

## BT7

### Induction of Serotonin Production in Human Pancreatic Neuroendocrine Tumors by Tryptophan Hydroxylase-1

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**Background:** Pancreatic neuroendocrine tumors (PNETs) frequently metastasize and produce hormones, causing debilitating symptoms. However, little is known about the malignant potential and clinical sequelae of PNETs producing serotonin and the molecular events underlying serotonin production. Two isoforms of tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin synthesis, exist – TPH-1 and TPH-2. *We sought to elucidate the malignant potential and clinical features of serotonin-producing PNETs and hypothesized that a single TPH isoform functions in serotonin synthesis.*

**Methods:** TPH-1 and TPH-2 expression levels were evaluated in PNETs (n=32) and normal pancreas (n=9) by quantitative RT-PCR. Serotonin expression was assessed in PNETs (n=21) by immunohistochemistry. The clinical and pathological features of patients who underwent resection were analyzed.

**Results:** In comparison to the expressive levels found in normal pancreas tissue, we detected elevated TPH-1 expression in almost half of PNETs (14/32, 43.8%, *Figure 1*). In contrast, we found very low levels of TPH-2 expression in all PNETs. We observed serotonin expression in one-third of PNETs (7/21, 33.3%). All serotonin-positive PNETs (7/7, 100%) expressed TPH1 but not TPH2. Most (10/14, 71.4%) TPH-1-positive PNETs were malignant, exhibiting either lymph node (4/14, 28.6%) or liver (6/14, 42.9%) metastases. A clinical syndrome due to hormonal excess was present in 35.6% (5/14) of TPH1-positive PNETs (gastrinoma in 1, insulinoma in 2, glucagonoma in 2). No patient had classical carcinoid syndrome.

**Conclusion:** In this study, we found that TPH-1 and serotonin are expressed in many PNETs. Importantly, we conclude that TPH-1, but not TPH-2, is required for serotonin production in PNETs. Most serotonin-producing PNETs are malignant, and despite the presence of liver metastases, none of the patients had carcinoid syndrome. Rather, sequelae attributed to other hormones were observed.

**Figure 1. Relative TPH-1 mRNA levels**

**TPH-1 mRNA expression, value relative to BON cell line. Assayed via real-time PCR**

