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MicroRNA-Based Classification of Neuroendocrine Neoplasms

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BACKGROUND: Neuroendocrine neoplasms (NENs) are clinically diverse tumors that lack a single defining molecular marker. microRNAs (miRNAs) are small RNA molecules that are excellent biomarkers due to their stability, abundance, cell-type- and disease-stage specificity. To date, there are no comprehensive miRNA profiling studies of multiple NEN pathological types. Given their utility in cancer classification, we hypothesized that miRNAs can be used to define and classify NENs.

METHODS: Comprehensive miRNA expression profiles for 221 archived NEN samples, representing 15 different pathological types, and 114 non-NEN controls were generated through barcoded small RNA sequencing. Following data quality control, we compared miRNA expression in NEN and non-NEN samples through high expression analyses and built a hierarchical machine-learning model for NEN classification.

RESULTS: miR-375 was abundantly expressed in all NENs and significantly higher in NEN compared to non-NEN tissues. Within NENs, machine learning models identified 17 miRNAs that could accurately discriminate all 15 pathological types. These miRNAs were subsequently used in a multi-layer machine-learning model that separates NENs on developmental (epithelium vs. neuroectoderm) and anatomic origin, with 97-100% accuracy at each layer of the classifier.

CONCLUSION: We provide compelling evidence that miR-375 is a universal mono-analyte marker of NEN tissue differentiation. We also show that NENs can be accurately classified through high quality miRNA expression profiling and machine-learning models. We plan to leverage our findings to improve NEN detection and to advance our knowledge of neuroendocrine tumorigenesis.