Editorial



# Another step in understanding the genomic classification of prostate cancer

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*Comment on:* Boysen G, Rodrigues DN, Rescigno P, *et al.* SPOP-Mutated/CHD1-Deleted Lethal Prostate Cancer and Abiraterone Sensitivity. Clin Cancer Res 2018;24:5585-93.

Received: 06 November 2018; Accepted: 29 November 2018; Published: 12 December 2018.

doi: 10.21037/amj.2018.12.01

**View this article at:** http://dx.doi.org/10.21037/amj.2018.12.01

## Background of genomics in prostate cancer

Prostate cancer is a leading cause of cancer death in the United States. This lethal disease is very heterogeneous both genomically and clinically. Even patients with advanced disease may have very different clinical course as well as varied responses to our most novel therapies. As in most cancers, improved knowledge of the genomic landscape may lead to improved prognostication and an enhanced selection of therapies specific to particular subtypes which would improve the patient experience. The referenced article by Boysen *et al.* (1) has contributed to an improved understanding of the clinical genomics of prostate cancer.

Investigators have identified multiple genomic alterations in archival patient samples of primary tumors or in autopsy studies. The characterization of genomic changes in more advanced prostate cancer is limited due to challenges in obtaining adequate tumor tissue, which largely is in the bone (2). Yet using selected prospective cohorts, and autopsy results, alterations within the chromodomain helicase DNA binding protein 1 (CHD1) and mutations in the gene encoding the Speckle-Type POZ protein (SPOP) have been cited as frequently as 29% of the time in prostate cancer (3). CHD1 plays a role in maintaining open chromatin, DNA repair, as well as transcription. SPOP is partly involved in controlling the stability of the androgen receptor (AR). These two alterations generally occur in parallel and mechanistically may be implicated in drug resistance and prostate cancer progression to the castration resistant state. There is a need for further understanding of how CHD1 loss and *SPOP* mutation contribute to a distinctive genomic subclass of prostate cancer. The article accompanying this editorial further characterizes CHD1 and SPOP alterations in prostate cancer using prospective samples obtained from patients with hormone sensitive prostate cancer, and later during castration resistant disease.

## Approach of the de Bono group (1)

The authors of this study identified 89 patients for whom they had tumor samples obtained within the hormone sensitive and castration resistant settings. The authors analyzed biopsies from bone, lymph node and liver metastases of patients in order to further describe the genomic and clinical characteristics of CHD1 loss, *SPOP* mutated metastatic prostate cancer. CHD1, PTEN, ERG expression, and *SPOP* status was evaluated using next generation sequencing, immunohistochemical (IHC) staining and fluorescent *in situ* hybridization.

In addition, the research team established and validated an assay for analysis of CHD1 protein loss using archival tissue. The loss of this protein was analyzed via IHC staining and compared to *CHD1* gene copy number expression by FISH and found to be strongly associated. They then used this assay in matched patient cases and detected CHD1 loss in 15% and 17% of both hormone sensitive and castration resistant biopsy, respectively. Single cell analysis of CHD1 protein expression in matched samples did not reveal any significant change in matched samples from the hormone-sensitive prostate cancer (HSPC) and castration-resistant

prostate cancer (CRPC) timepoints. Notably, previous work had suggested CHD1 differed in hormone sensitive versus castration resistant prostate cancer. The use of these matched samples suggests a sampling difference in those investigations rather than an active evolution.

The authors further described an association of *SPOP* mutations with copy number changes rather than mutational burden. Twenty-two of the 89 patient samples had somatic mutations with most previously known within the Y83-F102 and F125-F133 residues. Six other mutations were identified and not previously reported in prostate cancer. There was 100% correlation between CHD1 loss and SPOP mutation. Similarly, there was a mutually exclusive ERG overexpression, CHD1 loss and SPOP mutation noted in the CRPC cohort.

### *Use as a biomarker*

These genomic changes were then correlated with clinical history in order to evaluate their prognostic and predictive strengths. As in many cancers, there is a need for improved subtyping of prostate cancer in order to better identify populations which may respond to treatments, or identify potential drivers of disease progression which may be targeted with therapy. CHD1 loss and *SPOP* mutations were not found to have any significant association with important clinical outcomes of overall survival and time to castration resistance. The investigators then evaluated how these alterations predicted response to abiraterone acetate. Abiraterone acetate is a novel agent which has improved survival outcomes both in the hormone sensitive and castration resistant setting. However, response rates are quite variable to this agent (4-6). Mutations in *SPOP* have been associated with very high AR transcription compared to other prostate cancer subtypes (7). The authors found that patients with an SPOP mutation had improved rates of prostate-specific antigen (PSA) response (P=0.001), defined as a reduction of at least 50% in PSA. In addition, these patients experienced a longer response to abiraterone therapy, P=0.002. This is exciting data yet will require further validation in prospective study.

## Clinical relevance and summary

Overall the authors performed a well-executed characterization of two known important genomic alterations in prostate cancer. While a single institution experience, the utility of hormone sensitive and castration resistant patient matched samples can not be discounted. This work has offered important insight into both the genomic landscape of prostate cancer as well as potential predictive markers of response to abiraterone acetate. This also should be validated in prospective work yet contributes to filling the gaps in our ability to provide individualized care. With emerging evidence of the importance of DNA repair defects in prostate cancer and the subsequent impact on therapeutic choices, there is further evidence that better classification of this disease could lead to improved treatment options for patients. The ability to predict response as well as prognosticate disease progression continues to be of primary importance and need within prostate cancer. These authors have further contributed to our knowledge of these alterations as work continues to enhance a precision medicine framework for both characterizing metastatic prostate cancer and aiding in treatment assignment.

## Acknowledgements

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Xiao Li (Department of Urologic Surgery, the Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing, China).

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.12.01). The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2018.12.01
**Cite this article as:** Kessler ER. Another step in understanding the genomic classification of prostate cancer. AME Med J 2018;3:113.

 