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Germline Pathogenic Variants in Patients with High-Grade (G3) Metastatic Gastroenteropancreatic (GEP) Neuroendocrine Neoplasms (NENs)

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BACKGROUND

The incidence of germline pathogenic/likely pathogenic variants (P/LPV) is relatively well described in low grade well differentiated neuroendocrine tumors (NETs). However, germline findings in G3 NENs including grade 3 NETs (G3NET) and poorly differentiated neuroendocrine carcinoma (NEC) is gravely understudied, and guidance related to germline testing in G3NEN is lacking.

METHODS

An IRB approved, single institution, retrospective chart review was performed in patients with metastatic G3NEN of gastro enteropancreatic (GEP) origin and unknown primary in whom both tumor DNA sequencing and germline testing were performed as part of clinical care. Pathology reports and clinical history were reviewed by one pathologist to best reclassify as G3NETs, NECs or ambiguous G3NEN. Data were collected from germline and tumor molecular sequencing reports. In patients harboring a germline P/LPV, somatic P/LPV were evaluated.

RESULTS

Among 88 UCSF patients with G3NEN, 15 (17%) had germline P/LPV (13 patients with one and 2 with 2); see Table for details. Median age at the time of metastatic G3NEN was 58 years (range 26-84). Primary tumor sites: pancreas (N=30), colorectum (CR) (N=23), other gastrointestinal (GI) (N=14), and unknown (N=21). Histologic subtypes: 34 NEC, 24 G3NET, and 30 ambiguous G3NEN. Fifteen of 17 total germline P/LPV were also evaluable on somatic panels and 10 (67%) were present in the tumor with high mutant allele frequency (maf), suggesting a role in tumorigenesis. Five of 15 germline P/LPV (33%, 2 MUTYH, 1 BRCA1, 1 APC, and 1 PALB2) were not present or had significantly decreased maf in the tumor, arguing against a role in tumorigenesis.

*Table: Germline P/LPV in G3NENs [Note: ** not sequenced in tumor]*

Gene	Mutated in germline (n)	Mutated in tumor (n)	Differentiation	Site
MUTYH	4	2	1 NEC 3 Ambiguous	2 Pancreas 2 Unknown
BRCA1	2	1	1 NEC 1 ambiguous	1 Pancreas 1 GI
APC	2	1	NEC	1 CR 1 GI
BRCA2	1	1	Ambiguous	CR
MLH1	1	1	NEC	CR
MSH6	1	1	Ambiguous	CR
NTHL1**	1	**	Ambiguous	Pancreas
PALB2	1	0	NET	CR
ATM, NBM**	1	1 (ATM)	NEC	GI
CHEK2 and MEN1	1	1 (CHEK2 & MEN1)	NET	Pancreas

CONCLUSIONS

Germline P/LPV were identified in 17% of patients with GEP G3NENs, with 67% present at high maf in the tumor-supporting a role in G3NEN pathogenesis and with potential therapeutic implications in some cases. The findings suggest a role for germline genetic testing in all patients with G3NEN.

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