

5 - Colorectal mixed adenoneuroendocrine carcinomas and neuroendocrine carcinomas are genetically closely related to colorectal adenocarcinomas.

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Colorectal mixed adenoneuroendocrine carcinomas are rare and clinically aggressive neoplasms with considerable morphological heterogeneity. Data on their genomic characteristics and molecular associations to either conventional colorectal adenocarcinomas or poorly differentiated neuroendocrine neoplasms is still scarce, hampering optimized patient treatment and care. Tissue from 19 colorectal mixed adenoneuroendocrine carcinomas and eight colorectal poorly differentiated neuroendocrine neoplasms (neuroendocrine carcinomas) was microdissected and subjected to next-generation sequencing using a colorectal adenocarcinoma-specific panel comprising 196 amplicons covering 32 genes linked to colorectal adenocarcinoma, and poorly differentiated neuroendocrine neoplasm tumorigenesis. Mixed adenoneuroendocrine carcinomas were also examined for microsatellite instability and MLH-1 promoter methylation status. In three mixed adenoneuroendocrine carcinomas, exocrine and endocrine components were analyzed separately. Genetic testing of colorectal mixed adenoneuroendocrine carcinomas identified 43 somatic mutations clustering in 13/32 genes. Sixteen (84%) tumors harbored at least one somatic mutation, two tumors (11%) displayed high microsatellite instability. Compared with colorectal adenocarcinomas, mixed adenoneuroendocrine carcinomas were more frequently BRAF (37%; $P=0.006$), and less frequently KRAS (21%; $P=0.043$) and APC (16%; $P=0.001$) mutated. Point mutations in neuroendocrine neoplasm-related genes like RB1 or RET were not detected, but one tumor harbored a heterozygous RB1 deletion. Separately analyzed adenocarcinoma and neuroendocrine carcinoma components revealed a shared mutational trunk of driver genes involved in colorectal adenocarcinoma carcinogenesis. Colorectal neuroendocrine carcinomas were similar in their mutation profile to colorectal adenocarcinomas, but compared with mixed adenoneuroendocrine carcinomas, had a higher rate of APC mutations ($P=0.027$).

Our data indicate that colorectal mixed adenoneuroendocrine carcinomas and neuroendocrine carcinomas are genetically closely related to colorectal adenocarcinomas, suggesting that the cells giving rise to these tumors primarily have an intestinal coinage. The identification of BRAF mutations and the frequently present KRAS wild-type status principally render some mixed adenoneuroendocrine carcinomas eligible to targeted treatment strategies used for colorectal adenocarcinomas.