Inherited syndromes involving pancreatic neuroendocrine tumors

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Abstract: Inherited syndromes are important to recognize in the setting of a pancreatic neuroendocrine tumor (PNET) as there are significant implications for the patient's medical management and opportunity for early detection of subsequent manifestations. Although most PNETs are sporadic, approximately 10% are due to an inherited syndrome, which include multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 4 (MEN4), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC). The general hallmarks of a hereditary endocrine neoplasia predisposition syndrome include any one of the following: multiple primary tumors (in the same or different organs), rare tumors (prevalence of less than 1 in 1,000 people in the general population), earlier age of diagnosis (usually under the age of 40), characteristic pattern of disease in the individual or family (phenotype and inheritance pattern). These syndromes are monogenic (due to a single gene disorder), highly penetrant (with all carriers of the disease exhibiting at least part of the phenotype) and can display variable expressivity (where affected individuals may have different presentations and features of the disease). A thoughtful approach to management is required, even if the presenting symptom is resolved, as these syndromes often involve multi-organ disease with a lifelong risk for tumor development. Additionally, the natural history of tumors in the setting of a hereditary condition may be different than would be expected in a sporadic form of the disease. For example, in some circumstances the risk of metastatic disease is lower, and therefor longer observation is the preferred approach over early surgical intervention. The unique aspects to management, challenges in hereditary disease recognition and accurate diagnosis, and rarity of these syndromes are all reasons to support referral to high-volume centers with the experience and knowledge to treat patients with hereditary endocrine neoplasia syndromes.

Keywords: Multiple endocrine neoplasia type 1 (MEN1); von Hippel-Lindau disease (VHL); neuroendocrine tumor; pancreatic neoplasms; genetic counseling

Multiple endocrine neoplasia type 1 (MEN1) is one of the most well-known hereditary endocrine syndromes, first described in 1903 with an estimated prevalence of 2 per 100,000 in the general population (1,2). However, in patients with gastrinomas the incidence of MEN1 is 16–38%, which highlights the opportunity for syndrome recognition in this disease population (3-5). The clinical diagnostic criteria include: a patient with two or more classic MEN1-associated tumors (parathyroid, gastroenteropancreatic neuroendocrine, pituitary) or a patient with a single MEN1-associated tumor and a first-degree relative with MEN1 (6). A molecular

diagnosis is given when a pathogenic variant in the *MEN1* gene is identified, genetic testing criteria are provided in *Figure 1* (6,7).

As MEN1 syndrome is inherited in an autosomal dominant pattern, there is a 50% chance for affected individuals to pass the disease on to each offspring. Approximately 10% of cases are considered sporadic, where neither parent has any manifestations of MEN1. Since the majority of cases are familial, it is appropriate to consider non-paternity and occult or unreported disease in a parent if no family history is reported. MEN1 syndrome is also a

Individuals meeting any one of the following should be referred for genetic counseling and gene testing:
- Patient meeting MEN1 clinical diagnostic criteria
- First degree relative of patient with MEN1 syndrome
- Parathyroid adenoma diagnosed before age 30
- Multiple parathyroid adenomas
- Gastrinoma or multiple PNET at any age
- Single PNET diagnosed before age 20
- Female with thymic NET
- One classic MEN1-associated tumor (parathyroid, GEP-NET, pituitary) and one nonclassic feature (carcinoid, dermatologic features or adrenal tumor)

Figure 1 MEN1 genetic testing criteria. MEN1, multiple endocrine neoplasia type 1.

Table 1 Features of multiple endocrine neoplasia type 1 syndrome

Finding	Frequency	Comments
Primary HPT	Over 90%	By age 60, yet onset typically 20–25 yrs
GEP-NETs	Up to70%	Gastrinoma (~40%)
		Insulinoma (~10%)
		Glucagonoma (~2%)
		VIPoma (~2%)
Pituitary adenoma	30–40%	Prolactinoma (20%)
		May be larger and more aggressive
Carcinoid tumors	~10%	Bronchial/thymic/gastric
Dermatologic findings	~80%	Angiofibromas (85%)
		Lipomas (30%)
		Collagenomas (70%)
Adrenal tumors	20–40%	Typically adrenal cortical adenomas, rarely hormone secreting

HPT, hyperparathyroidism; GEP-NET, gastroenteropancreatic neuroendocrine tumor.

highly penetrant disease, over 90% individuals with MEN1 syndrome develop hyperparathyroidism by the age of 60, nearly 70% develop gastroenteropancreatic neuroendocrine tumors (GEP-NET), and 30% to 40% develop pituitary adenoma (*Table 1*) (8,9). The first presenting manifestation in individuals with MEN1 is typically hyperparathyroidism which is often multiglandular disease. Gastrinoma is the most commonly identified GEP-NET, seen in approximately 40% of patients with MEN1 syndrome, followed by insulinoma at a 10% frequency (6). Cutaneous manifestations are common in MEN1 syndrome and include facial angiofibromas, collagenomas and lipomas. Individuals with MEN1 syndrome also have an increased risk for developing thymic and bronchial carcinoid tumors, adrenocortical tumors (mostly nonfunctioning) and meningiomas. Comprehensive guidelines for screening and management of MEN1 syndrome are available from expert sources including The Endocrine Society and The National Comprehensive Cancer Network (6,10).

MEN1 is a tumor suppressor gene, identified in 1997 at the 11q13.1 locus, encoding the menin protein consisting of 10 exons and 610 amino acids. Menin localizes to the nucleus and is involved in several important cell functions including transcriptional regulation, genome stability, cell division, and proliferation. Over 250 germline pathogenic/likely-pathogenic variants in the *MEN1* gene have been reported in the ClinVar database (11). There are no known specific mutational hot spots and pathogenic variants are found in all the coding exons. Frameshift and nonsense variants, which generate a truncated menin protein, are the most frequent type of variant identified in MEN1 syndrome (12-14). Most recently a genotype-phenotype association was reported for large rearrangements in the *MEN1* gene and an earlier onset of disease when compared with patients who harbored truncating or missense variants (15).

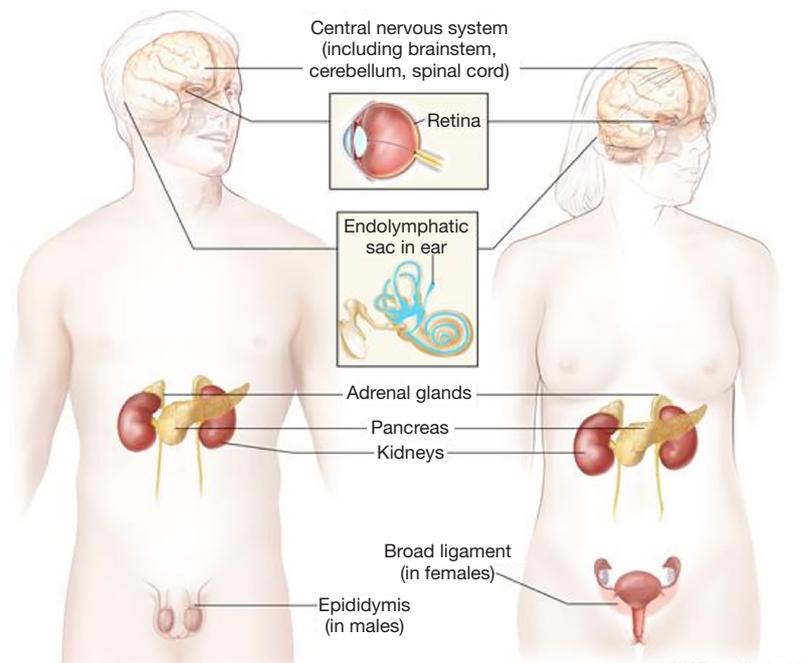The current genetic testing technologies, including

Figure 2 Areas of the body affected by von Hippel-Lindau disease. For the National Cancer Institute © (2020) Terese Winslow LLC, U.S. Govt. has certain rights.

MEN1 gene sequencing and deletion/duplication analysis, identify a pathogenic variant in approximately 90% of familial cases and 65% in apparently sporadic instances of MEN1 syndrome. Unidentified causative variants may exist in non-coding and regulatory regions in and around the *MEN1* gene, these areas of the genome are not analyzed in routine clinical genetic testing. It is also possible, in the case of sporadic MEN1 syndrome, that the condition is not due to a genetic cause, but rather an incidental co-occurrence of 2 endocrine tumors. Subsequent research in familial cases of phenotypic MEN1 syndrome with no previously identified causative gene variant led to the discovery of MEN4 syndrome. Patients with MEN4 are identified as having a pathogenic variant in the cyclin-dependent kinase (CDK) inhibitor 1b gene (*CDKN1B*) and not in the *MEN1* gene (16-18). As there are a limited number of published MEN4 syndrome cases to date, the natural history, penetrance and expressivity of the disease is uncertain (19). Primary hyperparathyroidism is the most commonly reported manifestation in MEN4 syndrome patients, yet GEP-NETs, pituitary tumors, carcinoid tumor have also been observed (19-24).

von Hippel Lindau (VHL) disease is a multifaceted tumor predisposition syndrome, with the symptoms first described in the early 1800s (25). The VHL tumor spectrum includes malignant and benign tumors comprised of: renal cell carcinoma, pheochromocytoma, serous cystadenoma and neuroendocrine tumors of the pancreas, endolymphatic sac tumors, epididymal and broad ligament cysts and hemangioblastomas of the retina and central nervous system (*Figure 2*). The *VHL* gene is a tumor suppressor with many functions, cloned in 1993 on the short of chromosome 3, consisting of 3 exons and 213 amino acids (26). Pathogenic variants in the *VHL* gene are the only known cause of VHL syndrome and can be identified through gene sequencing and deletion/duplication analysis in up to 100% of individuals meeting the clinical diagnostic criteria (26,27). Over 250 pathogenic/likely pathogenic variants have been described in the ClinVar database and detailed in the medical literature (11,28,29). Genetic testing is highly reliable and should be offered to individuals meeting diagnostic criteria (*Figure 3*) (26). Additionally, unexpected germline *VHL* pathogenic variants have been identified at a high rate in seemingly sporadic tumors, leading to the recommendation for offering genetic testing in simplex cases of retinal or brain/spinal cord hemangioblastomas, pheochromocytoma or endolymphatic sac tumors, as well as clear-cell renal carcinoma with any of the following

- Simplex case (no family history), individual with <u>two or more</u> of the following:
  - Two or more hemangioblastomas of the retina, spine, or brain or a single hemangioblastoma in association with a visceral manifestation (e.g., multiple kidney or pancreatic cysts)
  - Renal cell carcinoma
  - Paraganglioma or pheochromocytoma
  - Less commonly, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumors of the pancreas
- Familial case (known relative with VHL), individual with <u>one or more</u> of the following:
  - Retinal angioma
  - Spinal or cerebellar hemangioblastoma
  - Paraganglioma or pheochromocytoma
  - Renal cell carcinoma
  - Multiple renal and pancreatic cysts

Figure 3 VHL diagnostic criteria. VHL, von Hippel-Lindau disease.

features: diagnosed at an age ≤46 years, bilateral or multifocal tumors, or ≥1 close relatives with clear-cell renal carcinoma (30).

The incidence of VHL syndrome is approximately 1 in 36,000, the inheritance pattern is autosomal dominant, yet a *de novo* occurrence seen in 3–20% of cases (28,31). The condition is highly penetrant, with 90% of affected individuals displaying symptoms by 65 years of age (32,33). Although the disease has variable expressivity, some genotype-phenotype associations are appreciated (34-36). Large deletions and truncating pathogenic variants in the *VHL* gene are associated with a lower risk for pheochromocytoma, whereas missense pathogenic variants, at codon 167 especially, are associated with a high risk (36,37). However, at this time it is recommended that all individuals with a diagnosis of VHL syndrome follow the same surveillance protocol, as the understanding of genotype and phenotype implications is still evolving. Medical management recommendations have been developed through expert consensus and updated based on published outcomes of comprehensive surveillance programs (38,39).

The prevalence of PNET in individuals with VHL syndrome ranges from 9% to 17% and the tumors are most often nonfunctional and may be numerous (40-42). Risk factors for PNET metastasis in VHL syndrome include: greatest tumor diameter >3 cm, blood type O, tumor doubling time <500 days, and pathogenic missense variants or any pathogenic variant in exon 3 of the *VHL* gene (43-46). PNETs in the setting of VHL syndrome typically have a better prognosis compared to sporadic PNETs (47). Cystic lesions in the pancreas are common and nearly always benign (40). The pancreatic lesions that can be seen in VHL syndrome are almost never the presenting feature in an individual, rather they are discovered incidentally during surveillance for individuals known to have disease (48).

Less commonly, pancreatic involvement in neurofibromatosis (NF1) and tuberous sclerosis complex (TSC) may be observed. NF1 is an autosomal dominant tumor predisposition syndrome that has a population frequency of 1 in 3,000 births with half of cases due to a *de novo* mutation (49). NF1 syndrome is caused by germline pathogenic variants in the *NF1* gene, which is a tumor suppressor located on chromosome 17q encoding for the neurofibromin protein (50,51). Manifestations of NF1 involve multiple organs, there is highly variable expressivity, but the condition is predominantly characterized by nervous system involvement including neurofibromas and cutaneous findings. GEP-NET tumors may be reported in up to 10% of patients with NF1 syndrome, most frequently nonfunctioning somatostatinomas arising from the duodenum where there is risk for obstruction (52-54). The somatostatinoma histologic features are characteristic with glandular formation and psammomatous calcifications (55). These tumors are not a significant cause of mortality in patients with NF1 but do increase morbidity (56).

TSC is an autosomal-dominant syndrome characterized by the development of hamartomas in almost every organ, disabling neurologic disorders, and dermatologic features (57). Both functional and nonfunctional PNETs are a rare manifestation, involved in only 1% of cases (56,58). TSC is caused by pathogenic variants in either the *TSC1* gene, which encodes hamartin or the *TSC2* gene, which encode tuberin (59).

Given the complexities of these multi-organ hereditary syndromes, a multidisciplinary approach to care coordination is essential for optimal patient outcomes. Although no gene-therapy nor preventative treatment is yet available for these syndromes, comprehensive surveillance programs can lead to reduced morbidity and mortality through early detection and appropriately timed intervention (6,60-62). Since there are tumor risks for young children, genetic testing should be pursued early

in childhood, before the age of 5. Genetic counseling and testing are important for at risk relatives to identify carriers who require lifelong screening and noncarriers who can discontinue screening. Importantly, genetic counseling has been shown to improve adherence to genetic testing recommendations as genetic counselors aid in risk communication for family members, provide education, and work through barriers to genetic testing (63-65). All patients with a suspicion for a hereditary endocrine neoplasia syndrome should be referred for pre-test genetic counseling. Additionally, close family members should receive genetic counseling and genetic testing for risk stratification and appropriate management. When possible, it is ideal to begin the genetic testing process in an affected family member, as identification of a causative pathogenic variant in the index case can improve interpretation for family members and is more cost effective.

The discoveries and increased knowledge from our understanding of hereditary endocrine neoplasia syndromes provide a model to help scientists and clinicians have insight into the pathogenesis of sporadic PNETs as well. The observance of intrafamilial phenotypic variable expressivity in both MEN1 and VHL syndromes suggest the disease is influenced by environmental factors, personal risk factors and/or modifying genetic and epigenetic factors that have yet to be discovered. The era of precision medicine and somatic molecular analysis will bring identification of novel biomarkers for prognosis and new treatment targets for PNETs.

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Footnote

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