Mutation spectrum and rates of variants of uncertain significance among African American males undergoing prostate cancer germline testing: Need for equity in genetic testing

Veda N. Giri, MD, Rebecca Hartman, MPH, Mary Pritzlaff, MS, CGC, and Scott Keith, PhD

Background. Germline testing (GT) for prostate cancer (PCA) is central to metastatic disease management, PCA screening strategies, and hereditary cancer assessment. African American (AA) males have a higher burden of PCA, yet have lower engagement in germline testing which limits understanding of genetic contribution to PCA. Here we evaluated the germline spectrum of AA and White males with PCA undergoing clinical multigene panel testing (MGPT) to inform germline testing strategies with attention to equity.

Methods. Study participants included AA men and White men with PCA who underwent a 14-gene MGPT between April 2012 - December 2020 at a clinical diagnostic laboratory (Ambry Genetics). Exclusions were men with known pathogenic variants reported in their families or who had prior genetic testing. MGPT included: *ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53.* Sanger or next generation sequencing analysis was performed per standard clinical testing protocol. Variant classification was per ACMG 5-tier system. Descriptive statistics summarized results with counts and percentages for categorical variables and mean and standard deviation for continuous variables. Data were compared with Fisher's exact, Chi-squared, two proportion z-test, or two sample t-test, as appropriate. Significance level was set a priori at 0.05.

Results. The dataset included genetic and clinical data from 427 males who had undergone MGPT: White males (n=190; 45.5%) and AA males (n=237; 55.5%). Mean age at diagnosis was 59 $\pm$ 9.3 years. Among men whose Gleason score was indicated (72%), 47% had Gleason >=8. Majority of men indicated having a $1^{st}/2^{nd}$ degree relative with PCA (68.97%) or $1^{st}/2^{nd}$ degree relative with any cancer (99.2%). In the entire cohort, 8.2% tested positive for a pathogenic/likely pathogenic variant; AA males (n=14, 5.91%) and White males (n=21, 11.05%). VUS only was reported in 21.31% of the overall cohort with a significant difference noted between AA and White males (25.32% vs. 16.32%, respectively; p=0.0238). Mutation spectrum in AA males included: *BRCA2* (n=7), *PALB2 (n=3), ATM* (n=3), and *BRCA1* (n=1). Among White males, a wider spectrum of mutations was observed: *BRCA2* (n=6), *ATM* (n=5), *HOXB13* (n=5), *CHEK2* (n=2), *TP53* (n=1), and *NBN* (n=2). The proportion of AA males with multiple VUS was significantly higher than for Caucasian males (5.1% vs. 0.53%, p = 0.003).

Conclusions. Clinical germline testing among AA males reveals a narrow spectrum of mutations in key DNA repair genes, with important implications for precision therapy and hereditary cancer assessment. Furthermore, AA males had significantly higher rates of multiple VUS, indicating critical need for greater inclusion of diverse populations in genetic studies to discern the pathogenic spectrum contributing to PCA aggressiveness and risk.