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# Functional Genomics of Pancreatic Neuroendocrine Tumor Malignancy

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**BACKGROUND:** Pancreatic neuroendocrine tumors (PanNETs) are among one of the fastest growing cancer diagnoses due to improved detection of asymptomatic malignancies during cross-sectional imaging; however, it is difficult to determine which patients will develop malignant disease. Preliminary genomic analysis of primary PanNETs revealed a complex mutational landscape with four common oncogenic events; yet, critical activation pathways that correlate with tumor aggressiveness have yet to be elucidated. Therefore, pan-genomic analysis of both primary and metastatic PanNETs is necessary to understand which genes/pathways are deregulated in PanNET progression and lead to malignancy.

**METHODS:** We initiated a preliminary genomic sequencing study to evaluate mutations in a set of primary and metastatic PanNETs to determine genetic variants involved in metastasis to the liver. De-identified FFPE tumor samples were analyzed from patients who underwent surgical resection without receiving preoperative therapy. DNA was isolated and whole exome sequencing was performed using the Nextera Rapid Capture Exome Kit by Illumina on an Illumina HiSeq 2000/2500. The following criteria were used to define genetic variants: bidirectional, non-synonymous, 30X coverage, clean mapping in IGV, and a ≥ 5% alternate allele frequency.

**RESULTS:** There was no difference in tumor stage between non-metastatic PanNETs, PanNETs with lymph node metastases, and PanNETs with liver metastases. Non-metastatic tumors all classified as G1 whereas PanNETs with lymph node metastases were G1/G2 and PanNETs with liver metastases were

G2/G3. All PanNETs with liver metastases harbored a somatic mutation in the same histone modifying protein. This mutation was not identified in any non-metastatic PanNETs or PanNETs with lymph node metastases. Additionally, two-thirds of liver metastases contained a somatic mutation in the same FGF receptor family member.

**CONCLUSION:** We have discovered a novel marker that is a potential driver of PanNET liver metastasis along with an innovative signaling pathway that may sustain liver metastasis growth and survival.