Molecular Evidence for Independent Origin of Multifocal Neuroendocrine Tumors of the Enteropancreatic Axis

Terrence M. Katona, Timothy D. Jones, Mingsheng Wang, Fadi W. Abdul-Karim, Oscar W. Cummings, and Liang Cheng

Departments of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana and Department of Pathology, Case Western Reserve University, Cleveland, Ohio

Abstract

Neuroendocrine tumors of the enteropancreatic axis are often multifocal. We have investigated whether multifocal intestinal carcinoid tumors and multifocal pancreatic endocrine tumors arise independently or whether they originate from a single clone with subsequent intramural or intrapancreatic spread. Twenty-four cases, including 16 multifocal intestinal carcinoid tumors and eight multifocal pancreatic endocrine tumors, were studied. Genomic DNA samples were prepared from 72 distinct tumor nodules using laser capture microdissection. Loss of heterozygosity (LOH) assays were done using markers for putative tumor suppressor genes located on chromosomes 9p21 (p16), 11q13 (MEN1), 11q23 (SDHD), 16q21, 18q21, and 18q22-23. In addition, X chromosome inactivation analysis was done on the tumors from eight female patients. Twenty-two of 24 (92%) cases showed allelic loss in at least one tumor focus, including 15 of 16 (94%) cases of multifocal carcinoid tumors and 7 of 8 (88%) cases of multifocal pancreatic endocrine tumors. Eleven of 24 (46%) cases exhibited a different LOH pattern for each tumor. Additionally, 9 of 24 (38%) cases showed different LOH patterns among some of the coexisting tumors, whereas other coexisting tumors displayed the same allelic loss pattern. Two of 24 (8%) cases showed the same LOH pattern in every individual tumor. X chromosome inactivation analysis showed a discordant pattern of nonrandom X chromosome inactivation in two of six informative cases and concordant pattern of nonrandom X chromosome inactivation in the four remaining informative cases. Our data suggest that some multifocal neuroendocrine tumors of the enteropancreatic axis arise independently, whereas others originate as a single clone with subsequent local and discontinuous metastasis. (Cancer Res 2006; 66(9): 4936-42)

Introduction

Carcinoid tumors are relatively uncommon neoplasms that nonetheless comprise up to 85% of neuroendocrine gastrointestinal neoplasms (1). They most frequently occur in the midgut and develop from neuroendocrine cells that are normally and diffusely present in this location (2, 3). Unlike neuroendocrine tumors of the duodenum, stomach, and pancreas, midgut carcinoid tumors are not typically associated with multiple endocrine neoplasia type 1 (MEN1) or with neurofibromatosis (4). One feature of these tumors, occurring in up to 33% of intestinal carcinoid cases, is their tendency to present as multiple, discontinuous nodules within the mucosa and submucosa (5–7). Whether or not multifocal carcinoid tumors are monoclonal or independent in origin has not been fully elucidated (5, 8).

Pancreatic endocrine tumors (PET; islet cell tumors) similarly are uncommon, occurring in 0.4 to 1 per 100,000 persons. PETs comprise 1% of all pancreatic neoplasms although a prevalence as high as 15% of all pancreatic tumors has been described in one surgical series (9, 10). PETs are commonly seen in the setting of MEN1, with these patients having a propensity toward developing multifocal tumors, some of which may ultimately metastasize (11). Elucidating the clonal relationships of multifocal neuroendocrine tumors of the enteropancreatic axis could provide further insight into the genetic nature of these tumors and could potentially affect clinical and surgical management. In this study, we have investigated the pattern of allelic loss and X chromosome inactivation in the tumors from 16 patients with multifocal carcinoid tumors and from eight patients with multifocal pancreatic endocrine tumors to assess clonality of individual tumors.

Patients and Methods

Patients. Twenty-four patients (16 men and 8 women) with multifocal carcinoid or multifocal pancreatic endocrine tumors underwent resection between 1989 and 2005. Fourteen patients (nine men and five women) had midgut carcinoid tumors, including one case with tumors arising in the appendix and 13 cases with tumors located in the jejunum or ileum. One male patient had multifocal hindgut carcinoid tumors arising in the rectum. Another male patient had multifocal carcinoid tumors arising in the duodenum. Eight patients (five men and three women) had multifocal PETs. Two patients with multifocal PETs had functional tumors, including one gastrinoma and one insulinoma. Both the duodenal and pancreatic tumors are considered foregut neuroendocrine tumors. Eight of the patients (six men and two women) were known to have the MEN1 syndrome. All MEN1 patients had foregut neuroendocrine tumors, including one patient with multiple duodenal carcinoids and seven patients with multiple PETs.

The mean patient age was 52.5 years (range, 23-87 years). All patients had two or more tumors (range, 2-6) that were confined to either the intestine or the pancreas. The mean diameter of the largest tumor from each patient was 1.01 cm (median, 1.0 cm; range, 0.1-5.0 cm). The mean diameter of the largest intestinal carcinoid tumor from each patient was 1.05 cm (median, 1.1 cm; range, 0.2-2.5 cm). The mean diameter of the largest tumor from each pancreatic endocrine tumor was 0.96 cm (median, 0.6 cm; range, 0.1-5.0 cm).

Tissue samples and microdissection. Archival surgical materials from 16 patients (11 men and 5 women) with multifocal intestinal carcinoid tumors and from eight patients (five men and three women) with multifocal pancreatic endocrine tumors accessioned from 1989 to 2005 were retrieved from the surgical pathology files of the Indiana University
Medical Center (Indianapolis, IN) and the University Hospitals of Cleveland and Case Western Reserve University (Cleveland, OH). All cases labeled small bowel were from the jejunum and/or ileum. This study included a total of 74 separate neuroendocrine tumors, including 52 carcinoid tumors and 22 pancreatic endocrine tumors.

Histologic sections were prepared from formalin-fixed, paraffin-embedded tissue and were stained with H&E for microscopic evaluation. From these slides, the neuroendocrine neoplasms were reviewed by a single pathologist (L.C.). Laser-assisted microdissection of the separate tumors was done on unstained sections using a PixCell II Laser Capture Microdissection system (Arcturus Engineering, Mountain View, CA), as previously described (12–14). Approximately 400 to 1,000 cells of each tumor nodule were microdissected from the 5-μm histologic sections (Fig. 1). Normal tissue from each case was microdissected as a control.

Detection of loss of heterozygosity. The dissected cells were deparaffinized with xylene and ethyl alcohol. PCR was used to amplify genomic DNA at six specific loci on four different chromosomes: 9p (D9S171; p16 gene), 11q13 (D11S2072; MEN1 gene), 11q23 (D11S1986; SDHD gene), 16q (D16S422), and 18q (D18S541 and D18S541). Previous studies have shown that loss of heterozygosity (LOH) at these loci occurs frequently in midgut carcinoid tumors or PETs or both (3, 9, 10, 15–27). The tumor suppressor gene p16 is located at 9p21, and genetic aberrations of this gene have been detected in PETs (9, 18, 22). Additionally, up to 21% of foregut and midgut neuroendocrine tumors have shown losses of 9p by comparative genomic hybridization (CGH) analysis (21). Allelic losses at 11q13 (MEN1 gene) have been described in both sporadic and MEN1-associated PETs, with the latter showing LOH most frequently (9, 18, 22). In contrast, neuroendocrine tumors of the midgut and hindgut rarely manifest MEN1 mutations (21). Only a limited number of carcinoid tumors have exhibited LOH at 11q13 (21). Chromosomal region 11q23 (D11S1986) contains the putative tumor suppressor gene SDHD, which encodes a subunit of cytochrome b, a component of mitochondrial succinate-ubiquinone oxidoreductase (complex II). Losses of 11q have been shown in midgut carcinoid tumors by CGH and LOH methods (15, 17, 20). D’Adda et al. have shown that up to 52% of gastrointestinal neuroendocrine tumors and 28% to 69% of PETs have losses of 11q downstream from the MEN1 locus (23). The D16S422 locus is located at 16q21 within another putative tumor suppressor gene, the loss of which has been described in midgut carcinoid tumors and which may be correlated with a more aggressive phenotype (3, 16). The loss of chromosome 16q has been found in 29% of ileal carcinoids (20). The tumor suppressor genes DPC4/Smad4 and DCC are located at 18q21 (D18S541). LOH at these loci has been described in nonfunctioning PETs (9). A study of 25 nonfunctional PETs showed mutation or deletion of DPC4/Smad4 in 55% of cases (27). Another putative tumor suppressor gene may be present immediately downstream from the DPC4/Smad4 and DCC genes at 18q21 (15, 21). Loss of 18q22-23 (D18S514) is considered an “early and specific event” in the genesis of midgut carcinoids (16). CGH studies of gastrointestinal neuroendocrine tumors have shown nonspecific losses by DNA copy number changes on chromosome 18q in 18% to 43% of tumors (19, 21).

PCR amplification and gel electrophoresis were done as previously described (28, 29). PCRs for each polymorphic microsatellite marker were repeated at least twice and for certain cases up to five times from the same DNA preparations, and the same results were obtained. The criterion for allelic loss was complete or nearly complete absence of one allele in tumor DNA. DNA sampled from the cells of separate neuroendocrine neoplasms showing identical allelic loss patterns is compatible with a common clonal origin, whereas different patterns of allelic deletions are compatible with independent clonal origins of these tumors (13, 14, 28, 29).

Detection of X chromosome inactivation. X chromosome inactivation analysis was done on the neuroendocrine tumors from the eight female patients, including five midgut carcinoid cases and three pancreatic endocrine tumor cases, as previously described (30, 31). Tumors were considered to be of the same clonal origin if the same AR allelic inactivation pattern was detected in each separate neoplasm. Tumors were considered to be of independent origin if alternate predominance of AR alleles after HhaI digestion (different allelic inactivation patterns) was detected in each tumor (32–34).

Results

Twenty-two of 24 (92%) cases showed allelic loss in at least one tumor focus, including 15 of 16 (94%) multifocal carcinoid tumors and 7 of 8 (88%) multifocal pancreatic endocrine tumors (Table 1). The number of loci lost in a single tumor nodule ranged from one to six. Two of 24 (8%) cases showed the same LOH pattern in every individual tumor focus, consistent with a monoclonal origin. Eleven of 24 (46%) cases exhibited a different LOH pattern for each tumor, signifying that each arose independently (Fig. 2). Additionally, 9 of 24 (38%) cases showed different LOH patterns in some tumors, whereas other tumors in the same patient showed identical LOH patterns. This latter finding may indicate that within the same patient, some of the multifocal tumors are clonally
related, whereas other tumors arose independently. Two of 24 (8%) cases failed to display LOH at any of the six loci examined.

The frequency of allelic loss in the informative multifocal carcinoid tumors was 35% (17 of 49) with D9S171, 14% (7 of 49) with D11S2072, 28% (12 of 43) with D11S1986, 35% (15 of 43) with D16S422, 11% (5 of 47) with D18S64, and 41% (20 of 49) with D18S541. The frequency of allelic loss in the informative multifocal pancreatic endocrine tumors was 41% (9 of 22) with D9S171, 21% (3 of 14) with D11S2072, 41% (7 of 17) with D11S1986, 18% (4 of 22) with D16S422, 32% (7 of 22) with D18S64, and 14% (2 of 14) with D18S541.

The respective frequencies of LOH in informative MEN1-related foregut neuroendocrine tumors (seven patients with PETs and one patient with duodenal carcinoids) were 48% (12 of 25) with D9S171, 18% (3 of 17) with D11S2072, 45% (9 of 20) D11S1986, 16% (4 of 25) with D16S422, 28% (7 of 25) with D18S64, and 24% (4 of 17) with D18S541.

The allelic loss patterns at the six loci were variable among some of the multifocal carcinoid tumors and some of the multifocal PETs that were analyzed, consistent with independent origin. Other cases had multiple tumors with the same LOH pattern, indicative of a monoclonal origin. Some multifocal carcinoid tumors and some multifocal PETs displayed a mixed pattern with some tumors sharing an identical allelic loss pattern and other tumors displaying an alternate LOH pattern. In two patients with multifocal carcinoids (cases 4 and 13) and in one patient with multifocal PETs (case 23), each tumor displayed a unique LOH pattern; however, the separate tumors displayed a concordant, nonrandom inactivation pattern by X chromosome inactivation analysis, consistent with a monoclonal origin.

Four of 13 (31%) patients with multifocal midgut carcinoid tumors (excluding the appendical carcinoid case) displayed a different LOH pattern in each tumor, consistent with an independent origin for each tumor. Seven of 13 (54%) patients with multifocal midgut carcinoids exhibited a mixed pattern of monoclonal and independent origin of separate tumor foci by LOH analysis. One patient (case 14) with multiple midgut carcinoid tumors displayed a monoclonal origin for all multicentric tumors. One midgut carcinoid case (case 9) failed to show allelic loss at any of the six loci studied.

X chromosome inactivation analysis was informative for five carcinoid tumors and one pancreatic tumor. Three cases of multifocal carcinoid tumors (cases 4, 13, and 14) and one case (case 23) of multifocal pancreatic endocrine tumors showed a concordant pattern of nonrandom X chromosome inactivation among all coexisting tumors, consistent with a monoclonal origin. Two cases of multifocal carcinoid tumors (cases 5 and 24) displayed a discordant pattern of nonrandom X chromosome inactivation, consistent with an oligoclonal origin. Two of the three multifocal carcinoid tumor patients (cases 4 and 13) with a concordant pattern of nonrandom X chromosome inactivation had only two tumors.

The seven MEN1 patients with multifocal PETs were examined for LOH using all six microsatellite loci. Of these MEN1 patients, one patient (case 18) showed a monoclonal pattern on LOH analysis, three patients (cases 10, 15, and 16) showed an oligoclonal LOH pattern, two patients (cases 17 and 21) displayed a mixed pattern on LOH analysis, and one patient (case 11) manifested retention of heterozygosity at all six loci examined. One patient (case 23) with two multifocal PETs displayed an LOH pattern indicative of independent origin; however, the two tumors displayed a concordant pattern of nonrandom X chromosome inactivation.
Table 1. LOH analysis and X chromosome inactivation analysis of multifocal intestinal carcinoid tumors and multifocal pancreatic endocrine tumors

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Anatomic site and classification</th>
<th>Age</th>
<th>Sex</th>
<th>Tumors</th>
<th>Allelic loss/microsatellite markers</th>
<th>X chromosome*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p16/</td>
<td>SDHD/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D9S171</td>
<td>D11S1986</td>
</tr>
<tr>
<td>1</td>
<td>Rectum, hindgut</td>
<td>55</td>
<td>M</td>
<td>F1</td>
<td>▼ N ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>2</td>
<td>Appendix, midgut</td>
<td>87</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>3</td>
<td>Small bowel, midgut</td>
<td>68</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>4</td>
<td>Small bowel, midgut</td>
<td>71</td>
<td>F</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>5</td>
<td>Small bowel, midgut</td>
<td>73</td>
<td>F</td>
<td>F2</td>
<td>▼ ▼ ▼</td>
<td>N ▼ ▼ ▼</td>
</tr>
<tr>
<td>6</td>
<td>Small bowel, midgut</td>
<td>47</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>N ▼ ▼ ▼</td>
</tr>
<tr>
<td>7</td>
<td>Small bowel, midgut</td>
<td>50</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>N ▼ ▼ ▼</td>
</tr>
<tr>
<td>8</td>
<td>Small bowel, midgut</td>
<td>75</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>9</td>
<td>Ileum, midgut</td>
<td>44</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>12</td>
<td>Small bowel, midgut</td>
<td>65</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>13</td>
<td>Small bowel, midgut</td>
<td>42</td>
<td>F</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>14</td>
<td>Small bowel, midgut</td>
<td>37</td>
<td>F</td>
<td>F1</td>
<td>N ▼ ▼ ▼</td>
<td>N ▼ ▼ ▼</td>
</tr>
<tr>
<td>20</td>
<td>Small bowel, midgut</td>
<td>57</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>22</td>
<td>Ileum, midgut</td>
<td>96</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>N ▼ ▼ ▼</td>
</tr>
<tr>
<td>24</td>
<td>Small bowel, midgut</td>
<td>56</td>
<td>F</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>16</td>
<td>Duodenum, foregut, MEN1</td>
<td>43</td>
<td>M</td>
<td>F1</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
</tbody>
</table>

(Continued on the following page)
environment, one tumor may undergo selection under this exogenous growth stimulus and subsequently develop an invasive phenotype, which may ultimately metastasize. Clonality studies comparing multifocal midgut carcinoids with their distant and lymph node metastases could shed further light on this question. In a large series of 13,715 carcinoid tumors, up to 29% of individuals with a small bowel carcinoid tumor also developed a synchronous or metachronous noncarcinoid neoplasm elsewhere (7). This association could be due to the production of various trophic products by carcinoid tumors that may have stimulatory, potentially mitogenic, properties in numerous cell types (7).

Clinically apparent PETs are found in 30% to 50% of patients with MEN1 syndrome, and nearly all MEN1 patients harbor small, occult, nonfunctioning PETs (9, 35). Indeed, up to 25% of all PETs occur in MEN1 patients (36). Allelic losses involving the MEN1 gene at 11q13 are frequently the second insult in the classic Knudson "two-hit" hypothesis of tumorigenesis in patients with MEN1 syndrome (21). Moreover, LOH at 11q13 has been described in both sporadic and MEN1-related endocrine tumors (21). MEN1 patients typically develop neuroendocrine tumors of the foregut, such as PETs, gastric carcinoids, and bronchial carcinoids; however, similar tumors of the midgut and hindgut are not associated with this syndrome (35). Moreover, sporadic midgut and hindgut carcinoids seldom manifest LOH at 11q13 (35). Interestingly, in the current study, LOH at 11q13 was infrequently identified, regardless of the site of the tumor or the patient’s MEN1 status. The tumors from only one patient (case 18) with MEN1 syndrome showed LOH at this locus with each tumor having the same pattern of allelic loss. Three other patients (cases 1, 3, and 12) with sporadic multicentric carcinoids showed allelic loss at 11q13. These three patients displayed a different LOH pattern in each tumor, consistent with independent origin.

The clinical implications of our study become relevant in the planning of an appropriate surgical strategy. Subtotal distal pancreatectomy is the most frequent treatment choice for PETs. In a scenario in which multiple small discrete pancreatic endocrine tumors are present in an individual with a separate larger lesion, attempted enucleation of a presumed solitary PET may leave a small occult tumor behind in the residual pancreas. This possibility is especially relevant in the management of MEN1 patients, given their propensity toward tumor multifocality. This scenario may be lessened with the current implementation of intraoperative ultrasound to detect small, occult tumor foci during resection (11, 37–40). With some multifocal tumors arising independently, there is a greater probability that one neoplasm could develop genetic aberrations leading to a more aggressive phenotype. This conclusion is supported by the association of multifocality with poor prognosis (4). With the prediction of the malignant potential of PETs often difficult, complete excision of all tumor foci is paramount to prevent recurrence and to provide an accurate prognosis (41). Additionally, further elucidation of the genetic nature of PETs may permit greater accuracy in assessing their malignant potential.

### Table 1. LOH analysis and X chromosome inactivation analysis of multifocal intestinal carcinoid tumors and multifocal pancreatic endocrine tumors (Cont’d)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Anatomic site and classification</th>
<th>Age</th>
<th>Sex</th>
<th>Tumors</th>
<th>Allelic loss/microsatellite markers</th>
<th>X chromosome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Pancreas, foregut, MEN1</td>
<td>F</td>
<td>F1</td>
<td>N</td>
<td>p16/ D9S171, SDHD/ D11S1986, 11q3/ D11S2072, 16q/ D16S422, 18q21/ D18S64, 18q22-23/ D18S441</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>Pancreas, foregut, MEN1</td>
<td>34</td>
<td>M</td>
<td>F1</td>
<td>N</td>
<td>p16/ D9S171, SDHD/ D11S1986, 11q3/ D11S2072, 16q/ D16S422, 18q21/ D18S64, 18q22-23/ D18S441</td>
</tr>
<tr>
<td>17</td>
<td>Pancreas, foregut, MEN1</td>
<td>32</td>
<td>F</td>
<td>F1</td>
<td>N</td>
<td>p16/ D9S171, SDHD/ D11S1986, 11q3/ D11S2072, 16q/ D16S422, 18q21/ D18S64, 18q22-23/ D18S441</td>
</tr>
<tr>
<td>18</td>
<td>Pancreas, foregut, MEN1</td>
<td>54</td>
<td>M</td>
<td>F1</td>
<td>N</td>
<td>p16/ D9S171, SDHD/ D11S1986, 11q3/ D11S2072, 16q/ D16S422, 18q21/ D18S64, 18q22-23/ D18S441</td>
</tr>
<tr>
<td>23</td>
<td>Pancreas, foregut, MEN1</td>
<td>34</td>
<td>F</td>
<td>F1</td>
<td>N</td>
<td>p16/ D9S171, SDHD/ D11S1986, 11q3/ D11S2072, 16q/ D16S422, 18q21/ D18S64, 18q22-23/ D18S441</td>
</tr>
</tbody>
</table>

**Note:** ▼, loss of upper allele; ▲, loss of lower allele; †, both alleles present.

**Abbreviations:** FC, tumor focus; N, noninformative.

*X chromosome inactivation analysis (HUMARA).
Although there was evidence for an independent origin in some or all endocrine tumors in the majority of patients, some tumors seemed to share the same clonal origin. Some caveats must be considered regarding assessments of clonality based on X chromosome inactivation data. As mentioned above, the presence of a common X inactivation pattern is not unequivocal proof of a monoclonal origin. The possibility exists that the same X chromosome was inactivated in multiple tumors merely by coincidence. However, as the sample size increases and a greater number of tumors are found to share the same inactivation pattern, the probability of multiple tumors displaying the same pattern purely by chance becomes unlikely. For example, the probability that each individual tumor has the same inactivated X chromosome in a patient with three separate tumors is 1 in 8 \[\text{i.e., } (1/2)^3; \text{ ref. 5}\]. In our study, four patients (cases 4, 13, 14, and 23) having up to three separate informative tumors showed X inactivation patterns indicating a common clonal origin. The probability of this occurring by coincidence is remote. However, the conclusion that a shared X inactivation pattern indicates monoclonality has additional confounding factors. A group of genetically or epigenetically dissimilar cells can share a common X inactivation pattern before the onset of tumorigenesis and still give rise to subpopulations within that tumor (42).

Our data suggest that in the majority of patients with multifocal neuroendocrine tumors of the enteropancreatic axis, there is evidence of independent origin of at least some of the separate tumors by allelic loss analysis and/or X chromosome inactivation analysis. Our findings may be relevant in planning an appropriate treatment strategy and in providing accurate prognosis.

Acknowledgments

Received 11/22/2005; revised 2/7/2006; accepted 3/3/2006.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

References


Molecular Evidence for Independent Origin of Multifocal Neuroendocrine Tumors of the Enteropancreatic Axis

Terrence M. Katona, Timothy D. Jones, Mingsheng Wang, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/66/9/4936

Cited articles
This article cites 42 articles, 9 of which you can access for free at:
http://cancerres.aacrjournals.org/content/66/9/4936.full.html#ref-list-1

Citing articles
This article has been cited by 5 HighWire-hosted articles. Access the articles at:
/content/66/9/4936.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.