Leveraging population-specific genomic architecture to dissect rare genetic drivers of PC heritability

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Background:
Up to 60% of PC risk can be attributed to inherited genetic defects. Established Mendelian PC predisposition genes, such as BRCA1, BRCA2, HOXB13, and the DNA mismatch repair genes, only explain PC risk in roughly 8% and 12% of primary and metastatic PC patients respectively, clearly suggesting the presence of one or more undiscovered PC susceptibility defects. As most of the case-control studies, done so far to explore PC heritability, primarily included patients of European ancestry, additional genetic drivers of PC risk and heritability, that are rare in European patients but prevalent in other populations, are still to be discovered. Here, we leverage the concept of allelic genetic drift to explore novel PC risk determinants in Arab PC patients.

Methods:
This study enrolls PC patients from the indigenous Arab population regardless of their disease status, response to treatment, family history of cancer, and age of onset. Blood or sputum samples are collected from enrolled patients along with detailed clinical data covering disease progression, history of other primary cancers, family history of cancer or neoplastic disorders, and other relevant information. DNA extraction is done in a central laboratory to ensure high quality of extracted DNA. Whole-exome sequencing is done on germline DNA samples passing all QC metrics. Germline variant calling will then be performed on the aligned BAM files following Best Practices.

Results:
A total of 125 PC patients from the indigenous Arab population have been enrolled so far. The average age of PC diagnosis on our cohort was 66.4 (SD= 6.98; range: 55 to 82) years. The Median Gleason score (GS) was 7 (GS6: 23.2%, GS7:64.4%, GS8:8.7, GS9:10.1, GS10:2.9%, unknown GS:10.9%). A total of 103 (82.4%, 95% CI:75.72-89.08) patients had primary PC while 22 (17.6%, 95% CI:10.92-24.28) patients had evidence of metastatic disease. A total of 15 (12%, 95% CI: 6.30-17.70) patients had a history of PC in a first- or second-degree family member. Germline DNA extraction has been done on 69 samples, each of which resulted in 100 µl of 50 ng/µl yielding a total of 5 µg of DNA, which is sufficient for germline whole exome/genome sequencing at 50-150X coverage. A total of 500 patients are planned to be enrolled over the coming two years.

Conclusions:
Germline genomic analysis of large cohorts of patients from genetically distinct populations can uncover novel biological mechanisms underlying PC susceptibility in selected PC patients.

Conflict of Interest: none

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