Aberrant Menin expression is an early event in pancreatic neuroendocrine tumorigenesis.

Pancreatic neuroendocrine tumors (PanNETs) are the second most common pancreatic malignancy and cause significant morbidity and mortality. Neuroendocrine microadenomas have been proposed as a potential precursor lesion for sporadic PanNETs. In this study, we applied telomere-specific fluorescent in situ hybridization (FISH) to a series of well-characterized sporadic neuroendocrine microadenomas and investigated the prevalence of alterations in known PanNET driver genes (MEN1 and ATRX/DAXX) in these same tumors using immunohistochemistry for the encoded proteins. We identified aberrant Menin expression in 14 of 19 (74%) microadenomas, suggesting that alterations in Menin, at least a subset of which was likely due to somatic mutation, are early events in pancreatic neuroendocrine tumorigenesis. In contrast, none of the microadenomas met criteria for the alternative lengthening of telomeres phenotype (ALT) based on telomere FISH, a phenotype that is strongly correlated to ATRX or DAXX mutations. Two of 13 microadenomas (15%) were noted to have very rare abnormal bright telomere foci on FISH, suggestive of early ALT, but these lesions did not show loss of
ATRX or DAXX protein expression by immunohistochemistry. Overall, these data suggest that loss of Menin is an early event in pancreatic neuroendocrine tumorigenesis and that ATRX/DAXX loss and ALT are relatively late events.