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Differences in Tumor *VHL* Mutation and Hypoxia-inducible Factor 2 Expression Between African American and White Patients with Clear Cell Renal Cell Carcinoma

Catherine L. Callahan[a], **Lee Moore**[a], **Petra Lenz**[b], **W. Marston Linehan**[c], **Michael L. Nickerson**[d], **Nathaniel Rothman**[a,†], **Mark P. Purdue**[a,†,*]

[a]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

[b]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc., NCI Campus at Frederick, Frederick, MD, USA

[c]Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

[d]Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

VHL inactivation is a hallmark of clear cell renal cell carcinoma (ccRCC) development, resulting in constitutive upregulation of hypoxia-inducible factor (HIF)-mediated expression of vascular endothelial growth factor (VEGF) and other oncogenic factors [1]. An investigation within The Cancer Genome Atlas (TCGA) found evidence of racial differences in ccRCC tumor biology, with lower levels of *VHL* mutation and HIF expression in tumors from African American versus white patients (n = 19 and 419, respectively) [2]. We investigated this question by conducting an analysis of *VHL* mutation and HIF-1α and HIF-2α expression in ccRCC tissue from a larger case series of African American and white patients.

We tested formalin-fixed paraffin-embedded tumor tissue collected from ccRCC patients enrolled in a case-control study conducted in Chicago and Detroit investigating RCC risk factors in African American and white adults [3]. Following manual microdissection of tissue sections, areas containing at least 70% tumor cells were used for DNA extraction by standard phenol chloroform methods. *VHL* sequencing was performed using the Ion Torrent platform for tumor DNA from 167 patients (69 black and 98 white), while immunohistochemical staining for HIF-1α and HIF-2α was performed using standard avidin-biotin peroxidase methods for slides from 326 patients (87 black and 239 white). A nuclear staining algorithm (Aperio Technologies, Vista, CA, USA) was used to develop quantitative scoring models to compute the percentage of positive tumor cells

*Corresponding author. National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850, USA. Tel. +1 240 276 7265. purduem@mail.nih.gov (M.P. Purdue).

†These authors contributed equally to this work.

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for each marker and the staining intensity. We computed odds ratios and corresponding 95% confidence intervals comparing the frequencies of *VHL* mutation and HIF protein expression (categorized by tertiles) between African American and white patients, using unconditional logistic regression models.

We found the tumors of African American patients to have a significantly lower frequency of *VHL* mutation (32% vs 49%; $p = 0.03$; Table 1) and lower HIF-2α expression (16% vs 41% in the third tertile; $p_{trend} < 0.0001$) than those of white patients. These racial differences persisted after adjustment for patient and tumor characteristics ($p = 0.04$ and <0.0001, respectively). We did not observe notable differences in HIF-1α expression between racial groups.

Within this case series, which includes a substantially larger number of African American patients than investigated in TCGA [2], we have confirmed that *VHL* mutation and high HIF-2α expression are less frequent in ccRCC tumors of African American versus white patients. Further, we have demonstrated that these racial differences persist after adjustment for several patient and tumor characteristics, including chronic kidney disease (CKD). Our findings thus argue against differences in CKD-related RCC as an explanation for these results, as speculated in the earlier report [2]. More research is needed to better understand the factors underlying these differences.

It is unclear to what extent our findings, involving predominantly localized disease, are generalizable to patients with metastatic RCC. If so, it is plausible to suspect that African American patients may be less responsive to therapies targeting the *VHL*/*HIF* downstream genes, such as VEGF. Since African American patients had poorer RCC prognosis in the pretargeted therapy era [4], whether such racial differences in the current targeted treatment era exist is an important question for further investigation.

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Table 1 –

Different patterns of tumor *VHL* mutation and expression of hypoxia-inducible factor (HIF)-1 and HIF-2 between white and African American patients with clear cell renal cell carcinoma

	White *N* (%)	African American *N* (%)	Unadjusted			Adjusted[a]		
			OR	95% CI	*p* value	OR	95% CI	*p* value
VHL mutation								
No	50 (51)	47 (68)	1.00			1.00		
Yes	48 (49)	22 (32)	**0.49**	**0.26, 0.93**	**0.03**	**0.44**	**0.19, 0.98**	**0.04**
HIF-1α expression								
<27.9	76 (32)	33 (38)	1.00			1.00		
27.9–49.6	82 (34)	25 (29)	0.70	0.38, 1.29	0.25	0.97	0.47, 2.00	0.98
>49.6	81 (34)	29 (33)	0.83	0.46, 1.49	0.52	1.01	0.49, 2.08	0.94
					p_{trend} = 0.51			p_{trend} = .75
HIF-2α expression								
<5.0	67 (28)	42 (48)	1.00			1.00		
5.0–10.9	75 (31)	31 (36)	0.66	0.37, 1.17	0.50	0.72	0.37, 1.40	0.33
>10.9	97 (41)	14 (16)	**0.23**	**0.12, 0.46**	**0.02**	**0.21**	**0.09, 0.47**	**0.001**
					p_{trend} < 0.0001			**p_{trend} < 0.0001**

CI = confidence interval; OR = odds ratio. Note: bold text indicates statistically significant results ($p < 0.05$).

[a]Adjusted for age in years, body mass index, history of hypertension, history of chronic kidney disease, sex, smoking status, stage, grade, and tumor size.

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