Frequency and clinical correlates of somatic Ying Yang 1 mutations in sporadic insulinomas.

Abstract:
Insulinomas represent pancreatic neuroendocrine neoplasms that cause severe morbidity attributed to their often pronounced endocrine activity. Apart from hereditary forms such as multiple endocrine neoplasia type 1 (MEN-1), genetic causes for sporadic insulinoma development had remained obscure until recently. Applying next-generation sequencing methods, disease-causing genetic alterations have been identified in various endocrine tumors. Paired tumor and blood DNA from eight patients with sporadic insulinomas (five females and two malignant tumors) were analyzed by whole-exome sequencing. After this initial analysis, Ying Yang 1 (YY1) mutation status was assessed in a larger cohort of 39 additional insulinomas (including eight malignant and one liver metastasis) from three German hospitals by targeted sequencing. The mutation status was correlated with various clinical parameters. A range of one to 12 somatic genetic variants were identified by exome sequencing. A recurrent somatic Thr372Arg YY1 point mutation was detected in two patients of the initial cohort and four patients of the second cohort (total, six of 47; 13%). The presence of the
mutation was associated with a trend toward higher age (63.5 y; IQR, 48.0-74.0 vs 45.0 y; IQR, 33.0-63.0; P = .05), and all affected patients were females (six of six; P = .04). All other clinical parameters, including the presence of malignancy and metastatic spread, tumor localization, and hypoglycemic episodes were not different between YY1-mutated and nonmutated tumor carriers. The somatic Thr372Arg YY1 mutation is a relevant finding in female patients with sporadic insulinomas. The prevalence of this mutation in this Caucasian population is considerably lower compared to that of a recently described Asian cohort.