# NOVEL GERMLINE MUTATIONS IN PROSTATE CANCER – THE NEXT FRONTEIR IN PERSONALIZED THERAPY FOR ASIA AND BEYOND

**DAMIEN BOLTON PhD FRACS**

**Abstract**

*Introduction:* The role of *BRCA* genes in the development of prostate cancer is well established. Little is known though about non-*BRCA* germline pathogenic variants associated with familial PCa and their clinical phenotypes. This is of particular relevance in certain Asian ethnicities where prostate cancer has been shown to have especially high and lower incidences respectively.

*Aim:* We aimed to identify novel germline pathogenic variants in known cancer predisposition genes associated with multi-case PCa families from a variety of ethnicities, and to describe the resulting clinical phenotypes with respect to prostate cancer outcomes.

*Methods:* Germline DNA (gDNA) from 94 index cases with verified PCa was screened over an 84-cancer gene panel. Index cases arose from families with a strong history of breast and/or ovarian cancer (n=66), or multi-case PCa families (n=28). All families had at least two verified cases of prostatic adenocarcinoma. The phenotype of PCa associated with each gene was compared to *BRCA* 1 and 2 carriers, to non-mutation carriers from families with a positive history for breast/prostate cancer (*BRCAX* group, n=111) and to general population data.

*Results:* 22 Class 4/Class 5 (C4/C5) variants (23.4%) were identified in index cases. Six variants were not clinically notifiable and seven were identified in *BRCA1* (n=3) and *BRCA2* (n=4) genes. gDNA screening for the identified, family-specific mutation resulted in a final cohort of 15 non-*BRCA* men who were confirmed to carry the family-specific mutation in *ATM* (n= 9, mean age at diagnosis 65 years), *CHEK2* (n=2, mean age at diagnosis 68 years), and *HOXB13*84E (n=4, mean age at diagnosis 62 years). 13/15 (87%) of these prostate cancers were classified as D'Amico intermediate or high-risk. *ATM* and *CHEK2* mutation carriers demonstrated high-risk disease similar to our previously published *BRCA2* carriers (mean age at diagnosis 66yrs, and 79.5% D'Amico high risk). The *BRCAX* group also demonstrated a high proportion of high-risk PCa (53.2%) in contrast to general population characteristics (25%).

*Conclusions: ATM* and *CHEK2* carriers and the *BRCAX* cohort in this study more frequently demonstrated high-risk disease compared to PCa cases from a general population cohort. *HOXB*13 carriers demonstrated low-intermediate risk features of PCa. The increased frequency of these mutations in familial lines helps explain the variability in incidence of clinically significant prostate

cancer amongst different ethnicities. Targeted genetic testing of at-risk groups will help identify men with greater potential for prostate cancer specific mortality. More data correlating these rare genetic variants with clinical phenotypes and familial predisposition will also strengthen the clinical validity of these results and further establish the significance of these mutations in PCa detection and management.