Genomic determinants of prostate cancer in Zambian patients

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Background: Cancer represents an enormous burden on health, wellbeing, and healthcare sustainability. There is therefore an urgent need to improve the provision of cancer prevention and management strategies in low resource settings. The challenge could not be more urgent as soon a majority of new cancer diagnoses, will soon affect lower- and middle-income countries disproportionately affecting the global majority population who have been under-represented in cancer clinical trials. Prostate cancer (PCa) is the most common cancer in men, with predicted global increase of new cases to increase to 2.9 million cases annually by 2040 [1]. Furthermore, patients of African ancestry are diagnosed with PCa younger than white counterparts and the disease progresses more rapidly [2]. While the molecular basis of this difference is poorly understood, there is evidence that complex interactions of social determinants of health, combined with life experiences and environmental exposures influence genetic risk and this contributes to the observed inequities in outcomes experienced by PCa patients of African ancestry.

While advances in genomics are transforming the molecular understanding of PCa and this in turn is informing and improving cancer care for many patients in higher resource settings in the UK, Europe and USA, these advances have thus far not been widely available for indigenous African patients. Furthermore, the foundational knowledge required to understand the genetic diversity of African populations needed to underpin cancer precision medicine in patients of African ancestry is only now being established for certain African populations. For this reason, we completed genomic profiling of Zambian PCa patient specimens.

Methods: Genomic DNA was isolated from fresh frozen and formalin fixed paraffin embedded PCa specimens obtained from patients treated at the University Hospital, University of Zambia, Lusaka. Whole exome sequencing was completed, aligned to the human reference (GRCh38) genome using BWA and variants identified using the GATK Mutect2 best practices method. The resultant variants were compared to data obtained from the previously described TCGA-PRAD cohort and a Nigerian PCa cohort [3].

Results and Conclusions: This proof of principle study established the feasibility and workflows to complete WES in PCa patients in Zambia. Our preliminary study has identified differences in PCa-associated genetic variants in Zambian PCa patients as compared to the TCGA-PRAD cohort. Novel variants affecting DNA repair genes including in *BRCA1, BRCA2*, and *ATM* were common, as previously reported in Nigerian PCa patients [3]. Large scale studies are now required to better understand the molecular and genomic diversity of PCa in patients of African ancestry. The SAMBAI NCI-CRUK Cancer Grand Challenge project will establish how social determinants of health interact with environmental, genetic and other factors to establish the knowledge base required to inform new approaches and drive new clinical trials to improve PCa outcomes in patients of African ancestry.

References:

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