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MEN1 PNET Genotype/Phenotype- Is there any advance on predicting or preventing?

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MEN1: Prevalence and Diagnosis

Multiple endocrine neoplasia type 1 syndrome (MEN1) is a rare autosomal dominant disease caused by inactivating mutations in the tumor suppressor gene *MEN1*, which predisposes patients to the development of characteristic endocrine and non-endocrine tumors.[1–7] Classically, MEN1 is associated with primary hyperparathyroidism from multi-glandular hyperplastic parathyroid tumors, anterior pituitary adenomas, and entero-pancreatic neuroendocrine tumors.[3,7] Other tumors that have also been implicated in MEN1 include thymic, pulmonary, and gastric neuroendocrine tumors, adrenocortical tumors, (rarely) pheochromocytoma, central nervous system tumors including meningiomas, schwannomas, and ependymomas, and soft tissue tumors such as lipomas, leiomyomas, angiofibromas, collagenomas, and hibernomas; more recently, female MEN1 patients have been found to have increased risk of breast cancer.[8]

Though rare, with a prevalence of 3–20 cases per 100,000 individuals, the disease exhibits high age-dependent penetrance; over 50% of patients present with clinical features by age 20 years old, 95% by age 40,[1] and almost 100% by age 50.[9] There is no observed ethnic or racial pre-disposition, but some studies have shown a slight female predominance.[1,9]

According to the Clinical Practice Guidelines, MEN1 can be diagnosed if patients meet clinical (two or more principal MEN1-associated tumors), familial (one MEN1-associated tumor and a first-degree relative with MEN1), or genetic criteria (MEN1 mutation without clinical or biochemical manifestations).[7] It is most commonly encountered as an inherited autosomal dominant disorder, as is the case in over 90% of cases; however, *de novo MEN1*

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mutations can occur (<10%), whereby a *MEN1* mutation develops in the embryo.[3,10–11] As described in Knudson's two-hit hypothesis for tumor suppressor genes, the germline inactivating mutation creates heterozygosity of the gene, but it is the second somatic inactivating mutation to the remaining allele that leads to loss of heterozygosity and the development of tumors and the clinical manifestations of the disease.

MEN1: Menin

The *MEN1* tumor suppressor gene is located on chromosome 11q13.[1,3,5,12] The gene's 10 exons encode menin, a 610 amino acid, 67 kDa protein that is widely expressed and predominantly localizes to the nucleus, though some studies demonstrate some menin protein may associate with the cell membrane. Importantly, it contains three nuclear localization signals in the C-terminal region. The protein structurally encompasses a binding pocket that facilitates interactions with proteins such as transcription factors, histone modifiers, cytoskeletal proteins, and cytosolic cell signaling proteins.[1,5,13] Through inhibitory interactions with transcription factors JunD, the NFKB family, and the Smad family, and with activator of S-phase kinase (ASK), menin represses the activation of multiple pathways involved in cellular proliferation.[14] Additionally, menin interacts with histone methyltransferase mixed-lineage leukemia complexes,[13–18] enabling methylation of the lysine 4 residue on histone H3; this trimethylation of H3K4 (H3K4me3) subsequently facilitates the transcriptional activation of cyclin-dependent kinase inhibitors p18 and p27, preventing unopposed cell cycle progression. Its role in genome stability is implied through interactions with a subunit of replication protein A (RPA2) and FANCD2 protein, both of which are involved in DNA repair.[14] Menin also interacts directly with double-stranded DNA via its nuclear localization signals; it has been reported to cause upregulation of caspase 8 transcription and downregulation of insulin growth factor binding protein-2 (IGFBP-2) transcription. Further interactions and effects exist but have not been fully elucidated yet. Overall, menin has been shown to play a key regulatory role in cell cycle progression and proliferation.

MEN1: Clinical Manifestations

As stated previously, the principal MEN1 clinical manifestations are primary hyperparathyroidism, pituitary adenomas, and entero-pancreatic neuroendocrine tumors, which develop in 90%, 30–40%, and 30–70% of patients, respectively, by age 40.[3,7] Primary hyperparathyroidism is seen in 100% of patients by age 50 and is the most common first manifestation of the disease (90%).[4,6] Important differences exist between sporadic hyperparathyroidism and hyperparathyroidism secondary to MEN1. Unlike patients with sporadic primary hyperparathyroidism, patients with MEN1 commonly present at a younger age with no female gender predilection, in concordance with an autosomal dominant inheritance pattern.[3,9] Additionally, though patients with MEN1 tend to have lower calcium and PTH levels, the severity of bone mineral loss and nephrolithiasis is higher compared to sporadic hyperparathyroidism, and hyperparathyroidism associated with MEN1 is caused by multiple parathyroid gland hyperplasia rather than a solitary parathyroid adenoma,[3,9] though asymmetric hyperplasia can give the appearance of adenomas. In the setting of Zollinger-Ellison syndrome (ZES) caused by gastrinomas, which is the most common

functional pancreatic neuroendocrine tumor in MEN1, the correction of hypercalcemia with parathyroidectomy has been shown to reduce gastrin secretion and acid output.[19]

Anterior pituitary tumors are identified in about 30–40% of patients with MEN1, and while about two-thirds of patients have microadenomas, the rates of macroadenomas are higher in patients with MEN1 than in patients without the syndrome.[1,9] Prolactinomas are by far the most commonly encountered pituitary tumor in MEN1, with a prevalence of 65%, followed by somatotropinomas, ACTH-producing adenomas, and gonadotropin-producing adenomas; interestingly, adenomas secreting multiple hormones have been seen in up to 10% of MEN1-associated pituitary adenomas.[9] Of note, there is a documented familial MEN1 variant called the Burin variant with a high rate of prolactinomas but a low rate of entero-pancreatic neuroendocrine tumors, particularly gastrinomas which were seen in only 10% of the patient group.[20]

Entero-pancreatic neuroendocrine tumors are seen in 70–80% of patients with MEN1 and carry significant clinical importance as they are the most common cause of death in patients with MEN1 due to the risk of metastasis.[6,9] Most commonly observed are nonfunctional neuroendocrine tumors, which are seen in 55% of patients with MEN1; these carry a higher mortality rate than functional tumors, likely as a result of delayed diagnosis in the absence of clinical symptoms caused by abnormal hormone secretion. Of note, this group encompasses tumors that truly do not secrete hormones, tumors that secrete hormones at levels insufficient to cause a clinical syndrome, and tumors that secrete hormones that do not cause a clinical syndrome. The most common functional entero-pancreatic neuroendocrine tumor is gastrinomas, which are associated with ZES. Interestingly, they are not the most prevalent pancreatic neuroendocrine tumor in MEN1 patients and are, in fact, encountered as duodenal microtumors in 80% of MEN1-associated gastrinoma cases. Others include insulinomas, glucagonomas, VIPomas, and somatostatinomas. These will be discussed in greater detail in a later section of the review.

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine neoplasms (PanNENs) are composed of cancer cells that express both neuroendocrine markers (eg. chromogranin A and synaptophysin) and pancreatic tissue-specific markers; this subset of tumors has undergone multiple classification changes over the last two decades by the World Health Organization (WHO), most recently in 2017.[21] Currently, PanNENs are divided into well-differentiated pancreatic neuroendocrine tumors (PNETs) and poorly-differentiated pancreatic neuroendocrine carcinomas (PNECs). PNECs by definition have morphology demonstrating poor differentiation and high-grade (G3) proliferation criteria, ie. Ki67 staining index of >20% of ≥500 cells and mitotic count of >20 per 10 high-powered fields (HPF). In contrast, PNETs are subdivided into low-grade (G1), intermediate-grade (G2), and high-grade (G3) again based on proliferation markers Ki67 and mitotic index; this allows for the classification of a subset of PanNENs that are both well-differentiated and with high proliferation indices.

PNETs account for less than 3% of pancreatic neoplasms in the general population, with an incidence of 0.8 cases per 100,000 persons.[17,22–24] Only 5–10% arise in the setting

of predisposing genetic syndromes, which include MEN1, von Hippel Lindau syndrome (VHL), tuberous sclerosis complex (TSC), and neurofibromatosis type 1 (NF1).

In the general population, 15% of PNETs are functional and 85% are nonfunctional.[17] Functional PNETs are defined by the development of clinical symptoms rather than immunohistochemical findings, and nonfunctional PNETs are clinically silent, not necessarily nonsecretory. Nonfunctional PNETs carry a poorer prognosis, with 5-year survival rate of 30–40%, and are often not identified until their growth causes obstructive or compressive symptoms, at which point lymph node and liver metastases may be seen. Compared to sporadic PNETs, MEN1-associated PNETs are diagnosed at a younger age. In MEN1, PNETs have become more frequently identified and are now seen in up to 80% of patients, owing to increased and more effective surveillance strategies and modalities. Nonfunctional PNETs in the context of MEN1 are also most common (55% of cases), followed by insulinomas (7–31% of cases), and gastrinomas (5% of cases); glucagonomas (3–4% of cases), VIPomas (2% of cases), and somatostatinomas (2% of cases) are rare. Like the duodenal microgastrinomas commonly seen with MEN1-associated ZES, PNETs in MEN1 are much more commonly seen as multiple microadenomas (<0.5cm).[3,17] Solitary PNETs in MEN1 patients, which occur less than 13% of the time, are usually >2cm in size and nonfunctional.

The multifocal nature and genetic predisposition for the recurrence of MEN1-associated PNETs hold important implications for their treatment.[17,25] Currently, guidelines recommend observation for asymptomatic, nonfunctional PNETs that are less than 1 to 2 cm with surveillance imaging every 6 to 12 months to monitor size changes.[23,26–27] Increased tumor size correlates with metastases and intermediate or high grade with higher recurrence rate.[23,27] Because these tumors are often identified in young patients with multiple small tumors, complete surgical resection may entail major pancreatic resection with risks of pancreatic insufficiency and diabetes. Management of functional PNETs depends on tumor type and symptom.[3] Gastrinomas, which are most often seen in MEN1 as multiple microadenomas in the duodenum, are typically managed medically with proton pump inhibitors, histamine receptor blockers, and somatostatin analogs to control the effects of excess gastrin. At the time of diagnosis, gastrinomas are seen with lymph node metastases in 34–85% and liver metastases in 6–16% of cases. Surgical resection is indicated in cases with concomitant nonfunctional PNET that meets resection criteria (e.g. >2cm in size or doubles in size in 6 months). In contrast to gastrinomas, insulinomas are found as solitary tumors in 85%, multiple in 6–13%, and with other PNETs in 10% of cases. Although the tumors are usually small (<2cm) and metastatic disease is uncommon (4–14% of cases), medical management is typically unsuccessful in curtailing hyperinsulinism symptoms. The tumors are found in equal distribution in all regions of the pancreas, and surgical resection is indicated if the tumor(s) can be localized, as these PNETs can often be completely resected and achieve surgical cure without an extensive pancreatic resection, though the risk of recurrence remains. Glucagonomas and VIPomas are characteristically found in the body and tail of the pancreas. Glucagonomas are associated with necrolytic migratory erythema, weight loss, anemia, and stomatitis, and there is a 50–80% rate of metastatic disease at the time of diagnosis. VIPomas present with the classic triad of watery diarrhea, hypokalemia,

and achlorydia. Metastasis is common in patients with glucagonoma and VIPoma. Like insulinomas, both glucagonomas and VIPomas should be resected if localized.

Genotype-Phenotype Correlations in MEN1-associated PNETs:

Because entero-pancreatic neuroendocrine tumors are the most common cause of death in MEN1 patients due to the risk of metastatic disease,[6,9] it would be beneficial to identify prognostic factors that could help identify patients with MEN1 that may benefit for more aggressive screening, surveillance, and treatment for PNETs. For this reason, many studies have been performed in an attempt to establish genotype-phenotype correlations. However, unlike accurate genotype-phenotype correlation seen in *APC* and *RET*, that of *MEN1* remains unclear, partly due to the complex functions of menin, including epigenetic regulation of gene expression.

One of the first investigations by Bartsch *et al.* (2000) identified 21 patients with MEN1 and pancreaticoduodenal neuroendocrine tumors who had 14 different mutations and found that those with truncating nonsense mutations and frameshift mutations involving exons 2, 9, and 10, which comprise the N- and C-terminal regions, had significantly higher rates of malignant tumors, 55% compared to 10%.[28] Other studies have found that *MEN1* mutations in exons 2, 9, and 10 are the most common mutations seen in patients with MEN1-associated gastroenteropancreatic neuroendocrine tumors (GEP-NETs), but some studies show higher rates of frameshift mutations,[29] and others show higher rates of nonsense mutations.[4] Kövesdi *et al.* (2019) corroborated the finding of high frequency of frameshift and nonsense mutations in MEN-1 associated GEP-NETs, identifying a significantly higher rate of high-impact mutations, defined as frameshift mutations, nonsense mutations, a splice-site mutation, and a large deletion, compared to low-impact mutations, defined as missense mutations and in-frame deletions.[30]

Christakis *et al.* (2017) found that MEN1 patients with PNETs were more likely to have a mutation in exon 2 than in any other exon and more likely to have a frameshift mutation.[31] Deleterious exon 2 mutations were significantly more likely to be associated with malignant PNET and with distant metastasis from a PNET than deleterious mutations in exons 3–10, and they trended toward shorter overall survival.

In a comparison between hereditary and sporadic PNETs, one study with 58 patients with MEN1 found a strong negative correlation between frameshift or splice-site mutations and stage.[24] They also found that exon 5 mutations were diagnosed with PNETs at an earlier age than mutations in other locations, and they found that exon 2 mutations were associated with more frequent metastases.

Contrastingly, a 2014 study by Bartsch *et al.* did not identify any genotype-phenotype differences between the 36 truncating and 9 nontruncating *MEN1* mutations in their cohort of 71 patients.[32] They did, however, compare mutations affecting menin protein's interacting domains with JunD, Smad3, CHES1, and HDAC1 and found that mutations causing loss of interaction (LOI) with CHES1, which are encompassed in exons 9 and 10, were associated with significantly higher rates of functional PNETs, malignant PNETs, PNETs with distant metastasis, and PNET-related deaths. Another study by Thevenon *et al.*

(2013) examined 262 mutations in 806 MEN1 patients and found no genotype-phenotype correlations regarding PNETs but did identify an increased risk of overall MEN1-related death in mutations that caused LOI with JunD.[33]

In sum, genotype-phenotype correlations have yet to be firmly established in MEN1 PNETs. However, certain trends, such as truncating or deleterious mutations in exons 2, 9, and 10 have been documented in multiple studies (Table 2).

Epigenetic Mechanisms in MEN1-associated PNETs

While genotype-phenotype correlations in MEN1 PNETs have not been consistently demonstrated, other studies have begun exploring the impact of epigenetic changes on MEN1-associated PNETs and have yielded interesting results. DNA methylation is a well-documented epigenetic mechanism of gene expression silencing.[15,34] Methylation of CpG DNA sites in promoter regions is accomplished by DNA methyltransferase enzymes (DNMTs), and hypermethylation of tumor suppressor genes' promoter regions is often seen in the setting of cancer. In sporadic PNETs, the Ras-association domain gene family 1 (*RASSF1*) tumor suppressor gene promoter is the most commonly hypermethylated promoter region, seen in 75–83% of sporadic PNETs. Hypermethylation of the *RASSF1* promoter is more frequently identified in metastatic PNETs than nonmetastatic PNETs, implying a role in neuroendocrine tumor progression. Other hypermethylated genes have been implicated in sporadic PNETs but differentially depending on functional type; for example, *CDKN2A/p16INK4a* promoter hypermethylation and *IGF2* hypomethylation have been associated with gastrinomas.[15] *IGF2* hypermethylation is commonly identified in insulinomas, whereas *CDKN2A/p16INK4a* alterations are uncommon.[15]

MEN1-associated PNETs also exhibit hypermethylation of tumor suppressor genes but in different patterns than in sporadic PNETs. Conemans *et al.* (2018) showed no difference in cumulative methylation index (CMI) between MEN1-associated PNETs and sporadic PNETs, but hypermethylation of *CASP8*, *RASSF1_1*, and *RASSF1_2* were identified more often in MEN1-associated PNETs than sporadic PNETs.[35] MEN1 subgroup analyses revealed that nonfunctional MEN1-associated PNETs had higher CMI if they were >2 cm or had liver metastases and that MEN1 insulinomas more frequently had hypermethylation of *RASSF1_1* than nonfunctional PNETs (70% vs 47%) while nonfunctional PNETs more frequently had hypermethylation of *MGMT2* than insulinomas (44.7% vs 8.3%). Another study by Tirosh *et al.* (2020) included 96 NETS, of which 42 were from MEN1 patients and 24 were specifically MEN1-associated PNETs, and also showed MEN1-associated NETs and sporadic NETs had similar percentages of hypermethylated regions.[36] However, they identified different methylation profiles associated with NET location and found higher percentages of *APC* promoter hypermethylation in MEN1-associated NETs compared to sporadic NETs, though these were more often seen in gastric and duodenal NETs compared to small intestine NETs and PNETs. A smaller investigation focusing on nonfunctional PNETs compared nine sporadic, ten MEN1-associated, and ten VHL-associated tumors and found that MEN1-associated nonfunctional PNETs had significantly more hypermethylated genomic regions compared to the others, the majority of which were associated with downregulation of gene expression;[37] some of these downregulated genes include *RBM47*,

FAM3B, *ECHDC1*, *MPP2*, *JAK1*, *ATP11A*, *CDCA7L*. Of these, *RBM47* and *CDCA7L* are associated with other cancer types, *RBM47* with colorectal, breast, and lung cancer and *CDCA7L* with hepatocellular carcinoma. Subsequently activated pathways for MEN1-associated nonfunctional PNETs included VEGF signaling, neuronal pathways, insulin secretion regulation, and the phosphatidylinositol-4,5-bisphosphate (PIP2) related pathway. By contrast VHL-associated nonfunctional PNETs were more frequently associated with hypomethylation and activation of pathways involved in VEGF and beta cell development.

Chromatin remodeling via histone modifications is another epigenetic avenue under investigation. As stated previously, menin interacts with histone methyltransferase MLL complexes, facilitating trimethylation of H3K4 (H3K4me3), an activating epigenetic marker. *Men1* knockout mouse models have demonstrated a cooperative effect between MLL and menin where inactivation of MLL1, also known as KMT2A, in *Men1* knockout mice have reduced survival, and their pancreata show accelerated pancreatic islet tumor progression with tumors that were more frequently larger, more vascular, and more cellularly abnormal.[38] Another study using *Men1* knockout mice pancreata showed decreased islet tumorigenesis and prolonged survival with inactivation of retinoblastoma binding protein 2 (RBP2), an H3K4me3 demethylase,[39] suggesting that RBP2 is a downstream effector of menin. One interesting study further demonstrated this by showing that the deletion of RBP2 lead to a reversal in the downregulation of IGFBP2 in MEN1-deficient islets.[40]

MicroRNAs (miRNAs) are a class of small non-coding RNAs that downregulate or silence gene expression through.[12,18] Some studies have examined miRNA expression profiles in PNET patients, and while some intriguing results have revealed differential expression profiles in different types of GEP-NETs by location and identified miR-21 as a miRNA significantly upregulated in metastatic PNETs, none of these studies specifically examine MEN1-associated PNETs.[12]

Future Directions

Genotype-phenotype correlations in MEN1-associated PNETs remains an area of investigation. As a major cause of morbidity and mortality in patients with MEN1, identifying these correlations may assist in the screening, surveillance, and treatment recommendations for patients based on their genotypes. However, despite several attempts to identify clear associations, none have been firmly established, though trends have emerged. MEN1 patients with PNETs and deleterious mutations in exons 2, 9, and 10 may benefit from closer follow-up and surveillance, and perhaps more aggressive treatment.

Exploration into epigenetic factors has yielded interesting and promising early data. As this field expands and more investigations are performed with a specific focus on MEN1-associated PNETs, it is possible that new relationships will be identified. Additionally, as epigenetic changes are reversible, medications that target epigenetic regulatory modifications may become of interest. For example, azacitidine and decitabine, both of which are DNA methyltransferase inhibitors, are approved for the treatment of myelodysplastic syndrome.[39] Further investigation is needed to verify and elucidate the underlying causes of genotype-phenotype and epigenetic-phenotypic correlations that have been suggested.

Conclusions

One of the most common manifestations of MEN1 is PNET. Compared to sporadic PNETs, MEN1-associated PNETs tend to be multifocal with high rates of recurrence, often making complete surgical resection difficult or involving major organ resection. *MEN1* mutations in exons 2, 9, and 10 may be associated with increased risk for malignant PNETs, but clear genotype-phenotype correlations have yet to be validated. Further study into menin's role in gene expression through epigenetic modifications may provide additional clues to detect patients with MEN1-associated PNETs that are at greater risk of aggressive disease who subsequently may benefit from closer follow-up and treatment.

References:

1. Brandi ML, Agarwal SK, Perrier ND, Lines KE, Valk GD, Thakker RV. Multiple Endocrine Neoplasia Type 1: Latest Insights. Endocr Rev. 2021;42(2):133–170. doi:10.1210/endrev/bnaa031 [PubMed: 33249439]
2. de Laat JM, van der Luijt RB, Pieterman CR, et al. MEN1 redefined, a clinical comparison of mutation-positive and mutation-negative patients. BMC Med. 2016;14(1):182. Published 2016 Nov 15. doi:10.1186/s12916-016-0708-1 [PubMed: 27842554]
3. Kamilaris CDC, Stratakis CA. Multiple Endocrine Neoplasia Type 1 (MEN1): An Update and the Significance of Early Genetic and Clinical Diagnosis. Front Endocrinol (Lausanne). 2019;10:339. Published 2019 Jun 11. doi:10.3389/fendo.2019.00339 [PubMed: 31263451]
4. Marini F, Giusti F, Fossi C, et al. . Multiple endocrine neoplasia type 1: analysis of germline MEN1 mutations in the Italian multicenter MEN1 patient database [published correction appears in Endocrine. 2018 Jul 21;:]. Endocrine. 2018;62(1):215–233. doi:10.1007/s12020-018-1566-8 [PubMed: 29497973]
5. Falchetti A. Genetics of multiple endocrine neoplasia type 1 syndrome: what's new and what's old. F1000Res. 2017;6:F1000 Faculty Rev-73. Published 2017 Jan 24. doi:10.12688/f1000research.7230.1
6. Mele C, Mencarelli M, Caputo M, et al. Phenotypes Associated With MEN1 Syndrome: A Focus on Genotype-Phenotype Correlations. Front Endocrinol (Lausanne). 2020;11:591501. Published 2020 Nov 18. doi:10.3389/fendo.2020.591501
7. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990–3011. doi:10.1210/jc.2012-1230 [PubMed: 22723327]
8. van Leeuwaarde RS, Dreijerink KM, Ausems MG, et al. MEN1-Dependent Breast Cancer: Indication for Early Screening? Results From the Dutch MEN1 Study Group. J Clin Endocrinol Metab. 2017;102(6):2083–2090. doi:10.1210/jc.2016-3690 [PubMed: 28323962]
9. Al-Salameh A, Cadiot G, Calender A, Goudet P, Chanson P. Clinical aspects of multiple endocrine neoplasia type 1. Nat Rev Endocrinol. 2021;17(4):207–224. doi:10.1038/s41574-021-00468-3 [PubMed: 33564173]
10. Giusti F, Cianferotti L, Boaretto F, et al. Multiple endocrine neoplasia syndrome type 1: institution, management, and data analysis of a nationwide multicenter patient database. Endocrine. 2017;58(2):349–359. doi:10.1007/s12020-017-1234-4 [PubMed: 28132167]
11. Marini F, Carbonell Sala S, Falchetti A, Caramelli D, Brandi ML. The genetic ascertainment of multiple endocrine neoplasia type 1 syndrome by ancient DNA analysis. J Endocrinol Invest. 2008;31(10):905–909. doi:10.1007/BF03346440 [PubMed: 19092297]
12. Donati S, Ciuffi S, Marini F, et al. Multiple Endocrine Neoplasia Type 1: The Potential Role of microRNAs in the Management of the Syndrome. Int J Mol Sci. 2020;21(20):7592. Published 2020 Oct 14. doi:10.3390/ijms21207592 [PubMed: 33066578]

13. Lips CJ, Dreijerink KM, Höppener JW. Variable clinical expression in patients with a germline MEN1 disease gene mutation: clues to a genotype-phenotype correlation. Clinics (Sao Paulo). 2012;67 Suppl 1(Suppl 1):49–56. doi:10.6061/clinics/2012(sup01)10

14. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. Hum Mutat. 2008;29(1):22–32. doi:10.1002/humu.20605 [PubMed: 17879353]

15. Karpathakis A, Dibra H, Thirlwell C. Neuroendocrine tumours: cracking the epigenetic code. Endocr Relat Cancer. 2013;20(3):R65–R82. Published 2013 May 20. doi:10.1530/ERC-12-0338 [PubMed: 23429748]

16. Pipinikas CP, Berner AM, Sposito T, Thirlwell C. The evolving (epi)genetic landscape of pancreatic neuroendocrine tumours. Endocr Relat Cancer. 2019;26(9):R519–R544. doi:10.1530/ERC-19-0175 [PubMed: 31252410]

17. Marini F, Giusti F, Tonelli F, Brandi ML. Pancreatic Neuroendocrine Neoplasms in Multiple Endocrine Neoplasia Type 1. Int J Mol Sci. 2021;22(8):4041. Published 2021 Apr 14. doi:10.3390/ijms22084041 [PubMed: 33919851]

18. Iyer S, Agarwal SK. Epigenetic regulation in the tumorigenesis of MEN1-associated endocrine cell types. J Mol Endocrinol. 2018;61(1):R13–R24. doi:10.1530/JME-18-0050 [PubMed: 29615472]

19. Norton JA, Venzon DJ, Berna MJ, et al. . Prospective study of surgery for primary hyperparathyroidism (HPT) in multiple endocrine neoplasia-type 1 and Zollinger-Ellison syndrome: long-term outcome of a more virulent form of HPT. Ann Surg. 2008;247(3):501–510. doi:10.1097/SLA.0b013e31815efda5 [PubMed: 18376196]

20. Hao W, Skarulis MC, Simonds WF, et al. Multiple endocrine neoplasia type 1 variant with frequent prolactinoma and rare gastrinoma. J Clin Endocrinol Metab. 2004;89(8):3776–3784. doi:10.1210/jc.2003-031511 [PubMed: 15292304]

21. Inzani F, Petrone G, Rindi G. The New World Health Organization Classification for Pancreatic Neuroendocrine Neoplasia. Endocrinol Metab Clin North Am. 2018;47(3):463–470. doi:10.1016/j.ecl.2018.04.008 [PubMed: 30098710]

22. Partelli S, Giannone F, Schiavo Lena M, et al. Is the Real Prevalence of Pancreatic Neuroendocrine Tumors Underestimated? A Retrospective Study on a Large Series of Pancreatic Specimens. Neuroendocrinology. 2019;109(2):165–170. doi:10.1159/000499606 [PubMed: 31117106]

23. Howe JR, Merchant NB, Conrad C, et al. The North American Neuroendocrine Tumor Society Consensus Paper on the Surgical Management of Pancreatic Neuroendocrine Tumors. Pancreas. 2020;49(1):1–33. doi:10.1097/MPA.0000000000001454 [PubMed: 31856076]

24. Soczomski P, Jurecka-Lubieniecka B, Krzywon A, et al. A Direct Comparison of Patients With Hereditary and Sporadic Pancreatic Neuroendocrine Tumors: Evaluation of Clinical Course, Prognostic Factors and Genotype-Phenotype Correlations. Front Endocrinol (Lausanne). 2021;12:681013. Published 2021 May 28. doi:10.3389/fendo.2021.681013

25. Jensen RT, Norton JA. Treatment of Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1: Some Clarity But Continued Controversy. Pancreas. 2017;46(5):589–594. doi:10.1097/MPA.0000000000000825 [PubMed: 28426491]

26. Niederle B, Selberherr A, Bartsch DK, et al. Multiple Endocrine Neoplasia Type 1 and the Pancreas: Diagnosis and Treatment of Functioning and Non-Functioning Pancreatic and Duodenal Neuroendocrine Neoplasia within the MEN1 Syndrome - An International Consensus Statement. Neuroendocrinology. 2021;111(7):609–630. doi:10.1159/000511791 [PubMed: 32971521]

27. Sadowski SM, Pieterman CRC, Perrier ND, Triponez F, Valk GD. Prognostic factors for the outcome of nonfunctioning pancreatic neuroendocrine tumors in MEN1: a systematic review of literature. Endocr Relat Cancer. 2020;27(6):R145–R161. doi:10.1530/ERC-19-0372 [PubMed: 32229700]

28. Bartsch DK, Langer P, Wild A, et al. Pancreaticoduodenal endocrine tumors in multiple endocrine neoplasia type 1: surgery or surveillance?. Surgery. 2000;128(6):958–966. doi:10.1067/msy.2000.109727 [PubMed: 11114630]

29. Marini F, Giusti F, Brandi ML. Multiple endocrine neoplasia type 1: extensive analysis of a large database of Florentine patients. Orphanet J Rare Dis. 2018;13(1):205. Published 2018 Nov 14. doi:10.1186/s13023-018-0938-8 [PubMed: 30428914]

30. Kövesdi A, Tóth M, Butz H, et al. True MEN1 or phenocopy? Evidence for geno-phenotypic correlations in MEN1 syndrome. Endocrine. 2019;65(2):451–459. doi:10.1007/s12020-019-01932-x [PubMed: 31044390]

31. Christakis I, Qiu W, Hyde SM, et al. . Genotype-phenotype pancreatic neuroendocrine tumor relationship in multiple endocrine neoplasia type 1 patients: A 23-year experience at a single institution. Surgery. 2018;163(1):212–217. doi:10.1016/j.surg.2017.04.044 [PubMed: 29122330]

32. Bartsch DK, Slater EP, Albers M, et al. Higher risk of aggressive pancreatic neuroendocrine tumors in MEN1 patients with MEN1 mutations affecting the CHES1 interacting MENIN domain. J Clin Endocrinol Metab. 2014;99(11):E2387–E2391. doi:10.1210/jc.2013-4432 [PubMed: 25210877]

33. Thevenon J, Bourredjem A, Faivre L, et al. Higher risk of death among MEN1 patients with mutations in the JunD interacting domain: a Groupe d'etude des Tumeurs Endocrines (GTE) cohort study. Hum Mol Genet. 2013;22(10):1940–1948. doi:10.1093/hmg/ddt039 [PubMed: 23376981]

34. Tirosh A, Kebebew E. Genetic and epigenetic alterations in pancreatic neuroendocrine tumors. J Gastrointest Oncol. 2020;11(3):567–577. doi:10.21037/jgo.2020.03.11 [PubMed: 32655936]

35. Conemans EB, Lodewijk L, Moelans CB, et al. DNA methylation profiling in MEN1-related pancreatic neuroendocrine tumors reveals a potential epigenetic target for treatment. Eur J Endocrinol. 2018;179(3):153–160. doi:10.1530/EJE-18-0195 [PubMed: 29903750]

36. Tirosh A, Killian JK, Petersen D, et al. Distinct DNA Methylation Signatures in Neuroendocrine Tumors Specific for Primary Site and Inherited Predisposition. J Clin Endocrinol Metab. 2020;105(10):3285–3294. doi:10.1210/clinem/dgaa477 [PubMed: 32706863]

37. Tirosh A, Mukherjee S, Lack J, et al. Distinct genome-wide methylation patterns in sporadic and hereditary nonfunctioning pancreatic neuroendocrine tumors. Cancer. 2019;125(8):1247–1257. doi:10.1002/cncr.31930 [PubMed: 30620390]

38. Lin W, Francis JM, Li H, et al. . Kmt2a cooperates with menin to suppress tumorigenesis in mouse pancreatic islets. Cancer Biol Ther. 2016;17(12):1274–1281. doi:10.1080/15384047.2016.1250986 [PubMed: 27801610]

39. Lin W, Cao J, Liu J, et al. Loss of the retinoblastoma binding protein 2 (RBP2) histone demethylase suppresses tumorigenesis in mice lacking Rb1 or Men1. Proc Natl Acad Sci U S A. 2011;108(33):13379–13386. doi:10.1073/pnas.1110104108 [PubMed: 21788502]

40. Lin W, Watanabe H, Peng S, et al. Dynamic epigenetic regulation by menin during pancreatic islet tumor formation. Mol Cancer Res. 2015;13(4):689–698. doi:10.1158/1541-7786.MCR-14-0457 [PubMed: 25537453]

Synopsis:

Multiple endocrine neoplasia type 1 syndrome (MEN1) is a disease caused by mutations in the *MEN1* tumor suppressor gene leading to hyperparathyroidism, pituitary adenomas, and entero-pancreatic neuroendocrine tumors. Pancreatic neuroendocrine tumors (PNETs) are a major cause of mortality in patients with MEN1. Identification of consistent genotype-phenotype correlations has remained elusive, but *MEN1* mutations in exons 2, 9, and 10 may be associated with metastatic PNETs; patients with these mutations may benefit from more intensive surveillance and aggressive treatment. Additionally, epigenetic differences between MEN1-associated PNETs and sporadic PNETs are beginning to emerge, but further investigation is required to establish clear phenotypic associations.

Key Points:

1. MEN1 is classically characterized by hyperparathyroidism, pituitary adenomas, and entero-pancreatic neuroendocrine tumors.
2. Entero-pancreatic neuroendocrine tumors are the most common cause of death in patients with MEN1.
3. Menin is a ubiquitous protein that associates with many other proteins that control cell expression.
4. Genotype-phenotype associations have not been firmly established, but some studies indicate a correlation between mutations in exons 2, 9, and 10 and malignant PNETs in MEN1 patients.
5. Epigenetic studies have shown differences in DNA methylation between MEN1-associated PNETs and sporadic PNETs, but further investigation into DNA methylation, histone modification, and non-coding RNAs is needed to determine epigenetic-phenotypic associations.

Table 1.

Pancreatic neuroendocrine neoplasm classifications.

PanNENs	Differentiation	Proliferation Features		
		Grade	Ki67 (% per ≥500 cells)	Mitotic Count (per 10 HPF)
PNET	Well-differentiated	G1 (Low)	<3	<2
		G2 (Intermediate)	3–20	2–20
		G3 (High)	>20	>20
PNEC	Poorly-differentiated	G3 (High)	>20	>20

Table 2.

Summary of *MEN1* mutation characteristics in PNETs.

Study	Year	Mutation Type	Exon	Association
Bartsch *et al.*	2000	Truncating frameshift or nonsense	2, 9, 10	Increased risk of malignant PNET
Thevenon *et al.*	2013	Loss of interaction with JunD		Increased overall risk of MEN1-related death
Bartsch *et al.*	2014	Loss of interaction with CHES1	9, 10	Increased risk of functional PNET, malignant PNET, PNET with metastasis, and PNET-related death
Christakis *et al.*	2017	Deleterious	2	Increased risk of malignant PNET and PNET with metastasis
Marini *et al.*	2018	Frameshift	2, 9, 10	GEP-NET
Marini *et al.*	2018	Nonsense	2, 9, 10	GEP-NET
Kövesdi *et al.*	2019	Frameshift, nonsense, splice-site, large deletion		GEP-NET
Soczomski *et al.*	2021		5	Earlier age of PNET diagnosis
			2	Increased risk of PNET with metastasis