Prevalence and Implications of Germline Genetic Variants in Prostate Cancer

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BACKGROUND

Inherited genetic variants have considerable implications for prostate cancer staging, treatment, screening and genetic counseling of affected individuals and family members.

Prior publications have focused on specific patient populations and there are limited data on the prevalence of germline variants in individuals with prostate cancer across stage and ethnic groups.

The clinical impact of germline genetic testing on management of individuals with prostate cancer is not well defined.

OBJECTIVE

We report on a series of 3607 men with prostate cancer undergoing hereditary cancer testing at various stages of disease. We sought to define clinical factors associated with the presence of positive (Pathogenic, Likely Pathogenic or Increased Risk Allele) germline variants (PV) and their clinical significance.

METHODS

• De-identified personal and family history information was reviewed for 3607 consecutive men with prostate cancer undergoing germline genetic testing between 2013 and 2018.

• Genes analyzed were chosen at the discretion of the ordering clinician and varied from 2-80 genes. The 14 genes (Figure 1) included on a curated hereditary prostate cancer panel were requisitioned in 62% of cases.

• Extracted DNA was processed and subjected to paired-end sequencing on a next-generation sequencing platform. Variants were subjected to clinical interpretation using Sherlock, a schema refined from the American College of Medical Genetics and Genomics criteria.

• This study was performed under IRB approved protocol (Western IRB-1167406) allowing for evaluation of de-identified data.

RESULTS

• Among men with PV, the 10 most common genes were: BRCACA2, CHEK2, ATM, MUTYH, BRCAC1, HOXB13, APC, MSH2, TP53 and PMS2.

• 69% of PV occurred in genes other than BRCAC1/2.

• 66% of PV occurred in genes not included in the 2018 Prostate Cancer Genetic Testing Guidelines.

• Increased PV detection of a PV.

RESULTS

• Age at diagnosis (avg 60y) was distinct from age at testing (avg 67y), but did not correlate with the chance of a PV.

• The frequency of variants varied by ethnicity. Compared to other ethnic groups African Americans (OR=0.927, p<0.001) and Hispanics (OR>0.325, p<0.02) had a lower rate of PV.

• The rate of pathogenic germline variants in men with prostate cancer appears to be similar to other cancer types, such as breast and colorectal cancer, where germline testing is an established part of medical management.

• Individuals were identified from a clinical laboratory cohort implying a selection bias to this study. Other limitations include variability in the genes analyzed, limited availability of clinical and family history information, as well as the underrepresentation of men from non-White ethnic groups.

• Our data did not show significant associations between the presence of a positive germline variant and Gleason score, family history or age at testing. Further study on clinical indicators of hereditary risk is warranted.

• Germline genetic testing provides information that can significantly impact medical management including therapy, surveillance, counseling and identification of at-risk family members.

CONCLUSIONS

This presentation is based on data published in: Jama Genomics Sherloc generation Extracted panel Genes men data treatment, report 80 - with 14 % and 2,03% reevaluation of personal medical information was reviewed for 3607 consecutive men with prostate cancer undergoing germline genetic testing between 2013 and 2018. Genes analyzed were chosen at the discretion of the ordering clinician and varied from 2-80 genes. The 14 genes (Figure 1) included on a curated hereditary prostate cancer panel were requisitioned in 62% of cases. Extracted DNA was processed and subjected to paired-end sequencing on a next-generation sequencing platform. Variants were subjected to clinical interpretation using Sherlock, a schema refined from the American College of Medical Genetics and Genomics criteria. This study was performed under IRB approved protocol (Western IRB-1167406) allowing for evaluation of de-identified data.

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