available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Daniel A. Leongamornlert, Edward J. Saunders, Sarah Wakerell, et al., Germline DNA Repair Gene Mutations in Young-onset Prostate Cancer Cases in the UK: Evidence for a More Extensive Genetic Panel. Eur Urol 2019;76:329–37

Germline pathogenic gene mutations, including many within DNA repair genes (DRGs) such as *BRCA2*, *ATM*, *BRCA1*, and *CHEK2*, have been reported as being associated with prostate cancer (PC) risk, aggressiveness, prognosis, and treatment responses [1–3]. As a result, the National Comprehensive Cancer Network (NCCN) guidelines for early PC detection now recommend germline testing [4]. Several commercial companies currently offer germline tests with ~14 gene panels, including the four genes mentioned above, other DRGs, and *HOXB13*. However, with few exceptions, statistical evidence for most of the genes tested is lacking, largely because of low statistical power owing to the rarity of mutation carriers. This mixed evidence has created confusion among urologists as to which genes should be considered for clinical decision-making.

The paper by Leongamornlert and colleagues [5] attempted to address the confusion. By sequencing 164 DRGs for 1281 early-onset PC cases and 1160 controls and using a sophisticated ADA (adaptive combination of *p* values) statistical method, they discovered a set of 20 DRGs associated with PC susceptibility. They concluded, as reflected in the article title, that this was "evidence for a more extensive genetic panel". However, we believe that the ADA analysis is valid only to "nominate" candidate gene set for further validation, and does not provide "evidence" of its validity.

The ADA approach in essence selected all genes with higher numbers of protein truncating variants (PTVs) among cases compared to controls in the study population. It guarantees the identification of a best-performance gene set (higher frequency of PTVs among cases compared to controls) from the 164 DRGs even if none is truly associated with PC risk. The problem with this approach is also exemplified in the remaining genes, for which a converse trend is expected. This is confirmed by our reanalysis based on their data in Fig. 2A [5]. The frequency of PTVs for the remaining 144 DRGs was significantly lower among cases (6.5%) than among controls (9.1%; odds ratio [OR] 0.69; $p = 0.01$). It is apparent that we would not conclude that PTVs in the remaining DRGs are protective.

A more objective approach to test whether additional DRGs are involved in PC susceptibility is to exclude known PC risk-associated DRGs and compare the carrier rate of PTVs for the remaining DRGs as a group between cases and controls. For example, when we excluded the four commonly implicated DRGs for PC (*BRCA2*, *ATM*, *BRCA1*, and *CHEK2*), the carrier rate of PTVs for the remaining 160 DRGs was similar among cases (11.3%) and controls (10.6%; OR 1.08; $p = 0.57$). This suggests a lack of evidence that remaining DRGs, as a group, affect PC susceptibility. However, it is recognized that most studies, including the study by Leongamornlert et al., do not have statistical power to exclude the possibility that some individual DRGs affect PC risk.

It is important to distinguish three distinct purposes of germline testing for PC: to predict risk for men without a diagnosis of PC; to predict prognosis for patients with newly diagnosed PC; and to predict treatment responses for men with late-stage PC. Different purposes of germline testing may require different sets of genes. Efforts should be devoted to obtain evidence for the respective gene sets.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–53.
[2] Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2017;71:740–7.
[3] Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–708.
[4] Carroll PH, Mohler JL. NCCN guidelines updates: prostate cancer and prostate cancer early detection. J Natl Compr Cancer Netw 2018;16:620–3.
[5] Leongamornlert DA, Saunders EJ, Wakerell S, et al. Germline DNA repair gene mutations in young-onset prostate cancer cases in the

DOI of original article: https://doi.org/10.1016/j.eururo.2019.06.012.
https://doi.org/10.1016/j.eururo.2019.06.013

UK: evidence for a more extensive genetic panel. Eur Urol 2019;76:329–37.

Xiaoling Lin[a]
Brian T. Helfand[b]
Jianfeng Xu[a,b,*]

[a]*Fudan Institute of Urology, Huashan Hospital, Fudan University, Shanghai, PR China*

[b]*Program for Personalized Cancer Care, NorthShore University Health System, Evanston, IL, USA*

[*]Corresponding author. Program for Personalized Cancer Care, NorthShore University Health System, 1001 University Place, Evanston, IL 60201, USA.
E-mail address: jxu@northshore.org (J. Xu).

June 12, 2019