

**TITLE: Differences in the Mutation of Key Epigenetic Regulators and Oncogenes Between Black and White Patients with Pancreatic Neuroendocrine Tumors.**

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**BACKGROUND:** Disparate outcomes have been shown between Black and White patients with pancreatic neuroendocrine tumors (pNETs), but have historically been attributed to socioeconomic factors.<sup>1-5</sup> However, (epi)genetic abnormalities unique to Black patients with breast, prostate, colon, and endometrial cancer have been associated with differential outcomes, but have not been investigated in pNETs.<sup>6-14</sup>

**METHODS:** Mutational data were obtained from the AACR project GENIE database using cBioPortal. Protein expression of MEN1, which is altered by most mutations, was determined by immunohistochemistry in tissue microarrays (TMAs).<sup>15,16</sup> Stains were evaluated by a pathologist. Mutations and staining were compared between Black and White patients using Fisher's exact test.

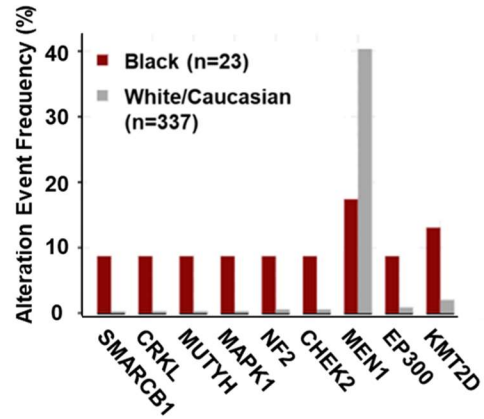
**RESULTS:** A total of 23 and 369 pNET specimens were identified in the AACR dataset from Black and White patients, respectively. Mutations evaluated included inframe insertions & deletions (INDELs), truncating mutations (nonsense, frameshift, non-start, non-stop, and splice site), and structural variants/fusions. Nine genes were found to be differentially mutated between groups (**Fig 1A**). Four of these genes have direct roles in epigenetic regulation (SMARCB1, MEN1, EP300, KMT2D). 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).

**CONCLUSION:** Unique mutational differences are present between Black and White patients with pNETs, many of which are in key epigenetic regulators. Further (epi)genetic sequencing efforts are warranted in Black patients with pNETs.

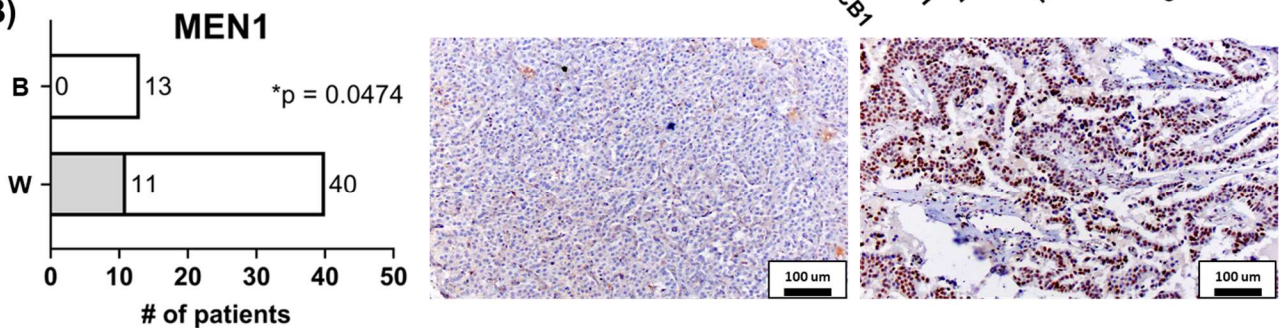
**A)**

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

\*Fisher's Exact Test



**B)**



**Figure 1. A)** Genes with significantly different rates of INDELS, frameshift, truncating, and structural mutations in pNETs from AACR Genie. **B)** Immunohistochemical staining of pNET TMAs for MEN 1. Loss of staining (gray) indicates protein-altering mutation.

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