval [CI]: 6.5–13%) patients, and one man had mutations in two genes. The 32 pathogenic mutations occurred in eight different genes, including *BRCA2* (20/32, 63% of total mutations), *BRCA1* (2/32, 6.3%), *ATM* (2/32, 6.3%), *GEN1* (2/32, 6.3%), *MSH6* (2/32, 6.3%), *MSH2* (2/32, 6.3%), *CHEK2* (1/32, 3.1%), and *FANCA* (1/32, 3.1%; Fig. 1A). Pathogenic variants were found in 12% (22/187) of metastatic cases, compared with 10% (3/30) in those with regional disease and 8.1% (6/74) in high-risk localized cases (Table 1). We found no statistically significant association between pathogenicity carrier status and age of onset, family cancer history, Gleason score, or PSA value at diagnosis (Table 1).

To determine the similarity and difference of mutation landscape in DRGs between Chinese and American populations, we compared mutation frequency in metastatic cases between our cohort and the cohort by Pritchard et al. [4] (Fig. 1B). Mutation frequencies in metastatic cases were similar between the two cohorts (12% vs 12%). Of note, only 14% (98/692) cases in the American cohort were older than 70 yr, while the proportion was 29% (55/187) in our cohort ($p < 0.001$). Next, we compared gene mutations in high-risk localized PCa patients between our cohort and the Cancer Genome Atlas (TCGA) data (Fig. 1C) [4]. Of the 337 men with high-risk localized disease in TCGA, 19 (5.6%) had deleterious germline DRG mutations. Similar results were achieved in our cohort (8.1%, $p = 0.4$). Our findings were consistent with the recent study published by Nicolosi et al. [10], which identified the frequency and distribution of germline variants in a multiethnic series of PCa patients, showing similar mutation prevalence between Asians (15%) and Whites (18%). The higher mutation frequencies in the Nicolosi et al's [10] study (17%) in comparison with the Pritchard et al's study [4] (12%), however, can be attributed to different definitions of pathogenicity used in the two studies (Sherloc criteria and ACMG criteria, respectively). Recognizing the potential importance of detecting variants of unknown significance (VUSs) [11], we analyzed VUSs in our cohort and reported the data in the Supplementary material.

Despite a similar prevalence of pathogenic mutations in DRGs between our cohort and the US cohort [4], a comparison of the distribution of specific DRG variants requires more work. *BRCA2* mutations are the most frequently mutated gene in both cohorts. Additionally, there are several genes in which mutations were found at low levels in the American cohorts, which were not observed in our cohort, such as *ATR*, *BRIP1*, and *FAM175A*. Undoubtedly, more patients and a larger panel are needed to evaluate a particular gene individually.

To our knowledge, our cohort is the largest Chinese PCa cohort reported to date for the purpose of elucidating the germline DRG mutation landscape. Importantly, for the first time, we show that in a population with a low PCa incidence and without widespread PSA screening, frequencies of germline DRG mutations in stratified risk groups were similar to those in Caucasian populations. Genome-wide association studies have identified approximately 100 common genetic variants associated with PCa risk. However, less than a dozen of these variants could be validated in Asian population [12]. Unlike the vast differences in common variants, our results showed that rare but high penetrance germline mutations with clinical implications demonstrated more similarities between Chinese and American patients. Intriguingly, African Americans with higher PCa incidence and mortality rates had a significantly lower germline DRG mutation prevalence according to a recent study (10% vs 18%) [10]. This fact highlights the

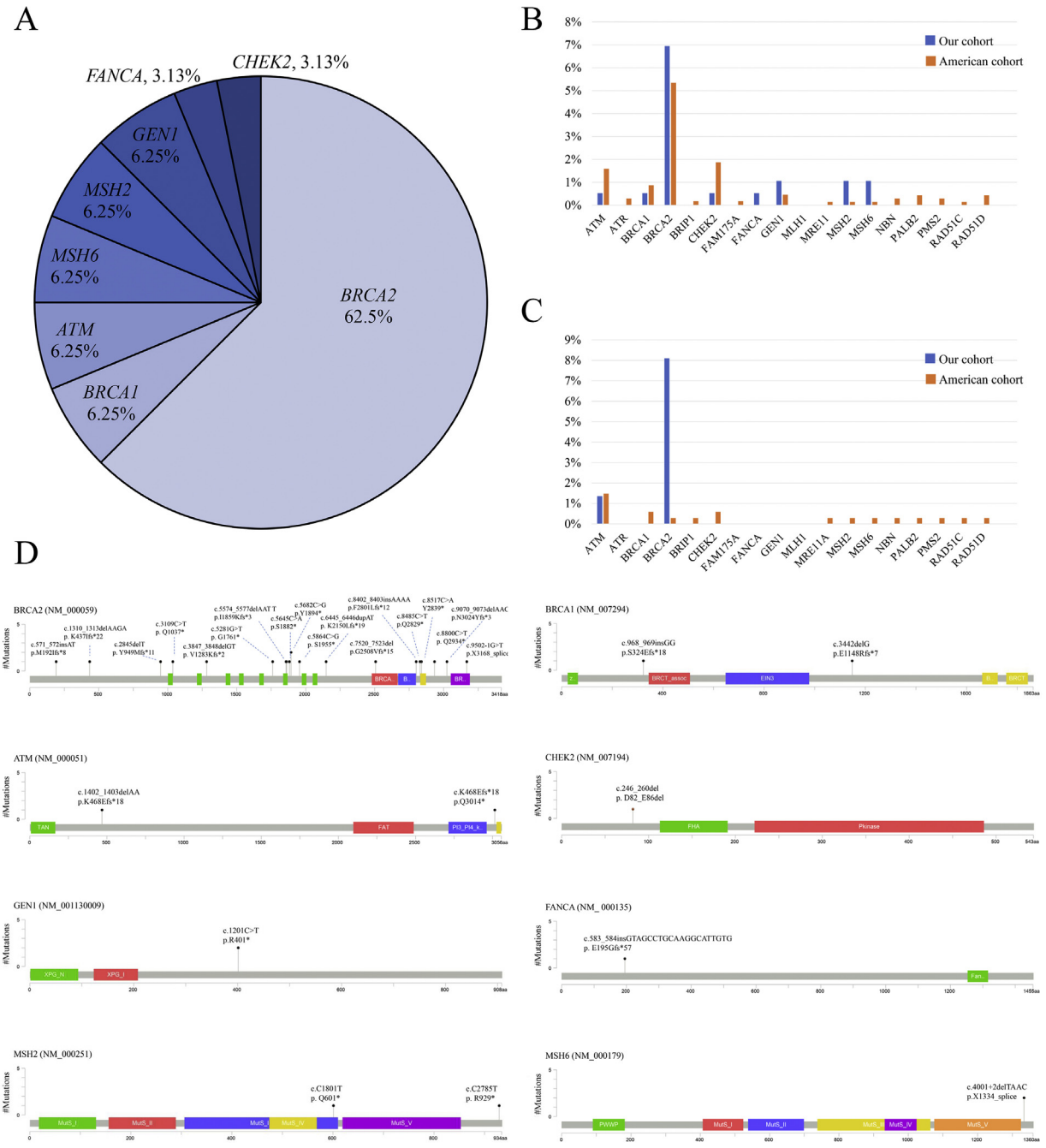

Fig. 1 – DRG mutation spectrum in our cohort. (A) Distribution of pathogenic germline mutations that occurred in eight genes, and the remaining 10 genes did not have any pathogenic mutations. (B) Comparison of pathogenic mutation frequency in patients with metastatic prostate cancer between our cohort and the American cohort. (C) Comparison of pathogenic mutation frequency in patients with high- to very-high-risk prostate cancer between our cohort and the American cohort. (D) Locations of pathogenic germline mutations in DRGs. Each mutation identified is shown by a lollipop plot. DRGs = DNA repair genes.

complexity of prostate carcinogenesis and emphasizes the importance of performing ethnicity-based studies [13,14].

Our study has several limitations. First, we chose 18 frequently mutated DRGs instead of all DRGs. This may cause omission of important findings. Furthermore, we refrained from performing a comprehensive analysis of the specific gene mutations due to a low frequency of each specific mutated gene. Finally, the retrospective design may lead to a selection bias, although all patients receiving genetic testing were included in the study.

In conclusion, our results elucidated the germline mutation landscape of DRGs in Chinese PCa patients. The observation of similar germline mutation rates between Chinese and Western PCa patients is interesting given a

Table 1 – Clinical characteristics of patients with prostate cancer

	Carrier	Noncarrier	*p* value
Total number	31	285	
Median Age at diagnosis, yr (IQR)	60 (54–67)	64 (57–70)	0.3
Gleason grade group			0.4
1	0.0% (0/31)	4.6% (13/285)	
2	3.0% (1/31)	8.4% (24/285)	
3	13% (4/31)	12% (34/285)	
4	19% (6/31)	28% (80/285)	
5	65% (20/31)	46% (130/285)	
Unknown	0.0% (0/31)	1.0% (4/285)	
Median baseline PSA, ng/ml (IQR)	100 (42–150)	56 (17–132)	0.13
Family history of cancers, *N* (%)	39% (12/31)	26% (74/285)	0.14
Risk group, *N* (%)			0.3
Low-intermediate[a]	0.0% (0/31)	9.0% (25/285)	
High to very high[b]	19% (6/31)	24% (68/285)	
Regional[c]	10% (3/31)	9.0% (27/285)	
Metastatic[d]	71% (22/31)	58% (165/285)	

PSA = prostate-specific antigen; IQR = interquartile range.
Risk group is categorized according to the NCCN guideline risk criteria.
[a] T1-T2c AND Gleason score ≤7 and PSA ≤20 ng/ml.
[b] T3-T4 OR Gleason score ≥8 or PSA >20 ng/ml.
[c] Any T, N1, M0.
[d] Any T, any N, M1.

large difference in PCa risk. We suggested to comprehensively analyze germline mutational details among different ethnicities to refine prevention, diagnosis, and management strategies for PCa in the setting of ethnic diversity.

Author contributions: Yao Zhu 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: Zhu, Wu, Ye.
Acquisition of data: Wei, Wu, Gu, Qin.
Analysis and interpretation of data: Wei, Wu, Dai, Lin.
Drafting of the manuscript: Wei, Wu, Zhu.
Critical revision of the manuscript for important intellectual content: Zhu, Freedland, Ye.
Statistical analysis: Wei, Wu, Gan.
Obtaining funding: Zhu, Ye.
Administrative, technical, or material support: Ye, Zhu, Gan.
Supervision: Ye, Zhu.
Other: None.

Financial disclosures: Yao Zhu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** This study was supported by Shanghai Rising Star Program (grant no. 16QA1401100), Fudan University Shanghai Cancer Center Fund (grant no. YJJQ201802), and Shanghai "Rising Stars of Medical Talent" Youth Development Program.

Acknowledgments: We wish to thank Professor Jun Luo for his kind review and suggestions to this work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.06.004.

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