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Molecular and Clinical Profiling of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): An Analysis of the Oncology Research Information Exchange Network Database

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BACKGROUND

The incidence of neuroendocrine tumors (NETs) is approximately 7 per 100,000 persons and rising. By location, tumors located in the gastroenteropancreatic (GEP) region, particularly midgut NETs, are most common. The Oncology Research Information Exchange Network (ORIEN) database contains complementary clinical, genomic, and transcriptomic profiling, providing opportunities to identify novel associations between molecular features and clinical outcomes.

METHODS

Survival analyses were performed using the Log-rank testing, and clinical features were evaluated using Wilcoxon and chi-squared tests. Mutational analyses utilized sample-level enrichments from whole exome sequencing data, and statistical tests were performed using the one-sided Fisher Exact test. Transcriptomic analyses utilized a student's t-test. We reviewed well-differentiated GEP-NET samples of these primary sites: pancreatic (n=121), small bowel (n=89), gastric (n=15), and colorectal (n=9). A p-value <0.05 was considered significant.

RESULTS

Across all GEP-NETs, the most common somatic mutations were *TTN* (29%), *MUC16* (25%), *TGIF2LX* (23%), *CCDC168* (21%), *MUC17* (18%), and *MEN1* (18%). The most common copy number amplifications were *MUC3A* (61%), *PRSS2* (32%), *ROCK1P1* (30%), and *MUC19* (30%).

NETs of small bowel origin had significantly higher rates of M1 stage than pancreatic NETs (p=0.02). Quantitative MSI by WES was significantly higher in pNETs compared to sbNETs ($p<0.001$). *MEN1* was the most common mutation in pNETs (35.6%). Mutations in *ARGAP* (23%), *CEP126* (22%), *MMP20* (17%), *CASP5* (17%), *DDI1* (15%), and *TRPC6* (15%) were the most common in sbNETs and none of these were

frequent in pNETs.

pNETS with a mutation in *ATRX* and/or *DAXX* had significantly higher rates of M1 disease than *ATRX/DAXXwt* pNETs (p=0.029). Specifically, the liver was a more common site of metastatic disease in *ATRX/DAXXmut* pNETS compared to *ATRX/DAXXwt*. More than 200 distinct mRNA expression levels by WES were significantly different between *ATRX/DAXXmut* and wt, potentially providing additional information on the prognostic role of *ATRX/DAXX* mutations in pNETs.

CONCLUSIONS

We report the first clinical, genomic, and transcriptomic analysis of ORIEN GEP-NET cases. These findings create multiple avenues for further investigation and reinforce the value of multi-institutional consortia such as ORIEN in deepening our knowledge of well-differentiated NETs.

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