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The Genomic Landscape of Small Intestine Neuroendocrine Tumors

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Background: Small intestine neuroendocrine tumors (SI-NET) are the commonest malignancy of the small bowel. SI-NET clinical trials target PI3K/Akt/mTOR signaling. Whether these or other genes are genetically altered is unclear.

Methods: We performed analysis of 48 SI-NET by massively parallel exome sequencing.

Results: An average of 0.1 somatic SNV were detected per 10^6 nucleotides (range 0-0.59), mostly transitions (C>T, A>G), resembling genetically stable cancers. 197 protein altering somatic SNV affected a preponderance of cancer genes including FGFR2, MEN1, HOOK3, EZH2, MLF1, CARD11, VHL, NONO, and SMAD1. Integrative analysis of SNV and somatic copy number variations identified recurrently mutated mechanisms of carcinogenesis: chromatin remodeling; DNA damage; apoptosis; RAS signaling; axon guidance. Candidate therapeutically relevant alterations were found in 35 patients including SRC, SMADs, AUROKA, EGFR, HSP90, and PDGFR. Mutually exclusive amplification of AKT1 or AKT2 was the most common event in the 16 patients with alterations of PI3K/Akt/mTOR.

Conclusion: Sequencing-based analysis may provide provisional grouping of SI-NET by therapeutic targets or deregulated pathways.