Article Review: Intrinsic Genomic Differences Between African American and White Patients With Clear Cell Carcinoma

Kimberly Deas, MS

Background

- Renal cell carcinoma is the 8th leading cause of cancer deaths in the United States.
- As is the case with other cancers, African Americans have disparate outcomes following diagnosis with clear cell renal carcinoma (ccRCC), the most common form of renal cancer.
- Despite a decade of new knowledge about the molecular drivers of renal call carcinoma, this study is the first to examine genomic and transcriptomic differences between African Americans and Caucasian patients.
- While VHL inactivation is known characterize the development of both sporadic and hereditary ccRCC, among African Americans, this tumor suppressor gene is mutated at a far lower rate.

Methods

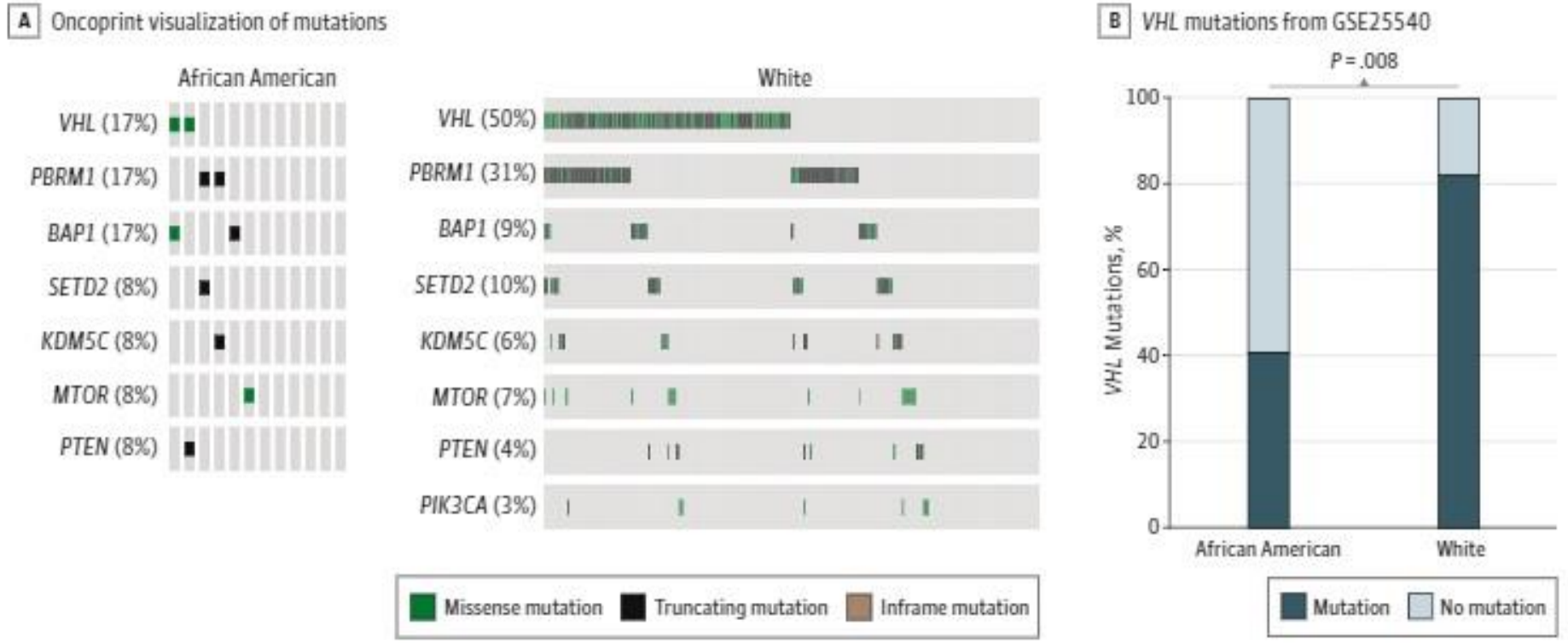
- The Cancer Genome Atlas (TCGA) was the primary source of the genomic data analyzed in this study. Somatic mutation data was obtained from the Gene Expression Omnibus (GEO) Data Set.
- After developing race specific gene lists, significant genes and corresponding fold changes were analyzed for predicted pathway activation and/or inhibition.
- GSEA was performed to examine tumor differences between African American and Caucasian patients.
- Patients were also classified by RNA subtype of ccRCC, ccA or ccB, using prediction analysis for microarrays (PAM) with heatmaps for visual display.
- Statistical analysis using either chi-squared or Fischer's exact tests, were used to determine differences in mutation rates by race.

Results:

- African American patients had far fewer VHL mutations than White patients at a rate of 17% and 50%, respectively.
- African American patients also had lower expression of VEGF ligands and receptors. This is important because most ccRCC therapies target the VEGF pathway, which is involved in tumor angiogenesis.
- VEGF and HIF signatures were also negatively enriched in African American patients. HIF is stabilized by VHL and targets the VEGF pathway.
- African American patients also express higher levels of ccB, the subtype of ccRCC which is associated with worst outcomes.

Results: Gene Mutations in RCC by Race

Figure 1. Gene Mutations in Clear Cell Renal Cell Carcinoma Tumors by Data Set Source and Race



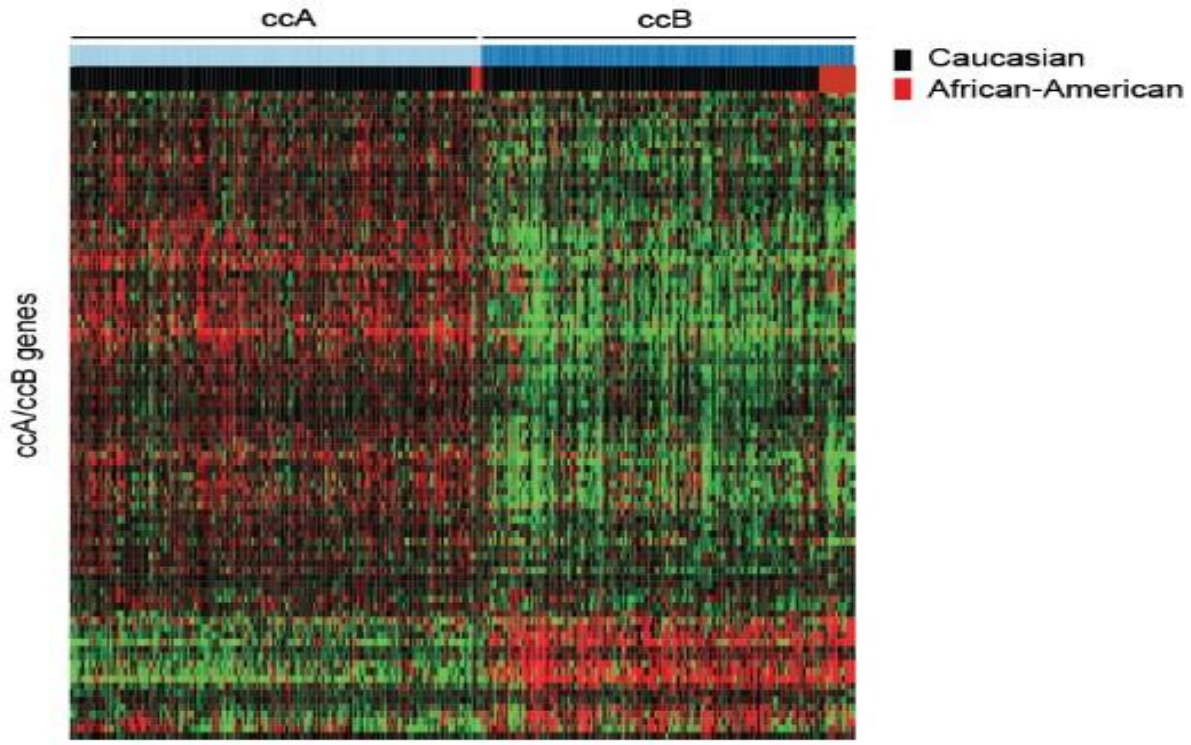
A, Mutations in significantly mutated genes according to the The Cancer Genome Atlas kidney clear cell data sets are shown by race. B, Frequency of *VHL* mutations in an independent data set[6] are shown by race.

Results: Mutation Frequency by Racial Group

A.

GENE	African American	White	Fisher's Exact (p-value)
VHL	2/12 (17%)	175/351 (50%)	0.036
PBRM1	2/12 (17%)	110/351(31%)	0.356
BAP1	2/12 (17%)	32/351(9%)	0.610
SETD2	1/12 (8%)	36/351(10%)	1.000
KDM5C	1/12 (8%)	22/351(6%)	1.000
PTEN	1/12 (8%)	14/351(4%)	0.402
MTOR	1/12 (8%)	23/351(7%)	1.000
TP53	0/12 (0%)	5/351(1%)	1.000
PIK3CA	0/12 (0%)	9/351(3%)	1.000

Results: Differential expression of ccRCC subtypes in African Americans and Caucasians



eFigure 3: Subtype classification of African-American (red) and Caucasian (black) patient tumors in TCGA: KIRC samples by ccA (light blue) and ccB (dark blue), heat map represents the list of genes used to classify subtype.

Conclusion:

- African American patients in this study have biologically distinct ccRCC compared to Caucasian patients as evidenced by the gene mutations associated with ccRCC and tumor subtype.
- Due to the presence of tumors that are both HIF and VEGF independent, VEGF-targeted therapies that are common in treating ccRCC, are ineffective and may contribute greatly to the disparate outcomes seen in African Americans with ccRCC.
- While differences in tumor biology may account for a significant portion of the poor outcomes of African Americans with ccRCC, the authors acknowledge that disparate health care delivery may also play a major role.
- Other comorbid conditions are also plausible contributors to poorer survival among African Americans, including end stage renal disease and hypertension.

Future Considerations:

- While the results of this study are promising as it relates to understanding the role of biology in understanding disparities in ccRCC, a larger sample size would better substantiate the findings in this study.
- The top mutated genes in ccRCC according to the TCGA database, differs considerably between African Americans and Caucasians. This difference could account for the disparate outcomes of African Americans following treatment for ccRCC.
- The relationship between comorbid conditions like hypertension and ccRCC likely contributes disparities and may also offer clues about the treatment resistance.

References:

1. Krishnan B, Rose TL, Kardos J, Milowsky MI, Kim WY. Intrinsic Genomic Differences Between African American and White Patients With Clear Cell Renal Cell Carcinoma. JAMA Oncol. 2016 Mar 24.
2. Rose TL, Deal AM, Krishnan B, Nielsen ME, Smith AB, Kim WY, Milowsky MI. Racial disparities in survival among patients with advanced renal cell carcinoma in the targeted therapy era. Cancer. 2016 Oct;122(19):2988-95