Role of the Y-chromosome in ethnic disparities and prostate cancer presentation

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Background
The Y chromosome (chrY) is notoriously difficult to investigate due to its highly repetitive nature. As such, it is mostly ignored in many genomic investigations into associations with disease, including prostate cancer (PCa). A highly heritable cancer, PCa presents with significant ethnic disparity, with African men at greatest risk of associated mortality. Yet, both chrY investigation and African inclusion are severely lacking.

Method
A unique multi-ethnic PCa resource (106 African, 57 European) was used for this study, comprised of whole genome sequences from the blood and tumour. We tested for association between high-risk PCa (HRPCa) with Y-haplogroups or phylogenies, and interrogated the data for chrY germline and somatic single nucleotide variants (SNVs) and copy number variants (CNVs) between ethnicities. Copy number calls were determined by the consensus between three callers (GATK gCNV, cn.MOPS, CNVkit) for the germline dataset, and two callers (GATK gCNV, CNVkit) for the somatic dataset.

Results
No significant associations between Y lineages and HRPCa were found, however significant uncaptured variation was identified among African haplogroups. Potentially deleterious germline variants were found in both European (one in *TBL1Y*, three in *USP9Y*) and African patients (one in *UTY* and one in *KDM5D*). Somatic copy number alterations were more common in HRPCa patients, and present in more genes in African tumours (166 RNA and protein-coding genes) than European tumours (58 genes). However, shared alterations between ethnicities were noted in *DDX3Y* and *USP9Y*, while losses in *KDM5D*, *PCDH11Y* and *RBMY* genes were more prevalent in African tumours.

Conclusions
Overall, we report the inherited and acquired variation in the chrY landscape between ethnicities. The differences in somatic copy number alterations between African and European tumours point towards pathways for treatment-resistant tumours in African patients, a possible contributor to the worsened PCa mortality rates for African men. As there were a greater number of genes altered in African tumours, further work is needed to explore epigenetic and expression differences for how this variation may impact tumour progression.

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Conflicts of Interest Disclosure Statement
The authors declare no conflicts of interest.