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Germline Testing identifies Pathogenic/Likely Pathogenic Variants in Patients with Pancreatic Neuroendocrine Tumors

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BACKGROUND

10% of pancreatic neuroendocrine tumors (pNETs) are thought to be related to inherited syndromes, (MEN1, MEN4, VHL, NF1 and TSC). Growing evidence suggests, that clinically sporadic appearing pNETs can harbor germline mutations. Here, we report the prevalence of pathological/likely pathological germline variants (P/LP) in 2 cohorts: 1) High-risk and 2) Unselected.

METHODS

We retrospectively collected clinical data of pNET patients seen at MD Anderson Cancer Center (MDACC) and Johns Hopkins Hospital (JHH). High-risk cohort included 132 patients seen at MDACC, who underwent germline testing based on high-risk criteria such as early onset, personal or family history of cancer and syndromic features between 2013 -2019. The unselected cohort included 106 patients seen at JHH, who underwent germline testing following their diagnosis of pNETs between 2020 to 2022

RESULTS

In high-risk cohort, 33% (n= 44) had P/LP mutations, and 17 % (n= 22) had a variant of unknown significance (VUS). Majority of them had a mutation in MEN1 56% (n= 25), followed by DNA Repair pathway 18% (n= 8), Colon cancer genes 11% (n= 5) , VHL 11% (n= 5) and AXIN2 2%(n= 1). Patients with P/LPs mutations were younger (45 years vs 50 years p=0.002). In the unselected cohort (n= 106), 21% (n= 22) had P/LP, 28 % (n = 30) had a VUS. P/LP were noted in DNA Repair pathway 40% (n= 9), MEN1 36% (n= 8), Colon cancer related genes 9% (n= 2) ,VHL 5% (n= 1) , RET 5% (n= 1) and PRSS1 5% (n= 1). Testing was performed using multigene panel testing in 93% of the patients. Multifocal tumors correlated with the presence of P/LP (p=0.0035).

The presence of MEN1 germline mutation correlated with younger age (40 vs 56 years) (p=0.0012). presence of multifocal tumors (p=<0.0001), and WHO grade 1 histology (p= 0.0078). Paired somatic testing in the unselected cohort identified that >70% of patients with P/LP had matching somatic mutations in the tumor specimen.

CONCLUSIONS

P/LP are prevalent in patients with sporadic pNET irrespective of high-risk features. We identified a high number of mutations in the DNA repair pathway and lynch syndrome associated genes, not previously described, which could affect subsequent therapies and surveillance for patients and their family members. The high concordance of somatic and germline mutations suggest that P/LP can often be the initiating drivers of pNET development. The findings support upfront universal germline testing in all patients with diagnosis of pNETs.

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