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Expanding Role of Germline DNA Repair Alterations in Prostate Cancer Risk and Early Onset

Karen E. Knudsen [a,*], ***Felix Y. Feng*** [b]

[a] *Departments of Cancer Biology, Urology, Radiation Oncology, and Medical Oncology and Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA;* [b] *Departments of Radiation Oncology, Urology, and Medicine and Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San Francisco, CA, USA*

Prostate cancer (PC) remains a major worldwide health burden, accounting for more than 300 000 deaths per year. While it has long been appreciated that heritable genetic factors contribute to PC risk, factors underlying early-onset disease remain less well defined. The study by Leongamornlert et al. [1] in this issue of *European Urology* extends recent findings implicating germline mutations in DNA repair genes associated with PC predisposition [2–4] and sheds new light on the genetics of the risk of early onset.

In brief, a targeted panel of 167 DNA repair and eight additional candidate PC risk genes derived from a literature review was assessed in a UK-based cohort of 1281 early-onset cases (defined as diagnosed at or before 60 yr of age) and 1160 selected controls. It should be noted that while the cohort of DNA repair genes was exhaustive, one major DNA repair gene previously linked to aggressive prostate cancer (*PRKDC*, which encodes the catalytic subunit of DNAPK [5]) was streamlined from analyses because of technical difficulty. For the remaining DNA repair and candidate genes, two endpoints were considered: (1) incidence in cases versus controls; and (2) association with "aggressive" disease, defined as Gleason grade $\geq$8.

Gene-level SKAT-O analyses were initially used to identify germline alterations associated with risk. Analyses were restricted to genes with two or more tier 1 or tier 2 variants; these analyses identified alterations in two genes associated with PC predisposition (*HOXB13* and *POLL*) and two associated with Gleason $\geq$8 disease (*NBN* and *XPC*). These provocative findings add to the current set of risk alleles that have been recommended for panel testing [6], which include *HOXB13* and *NBN* but lack recommendations for *XPC* and *POLL*. Functionally, *HOXB13* encodes a transcription factor that has a major role in controlling androgen receptor (AR) activity, among other effects [7]. As it has been shown that AR regulates the expression of double-strand DNA-break repair factors [8,9], the contribution of these or other activities of *HOXB13* in modifying early-onset PC predisposition will be an important area of study. *POLL* encodes DNA polymerase lambda and plays a role in multiple DNA repair processes, including nonhomologous end joining [10]. *NBN* encodes a key component of the MRN complex (MRE11-RAD50-NBN), which plays complex roles in double-strand DNA-break repair, telomere maintenance, DNA recombination, and cell-cycle checkpoint control. It is of interest that *NBN* is the only gene component in the complex that was significantly associated with PC risk, thus raising the question as to how observed *NBN*-specific alternations influence MRN-dependent genomic integrity. Finally, the DNA repair factor XPC plays very different roles that are integral to global genome nucleotide excision repair, in which XPC senses DNA damage and is the DNA-binding component of the overall XPC complex [11]. These collective findings reveal that perturbations in a wide spectrum of DNA repair processes probably contribute to early-onset PC.

Additional gene discovery analyses used ADA to identify candidate gene sets rather than individual variants. In these analyses, 233 unique protein-truncating variants (PTVs) with a minor allele frequency of <0.5% were identified in 97 genes, of which 57 PTVs arose in a discrete set of

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* Corresponding author. Department of Cancer Biology, Thomas Jefferson University, 233 South 10th Street, Philadelphia, PA 19107, USA.
Tel. +1 215 5038574; Fax: +1 215 5030622.
E-mail addresses: karen.knudsen@jefferson.edu, elizabeth.schade@jefferson.edu (K.E. Knudsen).

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15 genes. Of these, the greatest enrichment was observed for five genes previously identified as associated with PC risk (*ATM*, *BRCA1*, *BRCA2*, *CHEK1*, and *GEN1*) [1], which suggests that alterations in these factors play a broad role in PC risk, irrespective of the age of onset. From the PTVs, analyses at the gene-set level identified 20 genes associated with higher risk of PC predisposition (*BRCA1*, *BRCA2*, *ATM*, *CHEK 2*, *MSH2*, *GEN1*, *RNASEL*, *BLM*, *CDC25C*, *ERCC3*, *LIG4*, *MSH5*, *NEIL2*, *NHEJ1*, *PARP2*, *POLD1*, *POLE*, *POLM*, *RECQL4*, and *TDP1*) and four genes associated with both higher risk and aggressive disease (*BRCA2*, *CHEK2*, *MSH2*, and *ERCC2*), of which three overlapped with the disposition set, thus culminating in a proposed 23-gene panel that may provide information on the risk of early onset. It is hoped that future studies delving into the functional consequence of the PTVs will provide new insights into the molecular basis of early-onset predisposition and/or the risk of developing aggressive PC.

Although these exciting findings provide a major new insight into the genetics of young-onset PC and refinement of genetic testing panels, a number of additional considerations remain. In the study by Leongamornlert et al. [1], early onset was defined as $\leq$60 yr in a UK-based population. It would be of interest to determine whether the genetic panel can be further refined using a younger cohort (eg, $\leq$55 yr) and to assess how the panel performs in a cohort with greater diversity, including men of non-European descent. As the authors note, a caveat of the study is that the control cohort consisted of a screened population (with PSA of $<$0.5 ng/ml), thus providing a future opportunity for testing of the panel in an unscreened control-arm cohort. In addition, it is unclear whether these genetic alterations will predispose patients to specific PC subtypes, and whether they will have treatment implications. Furthermore, expanding the definition of aggressiveness to include later development of non-organ-confined disease may facilitate the capacity to refine the panel for genetic alterations associated with clinical progression in men with early-onset PC. Formal testing of these concepts and evaluation in larger prospective studies will aid in refining and defining the impact of the young-onset PC genetic risk panel.

Conflicts of interest: Karen E. Knudsen has received research support from Celgene and CellCentric and is a consultant for CellCentric, Sanofi, Atrin, Celgene, Janssen, and Genentech. Felix Y. Feng has nothing to disclose.

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