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The *MEN1* Gene and Pituitary Tumours

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Abstract

Sporadic multiple endocrine neoplasia type 1 (MEN1) is defined as the occurrence of tumours in two of three main endocrine tissue types: parathyroid, pituitary and pancreaticoduodenal. A prolactinoma variant or Burin variant of MEN1 was found to occur in three large kindreds, with more prolactinomas and fewer gastrinomas than typical MEN1. MEN1 tumours differ from common tumours by showing features from the *MEN1* gene (e.g. larger pituitary tumours). They also show various expressions of tumour multiplicity; however, pituitary tumour in MEN1 is usually solitary. Diagnosis in MEN1 carriers during childhood is not directed at cancers but at benign morbid tumours. Morbid prolactinoma occurred at the age of 5 years in one MEN1 individual; hence, this is the earliest age at which to recommend tumour surveillance in carriers. The *MEN1* gene shows biallelic inactivation in 30% of some types of common variety endocrine tumours (e.g. parathyroid adenoma, gastrinoma, insulinoma and bronchial carcinoid), but in only 1–5% of common pituitary tumours. Heterozygous knockout of *MEN1* in mice provides a robust model of MEN1 and has been found to support further research on anti-angiogenesis therapy for pituitary tumours. The rarity of *MEN1* mutations in some MEN1-like states aids the identification of other mutated genes, such as *AIP*, *HRPT2* and *p27^{Kip1}*. We present recent clinical and basic findings about the *MEN1* gene, particularly concerning hereditary vs. common variety pituitary tumours.

Keywords

Angiogenesis; MEN1; Mouse; p27^{Kip1}; Pituitary tumour; Prolactinoma; Tumour suppressor

MEN1 and MEN1-Like States

MEN1

Multiple endocrine neoplasia type 1 (MEN1) is defined as tumours in two of its three main endocrine tissues: parathyroid, pituitary and pancreaticoduodenal [1], with familial MEN1 defined as MEN1 plus one first-degree relative with a tumour in one of these three tissues. MEN1 is the most heterogeneous of tumour syndromes, causing tumours among 25 mainly endocrine tissues (table 1) [2]. Its prevalence is only 1 in 30,000, but the gene is central to

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many common tumours. 'MEN1-like' is a much broader term than MEN1 for sporadic or hereditary states with a tumour in as few as one of the three main tissues. Several such states are discussed in this article.

Typically, each MEN1 tissue with a tumour or at risk of a tumour must be managed independently. Anterior pituitary tumour in MEN1 has an age and sex distribution and hormone profile similar to those of common variety pituitary tumours [3]. Typical onset is from the ages of 30–35 years, with nearly maximal penetrance of 50% by age 50 years among carriers. Management is similar to that for sporadic pituitary tumour, but treatments in MEN1 seem less effective [3].

Prolactinoma Variant of MEN1

A high prevalence of prolactinoma was found in four large MEN1 families located near the Burin Peninsula of Newfoundland, Canada [4]. This has been termed the prolactinoma variant or the Burin variant of MEN1. These four Newfoundland families share an identical mutation in the *MEN1* gene and have an identical 11q13 haplotype about the gene [5, 6], implying that they must be descended from a common founder. The prolactinoma variant of MEN1 should be diagnosed only in a large family; such features in a small family cannot be distinguished from random expression of typical MEN1. Three very large families (scoring the Newfoundland cluster as one huge family) have this phenotype (fig. 1) [7]. Unlike typical MEN1, they show a lower prevalence of gastrinoma (10 vs. 42%, $p < 0.01$) and higher prevalence of prolactinoma (40 vs. 22%, $p < 0.01$). The three families do not share a common *MEN1* mutation pattern or a common environmental feature. We speculate that each family has a similar, tightly linked polymorphism in or near the *MEN1* gene at 11q13 [8] that affects expression of the MEN1 syndrome. Although the seeming proximity of the *AIP* gene (also at 11q13) is intriguing, this cannot be the explanation because the substantial subchromosomal distance of *AIP* from *MEN1* (elaborated below) indicates that any polymorphism within the *AIP* gene must segregate away from the *MEN1* gene in these large families [9].

Familial Isolated Pituitary Tumour

Isolated pituitary tumour is a MEN1-like state that can occur in families and that is linked to 11q13 [10]. In this state, growth hormone (GH) is often oversecreted. In theory, such a syndrome could be caused by the *MEN1* gene also at 11q13, but *MEN1* mutation has not been observed in over 100 families [10]. Indeed, the cause of isolated pituitary tumour in 15% of these families is the *AIP* gene [9]. Although in this gene the subchromosomal locus is close to the *MEN1* gene and is separated by 2.7 million bases, this proximity seems to be a random coincidence. Familial isolated pituitary tumour and its gene are covered separately in detail [11].

Familial Isolated Parathyroid Tumour

Isolated parathyroid tumour is another MEN1-like state that can occur in families. *MEN1* mutation accounts for some 5% of these families, and there is no specific *MEN1* genotype [12, 13]. Other similarly uncommon causes are mutation of the *CASR* or *HRPT2* genes [12–14]. Each of these three genes causes a characteristic syndrome in and beyond the

parathyroids; however, each can also present in an incomplete form as familial isolated hyperparathyroidism. In most affected families, isolated hyperparathyroidism is probably caused by unidentified genes, although genetic linkage suggests the involvement of a locus at chromosome 2p [15].

Familial Isolated Carcinoid Tumour

Carcinoid of the foregut occurs in 16% of MEN1 cases (table 1) [2]. A few small MEN1 families have shown a modest clustering of these carcinoids without a specific *MEN1* genotype [16].

Isolated carcinoid tumour has been reported in a few kindreds, mainly with only two to three affected members [17–19]. The carcinoids in these families have been located mainly in the duodenum, lung and colon, with a repetition of organ location evident in few families [17, 19]. Epidemiological studies of carcinoid suggest that familial clustering is more frequent than reported [20]. No germline *MEN1* mutation has been reported in a family with isolated carcinoid.

MEN1-Like State from p27 Mutation (MEN4)

Mice with combined knockouts of the *p18^{INK4c}* (*CDKN2C*) and *p27^{Kip1}* (*CDKN1B*) cyclin-dependent kinase inhibitor (CDKI) genes express combinations of the tumours of MEN1 and MEN2 [21]. A strain of rat, termed MENX, was discovered with similar combined tumours. MENX is caused by homozygous inactivating mutation of *p27* [22]. The same group reported one human index case and relatives with MEN1, caused by heterozygous mutation of *p27* [22]. Subsequently, another MEN1 case with mutation of *p27* was reported [23]. Considering the few cases identified, the full spectrum of this *p27* gene-related syndrome remains to be established. Notably, three of the four affected cases in these two families had a pituitary tumour (two GH, one adrenocorticotrophic hormone [ACTH]). Because of this preponderance of pituitary tumours and because sporadic MEN1 cases with both parathyroid and pituitary tumour have had a particularly low finding (7%) of *MEN1* mutation (fig. 2), we screened 34 such index cases, each lacking *MEN1* mutation, but found no *p27* mutation [24]. Thus, *p27* mutation is likely to cause 1% or less in this MEN1 category. In OMIM (Online Mendelian Inheritance of Man), this rare *p27* syndrome is termed MEN4 [25]. Subsequently, three more of the remaining six CDKI genes have been similarly implicated [26].

Endocrine Tumours Differ in MEN1 vs. in Other States

Single Tumour Reflects Its Main Gene

Pituitary Tumours: Tumours, and particularly cancers, can have mutations in several genes [27], and sometimes one gene, such as *MEN1*, dominates the clinical expression.

Size.: Pituitary tumours in MEN1 are larger than common variety pituitary tumours, with macroadenoma in 85% of the MEN1 cases compared with 42% of the common variety cases [3].

Hormone Profile.: MEN1 pituitary tumours show the following hormone profile: prolactin (62%), GH (9%), ACTH (4%), co-secreting mostly with prolactin (10%) and non-secreting (15%) [3]. This profile is similar to that of common variety pituitary tumours, but different from the profiles of other hereditary pituitary tumours (from *GNAS*, *AIP* or *PRKAR1A*) that secrete mainly GH.

Tumours Other than Pituitary

Location.: Carcinoid tumour in MEN1 has unusual locations in the foregut (table 1), unlike common variety carcinoid, which is mainly in the mid- or hindgut.

Pathology.: Hereditary parathyroid tumours have a wide spectrum of pathologies with syndrome specificity [27]. The extremes of the spectrum are near-normal parathyroid pathology in familial hypocalciuric hypercalcaemia and parathyroid cancer in 20% of cases with hyper-parathyroid jaw tumour syndrome [28]. The parathyroid tumour of MEN1 is in the middle of this spectrum, resembling common variety adenoma.

Tumour Multiplicity

Tumour multiplicity is a feature of most hereditary tumours. It reflects the germline mutation in all cells of a tumour target tissue, making each cell susceptible to hyperfunction. In MEN1, this multiplicity is seen at four levels:

1. *Hyperplasia as tumour precursor.* Hyperplasia is a histological diagnosis, well recognized in some hereditary tumours [29]. It is not well recognized as a tumour precursor state in most MEN1 tumours, including the pituitary. However, it is a striking feature of the pancreatic islets of mice with MEN1 [30–32], and is a less-evident feature in the gastrin cells of MEN1 in man [33].
2. *Tumour in multiple tissues.* MEN1 has tumours in about 25 endocrine and even non-endocrine tissue types (table 1).
3. *Tumour in a dispersed tissue.* The normal gastrin cells are dispersed in the submucosa of the duodenum. MEN1 patients show multiple microgastrinomas in this tissue [33].
4. *Tumour in a continuous tissue.* The parathyroid gland is quite homogeneous. Multiple tumour nodules, presumably from distinct clones, sometimes arise there in MEN1 [2].

Tumour treatments in MEN1 must be inclusive (i.e. developed to address all of the multiple tumours in an affected organ). These treatments vary from total resection (for thymus) and subtotal resection (for parathyroids), to no resection (drug treatment with acid-pump blockers for gastrin cells).

Pituitary Breaks the Rule of Tumour Multiplicity

Multiple tumours of the pituitary are rare in common variety disease [34] and surprisingly rare even in MEN1 [35, 36]. This is particularly notable since pituitary tumours have a very high penetrance in MEN1 (table 1) and multiple pituitary tumours could easily be imaged by

magnetic resonance imaging. We speculate that a dominant pituitary tumour in MEN1 releases factors that inhibit the growth of nearby pituitary tissues. This could be related to the process of oncogene-induced cell senescence [37].

Preventing Morbidity in MEN1

Preventing or Treating Cancer

Prevention or cure of C-cell cancer has long been possible in MEN2, based on early diagnosis using calcitonin assays and, more recently, using *RET* sequencing [2]. This treatment is mainly based on a favourable location (inside the thyroid gland) of the tumour target tissue.

Twenty-five percent of MEN1 cases will die from a MEN1-related cancer [2]. Although diagnosis by *MEN1* gene testing during childhood is widely available, cancer prevention at any age has not been practical in MEN1 because of the problematic foregut locations of duodenopancreatic and carcinoid tumours.

Preventing and Treating Benign but Morbid Disease

Once a patient is diagnosed as a likely *MEN1* carrier, rather complex protocols for periodic tumour surveillance can help to recognize tumour emergence (table 2). The age at which to begin such periodic monitoring should be determined, in part, by the age at which morbid disease might be treated successfully. In MEN1, there have been two cases of insulinoma at age 6 years [38, 39] and one with pituitary macroadenoma, secreting prolactin and GH, at age 5 years or earlier [40].

Families and physicians face a difficult decision: should a young child at 50% risk of the mutation undergo *MEN1* sequencing and then periodic monitoring for benign but morbid tumours that are very rare in early childhood? Is it preferable to accept the possibility that the rare tumour might not occur or might be recognized early by sensitivity to its symptoms? We generally recommend periodic surveillance for tumours in known MEN1 carriers, beginning at age 5 years (table 2).

Exploiting *MEN1* and Related Genes

Rodent Models and Cell-Cycle Genes

Mice and rats with combined knockouts of *p18* and *p27* CDKIs provide a model for MEN1 and MEN2 (see above [21, 22]). Mice have also been engineered to express inactivation of one copy of the *MEN1* gene [30–32]; these provide a robust model of MEN1 with pituitary tumour, parathyroid tumour, insulinoma and other tumours. Unlike the pituitary tumours of the intermediate lobe of mice with *Rb1* inactivation, the pituitary tumours from *MEN1* mutation are mainly prolactinomas. In mice, knockout of *MEN1* synergizes with knockout of *p18* in pituitary and other tumorigenesis, but not with knockout of *p27* or *Rb1* [41–43]. MEN1 mice have been used to test the efficacy of a monoclonal antibody to vascular endothelial growth factor A, which was subsequently found to inhibit pituitary tumour growth, inhibit growth of pituitary tumour as implants and cause less elevation in serum prolactin concentration. There was similar efficacy against islet tumours [44]. Such studies

suggest the importance of the vascular component of some or even all tumours in MEN1 [45].

Role in Common Tumours

Often the gene for a rare hereditary disorder also has important roles in common tumours of similar types. Thus, the *RET* gene is implicated in common pheochromocytoma, common C-cell cancer and papillary thyroid cancer (the latter as the *RET-PTC* rearrangements) [2].

The *MEN1* gene is the initiator in about 30% of all common parathyroid adenomas, gastrinomas, insulinomas and bronchial carcinoid tumours (fig. 3) [2]. Surprisingly, it initiates only 1–5% of common pituitary tumours [46]. The finding of *MEN1* mutation in many common endocrine tumours suggests that identifying the menin pathway could lead to the development of drugs for treating many tumours.

MEN1 Mutation in Probands

The germline *MEN1* sequence test is the gold standard for identifying MEN1 carriers among probands with MEN1-like features [2, 47]. If a mutation is identified, then simplified DNA testing can be discussed with relatives.

Recognizing MEN1-Like States Caused by Other Genes

MEN1 sequence testing has led to the recognition of states in which *MEN1* mutation seems deficient (fig. 2) [2, 47]. For example, 30% of patients with typical MEN1 do not have an identifiable *MEN1* mutation. This could reflect a MEN1 mutation invisible to current methods of detection or a mutation in other gene(s) [2, 26].

Menin Molecular Pathway

The *MEN1* gene encodes menin, a protein of 610 amino acids. Other than several nuclear localization sequences, menin has no homologies or recognizable domains. Efforts to understand its molecular pathway have begun with protein partnering methods. Some 25 menin partners have been identified [48]; none have been shown conclusively to be important in pathophysiology. MLL and junD have received the most attention. A tumorigenic mechanism has been proposed for each, independent of the other. Each mechanism must begin with the inactivation of both copies of the *MEN1* gene. Menin inactivation can switch junD from growth suppressor to growth promoter [49, 50]. Alternately, menin inactivation can destabilize the MLL-COMPASS complex and thereby stop its transcriptional activation of *p18* and *p27*, each of which is a growth suppressor [51–53].

Conclusion

Germline heterozygous loss of function of the *MEN1* gene gives a high penetrance for development of tumour of the anterior pituitary, mainly prolactinoma. This is also expressed in mouse models. Among all pituitary tumour syndromes, only MEN1 in man or mouse shows a hormonal profile similar to that of common pituitary tumours. However, biallelic somatic mutation of *MEN1* is rare in common variety pituitary tumours. Future research

must explore other mechanisms of *MEN1* gene inactivation in common variety tumours of the pituitary. This would include epigenetic changes, such as promoter methylation, dysregulation of menin protein [54] and other changes in menin pathways. The principal clinical and therapeutic implications are summarized in table 3.

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Fig. 1.

Prevalence of gastrinoma and prolactinoma in seven reviews of typical MEN1 (♦) versus in three large kindreds with the prolactinoma or Burin variant of MEN1 [7]. The low prevalence of gastrinoma in the so-called prolactinoma variant kindreds is particularly striking.

Fig. 2.

Estimates of the prevalences of *MEN1* mutation in selected clinical groups. Each group fits the broad definition of MEN1 or MEN1-like, but mutation prevalences differ dramatically, justifying the logarithmic scale. The group of sporadic cases with both parathyroid (PTH) and pituitary (Pitu) tumour is circled because of its meeting the formal definition of MEN1 but having a particularly low prevalence (7%) of identified *MEN1* mutation.

Fig. 3.

Contributions from inactivation of the *MEN1* gene in groups with common variety endocrine tumour (i.e. no DNA or kindred evidence of MEN1). Inactivation of the *MEN1* gene is found as small mutations in the *MEN1* gene sequence and as large subchromosomal losses, the latter determined by loss of heterozygosity at 11q13. Modified from Gagel and Marx [2].

Table 1.

Tissue selectivity of tumours in probands and families with MEN I

<i>Hormone-secreting tumours</i>	
Parathyroid adenoma (90%)	Anterior pituitary tumour
Pancreaticoduodenal tumour	Prolactinoma (20%)
Gastrinoma (40%)	Other growth hormone + prolactin (5%)
Insulinoma (10%)	Growth hormone (5%), NF (5%)
NF, also pancreatic polypeptide (20%)	ACTH (2%) or TSH (rare)
Glucagon, vasoactive intestinal polypeptide, somatostatin, etc. (2%)	Adrenal
Foregut carcinoid	Cortex NF (25%)
Thymic carcinoid NF (4%)	Medulla (1%)
Bronchial carcinoid NF (2%)	
Gastric enterochromaffin-like NF (10%)	
<i>Hormone non-secreting tumours</i>	
Facial angiofibroma (85%)	Leiomyoma
Truncal collagenoma (70%)	Uterus in female (30%?)
Lipoma (30%)	Oesophagus (5%)
Meningioma (5%)	Ependymoma (1%)
Barrett's oesophagus (5%)	

NF = Non-functioning; TSH = thyroid-stimulating hormone. Percentages in parentheses/brackets indicate penetrance at age 40 years. Terms in bold font indicate tumour type with malignant potential for 25% or more of cases. Modified from Gagel and Marx [2].

Protocol for periodic surveys for donor emergence in a known or highly likely carrier of MEN1. A positive result should lead to further considerations, regarding false-positives or additional tests for confirmations

Table 2.

Tumour	Age to begin (year)	Biochemical tests (annually)	Imaging tests (every 3–5 years)
Anterior pituitary	5	Prolactin, IGF-I	MRI
Parathyroid	5	Calcium, PTH	None
Insulinoma	5	Fasting glucose	None
Gastrinoma	20	Gastrin	None
Other gastrointestinal	20	None ^a	CAT or MRI, Octreoscan ^b
Foregut carcinoid	20	None ^a	CAT ^b during gastroscopy

CAT = Computerized axial tomography; IGF-I, insulin-like growth factor I; MRI = magnetic resonance imaging; PTH = parathyroid hormone.

^aChromogranin A has some utility in following a large endocrine tumour burden. It has not been shown to be useful in screening for small tumours.

^bNew tests such as ¹⁸F-fluorodopa positron emission tomography or endoscopic ultrasound are promising. Modified from Gagel and Marx [2].

Table 3.**Clinical and therapeutic implications**

Clinical

- The MEN1 syndrome causes tumours in more tissue types than any other syndrome
- Pituitary tumours in MEN1 have the same hormonal profile as sporadic pituitary tumours. All other pituitary tumour syndromes (isolated pituitary tumours, Carney complex, McCune-Albright) favour GH tumours
- Pituitary tumours are larger in MEN1 cases than in sporadic cases
- Germline mutation is the basis for multiplicity of hereditary tumours. Surprisingly, pituitary tumour in MEN1 is rarely multiple
- Most cases of MEN1 have a germline *MEN1* mutation. About 1% have *p27* mutation

Therapeutic

- The *MEN1* gene contributes by mutation to tumorigenesis in many tissues, mainly endocrine. *MEN1* mutation is less frequent in sporadic tumours of pituitary tissue than of other endocrine tissues. Detecting such a mutation is not important in clinical practice
 - More importantly, understanding the molecular pathway of *MEN1* and its encoded menin could lead to new drugs for many endocrine tumours
 - Germline *MEN1* mutation testing can provide useful information for patients and caregivers
 - For example, early diagnosis of MEN1 cannot guide the prevention of MEN1 cancers due to their critical locations. However, it can lead to the monitoring for emergence of morbid but treatable tumours, such as macro-prolactinoma
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