THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department of Surgery

Differences in the Mutation of Key Epigenetic Regulators & Oncogenes Between Black and White Patients with Pancreatic Neuroendocrine Tumors

Brendon Herring[1], Catesby Mallard[1],Rachael Guenter[1], Selwyn Vickers[1], Herbert Chen[1], Goo Lee[2], Deepti Dhall[2], Clayton Yates[3], J. Bart Rose[1]
University of Alabama at Birmingham, Departments of [1]Surgery and [2]Pathology; [3]Tuskegee University, Department of Biology

UAB MSTP MEDICAL SCIENTIST TRAINING PROGRAM

Introduction

1. Disparate outcomes have been shown between Black and White patients with pancreatic neuroendocrine tumors (pNETs), but have historically been attributed to socioeconomic factors.[1-5]

2. Recent analyses of our institutional database performed by our lab found that tumor size was a significant predictor of recurrence-free survival in patients with pNETs.[1] We then found that Black patients had significantly larger tumor sizes compared to White patients in our dataset. These data indicated that there may be biological differences in the tumors occurring in these two populations.[1]

3. Epigenetics is an area of known variation between racial groups. Interracial variation in epigenetics is present in healthy tissue, and specific epigenetic differences between Black and White patients have been linked to racial disparities in breast, colon, endometrial, and prostate cancer, among others.[6-14]

Figure 1. A) pNET survival based on tumor size and B) Differences in tumor size at resection between Black and White pNET patients[1]

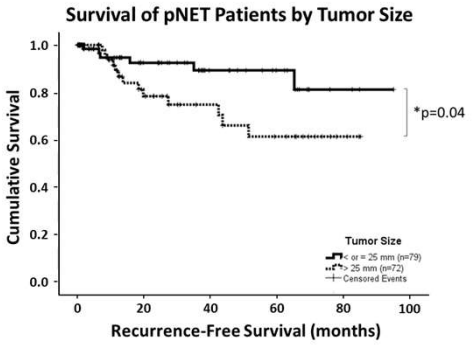


Table 1

	White (n=114)	African American (n=37)	Sig.
Sex[a]			P=0.02*
Male (n=79)	66 (58%)	13 (35%)	
Female (n=72)	48 (42%)	24 (65%)	
Age (years)[b,c]	65 (55-70)	60 (47-66)	p=0.03*
Tumor Size (mm)[b,c]	23 (15-37)	30 (20-60)	p=0.02*
Metastatic[a]	38 (40%)	16 (53%)	p=0.10

All are reported as median, IQR (interquartile range)
[a]Chi-Squared test; [b]Mann-Whitney U; [c]median, interquartile range

Results

Figure 2. A) Lack of representation of Black subjects in pNET genomic studies. B) Differentially mutated genes between Black and White patients with pNETs

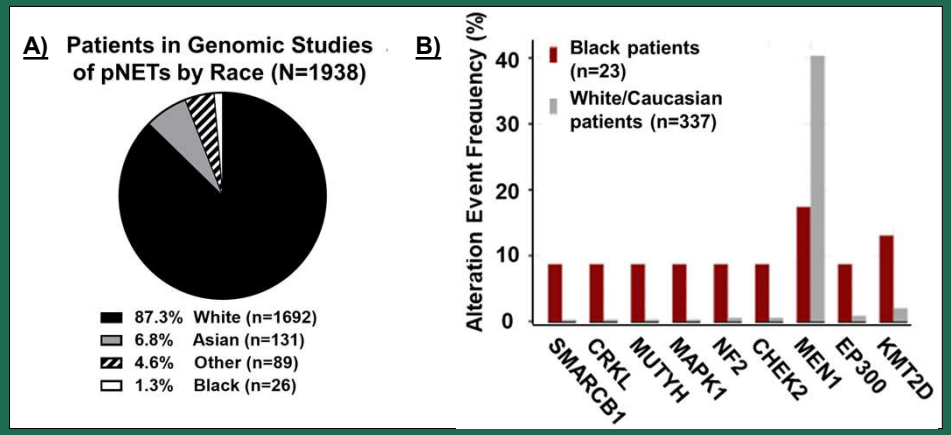


Figure 3. Statistics of differentially mutated genes between Black & White patients with pNETs, depicting enrichment for mutations in epigenetic modulators

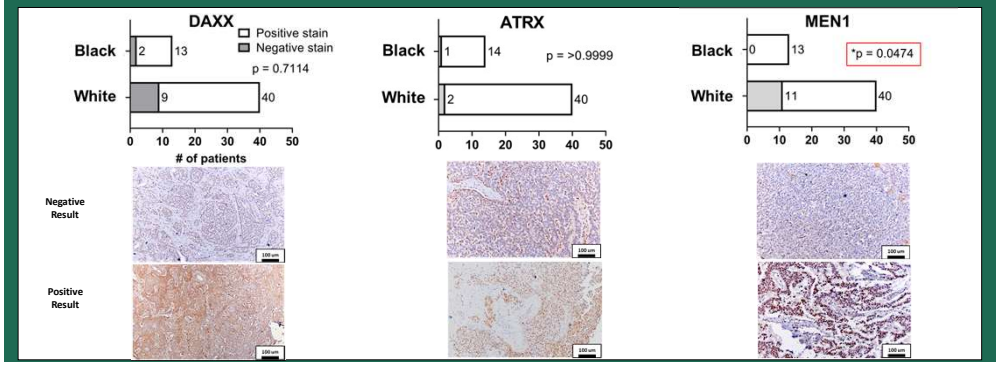
Gene	Black	White	p-Value	Enriched in
CRKL	2 (8.70%)	1 (0.29%)	0.0107	Black
MAPK1	2 (8.70%)	1 (0.30%)	0.0114	Black
MUTYH	2 (8.70%)	1 (0.29%)	0.0107	Black
CHEK2	2 (8.70%)	2 (0.57%)	0.0202	Black
NF2	2 (8.70%)	2 (0.56%)	0.0195	Black
SMARCB1	2 (8.70%)	1 (0.27%)	9.55E-03	Black
EP300	2 (8.70%)	3 (0.86%)	0.033	Black
KMT2D	3 (13.04%)	7 (2.02%)	0.019	Black
MEN1	4 (17.39%)	140 (40.35%)	0.021	White

Epigenetic modulators

*Fisher's exact test

AACR American Association for Cancer Research FINDING CURES TOGETHER
PROJECT GENIE Genomics Evidence Neoplasia Information Exchange

Figure 4. TMAs of resected human pNETs (G1 & G2) were immunohistochemically evaluated for DAXX, ATRX and MEN1 mutations, finding a significant enrichment for MEN1 mutations in White patients compared to Black patients, as depicted by negative staining result.



Methods

Pancreatic NET mutational data from Black and White patients were obtained from the AACR project GENIE database and screened for in-frame INDELs, frameshift, truncating, and splice-site mutations as well as structural variants. Differences in mutation between Black and White patients were assessed by Fisher's exact test with Bonferroni correction.

Protein expression of MEN1, DAXX, and ATRX, which are the most frequently mutated genes in pancreatic NETs, was determined by immunohistochemistry in tissue microarrays (TMAs). Mutations in these proteins are detectable by IHC in most cases, presenting as a specific loss of nuclear staining.[15,16] Stains were evaluated by a pathologist for quality and interpretation. Differences between groups were evaluated by Fisher's exact test.

Conclusions

1. Nine genes were found to be differentially mutated between groups. Four of these genes have direct roles in epigenetic regulation (SMARCB1, MEN1, EP300, KMT2D).

2. Loss of MEN1 protein expression (Fig 1B) was found in 11/40 (28%) of White patients, but was not identified in Black patients (p=0.047). There is little representation of racial minorities in genomic studies of GEP-NENs.

3. These data indicate that there are differences in the mutation of key genes in pNETs between Black and White patients

4. Differences at the genomic, transcriptomic, and epigenetic level may be influencing the pathogenesis and progression of pNETs in these populations, contributing to racial disparities in disease outcomes. These data also indicate that Black subjects must be included in further genomic studies of pNETs to uncover these differences.

Funding:
T32GM008361-28, MEDICAL SCIENTIST TRAINING PROGRAM (MSTP), National Institute of General Medical Sciences

https://sites.uab.edu/neuroendocrinesurgerylab/