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Biological Determinants of Kidney Cancer Health Disparities

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TECHNICAL ABSTRACT

Background: Kidney cancer ranks as a top 10 leading site of new cancer cases (~64,000), killing ~15,000 people in the U.S. each year. Renal cell carcinoma (RCC) is the most common type of kidney cancer (~90% cases). RCC subtypes each have a different histology, clinical course, and response to therapy, in addition to distinctive genetic and genomic alterations. African Americans (AAs) have higher incidence rates of RCC than European Americans (EAs) for reasons that are unclear. Population-specific somatic mutation drivers in clear cell RCC (ccRCC) from AAs compared with EAs have been identified. Other genomic determinants of this cancer health disparity, such as somatic copy number variations (SCNVs), have been largely understudied. Recurrent SCNVs (e.g., 5q amplifications, 3p and 14q deletions) have been detected in kidney cancer genomes from EA patients, which functionally impact clinically relevant genes that correlate with treatment response (e.g., VHL SCNAs in ccRCC can predict response to VEGF and mTOR targeted therapies). Few studies have profiled SCNV drivers of kidney cancer in diverse populations, including AAs.

Hypothesis: RCC tumors from AA and EA patients have distinct SCNV, loss of heterozygosity (LOH), and chromothripsis profiles that cause clinically relevant gene expression changes.

Specific Aims: The first aim will identify and validate population-specific SCNV, LOH, and chromothripsis profiles across the genome between AAs and EAs with RCC. The second aim will determine if these population-specific genomic signatures correlate with clinically actionable gene expression, disease-specific survival, and other clinical features.

Study Design: DNA and RNA pairs will be extracted from fresh frozen and FFPE RCC samples in both The Cancer Genome Atlas (TCGA) discovery and Cooperative Human Tissue Network (CHTN) validation cohorts. Three histologies will be studied in the TCGA cohort, including clear cell (n = 56 AAs, 466 EAs), papillary (n = 61 AAs, 207 EAs), and chromophobe (n = 12 AAs, 95 EAs) RCC. The CHTN validation study will be performed in the histology with the most significant findings (n = 20 AAs, 20 EAs). Affymetrix SNP 6.0 and OncoScan CNV Plus (the highest-resolution whole-genome SCNV microarray-based assay currently available) data will be integrated with mRNA-sequencing data to test for the functional significance of any population-specific genomic differences identified.

Innovation: First, this work goes beyond a panel of known kidney cancer driver genes and adopts a genome-wide approach to search for new candidate drivers in AAs. Second, the proposed study measures racial differences of genomic instability in two ways, using a traditional LOH approach and a novel chromothripsis or “chromosome shattering” analysis. Third, this project will incorporate genetic ancestry (a biological construct), in addition to self-reported race (a social construct), to determine if increased ancestry is associated with increased RCC rates.

Impact: The discovery of novel population-specific SCNV drivers can be leveraged to improve diagnostic and prognostic biomarker development and targeted therapies for both AA and EA patients. Classifying kidney tumors based on their degree of chromothripsis or predisposition due to degree of genetic ancestry would also help to refine current disease classification paradigms.

Back to Search Results

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