Dear Editor,

Germline deleterious alterations interrupting the function of DNA damage repair (DDR) have proven to be related to a high risk of prostate cancer (PCa), which are recommended for testing in general practice. Moreover, the genetic background has recently emerged as a potential factor in racial diversity, especially in the epidemiology of PCa. Since our understanding of the genomics was mostly derived from the Caucasian population, we conducted a real-world multicenter retrospective study of 490 patients with PCa across distinct clinical states in order to better elucidate the prevalence and clinical implication of rare germline deleterious alterations in Chinese men.

A total of 490 patients with PCa, including 181 patients with localized PCa, 156 patients with metastatic hormone-sensitive PCa, 147 patients with metastatic castration-resistant PCa, and 6 patients with neuroendocrine-differentiated PCa, were included in the present study (Figure 1A and Table 1). To explore the landscape of germline deleterious alterations, targeted gene sequencing of 50 genes covering DDR pathway genes and HOXB13 was performed. In addition, concurrent HSD3BI genotypes were detected in 348 patients. Detailed sequencing and bioinformatics are summarized in Supplementary Methods.

Although the distinctiveness in genetic background might play an essential role in the ethnic disparity in the same disease, the similar prevalence of germline deleterious alterations in DDR pathway genes between the Chinese and American populations has been reported a prior single-center study. However, due to its relatively small sample size and limited detected genes, the ethnic differences in the germline genomes still remain to be further elucidated. To better determine the inter-racial heterogeneity in the genomics, we compared the incidence of germline DDR pathway gene alterations in our cohort with the unselected cohort by Nicolosi et al. study. (Figure 1C). Germline deleterious alterations in PALB2, interrupting the recombinational repair and the tumor suppression function, were associated with increased risk of various malignancies. However, the molecular pattern of germline PALB2 alteration and its prognostic value need to be further elucidated. Similar to PALB2, CHEK2 plays an important role in DDR and germline deleterious alterations in CHEK2 may lead to the carcinogenesis of normal prostate cell. Further studies need to be conducted in a larger Chinese population to characterize possible alteration-specific risks of CHEK2 due to its low incidence.

Furthermore, a notable distinction of our cohort was the absence of HOXB13 p.G84E mutation compared to 0.9% in the cohort by Nicolosi et al. study (p = 0.02) (Figure 1C). HOXB13 plays essential roles in prostate-lineage differentiation and tumorigenesis, which is recommended for family counseling. Specially, the missense mutation G84E in the Caucasian populations has been identified to be strongly associated with increased PCa susceptibility, early onset, and aggressive disease. However, we failed to detect G84E in any of the 490 studied patients, instead, we found other four mutation sites, including G135E. The locations of germline deleterious alterations in the five most frequently altered genes are shown in Figure 2A. Since the recurrent mutation G135E was a founder mutation in a Chinese cohort, our results provided substantial support...
to the fact that HOXB13 p.G135E may be a prominent signature in the Chinese population. Although few PCa risk-associated rare mutations in HOXB13 have been identified to date, it is expected that additional mutations, such as G135E, will be found in ongoing studies in order to better understand the genetic mechanism underlying PCa.

Additionally, concurrent HSD3B1 genotype was detected in 348 (71.0%) of the 490 studied patients. To our knowledge, it was the first time to report the genotype of HSD3B1 in the Chinese population. We compared the alteration frequencies of HSD3B1 with the cohort by Hearn et al. study, surprisingly finding a relatively lower incidence of HSD3B1 c.1245C > A alteration, especially homozygous HSD3B1 (1245CC) alteration (0.8% in our cohort vs. 7.4% in the cohort by Hearn et al. study, p < 0.001) (Figure 1D). HSD3B1 is responsible for the transformation of steroidal precursors into potent androgens. In addition, HSD3B1 c.1245A > C was associated with rapid resistance to androgen deprivation therapy but was sensitive to abiraterone. The rare homozygous alteration of HSD3B1 in our cohort was also of interest, which might partly interpret the distinct efficacy of conventional hormonal therapy in the Asian population.  

Next, we examined the predictive value of germline deleterious alterations in DDR pathway genes. Our results suggested that the germline status of DDR pathway genes was associated with severe disease phenotype and shorter time to castration resistance (18.0 months in the gDDR altered group vs. 23.0 months in the gDDR wild-type group, p < 0.001) (Figure 2B). Specifically, patients harboring deleterious germline BRCA2 mutation has emerged as a distinct subset with inferior outcomes (15.5 months in the gBRCA2 altered group vs. 22.0 months in the gBRCA2 wild-type group, p = 0.0059) (Figure 2C). Nevertheless, recent evidence suggested that those patients harboring germline DDR defect could experience superior clinical outcomes from poly (ADP-ribose) polymerase inhibitors or platinum-combined chemotherapy. Thus, we inferred that the patients with metastatic PCa harboring germline deleterious alterations in DDR pathway genes might
TABLE 1  Clinical characteristics of the 490 studied patients

| Clinical characteristics at onset time | Overall (n = 490) | gDDR altered (n = 81) | gDDR wild-type (n = 409) | p value |
|----------------------------------------|-------------------|-----------------------|--------------------------|--------|
| Median age (IQR), year                 | 67 (62-72)        | 66 (61-71)            | 68 (63-72)               | 0.0830 |
| PSA, n (%)                             |                   |                       |                          |        |
| 0-20 ng/ml                             | 166 (33.9)        | 17 (20.1)             | 149 (36.3)               | 0.0075 |
| 20-100 ng/ml                           | 139 (28.4)        | 22 (27.2)             | 117 (28.7)               |        |
| > 100 mg/ml                            | 185 (37.8)        | 42 (51.9)             | 143 (35.1)               |        |
| Gleason score, n (%)                   |                   |                       |                          | 0.0095 |
| 6                                      | 22 (4.5)          | 1 (1.2)               | 21 (5.1)                 |        |
| 7                                      | 137 (28.0)        | 12 (14.8)             | 125 (30.6)               |        |
| 8                                      | 158 (32.2)        | 27 (33.3)             | 131 (32.0)               |        |
| 9                                      | 136 (27.8)        | 32 (39.5)             | 104 (25.4)               |        |
| 10                                     | 31 (6.3)          | 7 (8.6)               | 24 (5.9)                 |        |
| Neuroendocrine                          |                   |                       |                          |        |
| Metastasis, n (%)                      |                   |                       |                          | 0.0149 |
| Nonmetastasis                          | 237 (48.4)        | 29 (35.8)             | 208 (50.9)               |        |
| With metastasis                        | 253 (51.6)        | 52 (64.2)             | 201 (49.1)               |        |
| Lymph node                              | 32                | 6                     | 26                       |        |
| Bone                                    | 215               | 44                    | 171                      |        |
| Visceral                                | 6                 | 2                     | 4                        |        |
| Family history of malignant tumors, n (%)| 36 (7.3)         | 6 (7.4)               | 30 (7.3)                 | >0.9999|

benefit more from intensive combination therapy, instead of androgen deprivation therapy alone.

In conclusion, we investigated the genomic landscape of rare germline alterations in the Chinese population and highlighted the prognostic value of germline DDR status in general practice. Comparative analysis of the genomic data from our cohort and Caucasian cohorts revealed the interracial diversity in genetic background, suggesting that PALB2 might be an underlying genomic signature in Chinese population. Especially, the frequency and unique pattern of HOXB13 p.G135E and HSD3B1 c.1245A > C were unique in the Chinese population. In brief, further investigations by incorporating the genetic background might be helpful to understand the racial diversity and establish therapeutic interventions.

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Xiaochen Fei1,*
Liancheng Fan1,*
Wei Chen1,*
Wei Chen3
Yiming Gong1
Xinxing Du1
Yanqing Wang1
Yinjie Zhu1
Jiahua Pan1
Fangqin Wang4
Wanbing Zhao4
Tongtong Liu4
Yining Yang4
Baijun Dong1
Wei Xue1

1 Department of Urology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
FIGURE 2  The locations of germline deleterious alterations in the five most frequently altered genes and the association between rare germline deleterious alterations and the time to castration resistance among the patients with metastatic castration-resistant PCa. (A) Locations of germline deleterious alterations and domains in proteins encoded by the five frequently altered genes are shown by lollipop structures. Protein domains are shown by different colors. On the graph of each gene, the x axis reflects the number of amino acid residues, and the y axis represents the total number of identified germline deleterious alterations. (B) Kaplan–Meier curves for time to castration resistance in patients with germline DDR alteration and germline DDR wild-type. (C) Kaplan–Meier curves for time to castration resistance in patients with germline BRCA2 alteration and germline BRCA2 wild-type

REFERENCES

1. Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17:479-505.
2. Zhu Y, Mo M, Wei Y, et al. Epidemiology and genomics of prostate cancer in Asian men. Nat Rev Urol. 2021;18:282-301.
3. Wei Y, Wu J, Gu W, et al. Germline DNA repair gene mutation landscape in Chinese prostate cancer patients. Eur Urol. 2019;76:280-283.
4. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol. 2019;5:523-528.
5. Yang X, Leslie G, Doroszuk A, et al. Cancer risks associated with germline PALB2 pathogenic variants: an international study of 524 families. J Clin Oncol. 2020;38:674-685.
6. Dong X, Wang L, Taniguchi K, et al. Mutations in CHEK2 associated with prostate cancer risk. Am J Hum Genet. 2003;72:270-280.
7. Li B, Huang Q, Wei GH. The role of HOX transcription factors in cancer predisposition and progression. Cancers (Basel). 2019; 11(4):528.

8. Lin X, Qu L, Chen Z, et al. A novel germline mutation in HOXB13 is associated with prostate cancer risk in Chinese men. Prostate. 2013;73:169-175.

9. Hearn JWD, AbuAli G, Reichard CA, et al. HSD3B1 and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study. Lancet Oncol. 2016;17:1435-1444.

10. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382:2091-2102.

**SUPPORTING INFORMATION**

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