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# Neuroendocrine Neoplasms Associated with Germline Pathogenic Variants in the Homologous Recombination Pathway

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## Abstract

Neuroendocrine neoplasms (NENs) have been primarily associated with germline pathogenic variants in genes involved in chromatin remodeling (*MEN1*), cell cycle control (*CDKN1B*), PI3K/mTOR signaling (*TSC1/2, PTEN*) as well as pseudohypoxia (*VHL, SDHx*). Recent work has implicated various genes involved in DNA repair pathways in the pathophysiology of a subset of pancreatic neuroendocrine neoplasms, including *BRCA2*, via the homologous recombination pathway (HRD). To date, germline variants in other HRD pathway genes have not been described to contribute to NEN. *PALB2*, *RAD51C*, and *BARD1* are additional tumor suppressor genes which also mediate repair of double stranded DNA breaks through the HRD pathway and are implicated in hereditary breast (*PALB2*; *BARD1*) and ovarian (*RAD51C*) cancer. Here we report three cases of NEN associated with germline pathogenic variants in *PALB2* (pancreatic NEN), *RAD51C* (thymic NEN), and *BARD1* (pancreaticoduodenal NEN) respectively, further linking the DNA repair pathway to NENs.

## Introduction/Background

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of neoplasms that collectively have an annual incidence of 5.25 per 100,000 [1]. In two-thirds of cases, tumors arise from the neuroendocrine cells of the gastro-entero-pancreatic sites and, in one-third of cases, the bronchopulmonary tree and thymus [1]. Other reported sites of origin for NEN commonly include the adrenal, thyroid, parathyroid, pituitary, sympathetic/parasympathetic ganglia, and, in rare cases, the ovary and testis as well as the middle ear [2].

In recent years, high-throughput genomic studies of epithelial NENs (neuroendocrine tumors/NETs and neuroendocrine carcinomas/NECs) have confirmed various genomic mechanisms contributing to their pathogenesis. These mechanisms include chromosomal aberrations, somatic and germline mutations, epigenetic modifications, and differing miRNA expression profiles [2]. An increased understanding of the interplay between these mechanisms is still needed and will inevitably lend itself to better classification and treatment of these tumor types.

Well established hereditary (germline) genetic syndromes which are associated with NENs include multiple endocrine neoplasia type 1, type 2, and type 4 (caused by pathogenic variants in *MEN1*, *RET*, and *CDKN1B* respectively), Von Hippel Lindau disease (*VHL*), tuberous sclerosis complex (*TSC1/2*), and, rarely, neurofibromatosis type 1 (*NF1*) [3]. In addition to NENs occurring in the setting of Cowden syndrome (*PTEN*) [4], recent evidence has implicated NENs in extra-colonic manifestations of Lynch syndrome [5–7] and succinate dehydrogenase (*SDHx*)-associated disease [8]. Recent studies have shown that pancreatic NENs can be associated with germline pathogenic variants in genes involved DNA damage repair (*MUTYH*, *CHEK2*, *BRCA2*) [2, 3]. Another group has since identified a germline *BRCA2* pathogenic variant in a woman with non-small cell ovarian NEN [9]. Interestingly, the Scarpa study also found a larger-than-

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expected proportion of germline pathogenic variants in patients with seemingly sporadic pancreatic NENs, 17% as compared to the previously reported 10%, suggesting that family histories may be less striking in germline NEN cases [2, 3].

While a role for the homologous recombination repair of double-stranded DNA (HRD) pathway in the pathogenesis of NENs has been recently suggested, pathogenic germline variants in HRD-related genes other than *BRCA2* have not been reported. One study did identify a tumor somatic (non-germline) *PALB2* pathogenic variant in an individual with a synchronous pancreatic adenocarcinoma and pancreatic NEN [10]. Here, we describe three separate cases of NEN associated with germline pathogenic variants in additional HRD-related genes. This includes *PALB2* in a pancreatic NEN, *RAD51C* in a thymic NEN, and *BARD1* in a pancreaticoduodenal NEN, further linking the DNA repair pathway to NENs.

## Case 1

A 45-year-old man who initially presented with a progressive pain in his right shoulder, chest, and right abdomen and was investigated with an abdominal ultrasound which identified multiple liver lesions. Subsequent CT scanning of his chest, abdomen, and pelvis showed extensive liver metastases, abdominal/retroperitoneal lymphadenopathy and a 1.7-cm pancreatic mass. The liver biopsy from segment 5 identified a poorly differentiated NEC. The tumor was positive for chromogranin-A, synaptophysin, CDX-2, and somatostatin, and was negative for insulin, glucagon, pancreatic polypeptide, calcitonin, and TTF-1 (Fig. 1-Pathology Case 1). Expression for mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) was normal. The MIB-1 labeling index was 80% in hot spots (Fig. 1-Pathology Case 1). The overall findings were

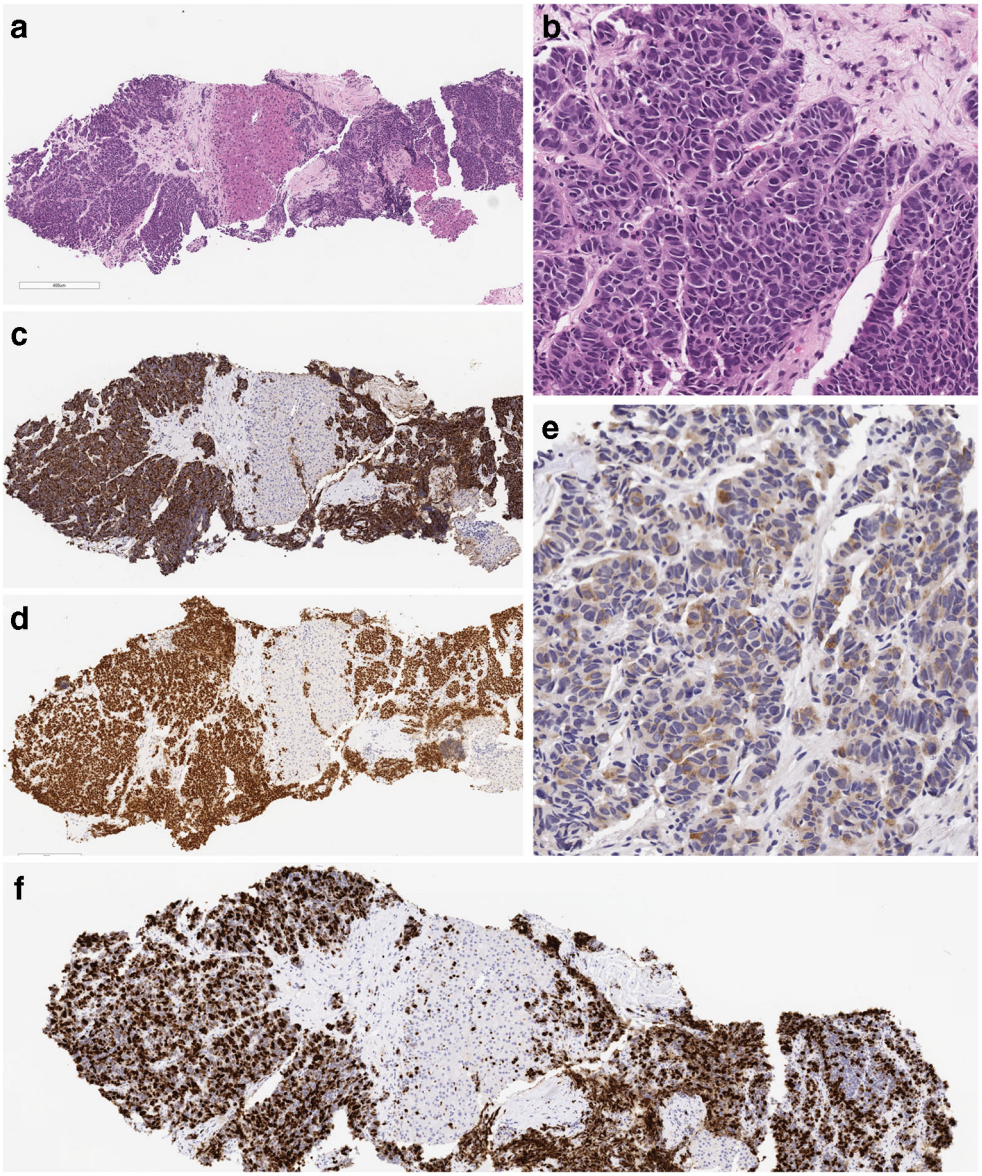


**Fig. 1** Histopathological features of liver metastasis (case 1). The core biopsy shows a metastatic poorly differentiated neuroendocrine carcinoma (**a**, **b**) that was positive for chromogranin-A (**c**) and CDX-2 (**d**). The tumor was also variably positive for somatostatin (**e**). The MIB-1 labeling index was 80% (**f**)

considered consistent with metastatic pancreatic NEC (WHO Grade 3) that was immunoreactive for somatostatin. Biochemical testing for somatostatin was not performed; thus, the status of functionality was unknown. Subsequently, the patient presented with brain metastases followed by symptoms and signs suggestive of cord compression at the lower lumbar spine within 7 months after his liver biopsy.

A review of our patient's family history was significant for a 13-year-old daughter with unilateral right retinoblastoma diagnosed at age 2.5 years. Analysis of the retinoblastoma tissue revealed homozygous hypermethylation of the *RB1* gene promoter and *RB1* gene testing in her germline was negative for *RB1* pathogenic variants. Interestingly, the patient's father had a resection of an adrenocortical adenoma at the age of 62 years. Other notable malignancies included a mother with thyroid cancer at 35 years and a maternal grandfather with gastric cancer in his 50s. Information about our patient's maternal side of the family was otherwise limited, as his mother was adopted. Our patient was from the Canadian Maritimes and reported Ukrainian and Ashkenazi Jewish descent. There was no other family history of cancer, including breast, ovarian, pancreatic, colon, or other (Fig. 2a).

A germline gene panel was requested (sequencing and copy number analysis) for *APC*, *ATM*, *BARD1*, *BMPR1A*,

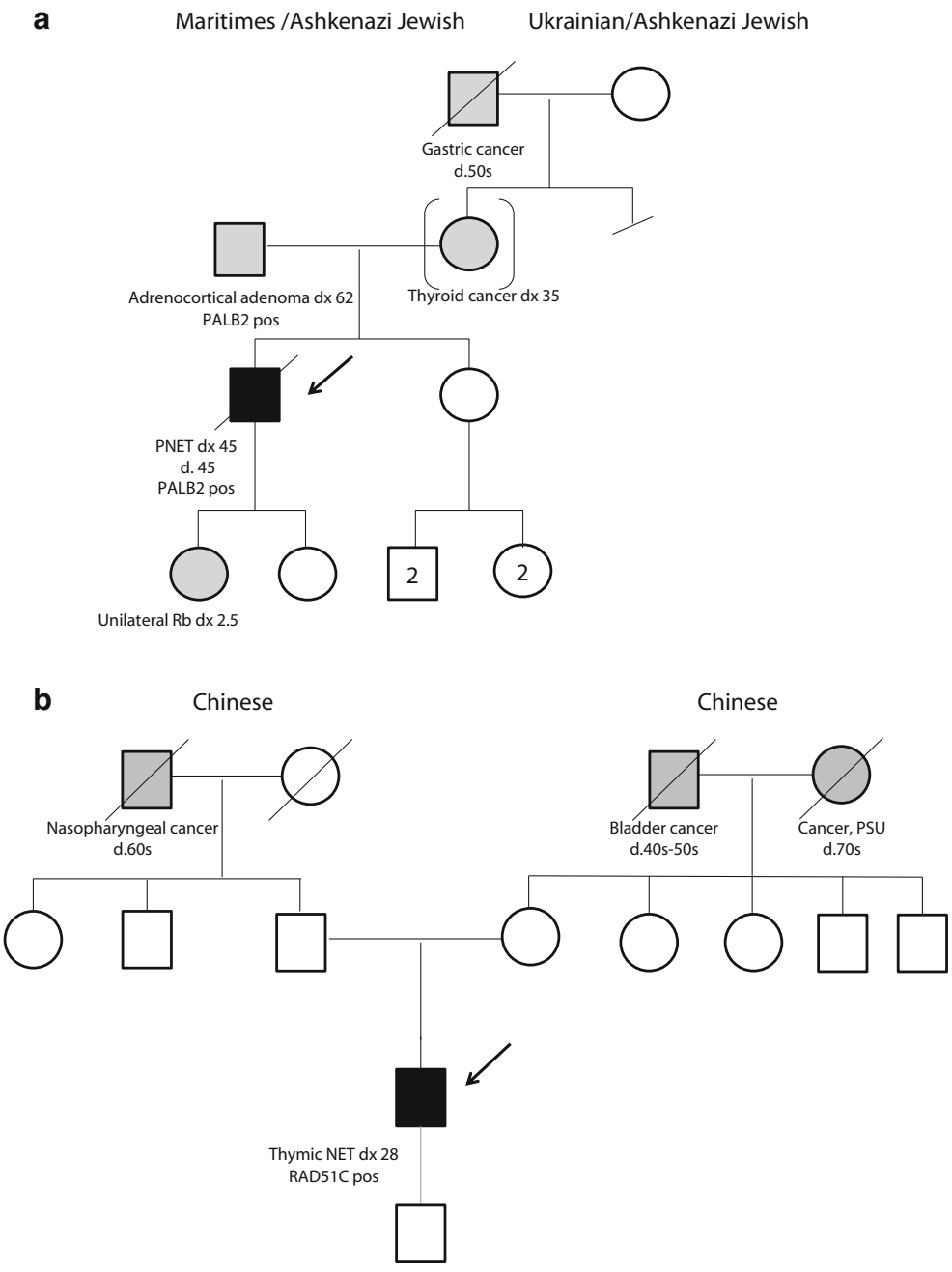


**Fig. 2** **a**, **b** Three generational pedigree. Square, male; circle, female; white-filled square/circle, no relevant disease; strikethrough, deceased; filled gray square/circle, other tumor type; black square, pancreatic NET (**a**) or thymic NET (**b**). Age of tumor diagnosis and age of death provided, where known. PALB2 positive (**a**) and RAD51C positive (**b**) genetic test result indicated

*BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN1B*, *CDKN2A-P16*, *CDKN2A-P14*, *CHEK2*, *CTNNA1*, *EPCAM*, *GREM1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *SDHB*, *SMAD4*, *STK11*, *TP53*, *TSC1*, *TSC2*, and *VHL*. The results revealed a rare pathogenic frameshift variant in exon 5 of the *PALB2* gene denoted as c.2325dupA, p.Phe776Ilefs*26. This specific variant has been previously reported in an individual with hereditary breast and ovarian cancer syndrome [11]. Familial testing of this *PALB2* variant was also observed in the patient's father, who had the adrenocortical adenoma.

## Case 2

A 29-year-old man who presented with persistent cervical lymphadenopathy and was found to have a large mediastinal NET with widespread metastatic disease affecting bone, retroperitoneum, and pancreas. The mediastinal tumor debulking specimen identified an angioinvasive and widely invasive well differentiated NET with intermediate grade proliferative features (Atypical Carcinoid Tumor based on the 2015 WHO classification of thymic NETs) involving the thymus. The MIB-1 labeling index was 16.5% in hot spots. The

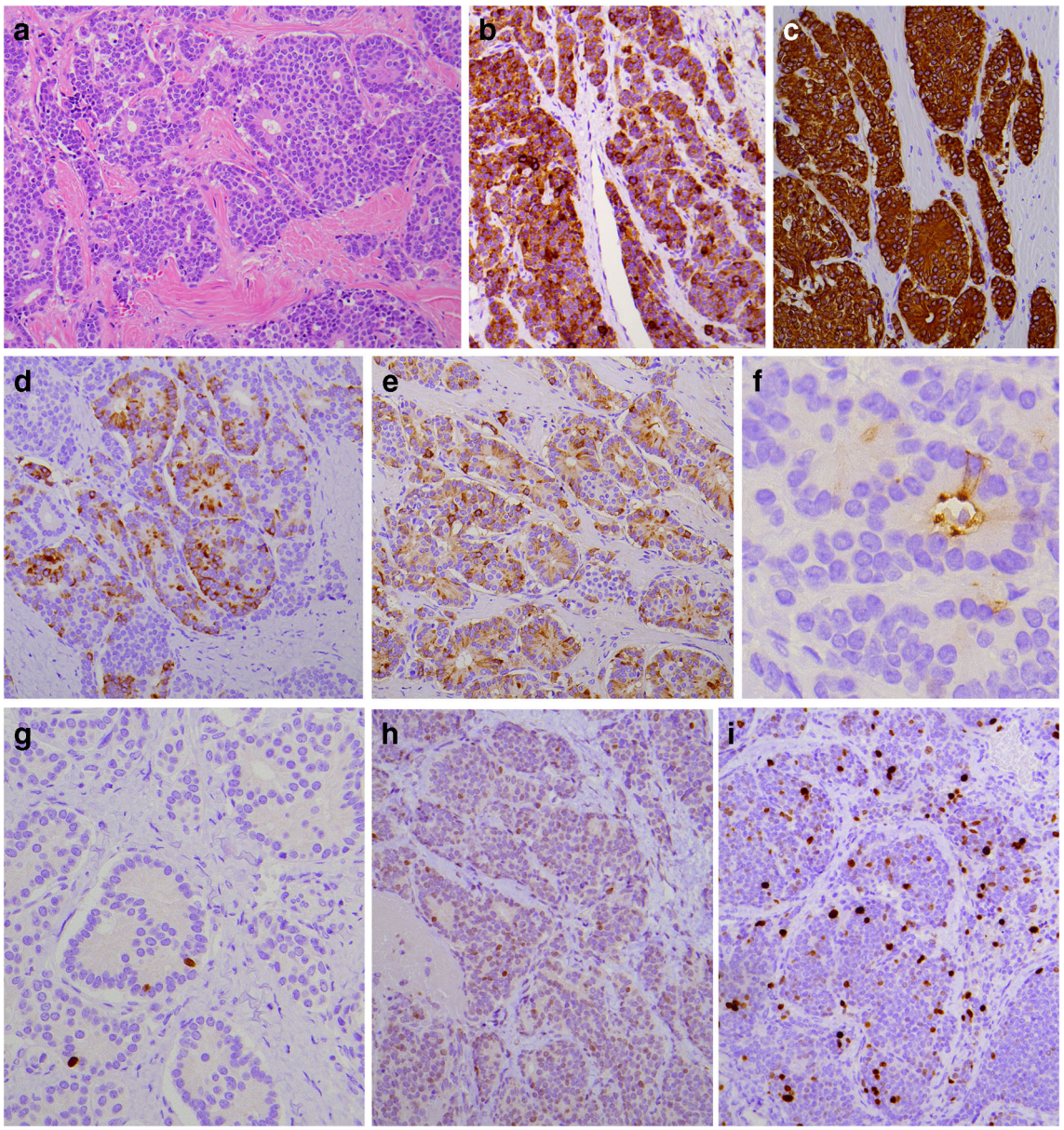


**Fig. 3** Histopathological features of mediastinal mass (case 2). The debulking thymic tumor resection specimen showed a well differentiated neuroendocrine tumor that exhibited a growth pattern with nests, trabeculae, and acini (**a**). The tumor was diffusely positive for chromogranin-A (**b**) and CAM5.2 (**c**). Variable immunoreactivity for calcitonin (**d**) and somatostatin (**e**) was noted. Monoclonal CEA (**f**) and TTF-1 (clone: SPT24) (**g**) were identified in less than 10 tumor cells. Staining for p53 was wild-type (**h**). The MIB-1 labeling index was 16.5% in this specimen

mitotic activity was 3.6 per 2 $mm^2$, based on 18 per 10 $mm^2$. The tumor was positive for chromogranin-A, synaptophysin, CAM5.2, monoclonal CEA (very focal), calcitonin (variable), and somatostatin (variable), and was negative for PAX8, CDX-2, GATA-3, parathyroid hormone, insulin, glucagon, pancreatic polypeptide, and peptide-YY. TTF-1 (clone: SPT24) showed scattered nuclear reactivity in the tumor cells (Fig. 3-Pathology Case 2) as well as a very few cells in the nontumorous thymic epithelium. The nontumorous thymic epithelium also showed variable reactivity for monoclonal CEA. Staining for p53 was wild-type. There was no loss of protein expression for p27 (protein encoded by *CDKN1B*), SDHB, and MMR (MLH1, MSH2, MSH6, PMS2) proteins. Menin immunohistochemistry showed reduced expression but no evidence of global loss. The very focal extent of expression for monoclonal CEA excluded the possibility of a medullary thyroid carcinoma. TTF-1 expression was reported in thymic neoplasms (thymomas and thymic carcinoid tumors) especially when using the clone SPT24 [12, 13]. The overall clinicopathological findings were consistent with a primary thymic origin of this NET. The right neck dissection showed nine metastatic lymph nodes with a well differentiated NET with somatostatin expression. The MIB-1 labeling index was as high as 27%. Staining for p53 was wild-type. The mitotic activity was 14 per 2 $mm^2$. These findings were considered as a tumor progression to a well differentiated NET with high grade proliferative features (Grade 3 NET).

A review of this patient's family history is significant for a mother, 2 maternal aunts, and 1 maternal uncle with nephritis, bladder cancer in a maternal grandfather who died in his 40–50s, and a maternal grandmother with extensive metastatic cancer with primary site unknown in the 70s, and nasopharyngeal cancer in his paternal grandfather who died at the age of 60 years. The patient's ethnic background is Chinese (Fig. 2b).

The same germline gene panel was requested and revealed a likely pathogenic variant in the *RAD51C* gene denoted as c.838-?_965+?dup (exon6_7dup). This variant is expected to disrupt the normal function of the RAD51C protein.

### Case 3

A 44-year-old woman presented with a history of chronic and relapsing abdominal pain with radiation to the back. Following an abdominal ultrasound, the CT scan identified a pancreaticoduodenal mass along with abdominal nodal and hepatic metastases. The MRI confirmed the presence of a 2.6 × 1.7 cm mass, predominantly in the lumen of the proximal duodenum and multiple liver and nodal metastases (mesenteric and peripancreatic). The liver biopsy identified an epithelial neoplasm that was diffusely positive for chromogranin-A, synaptophysin, somatostatin, CDX-2, and CAM5.2, and negative for serotonin, insulin, glucagon, and pancreatic polypeptide (Fig. 4-Pathology Case 3). There was no necrosis. The mitotic activity was 0.2 per 2 $mm^2$. The MIB-1 labeling index was 2.7%. The overall findings were those of a metastatic well differentiated neuroendocrine tumor with low grade proliferative features (Grade 1 NET). CA19-9 and 5-HIAA were normal. The patient is currently managed with ongoing lanreotide injections. A review of this patient's family history is unremarkable. Her ethnic background is Chinese.

The same germline gene panel was completed for this patient and revealed a pathogenic variant in the *BARD1* gene denoted as c.69_70delins25 (p.Ala25Glyfs*41). While novel, this specific variant is expected to cause premature termination of protein synthesis and is predicted to be pathogenic.

## Discussion

Our understanding of the pathogenesis of NENs continues to evolve as the cost associated with genome-wide screening declines [14]. In cases of NENs not clearly associated with a syndromic presentation or in the absence of some histopathological and/or immunohistochemical findings suggestive of germline predisposition [15], no standardized genetic testing approach currently exists. The advent of gene panel testing may provide an opportunity to interrogate multiple genes at a marginal increase in cost. Currently, known germline genes associated with NENs include *TSC1*, *TSC2*, *VHL*, *MEN1*, *CDKN1B*, *NF1*, *RET*, *SDHB*, *BRCA2*, *CHEK2*, and *MUTYH*. However, there are no clinical guidelines to inform genetic testing strategies. Given the progress in the understanding of the genetics of NENs and the emerging involvement of the HRD pathway in its pathogenesis, gene panel testing may provide an opportunity to detect clinically actionable variants irrespective of family history. Here, we characterize three separate cases of NEN associated with three HRD-related genes: *PALB2*, *RAD51C*, and *BARD1*. To our knowledge, this is the first series describing an association between NENs and inherited (germline) *PALB2*, *RAD51C*, and *BARD1* pathogenic variants.

The *PALB2* (Partner and Localizer of *BRCA2*), *RAD51C*, and *BARD1* (*BRCA1*-associated Ring Domain 1) genes are tumor suppressor genes which mediate DNA damage repair via homologous recombination repair of double-stranded DNA breaks via the *BRCA*-associated pathway [16, 17]. Published literature suggests that the general population carrier frequency of pathogenic variants is ~1/1300 (0.08%) for *PALB2*, ~1/1400 (0.07%) for *RAD51C* [18–21], and ~1/1400 (0.7%) for *BARD1* (extrapolated from the Exome Aggregation Consortium database). Germline pathogenic variants in *PALB2* and *RAD51C* in a homozygous (biallelic) state lead to the childhood disorder, Fanconi anemia, (*PALB2*-Fanconi complementation group N; *RAD51C*-Fanconi

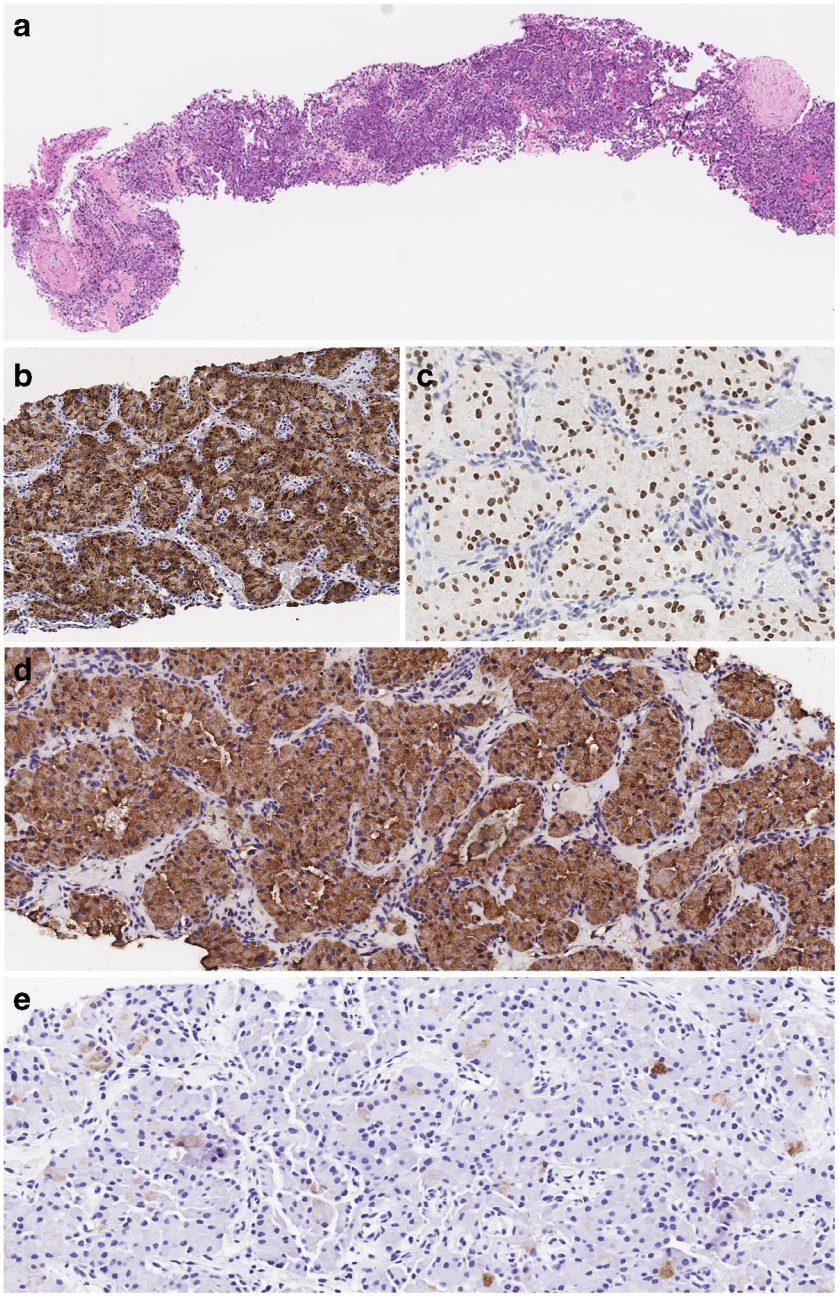


**Fig. 4** Histopathological features of metastatic neuroendocrine tumor in the liver (case 3). The specimen showed a well differentiated neuroendocrine tumor (**a**). The tumor exhibited low grade proliferative features. The tumor cells were diffusely positive for chromogranin-A (**b**), synaptophysin, CAM5.2, CDX-2 (**c**), and somatostatin (**d**). Scattered tumor cells were also positive for gastrin (**e**)

complementation group O) [22]. This is characterized by congenital anomalies, short stature, and bone marrow failure and identification of carriers may play a role in in family planning. Importantly, germline pathogenic variants in *PALB2* in a heterozygous state predispose to a 35% lifetime risk of breast cancer and account for 3–4% of familial cases of pancreatic adenocarcinoma [18, 23–26]. *PALB2*-associated breast cancer is linked to a poor prognosis [27] and *PALB2*-associated pancreatic adenocarcinoma is highly penetrant [28, 29]. Heterozygous pathogenic variants in *RAD51C* have recently been characterized to confer a moderately increased risk of ovarian cancer [30–33]. Heterozygous germline pathogenic variants in *BARD1* confer a moderately increased risk of breast cancer [34, 35].

The field of NENs is still evolving. From a pathological perspective, the common finding of somatostatin expression in all presented NENs is of interest. While somatostatin can be expressed in various NENs, further investigations are needed to clarify the possible link of the HRD pathway in somatostatin-expressing NENs. Another interesting finding of the presented cases was the

occurrence of the phenomenon of "grade 3 NET" in metastatic clones of a well differentiated thymic NET in the second case. From a diagnostic perspective, we believe that such cases should not be classified as a large cell NEC based solely on the mitotic activity. The assessment of the cytomorphology, the relatively low MIB-1 labeling index (less than 55%), and the status of other immunohistochemical biomarkers (e.g., p53, RB1) are all critical elements that the diagnostician should consider in this distinction [36].

## Conclusion

Given the relative low cost and pervasive nature of germline cancer gene panels, along with the emerging evidence of the HRD pathway in NEN, we suggest that a comprehensive germline testing approach in patients with NENs should be considered, including seemingly sporadic cases. The identification of pathogenic germline variants of the HRD pathway would have important implications for cancer surveillance in patients and their at-risk relatives and may also provide additional targeted therapeutic options. In general, women with pathogenic germline *PALB2* or *BARD1* variants should begin high-risk breast cancer screening while women with pathogenic *RAD51C* variants should also be offered prophylactic oophorectomy after menopause [30]. Given the low population frequency of pathogenic germline variants in the *PALB2*, *RAD51C*, and *BARD1* genes, we believe our findings contribute to the emerging spectrum of cancers associated with germline pathogenic variants in HRD-related genes. Finally, identifying patients with NENs related to aberrations in the *BRCA*-associated pathway may also benefit from alternative precision cancer therapies, such as poly (ADP-ribose) polymerase (PARP) inhibitors which target the HRD pathway [37].

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### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.



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