Summary

Significant racial disparities exist in kidney cancer, including early disease onset, a distinct histological distribution, and poorer disease outcome for African Americans, even when controlling for treatment. No study has yet evaluated a biological cause of racial disparities in kidney cancer. Here, we intend to investigate whether these disparities have a genetic basis in clear cell (ccRCC) and papillary (pRCC) renal cell carcinoma by focusing on two major kidney cancer genes, *MET* and *VHL*. Our first aim is to perform whole-genome sequencing (WGS) of 15 African Americans with ccRCC, thus increasing the size of this cohort in The Cancer Genome Atlas (TCGA) and complementing existing TCGA kidney cancer cohorts. Using the updated TCGA ccRCC and pRCC cohorts, we will then perform high-quality mutation calls for structural and genomic variations including single nucleotide polymorphisms, deletions, insertions, inversions, and copy number variations. Our second aim is to assemble a comprehensive list of somatic and germline mutations associated directly or indirectly with *MET* and *VHL* (what we term the 'METome' and 'VHLome') and prioritize regions according to greatest impact and racial disparity. We will begin constructing the METome and VHLome by finding all annotations of molecular interactions and regulatory relationships for these genes. We will leverage a novel pipeline that includes i) FunSeq, a sophisticated algorithm that prioritizes high functional impact variants and ii) LARVA, a burden test algorithm that identifies significant mutation enrichment in non-coding elements by considering covariates such as mutation rate and replication time. We will then identify racial disparities across i) germline mutations in coding regions using WGS and whole-exome sequencing data, ii) genomic regions with higher mutational burdens, iii) germline mutations in non-coding prioritized regions using WGS data, and iv) somatic mutations in prioritized regions. In our third aim, we will validate our prioritized racially disparate regions using a large, independent cohort, balanced to include an equal number of ccRCC and pRCC tumors from Caucasian and African-American patients. We will genotype patients from this validation cohort using PCR-mass spectroscopy. Finally, in our fourth aim we will use CRISPR/Cas to functionally validate a selected subset of mutations in genotyped immortalized cell lines. We will determine the effects of gene and protein expression alterations on proliferation, invasion, migration, and anchorage-independent growth. These studies will not only provide insight into genomic differences underlying the racial disparities in kidney cancer, but will also make a large set of data readily available to other scientists.