Multiple endocrine neoplasia type 1 (MEN1): Not only inherited endocrine tumors

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Abstract: MEN 1 is a rare hereditary cancer syndrome which manifests a variety of endocrine and non-endocrine neoplasms and lesions. Growing knowledge of this condition in both its molecular genetic underpinnings and its clinical implications have affected the entire spectrum of the clinical management of MEN patients. The *MEN1* gene is a tumor suppressor gene, and mutations in it account for the development of the MEN1 clinical syndrome through impairment of several cell functions, such as cell proliferations, cell growth control, apoptosis, DNA replication and repair, gene expression, transcriptional machinery control, and hormone secretion. Currently, DNA testing makes possible the early identification of germline mutations in asymptomatic mutation carriers. The ever increasing combination of genetic and clinical tools will allow early detection of MEN1-associated neoplasms, potentially improving clinical outcomes and quality of life for both affected patients and their relatives. *Genet Med* 2009;11(12):825–835.

Key Words: *MEN1*, *menin*, neuroendocrine tumors, familial endocrine cancer syndrome

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The multiple endocrine neoplasia type 1 (MEN1) syndrome (MIM#131100) was originally described at the beginning of the past century at the autopsy of a patient concurrently exhibiting acromegaly and multiglandular parathyroid abnormalities.¹ At the end of the 1920s, the presence of the “classical” P-triad (Parathyroid, Pancreatic, and Pituitary adenomas) was reported in a patient.² In 1953, a first review of related syndromes in 14 cases was published.³ Up to this period, the existence of the syndrome as a distinct clinical entity had not been assumed or suspected. In 1954, Wermer⁴ was the first to suggest that the P-triad could represent a trait inherited in an autosomal dominant manner with high penetrance. This insight is honored by also referring to MEN1 as Wermer syndrome.

However, it was not until the 1960s and later, when radioimmunoassays for hormonal and peptidic products of the affected endocrine tissues were developed,^{5–7} that more careful definitions of the details of the clinical features of the disorder could be made. The clinical management of individuals with MEN1 has greatly benefited from the advances in knowledge of either surgical or pharmacological interventions or molecular mechanisms underlying the tumorigenesis of the sporadic, non-syndromic, and counterparts of those endocrine tumors known to be associated with the MEN1 syndrome.^{8–10}

Today, it has been well established that MEN1 syndrome may present with a varying combination of more than 20 endocrine and nonendocrine tumors, other than combinations of parathyroid adenoma(s), gastrinoma(s), and prolactinoma.¹¹

In fact, other endocrine and nonendocrine neoplasms such as foregut carcinoid, central nervous system (CNS) tumors, leiomyomas, lipomas, and particularly skin tumors have also been demonstrated to be common. Furthermore, other endocrine and nonendocrine tissues can be affected but with a lower frequency (Table 1). In this review, we update genetic and clinical aspects.

Table 1 MEN1-related endocrine tumors (prevalence at 40 years)

Parathyroid adenomas	Multiglandular disease (90%; 100% at 50 yr)
GEP	Gastrinoma(s) (40%)
	Insulinoma (10%)
	Others (VIPoma, PPoma, SSoma, glucagonoma) (2%)
	Nonfunctioning (20%; 34% at 50 yr)
Anterior pituitary	Functioning: PRLoma (20%)
	GH (5%), GH/PRL (5%), TSH (rare), ACTH (2%) secreting
	Nonfunctioning (17%)
Foregut carcinoids	Thymic (2%)
	Bronchial (2%)
	Gastric (ECLoma) (10%)
Adrenocortical gland	Nonfunctioning (20–40%)
	Cortisol (rare), aldosterone (rare) secreting
	Pheochromocytoma (<1%)

ECL, enterochromaffin like; TSH, thyroid-stimulating hormone; GEP, gastro-entero-pancreatic tract; PP, pancreatic polypeptide; SS, somatostatin.

FAMILIAL/SIMPLEX MEN1 CASES AND THEIR DEFINITION

Despite extreme variation in the range of tumors which occur, MEN1 can be practically regarded as a disease with two of three principal MEN1-related endocrine tumors (parathyroid, pituitary and gastro-entero-pancreatic [GEP] tract [neuro]endocrine tumors).

The familial form of MEN1 syndrome occurs with a significantly higher frequency, approximately 90%, than the simplex form (only one affected individual without evidence of a positive familial history), that occurs approximately in 10% of cases. The familial form is defined as MEN1 syndrome in an individual who has either at least one first-degree relative with at least one of the main endocrine tumors or only one organ involvement and a MEN1 disease-causing germline mutation.¹²

CLINICAL ASPECTS OF MEN1 SYNDROME

Clinical diagnosis

Diagnosis of MEN1-associated endocrine tumors is easier if there is evidence of hormonal overproduction by the tumor than through identification of symptoms related to the growth of the tumor itself.

MEN1-associated endocrine tumors

Most of the tumors in MEN1 are benign, even if some GEP neuroendocrine tumors (mainly gastrinomas) and foregut carcinoids are often malignant. Although often regarded as a treatable endocrinopathy, MEN1 can also be regarded as a cancer syndrome lacking effective prevention or cure for associated malignancies. Tables 1 and 2 describe the MEN1-associated endocrine and nonendocrine tumors and their penetrance esti-

Table 2 MEN1-related nonendocrine tumors and their prevalence at 40 years

Cutaneous tumors	Facial angiofibromas (85%)
	Collagenomas (70%)
	Lipomas (30%)
Central nervous system	Meningiomas (5–8%)
	Ependymomas (1%)
Others	Leyomiomas (10%)

mated at 40 years of age, Table 3 reports the salient clinical manifestations of MEN1-associated (neuro)endocrine tumors.

Parathyroid tumors

Primary hyperparathyroidism (PHPT) is the main MEN1-associated endocrinopathy occurring in 90% of individuals between ages 20 and 25 years and manifests as hypercalcemia in 100% of affected individuals by age 50 years (high penetrance); hypercalcemia may cause lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, diuresis, dehydration, hypercalciuria, kidney stones, increased bone resorption and increased fracture risk, hypertension, and shortened QT interval. However, MEN1-PHPT is frequently asymptomatic for a long period of time.¹³

The MEN1 parathyroid disease is a multiglandular disorder with enlargement of all the parathyroid glands occurring asynchronously and asymmetrically.¹⁴

Risk of malignant progression

Malignant progression of parathyroid tumors is not a frequent feature of MEN1 syndrome, even if some reports described the presence of parathyroid carcinoma in patients with MEN1.^{15–17}

Pituitary tumors

Pituitary tumors may occur as the first clinical manifestation of MEN1 syndrome in 25% of simplex and in 10% of familial cases. Verges et al.¹⁸ reported that pituitary involvement was the initial manifestation of MEN1 syndrome in 17% of individuals and that pituitary adenomas were significantly more frequent in women than in men. The occurrence of anterior pituitary tumors in MEN1 syndrome may range between 10 and 60% depending on the study.¹² Between 65¹² and 85%¹⁸ of pituitary tumors in MEN1 syndrome are represented by macroadenomas and plurihormonal adenomas can occur more frequently than monohormonal adenomas in MEN1. A patient with MEN1 and two simultaneously occurring pituitary tumors (one gonadotrope macroadenoma and one corticotrope microadenoma) has been also reported.¹⁹ Recently, an unusual association between the growth hormone (GH) and prolactin (PRL) plurihormonality with follicle-stimulating hormone, luteinizing hormone, or adrenocorticotrophic hormone (ACTH) has been reported to be more frequent in MEN1 tumors than non-MEN1 controls.²⁰

Pituitary tumors are mainly functioning tumors and prolactinoma is the most common among them, manifesting as oligomenorrhea/amenorrhea and galactorrhea in women and sexual dysfunction and, more rarely, gynecomastia in men. In some families, including four families from Newfoundland reported as the so-called MEN1_{Burin} variant, prolactinoma is unusually common.²¹ Hypercortisolism occurs in ACTH-secreting tu-

Table 3 Salient clinical manifestations of MEN1-associated (neuro)endocrine tumors

Endocrine tumor	Hormone	Clinical manifestations (signs/symptoms)
PHPT (multiglandular disease)	PTH	Hypercalcemia (lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, diuresis, dehydration, hypercalciuria, kidney stones, increased bone resorption and increased fracture risk, hypertension, and shortened QT interval)
Pituitary	PRL (more frequent)	Hyperprolactinemia (oligomenorrhea/amenorrhea and galactorrhea in women; sexual dysfunction and, more rarely, gynecomastia in men)
	GH	Gigantism (prepuberal age)/acromegaly (postpuberal age)
	ACTH (rare)	Hypercortisolism
	FSH, LH (rare)	FSH, LH hypersecretion symptoms vanished and aspecific (age dependent)
	TSH (rare)	Hyperthyroidism (inappropriate secretion of TSH)
GEP neuroendocrine tract	Gastrin	ZES (multiple duodenal ulcers; upper abdominal pain [epigastric pain generally occurring 2 or more hours after meals] [less frequent right upper quadrant, chest, or back pain]; diarrhea; esophageal reflux; acid-peptic ulcers; ulcer perforation; heartburn and weight loss; vomiting related to partial or complete gastric outlet obstruction; hematemesis or melena caused by gastrointestinal bleeding)
	Insulin	Hyperinsulinism (hypoglycemia during fasting; headache; confusion; visual disturbances; motor weakness; paresis; ataxia; marked changes in personality with possible progression to the loss of consciousness; convulsions; coma; less frequent signs of sympathetic stimulation [lipotimia, weakness, tremor, palpitation, sweating, anger, and nervousness])
	Glucagon	Hyperglycemia; anorexia; glossitis; anemia; diarrhea; venous thrombosis; necrolytic migratory erythema; skin rash
	VIP	Watery diarrhea; hypokalemia; achlorhydria
	Somatostatin	Diabetes; diarrhea/steatorrhea; gallbladder disease; hypochlorhydria; weight loss
	GRF	Acromegaly
Carcinoid(s) (mainly nonfunctioning)	ACTH	Hypercortisolism
	Calcitonin	Diarrhea; skin rash
	Serotonin/histamine	Diarrhea; skin rash
	GH	Acromegaly
Adrenocortical (mainly nonfunctioning)	Cortisol	Hypercortisolism
	Aldosterone	Hyperaldosteronism

PTH, parathormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; GRF, GH-releasing factor; TSH, thyroid-stimulating hormone.

mors^{22,23} and gigantism/acromegaly occur in children/adults with GH-secreting tumors.²⁴ Symptoms such as nerve compression, headache, and hypopituitarism may also result from pituitary mass effects.^{25,26}

Risk of malignant progression

Although the MEN1 French-Belgian Registry reported that 32% of pituitary macroadenomas were locally invasive, malignant degeneration of MEN1-associated pituitary tumors is an infrequent event.¹⁸ However, recently, it has been described a metastatic PRL-oma, presenting as a cervical spinal cord tumor, in one MEN1 affected individual.²⁷

Well-differentiated endocrine tumors of the GEP tract

They include neuroendocrine tumors of the stomach, duodenum, pancreas, and the intestinal tract.²⁸ These tumors may

clinically manifest as Zollinger-Ellison syndrome (ZES) resulting from gastrinoma(s); hypoglycemia resulting from an insulinoma; hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, and skin rash resulting from a glucagonoma; and watery diarrhea, hypokalemia, and achlorhydria syndrome resulting from a vasoactive intestinal peptide (VIP) secreting tumor, VIPoma.

Adrenocortical tumors are frequently nonfunctioning neoplasms but sometimes are associated with primary hypercortisolism or hyperaldosteronism.

Carcinoid tumors are generally nonhormone-secreting tumors, and they manifest as a large mass after 50 years of age.

Gastrinoma(s)

Approximately 40% of individuals with MEN1 syndrome have gastrinoma(s), which manifests as ZES. Clinical findings

can include upper abdominal pain, diarrhea, esophageal reflux, and acid-peptic ulcers; if not properly diagnosed or treated, as occurred in the past, ulcer perforation can develop from hypergastrinemia, even without prior symptoms. Heartburn and weight loss, which are less commonly reported, may be also described. ZES-associated hypergastrinemia may result in multiple duodenal ulcers; epigastric pain generally occurs 2 or more hours after meals or at night and may be relieved by eating. However, the pain may also be in the right upper quadrant, chest, or back. Vomiting may be related to partial or complete gastric outlet obstruction; hematemesis or melena may result from gastrointestinal bleeding. ZES usually occurs before 40 years of age.²⁹ In the MEN1_{Burin} variant, the prevalence of gastrinoma is lower than in classical MEN1.³⁰

At pathology, multiple small (<1 cm in diameter) gastrinomas are typically observed in the duodenal submucosa. In particular, more than 80% of MEN1 gastrinomas are commonly found within the first and second duodenum portion,³¹ likely arising from multifocal/hyperplastic proliferations of gastrin-producing cells. MEN1 duodenal gastrinomas are associated with diffuse hyperplastic changes of gastrin cells and multicenter microtumors (<1 mm) producing gastrin.³²

About 50% of duodenal microgastrinomas exhibit loss of heterozygosity at *MEN1* locus and thus might represent the initial tumors.³³ In fact, multifocal duodenal endocrine tumors are presumably arising by independent clonal events after the germline *MEN1* mutation.³⁴ Such precursor lesions are not reported in sporadic, non-MEN1, gastrinomas.³³ Pancreatic gastrinomas are extremely rare in patients with MEN1.³⁵

Risk of malignant progression

MEN1-gastrinomas usually include a malignant component and in approximately 50% of subjects with MEN1 has metastasized before diagnosis.^{12,31,36} Individuals with liver metastases have a poor prognosis for survival; this contrasts with nodal metastases, which do not seem to negatively influence prognosis.

Insulinoma

The age of onset of MEN1-insulinoma, clinically evidenced as recurrent fasting hypoglycaemic crises, is generally one decade earlier than the sporadic counterpart.³⁷

At pathology, generally a single tumor occurs in the setting of multiple islet macroadenomas.¹² Tumors responsible for hyperinsulinism are usually about 1–4 cm in diameter.³⁸

Risk of malignant progression

MEN1-insulinomas are almost always benign.³⁹

Rare functioning GEP tumors

They include VIPomas, glucagonomas, somatostatinomas, or GH-releasing factoromas, usually exhibiting a large diameter (>3 cm).³⁵ Recently, cervical metastases of glucagonoma in a patient with MEN1 have been reported. After a pancreatoduodenectomy, the patient recovered well and remained asymptomatic.⁴⁰

Nonsecreting GEP tract tumors

They are frequent in MEN1 syndrome. A prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreatic tumors in patients with MEN1 suggested that their frequency is higher (55%) than previously thought.⁴¹ The penetrance of these tumors has been reported to be 34% at the age of 50 years in patients with MEN1 from the French Endocrine Tumor Study Group, indicating them as the most frequent

pancreaticoduodenal tumor in patients with MEN1. Average life expectancy for patients with these tumors was shorter than that for patients with MEN1 who did not have pancreaticoduodenal tumors.⁴²

Risk of malignant progression

Interestingly, a long-term follow-up study in Japanese patients with MEN1 revealed that nonfunctioning pancreatic tumors, smaller than 20 mm in diameter, did not show any apparent growth over a long monitoring period without metastasizing to regional lymph nodes or the liver.⁴³

Carcinoid tumors

Thymic, bronchial, and type II gastric enterochromaffin-like carcinoids occur approximately in 10% of individuals with MEN1 syndrome. They rarely oversecrete ACTH, calcitonin, or GH-releasing factor; similarly, they rarely oversecrete serotonin or histamine and rarely cause the carcinoid syndrome. However, GH production by a thymic carcinoid causing acromegaly has been reported⁴⁴ as also Cushing syndrome due to ACTH-producing thymic carcinoids.^{45,46} The clinical course of carcinoid tumors is often indolent, but it can also be aggressive and resistant to therapy.⁴⁷

Thymic carcinoid tumors are generally a late manifestation of MEN1 syndrome because no affected individuals had thymic carcinoid as the initial manifestation of MEN1 syndrome.⁴⁸

Risk of malignant progression

They commonly present at an advanced stage as a large invasive mass and are more prevalent in men than in women.⁴⁹ The MEN1-associated thymic carcinoids tend to be aggressive and highly lethal, particularly in men who are smokers.^{48,50,51} Recently, a spinal metastasis of a carcinoid tumor has been also reported in a patient with MEN1.⁵²

On the other hand, bronchial carcinoids are more prevalent in women than in men. Bronchial carcinoids, often multicentric, may exhibit both synchronous and metachronous occurrence. In contrast to thymic carcinoids, most bronchial carcinoids usually behave indolently, albeit with the potential for local mass effect, metastasis, and recurrence after their resection.⁵³

Gastric carcinoids have a mean age at diagnosis of 50 years. In up to 15% of individuals with MEN1 syndrome, they are recognized incidentally during endoscopy.^{54–56}

Adrenocortical tumors

In MEN1, they are generally nonfunctioning but rarely may be associated with elevated serum concentrations of cortisol or aldosterone.^{57–59} Mono- or bilateral adrenocortical tumors are present in 20–40% of individuals with MEN1 syndrome.⁶⁰

Risk of malignant progression

Their cancer progression risk is very low. Recently, a prospective study confirmed that adrenal lesions were invariably nonfunctional, and no malignant transformation was reported.⁶¹

MEN1-associated nonendocrine tumors

Nonendocrine tumors associated with MEN1 syndrome include skin tumors such as facial angiofibromas, collagenomas, lipomas, CNS tumors such as meningiomas, ependymomas, and leiomyomas.¹³ Table 2 describes the MEN1-associated endocrine tumors and their penetrance estimated at the age of 40 years.

Skin tumors

Facial angiofibromas are benign tumors, comprised of blood vessels and connective tissue, consisting of acneiform papules that do not regress and may extend across the vermilion border of the lips.

Collagenomas are generally multiple, skin-colored, sometimes hypopigmented, cutaneous nodules, symmetrically arranged on the trunk, neck, and upper limbs. They are typically asymptomatic, rounded, and firm-elastic, from a few millimeters to several centimeters in size.

Lipomas consist of multiple benign fatty tissue tumors found anywhere that fat is located. They are generally subcutaneous or, rarely, visceral.

Because multiple facial angiofibromas have been reported in 88%, collagenomas in 72%, café au lait macules in 38%, lipomas in 34%, confetti-like hypopigmented macules in 6%, and multiple gingival papules in 6%, it has been suggested that these cutaneous findings may be helpful in the diagnosis of individuals with MEN1 syndrome before manifestations of hormone-secreting tumors appear.^{62,63} Although a rapid growth of protuberant collagenomas seems to be unusual in MEN1, a patient with MEN1 exhibiting rapid growth of multiple collagenomas, after pancreatic enucleation of a VIPoma and excision of multiple pancreatic masses, has been reported, suggesting that MEN1 be considered in patients with apparent eruptive collagenoma(s).⁶⁴

CNS tumors

The presence of a meningioma has been reported in 8% of 74 individuals with MEN1⁶³; the meningiomas were mainly asymptomatic and 60% showed no growth. Ependymoma has been described in 1% of subjects with MEN1.⁶⁵

Leiomyomas

They are benign neoplasms derived from smooth (nonstriated) muscle.^{66,67}

GENETIC ASPECTS OF MEN1 SYNDROME

Chromosomal location of the *MEN1* gene and model for the related tumorigenesis

Combined studies of both linkage in MEN1 kindreds,⁶⁸ and microdeletion analysis in tumors^{68–70} demonstrated that the MEN1 trait was closely linked to *PYGM* gene, encoding for muscle phosphorylase, at chromosome 11q13. The proposed model for tumorigenesis in familial MEN1 is, according to Knudson's "two hits" hypothesis,⁷¹ a mutated *MEN1* copy is inherited at the germline level from the affected parent (first hit), whereas the wild-type copy, inherited from the healthy parent, is lost at the somatic level (second hit), resulting in a tumor. This mechanism is supported by the observation of loss of heterozygosity or allelic loss when tumor DNA is compared with constitutive DNA (Fig. 1). These findings strongly suggested gene inactivation as the mechanism of tumorigenesis for MEN1.

MEN1 gene and its mutations

In 1997, the *MEN1* gene was identified by positional cloning^{72,73} and is the only gene known to be associated with MEN1 syndrome.

The gene spans 9 kb and consists of 10 exons with an 1830-bp coding region (Fig. 2) that encodes a novel 610-amino acid protein, referred to as menin. The first exon and part of exon 10 are untranslated. A major transcript of 2.8 kb has been

Fig. 1. Example of a loss of heterozygosity or allelic loss at 11q13 region in DNA from a MEN1-associated tumor (T) with respect to the retention of both alleles in the constitutive (C) DNA. The lost allele derives from the healthy, unaffected, parent. Consequently, such a finding suggests the loss of a tumor suppressor gene.

described in a large variety of human tissues (pancreas, thymus, adrenal glands, thyroid, testis, leukocytes, heart, brain, lung, muscle, small intestine, liver, and kidney).⁷³ Moreover, an additional transcript of approximately 4 kb has been detected in pancreas and thymus, suggesting a tissue-specific alternative splicing.⁷³

More than 1000 different germline *MEN1* mutations are scattered in and around the open reading frame without significant clustering that corresponds to functional domains of the protein.^{18,72,74–93} Of all mutations, about 25% are nonsense, 45% are deletions, 15% are insertions, <5% are splice site mutations, and 10% are missense mutations. Twenty-four normal variants (polymorphisms) have been described.⁷⁴ Most germline or somatic mutations in the *MEN1* gene predict truncation or absence of encoded menin. Neither the finding of a tumor suppressor mechanism nor the identification of binding partners has established the ultimate pathways of menin action in normal tissues or in tumors.⁹³

MEN1 germline mutations are identified by sequencing analysis in about 80–90% of probands with familial MEN1 syndrome¹² and about 65% of individuals with simplex MEN1 syndrome (88 < 32). Approximately 45% of germline mutations detected by a sequence analysis are small deletions and approximately 15% are small insertions.¹² Intronic *MEN1* mutations have been also reported in the literature, representing splicing-affecting genomic variants that are likely to be of significance in the 10% of patients with MEN1 who do not have coding region mutations.^{94,95} Recently, a new intronic mutation, at intron 3 of the *MEN1* gene, has been described to be associated with PRL-oma, decreased familial penetrance, and variable effects on *MEN1* mRNA and menin.⁹⁶

Different mutation detection rates have been reported in different series, and the likelihood of detecting a *MEN1* mutation is higher in individuals with more main tumors (parathyroid, pancreatic, and pituitary), especially those from families with hyperparathyroidism and pancreatic islet tumors.^{97,98} In particular, it has been described that pancreatic manifestations were significantly linked with the probability of mutation and within a sporadic context with at least two established manifestations of MEN1, the overall probability of identifying a mutation was 26%, warranting MEN1 genotypic analysis.⁹⁹ *MEN1* genetic screening should also be offered to patients with PHPT or gastrinomas after thorough investigation into the family history, whereas sporadic carcinoid tumors or primary prolactinomas are rarely associated with germline *MEN1* mutations.¹⁰⁰

Simplex MEN1 cases are less likely to test positive than familial cases, in part because some of these simplex cases are caused by somatic mosaicism.⁹⁸ Individuals who have a single MEN1-related tumor and no family history of MEN1 syndrome rarely have germline *MEN1* mutations.⁹⁷

Fig. 2. Schematic representation of the *MEN1* gene. White boxes indicate exons, horizontal bars indicate introns, gray boxes represent untranslated regions (UTRs). Vertical bold black bars (A-I) above the gene represent the site of the nine most common germline mutations, potential mutational hot spots (frequency > 1.5%), length of bars indicates the mutation frequency according to the scale shown on the left (see also Ref. 74). Vertical black bar below the gene indicate the founder mutations in very large *MEN1* families (see also Ref. 111).

Approximately, 1–3% of *MEN1* germline mutations may consist of large deletions, detectable by a Southern blot analysis or other gene dosage procedures (i.e., polymerase chain reaction based).^{97,98,101–103} Multiplex ligation-dependent probe amplification assay may detect large deletions (4%) as germline mutations in *MEN1*.¹⁰⁴ Through polymorphism analyses, gene dose assay and nucleotide sequencing, a large germline deletion of approximately 29 kbp spanning the whole *MEN1* gene has been identified in one patient with a positive familial history for *MEN1* whose germline *MEN1* mutation was undetectable by a conventional sequencing analysis.¹⁰⁵

Moreover, through the application of a forensic technique for ancient DNA by 11q13 haplotype-based analysis, in eight living and one deceased member of a *MEN1* Italian family lacking of detection of any germline mutation of the *MEN1* gene, it has been possible to identify the familial disease-associated haplotype, demonstrating that *MEN1* disease haplotype family history can be reconstructed even when one or more family members are deceased.¹⁰⁶

Finally, linkage analysis may be used in certain families if a disease-causing mutation is not identified using a sequence analysis or targeted mutation analysis or multiplex ligation-dependent probe amplification analysis.

Founding *MEN1* mutations

To date, 13 *MEN1* founding mutations have been described in European (France, Finland, and Sweden), North American (United States and Canada), South American (Brazil), and Oceania (Australia) kindreds^{107–114} (Fig. 2). Founder effect has been reported as the result of combination of either genetic or clinical studies. Genealogical data, common geographic origin, common *MEN1* mutations, and common haplotypes were described for each *MEN1* family.

MEN1 variants and phenocopies

MEN1 variants manifest as different clinical consequences from mutations in the *MEN1* gene. For example, familial isolated hyperparathyroidism, in which germline mutations in *MEN1* gene have been reported, only results in parathyroid dysregulation. On the other hand, *MEN1* phenocopies occur when a clinical presentation resembles *MEN1* but does not result from an alteration in the *MEN1* gene. An example of such a situation would be a family with familial isolated hyperparathyroidism who has negative *MEN1* mutation analysis but a mutation in a different familial hyperparathyroidism related gene, such as the *calcium sensing receptor gene (CaSR)*.¹¹⁵

Recently, germline mutations in the *CDKN1B/p27* gene, encoding a protein belonging to the Cip/Kip family members of cyclin-dependent kinase inhibitor (CDKI) family, have been reported¹¹⁶ in an *MEN1*-like state featured by familial occurrence of PHPT and pituitary tumors, known as *MEN4* syndrome. Such heterogeneity highlights the need for caution in interpretation of negative mutational analyses. Agarwal et al.¹¹⁷ have demonstrated that germline *CDKN1B/p27* mutations are associated in a small, but important, fraction of cases with *MEN1* and related states.

Menin is mainly located in the nucleus^{93,118} and its C-terminal part contains sequences, overlapping with nuclear localization domains, essential for the regulation of gene expression.¹¹⁸ It has been recently demonstrated that a splicing mutation of *MEN1* alters the splice acceptor site of intron 9 that promotes an incorrect splicing, generating aberrant proteins without the nuclear localization signals necessary for the normal menin translocation to the nucleus.¹¹⁹ Menin is widely expressed and may play different roles in different tissues. It is probably involved in the physiological regulation of several cell functions, including DNA replication and repair, as also in transcriptional machinery.

Menin may inhibit JunD-mediated transcriptional activation, because studies of deletion mutants have shown the existence of interacting regions of both proteins. Menin could inhibit JunD-mediated transcription by modification of chromatin structure recruiting a specific histone deacetylase targeted to a promoter by binding JunD. Moreover, when compared with controls, lymphocytes from individuals with a heterozygous *MEN1* mutation show both premature division of the centromere and hypersensitivity to alkylating agents. Thus, menin could be a negative regulator of cell proliferation after DNA damage. Menin has been reported to interact with a multitude of proteins, other than JunD, including SMAD family members, Pcm, NFκB, FANCD2, RPA2, NMMHC II-A, GFAP, vimentin, p53, and Hsp70, although to date none of the interacting partners have been directly proved important in *MEN1* pathophysiology.^{120–137} It has been hypothesized that menin may mediate its tumor suppressor action by regulating histone methylation in promoters of *HOX* genes and/or *CDKN2C/p18*, *CDKN1B/p27*, and possibly other *CDKIs*.^{138,139} Consistent with this hypothesis, H3 K4 methylation and expression of p18 and p27 were shown to be dependent on menin in pancreatic islets.¹³⁹ An additional clue for a role of p18 and p27 in *MEN1* pathophysiology comes from the studies in knockout mice,¹⁴⁰ in which the simultaneous loss of p18 and p27, *CDKI*, leads to a tumor spectrum similar to that in human *MEN1* and *MEN2* patients, including tumors in the pituitary, parathyroid, thyroid, endocrine pancreas, stomach, and duodenum. Moreover, a physiological role for menin has been postulated either in bone development or hematopoiesis, also regulating lymphoid progenitors.^{124,129,136,141} However, it still remains to be delineated what determines the tissue-specific activities of menin and whether the menin–MLL–Hox pathway has a role in suppressing tumorigenesis in endocrine organ.

Through serial analysis of chromatin occupancy, a method combining chromatin immunoprecipitation with serial analysis of gene expression, hundreds of menin-occupied genomic sites were identified in promoter regions, near the 3' end of genes, or inside genes, extending other data about menin recruitments to many sites of transcriptional activity. Moreover, a large number of menin-occupied sites were located outside known gene regions.¹³¹ Interestingly, it has been shown that wild-type menin, but not *MEN1* disease-derived mutants, physically interacts with p53 and that ectopic menin expression in insulinoma cells enhances γ-irradiation-induced apoptosis, p21 expression and proliferation inhibition. Because activated p53 normally stimulates transcription of p21, a *CDKI* and an inhibitor of cell proliferation, and also multiple Bcl-2 homology domain-containing proapoptotic proteins such as PUMA, these findings could explain how menin, at least in part, regulates proliferation and apoptosis of endocrine cell through an interaction with p53.¹⁴² However, although many menin-interacting pathways have been described, it is highly likely that only a few basilar molecular pathways are involved in menin-dependent tumorigenesis.

Genotype-phenotype correlations

With the exception of the *MEN1*_{Burin} variant, a phenotype reported in four kindreds from Newfoundland and in one from Mauritius, where a higher prevalence for prolactinoma has been described,²¹ no genotype-phenotype correlations have been clearly reported in *MEN1* syndrome,^{74,90,91,110} even if a statistically not significant trend for a high prevalence of truncating mutations in *MEN1*-related thymic carcinoids has been described.¹⁴³

Genetic counseling and DNA test

As mentioned earlier, *MEN1* syndrome is inherited in an autosomal dominant manner. Consequently, each child of an individual with *MEN1* syndrome has a 50% chance of inheriting the disease-causing mutation. In general, the risk to other family members depends on the status of the proband's parents. If a parent is found to be affected and/or to have a disease-causing mutation, his or her family members are at risk.

Although approximately 90% of individuals diagnosed with *MEN1* syndrome have an affected parent, the family history may seem to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.¹³ The penetrance of this syndrome approaches 100% with increasing age and with a variable expression (different clinical phenotypes in affected members within a *MEN1* kindred, in terms of tumor localization, onset age, and clinical aggressiveness). Variable expression is frequently observed among members from different *MEN1* families sharing a common *MEN1* mutation. Because there are no definitive data on cell tissue-specific interactions between menin and proteins involved in regulating the growth and cellular functions, or on the existence of gene modifiers of the age of onset, such a variable expression cannot be currently explained. However, according to the above described roles played by menin in regulation of transcription, genome stability, cell division and proliferation, in the control of DNA repair and genome stability, it could be hypothesized that accumulation of randomly occurring genetic damage at the cellular level could foster tumorigenesis in different organs or tissue.

On the other hand, the possible existence of cell-specific factors for menin could explain a permissive endocrine environment for *MEN1* tumorigenesis. As recently reported in an animal model, ability of menin in the maintenance of both cellular and microenvironment integrity could account for the endocrine-restrictive nature of the *MEN1* syndrome.¹⁴⁴

Counseling of patients and closely related family members has a central role in the management of hereditary diseases, such as *MEN1* syndrome. In fact, subjects with a genetic predisposition for this tumor syndrome may greatly benefit from early identification, especially at a presymptomatic stage by a DNA analysis. After the genetic status is disclosed, *MEN1* gene carriers have to be followed by a periodic clinical tumor surveillance for expression of the disease as well as recurrence after treatment or progression of the disease, because the knowledge about carrier status enables early diagnosis and intervention, as reported in the literature.^{13,145} Moreover, no less important is the fact that knowledge decreases uncertainty and anxiety and assists in making decisions about lifetime plans.

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. The latter comprises subjects who have inherited the *MEN1* mutation from one affected parent or are the relatives of subjects clinically defined as suffering from *MEN1* and in which the germline mutation has not been identified.

The advantages of DNA analysis are that it requires a single blood sample and does not need to be repeated in theory, because the analysis is independent of the age of the individual and provides an objective result. Requests for prenatal testing for conditions such as *MEN1* syndrome that do not affect intellect and have some treatment available are not common, and an universal consensus on the opportunity to perform such a diagnosis in

MEN1 does not exist. Moreover, there may be no role for genetic testing if there is no planned pregnancy in the future.

DNA test in MEN1 may be undertaken in children within the first decade because tumors such as insulinoma and pituitary adenomas have developed in some children by the age of 5 years.^{24,145} Moreover, it has been reported that genetically diagnosed patients already harbored manifestations at the time of diagnosis confirming that screening for a *MEN1* mutation should be done at an early age.¹⁴⁶

Unfortunately, the great diversity together with widely scattered locations of the *MEN1* mutations⁷⁴ and a lack of genotype–phenotype correlation, make such mutational screening time consuming, arduous, and expensive.⁷⁴ An appropriate intervention in the form of clinical-biochemical testing, or treatment, or both, has been considered.¹⁴⁵ Tables 4 and 5 summarize a minimal clinical surveillance for subjects known to have MEN1 on genetic and/or clinical basis (Table 4) and for individuals at 50% risk of having MEN1 syndrome whose genetic status is unknown (Table 5). In many centers following subjects with MEN1, there is an integrated program of both mutational analysis, to identify mutant gene carriers, and clinical-biochemical screening, to detect the development of tumors.¹⁴⁵ Although currently a DNA test identifying an individual as a mutant gene carrier does not usually lead to immediate medical or surgical treatment, it suggests a precocious and frequent clinical screening, whereas a DNA result indicating that an individual is not at risk will suggest no further clinical investigations. However, because of the current inability to individually predict tumor penetrance and malignancy, lifelong follow-up of *MEN1* carriers is strongly recommended to prevent tumor morbidity.

Finally, we believe that it is important that the medical counselor has to be involved either in clinical network or in informing the family doctor. Moreover, it is important that the

Table 5 Clinical screening for individuals at 50% risk of having MEN1 syndrome whose genetic status is unknown (first-degree relative without gene testing, member of a clinical group at risk)

At baseline

Physical examination (considering search for skin tumors)

Genetic testing and counseling

Biochemical investigations. Yearly (beginning at the specified age)^a

Serum concentration of prolactin, IGF-1 (from the age of 5 yr)^a

Fasting total serum calcium concentration (corrected for albumin) and/or ionized-serum calcium concentration form (from the age 8 yr)^a

Fasting serum concentration of intact (full length) PTH (from the age 8 yr)^a

Fasting and/or stimulated serum gastrin concentration if individual has symptoms of ZES (reflux or diarrhea) (from the age of 20 yr)^a

Glycemia, fasting insulin, proinsulin (from the age of 5 yr)^a

To be considered: biochemical tests: pancreatic polypeptide; imaging: (a) abdominal imaging and (b) head MRI

Life span follow-up clinical testing at 3- to 5-yr intervals

^aRef. 145.

IGF, insulin-like growth factor; PTH, parathormone; MRI, magnetic resonance imaging.

Table 4 Minimal clinical surveillance for subjects known to have MEN1 (positive gene test, affected kindred member, affected index patient)

Biochemical investigations (beginning in the childhood, as soon as 5 yr of age)

On annual basis

Physical examination (considering search for skin tumors)

Fasting total serum calcium (corrected for albumin) and/or ionized calcium (from the age of 8 yr)^a

Glycemia, fasting insulin, proinsulin (from the age of 5 yr)^a

Fasting and/or stimulated gastrin (from the age of 20 yr)^a

Prolactin, IGF-1 (from the age of 5 yr)^a

To be considered: fasting intact PTH

Imaging

Yearly to every 3–5 yr (it depends on the biochemical evidence of a neoplasia and/or signs and symptoms of an MEN1-related tumor)

Abdominal CT or MRI (from the age of 20 yr)^a

Head MR (from the age of 5 yr)^a

To be considered: yearly chest CT, somatostatin receptor scintigraphy (SRS) octreotide scan

^aRef. 145.

IGF, insulin-like growth factor; PTH, parathormone; CT, computed tomography; MRI, magnetic resonance imaging.

medical counselor be familiar with both basic and clinical research, especially in light of new potential therapeutic strategies that may be offered soon in patients with MEN1.

MORBIDITY AND MORTALITY OF MEN1 SYNDROME

In the past 10 years, the improved knowledge of MEN1 syndrome-associated clinical manifestations, facilitated by an early diagnosis of MEN1 syndrome-associated tumors, and treatment of metabolic complications of MEN1, has virtually eliminated ZES and/or complicated PHPT as causes of death. Interestingly, according to a study performed in a single large MEN1 pedigree from Oceania, diabetes and impaired fasting glucose significantly occurred more frequently among patients with MEN1 than controls and was associated with uncontrolled hyperparathyroidism and evidence of enteropancreatic hyperstimulation.¹⁴⁷ Although such findings need to be repeated in subjects with MEN1 from other ethnicities, they may suggest physicians to look more carefully for glucose homeostasis impairment in all patients with MEN1.

Nonetheless, individuals with MEN1 syndrome have a significantly increased risk of premature death, justifying surveillance of those with *MEN1* mutations and/or a family history of MEN1 syndrome.¹⁴⁸ Longer life expectancy in MEN1 syndrome is likely to result in a rising cumulative morbidity and mortality from MEN1 syndrome-associated malignancies, which currently account for approximately 30% of deaths in MEN1 syndrome.

Gene testing decreased the morbidity and mortality associated with MEN1. In a multicenter study on 258 *MEN1* gene carriers, it has been reported “as a result of differential tumor detection, *MEN1* carriers born during the second half of the 20th century tend to have their tumors diagnosed earlier than carriers of the same age born in the first half.”¹⁴⁹

A prospective clinical study on *MEN1* mutant gene carriers revealed that biochemical evidence of neoplasia could be identified on average 10 years after evidence of clinical disease, allowing for early surgery. Thus, mutation positive individuals should undergo a focused surveillance for early identification of potentially malignant neuroendocrine tumors because of the potential for morbidity and mortality related to the syndrome.¹⁵⁰

CONCLUSIONS

Since the discovery of the *MEN1* gene, changes in clinical management have occurred. Unfortunately, neither the finding of a tumor suppressor mechanism nor the identification of binding partners has established the ultimate pathways of menin action in normal tissues or in tumors.⁹³ However, identification of several menin interacting partners strongly contribute to increase the knowledge of the pathophysiological actions of menin, but more studies are necessary to clearly elucidate both the molecular mechanisms underlying *MEN1*-associated tumorigenesis and the role(s) played by menin in tumor development. In the near future, there are prospects for novel treatments based on DNA, RNA, or even other small molecules. Further studies on the intricate molecular pathway networks of menin will be helpful to design novel therapeutic modalities.

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REFERENCES

- Erdheim J. Zur normalen und pathologischen histologie der glandula thyroidea, parathyroidea, und hypophysis. *Beitr Pathol Anat* 1903;33:158–236.
- Cushing H, Davidoff LM. Studies in acromegaly V. The pathological finding in four autopsied cases of acromegaly with a discussion of their significance. Monograph, New York, NY: Rockefeller Institute for Medical Research; 1927:22.
- Underdahl LO, Woolner LB, Black BM. Multiple endocrine adenomas: report of eight cases in which the parathyroids, pituitary and pancreatic islets were involved. *J Clin Endocrinol Metab* 1953;13:20–25.
- Wermer P. Genetic aspects of adenomatosis of endocrine glands. *Am J Med* 1954;16:363.
- Yalow RS. Radioimmunoassay: a probe for the fine structure of biologic systems. *Science* 1978;200:1236–1245.
- Malarkey WB. Prolactin and the diagnosis of pituitary tumors. *Annu Rev Med* 1979;30:249–258.
- Nussbaum SR, Potts JT Jr. Immunoassays for parathyroid hormone 1–84 in the diagnosis of hyperparathyroidism. *J Bone Miner Res* 1991;6:S43–S50.
- Albright F, Ellsworth R, Loriaux DL eds. *Uncharted Seas*. Portland, OR: Kalmia Press; 1990.
- Bevan JS, Webster J, Burke W, Scanlon MF. Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev* 1992;13:220–240.
- Schmid JR, Labhart A, Rossier PH. Relationship of multiple endocrine adenomas to the syndrome of ulcerogenic islet cell adenomas (Zollinger-Ellison). Occurrence of both syndromes in one family. *Am J Med* 1961;31:343–348.
- Gagel RF, Marx SJ. Multiple endocrine neoplasia. In: Larsen PR, Kronenberg H, Melmed S, Polonsky K, editors. *Williams textbook of endocrinology*, 11th ed. Orlando, FL: WB Saunders & Company, 2007.
- Brandi ML, Bordin C, Tonelli F, et al. Multiple endocrine neoplasia type 1. In: Bilezikian JP, Raisz GA, Rodan LG, editors. *Principles of bone biology*, 3rd ed. San Diego, CA: Academic Press, 2008:1345–1374. Chapter 62.
- Falchetti A, Marini F, Brandi ML. Multiple endocrine neoplasia type 1. In: GeneReviews at GeneTests: Medical Genetics Information Resource [database online]. Copyright, University of Washington, Seattle, 1997–2005. Available at: <http://www.genetests.org>. Accessed August 2005.
- Marx SJ. Multiple endocrine neoplasia type 1. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001.
- Sato M, Miyauchi A, Namiura H, et al. A newly recognized germline mutation of *MEN1* gene identified in a patient with parathyroid adenoma and carcinoma. *Endocrine* 2000;12:223–226.
- Dionisi S, Minisola S, Pepe J, et al. Concurrent parathyroid adenomas and carcinoma in the setting of multiple endocrine neoplasia type 1: presentation as hypercalcemic crisis. *Mayo Clin Proc* 2002;77:866–869.
- Agha A, Carpenter R, Bhattacharya S, Edmonson SJ, Carlsen E, Monson JP. Parathyroid carcinoma in multiple endocrine neoplasia type 1 (*MEN1*) syndrome: two case reports of an unrecognized entity. *J Endocrinol Invest* 2007;30:145–149.
- Verges B, Boureille F, Goudet P, et al. Pituitary disease in *MEN1* type 1 (*MEN1*): data from the France-Belgium *MEN1* multicenter study. *J Clin Endocrinol Metab* 2002;87:457–465.
- Al Ibrahim NY, Rambaldini G, Ezzat S, Asa SL. Complex endocrinopathies in *MEN-1*: diagnostic dilemmas in endocrine oncology. *Endocr Pathol* 2007;18:37–41.
- Trouillas J, Labat-Moleur F, Sturm N, et al. Pituitary tumors and hyperplasia in multiple endocrine neoplasia type 1 syndrome (*MEN1*): a case-control study in a series of 77 patients versus 2509 non-*MEN1* patients. *Am J Surg Pathol* 2008;32:534–543.
- Farid NR, Buehler S, Russell NA, Maroun FB, Allerdice P, Smyth HS. Prolactinomas in familial multiple endocrine neoplasia syndrome type 1. Relationship to HLA and carcinoid tumors. *Am J Med* 1980;69:874–880.
- Rix M, Hertel NT, Nielsen FC, et al. Cushing's disease in childhood as the first manifestation of multiple endocrine neoplasia syndrome type 1. *Eur J Endocrinol* 2004;151:709–715.
- Matsuzaki LN, Canto-Costa MH, Hauache OM. Cushing's disease as the first clinical manifestation of multiple endocrine neoplasia type 1 (*MEN1*) associated with an R460X mutation of the *MEN1* gene. *Clin Endocrinol (Oxf)* 2004;60:142–143.
- Stratakis CA, Schussheim DH, Freedman SM, et al. Pituitary macroadenoma in a 5-year-old: an early expression of multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2000;85:4776–4780.
- Yoshimoto K, Saito S. [Clinical characteristics in multiple endocrine neoplasia type 1 in Japan: a review of 106 patients]. *Nippon Naibunpi Gakkai Zasshi* 1991;67:764–774 (in Japanese).
- Carty SE, Helm AK, Amico JA, et al. The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. *Surgery* 1998;124:1106–1114.
- Gordon MV, Varma D, McLean CA, Bittar RG, Burgess JR, Topliss DJ. Metastatic prolactinoma presenting as a cervical spinal cord tumour in multiple endocrine neoplasia type one (*MEN-1*). *Clin Endocrinol (Oxf)* 2007;66:150–152.
- Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann NY Acad Sci* 2004;1014:13–1027.
- Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. *Medicine (Baltimore)* 2004;83:43–83.
- Hao W, Skarulis MC, Simonds WF, et al. Multiple endocrine neoplasia type 1 variant with frequent prolactinoma and rare gastrinoma. *J Clin Endocrinol Metab* 2004;89:3776–3784.
- Hoffmann KM, Furukawa M, Jensen RT. Duodenal neuroendocrine tumors: classification, functional syndromes, diagnosis and medical treatment. *Best Pract Res Clin Gastroenterol* 2005;19:675–697.
- Anlauf M, Perren A, Meyer CL, et al. Precursor lesions in patients with multiple endocrine neoplasia type 1-associated duodenal gastrinomas. *Gastroenterology* 2005;128:1187–1198.
- Anlauf M, Perren A, Klöppel G. Endocrine precursor lesions and microadenomas of the duodenum and pancreas with and without *MEN1*: criteria, molecular concepts and clinical significance. *Pathobiology* 2007;74:279–284.
- Anlauf M, Bauersfeld J, Raffel A, et al. Insulinomatosis: a multicentric insulinoma disease that frequently causes early recurrent hyperinsulinemic hypoglycemia. *Am J Surg Pathol* 2009;33:339–346.
- Anlauf M, Perren A, Henopp T, et al. Allelic deletion of the *MEN1* gene in duodenal gastrin and somatostatin cell neoplasms and their precursor lesions. *Gut* 2007;56:637–644.
- Fendrich V, Langer P, Waldmann J, Bartsch DK, Rothmund M. Management of sporadic and multiple endocrine neoplasia type 1 gastrinomas. *Br J Surg* 2007;94:1331–1341.
- Marx SJ, Agarwal SK, Kester MB, et al. Multiple endocrine neoplasia type 1: clinical and genetic features of the hereditary endocrine neoplasias. *Recent Prog Horm Res* 1999;54:397–438.
- Grams D, Skogseid B, Wilander E, et al. Pancreatic tumors in multiple endocrine neoplasia type 1: clinical presentation and surgical treatment. *World J Surg* 1992;16:611–618.
- Mignon M, Ruzsiewski P, Podevin P, et al. Current approach to the management of gastrinoma and insulinoma in adults with multiple endocrine neoplasia type 1. *World J Surg* 1993;17:489–497.
- Butte JM, Montero PH, Solar A, et al. Cervical metastases of glucagonoma in a patient with multiple endocrine neoplasia type 1: report of a case. *Surg Today* 2008;38:1137–1143.
- Thomas-Marques L, Murat A, Delemer B, et al. Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreatic

- coduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. *Am J Gastroenterol* 2006;101:266–273.
42. Triponez F, Dossse D, Goudet P, et al. Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. *Ann Surg* 2006;243:265–272.
 43. Sakurai A, Katai M, Yamashita K, Mori J, Fukushima Y, Hashizume K. Long-term follow-up of patients with multiple endocrine neoplasia type 1. *Endocr J* 2007;54:295–302.
 44. Boix E, Pico A, Pinedo R, Aranda I, Kovacs K. Ectopic growth hormone-releasing hormone secretion by thymic carcinoid tumour. *Clin Endocrinol (Oxf)* 2002;57:131–134.
 45. Takagi J, Otake K, Morishita M, et al. Multiple endocrine neoplasia type I and Cushing's syndrome due to an aggressive ACTH producing thymic carcinoid. *Intern Med* 2006;45:81–86.
 46. Yano M, Fukai I, Kobayashi Y, et al. ACTH-secreting thymic carcinoid associated with multiple endocrine neoplasia type 1. *Ann Thorac Surg* 2006;81:366–368.
 47. Schnirer IL, Yao JC, Ajani JA. Carcinoid—a comprehensive review. *Acta Oncol* 2003;42:672–692.
 48. Gibril F, Chen YJ, Schrupp DS, et al. Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2003;88:1066–1081.
 49. Teh BT, McArdle J, Chan SP, et al. Clinicopathologic studies of thymic carcinoids in multiple endocrine neoplasia type 1. *Medicine (Baltimore)* 1997;76:21–29.
 50. Ferolla P, Falchetti A, Filosso P, et al. Thymic Neuroendocrine Carcinoma (Carcinoid) in MEN1 Syndrome: the Italian series. *J Clin Endocrinol Metab* 2005;90:2603–2609.
 51. Goudet P, Murat A, Cardot-Bauters C, et al. Thymic neuroendocrine tumors in multiple endocrine neoplasia type 1: a comparative study on 21 cases among a series of 761 MEN1 from the GTE (Groupe des Tumeurs Endocrines). *World J Surg* 2009;33:1197–1207.
 52. Tanabe M, Akatsuka K, Umeda S, et al. Metastasis of carcinoid to the arch of the axis in a multiple endocrine neoplasia patient: a case report. *Spine J* 2008;8:841–844.
 53. Sachithanandan N, Harle RA, Burgess JR. Bronchopulmonary carcinoid in multiple endocrine neoplasia type 1. *Cancer* 2005;103:509–515.
 54. Benya RV, Metz DC, Hijazi YJ, Fishbeyn VA, Pisegna JR, Jensen RT. Fine needle aspiration cytology of submucosal nodules in patients with Zollinger-Ellison syndrome. *Am J Gastroenterol* 1993;88:258–265.
 55. Bordi C, D'Adda T, Azzoni C, Ferraro G. Pathogenesis of ECL cell tumors in humans. *Yale J Biol Med* 1998;71:273–284.
 56. Gibril F, Reynolds JC, Lubensky JA, et al. Ability of somatostatin receptor scintigraphy to identify patients with gastric carcinoids: a prospective study. *J Nucl Med* 2000;41:1646–1656.
 57. Beckers A, Abs R, Willems PJ, et al. Aldosterone-secreting adrenal adenoma as part of multiple endocrine neoplasia type 1 (MEN1): loss of heterozygosity for polymorphic chromosome 11 deoxyribonucleic acid markers, including the MEN1 locus. *J Clin Endocrinol Metab* 1992;75:564–570.
 58. Skogseid B, Larsson C, Lindgren PG, et al. Clinical and genetic features of adrenocortical lesions in multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 1992;75:76–81.
 59. Honda M, Tsukada T, Horiuchi T, et al. Primary hyperparathyroidism associated with aldosterone-producing adrenocortical adenoma and breast cancer: relation to MEN1 gene. *Intern Med* 2004;43:310–314.
 60. Skogseid B, Rastad J, Gobl A, et al. Adrenal lesion in multiple endocrine neoplasia type 1. *Surgery* 1995;118:1077–1082.
 61. Waldmann J, Fendrich V, Habbe N, et al. Screening of patients with multiple endocrine neoplasia type 1 (MEN-1): a critical analysis of its value. *World J Surg* 2009;33:1208–1218.
 62. Darling TN, Skarulis MC, Steinberg SM, Marx SJ, Spiegel AM, Turner M. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol* 1997;133:853–857.
 63. Asgharian B, Turner ML, Gibril F, Entsuah LK, Serrano J, Jensen RT. Cutaneous tumors in patients with multiple endocrine neoplasia type 1 (MEN1) and gastrinomas: prospective study of frequency and development of criteria with high sensitivity and specificity for MEN1. *J Clin Endocrinol Metab* 2004;89:5328–5336.
 64. Xia Y, Darling TN. Rapidly growing collagenomas in multiple endocrine neoplasia type 1. *J Am Acad Dermatol* 2007;56:877–880.
 65. Kato H, Uchimura I, Morohoshi M, et al. Multiple endocrine neoplasia type 1 associated with spinal ependymoma. *Intern Med* 1996;35:285–289.
 66. McKeedy JL, Li X, Zhuang Z, et al. Multiple leiomyomas of the esophagus, lung, and uterus in multiple endocrine neoplasia type 1. *Am J Pathol* 2001;159:1121–1127.
 67. Ikota H, Tanimoto A, Komatsu H, Ozawa Y, Matsushita H. Ureteral leiomyoma causing hydronephrosis in Type 1 multiple endocrine neoplasia. *Pathol Int* 2004;54:457–459.
 68. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjöld M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. *Nature* 1988;332:85–87.
 69. Friedman E, Sakaguchi K, Bale AE, et al. Clonality of parathyroid tumors in familial multiple endocrine neoplasia type 1. *N Engl J Med* 1989;321:213–218.
 70. Emmert-Buck MR, Lubensky IA, Dong Q, et al. Localization of the multiple endocrine neoplasia type 1 (MEN1) gene based on tumor loss of heterozygosity analysis. *Cancer Res* 1997;57:1855–1858.
 71. Knudson AG. Antioncogenes and human cancer. *Proc Natl Acad Sci USA* 1993;90:10914–10921.
 72. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997;276:404–407.
 73. Lemmens I, Van de Ven WJ, Kas K, et al. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene. The European Consortium on MEN1. *Hum Mol Genet* 1997;6:1177–1183.
 74. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. *Hum Mutat* 2008;29:22–32.
 75. Agarwal SK, Kester MB, Debelenko LV, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet* 1997;6:1169–1175.
 76. Heppner C, Kester MB, Agarwal SK, et al. Somatic mutation of the MEN1 gene in parathyroid tumours. *Nat Genet* 1997;16:375–378.
 77. Bassett JH, Forbes SA, Pannett AA, et al. Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet* 1998;62:232–244.
 78. Carling T, Correa P, Hessman O, et al. Parathyroid MEN1 gene mutations in relation to clinical characteristics of nonfamilial primary hyperparathyroidism. *J Clin Endocrinol Metab* 1998;83:2960–2963.
 79. Farnebo F, Teh BT, Kytölä S, et al. Alterations of the MEN1 gene in sporadic parathyroid tumors. *J Clin Endocrinol Metab* 1998;83:2627–2630.
 80. Giraud S, Zhang CX, Serova-Sinilnikova O, et al. Germ-line mutation analysis in patients with multiple endocrine neoplasia type 1 and related disorders. *Am J Hum Genet* 1998;63:455–467.
 81. Sato M, Matsubara S, Miyauchi A, et al. Identification of five novel germline mutations of the MEN1 gene in Japanese multiple endocrine neoplasia type 1 (MEN1) families. *J Med Genet* 1998;35:915–919.
 82. Teh BT, Kytölä S, Farnebo F, et al. Mutation analysis of the MEN1 gene in multiple endocrine neoplasia type 1, familial acromegaly and familial isolated hyperparathyroidism. *J Clin Endocrinol Metab* 1998;83:2621–2626.
 83. Vortmeyer AO, Böni R, Pak E, Pack S, Zhuang Z. Multiple endocrine neoplasia 1 gene alterations in MEN1-associated and sporadic lipomas. *J Natl Cancer Inst* 1998;90:398–399.
 84. Cebrían A, Herrera-Pombo JL, Díez JJ, et al. Genetic and clinical analysis in 10 Spanish patients with multiple endocrine neoplasia type 1. *Eur J Hum Genet* 1999;7:585–589.
 85. Morelli A, Falchetti A, Martinetti V, et al. MEN1 gene mutation analysis in Italian patients with multiple endocrine neoplasia type 1. *Eur J Endocrinol* 2000;142:131–137.
 86. Tahara H, Imanishi Y, Yamada T, et al. Rare somatic inactivation of the multiple endocrine neoplasia type 1 gene in secondary hyperparathyroidism of uremia. *J Clin Endocrinol Metab* 2000;85:4113–4117.
 87. Guo SS, Sawicki MP. Molecular and genetic mechanisms of tumorigenesis in multiple endocrine neoplasia type-1. *Mol Endocrinol* 2001;15:1653–1664.
 88. Pannett AA, Thakker RV. Somatic mutations in MEN type 1 tumors, consistent with the Knudson “two-hit” hypothesis. *J Clin Endocrinol Metab* 2001;86:4371–4374.
 89. Sato M, Matsubara S, Murao K, Ishida T, Takahara J. Multiple endocrine neoplasia type 1: usefulness of genetic tests in atypical cases. *Intern Med* 2001;40:461–462.
 90. Turner JJ, Leotlela PD, Pannett AA, et al. Frequent occurrence of an intron 4 mutation in multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2002;87:2688–2693.
 91. Wautot V, Vercherat C, Lespinasse J, et al. Germline mutation profile of MEN1 in multiple endocrine neoplasia type 1: search for correlation between phenotype and the functional domains of the MEN1 protein. *Hum Mutat* 2002;20:35–47.
 92. Park JH, Kim JJ, Kang HC, et al. Germline mutations of the MEN1 gene in Korean families with multiple endocrine neoplasia type 1 (MEN1) or MEN1-related disorders. *Clin Genet* 2003;64:48–53.
 93. Agarwal SK, Lee Burns A, Sukhodolets KE, et al. Molecular pathology of the MEN1 gene. *Ann NY Acad Sci* 2004;1014:189–198.
 94. Raghavan R, Shah S, Kondkar AA, et al. MEN1 935–1G>C splicing mutation in an Indian patient with multiple endocrine neoplasia type 1. *Mol Diagn Ther* 2007;11:129–131.
 95. Lemos MC, Harding B, Shalet SM, Thakker RV. A novel MEN1 intronic mutation associated with multiple endocrine neoplasia type 1. *Clin Endocrinol (Oxf)* 2007;66:709–713.
 96. Drori-Herishanu L, Horvath A, Nesterova M, et al. An Intronic Mutation is Associated with Prolactinoma in a Young Boy, Decreased Penetrance in his

- Large Family, and Variable Effects on MEN1 mRNA and Protein. *Horm Metab Res* 2009;41:630–634.
97. Ellard S, Hattersley AT, Brewer CM, Vaidya B. Detection of an MEN1 gene mutation depends on clinical features and supports current referral criteria for diagnostic molecular genetic testing. *Clin Endocrinol (Oxf)* 2005;62:169–175.
 98. Klein RD, Salih S, Bessoni J, Bale AE. Clinical testing for multiple endocrine neoplasia type 1 in a DNA diagnostic laboratory. *Genet Med* 2005;7:131–138.
 99. Odou MF, Cardot-Bauters C, Vantyghem MC, et al. Contribution of genetic analysis in screening for MEN1 among patients with sporadic disease and one or more typical manifestation. *Ann Endocrinol (Paris)* 2006;67:581–587.
 100. Jäger AC, Friis-Hansen L, Hansen TV, et al. Characteristics of the Danish families with multiple endocrine neoplasia type 1. *Mol Cell Endocrinol* 2006;249:123–132.
 101. Kishi M, Tsukada T, Shimizu S, et al. A large germline deletion of the MEN1 gene in a family with multiple endocrine neoplasia type 1. *Jpn J Cancer Res* 1998;89:1–5.
 102. Bergman L, Teh B, Cardinal J, et al. Identification of MEN1 gene mutations in families with MEN 1 and related disorders. *Br J Cancer* 2000;83:1009–1014.
 103. Cavaco BM, Domingues R, Bacelar MC, et al. Mutational analysis of Portuguese families with multiple endocrine neoplasia type 1 reveals large germline deletions. *Clin Endocrinol (Oxf)* 2002;56:465–473.
 104. Tham E, Grandell U, Lindgren E, Toss G, Skogseid B, Nordenskjöld M. Clinical testing for mutations in the MEN1 gene in Sweden: a report on 200 unrelated cases. *J Clin Endocrinol Metab* 2008;92:3389–3395.
 105. Fukuchi A, Nagamura Y, Yaguchi H, Ohkura N, Obara T, Tsukada T. A whole MEN1 gene deletion flanked by Alu repeats in a family with multiple endocrine neoplasia type 1. *Jpn J Clin Oncol* 2006;36:739–744.
 106. Marini F, Carbonell Sala S, Falchetti A, Caramelli D, Brandi ML. The genetic ascertainment of multiple endocrine neoplasia type 1 syndrome by ancient DNA analysis. *J Endocrinol Invest* 2008;31:905–909.
 107. Vasen HF, Lamers CB, Lips CJ. Screening for multiple endocrine neoplasia syndrome type I. *Arch Int Med* 1989;149:2717–2722.
 108. Kytölä S, Villablanca A, Ebeling T, et al. Founder effect in multiple endocrine neoplasia type 1 (MEN 1) in Finland. *J Med Genet* 2001;38:185–189.
 109. Burgess JR, David R, Greenaway TM, Parameswaran V, Shepherd JJ. Osteoporosis in multiple endocrine neoplasia type 1: severity, clinical significance, relationship to primary hyperparathyroidism, and response to parathyroidectomy. *Arch Surg* 1999;134:1119–1123.
 110. Kouvaraki MA, Shapiro SE, Cote GJ, et al. Management of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. *World J Surg* 2006;30:643–653.
 111. Toledo RA, Lourenco DM, Coutinho FL, et al. Novel MEN1 germline mutations in Brazilian families with multiple endocrine neoplasia type 1. *Clin Endocrinol (Oxf)* 2007;67:377–384.
 112. Lourenço DM Jr, Toledo RA, Coutinho FL, et al. The impact of clinical and genetic screenings on the management of the multiple endocrine neoplasia type 1. *Clinics (Sao Paulo)* 2007;62:465–476.
 113. WHO. Technical report series 843. Geneva: World Health Organization, 1994:5–48.
 114. Lourenço DM Jr, Toledo RA, Mackowiak II, et al. Multiple endocrine neoplasia type 1 in Brazil: MEN1 founding mutation, clinical features, and bone mineral density profile. *Eur J Endocrinol* 2008;159:259–274.
 115. Falchetti A, Brandi ML. Multiple endocrine neoplasia type I variants and phenocopies: more than a nosological issue? *J Clin Endocrinol Metab* 2009;94:1518–1520.
 116. Pellegata NS, Quintanilla-Martinez L, Siggelkow H, et al. Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc Natl Acad Sci USA* 2006;103:15558–15563.
 117. Agarwal SK, Mateo CM, Marx SJ. Rare germline mutations in cyclin-dependent kinase inhibitor genes in multiple endocrine neoplasia type 1 and related states. *J Clin Endocrinol Metab* 2009;94:1826–1834.
 118. La P, Desmond A, Hou Z, Silva AC, Schnepf RW, Hua X. Tumor suppressor menin: the essential role of nuclear localization signal domains in coordinating gene expression. *Oncogene* 2006;25:3537–3546.
 119. Tala HP, Carvajal CA, González AA, et al. New splicing mutation of MEN1 gene affecting the translocation of menin to the nucleus. *J Endocrinol Invest* 2006;29:888–893.
 120. Sowa H, Kaji H, Hendy GN, et al. Menin is required for bone morphogenetic protein 2- and transforming growth factor β -regulated osteoblastic differentiation through interaction with Smads and Runx2. *J Biol Chem* 2004;279:40267–40275.
 121. Sowa H, Kaji H, Kitazawa R, et al. Menin inactivation leads to loss of transforming growth factor beta inhibition of parathyroid cell proliferation and parathyroid hormone secretion. *Cancer Res* 2004;64:2222–2228.
 122. Lacerte A, Lee EH, Reynaud R, et al. Activin inhibits pituitary prolactin expression and cell growth through Smads, Pit-1 and menin. *Mol Endocrinol* 2004;18:1558–1569.
 123. Hendy GN, Kaji H, Sowa H, Lebrun JJ, Canaff L. Menin and TGF- β superfamily member signaling via the Smad pathway in pituitary, parathyroid and osteoblast. *Horm Metab Res* 2005;37:375–379.
 124. Chen YX, Yan J, Keeshan K, et al. The tumor suppressor menin regulates hematopoiesis and myeloid transformation by influencing Hox gene expression. *Proc Natl Acad Sci USA* 2006;103:1018–1023.
 125. Balogh K, Rácz K, Patócs A, Hunyady L. Menin and its interacting proteins: elucidation of menin function. *Trends Endocrinol Metab* 2006;17:357–364.
 126. Drejerink KM, Mulder KW, Winkler GS, Höppener JW, Lips CJ, Timmers HT. Menin links estrogen receptor activation to histone H3K4 trimethylation. *Cancer Res* 2006;66:4929–4935.
 127. MacConaill LE, Hughes CM, Rozenblatt-Rosen O, Nannepaga S, Meyer-son M. Phosphorylation of the menin tumor suppressor protein on serine 543 and serine 583. *Mol Cancer Res* 2006;4:793–801.
 128. Farley SM, Chen G, Guo S, et al. Menin localizes to chromatin through an ATR-CHK1 mediated pathway after UV-induced DNA damage. *J Surg Res* 2006;133:29–37.
 129. Caslini C, Yang Z, El-Osta M, Milne TA, Slany RK, Hess JL. Interaction of MLL amino terminal sequences with menin is required for transformation. *Cancer Res* 2007;67:7275–7283.
 130. La P, Yang Y, Karnik SK, et al. Menin-mediated caspase 8 expression in suppressing multiple endocrine neoplasia type 1. *J Biol Chem* 2007;282:31332–31340.
 131. Agarwal SK, Impey S, McWeeney S, et al. Distribution of menin-occupied regions in chromatin specifies a broad role of menin in transcriptional regulation. *Neoplasia* 2007;9:101–107.
 132. Theillaumas A, Blanc M, Couderc C, et al. Relation between menin expression and NF- κ B activity in an intestinal cell line. *Mol Cell Endocrinol* 2008;291:109–115.
 133. Yokoyama A, Cleary ML. Menin critically links MLL proteins with LEDGF on cancer-associated target genes. *Cancer Cell* 2008;14:36–46.
 134. Marek LR, Kottmann MC, Glazer PM, Bale AE. MEN1 and FANCD2 mediate distinct mechanisms of DNA crosslink repair. *DNA Repair (Amst)* 2008;7:476–486.
 135. Bazzi W, Renon M, Vercherat C, et al. MEN1 missense mutations impair sensitization to apoptosis induced by wild-type menin in endocrine pancreatic tumor cells. *Gastroenterology* 2008;135:1698–1709.
 136. Maillard I, Chen YX, Friedman A, et al. Menin regulates the function of hematopoietic stem cells and lymphoid progenitors. *Blood* 2009;113:1661–1669.
 137. Yan J, Yang Y, Zhang H, et al. Menin interacts with IQGAP1 to enhance intercellular adhesion of beta-cells. *Oncogene* 2009;28:973–982.
 138. Milne TA, Dou Y, Martin ME, Brock HW, Roeder RG, Hess JL. MLL associates specifically with a subset of transcriptionally active target genes. *Proc Natl Acad Sci USA* 2005;102:14765–14770.
 139. Karnik SK, Hughes CM, Gu X, et al. Menin regulates pancreatic islet growth by promoting histone methylation and expression of genes encoding p27Kip1 and p18INK4c. *Proc Natl Acad Sci USA* 2005;102:14659–14664.
 140. Scacheri PC, Davis S, Odom DT, et al. Genome-wide analysis of menin binding provides insights into MEN1 tumorigenesis. *PLoS Genet* 2006;2:e51.
 141. Naito J, Kaji H, Sowa H, Hendy GN, Sugimoto T, Chihara K. Menin suppresses osteoblast differentiation by antagonizing the AP-1 factor, JunD. *J Biol Chem* 2005;280:4785–4791.
 142. Bazzi W, Renon M, Vercherat C, et al. MEN1 missense mutations impair sensitization to apoptosis induced by wild-type menin in endocrine pancreatic tumor cells. *Gastroenterology* 2008;135:1698–1709.
 143. Lim LC, Tan MH, Eng C, Teh BT, Rajasooriya RC. Thymic carcinoid in multiple endocrine neoplasia 1: genotype-phenotype correlation and prevention. *J Intern Med* 2006;259:428–432.
 144. Shen HC, He M, Powell A, et al. Recapitulation of pancreatic neuroendocrine tumors in human multiple endocrine neoplasia type I syndrome via Pdx1-directed inactivation of Men1. *Cancer Res* 2009;69:1858–1866.
 145. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658–5671.
 146. Pieterman CR, Schreinemakers JM, Koppeschaar HP, et al. Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome. *Clin Endocrinol (Oxf)* 2009;70:575–581.
 147. McCallum RW, Parameswaran V, Burgess JR. Multiple endocrine neoplasia type 1 (MEN 1) is associated with an increased prevalence of diabetes mellitus and impaired fasting glucose. *Clin Endocrinol (Oxf)* 2006;65:163–168.
 148. Geerdink EA, Van der Luijt RB, Lips CJ. Do patients with multiple endocrine neoplasia syndrome type 1 benefit from periodical screening? *Eur J Endocrinol* 2003;149:577–582.
 149. Machens A, Schaaf L, Karges W, et al. Age-related penetrance of endocrine tumours in multiple endocrine neoplasia type 1 (MEN1): a multicentre study of 258 gene carriers. *Clin Endocrinol (Oxf)* 2007;67:613–622.
 150. Lairmore TC, Piersall LD, DeBenedetti MK, et al. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). *Ann Surg* 2004;239:637–645.