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Multiple Endocrine Neoplasia Type 4

Synonyms: MEN4, *CDKN1B*-Related Multiple Endocrine Neoplasia

Pamela Brock, MS, CGC[1] and Lawrence Kirschner, MD, PhD[1]

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Summary

Clinical characteristics

Multiple endocrine neoplasia type 4 (MEN4) is characterized by the development of endocrine tumors, especially those involving the parathyroid and/or pituitary gland. Parathyroid adenomas and parathyroid hyperplasia manifest as hypercalcemia (primary hyperparathyroidism) as a result of the overproduction of parathyroid hormone. Anterior pituitary adenomas can secrete adrenocorticotrophic hormone (ACTH), growth hormone (GH), prolactin, or are nonfunctional (nonsecreting) adenomas. Well-differentiated endocrine tumors of the gastroenteropancreatic tract, carcinoid tumors, and adrenocortical tumors can also occur.

Diagnosis/testing

The diagnosis of MEN4 is established in a proband with a germline heterozygous pathogenic variant in *CDKN1B* identified by molecular genetic testing.

Management

Treatment of manifestations: Parathyroidectomy for primary hyperparathyroidism; cinacalcet may be considered in those with symptomatic hypercalcemia who are not surgical candidates; surgical resection for pituitary adenomas that secrete ACTH or GH; cabergoline for prolactin-secreting tumors; surgical resection for neuroendocrine and carcinoid tumors if possible; some individuals may be treated with somatostatin analogs; proton pump inhibitors for individuals with gastrin-secreting tumors.

Surveillance: Biennial serum calcium and gastrin starting at age 25 years; IGF-1 and prolactin every three to five years or as symptoms indicate, starting at age 25 years; pituitary MRI every five years starting at age 25 years; abdominal MRI or CT every five years starting at age 25 years and increasing frequency to every 2.5 years starting at age 40 years.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *CDKN1B* pathogenic

Author Affiliation: 1 The Ohio State University Comprehensive Cancer Center, Columbus, Ohio; Email: pamela.brock@osumc.edu; Email: lawrence.kirschner@osumc.edu.

variant in the family in order to identify as early as possible those who would benefit from prompt initiation of surveillance and treatment.

Genetic counseling

MEN4 is inherited in an autosomal dominant manner. Most individuals diagnosed with MEN4 have an affected parent; some individuals diagnosed with MEN4 may have the disorder as the result of a *de novo CDKN1B* pathogenic variant. Each child of an individual with MEN4 has a 50% chance of inheriting the *CDKN1B* pathogenic variant. Once the *CDKN1B* pathogenic variant has been identified in an affected family member, testing of at-risk asymptomatic family members (strongly recommended for all first-degree relatives of an affected person with an identified *CDKN1B* pathogenic variant) and prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Multiple endocrine neoplasia type 4 (MEN4) **should be suspected** in individuals with multiple/multifocal or early-onset endocrine tumors, especially those involving the parathyroid and/or pituitary gland (see Clinical Description). Varying combinations of tumors have been reported in individuals with MEN4; therefore, no clinical criteria or definition can capture all affected individuals.

Parathyroid tumors manifest as hypercalcemia (primary hyperparathyroidism [PHPT]) as a result of the overproduction of parathyroid hormone. Individuals with PHPT may be asymptomatic or may present with nephrolithiasis, reduced bone mass, fatigue, muscle weakness, bone or joint pain, and/or constipation.

Anterior pituitary adenomas

- Adrenocorticotrophic hormone-secreting anterior pituitary adenomas are mostly associated with Cushing disease.
- Growth hormone-secreting anterior pituitary adenomas cause gigantism in children and signs and symptoms of acromegaly in adults.
- Prolactinomas (prolactin-secreting anterior pituitary adenomas) manifest as oligomenorrhea/amenorrhea and galactorrhea in females, and sexual dysfunction and (more rarely) gynecomastia in males.
- Nonfunctioning (nonsecreting) anterior pituitary adenomas manifest as enlarging tumors, compressing adjacent structures such as the optic chiasm and causing visual disturbances, headaches, and/or hypopituitarism.

Note: The imaging test of choice for all types of pituitary tumors is MRI.

Well-differentiated endocrine tumors of the gastroenteropancreatic tract (including tumors of the stomach, duodenum, pancreas, and intestinal tract) manifest as the following clinical presentations (from most to least frequent):

- Nonfunctioning pancreatic endocrine tumors are the most frequently seen tumors in MEN4. They are not found during biochemical testing but may be detected on abdominal imaging studies (CT, MRI, ultrasound) performed for other specific indications.
- Zollinger-Ellison syndrome (ZES; peptic ulcer with or without chronic diarrhea) resulting from a gastrin-secreting duodenal mucosal tumor (gastrinoma)

Note: Endoscopic ultrasound examination is the most sensitive imaging procedure for the detection of small (≤10 mm) pancreatic endocrine tumors in asymptomatic individuals with multiple endocrine neoplasia type 1 (MEN1) [Jensen 1999]; however, this has not been directly evaluated in individuals with MEN4.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

No clinical diagnostic criteria can accurately distinguish MEN4 from multiple MEN1 or coincidental tumor co-occurrence. Therefore, the diagnosis of MEN4 **is established** in a proband with a germline heterozygous pathogenic (or likely pathogenic) variant in *CDKN1B* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *CDKN1B* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include single-gene testing and a multigene panel depending on the phenotype.

- **Single-gene testing.** Sequence analysis of *CDKN1B* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *CDKN1B* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Multiple Endocrine Neoplasia Type 4

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CDKN1B	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	2 individuals [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Grey et al [2013]; Authors, unpublished data

Clinical Characteristics

Clinical Description

Multiple endocrine neoplasia type 4 (MEN4) is characterized by the development of endocrine tumors, especially those involving the parathyroid and/or pituitary gland. The clinical presentation has significant overlap with multiple endocrine neoplasia type 1 (MEN1). While there are some conflicting reports, most indicate that, by comparison, MEN4 is more attenuated, with lower penetrance and later ages of diagnosis [Alrezk et al 2017, Singeisen et al 2023]. The mean age of first endocrine tumor presentation is 43.5 years (range: 5-76 years) [Singeisen et al 2023], compared to 31.8 years (range: 9-71 years) in MEN1 [Marini et al 2018].

To date, 65 individuals have been identified with a disease-causing variant in *CDKN1B* [Singeisen et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Endocrine Tumor Types in Multiple Endocrine Neoplasia Type 4

Tumor Type	Prevalence of Tumor Type in Persons w/ MEN4	Tumor Subtypes	Hormone Secreting	Comments
Parathyroid tumor / PHPT	55%-80%	NA	Yes	86% are single adenomas; parathyroid hyperplasia in 14%
Anterior pituitary	30%-45%	ACTH secreting	Yes	Of anterior pituitary tumors: 33% secrete ACTH; 24% PRL; 19% GH; 24% are NFAs
		Prolactinoma	Yes	
		GH secreting	Yes	
		Nonfunctioning	No	
Well-differentiated GEP-NET	14%-25%	Gastrinoma	Yes	Of GEP-NETs: 33% are gastrinomas; 66% are nonfunctioning
		Nonfunctioning	No	
Carcinoid	4%-7%	Thymus/lung	No	
		Small bowel	No	
Adrenocortical	4%-7%	Cortisol secreting	Yes	
		Nonfunctioning	No	

Based on Alrezk et al [2017] and Singeisen et al [2023]
ACTH = adrenocorticotrophic hormone; GEP-NET = gastroenteropancreatic neuroendocrine tumor; GH = growth hormone; NA = not applicable; NFA = nonfunctioning adenoma; PHPT = primary hyperparathyroidism; PRL = prolactin

Primary hyperparathyroidism (PHPT). MEN4-associated PHPT is often mild, with hypercalcemia often detected in asymptomatic individuals. PHPT is the most common MEN4-associated endocrinopathy and is the first manifestation in approximately 56% of individuals. The pathology most often shows a single adenoma. The median age of PHPT diagnosis in individuals with MEN4 is 51 years (range: 15-74 years). Multiglandular disease or recurrent PHPT are much less common in MEN4 (14% and 6%, respectively) compared to MEN1. MEN4-associated PHPT has been reported more often in women than in men (80% vs 58%) [Singeisen et al 2023].

Anterior pituitary adenomas are the second most common feature in MEN4 and are the presenting feature in approximately 23% of individuals. MEN4-associated anterior pituitary adenomas are more likely to be microadenomas. The median age of MEN4-associated anterior pituitary adenoma diagnosis is 39 years (range: 5-79 years). Adrenocorticotrophic hormone-secreting adenomas leading to hypercortisolism and Cushing disease are the most common, followed by prolactinomas and nonfunctional tumors [Singeisen et al 2023].

A study of mostly children with Cushing disease identified *CDKN1B* variants in up to 2.6% of individuals [Chasseloup et al 2020].

Well-differentiated neuroendocrine tumors of the gastroenteropancreatic tract (GEP-NET). Nonfunctioning GEP tract tumors are the most frequent type of neuroendocrine tumor in MEN4, followed by gastrin-secreting tumors (gastrinomas). Most GEP-NETs occur in the pancreas; however, gastric tumors have also been reported. MEN4-associated GEP-NETs are less likely to be multifocal. Furthermore, the age of tumor diagnosis is considerably later than the age of tumor diagnosis in those with MEN1, with the youngest reported MEN4-associated pancreatic neuroendocrine tumor diagnosed at age 42 years. However, approximately half of GEP-NETs are metastatic at diagnosis [Singeisen et al 2023]. A lack of standardized screening guidance for individuals with MEN4 may contribute to this finding.

Carcinoid tumors. Approximately 4%-7% of individuals with MEN4 develop carcinoid tumors of the thymus, bronchus, and ileum, some of which were metastatic at the time of diagnosis [Singeisen et al 2023].

Adrenocortical tumors. Approximately 4%-7% of individuals with MEN4 develop adrenocortical tumors, which are either nonfunctional or cortisol secreting [Singeisen et al 2023].

Other. Singeisen et al [2023] reported papillary thyroid cancer in 8% of individuals with MEN4. Three of four individuals had multifocal thyroid cancer, and all four individuals were women who were diagnosed with papillary thyroid cancer in their fifties or sixties. This may represent an emerging association, but further research is needed in this area.

Individuals with MEN4 have been found to have breast cancer, colon cancer, testicular cancer, prostate cancer, cervical neuroendocrine carcinoma, meningioma, and renal angiomyolipoma. Further research is needed to determine if these tumors are part of the phenotype or occurred by coincidence in an individual with MEN4.

Chevalier et al [2020] also reported a possible association between germline *CDNK1B* variants and autoimmune disease. Further research is needed to determine if risk of autoimmune disease is part of the MEN4 phenotype.

Cutaneous manifestations associated with MEN1 have not been reported in individuals with MEN4. Further research is needed to determine if cutaneous tumors are absent from the MEN4 phenotype versus underassessed in clinical reports.

Genotype-Phenotype Correlations

A recent report suggested that individuals with *CDKN1B* indels have a higher incidence of PHPT [Halperin et al 2022]. The same study found that individuals with variants in codons 94-96 had a higher risk of developing PHPT and pituitary adenomas compared to individuals with other *CDKN1B* pathogenic variants.

Penetrance

Penetrance is reduced and age related.

Prevalence

MEN4 is likely both rare and underdiagnosed. To date, 65 individuals have been reported with a disease-causing variant in *CDKN1B* [Singeisen et al 2023]. However, 13 of these individuals belong to a large Danish family [Frederiksen et al 2019]. A further complication is that many case reports describe individuals with MEN4 whose *CDKN1B* variant is currently classified as a variant of uncertain significance.

Disease-causing variants in *CDKN1B* have been identified in a very small percentage (<5%) of individuals with features suggestive of MEN1 and negative MEN1 molecular testing [Georgitsi et al 2007, Agarwal et al 2009, Molatore et al 2010].

Genetically Related (Allelic) Disorders

Grey et al [2013] reported a child with overgrowth/macrocephaly, strabismus, and neurodevelopmental delay who had reduced CDKN1B expression, presumably due to biallelic loss of the *CDKN1B* gene as a result of a maternally inherited contiguous gene deletion and a *de novo* promotor variant on the paternally inherited allele. The authors suggest an autosomal recessive disease mechanism.

Sporadic tumors (including breast cancer, prostate cancer, neuroendocrine tumors, and others) occurring as single tumors in the absence of any other findings of multiple endocrine neoplasia type 4 frequently contain a somatic pathogenic variant in *CDKN1B* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Table 3a. Hereditary Cancer Syndromes in the Differential Diagnosis of Multiple Endocrine Neoplasia Type 4

Gene	Disorder	MOI	Overlapping Feature(s)	Distinguishing Features
AIP	*AIP*-related pituitary adenoma predisposition (PAP) & multiple types of pituitary adenoma (PITA1) (See *AIP* Familial Isolated Pituitary Adenomas.)	AD	Pituitary adenomas	• Earlier onset pituitary tumors in *AIP*-assoc PAP than in MEN4 • *MEN4*-assoc tumors are predominantly ACTH-secreting adenomas. • *AIP*-assoc tumors are predominantly GH-secreting adenomas.
GPR101	Pituitary adenoma 2, GH-secreting (PITA2) (OMIM 300943)	XL	GH-secreting pituitary adenoma	• Not assoc w/other endocrinopathies typical of MEN4 • Not assoc w/GEP-NETs
CDH23	Pituitary adenoma 5, multiple types (PITA5) (OMIM 617540)	AD	GH-secreting & nonfunctional pituitary adenomas in familial pituitary adenoma types; GH-secreting, nonfunctional, PRL-secreting, ACTH-secreting, TSH-secreting, & plurihormonal (GH & TSH) tumors in sporadic pituitary adenoma types	• Not assoc w/other endocrinopathies typical of MEN4 • Not assoc w/GEP-NETs
CASR [1] *CDC73* [2] *GCM2* *MEN1*	Familial isolated primary hyperparathyroidism (FIHP) [3] (OMIM 145980, 145000, 617343)	AD	Parathyroid adenoma or hyperplasia	• Not assoc w/other endocrinopathies typical of MEN4 • Not assoc w/pituitary tumors or GEP-NETs
MEN1	Multiple endocrine neoplasia type 1 (MEN1)	AD	All features	See Clinical Description for comparison of MEN1 & MEN4.

Table 3a. continued from previous page.

Gene	Disorder	MOI	Overlapping Feature(s)	Distinguishing Features
RET	Multiple endocrine neoplasia type 2A (MEN2A)	AD	PHPT (in ~20%-30% of persons w/MEN2A); hypercalciuria & renal calculi (in some)	• MEN2A is assoc w/medullary thyroid carcinoma & pheochromocytoma. • MEN2A-assoc PHPT is less penetrant than MEN4-assoc PHPT.

ACTH = adrenocorticotropic hormone; AD = autosomal dominant; GEP-NET = gastroenteropancreatic neuroendocrine tumor; GH = growth hormone; MEN4 = multiple endocrine neoplasia type 4; MOI = mode of inheritance; PHPT = primary hyperparathyroidism; PRL = prolactin; TSH = thyroid-stimulating hormone; XL = X-linked

1. Between 14% and 18% of families with FIHP have identifiable *CASR* pathogenic variants [Simonds et al 2002, Warner et al 2004]. *CASR* pathogenic variants have also been identified in individuals with familial hypocalciuric hypercalcemia (OMIM 601198) and neonatal severe primary hyperparathyroidism (OMIM 239200).

2. Pathogenic variants in *CDC73* are associated with hyperparathyroidism-jaw tumor syndrome (see *CDC73*-Related Disorders). Of note, Warner et al [2004] did not identify any *CDC73* pathogenic variants in 22 individuals with FIHP.

3. FIHP is characterized by parathyroid adenoma or hyperplasia without other associated endocrinopathies in two or more individuals in one family.

Sporadic primary hyperparathyroidism (PHPT), generally caused by a single parathyroid adenoma, refers to PHPT that is not inherited. The peak incidence of sporadic PHPT is in the sixth decade, which is similar to the mean age of diagnosis in multiple endocrine neoplasia type 4 (MEN4) [Singeisen et al 2023].

Table 3b. Differential Diagnosis of Multiple Endocrine Neoplasia Type 4-Associated Clinical Features

Clinical Feature	Comments
Pituitary tumors	If multiple pituitary adenomas: see Table 3a
Zollinger-Ellison syndrome (ZES)	Gastrinomas may also be present in MEN1, TSC, & NF1.
Nonfunctioning neuroendocrine tumors	May also be present in MEN1 (20%-55%), VHL (10%-17%), & NF1
Carcinoid tumors	When **not** assoc w/MEN4: usually occur in derivatives of the midgut & hindgut & secrete serotonin (5-hydroxytryptamine)

MEN1 = multiple endocrine neoplasia type 1; MEN4 = multiple endocrine neoplasia type 4; NF1 = neurofibromatosis 1; TSC = tuberous sclerosis complex; VHL = von Hippel-Lindau syndrome

Management

No consensus clinical practice guidelines for multiple endocrine neoplasia type 4 (MEN4) have been established. Given the clinical overlap with multiple endocrine neoplasia type 1 (MEN1), MEN1-related screening can be used as a guide, keeping in mind that MEN4 is more attenuated, with lower penetrance and later age at tumor diagnosis.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MEN4, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Multiple Endocrine Neoplasia Type 4: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
General	• Referral to endocrinologist w/experience in MEN • Assess for clinical manifestations of endocrine tumors (e.g., kidney stones, signs of cortisol, GH, or prolactin excess, excessive nausea, vomiting, or diarrhea)	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
PHPT	Serum calcium	In those age ≥25 yrs
	Further testing (e.g., PTH, vitamin D, 24-hr urine calcium) & referral to surgery for those w/laboratory findings of PHPT.	
Pituitary adenoma	• Pituitary MRI • Serum hormone testing (ACTH, cortisol, IGF-1, prolactin) guided by clinical suspicion	In those age ≥25 yrs
	Dynamic testing of GH or cortisol axis may be needed if screening tests indicate possible hormonal abnormalities (e.g., glucose suppression test for ↑ GH/IGF-1 or dexamethasone suppression testing for ↑ cortisol).	
Neuroendocrine tumor	• Abdominal imaging (e.g., contrast-enhanced CT or MRI) • Note: Endoscopic ultrasound is more sensitive but more invasive.	In those age ≥25 yrs
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of MEN4 to facilitate medical & personal decision making

ACTH = adrenocorticotrophic hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; MEN = multiple endocrine neoplasia; MEN4 = multiple endocrine neoplasia type 4; MOI = mode of inheritance; PHPT = primary hyperparathyroidism; PTH = parathyroid hormone

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Multiple Endocrine Neoplasia Type 4: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
PHPT	Parathyroidectomy [1]	Medical therapy (cinacalcet) can be considered in those w/symptomatic hypercalcemia who are not surgical candidates.
Pituitary adenoma	• Pituitary surgery for ACTH- or GH-secreting tumors • Cabergoline for PRL-secreting tumors	Pituitary surgery should be carried out by surgeon w/pituitary expertise.
Neuroendocrine tumors & carcinoids	• Surgical resection if possible • Consider referral to medical oncologist. • Some persons may be treated w/somatostatin analogs. • Persons w/gastrin-secreting tumors can be treated w/proton pump inhibitors.	

ACTH = adrenocorticotrophic hormone; GH = growth hormone; PHPT = primary hyperparathyroidism; PRL = prolactin

1. For further treatment details see Multiple Endocrine Neoplasia Type 1, Treatment of Manifestations, PHPT.

Surveillance

Table 6. Multiple Endocrine Neoplasia Type 4: Recommended Surveillance

System/Concern	Evaluation	Frequency [1]
PHPT	• Serum calcium • PTH & vitamin D measurement may also be considered to ensure sufficiency.	Biennially (every 2 yrs) starting at age 25 yrs

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency [1]
Pituitary adenoma	Serum IGF-1 & prolactin	Every 3-5 yrs or as symptoms indicate, starting at age 25 yrs
	Pituitary MRI	Imaging every 5 yrs starting at age 25 yrs
	If clinical concern for Cushing disease, perform 24-hr urine free cortisol, late night salivary cortisol, &/or 1 mg overnight dexamethasone suppression test.	
Neuroendocrine tumors & carcinoids	Serum gastrin	Biannually starting at age 25 yrs
	Abdominal MRI (or CT)	Imaging every 5 yrs starting at age 25 yrs, increasing to every 2.5 yrs at age 40 yrs

IGF-1 = insulin-like growth factor 1; PHPT = primary hyperparathyroidism; PTH = parathyroid hormone
1. Abnormal findings would indicate the need for more frequent follow up (current multiple endocrine neoplasia type 1 treatment guidelines can be used as a guide).

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *CDKN1B* pathogenic variant in the family in order to identify as early as possible those who would benefit from prompt initiation of surveillance and treatment. Early detection and treatment of the potentially malignant neuroendocrine tumors should reduce the morbidity and mortality of MEN4.

When molecular genetic testing for a *CDKN1B* pathogenic variant is not possible or is not informative, individuals at 50% risk (i.e., first-degree relatives of an individual with MEN4) should undergo surveillance.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Multiple endocrine neoplasia type 4 (MEN4) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with MEN4 have an affected parent.

- Some individuals diagnosed with MEN4 may have the disorder as the result of a *de novo CDKN1B* pathogenic variant. The proportion of MEN4 caused by a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status, determine their need for appropriate clinical surveillance (see Management), and allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with MEN4 may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. However, penetrance appears to be reduced (see Penetrance), and the types of MEN4-related tumors can vary among affected family members.
- If the *CDKN1B* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *CDKN1B* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for MEN4 because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with MEN4 has a 50% chance of inheriting the *CDKN1B* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *CDKN1B* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Testing of at-risk asymptomatic individuals. Molecular genetic testing of at-risk asymptomatic family members is strongly recommended for all first-degree relatives of an affected person with an identified *CDKN1B* pathogenic variant so that individuals with a *CDKN1B* pathogenic variant can receive the appropriate clinical surveillance (see Management). Given the apparently low risk of childhood tumors and the emerging nature of associated risks, it may be appropriate to follow the American Society of Clinical Oncology (ASCO) recommendation to delay genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing [American Society of Clinical Oncology 2003]. Education and genetic counseling of all at-risk individuals and their families prior to genetic testing is appropriate.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CDKN1B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association for Multiple Endocrine Neoplasia Disorders (AMEND)**
  United Kingdom
  Email: info@amend.org.uk
  www.amend.org.uk

- **MedlinePlus**
  Multiple endocrine neoplasia

- **American Multiple Endocrine Neoplasia Support**
  Phone: 865-283-5842
  Email: Info@amensupport.org
  AMEN SUPPORT

- **AMEND Research Registry**
  Association for Multiple Endocrine Neoplasia Disorders
  United Kingdom
  Email: jo.grey@amend.org.uk
  UK National MEN1 & PNET Research Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Multiple Endocrine Neoplasia Type 4: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CDKN1B	12p13.1	Cyclin-dependent kinase inhibitor 1B	CDKN1B database	CDKN1B	CDKN1B

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Multiple Endocrine Neoplasia Type 4 (View All in OMIM)

600778	CYCLIN-DEPENDENT KINASE INHIBITOR 1B; CDKN1B
610755	MULTIPLE ENDOCRINE NEOPLASIA, TYPE IV; MEN4

Molecular Pathogenesis

CDKN1B encodes the p27 nuclear protein, which is a cyclin-dependent kinase inhibitor that blocks cell cycle progression from the G1 to S phase. *CDKN1B* acts as a tumor suppressor gene.

Mechanism of disease causation. Most reports suggest that the mechanism of tumorigenesis is loss or reduced p27. In many MEN4-related tumors, there is no loss of heterozygosity or acquired second hit. Further research is needed to determine whether the mechanism of disease causation is haploinsufficiency versus loss of function due to epigenetic silencing of *CDKN1B* in addition to a germline variant.

***CDKN1B*-specific laboratory technical considerations.** *CDKN1B* variants with functional evidence of pathogenicity have been reported to exist outside the coding region of the gene, such as in the 5' UTR [Chasseloup et al 2020, Singeisen et al 2023].

Chapter Notes

Revision History

- 21 September 2023 (sw) Review posted live
- 3 March 2023 (pb) Original submission

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