Race Disparities in Peptide Profiles of North American and Kenyan Wilms Tumor Specimens

Jaime M Libes, MD, Erin H Seeley, PhD, Ming Li, PhD, Jason R Axt, MD, Janene Pierce, MS, Hernan Correa, MD, Mark Newton, MD, Erik Hansen, MD, Audra Judd, Hayes McDonald, PhD, Richard M Caprioli, PhD, Arlene Naranjo, PhD, Vicki Huff, PhD, James A O'Neill Jr, MD, FACS, Harold N Lovvorn III, MD, FACS, on behalf of the Kenyan Wilms Tumor Consortium

BACKGROUND: Wilms tumor (WT) is the most common childhood kidney cancer worldwide and arises in children of black African ancestry with greater frequency and severity than other race groups. A biologic basis for this pediatric cancer disparity has not been previously determined. We hypothesized that unique molecular fingerprints might underlie the variable incidence and distinct disease characteristics of WT observed between race groups.

STUDY DESIGN: To evaluate molecular disparities between WTs of different race groups, the Children's Oncology Group provided 80 favorable histology specimens divided evenly between black and white patients and matched for disease characteristics. As a surrogate of black sub-Saharan African patients, we also analyzed 18 Kenyan WT specimens. Tissues were probed for peptide profiles using matrix-assisted laser desorption ionization time of flight imaging mass spectrometry. To control for histologic variability within and between specimens, cellular regions were analyzed separately as triphasic (containing blastema, epithelia, and stroma), blastema only, and stroma only. Data were queried using ClinProTools and statistically analyzed.

RESULTS: Peptide profiles, detected in triphasic WT regions, recognized race with good accuracy, which increased for blastema- or stroma-only regions. Peptide profiles from North American WTs differed between black and white race groups but were far more similar in composition than Kenyan specimens. Individual peptides were identified that also associated with WT patient and disease characteristics (eg, treatment failure and stage). Statistically significant peptide fragments were used to sequence proteins, revealing specific cellular signaling pathways and candidate drug targets.

CONCLUSIONS: Wilms tumor specimens arising among different race groups show unique molecular fingerprints that could explain disparate incidences and biologic behavior and that could reveal novel therapeutic targets. (J Am Coll Surg 2014;218:707–722. © 2014 by the American College of Surgeons)

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The members of the Kenyan Wilms Tumor Consortium are listed in the Appendix.

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From the Division of Pediatric Hematology and Oncology (Libes), Department of Biochemistry, Mass Spectrometry Research Center, Tissue Core (Seeley, Judd, Caprioli) and Proteomics Laboratory (McDonald), Department of Biostatistics (Li), Department of Pediatric Surgery (Axt, Pierce, Hansen, O'Neill, Lovvorn), Department of Pathology (Correa), Division of Pediatric Anesthesiology (Newton), Vanderbilt University School of Medicine, Nashville, TN, Kijabe Mission Hospital, Kenya (Newton, Hansen, O'Neill), and Children's Oncology Group Statistics and Data Center, Department of Biostatistics, University of Florida, Gainseville, FL (Naranjo, Huff).

Correspondence address: Harold N Lovvorn III, MD, FACS, The Monroe Carell Jr Children's Hospital at Vanderbilt, Department of Pediatric Surgery, Vanderbilt University School of Medicine, 2200 Children's Way, Doctor's Office Tower, Suite 7102, Nashville, TN 37232-9780. email: harold.lovvorn@vanderbilt.edu

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Abbreviations and Acronyms

COG	= Children's Oncology Group
FH	= favorable histology
IMS	= imaging mass spectrometry
KWT	= Kenyan Wilms tumor
LC-MS/MS	= liquid chromatography mass spectrometry
LOH	= loss of heterozygosity
MALDI-TOF	= matrix-assisted laser desorption ionization time of flight
NAWT	= North American Wilms tumor
WT	= Wilms tumor

Wilms tumor (WT) is the most common childhood kidney cancer worldwide, and its incidence varies according to race.[1-5] When comparing North American race groups, WT develops in black children of sub-Saharan African ancestry at the highest rate (11 cases per million children younger than 15 years of age); white children show an intermediate rate (8.5 cases per million younger than 15 years); and children of Asian descent show the lowest rate (3 cases per million younger than 15 years).[4,6,7] Moreover, in the seminal analysis of the Greater Delaware Valley Pediatric Tumor Registry (ie, the region surrounding Philadelphia, PA), WT not only developed in black children at a nearly 2-fold greater rate than in white children, but also showed a higher frequency of congenital anomalies known to cluster with WT, which have since been linked to specific genetic mutations (eg, loss of heterozygosity at *WT1* and loss of imprinting at *H19-IGF2* or *WT2*).[8,9] This cancer predisposition appears to follow black children through generations regardless of geographical immigration away from sub-Saharan Africa.[10] Importantly, WT continues to burden black children born and living in developing or low-income African countries, where resources to treat this disease effectively are often limited, abandonment of care is common, and therapy does not follow standardized protocols.[11-15] For example, WT is the third most commonly diagnosed childhood cancer in Kenya, behind only lymphoma and leukemia, and where, alarmingly, 2-year survival currently approaches 50% at best.[11] In contrast, owing to treatment optimization strategies during the past 4 decades, WT survival in North America and other developed nations now exceeds 90% at 5 years.[16] Taken together, these observations suggest that black children might harbor a heritable molecular predisposition to develop WT. Despite consistent epidemiologic documentation of this childhood cancer disparity both in North America and globally, little has been published about a potential biologic basis to explain the different incidence rates according to race and ancestry.

Although race disparities in survival from WT previously existed in the United States, as black children typically fared worse, current outcomes comparing blacks with whites now have approximated one another.[4,5,17,18] The disparity in incidence remains, suggesting a biologic predisposition. Societal and socioeconomic barriers likely explain, in part, the once disparate outcomes between black and white WT patients, yet genetic and molecular events more probably influence the recognized, increased risk among black children of this potentially lethal childhood cancer developing.

The Children's Oncology Group (COG) 2013 Blueprint for Research of Renal Tumors calls for investigators to identify new targets and strategies in WT therapy to close the persistent survival gap, to reduce late toxic side effects for survivors, and to optimize therapy for children having treatment-resistant favorable histology (FH) disease.[19] One current focus in translational cancer biology is to personalize therapy for individual patients having unique genetic mutations and potential pharmacogenetic variations in responsiveness to established standard therapies. Clues to personalize therapy for any cancer, and specifically WT, might well originate with race group status, if core biologic differences are found to exist.

The purpose of this study was to explore, at the molecular level, the well-documented disparity in WT incidence that separates along race group status but for which a biologic explanation remains unknown. In a previous pilot study seeking to explain potential biologic differences in WT between race groups, we observed unique peptide profiles that can discriminate specimens according to race, but the power of that study was too low to draw substantial conclusions or to identify specific mechanistic pathways.[20] These current studies were designed to build on those preliminary findings and to test the hypotheses that WT specimens express a molecular fingerprint specific to race and that these profiles might reveal candidate targets as an initial step to personalize therapy.

METHODS

North American Wilms tumor specimens

To compare peptide composition between black and white WT patients residing in North America, the COG provided 80 FH specimens (ie, no anaplasia) divided evenly between either race group (n = 40), and relatively evenly between treatment success (n = 42) and failure (n = 38; Table 1). The COG matched these FH WT specimens for age, sex, stage, and loss of heterozygosity (LOH) at 1p and 16q, which, when both mutations are found in combination, portend considerably worse outcomes, increase risk stratification, and call for intensified therapy. Because