Multiple endocrine neoplasia type 1 : from bedside to benchside

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Abstract: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by the combined occurrence of parathyroid, pancreatic endocrine, and anterior pituitary tumors. MEN1 has two characteristics ; a hormone excess and a sometimes lethal outcome due to malignant tumors. The recent identification of the *MEN1* gene has opened the door to a much deeper understanding of this syndrome. Germline *MEN1* mutations have been identified in most MEN1 families. They were not found, however, in families with familial pituitary tumors. Thus, studies with the *MEN1* gene helped to establish that mutation of some other gene(s) is likely causative of the MEN1 phenocopy. These recent advances provide for the identification of mutant *MEN1* gene carriers who are at a high risk of developing MEN1. The protein encoded by the *MEN1* gene has been shown to function in the regulation of JunD-activated transcription but much still remains to be elucidated. J. Med. Invest. 47 : 108-117, 2000

Key words **:** *MEN1, menin, pituitary tumors, parathyroid tumors, pancreatic endocrine tumors*

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is characterized by the combined occurrence of tumors of parathyroid glands, pancreatic endocrine and anterior pituitary. The "multiple" designation refers both to the occurrence of tumors in multiple endocrine organs (e.g., parathyroid tumors plus pancreatic endocrine tumors) and to the occurrence of multiple tumors in the involved endocrine organ (e.g., multiple pancreatic endocrine tumors). MEN1 is inherited in an autosomal dominant fashion with high penetrance, or may occur sporadically i.e. without a family history. Defining the features of disease manifestation in MEN1 has improved patient management and treatment. In this review, the clinical features of MEN1 including those of Japanese patients and the genetic features of MEN1 will be discussed.

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Clinical features of MEN1

The clinical manifestations of MEN1 are related to the sites of tumors and mainly to their secreted hormones. In addition to the triad of parathyroid, pancreatic and pituitary tumors, which constitute the major components of MEN1, adrenocortical, carcinoid, and lipomatous tumors have also been described (1-4). Accurate data on the population prevalence of MEN1 do not exist. The prevalence of MEN1 has been estimated as 2-10 per 100,000 based on biochemical data (1). The most precise data may be derived from patients having at least one endocrinopathy. Evidence of MEN1 is detected in the following unselected patients : 2% to 18% with primary hyperparathyroidism, 15% to 40% with Zollinger-Ellison syndrome, 4% with insulinoma, and 2% to 5% with pituitary adenomas (1, 3).

The clinical course of MEN1 over a patient's life time can be quite variable. Clinically, overt MEN1 is usually recognized during the fourth or fifth decade of life. Intra-as well as interfamily comparison

of the clinical course of the syndrome shows great variability in the age and pattern of disease expression. MEN1 tumors except for pituitary tumors begin approximately one or two decades earlier than sporadic tumors. Tumor multiplicity in one endocrine organ in MEN1 is most evident in the parathyroid glands and endocrine pancreas. In contrast, reports describing multiple pituitary adenomas in MEN1 are rare (5-7). The mutant *MEN1* gene has a high age-related penetrance (i.e. the proportion of gene carriers manifesting symptoms or signs of the disease by a given age), being>50% penetrant by 20 years of age and >95% penetrant by 40 years (8).

Primary hyperparathyroidism is the most common manifestation of MEN1 and occurs in more than 95% of all MEN1 patients (1-4). Hyperparathyroidism is typically the first manifestation of MEN1. Multiple parathyroid glands are enlarged in association with primary hyperparathyroidism in MEN1, and the enlargement is usually quite asymmetric. Surgical removal of the abnormally overactive parathyroids is the definitive treatment.

The incidence of pancreatic endocrine tumors in MEN1 patients varies from 30 to 80% (1-4). The majority of these tumors produce excessive amounts of hormone, for example gastrin, insulin, glucagon or vasoactive intestinal polypeptide (VIP). Gastrinomas (with the Zollinger-Ellison syndrome), which generally originate in the pancreas or duodenum, represent approximately 50% of all pancreatic endocrine tumors in MEN1, and are the major cause of disease-related death in MEN1 patients. The ideal treatment for a non-metastatic gastrinoma is surgical excision. Medical treatment of MEN1 patients with Zollinger-Ellison syndrome is achieved using proton-pump inhibitors. Insulinomas represent one-third of all pancreatic endocrine tumors in MEN1 patients. Patients with an insulinoma present with hypoglycemic symptoms. Endoscopic ultrasound and selective arterial infusion of calcium have been suggested as effective in localizing insulinomas. Surgical treatment has been more often successful.

The incidence of pituitary tumors in MEN1 patients varies from 15 to 60% in different series (1-4). The widely varying prevalence rate for pituitary tumors in MEN1 among reports may be tied to biases in patient selection and to the methods used to test patients for the feature. The majority of pituitary adenomas are prolactinomas, followed by growth hormone (GH)-secreting tumors, non-functioning tumors, and adenocorticotrophin-secreting tumors. The clinical manifestations depend upon the size of the pituitary tumor and its product of secretion. Treatment of pituitary tumors in MEN1 patients is, in principle, the same as for sporadic tumors.

Adrenocortical tumors, carcinoid tumors, and lipomas have also been observed in association with MEN1 (1-4). The carcinoid tumor may be located in the bronchi, the gastrointestinal tract, the pancreas, or the thymus. Thymic and bronchial carcinoid tumors have malignant potential.

Review of MEN1 patients in Japan

To clarify the clinical features of MEN1 in Japan, we searched case reports of MEN1 (9, 10). In practice, a working definition of MEN1 is a case with at least two of the three main endocrine expressions of MEN1. The study included case reports of autopsy. One hundred and forty-three patients were reported from 1966 to 1995 : 59 patients from 27 families (familial type) and 84 patients without family history (sporadic type). The mean age of diagnosis of MEN1 was 41.3 (range 14-74) years in familial MEN1 and 45.8 (range 9-86) years in sporadic MEN1.

At diagnosis of MEN1, parathyroid tumors were present in 89%, pancreatic endocrine tumors in 67%, pituitary tumors in 62%, adrenocortical tumors in 20%, thyroid tumors in 22%, carcinoid tumors in 8%, and lipoma in 3% of patients. The pattern of gland involvement in MEN1 is shown in Table 1. In pituitary tumors,46% of patients showed visual field disturbance, exhibited hypopituitarism, or were nonsymptomatic. The remainder showed acromegaly or gigantism, amenorrhoea-galactorrhea syndrome, or Cushing disease (Table 2). As described above, prolactinomas were most common in Caucasians (1-4). Larger numbers of sporadic MEN1 cases or autopsy cases in our Japanese cases than in Caucasian populations may be related to the different prevalence rate for subtypes of pituitary tumors. In pancreatic endocrine tumors, Zollinger-Ellison syndrome due to gastrinomas was most common, followed by hypoglycemia due to insulinomas (Table 3). VIP, parathyroid hormone-related protein (PTHrP), and growth hormone-releasing hormone (GHRH)-secreting pancreatic tumors were seen less frequently (11). Clinical manifestations of primary hyperparathyroidism as part of MEN1 are shown in Table 4. Our results suggest that the prevalence of MEN1 is lower in Japan. However, MEN1 seems not to be rare in Japan, because Japanese MEN1 case reports have progressively increased since the recent discovery of the *MEN1*

Table 1. Pattern of gland involvement in MEN1 ; evaluation of 143 MEN1 cases reported in the literature 1966-1995 in Japan

Pattern of involvement	Number of patients	(%)
Parathyroids, pituitary, and endocrine pancreas	48	34
Parathyroids and endocrine pancreas	37	26
Parathyroids and pituitary	27	19
Pituitary and endocrine pancreas	9	6
Parathyroids*	16	11
Pituitary*	4	3
Endocrine pancreas*	2	1

* cases with family history

Table 2. Clinical syndromes caused by pituitary tumors in MEN1

Clinical manifestation	Number of patients	(%)
Acromegaly	21	26
Gigantism	1	1
Amenorrhea-galactorrhea	16	20
Cushing disease	6	7
Hypopituitarism	1	1
Local signs of tumor growth	14	17
Asymptomatic tumors	23	28

Table 3. Clinical syndromes and symptoms caused by pancreatic endocrine tumors in MEN1

Clinical manifestation	Number of patients	(%)
Zollinger-Ellison syndrome	37	50
Hypoglycemia	30	41
WDHA syndrome	4	5
Ectopic GHRH syndrome	2	3
Hypercalcemia by PTHrP producing tumor	1	1

Table 4. Clinical manifestation of primary hyperparathyroidism as a part of MEN1

Clinical presentation	Number of patients	(%)
Biochemical hyperparathyroidism	59	57
Urolithiasis	36	35
Bone disease (ostitis fibrosa)	21	18
Hyperparathyroid crisis	3	3
Acute pancreatitis	1	1

gene.

Mapping and identification of the MEN1 gene

The gene for MEN1 was assigned to chromosome 11q13 by linkage analysis in 1988 (12). By comparing constitutional and tumor tissue genotypes of pancreatic endocrine tumors as well as parathyroid tumors, loss of heterozygosity (LOH) involving polymorphic loci from chromosome 11 in tumors was frequently disclosed (13-16) (Figure 1). Regarding pituitary tumors, we first reported LOH on chromosome 11 in a GH and prolactin-secreting adenoma (17). In addition, we first reported common LOH on chromosome 11 in tumors in three separate organs in an MEN1 patient (5).

The lost allele was found to be consistently derived from the unaffected parent, leaving only the mutated *MEN1* allele in the tumors (Figure 2). LOH studies in MEN1-associated tumors and sporadic endocrine tumors helped to narrow the location of the *MEN1* gene to within an area of 600-kb (18, 19). Focusing on this smaller region, 12 transcripts were identified and mapped.

The *MEN1* gene was finally identified because it was the one that contained mutations in most DNAs from MEN1 patients (20, 21). The gene consists of 10 exons (one untranslated) with a 1,830 bp coding region (Figure 3). It encodes a 610 amino acid protein, referred to as menin (20). Expression of the *MEN1* gene has been identified in all normal tissues tested, and is not restricted to target organs of MEN1.

Germline mutations in MEN1 cases

Except for one large 11q13 deletion (22), recognized *MEN1* mutations have been single-base substitutions, small insertions, or small deletions. Pannett and Thakker summarized the reported germline mutations of the *MEN1* gene (4). In 262 patients, 22% are nonsense mutations, 48% are frameshift

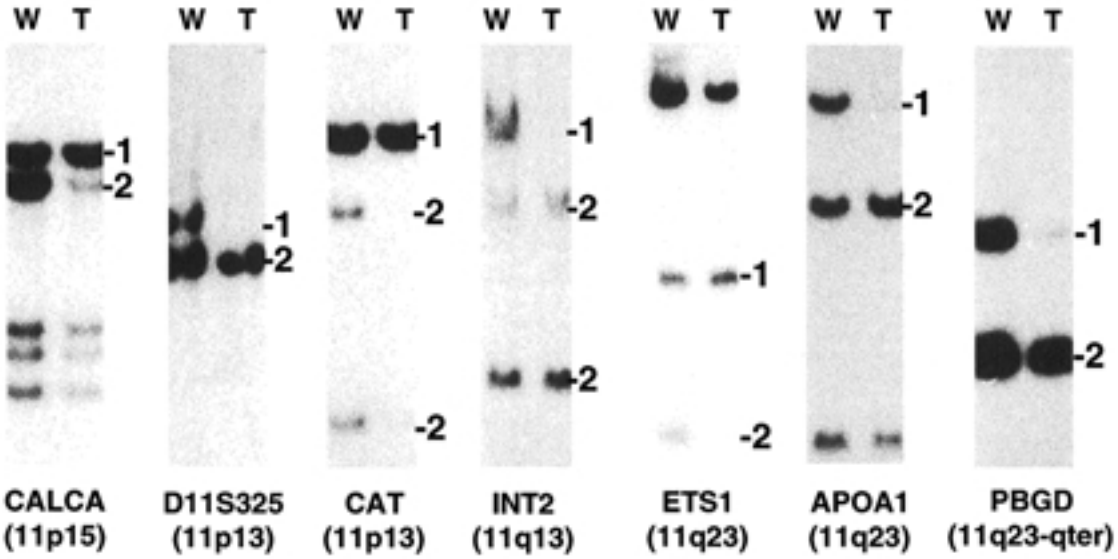

Fig.1. Loss of alleles on chromosome 11 in an insulinoma from a patient with MEN1. The restriction fragment length polymorphisms (RFLPs) obtained from the patient's leukocytes (W) and insulinoma (T) DNA using the probes CALCA, D11S325, CAT, INT 2, ETS1, APOA1, and PBGD are shown. For example, the leukocytes are heterozygous in the CALCA locus (allele 1, 2), but the tumor cells lost allele 2. Similar losses of alleles are detected by the use of other DNA probes, and an extensive loss of alleles involving the whole of chromosome 11 is observed. The patient corresponds to case number 7 in Table 2 of reference 23.

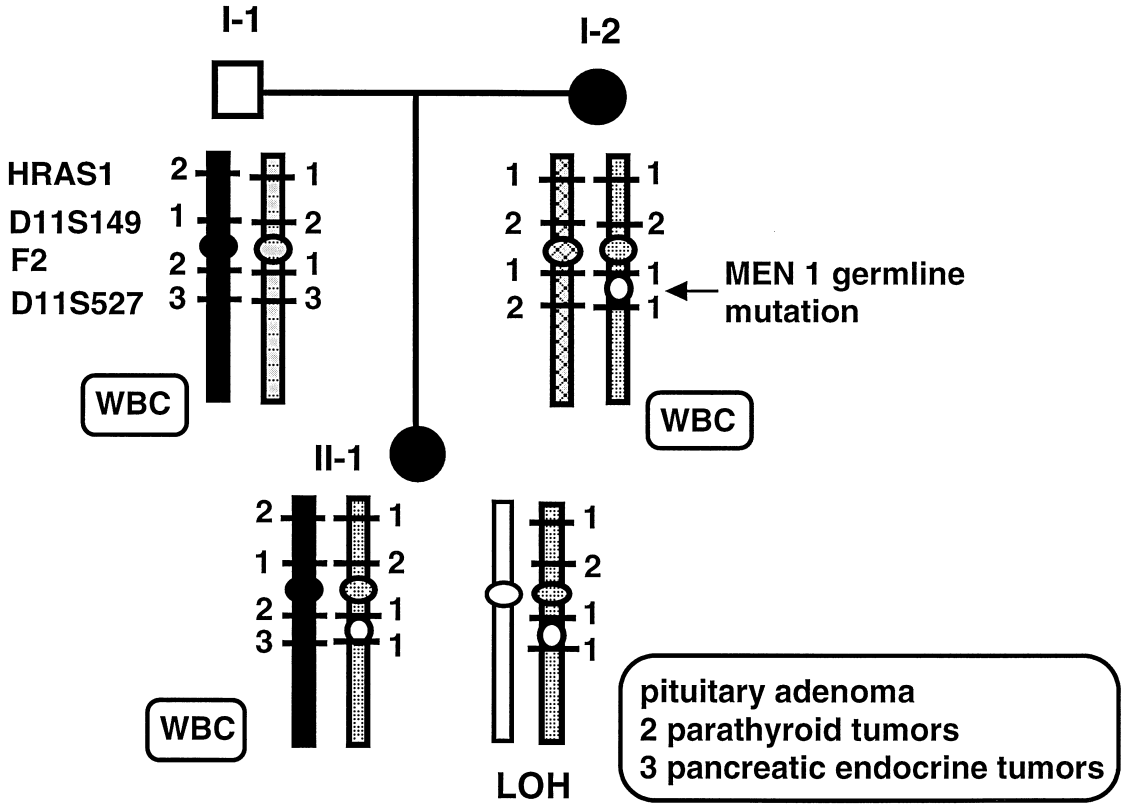

Fig. 2. Combined pedigree and tumor analysis. The alleles obtained with probes from HRAS1, D11S149, F2, and D11S527 on chromosome 11 in patient II-1 and her parents (I-1 and I-2). The alleles were obtained by Southern blot analysis, polymerase chain reaction-RFLP, or microsatellite analysis of leukocytes and pituitary adenomas, parathyroid tumors, and pancreatic endocrine tumors. The mother (I-2) was affected and the father (I-1) was unaffected. The leukocyte genotype of the affected daughter (II-1) was heterozygous at all 4 loci. An examination of tumor genotypes indicated hemizygosity with the loss of the paternal chromosome 11. The patients II-1 and I-2 correspond to case numbers 2 and 3, respectively, in Table 2 of reference 23.

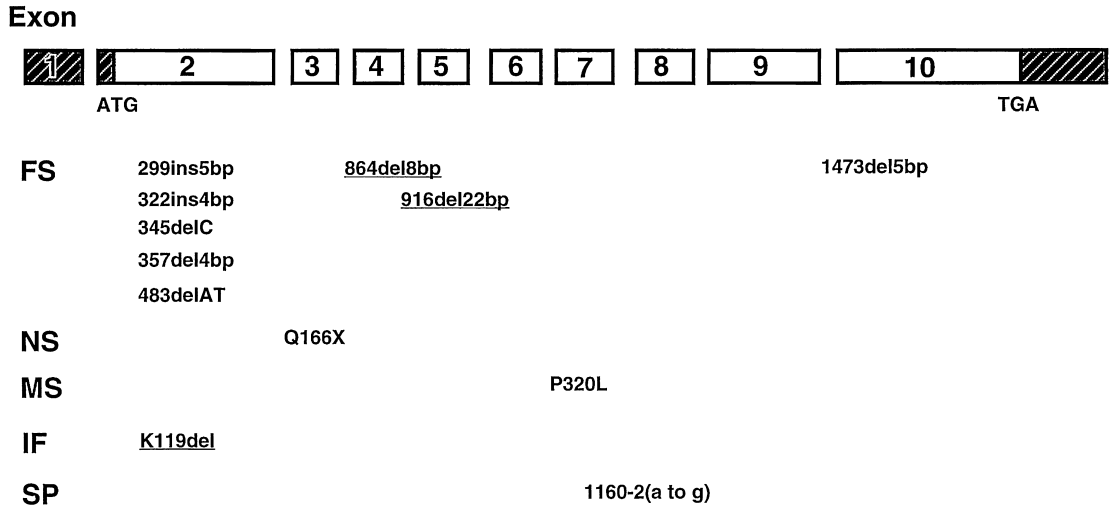

Fig. 3. Schematic representation of the mutations identified in the *MEN1* gene. Exon 1, the 5' part of exon 2, and the distal part of exon 10 (diagonally hatched box) are untranslated regions of the gene. The coding regions of the gene are denoted by a nonhatched box. The start (ATG) and the stop (TGA) codons are indicated within exon 2 and exon 10, respectively. The locations of the mutations are shown under the gene structure. FS, frameshift mutation ; NS, nonsense mutation ; MS, missense mutation ; IF, in-frame deletion ; SP, splice site mutation. Underlined mutations denote somatic mutations.

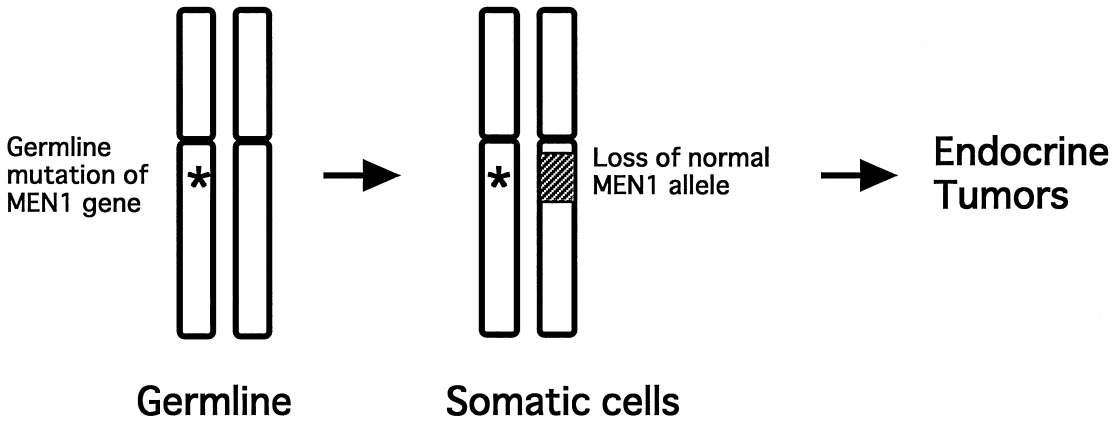

Fig. 4. Inactivation of both copies of the *MEN1* gene contributes to tumorigenesis in MEN1. Patients are born heterozygous for the mutant allele of *MEN1* (star). In endocrine cells, a second somatic mutation, in this example a partial deletion of chromosome 11 (striped), results in loss of the normal *MEN1* allele. Sequential inactivation of both copies of the *MEN1* gene leads to endocrine tumors.

deletions or insertions, 8% are in-frame deletions or insertions, 5% are donor-splice site mutations and 17% are missense mutations. Germline mutations in our Japanese MEN1 patients and somatic mutations in a sporadic pituitary adenoma and parathyroid tumor were identified (Figure 3) (23). Diversity of *MEN1* mutations was observed in Japanese MEN1 patients, as reported in Caucasians (4). Approximately 10% of the *MEN1* mutations arise de novo and may be transmitted to subsequent generations (8, 24). Mutations in the coding region of the *MEN 1* gene were not detected in 5% to 10% of MEN1 patients (8, 21, 24, 25). It is possible that additional mutations in the promoter or untranslated regions or a large germline deletion involving the *MEN1* gene might occur. The mutations are not only diverse in their types but scattered throughout the coding region of the *MEN1* gene. Despite the identification of a large number of mutations, no clear phenotype-genotype correlation has yet been discerned.

LOH on 11q13 was detected in MEN1-associated tumors of our MEN1 patients (5, 13, 16, 17, 23). Evidence that *MEN1* is a tumor suppressor gene has been provided by the demonstration of somatic genetic alterations (LOH on 11q13) in MEN1 tumors, which would inactivate the remaining normal allele and so unmask the inherited *MEN1* mutation on the other allele (Figure 4).

Prolactinoma dominant of MEN1 family

Three families with the prolactinoma variant of MEN1, which is characterized by hyperparathyroidism (88-100%), high penetrance of prolactinoma (37-75%), and infrequent expression of gastrinoma (2.5-12%), were reported (26). Of these three families, two had different *MEN1* mutations (Y312X and R460X). The third family showed no mutations but tight linkage of MEN1 to 11q13 (27). We reported an unusual MEN1 family in which four of five mutation carriers were affected and have developed prolactinoma (28). Our cases, which were initially considered as familial prolactinomas, later were found to show unusual features of MEN1. Parathyroid tumors are usually the first manifestation of MEN1 (1-4). However, prolactinomas were the first lesion diagnosed in this family. Detection of germline mutation of 357del4 in the family prompted us to carefully examine MEN1 phenotypes. Genetic examinations are useful as diagnostic tools for any rare or unusual cases of MEN1. The 357del4 were encountered frequently in many MEN1 patients (4). Because there were no prominent clinical features in families with the deletion, unknown genetic factors other than *MEN1* mutation may contribute to a prolactinoma-dominant phenotype.

Familial isolated hyperparathyroidism

Familial hyperparathyroidism may occur as familial isolated hyperparathyroidism (FIHP) or as part of an inherited syndrome, in particular MEN1, MEN2A, and hyperparathyroidism-jaw tumor syndrome. Families with FIHP were reported to have no *MEN1* germline mutations by several groups (23, 24, 29, 30). However, some of the FIHP families had a milder variant of MEN1, which is associated with a functionally milder missense mutation (31-35).

Familial pituitary tumors

Familial pituitary tumors are defined as the occurrence of at least 2 cases of pituitary tumors in a family that does not exhibit any other manifestations of MEN1 or Carney complex. Familial pituitary tumors are extremely rare. Only 85 cases occurring in 36 families have been reported in the literature. In our review of familial pituitary tumors, 74% of cases were acromegaly or gigantism. Furthermore, 23 families showed familial GH-producing tumors. This incidence of GH-secreting tumors in familial pituitary tumors is much higher than the 4-27% in MEN1 patients with pituitary tumors (1, 2, 4, Table 2). In addition, the majority of reported cases showing acromegaly or gigantism are diagnosed before the age of 30 years. We reported 2 brothers with GH-secreting adenomas that exhibited LOH at 11q13 (23, 38). Recently, Gadelha et al. also demonstrated LOH at 11q13 in all GH-secreting adenomas from 2 families with familial GH-producing tumors (39). Therefore, familial pituitary tumors were considered a candidate for phenotypic variants of MEN1. However, we demonstrated no germline *MEN1* mutations in 3 families with familial pituitary tumors (23). The result was confirmed in several laboratories (30, 32, 36, 37). These findings suggest the presence of another tumor suppressor gene located at 11q13. Taken together, familial pituitary tumors seem to be a different clinical entity from MEN1.

MEN1 phenocopy without germline *MEN1* mutation

Phenocopies have to be considered carefully in MEN1, because of the high frequency of common lesions such as primary hyperparathyroidism and prolactinoma in the non-MEN1 population. We present a patient showing primary hyperparathyroidism and prolactinoma as an example. She did not show any family history of endocrine tumors. No germline mutations of the *MEN1* were detected, however, two independent somatic mutations of the *MEN1* gene (K119del and 864del8bp) were identified in the parathyroid tumor (Figure 3). Whether both alleles of *MEN1* are inactivated by the two independent somatic mutations or not remains to be elucidated. Because the prolactinoma responded well to bromocriptine therapy, surgical intervention is not necessary at present.

Somatic MEN1 mutations in sporadic endocrine tumors

Previous studies on sporadic non-MEN1 endocrine tumors showed that LOH involving 11q13 occurs in 5% to 50% of cases, implying that somatic mutations of the *MEN1* gene contribute to the etiology of these tumors (14, 15). Subsequent studies detected somatic *MEN1* mutations in 13% of sporadic parathyroid tumors, 39% of gastrinomas, 17% of insulinomas, and 36% of bronchial carcinoid tumors (4). However, we revealed that somatic *MEN1* mu-

tations in sporadic pituitary tumors were very infrequent at 3% (40). The result was confirmed in several laboratories (41, 42). In distribution and type, somatic mutations of the *MEN1* gene were similar to germline mutations. The observation that the tumors having a somatic *MEN1* mutation had 11q13 LOH suggested that inactivation of the *MEN1* gene contributes to tumorigenesis in a subset of sporadic endocrine tumors.

Function of menin

Initial analysis of the predicted amino acid sequence did not reveal homology to any other protein, sequence motif, or signal peptide (20). Menin is primarily located in the nucleus (43). Using a yeast 2-hybrid screen with menin as the bait, Agarwal et al. found that menin directly interacts with JunD, to repress transcriptional activation mediated by JunD (44). Several naturally occurring and clustered *MEN1* missense mutations disrupted menin interaction with JunD. It is hoped that future study of the *MEN1* gene product and the biochemical pathways in which it functions will shed light upon the reasons why endocrine tissues are preferentially susceptible to loss of menin function, and may also suggest new approaches to prevention or treatment of MEN1-associated tumors.

Genetic screening in MEN1

Genetic testing for germline mutations of the *MEN1* gene is a good way to clarify the diagnosis in an index patient. Because the great diversity and widely scattered locations of the *MEN1* mutations and lack of genotype-phenotype correlations make such mutational screening time-consuming and expensive, genetic testing is not widely available. However, a DNA test that indicates an individual is not at risk would rule out the need for further clinical investigations. At present, it is suggested that mutant gene carriers should undergo biochemical screening at least once per annum, and also have pituitary and abdominal imaging. Genetic testing in patients with sporadic endocrine tumors should be performed, 1) in patients with two or more MEN1-associated tumors, 2) in patients with multiple parathyroid tumors, and 3) in patients with Zollinger-Ellison syndrome, 15% to 40% of whom will have coexistent MEN1.

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