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Germline Cancer Testing in Unselected Patients with Neuroendocrine Neoplasms: A Multi-center Prospective Study

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BACKGROUND

Neuroendocrine neoplasms (NEN) are known to be associated with specific familial syndromes. However, the incidence of pathogenic germline variants (PGVs) in unselected NEN patients is unknown. In this study, we aim to determine the prevalence and clinical utility of PGVs in unselected NEN patients using universal a genetic testing approach.

METHODS

We undertook a prospective study of germline genetic testing using a > 80 gene next-generation sequencing panel among NEN patients receiving care at Mayo Clinic Cancer Center (3 sites) between April 1, 2018, and June 20, 2022. Patients were not selected based on cancer stage, family history of cancer, ethnicity, or age. Family cascade testing was offered at no charge. Data were analyzed using descriptive statistics to look for trends across patient characteristics and results of the germline genetic testing.

RESULTS

A total of 55 patients with NEN were evaluated. Median age was 56.1 years, 49.1% were male, 87.3% were white. Most patients (69%) had pancreatic primary and 18% had a small bowel primary. Most patients (96%) had well-differentiated NEN. Thirty-four (61.8%) patients had metastatic disease at presentation. Family history of NEN was reported in 8% (4/50) patients. PGVs were detected in 14.5% (n=8) of patients. The prevalence of PGVs was 15.7% (6/38) in pancreatic primary, 11.7% (2/17) in non-pancreatic primary. PGVs detected were the following: *APC* (1), *ATM* (1), *CHEK2* (1), *MEN1* (1), *MITF* (1), *MLH1* (1), and *MUTYH* (2). VUS results are summarized in the table. Overall, a VUS was found in 38% (21/55) of the patients. Five patients had findings in mismatch repair genes (MMR): one patient had a PGV in *MLH1*, 3 patients with VUS in *MSH6,* and one patient with a VUS in *MSH2*. MMR protein testing was done in 3/4 VUS patients, and was MMR deficient in 2 of them.

	VUS (N=34)
ALK	2
APC	1
ATM	1
BRIP1	2
CASR	2
CDH1	1
CHEK2	0
CTNNA1	1
DICER1	1
EGFR	1
FLCN	1
MEN1	1
MITF	0
MLH1	0
MSH2	1
MSH6	3
MUTYH	1
NBN	1
NTHL1	1
PALB2	1
PDGFRA	1
POLD1	1
RAD50	1
RECQL4	3
RET	1
SMARCA4	1
STK11	1
TERC	1
WRN	2

CONCLUSIONS

Universal multi-gene panel testing in NEN was associated with detection of heritable mutations in 15% of patients. Alterations in MMR genes were found in 9% of patients which highlights the importance of germline testing for familial counseling and treatment selection.

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