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Multiple Endocrine Neoplasia Type 2

Synonyms: MEN2, MEN2 Syndrome

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Summary

Clinical characteristics

Multiple endocrine neoplasia type 2 (MEN2) includes the following phenotypes: MEN2A, familial medullary thyroid carcinoma (FMTC, which may be a variant of MEN2A), and MEN2B. All three phenotypes involve high risk for development of medullary carcinoma of the thyroid (MTC); MEN2A and MEN2B involve an increased risk for pheochromocytoma; MEN2A involves an increased risk for parathyroid adenoma or hyperplasia. Additional features of MEN2B include mucosal neuromas of the lips and tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the gastrointestinal tract, and a marfanoid habitus. MTC typically occurs in early childhood in MEN2B, early adulthood in MEN2A, and middle age in FMTC.

Diagnosis/testing

The diagnosis of MEN2 is established in a proband who fulfills existing clinical diagnostic criteria or by identification of a heterozygous germline gain-of-function variant in *RET* on molecular genetic testing. Molecular genetic testing is recommended in all individuals with a clinical diagnosis due to genotype-specific surveillance and treatment recommendations and to allow family studies.

Management

Targeted therapy: Prophylactic thyroidectomy for individuals with an identified germline *RET* pathogenic variant.

Supportive care: Measurement of plasma free metanephrines or 24-hour urine for fractionated metanephrines to evaluate for functioning pheochromocytoma prior to any surgery in individuals with MEN2A, MEN2B, or FMTC. Adrenalectomy prior to thyroidectomy in any individual with pheochromocytoma identified. Treatment for MTC is surgical removal of the thyroid gland and lymph node dissection. External beam radiation therapy or intensity-modulated radiation therapy can be considered for incomplete tumor resection or extrathyroidal

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extension with positive margins. Kinase inhibitors may be considered in those with metastatic MTC. Standard treatment for hypothyroidism following thyroidectomy. Treatment of hypertension prior to adrenalectomy or management of hypertension during surgery. Resection of pheochromocytomas by adrenalectomy. Primary hyperparathyroidism is treated with surgery to remove one or more parathyroid glands or, more rarely, with medications to reduce parathyroid hormone secretion.

Surveillance: Annual measurement of serum calcitonin concentration in those who have not had prophylactic thyroidectomy and to detect residual or recurrent MTC after thyroidectomy, even if thyroidectomy was performed prior to biochemical evidence of disease. Annual plasma free metanephrines or 24-hour urine for fractionated metanephrines for those with a germline *RET* pathogenic variant whose initial screening results are negative for pheochromocytoma. Annual albumin-corrected calcium or ionized calcium for individuals with MEN2A/FMTC whose initial screening results are negative for hyperparathyroidism. Age of initiation of surveillance for pheochromocytoma and hyperparathyroidism is determined by the specific germline *RET* pathogenic variant identified.

Agents/circumstances to avoid: Dopamine D_2 receptor antagonists and beta-adrenergic receptor antagonists present a high risk for adverse reactions in individuals with pheochromocytoma.

Evaluation of relatives at risk: RET molecular genetic testing should be offered to all at-risk members of kindreds in which a germline *RET* pathogenic variant has been identified. When an individual with MEN2 refuses to notify at-risk family members, the physician should consider consulting a clinical ethicist to determine if the physician has the ethical obligation to warn the at-risk family members.

Pregnancy management: Women with MEN2 should be screened for pheochromocytoma prior to a planned pregnancy or as early as possible during an unplanned pregnancy.

Genetic counseling

All MEN2 phenotypes are inherited in an autosomal dominant manner. Up to 95% of individuals diagnosed with MEN2A and 50% of individuals diagnosed with MEN2B have an affected parent. (By definition, individuals with FMTC have multiple family members who are affected.) Approximately 5%-9% of individuals with MEN2A and 50% of individuals with MEN2B have the disorder as the result of a *de novo* germline pathogenic variant. Each child of an individual with MEN2 has a 50% chance of inheriting the *RET* pathogenic variant. Once the *RET* pathogenic variant has been identified in an affected family member, molecular genetic testing of at-risk asymptomatic family members and prenatal and preimplantation genetic testing for MEN2 are possible.

GeneReview Scope

Multiple Endocrine Neoplasia Type 2: Included Phenotypes
• Multiple endocrine neoplasia type 2A (MEN2A) • Familial medullary thyroid carcinoma (FMTC) • Multiple endocrine neoplasia type 2B (MEN2B)

For synonyms and outdated names see Nomenclature.

Diagnosis

Clinical diagnostic criteria for multiple endocrine neoplasia type 2 (MEN2) have been published [Kloos et al 2009, Wells et al 2015, National Comprehensive Cancer Network 2022]; see Establishing the Diagnosis.

Suggestive Findings

MEN2 includes the phenotypes MEN2A; familial medullary thyroid carcinoma (FMTC), which may itself be a variant of MEN2A; and MEN2B.

MEN2A **should be suspected** in individuals with one or more specific endocrine tumor(s): medullary thyroid carcinoma (MTC), pheochromocytoma, or parathyroid adenoma/hyperplasia.

FMTC **should be suspected** in families with more than one individual diagnosed with MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia.

MEN2B **should be suspected** in individuals with distinctive facies including lip mucosal neuromas resulting in thick vermilion of the upper and lower lip, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, marfanoid habitus, and MTC.

Establishing the Diagnosis

The clinical diagnosis of MEN2 **can be established** in a proband based on clinical diagnostic criteria [Kloos et al 2009, Wells et al 2015, National Comprehensive Cancer Network 2022], or the molecular diagnosis can be established in a proband with suggestive findings and a heterozygous germline gain-of-function pathogenic (or likely pathogenic) variant in *RET* identified by molecular genetic testing (see Table 1). Molecular genetic testing is recommended in all individuals with a clinical diagnosis due to genotype-specific surveillance and treatment recommendations and to allow family studies.

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 *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *RET* variant of uncertain significance does not establish or rule out the diagnosis.

Clinical Diagnosis

MEN2A is diagnosed clinically by the occurrence of two or more specific endocrine tumors (MTC, pheochromocytoma, or parathyroid adenoma/hyperplasia) in a single individual or in close relatives.

FMTC is diagnosed clinically in families with two or more individuals with MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia.

MEN2B is diagnosed clinically by the presence of early-onset MTC, mucosal neuromas of the lips and tongue, as well as medullated corneal nerve fibers, distinctive facies with enlarged lips, and an asthenic, marfanoid body habitus.

Molecular Diagnosis

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *RET* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. Typically, if 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; however, to date such variants have not been identified as a cause of this disorder.
    - **Select-exon testing** can be considered first in those with suspected **MEN2A** or **FMTC**. The majority of pathogenic variants occur in exons 10, 11, and 13-16 (see Table 1 and Table 3). Sequence analysis

of select exons and targeted analysis for pathogenic variants may be offered by some laboratories. If no pathogenic variant is found by select-exon testing, full-gene sequencing of *RET* as part of a multigene panel should be considered next.

- **Targeted analysis** for *RET* pathogenic variants p.Met918Thr and p.Ala883Phe can be considered first in those with suspected **MEN2B.**

- **A cancer predisposition multigene panel** that includes *RET* and other genes of interest (see Differential Diagnosis) may 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 2

Gene [1]	Method [2]	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method		
		MEN2A	FMTC	MEN2B
RET	Sequence analysis [4, 5]	>98% [6]	>95% [6, 7]	>98% [6, 8]
	Sequence analysis of select exons assoc w/MEN2A or FMTC	98% [6, 9]	95% [6, 7]	NA
	Targeted analysis for pathogenic variants assoc w/MEN2B [10]	NA	NA	98% [6, 8]

FMTC = familial medullary thyroid carcinoma; MEN2A = multiple endocrine neoplasia type 2A; MEN2B = multiple endocrine neoplasia type 2B; NA = not applicable

1. See Table A. Genes and Databases for chromosome locus and protein.

2. Since MEN2 occurs through a gain-of-function mechanism, gene-targeted deletion/duplication analysis is not indicated.

3. See Molecular Genetics for information on variants detected in this gene.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants, and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

5. Sequence analysis of all *RET* exons may be performed instead of sequencing of select exons. If sequencing of select exons has been previously performed with no pathogenic variant detected, a multigene panel including *RET* is recommended (see Establishing the Diagnosis).

6. Zbuk & Eng [2007], Romei et al [2016], Elisei et al [2019]

7. Pathogenic variants of codons 618, 620, and 634 each account for 20%-30% of pathogenic variants. Other pathogenic variants in exons 5, 8, 10, 11, and 13-16 appear to account for a small percentage of pathogenic variants in families with FMTC, with an important minority affecting codons 768 and 804 [Wells et al 2015, Romei et al 2016, Elisei et al 2019].

8. Approximately 95% of individuals have a pathogenic variant at codon 918 in exon 16 [Eng et al 1996, Wells et al 2015]. A pathogenic variant in exon 15 has been identified in several affected individuals [Gimm et al 1997, Smith et al 1997, Wells et al 2015, Salvatore et al 2021].

9. Pathogenic variants in exons 10 and 11 [Eng et al 1996, Wells et al 2015, Romei et al 2016, Elisei et al 2019]

10. Pathogenic variants typically detected: p.Met918Thr, p.Ala883Phe. Note: Pathogenic variants included in a panel may vary by laboratory.

Clinical Characteristics

Clinical Description

The endocrine disorders observed in multiple endocrine neoplasia type 2 (MEN2) are: medullary thyroid carcinoma (MTC) and/or its precursor, C-cell hyperplasia (CCH); pheochromocytoma; and parathyroid adenoma or hyperplasia.

MTC and CCH

Clinical findings. MTC in persons with MEN2 typically presents at a younger age than sporadic MTC and is more often associated with CCH as well as multifocality or bilaterality.

- Symptoms of MTC include neck mass or neck pain prior to age 35 years. Diarrhea (the most frequent systemic symptom) occurs in affected individuals with a plasma calcitonin concentration >10 ng/mL and implies a poor prognosis [Wells et al 2015, Jayasinghe et al 2022].
- Up to 70% of individuals with a palpable thyroid mass or diarrhea already have cervical lymph node metastases [Moley 2010, Wells et al 2015]. Metastatic spread to regional lymph nodes (e.g., parathyroid, paratracheal, jugular chain, upper mediastinum) or to distant sites including the liver, lungs, or bone is also common in symptomatic individuals [Moley 2010, Wells et al 2015].
- About 20%-30% of all individuals with MTC have a germline *RET* pathogenic variant [Wells et al 2015, Salvatore et al 2021, Angelousi et al 2022]. In a large series of individuals with simplex MTC (i.e., no known family history of MTC or personal history of other endocrine disease), approximately 6%-7% had a germline *RET* pathogenic variant [Elisei et al 2019].

Biochemical findings. MTC and CCH are suspected in the presence of an elevated plasma calcitonin concentration, a sensitive and specific marker. In provocative testing, plasma calcitonin concentration is measured before (basal level), then two and five minutes after intravenous administration of calcium (stimulated level). Other calcitonin secretagogues such as pentagastrin (available in Europe, limited in the United States) are also used [Wells et al 2015].

Note: All individuals with an MTC-predisposing *RET* pathogenic variant who have not undergone prophylactic thyroidectomy demonstrate biochemical evidence of MTC by age 35 years [DeLellis et al 2004].

Approximately 50% of individuals diagnosed with MTC who have undergone total thyroidectomy and neck nodal dissections have recurrent disease [Cohen & Moley 2003]. Furthermore, thyroid glands removed from individuals with a germline *RET* pathogenic variant who had normal plasma calcitonin concentrations have been found to contain MTC [Skinner et al 1996].

Histology. MTC originates in calcitonin-producing cells (C cells) of the thyroid gland. MTC is diagnosed histologically when nests of C cells appear to extend beyond the basement membrane and to infiltrate and destroy thyroid follicles. Immunohistochemistry for calcitonin expression may be performed as a pathologic diagnostic adjunct.

CCH is diagnosed histologically by the presence of an increased number of diffusely scattered or clustered C cells. In MEN2, the age of transformation from CCH to MTC varies with different germline *RET* pathogenic variants [Wells et al 2015, Salvatore et al 2021].

Pheochromocytoma

Clinical findings. Pheochromocytomas in individuals with MEN2 are often bilateral. Although pheochromocytomas in individuals with MEN2 rarely metastasize, they can be lethal because of intractable hypertension or anesthesia-induced hypertensive crises. Head and neck paraganglioma have been reported in

individuals with MEN2; however, paragangliomas in individuals with MEN2 are nearly always adrenal (i.e., pheochromocytomas). Individuals with a confirmed germline *RET* pathogenic variant who present with head and neck paraganglioma all have a personal and/or family history consistent with MEN2 [Boedeker et al 2009].

Biochemical findings. Pheochromocytoma is suspected when biochemical screening reveals elevated excretion of catecholamines and catecholamine metabolites (e.g., norepinephrine, epinephrine, metanephrine, and vanillylmandelic acid) in plasma or 24-hour urine collections [Pacak et al 2005, Ilias & Pacak 2009]. In individuals with MEN2, pheochromocytomas consistently produce epinephrine or epinephrine and norepinephrine [Ilias & Pacak 2009].

Imaging. Abdominal MRI and/or CT is performed if plasma or urinary catecholamine values are increased or if a pheochromocytoma is suspected clinically. MRI is more sensitive than CT in detection of a pheochromocytoma.

[^{18}F]-fluorodopamine ([^{18}F]DA) PET is the best overall imaging modality in the localization of pheochromocytomas. If [^{18}F]DA PET is unavailable, MIBG (^{123}I- or ^{131}I-labeled metaiodobenzylguanidine) scintigraphy should be used to further evaluate individuals with biochemical or radiographic evidence of pheochromocytoma [Ilias et al 2008]. ^{68}Ga-DOTATATE-PET-CT results correlate best with biochemical parameters (reviewed in Neumann et al [2019]).

Parathyroid Abnormalities

Clinical findings. Parathyroid abnormalities can range from benign parathyroid adenomas to clinically evident hyperparathyroidism (HPT) with hypercalcemia and kidney stones.

Biochemical findings. Parathyroid abnormalities are present when elevated serum calcium occurs simultaneously with elevated or high-normal parathyroid hormone.

Imaging. Postoperative parathyroid localizing studies with ^{99m}Tc-sestamibi scintigraphy and neck ultrasound may be helpful if HPT recurs. For preoperative adenoma localization, three-dimensional single-photon emission CT (SPECT) may also be used [Brenner & Jacene 2008].

MEN2 Phenotypes

MEN2 is classified into three phenotypes: MEN2A, familial medullary thyroid carcinoma (FMTC, which is now considered a variant of MEN2A), and MEN2B (see Table 2). All three phenotypes involve high risk for MTC; individuals with MEN2A and MEN2B are at increased risk for pheochromocytoma; individuals with MEN2A are at increased risk for parathyroid hyperplasia or adenoma. Classifying an individual or family by MEN2 phenotype is useful for determining prognosis and management.

Table 2. Incidence of Select Clinical Manifestations by Multiple Endocrine Neoplasia Type 2 Phenotype

Phenotype	Medullary Thyroid Carcinoma	Pheochromocytoma	Parathyroid Disease
MEN2A	95%	50%	20%-30%
FMTC	100%	<1% [1]	<1% [1]
MEN2B	100%	50%	<1%

FMTC = familial medullary thyroid carcinoma; MEN2A = multiple endocrine neoplasia type 2A; MEN2B = multiple endocrine neoplasia type 2B

Reviewed in Neumann et al [2019]

1. FMTC is not associated with an increased risk for pheochromocytoma or parathyroid disease, and risk of pheochromocytoma and parathyroid disease are similar to the general population. Individuals with presumed FMTC who develop pheochromocytoma or parathyroid disease are instead more likely to have MEN2A.

MEN2A. The MEN2A phenotype occurs in approximately 70%-80% of individuals with MEN2. MTC is generally the first manifestation of MEN2A.

Pheochromocytomas usually present after MTC or concomitantly; however, they are the first manifestation in 13%-27% of individuals with MEN2A [Inabnet et al 2000, Rodriguez et al 2008]. Pheochromocytomas in persons with MEN2A are diagnosed at an earlier age, have subtler symptoms, and are more likely to be bilateral than sporadic pheochromocytomas [Pomares et al 1998, Pacak et al 2005]. Malignant transformation occurs in about 4% of individuals [Modigliani et al 1995]. Since pheochromocytoma can be the first manifestation of MEN2A, the diagnosis of pheochromocytoma in an individual warrants further investigation for MEN2A [Neumann et al 2019].

HPT in MEN2A is typically mild and may be due to a single parathyroid adenoma or due to marked parathyroid hyperplasia. Most individuals with HPT have no symptoms; however, hypercalciuria and renal calculi may occur [Brandi et al 2001]. HPT usually presents many years after the diagnosis of MTC; the average age at onset is 38 years [Kloos et al 2009].

A small number of families with MEN2A have pruritic cutaneous lichen amyloidosis, also known as cutaneous lichen amyloidosis. This lichenoid skin lesion is located over the upper portion of the back and may appear before the onset of MTC [Seri et al 1997].

FMTC. The FMTC phenotype occurs in approximately 10%-20% of individuals with MEN2. By definition, MTC is the only clinical manifestation of FMTC. Currently, FMTC is viewed as a variant of MEN2A with decreased penetrance of pheochromocytoma and HPT rather than a distinct subtype [Wells et al 2015]. To avoid erroneously dismissing a risk for pheochromocytoma, individuals with the FMTC phenotype should still undergo screening appropriate for MEN2A, in case of incorrect or premature classification of an individual or family (see Surveillance).

The age of onset of MTC is later in FMTC and the penetrance of MTC is lower than that observed in MEN2A and MEN2B [Eng et al 1996, Machens et al 2001, Zbuk & Eng 2007, Wells et al 2015].

MEN2B. The MEN2B phenotype accounts for approximately 5% of MEN2. MEN2B is characterized by the early development of an aggressive form of MTC in all affected individuals [Skinner et al 1996]. Individuals with MEN2B who do not undergo thyroidectomy before age one year are likely to develop metastatic MTC at an early age. Prior to intervention with early prophylactic thyroidectomy, the median age of death in individuals with MEN2B was 25 years (range: 0.5-66) [Castinetti et al 2019].

Pheochromocytomas occur in 50% of individuals with MEN2B; about half are multiple and often bilateral. Individuals with an undiagnosed pheochromocytoma may die from a cardiovascular hypertensive crisis perioperatively.

MEN2B is not associated with an increased risk for clinically significant parathyroid disease.

Individuals with MEN2B may be identified in infancy or early childhood by a distinctive facial appearance and the presence of mucosal neuromas on the anterior dorsal surface of the tongue, palate, or pharynx. The lips become prominent (or "blubbery") over time, and submucosal nodules may be present on the vermilion border of the lips. Neuromas of the eyelids may cause thickening and eversion of the upper eyelid margins. Prominent thickened corneal nerves may be seen by slit lamp examination.

About 40% of affected individuals have diffuse ganglioneuromatosis of the gastrointestinal tract. Associated symptoms include abdominal distention, megacolon, constipation, or diarrhea. In one study of 19 individuals with MEN2B, 84% reported gastrointestinal symptoms beginning in infancy or early childhood [Wray et al 2008].

About 75% of affected individuals have a marfanoid habitus, often with kyphoscoliosis or lordosis, joint laxity, and decreased subcutaneous fat. Proximal muscle wasting and weakness can also be seen.

Genotype-Phenotype Correlations

p.Cys609, p.Cys611, p.Cys618, and p.Cys620. Pathogenic variants involving the cysteine codons 609, 611, 618, and 620 in exon 10 of *RET* are associated with MEN2A, FMTC, and Hirschsprung disease [Mulligan et al 1994, Decker et al 1998, Romeo et al 1998, Inoue et al 1999, Takahashi et al 1999]. A pathogenic variant in one of these codons is detected in about 10% of families with MEN2A and more than 50% of families with FMTC; these pathogenic variants are associated with low transforming activity of *RET* [Takahashi et al 1998, Hansford & Mulligan 2000].

p.Cys634. Any *RET* pathogenic variant at codon 634 in exon 11 results in a higher incidence of pheochromocytomas and HPT [Eng et al 1996, Yip et al 2003, Zbuk & Eng 2007, Wells et al 2015].

- A report of 12 Brazilian families indicated that p.Cys634Arg is associated with a higher probability of having metastases at diagnosis than other codon 634 pathogenic variants [Puñales et al 2003].
- Codon 634 pathogenic variants are also associated with development of cutaneous lichen amyloidosis [Seri et al 1997]. Among 25 individuals from three families with a codon 634 pathogenic variant, 36% had cutaneous lichen amyloidosis [Verga et al 2003].
- While 25% of FMTC kindreds have a pathogenic variant in codon 634, p.Cys634Arg pathogenic variants are virtually absent in this subtype [Hansford & Mulligan 2000, Zbuk & Eng 2007].

p.Leu790, p.Val804. In addition to an association with MTC, pathogenic variants in codons 790 or 804 may be associated with papillary thyroid carcinoma [Brauckhoff et al 2002]. In an additional study of 24 individuals with a germline *RET* pathogenic variant and concomitant MTC and papillary thyroid cancer, p.Val804Met was the most frequently reported variant at 33% [Appetecchia et al 2019].

p.Val804. Initially thought to be associated with MTC only, pathogenic variants at codon 804 in exon 14 (e.g., p.Val804Leu and p.Val804Met) were subsequently identified in individuals with pheochromocytoma [Nilsson et al 1999, Høie et al 2000, Gibelin et al 2004, Jimenez et al 2004a]. Disease expression of pathogenic variants at codon 804 has been shown to be highly variable, even within the same family [Feldman et al 2000, Frohnauer & Decker 2000]. Some individuals with such pathogenic variants have had MTC at age five years and fatal metastatic MTC at age 12 years, whereas other individuals with the same pathogenic variant have been shown to have normal thyroid histology at age 27 years, normal biochemical screening at age 40 years, and no clinical evidence of MTC at age 86 years. In another large family with a high level of consanguinity, biochemical testing indicated expression of thyroid disease in individuals homozygous but not heterozygous for p.Val804Met [Lecube et al 2002]. Cutaneous lichen amyloidosis in association with a p.Val804Met has been reported in one individual [Rothberg et al 2009].

p.Met918Thr. *RET* germline pathogenic variant p.Met918Thr is only associated with MEN2B; however, somatic pathogenic variants at this codon are frequently observed in MTC in individuals with no known family history of MTC, and are overrepresented in individuals with sporadic MTC who have a *RET* germline variant affecting p.Ser836 [Gimm et al 1999].

The American Thyroid Association Guidelines Task Force has classified pathogenic variants based on their risk for aggressive MTC [Wells et al 2015]. The classification may be used in (1) predicting phenotype and (2) recommendations regarding the ages at which to (a) perform prophylactic thyroidectomy and (b) begin biochemical screening for pheochromocytoma and HPT (see Table 6 and Surveillance).

Table 3. Multiple Endocrine Neoplasia Type 2: Genotype-Phenotype Correlations

Affected Codon / Predicted Protein Change	Exon	ATA Risk of MTC	MEN2 Subtype	PCC	HPT	Additional Clinical Features
p.Cys609	10	MOD	MEN2A; FMTC	+	+	HSCR
p.Cys611	10	MOD	MEN2A; FMTC	+	+	HSCR
p.Cys618	10	MOD	MEN2A; FMTC	+	+	HSCR
p.Cys620	10	MOD	MEN2A; FMTC	+	+	HSCR
p.Cys630	11	MOD	MEN2A	+	+	–
p.Cys634	11	H	MEN2A	+	+	CLA
p.Leu790	13	MOD	MEN2A	+	–	PTC
p.Val804Leu	14	MOD	MEN2A	+	+	–
p.Val804Met	14	MOD	MEN2A	+	+	PTC; CLA
p.Ala883Phe	15	H	MEN2B	+	–	–
p.Met918Thr	16	HST	MEN2B	+	–	–

+ = present; – = absent; ATA = American Thyroid Association; CLA = cutaneous lichen amyloidosis; FMTC = familial medullary thyroid carcinoma; H = high risk: HPT = hyperparathyroidism; HST = highest risk; HSCR = Hirschsprung disease; MEN2 = multiple endocrine neoplasia; MEN2A = multiple endocrine neoplasia type 2A; MEN2B = multiple endocrine neoplasia type 2B; MOD = moderate risk; MTC = medullary thyroid carcinoma; PCC = pheochromocytoma; PTC = papillary thyroid cancer

Penetrance

Penetrance of some *RET* pathogenic variants is incomplete, as the incidence of MTC, pheochromocytoma, and parathyroid disease varies by MEN2 phenotype (see Table 2).

Nomenclature

MEN2A is also referred to as Sipple syndrome.

Mucosal neuroma syndrome is a synonym for MEN2B. MEN2B was initially called Wagenmann-Froboese syndrome [Morrison & Nevin 1996].

Prevalence

The prevalence of MEN2 has been estimated at 1:35,000 [DeLellis et al 2004].

Genetically Related (Allelic) Disorders

Hirschsprung disease (HSCR) (OMIM 142623). Heterozygous germline *RET* pathogenic variants are associated with HSCR, a disorder of the enteric plexus of the colon that typically results in enlargement of the bowel and constipation or obstipation in neonates. About 50% of familial cases and 35% of simplex cases (i.e., a single occurrence in a family) of HSCR are caused by a germline heterozygous loss-of-function variant in *RET* (see Molecular Genetics). Germline pathogenic variants causing HSCR occur throughout the coding sequence of *RET*. Families and individuals with a germline *RET* pathogenic variant in exon 10, especially affecting codons 618 and 620, often cosegregate MEN2A/FMTC and HSCR [Eng et al 1996, Wells et al 2015].

Sporadic tumors. Approximately 20%-40% of papillary thyroid carcinoma occurring in the absence of any other findings of MEN2 is associated with somatic gene rearrangements that cause juxtaposition of the tyrosine kinase domain of *RET* to various gene partners. Medullary thyroid carcinoma and pheochromocytoma also frequently

contain a somatic pathogenic variant in *RET*. Lung adenocarcinoma and chronic myelomonocytic leukemia can also contain somatic activating *RET* translocations that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable (see Differential Diagnosis, **Medullary thyroid carcinoma** and **Pheochromocytoma**).

Differential Diagnosis

Medullary thyroid carcinoma (MTC) accounts for approximately 10% of new thyroid cancer diagnoses in the United States. Sporadic MTC (i.e., the chance occurrence of MTC in a single family member that is not expected to recur in other family members) tends to be unifocal, have a later age of onset, and lack C-cell hyperplasia (CCH) [Kloos et al 2009]. A somatic *RET* pathogenic variant, in the absence of a *RET* germline pathogenic variant, is identified in 40%-50% of MTCs [Schilling et al 2001, de Groot et al 2006, Dvorakova et al 2008, Elisei et al 2008]. The somatic p.Met918Thr variant is the most common; variants at other codons as well as small in-frame deletions have been reported [de Groot et al 2006]. Tumors with a somatic codon 918 variant appear to be more aggressive [Schilling et al 2001, Elisei et al 2008].

C-cell hyperplasia (CCH). CCH associated with a positive calcitonin stimulation test occurs in about 5% of the general population. Serum calcitonin levels may be elevated in persons with chronic kidney failure, sepsis, neuroendocrine tumors of the lung or gastrointestinal tract, hypergastrinemia, mastocytosis, autoimmune thyroid disease, and type 1A pseudohypoparathyroidism [Costante et al 2009].

Secondary CCH has been described occasionally in the setting of aging and hyperparathyroidism (HPT). Secondary CCH rarely transforms to MTC and is not related to MEN2.

Pheochromocytoma. Up to 25% of individuals with pheochromocytoma and no known family history of pheochromocytoma have a heterozygous germline pathogenic variant in one of several genes: *RET*, *VHL*, *SDHD*, or *SDHB* [Neumann et al 2002, Bryant et al 2003, Neumann et al 2004]. Approximately 5% of individuals with nonsyndromic pheochromocytoma and no family history of pheochromocytoma were heterozygous for a germline *RET* pathogenic variant [Neumann et al 2002]. See Table 4 for genes associated with susceptibility for pheochromocytoma.

Evaluation of biochemical features can help differentiate MEN2-associated pheochromocytoma. Pacak et al [2005] compared biochemical profiles for inherited and sporadic pheochromocytoma and found that MEN2 can be ruled out in pheochromocytomas that exclusively produce normetanephrine.

Table 4. Pheochromocytoma Susceptibility Genes in the Differential Diagnosis of Multiple Endocrine Neoplasia Type 2

Gene(s)	Disorder	Key Features	Comment
VHL	Von Hippel-Lindau syndrome (VHL syndrome)	Hemangioblastomas of the brain, spinal cord, & retina; renal cysts & clear cell renal cell carcinoma; PCC, pancreatic cysts, & neuroendocrine tumors; endolymphatic sac tumors; & epididymal & broad ligament cysts	VHL can present w/familial PCC or nonsyndromic PCC; PCCs can be unilateral or bilateral & are usually benign, but malignant behavior has been reported.
MAX *SDHA* *SDHAF2* *SDHB* *SDHC* *SDHD* *TMEM127* [1]	Hereditary PGL-PCC syndrome	PGLs & PCCs; additional tumors: GI stromal tumors, pulmonary chondromas, renal clear cell carcinoma, papillary thyroid carcinoma, pituitary adenomas, & neuroendocrine tumors	While head & neck PGLs are common in persons w/hereditary PGL-PCC syndrome, they are extremely rare in MEN2 [2]

Table 4. continued from previous page.

Gene(s)	Disorder	Key Features	Comment
NF1	Neurofibromatosis type 1 (NF1)	Most persons w/NF1 can be diagnosed based on clinical features (multiple café au lait macules, intertriginous freckling, multiple cutaneous neurofibromas, & learning disability or neurobehavioral manifestations).	Although much more frequent in people w/NF1 than in the general population, PCCs or PGLs are found in <1% of adults w/NF1; these tumors are usually asymptomatic, but they can cause arterial hypertension.

GI = gastrointestinal; MEN2 = multiple endocrine neoplasia type 2; PCC = pheochromocytoma; PGL = paraganglioma
1. Listed genes represent the core genes associated with hereditary PGL-PCC syndrome. *EGLN1*, *EGLN2*, *EPAS1*, *KIF1B*, *KMT2D*, and additional genes have been reported to be associated with hereditary PGL/PCC; their clinical significance is as yet unclear.
2. Boedeker et al [2009]

Multiple endocrine neoplasia type 1 (MEN1). This endocrinopathy is genetically and clinically distinct from MEN2; the similar nomenclature for MEN1 and MEN2 may cause confusion. MEN1 includes varying combinations of more than 20 endocrine tumors (e.g., parathyroid, pituitary, carcinoid, and adrenocortical tumors) and non-endocrine tumors (e.g., facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas). MEN1 is caused by a germline pathogenic variant in *MEN1* and inherited in an autosomal dominant manner.

Multiple endocrine neoplasia type 4 (MEN4). While pheochromocytomas developed in the MENX rat model, humans with heterozygous pathogenic variants in *CDKN1B* tend to have a phenotype similar to MEN1, with a high incidence of pituitary tumors and primary HPT [Lee & Pellegata 2013].

Management

Clinical practice guidelines for multiple endocrine neoplasia type 2 (MEN2) have been published [Wells et al 2015, National Comprehensive Cancer Network 2022].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MEN2, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Multiple Endocrine Neoplasia Type 2: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Endocrine	Referral to endocrinologist	
	Biochemical evals: • Plasma calcitonin • Plasma CEA • Plasma free metanephrines or 24-hour urine fractionated metanephrines • Serum calcium followed by parathyroid hormone & 25-hydroxyvitamin D if calcium is ↑	
	Eval for metastatic disease in persons w/MTC • CT w/contrast of chest & abdomen • MRI of liver in presence of nodal disease or calcitonin >400 pg/mL	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of MEN2 to facilitate medical & personal decision making

CEA = carcinoembryonic antigen; MEN2 = multiple endocrine neoplasia type 2; MOI = mode of inheritance; MTC = medullary thyroid carcinoma

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

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Prophylactic thyroidectomy is the primary preventive measure for individuals with an identified germline *RET* pathogenic variant [Cohen & Moley 2003, Kloos et al 2009]. Thyroidectomy for C-cell hyperplasia, before progression to invasive medullary thyroid carcinoma (MTC), may allow surgery to be limited to thyroidectomy with sparing of lymph nodes [Brandi et al 2001, Kahraman et al 2003]. Prophylactic thyroidectomy is safe for all age groups; however, the timing of the surgery is controversial. According to the American Thyroid Association Guidelines Task Force consensus statement, the age at which prophylactic thyroidectomy is performed can be guided by the codon position of the *RET* pathogenic variant (see Table 6 and Genotype-Phenotype Correlations) [Wells et al 2015]. These guidelines continue to be modified as more data become available.

Note: Prophylactic thyroidectomy is not routinely offered to at-risk individuals in whom the disorder has not been confirmed.

Table 6. Risk of Aggressive Medullary Thyroid Carcinoma by *RET* Genotype and Recommended Interventions

Risk of MTC	Pathogenic Variants [1]	Recommended Age for Prophylactic Thyroidectomy
HST	p.Met918Thr	As soon as possible in 1st yr of life
H	p.Cys634Arg p.Cys634Gly p.Cys634Phe p.Cys634Ser p.Cys634Trp p.Cys634Tyr p.Ala883Phe	Age <5 yrs
MOD	Any other *RET* gain-of-function pathogenic variant	May delay until age >5 yrs if criteria met [2]

Adapted from Wells et al [2015]

H = high risk; HST = highest risk; MOD = moderate risk; MTC = medullary thyroid carcinoma

1. See Molecular Genetics, Table 9 for details of pathogenic variants.

2. Criteria: normal annual basal and or stimulated serum calcitonin; normal annual neck ultrasound examination; family history of less aggressive MTC

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in endocrinology, endocrine surgery, and medical genetics (see Table 7) [National Comprehensive Cancer Network 2022].

Table 7. Multiple Endocrine Neoplasia Type 2: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Prior to any surgery to avoid intraoperative catecholamine crisis	• Measurement of plasma free metanephrines or 24-hour urine for fractionated metanephrines to evaluate for functioning PCC prior to any surgery in persons w/MEN2A, MEN2B, or FMTC • If PCC is detected, adrenalectomy before thyroidectomy to avoid intraoperative catecholamine crisis	In a prospective study of at-risk family members w/*RET* pathogenic variant, 8% had PCC detected at the same time as MTC. [1]
MTC	• Standard treatment for MTC is surgical removal of thyroid & lymph node dissection. • Consider external beam radiation therapy or intensity-modulated radiation therapy for incomplete tumor resection or extrathyroidal extension w/ positive margins.	Parathyroidectomy is not typically performed at time of thyroidectomy unless there is evidence of HPT. [2]
	• Consider multikinase inhibitors (first line; vandetanib & cabozantinib) & RET-selective inhibitors (second line; selpercatinib [LOXO-292] & pralsetinib [BLU-667]) in those w/metastatic MTC. • Consider anti-PD-1 antibody pembrolizumab for persons w/metastatic, tumor mutational burden-high disease (tumors with ≥10 mutations/megabase) that has progressed on first-line treatment. [3]	Kinase inhibitors have improved progression-free survival & in some persons cause disease regression in unresectable or advanced metastatic MTC. [4]
Hypothyroidism following thyroidectomy	Standard treatment w/thyroid hormone replacement therapy	
PCC	Treatment of hypertension prior to adrenalectomy often w/ α- & β-adrenergic receptor blockade [5]	Some centers use nitroprusside to control blood pressure during surgery & do not pretreat w/α-blockade. [5]
	Resection by adrenalectomy, which may be performed using video-assisted laparoscopy	Most experts recommend unilateral adrenalectomy for unilateral PCC & cortical-sparing adrenal surgery w/close monitoring of the remnant tissue in persons w/1 remaining adrenal gland or bilateral PCC. [6]

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Parathyroid adenoma or hyperplasia	Treatment options for those diagnosed w/HPT at time of thyroidectomy: • Resection of visibly enlarged parathyroid gland(s) • Subtotal parathyroidectomy • Total parathyroidectomy w/forearm autograft [7]	However, in most persons w/MEN2A, HPT is diagnosed many years after thyroidectomy.
	In persons w/primary HPT who have undergone prior thyroidectomy: • Preoperative localization w/excision of localized hypertrophied parathyroid gland(s) w/subtotal parathyroidectomy or total parathyroidectomy w/ forearm autotransplantation in those w/4-gland disease • Consider medications to control primary HPT in persons w/high risk of surgical mortality, limited life expectancy, or persistent or recurrent primary HPT after one or more surgical attempts. [2]	

FMTC = familial medullary thyroid carcinoma; HPT = hyperparathyroidism; MEN2A = multiple endocrine neoplasia type 2A; MEN2B = multiple endocrine neoplasia type 2B; MTC = medullary thyroid carcinoma; PCC = pheochromocytoma

1. Nguyen et al [2001]
2. Wells et al [2015]
3. National Comprehensive Cancer Network [2022]
4. Wells et al [2012], Elisei et al [2013], Subbiah et al [2018], Wirth et al [2020]
5. Neumann et al [2019]
6. Kloos et al [2009], Neumann et al [2019]
7. Wells et al [2015], National Comprehensive Cancer Network [2022]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8 are recommended [Wells et al 2015, Neumann et al 2019, National Comprehensive Cancer Network 2022].

Table 8. Multiple Endocrine Neoplasia Type 2: Recommended Surveillance

System/Concern	Evaluation	Frequency
MTC	Serum calcitonin	In those who have not had prophylactic thyroidectomy: • **MEN2A/FMTC:** annually beginning at age 3-5 yrs • **MEN2B:** annually beginning at age 6 mos [1]
		In persons after thyroidectomy: 3 mos postoperatively, followed by annually; more frequently in those w/residual MTC [2]
	Plasma CEA	In persons after thyroidectomy: 3 mos postoperatively, followed by annually; more frequently in those w/residual MTC [2]

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
PCC	Plasma free metanephrines or 24-hour urine for fractionated metanephrines	In all persons prior to any surgery
	• Plasma free metanephrines or 24-hour urine for fractionated metanephrines • MRI &/or CT if biochemical results are abnormal	• **MEN2A/FMTC:** annually beginning at age 11 yrs in persons w/ATA H *RET* pathogenic variant; annually beginning at age 16 yrs in persons w/ATA MOD *RET* pathogenic variant • **MEN2B:** annually beginning at age 11 yrs • **Women:** prior to a planned pregnancy, or as early as possible during an unplanned pregnancy
	Other screening studies, such as scintigraphy or positron emission tomography	As needed
Parathyroid adenoma or hyperplasia	Albumin-corrected calcium or ionized calcium	In those who have not had parathyroidectomy & parathyroid autotransplantation: • **MEN2A/FMTC:** annually beginning at age 11 yrs in persons w/ATA H *RET* pathogenic variant; annually beginning at age 16 yrs in persons w/ATA MOD *RET* pathogenic variant • **MEN2B:** no screening necessary

ATA = American Thyroid Association; CEA = carcinoembryonic antigen; H = high risk; MOD = moderate risk; MTC = medullary thyroid carcinoma; PCC = pheochromocytoma

1. Caution should be used in interpreting calcitonin results for children younger than age three years, especially those younger than age six months [Kloos et al 2009].

2. Continued monitoring for residual or recurrent MTC is indicated after thyroidectomy, even if thyroidectomy is performed prior to biochemical evidence of disease.

Agents/Circumstances to Avoid

Dopamine D_2 receptor antagonists (e.g., metoclopramide and veralipride) and beta-adrenergic receptor antagonists (β-blockers) have a high potential to cause an adverse reaction in individuals with pheochromocytoma.

Other medications including monoamine oxidase inhibitors, sympathomimetics (e.g., ephedrine), and certain peptide and corticosteroid hormones may also cause complications; tricyclic antidepressants are inconsistent in causing adverse reactions [Eisenhofer et al 2007].

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures [Robson et al 2015]. Predictive genetic testing in asymptomatic at-risk relatives for MEN2 promotes earlier diagnosis and implementation of appropriate screening and surveillance. This has the potential to improve clinical outcomes by allowing for prophylactic removal of the thyroid gland prior to malignant transformation of C-cell hyperplasia, earlier diagnosis of MTC if already present, and earlier diagnosis of additional phenotypes including pheochromocytoma and hyperparathyroidism (HPT). Evaluations can include:

- Molecular genetic testing if the *RET* pathogenic variant in the family is known:
  - **MEN2A.** *RET* molecular genetic testing should be offered to at-risk children by age five years. The finding of MTC in the thyroid of a 12-month-old child with a germline *RET* pathogenic variant

suggests that molecular genetic testing should be performed even earlier when possible [Machens et al 2004].
    - **Familial medullary thyroid carcinoma (FMTC).** Recommendations for families with known FMTC are the same as for MEN2A.
    - **MEN2B.** *RET* molecular genetic testing should be performed as soon as possible after birth in all children known to be at risk [Wells et al 2015, National Comprehensive Cancer Network 2022].
- The following screening of at-risk family members if the pathogenic variant in the family is not known:
    - Neck ultrasound examination and basal and/or stimulated calcitonin measurements for MTC
    - Annual albumin-corrected calcium or ionized calcium for HPT
    - Annual measurement of plasma free metanephrines or 24-hour urine for fractionated metanephrines as appropriate [Wells et al 2015] for pheochromocytoma

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

Pregnancy Management

Women with MEN2 should be screened for pheochromocytoma prior to a planned pregnancy, or as early as possible during an unplanned pregnancy [Wells et al 2015].

Therapies Under Investigation

Clinical trials of multikinase inhibitors such as sorafenib, sunitinib, and regorafenib are currently under way. National Comprehensive Cancer Network and American Thyroid Association guidelines recommend consideration of clinical trial participation for individuals who fail standard treatment with a tyrosine kinase inhibitor such as vandetanib or cabozantinib [Wells et al 2015, National Comprehensive Cancer Network 2022]. Newer RET-selective inhibitors including selpercatinib (LOXO-292) & pralsetinib (BLU-667) are now approved as second-line treatment for metastatic MTC after failure of first-line multikinase inhibitors (see Treatment of Manifestations).

Sorafenib is FDA approved for use in renal cell and hepatocellular carcinoma. A meta-analysis including eight clinical trials and 101 individuals with metastatic MTC treated with sorafenib demonstrated a partial response of 21% and 58% stable disease [Vuong et al 2019]. A small Phase II trial of treatment with sunitinib demonstrated objective response in three (50%) of six individuals with metastatic MTC and stable disease in two individuals [Carr et al 2010].

Clinical trials of immune checkpoint inhibitors such as pembrolizumab, nivolumab, and ipilimumab are currently under way [Lorch et al 2020, Angelousi et al 2022]. National Comprehensive Cancer Network guidelines recommend consideration of pembrolizumab for individuals with metastatic, tumor mutational burden-high disease that has progressed on first-line treatment [National Comprehensive Cancer Network 2022].

Several studies have investigated peptide receptor radionuclide therapy (PRRT), targeting somatostatin receptors with radionuclides such as ^{177}lutetium, ^{90}yttrium, and ^{111}indium for individuals with advanced or metastatic MTC [Grossrubatscher et al 2020, Parghane et al 2020, Angelousi et al 2022]. A review of more than 200 individuals with MTC treated with PRRT with somatostatin analogs showed efficacy in treatment with a favorable radiologic response in greater than 60% of individuals [Grossrubatscher et al 2020]. Clinical trials investigating ^{177}lutetium and ^{90}yttrium are ongoing.

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.

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

All of the multiple endocrine neoplasia type 2 (MEN2) subtypes – MEN2A, familial medullary thyroid carcinoma (FMTC), and MEN2B – are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The proportion of individuals with MEN2 who have an affected parent varies by subtype:
  - Up to 95% of individuals diagnosed with MEN2A have an affected parent.
  - By definition, individuals with FMTC have multiple family members who are affected.
  - 50% of individuals diagnosed with MEN2B have an affected parent.
- A proband with MEN2A or MEN2B may have the disorder as the result of a *de novo* germline *RET* pathogenic variant.
  - The proportion of individuals with MEN2A caused by a *de novo* germline pathogenic variant is approximately 5%-9% [Wells et al 2015].
  - The proportion of individuals with MEN2B caused by a *de novo* germline pathogenic variant is 50%. The majority of *de novo* pathogenic variants are paternal in origin, but maternal origin has been reported.
- It is appropriate to evaluate the parents of an individual with MEN2A or MEN2B for manifestations of the disorder and to offer molecular genetic testing if the *RET* pathogenic variant has been identified in the proband (see Establishing the Diagnosis).
- If the proband has a known germline *RET* pathogenic variant that cannot be 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.
- Recommendations for the evaluation of parents of a proband with a clinical diagnosis of MEN2 and an undetectable *RET* pathogenic variant include thyroid ultrasound and biochemical screening for medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism.
- The family history of some individuals diagnosed with MEN2A or MEN2B may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before onset of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of a 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%.
- The penetrance for MTC, pheochromocytoma, and parathyroid disease varies by MEN2 subtype (see Table 2). Sibs who inherit a familial *RET* pathogenic variant typically manifest the same MEN2 subtype as other affected family members (see Genotype-Phenotype Correlations).
- If the proband has a known *RET* pathogenic variant that 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 are clinically unaffected but their genetic status is unknown, sibs are still at increased risk for MEN2 because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with MEN2 has a 50% chance of inheriting the *RET* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a germline *RET* pathogenic variant, the parent's family members are at increased risk.

Related Genetic Counseling Issues

Testing of at-risk 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 germline *RET* pathogenic variant. Predictive genetic testing in asymptomatic relatives at risk for MEN2 promotes earlier diagnosis and implementation of appropriate screening and surveillance. This has the potential to improve clinical outcomes by allowing for prophylactic removal of the thyroid gland prior to malignant transformation of C-cell hyperplasia, earlier diagnosis of MTC if already present, and earlier diagnosis of additional phenotypes including pheochromocytoma and hyperparathyroidism.
- Because early detection of at-risk individuals affects medical management, testing of asymptomatic children is beneficial [Robson et al 2015]. Molecular genetic testing should be performed in at-risk individuals by age five years in families with MEN2A and FMTC and as soon as possible after birth in families with MEN2B so that individuals with a *RET* pathogenic variant can receive appropriate preventative measures, surveillance, and treatment (see Management). When a known pathogenic variant is not identified, linkage analysis can be considered in families with more than one affected family member from different generations. Education and genetic counseling of at-risk children and their parents prior to genetic testing are appropriate.
- See also Management, Evaluation of Relatives at Risk for information on evaluating and screening at-risk relatives for the purpose of early diagnosis and treatment.

Individuals with simplex MTC and no identifiable *RET* germline pathogenic variant. The probability that the offspring of an individual with simplex MTC (i.e., no known family history of MTC) and no identifiable *RET* germline pathogenic variant would inherit a *RET* pathogenic variant is 0.15%-0.18% [Romei et al 2016]. This is based on empiric data indicating that 6%-7% of individuals with simplex MTC have a germline *RET* pathogenic variant and the possibility of a false negative molecular genetic test result in an individual with a germline *RET* pathogenic variant (the pathogenic variant detection rate for *RET* is approximately 95%).

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 – Health Professional Version (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and availability of prenatal/preimplantation genetic testing is 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *RET* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for MEN2 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
- **Associazione Italiana Neoplasie Endocrine Multiple (AIMEN 1 & 2)**
  Italy
  Phone: 347 4561588
  Email: info@aimen.it
  www.aimen.it
- **MedlinePlus**
  Multiple endocrine neoplasia
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **American Multiple Endocrine Neoplasia Support**
  Phone: 865-283-5842
  Email: Info@amensupport.org
  AMEN SUPPORT

- **CancerNetwork.com**
  www.cancernetwork.com
- **National Cancer Institute (NCI)**
  Phone: 800-422-6237
  Email: NCIinfo@nih.gov
  cancer.gov
- **NCBI Genes and Disease**
  Multiple Endocrine Neoplasia
- **Pheo Para Alliance**
  Our mission is to empower patients with pheochromocytoma or paraganglioma, their families and medical professionals through advocacy, education and a global community of support, while helping to advance research that accelerates treatments and cures.
  www.pheopara.org
- **AMEND Research Registry**
  Association for Multiple Endocrine Neoplasia Disorders
  United Kingdom
  amend.org.uk

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 2: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
RET	10q11.21	Proto-oncogene tyrosine-protein kinase receptor ret	RET database	RET	RET

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 2 (View All in OMIM)

155240	THYROID CARCINOMA, FAMILIAL MEDULLARY; MTC
162300	MULTIPLE ENDOCRINE NEOPLASIA, TYPE IIB; MEN2B
164761	RET PROTOONCOGENE; RET
171400	MULTIPLE ENDOCRINE NEOPLASIA, TYPE IIA; MEN2A

Molecular Pathogenesis

RET encodes a receptor tyrosine kinase with extracellular, transmembrane, and intracellular domains. The extracellular domain consists of a calcium-binding cadherin-like domain and a cysteine-rich domain. The encoded protein plays a role in signal transduction by interaction with the glial-derived neurotropic factor (GDNF) family of ligands: GDNF, neurturin, persephin, and artemin. Ligand interaction is via the ligand-

binding GDNF family receptors (GFRα) to which RET protein binds the encoded protein complexes. Formation of a complex containing two RET protein molecules leads to RET autophosphorylation, RET kinase activation, and intracellular signaling whereby phosphorylated tyrosines become docking sites for intracellular signaling proteins [Salvatore et al 2021]. The RET tyrosine kinase catalytic core, which is located in the intracellular domain, causes downstream activation of the mitogen-activated protein (MAP) kinase signaling cascade [Salvatore et al 2021]. Pathogenic variants causing multiple endocrine neoplasia type 2 (MEN2) lead to constitutive activation (i.e., gain of function) of tyrosine kinase.

The most common pathogenic variants are non-conservative substitutions located in one of six cysteine codons in the extracellular domain of the encoded protein. They include codons 609, 611, 618, and 620 in exon 10 and codons 630 and 634 in exon 11 [Takahashi et al 1998, Wells et al 2015, Romei et al 2016, Elisei et al 2019]. All of these variants have been identified in families with MEN2A and some have been identified in families with familial medullary thyroid carcinoma (FMTC). Pathogenic variants in these sites have been detected in 98% of families with MEN2A [Eng et al 1996].

The risk for aggressive medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism can be estimated based on genotype (see Table 3 and Table 6).

Approximately 95% of all individuals with the MEN2B phenotype have a pathogenic variant in the tyrosine kinase domain of *RET* at codon 918 in exon 16, which substitutes a threonine for methionine [Eng et al 1996, Wells et al 2015]. A second pathogenic variant, p.Ala883Phe, resulting from a two-nucleotide indel, has been found in 2%-3% of individuals with MEN2B [Wells et al 2015, Salvatore et al 2021].

Two variants in *cis* configuration on one *RET* allele have been reported in individuals with MEN2B (see Table 9 for codon 804 in combination with 778, 805, 806, and 904) [Miyauchi et al 1999, Menko et al 2002, Cranston et al 2006, Wells et al 2015].

In addition to the pathogenic variants in the cysteine residues in exons 10 and 11 that have been found in families with MEN2A, pathogenic variants in codons 631, 768, 790, 804, 844, and 891, and others in exons 5, 8, 10, 11, and 13-16, have been identified in a small number of families [Hofstra et al 1997, Berndt et al 1998, Wells et al 2015].

A pathogenic variant at codon 603 was reported in one family and appeared to be associated with both MTC and papillary thyroid cancer [Rey et al 2001]. The pathogenic variant p.Arg912Pro appeared to be associated with FMTC in two families [Jimenez et al 2004b].

Rare families with two pathogenic variants in *cis* configuration have been reported; for example, alteration of both codons 634 and 635 in one family with MEN2A; alteration of both codons 804 and 844 in one family with FMTC [Bartsch et al 2000]; and alteration of codons 804 and 806 in an individual with MEN2B [Miyauchi et al 1999].

For families in which MEN2A and Hirschsprung disease (HSCR) cosegregate, models to explain how the same pathogenic variant can cause gain of function and loss of function have been proposed [Takahashi et al 1999].

Mechanism of disease causation. Gain of function. In MEN2A, the majority of pathogenic variants occur in the extracellular cysteine-rich domain, allowing for aberrant intermolecular disulfide bonds and resulting in ligand-independent RET kinase dimerization and subsequent constitutive activation of the RET kinase. In MEN2B, p.Met918Thr results in increased ATP binding and autophosphorylation and subsequent dimerization-independent activation of the RET kinase [Salvatore et al 2021].

Note: In contrast to the activating pathogenic variants in MEN2, pathogenic variants that cause HSCR result in a decrease in the transforming activity of RET because RET molecules are stuck in the endoplasmic reticulum and do not reach the cell surface [Iwashita et al 1996] (see Genetically Related Disorders).

Table 9. Notable *RET* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment
NM_020975.6 NP_066124.1	c.1825T>A	p.Cys609Ser	• See Genotype-Phenotype Correlations. • ATA MOD
	c.1825T>C	p.Cys609Arg	
	c.1825T>G	p.Cys609Gly	
	c.1826G>A	p.Cys609Tyr	
	c.1826G>T	p.Cys609Phe	
	c.1831T>A	p.Cys611Ser	
	c.1831T>C	p.Cys611Arg	
	c.1831T>G	p.Cys611Gly	
	c.1832G>A	p.Cys611Tyr	
	c.1832G>T	p.Cys611Phe	
	c.1833C>G	p.Cys611Trp	
	c.1852T>A	p.Cys618Ser	
	c.1852T>C	p.Cys618Arg	
	c.1852T>G	p.Cys618Gly	
	c.1853G>A	p.Cys618Tyr	
	c.1853G>T	p.Cys618Phe	
	c.1858T>A	p.Cys620Ser	
	c.1858T>C	p.Cys620Arg	
	c.1858T>G	p.Cys620Gly	
	c.1859G>A	p.Cys620Tyr	
	c.1859G>T	p.Cys620Phe	
	c.1860C>G	p.Cys620Trp	
	c.1888T>C	p.Cys630Arg	
	c.1889G>A	p.Cys630Tyr	
	c.1889G>C	p.Cys630Ser	
	c.1889G>T	p.Cys630Phe	
	c.1900T>C	p.Cys634Arg	• See Genotype-Phenotype Correlations. • ATA H
	c.1900T>A	p.Cys634Ser	
	c.1900T>G	p.Cys634Gly	
	c.1901G>A	p.Cys634Tyr	
	c.1901G>T	p.Cys634Phe	
	c.1902C>G	p.Cys634Trp	
	c.2304G>C	p.Glu768Asp	See Table 1, footnote 7.
	c.2370G>C	p.Leu790Phe	• See Genotype-Phenotype Correlations. • ATA MOD
	c.2410G>A	p.Val804Met	
	c.2410G>C	p.Val804Leu	

Table 9. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment
	c.2647_2648delGCinsTT	p.Ala883Phe	• See Genotype-Phenotype Correlations. • ATA H
	c.2735G>C	p.Arg912Pro	See Molecular Genetics.
	c.2753T>C	p.Met918Thr	• See Genotype-Phenotype Correlations. • ATA HST (See Table 6.)
	c.1842G>A	p.Val648Ile	• See Molecular Genetics. • Modifier & predisposition variants
	c.2071G>A	p.Gly691Ser	
	c.2508C>T	p.Ser836= [1]	
	c.2712C>G	p.Ser904= [1]	
NM_020975.6	c.74-126G>T (IVS1-126G>T)	--	

ATA = American Thyroid Association; H = high risk; HST = highest risk; MOD = moderate risk
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. The protein sequence has not been analyzed, but no change in the amino acid is expected.

Modifier and predisposition variants. It is speculated that some rare variants (e.g., p.Val648Ile) may modify the phenotype when inherited with a pathogenic variant [Nunes et al 2002].

Evidence suggests that other rare allelic variants may be predisposition factors. For example, p.Gly691Ser and p.Ser904= may be low-penetrance risk factors for development of MTC [Robledo et al 2003, Elisei et al 2004] and may predispose individuals with a pathogenic variant to an earlier age of onset of MEN2A [Gil et al 2002, Robledo et al 2003, Cardot-Bauters et al 2008]; however, this finding was not replicated in a larger study [Lesueur et al 2006]. The p.Ser904= variant has been associated with an increased risk for nonfamilial MTC in at least two studies [Gimm et al 1999, Ruiz et al 2001] but not in another [Berard et al 2004]. A meta-analysis of six allelic variants found a modest nonfamilial MTC association with p.Ser904= and a strong association with the promoter benign variant IVS1-126G>T [Figlioli et al 2013]. Inactivating *RET* variants may provide a protective effect against the development of MEN2 phenotypes, such as c.73+9277T>C. This variant disrupts the *RET* gene enhancer and may counteract the constitutive *RET* activation seen in MEN2; it is rarely present in individuals with MEN2 [Borun et al 2012, Kaczmarek-Ryś et al 2018].

Chapter Notes

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* Karen Snow-Bailey died on September 10, 2006. The following is excerpted from a tribute by Stephen N Thibodeau, PhD, of the Mayo Clinic, Rochester, MN:

"Karen was well known to so many of us, as she was an active member of the Association for Molecular Pathology (AMP)....In 1993, Karen joined the medical staff at the Mayo Clinic, where she was responsible for codirecting the Molecular Genetics Laboratory in the Department of Laboratory Medicine and Pathology....In 2002, Karen returned to New Zealand to be closer to family and became an international presence. Importantly, she began to have a tremendous influence in the development of diagnostic genetics services both in New Zealand and Australia....Karen was a scientist, an educator, and an artist....We will all miss Karen as a colleague, as a mentor to many, as an individual who had a vision for the future, but most importantly, as a warm and compassionate friend who cared for others."

[Reprinted from *J Mol Diagn* 2007, 9:133 with permission from the American Society for Investigative Pathology and the Association for Molecular Pathology]

Revision History

- 10 August 2023 (sw) Comprehensive update posted live
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