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Somatic genomic profiling of gastrointestinal neuroendocrine tumors: Implications for prognostication and therapeutic targeting

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BACKGROUND

The incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is rising, yet their biological heterogeneity and variable treatment response remain poorly understood. Comprehensive genomic characterization is needed to uncover somatic drivers and inform biomarker-driven therapeutic strategies.

METHODS

We performed next-generation sequencing (NGS) on tumor samples from 111 patients with confirmed GEP-NETs treated at Johns Hopkins Hospital between 2020 and 2022. Pathogenic and likely pathogenic mutations were identified using OncoKB, CHASMplus, and COSMIC databases. Mutational patterns were correlated with clinical characteristics and overall survival using univariate and multivariate analyses.

RESULTS

In this retrospective study of 111 patients with GEP-NETs, somatic pathogenic or likely pathogenic mutations were identified in 79% of cases. The most frequent alterations involved TP53 (19%), MEN1 (17%), and chromatin remodeling genes such as DAXX (9%) and ATRX (6%). Notably, 9% of patients harbored mutations typically associated with hematologic malignancies, a finding not widely reported in GEP-NETs. Distinct co-mutation patterns were observed between pNETs and non-pancreatic GI-NETs, including mutual exclusivity of MEN1 and TP53 mutations in pNETs. SHINYGO analysis revealed that GEP-NETs exhibit disrupted chromatin remodeling and DNA repair, with pancreatic primaries enriched for epigenetic modifiers and GI-NETs for Wnt signaling. Clinical correlation showed associations between poor tumor differentiation or high-grade disease and mutations in TP53(P=0.02), KRAS(P=0.009), BRAF (P=0.01) and CDKN2A(P=0.03). Survival analysis demonstrated that mutations in KRAS (HR 7.45, P=0.009), the DAXX/ATRX group (HR 3.57, P=0.04) and hematologic malignancy-associated genes (HR 4.39, P=0.03) were independently associated with worse overall survival. These findings highlight distinct genomic and clinical correlates in GEP-NETs with implications for risk stratification and targeted therapy development.

CONCLUSIONS

This study reveals distinct somatic mutation patterns in GEP-NETs that are associated with tumor differentiation, grade, primary site, and survival. The identification of hematologic malignancy-associated mutations in a subset of GEP-NETs suggests possible shared molecular phenotypes with poor prognostic implications. These findings support incorporating genomic profiling into routine clinical evaluation to improve risk stratification and guide precision therapy in GEP-NETs.

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