Performance of Multigene Panel Testing in Hereditary Prostate Cancer

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Introduction and Objective

Hereditary prostate cancer (HPC) is defined as ≥3 first degree relatives with prostate cancer (PC); 2 relatives diagnosed ≤ age 55; or PC in ≥3 generations. While men with HPC are at increased risk of developing tumors at an early age, the biologic potential and their aggressiveness have yet to be fully elucidated. Genes associated with HPC have been associated with lethal PC and impart increased risks of other cancers. Multi-gene panel tests (MGPTs) can identify the genetic etiology of HPC, but the overall frequency of gene mutations among men with HPC is not well described.

Methods

Men with PC underwent MGPT using a 14-gene targeted PC panel (N=62) or one of 10 other hereditary cancer panels (N=1169) at Ambry Genetics between 2012 and 2016. The mutation frequency (pathogenic or likely pathogenic variant(s) detected), ages and number of primary cancer diagnoses were assessed. Using Fisher's exact test, the performance of targeted PC MGPT among HPC cases was compared to other MGPTs, as was the performance of targeted PC MGPT among individuals who met HPC criteria compared to those who did not meet strict criteria.

Results

94 of 1231 (7.6%) PC cases referred for testing met HPC criteria, including 14 who underwent targeted PC MGPT and 80 who underwent other MGPT. Overall, 18.1% (n=17) of men with HPC had a germline mutation. There was no significant difference in the age of diagnosis or number of primary malignancies between mutation carriers and non-carriers. 21.4% of HPC cases tested positive on targeted PC MGPT (n=3/14) compared to 17.5% tested via other hereditary cancer panels (n=14/80) (p=0.7). Of 62 men from the overall cohort with targeted PC MGPT, there was no statistically significant difference in the mutation rate between men who met HPC criteria and those who did not (p=0.7).

Table 1: Targeted PC MGPT Results by Clinical History

Clinical History	**PC cases tested, N**	**Positive, n**	**Positive (%)**	**Mutations Detected**
Meets HPC	14	3	21.4	*BRCA2* (2*), HOXB13* (1)
Does not meet HPC				
At least one relative with PC	26	6	23.1	*BRCA2* (3), *BRCA1* (1), *CHEK2* (1), *HOXB13* (1)
No family history of PC	22	1	4.5	*PALB2* (1)

Conclusions

Less than ten percent of PC cases referred for MGPT met strict HPC criteria, and the yield of MGPT in PC cases meeting HPC criteria was similar to those not meeting criteria. This data supports an MGPT approach in cases where hereditary PC predisposition is suspected but strict HPC criteria are not met. Further analysis in a larger cohort may clarify the significance of these results.