Thoracic and duodenopancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1: natural history and function of menin in tumorigenesis

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Abstract
Mutations of the multiple endocrine neoplasia type 1 (MEN1) gene lead to loss of function of its protein product menin. In keeping with its tumor suppressor function in endocrine tissues, the majority of the MEN1-related neuroendocrine tumors (NETs) show loss of heterozygosity (LOH) on chromosome 11q13. In sporadic NETs, MEN1 mutations and LOH are also reported, indicating common pathways in tumor development. Prevalence of thymic NETs (thNETs) and pulmonary carcinoids in MEN1 patients is 2–8%. Pulmonary carcinoids may be underreported and research on natural history is limited, but disease-related mortality is low. thNETs have a high mortality rate. Duodenopancreatic NETs (dpNETs) are multiple, almost universally found at pathology, and associated with precursor lesions. Gastrinomas are usually located in the duodenal submucosa while other dpNETs are predominantly pancreatic. dpNETs are an important determinant of MEN1-related survival, with an estimated 10-year survival of 75%. Survival differs between subtypes and apart from tumor size there are no known prognostic factors. Natural history of nonfunctioning pancreatic NETs needs to be redefined because of increased detection of small tumors. MEN1-related gastrinomas seem to behave similar to their sporadic counterparts, while insulinomas seem to be more aggressive. Investigations into the molecular functions of menin have led to new insights into MEN1-related tumorigenesis. Menin is involved in gene transcription, both as an activator and repressor. It is part of chromatin-modifying protein complexes, indicating involvement of epigenetic pathways in MEN1-related NET development. Future basic and translational research aimed at NETs in large unbiased cohorts will clarify the role of menin in NET tumorigenesis and might lead to new therapeutic options.

Key Words
▶ multiple endocrine neoplasia type 1
▶ neuroendocrine tumors
▶ menin
▶ epigenetics
▶ natural history
▶ lung NET
▶ thymic NET
▶ duodenopancreatic NET
▶ pancreatic NET
▶ MEN1
Introduction

Thoracic and duodenopancreatic neuroendocrine tumors (dpNETs) can occur either sporadically or as a manifestation of an inherited syndrome, most importantly the multiple endocrine neoplasia type 1 (MEN1) syndrome. This is an autosomal dominantly inherited disease that is caused by germline mutations in the MEN1 gene. NETs associated with MEN1 are lung NETs, thymic NETs (thNETs), gastrin NETs, and dpNETs. MEN1-related NETs are an important cause of morbidity and presently malignant dpNETs and thNETs are the main cause of MEN1-related death (Schaal et al. 2007, Goudet et al. 2010).

In the past decade, understanding of the genetic and molecular aspects of NETs has increased and important steps have been made in the therapy of advanced disease. New tumor classification and staging systems have improved patient care and uniformity in patient selection for clinical trials. It is important to recognize similarities in the tumorigenesis of MEN1-related and sporadic NETs, because MEN1-related NETs may be regarded as a model for sporadic disease. On the other hand, it is also essential to be aware of potential differences in tumor behavior between these two entities, as this influences diagnostic and therapeutic strategies.

In this review, we provide a comprehensive overview of the literature concerning tumor development of MEN1-related dpNETs and thoracic NETs (Box 1). The complete spectrum, from epidemiologic characteristics and natural history to important molecular findings associated with loss of the MEN1 gene, is discussed. Differences between and similarities with their sporadic counterparts are highlighted. Table 1 provides a list of some of the abbreviations used in the text.

MEN1 gene

The MEN1 gene was initially localized to chromosome 11q13 by linkage analysis and tumor deletion mapping studies (Larsson et al. 1988, Friedman et al. 1989, Byström et al. 1990, Lubensky et al. 1996), which led to the identification of the gene in 1997 (Chandrasekharappa et al. 1997, Lemmens et al. 1997). More than 450 different germline MEN1 mutations have been identified in MEN1 patients (Lemos & Thakker 2008). MEN1 consists of ten exons and mutations are found scattered throughout the gene. The protein product is the 610-amino acid protein, called menin. Most MEN1 gene mutations are predicted to lead to truncation of the protein (Lemos & Thakker 2008). Missense mutations have been reported in about 20% of the cases. Both truncated and missense mutations result in reduced levels of protein due to proteolytic degradation via the ubiquitin–proteasome pathway (Yaguchi et al. 2004). A small percentage of patients who are considered to have the MEN1 syndrome (based on the clinical definition) may not harbor a germline mutation within the coding region of the MEN1 gene (Agarwal et al. 1997). Possibly, these patients have mutations in the promoter region or large deletions on chromosome 11q13 (Cavaco et al. 2002). Currently, in clinical practice, inconclusive DNA sequencing is followed by multiplex ligation-dependent probe amplification analysis for detection of large deletions. An alternative explanation for the MEN1 syndrome of these patients may include epigenetic silencing of MEN1 (e.g. by DNA methylation) or mutations in other genes, which cause MEN1-like manifestations.

The MEN1 gene is a tumor suppressor gene for endocrine tissues. According to Knudson’s ‘two-hit hypothesis’, biallelic inactivation of MEN1 is required for tumor development (Knudson 1971). This second hit typically involves large chromosomal deletions in chromosome 11q13. Loss of heterozygosity (LOH) of MEN1 is demonstrated in most reported MEN1-related pancreatic NETs (pNETs) (Lubensky et al. 1996, Debelenko et al. 1997b, Hessman et al. 2001, Perren et al. 2007). However, the frequency of LOH of chromosome 11q13 in MEN1-related primary duodenal gastrinomas is only 21–45% (Lubensky et al. 1996, Debelenko et al. 1997b). LOH of chromosome 11q13 has also been shown in MEN1-related pulmonary carcinoids (Debelenko et al. 1997b, Dong et al. 1997). Intriguingly, no LOH was found in thNETs (Teh et al. 1994, 1998, Hessman et al. 2001, Gibril et al. 2003). In these cases, other events might be involved in silencing the second MEN1 allele.

Box 1: Search strategy

The contents of this review are based on the experience of the authors and on an extensive search in PubMed. The following terms were used in the search string: ‘MEN1’ and all relevant synonyms OR ‘menin’ and all relevant synonyms. For lung NET, this search string was combined with ‘bronchial’ OR ‘pulmonary’ OR ‘lung’ (and relevant synonyms) AND ‘carcinoid’ OR ‘neuroendocrine’. For thNET this search string was combined with ‘thymic’ OR ‘thymus’ OR ‘mediastinal’ AND ‘carcinoid’ OR ‘neuroendocrine’. For dpNET, this search string was combined with all relevant synonyms for ‘pancreas’ and ‘duodenum’ AND all relevant synonyms for ‘neuroendocrine tumor’ OR ‘gastrinoma’ OR ‘insulinoma’ OR ‘glucagonoma’ OR ‘VIPoma’.

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Somatic mutations in MEN1-related tumors have been reported as an alternative mechanism leading to the inactivation of this second MEN1 allele (Pannett & Thakker 2001). Post-transcriptional reduction in menin levels by specific microRNAs may mimic the second hit (Luzi et al. 2012). In sporadic NETs, somatic mutations of the MEN1 gene have been found. The reported frequency for MEN1 mutations in sporadic pNETs is up to 44% in well-differentiated tumors (Jiao et al. 2011). In accordance with Knudson’s hypothesis, LOH of chromosome 11q13 is also observed in sporadic pNETs (Debelenko et al. 1997b, Hessman et al. 1998, Gortz et al. 1999). Also, in sporadic pulmonary carcinoids, mutations in the MEN1 gene and LOH of chromosome 11q13 are observed in sporadic pNETs (Debelenko et al. 1997b, Hessman et al. 1998, Gortz et al. 1999, Gortz et al. 1999, Petzmann et al. 2001, Vageli et al. 2006, Veschi et al. 2012) and up to 73% in a single report (Finkelstein et al. 1999). Apparently, MEN1-related tumors and their sporadic counterparts share common pathways in tumor development.

**Thoracic NETs in MEN1**

**Pathology and pathogenesis**

According to the World Health Organization, lung and thymus NETs are classified into typical carcinoids (TCs), atypical carcinoids (ACs), and high-grade neuroendocrine carcinomas based on mitotic count and the presence of necrosis (Travis et al. 2004). High-grade tumors are divided into large-cell neuroendocrine carcinomas and small-cell carcinomas. Small (<0.5 cm) pulmonary tumors with carcinoma morphology are called tumorlets (Travis et al. 2004). For thNETs, alternative grading systems exist, which is important to realize when comparing and interpreting results from different studies (Fukai et al. 1999, Moran & Suster 2000a, Gal et al. 2001, Gaur et al. 2010).

Pulmonary carcinoids have a different clinical presentation and genetic profile compared with high-grade tumors and must be regarded as a separate entity (Swarts et al. 2012). High-grade lung NETs are not seen in association with MEN1. Moreover, in contrast to sporadic pulmonary carcinoids, mutations in the MEN1 gene and LOH at chromosome 11q13 are rare in high-grade lung NETs (Swarts et al. 2012). This sharp distinction is absent in thNETs (Moran & Suster 2000b) and MEN1-related thNETs include both well- and poorly-differentiated neuroendocrine carcinomas.

The cell of origin for pulmonary carcinoids is thought to be the pulmonary neuroendocrine cell (Swarts et al. 2012), although, some suggest an uncommitted progenitor cell (Warren & Hammar 2006). Pulmonary neuroendocrine cells are evenly distributed throughout the airways, but absent from the alveoli, and comprise 0.4% of all lung epithelial cells (Boers et al. 1996). In response to various triggers, reactive neuroendocrine cell hyperplasia can occur, which is not associated with the development of pulmonary carcinoids. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), on the other hand, is a rare disorder that is considered preneoplastic to pulmonary carcinoids (Aguayo et al. 1992, Travis et al. 2004). Only one case of a MEN1-patient with DIPNECH has been published to date (Davies et al. 2007). However, in published cases of MEN1-related pulmonary carcinoids, pathology of surrounding lung tissue was not reported, so the true prevalence of DIPNECH among MEN1-patients is unknown.
The cell of origin for thNETs is not known and there are no known precursor lesions. thNETs were first described in 1972 and in the same year the association with MEN1 was reported (Rosai & Higa 1972, Rosai et al. 1972). It was then hypothesized that these tumors arise from neuroendocrine cells residing within the normal thymus. In different series, family clustering of MEN1-related thNETs was demonstrated (Teh et al. 1997, 1998, Ferolla et al. 2005, Goudet et al. 2009). In those series, no apparent MEN1 genotype–phenotype correlation was seen, suggesting the involvement of other genetic factors.

Epidemiology


The exact prevalence of pulmonary carcinoids in MEN1 is unknown. Commonly reported figures are 3–8% (Marx et al. 1998, Karges et al. 2000, Goudet et al. 2011). However, in a large Tasmanian family (n=129), prevalence among patients screened with thoracic computed tomography ranged from 11% if only pathology proven cases were included to 31% based on radiological findings (Sachithanandan et al. 2005). Reported age at diagnosis of MEN1-related pulmonary carcinoids is mid-forties (Sachithanandan et al. 2005). Although initially a female predominance was reported (Duh et al. 1987, Farhangi et al. 1987, Shepherd 1991, Sachithanandan et al. 2005), the prevalence appears to be equal between genders in a large recent study (Goudet et al. 2011).

Natural history and prognostic factors: pulmonary carcinoids

Very little is known about the natural course and prognosis of pulmonary carcinoids in MEN1. Evidence is limited to one small series and several case reports or descriptions, either separately published or mentioned within larger MEN1 patient series. Among sporadic pulmonary carcinoids, TCs are much more frequent than ACs (10–27% in series also including nonsurgical patients; Fink et al. 2001, Pusceddu et al. 2010, Naalsund et al. 2011, Okoye et al. 2013). This seems to be similar in MEN1, but classifications are rarely reported (Murat et al. 1997, Snabboon et al. 2005, Lourenco-Jr et al. 2007, Abe et al. 2008, Divisi et al. 2008, Matsuda et al. 2010, Montero et al. 2010). As in other MEN1 manifestations, multiplicity seems to be common in pulmonary carcinoids (Marx et al. 1998, Sachithanandan et al. 2005). In its sporadic counterpart, multiplicity is seen in <1–9% (Daddi et al. 2004, Garcia-Yuste et al. 2007, Ferolla et al. 2009, Okoye et al. 2013). Ectopic hormone production is not reported in MEN1-related pulmonary carcinoids, in contrast to sporadic disease (Boddaert et al. 2012, Garby et al. 2012, Simonds et al. 2012).

The overall survival of MEN1-related pulmonary carcinoids is unknown. In series focusing on MEN1-related mortality, 5–9% of the MEN1-related deaths occurring before 1990 were attributed to pulmonary carcinoids (Wilkinson et al. 1993, Goudet et al. 2010), with no deaths due to pulmonary carcinoids reported after 1990 (Geerdink et al. 2003, Wilson et al. 2008, Goudet et al. 2010). In line with these findings, pulmonary carcinoids do not give an increased risk of death in MEN1 patients (Goudet et al. 2010).


Given the paucity of data on pulmonary carcinoids in MEN1 and the absence of head-to-head comparisons, it is unclear whether the natural history differs between MEN1-related and sporadic pulmonary carcinoids. There are a few studies in sporadic tumors that show somatic
MEN1 mutations, LOH at 11q13, or reduced MEN1 gene expression to be an adverse prognostic factor (Debelenko et al. 1997a, Petzmann et al. 2001, Swarts et al. 2011).

Factors predicting development of metastases or survival are not known in MEN1-related pulmonary carcinoids. In their sporadic counterparts ACs, lymph node metastases, distant metastases, and higher proliferation rate (Ki67 labeling index or mitotic index) have been repeatedly identified as adverse prognostic factors (Cao et al. 2011, Daddi et al. 2013). Results on the prognostic values of gender, age, and tumor size are contradictory.

Natural history and prognostic factors: thNET

Six case series including more than five patients have been published on thNETs in MEN1 (Teh et al. 1997, 1998, Gibril et al. 2003, Ferolla et al. 2005, Goudet et al. 2009, Sakurai et al. 2013). In these series, classifications are often not reported (Teh et al. 1997, 1998, Gibril et al. 2003, Sakurai et al. 2013). When mentioned, 100% are AC in one series and 38% poorly differentiated neuroendocrine carcinomas in another (with the distinction between TC and AC for the other 62% not reported; Ferolla et al. 2005, Goudet et al. 2009). In sporadic thNETs the reported frequencies vary greatly, TCs are reported in 0–67% in different series and 81% in a literature review from 1999 (de Montpreville et al. 1996, Fukai et al. 1999, Soga et al. 1999, Moran & Suster 2000a, Gaur et al. 2010, Cardillo et al. 2012). Patient selection and differences in the use of grading systems may explain this variation. Cushing’s syndrome due to ectopic adrenocorticotropin hormone production is rare in MEN1-related thNETs (0–5%; Teh et al. 1997, 1998, Gibril et al. 2003, Ferolla et al. 2005, Goudet et al. 2009, Sakurai et al. 2013), but it has been observed in 5–31% of the sporadic cases (Moran & Suster 2000a, Kondo & Monden 2003, Cardillo et al. 2012).

Among the manifestations of the MEN1 syndrome, thNETs carry the highest risk of death (Goudet et al. 2010) with an estimated 10-year survival of 30–36% (Goudet et al. 2009, Sakurai et al. 2013). Although mortality is high, the course of MEN1-related thNETs may be protruded, with one series reporting a median survival of 9.6 years (Goudet et al. 2009). When comparing six MEN1 patients with thNETs with 22 patients with sporadic thNETs, Crona et al. (2013) found no survival difference between these groups.

In MEN1-related thNETs, 90% disease-related mortality was reported among patients with advanced stage disease in a series with a mean 3.6 years follow-up (Teh et al. 1997). In the other series, patients were followed for a mean 5–7 years and metastases occurred in 32–71% of the patients. Disease-related mortality in these series ranged from 0 to 43% (Teh et al. 1998, Gibril et al. 2003, Ferolla et al. 2005, Goudet et al. 2009, Sakurai et al. 2013). In one of the two series reporting no mortality, the majority was discovered incidentally at prophylactic thymectomy or by screening (Gibril et al. 2003).

No data are available on prognostic factors with regard to overall survival, recurrence, or metastases in MEN1 patients. In series reporting on sporadic thNETs, prognostic factors related to decreased survival are higher tumor grade, more advanced disease, higher Ki67 labeling index (cut-off 10%), and larger tumor size (Moran & Suster 2000a, Gal et al. 2001, Gaur et al. 2010, Cardillo et al. 2012, Crona et al. 2013).

dpNETs in MEN1

Pathology and pathogenesis

dpNETs are classified according to the European Neuroendocrine Tumor Society/World Health Organization grading system into three grades based on proliferation rate (Rindi et al. 2006, Bosman et al. 2010).

The hallmark of dpNETs in MEN1 is multiplicity, which is in contrast to the mostly solitary sporadic dpNETs (Thompson et al. 1984, Pipeleers-Marichal et al. 1993, Crippa et al. 2012). All histologic subtypes can occur in MEN1. At pathology, all MEN1 patients have multiple micro-adenomas (pNETs <5 mm without clinical syndrome) dispersed throughout the pancreas associated with one or more NETs ≥5 mm (Thompson et al. 1984, Kloppel et al. 1986, Le Bodic et al. 1996, Anlauf et al. 2006b). These multiple dpNETs in MEN1 arise from independent clonal events, as demonstrated by different allelic deletion and retention patterns in synchronous tumors (Debelenko et al. 1997b, Hessman et al. 1999, Perren et al. 2007). Apart from these tumors other lesions such as islet cell hyperplasia/enlargement, nesidioblastosis, and atypical or monohormonal endocrine cell clusters are frequently observed in the MEN1 pancreas, leading to different theories as to the cell of origin for pNETs (Thompson et al. 1984, Le Bodic et al. 1996, Vortmeyer et al. 2004, Perren et al. 2007). Normal pancreatic islets and alternatively ductal/acinar cells are proposed to be the precursor cells for pNETs (Vortmeyer et al. 2004, Perren et al. 2007).

Gastrinomas take a special place among the MEN1-related dpNETs, as the vast majority are not pancreatic but located submucosal in the duodenum (Pipeleers-Marichal...
et al. 1990). Sporadic gastrinomas are located in the duodenum less frequently than in MEN1 (Pipeleers-Marichal et al. 1990, Donow et al. 1991, Pipeleers-Marichal et al. 1993, Anlauf et al. 2006a). Duodenal NETs in MEN1 are almost always multiple, while sporadic duodenal NETs are usually solitary (Pipeleers-Marichal et al. 1990, Donow et al. 1991, Anlauf et al. 2006a). In MEN1, they are associated with multifocal hyperplasia of gastrin and somatostatin producing cells, which are proposed to be precursor lesions (Anlauf et al. 2005).

**Epidemiology**

The clinical prevalence of dpNETs in MEN1 is over 50% in recent large series (Goudet et al. 2011, Sakurai et al. 2012a) and the penetrance of clinically manifest dpNETs at the age of 80 is 84% (Triponez et al. 2006a).

dpNETs are classified as hormonally active or non-functioning (NF) based on the combination of clinical features, laboratory results, and findings at immunohistochemistry. In the MEN1 syndrome, synchronous dpNETs may secrete different hormones based on immunohistochemistry (Le Bodic et al. 1996, Anlauf et al. 2006b). As these findings do not always correlate with clinical symptoms, classifications should not be based on immunohistochemistry alone.

When sought for, additional NF-pNETs are found in all patients undergoing surgery for functional tumors, so the prevalence of NF-pNETs is probably equal to dpNETs in general (Tonelli et al. 2006, Lopez et al. 2011, Giudici et al. 2012). Gastrinoma is the most prevalent hormonally active dpNET (29–55% of all dpNETs in studies published in the last decade), followed by insulinoma (2–24%) and rare functioning tumors seen in <10% such as glucagonoma, vaso-active intestinal peptide-producing NET (VIPoma), and somatostatinoma. (Lourenco-Jr et al. 2007, Vierimaa et al. 2007, Pieterman et al. 2009, Waldmann et al. 2009, Goudet et al. 2011, Sakurai et al. 2012a). It is important to realize that 76% of all cases of growth hormone (GH)-releasing hormone-producing pNETs reported in literature are MEN1-related (Garby et al. 2012). This diagnosis should therefore always raise suspicion of an underlying MEN1 syndrome. Separating different types of dpNETs in MEN1 is somewhat artificial, because most patients with hormonally active tumors will harbor additional NF-pNETs (Tonelli et al. 2006, Lopez et al. 2011, Giudici et al. 2012), patients with NF-pNETs can develop hormonally active tumors (Thomas-Marques et al. 2006, Davi et al. 2011), and co-occurrence of different hormonally active tumors has also been described (Tonelli et al. 2006, Giudici et al. 2012).

MEN1-related dpNETs are seen one to two decades earlier than their sporadic counterparts (Jensen 1998, Nikfarjam et al. 2008, Anlauf et al. 2009, Crippa et al. 2012, Singh et al. 2012). Insulinomas have the lowest age of onset (patients are usually in their twenties to thirties at diagnosis), patients with gastrinomas and NF-pNETs are usually diagnosed in their thirties (Jensen 1998, Cougard et al. 2000, Triponez et al. 2006a, Sakurai et al. 2012b). At the age of 60, the penetrance of gastrinoma is significantly higher in men (55%) compared with women (33%), while the other dpNET types do not show gender differences (Goudet et al. 2011).

**Natural history**

dpNETs are the most important determinant of MEN1-related survival. In historical series, ulcer disease due to gastrinoma was the most important cause of MEN1-related death (Ballard et al. 1964), while this presently is malignant dpNETs (Schaaf et al. 2007, Goudet et al. 2010). In patients with MEN1-related dpNETs, estimated 10-year survival is 75% (Carty et al. 1998, Kouvaraki et al. 2006). Risk of death seems to differ between the various subtypes, with the rare functioning tumors presenting the highest risk followed by NF-pNETs and gastrinoma, while insulinomas do not seem to increase the risk of death (Goudet et al. 2010).

However, the natural history of NF-pNETs is not well-established yet. Estimated 10-year survival rates of 23–62% have been reported (Levy-Bohbot et al. 2004, Kouvaraki et al. 2006), whereas this was 100% in a recent series (Lopez et al. 2011). One has to keep in mind that with endoscopic ultrasound, more small NF-pNETs are currently diagnosed. They are usually indolent and demonstrate slow growth, with a doubling time of 5–10 years (Kann et al. 2013). In the largest reported series on NF-pNETs (n=108), metastases, mostly distant, are seen in 19% and disease-specific survival is 91% after a mean follow-up of 4 years (Triponez et al. 2006a). In smaller series from the last decade, distant metastases are reported in 6–22% (Bartsch et al. 2005, Davi et al. 2011, Lopez et al. 2012a).
2011), whereas in a report from 1992 distant metastases were observed in 57% (Grama et al. 1992). Mean tumor size in this latter series was 6.7 cm (Grama et al. 1992).

In MEN1-related insulinomas, reported survival rates in series with more than ten patients are 93–100% after 9–10 years of follow-up (Van Box Som et al. 1995, Cougard et al. 2000, Proye et al. 2004). Multiple insulinomas are seen in 25–83% (Van Box Som et al. 1995, Thompson 1998, Giudici et al. 2012), whereas in sporadic insulinomas multiplicity is seen in ~4% (Nikfarjam et al. 2008, Anlauf et al. 2009, Crippa et al. 2012).

Malignancy in MEN1-related insulinomas has been reported in 5–27% in series including more than ten patients (Cougard et al. 2000, Proye et al. 2004, Crippa et al. 2012). In these malignant insulinomas, liver metastases were only seen once (Proye et al. 2004).

The natural history of gastrinomas in MEN1 is difficult to establish for several reasons. First, gastrinomas in MEN1 are predominantly located in the duodenum (Pipeleers-Marichal et al. 1990). In series on MEN1-related gastrinomas, high rates of pancreatic tumors might be reported, but most of these will not be the gastrinomas. Rates of pancreatic gastrinomas are only 0–18% in series that include immunohistochemistry in the classification of pNETs as gastrinomas (Tonelli et al. 2006, Dickson et al. 2011, Imamura et al. 2011, Lopez et al. 2013). Second, MEN1-related gastrinomas are almost invariably accompanied by NF-pNETs (Thompson 1998, Dickson et al. 2011). If distant metastases arise, these can not only be caused by the gastrinoma, but also by the accompanying NF-pNETs and even by NETs of other locations, which cannot be separated if no pathology or immunohistochemistry results are available. Third, when interpreting the results of clinical series, it is important to realize that in surgical series synchronous metastases will most likely be underrepresented, since diffuse liver metastases are seen as a contra-indication for surgery, whereas in series with low surgical rates nodal status will most likely be underrepresented, because this is difficult to establish on imaging (Skogseid et al. 1998). Finally, since the publication of guidelines for periodic evaluation, MEN1 patients must be viewed as a screened population, making comparison with sporadic cases more difficult (Thakker et al. 2012).


Owing to its rarity, very few data are available on functioning pNETs other than gastrinomas and insulinomas. The largest combined experience comes from the French Endocrine Tumor Study Group, reporting on five glucagonomas, three VIPomas, and two somatostatinomas in MEN1, comprising 3.3% of the MEN1-related dpNETs (Levy-Bobbot et al. 2004). Four of these ten patients had liver metastases (40%). Ten-year survival was 54% (Levy-Bobbot et al. 2004).

### Natural history: comparison with sporadic dpNET

Some series including MEN1 and sporadic dpNETs of all subtypes report MEN1 to be associated with better survival. However, no separate baseline characteristics are provided for MEN1 patients, so selection bias cannot be excluded (Tomassetti et al. 2005, Fendrich et al. 2007, Rindi et al. 2012). In one study including only patients operated upon for advanced dpNETs (all subtypes), patients with MEN1 had a trend toward better survival and developed no new distant metastases, while 46% of the patients with sporadic dpNETs did develop new distant metastases (Fendrich et al. 2006). The meaning of these findings is difficult to discern, given the highly selected source population.

With regard to different subtypes of dpNETs, no studies are available comparing MEN1-related and sporadic NF-pNETs. In series comparing MEN1-related with sporadic insulinomas, a higher rate of malignancy was seen in MEN1 (Service et al. 1991, Anlauf et al. 2009, Goretzki et al. 2010, Crippa et al. 2012). On gastrinomas more data are available, mostly from different reports of the prospective study on Zollinger–Ellison syndrome by the National Institutes of Health (Weber et al. 1995, Jensen 1998, Norton et al. 1999, Yu et al. 1999). In two of these reports, MEN1 patients had a better overall survival than patients with sporadic gastrinomas but also less advanced disease at baseline, indicating potential lead-time bias (Weber et al. 1995, Jensen 1998). When comparing patients in the same stage of disease, no survival difference was observed between MEN1-related and sporadic gastrinomas (Weber et al. 1995, Norton et al. 1999). Several other studies also point...
to a similar natural course for MEN1-related and sporadic gastrinomas (Stabile & Passaro 1985, Ruszniewski et al. 1993, Yu et al. 1999, Ellison et al. 2006). In contrast, in one series a survival benefit was found for MEN1 patients, but separate baseline characteristics were not provided (Melvin et al. 1993). Another series also found survival benefit in MEN1, with no significant baseline differences in liver metastases (MEN1 6% vs sporadic 24%, P=0.24), but this might be due to the small number of patients and selection or referral bias cannot be excluded (Singh et al. 2012). Overall, the available data seem to point to a similar natural course for MEN1-related and sporadic gastrinoma.

Prognostic factors

The most important adverse prognostic factor related to overall survival in MEN1-related dpNETs is the presence of liver or other distant metastases (Stabile & Passaro 1985, Cadiot et al. 1999, Kouvaraki et al. 2006, Triponez et al. 2006a, Ito et al. 2013). In a series including all subtypes of dpNETs, the estimated 10-year survival for patients with distant metastases was 34% (Kouvaraki et al. 2006). In patients with diffuse liver metastases from gastrinoma, 10- and 15-year survival of 88 and 52% are reported, while in patients with metastases from NF-pNET 8-year survival was 34% (Norton et al. 2001, Triponez et al. 2006a). Lymph node metastases are not related to survival (Gibril et al. 2001, Kouvaraki et al. 2006, Ito et al. 2013). Contradictory evidence exists with regard to the prognostic value of age. An older age (Burgess et al. 1998a, Cadiot et al. 1999, Kouvaraki et al. 2006, Vierimaa et al. 2007) as well as a younger age are reported as adverse prognostic factors (Gibril et al. 2001, Ito et al. 2013). Reports regarding the prognostic significance of pancreatic tumor size vary. No relation between tumor size and metastases, malignancy or overall survival is found in several series reporting on MEN1-related dpNETs (hormonally active and NF; Grama et al. 1992, Lowney et al. 1998, Lairmore et al. 2000, Bartsch et al. 2005, Kouvaraki et al. 2006, Lopez et al. 2011). In the subset of NF-pNETs, larger tumor size was related to a higher rate of metastases and a decreased overall survival (Triponez et al. 2006a,b). In gastrinoma series, pancreatic tumor size >3 cm was found to be associated with an adverse outcome (Cadiot et al. 1999, Gibril et al. 2001, Ito et al. 2013). However, it is unclear if these pNETs used as prognostic indicator were all gastrinomas and not (in part) coexisting NF-pNETs. Moreover, results from liver biopsy immunohistochemistry are often not reported, so the origin of the metastases cannot be verified. In the natural course of gastrinoma, an aggressive and nonaggressive variant based on tumor growth can be distinguished, with high prognostic relevance (Weber et al. 1995, Sutliff et al. 1997, Yu et al. 1999, Gibril et al. 2001). In MEN1-related gastrinomas, aggressive disease is reported in 15% and in sporadic gastrinomas in ~25% (Yu et al. 1999, Gibril et al. 2001, Ito et al. 2013). In MEN1 patients, 5-year survival was 100% for patients with nonaggressive disease and 88% for patients with aggressive disease (Gibril et al. 2001). Factors found to be associated with aggressive disease were pancreatic tumor size, liver and bone metastases, markedly increased fasting gastrin level, and the presence of a gastric NET (Gibril et al. 2001).

Mitotic count or Ki67 labeling index has proved to be a very important prognostic factor in sporadic dpNETs (Ekeblad et al. 2008, Scarpa et al. 2010, Rindi et al. 2012), but no information is available for MEN1-related dpNETs.

With regard to the possible prognostic value of genotype, results are contradictory. Nonsense and frameshift mutations in exon 2, 9, and 10 were found to be associated with a more malignant dpNET phenotype (Bartsch et al. 2000, 2005) and inactivating and frameshift mutations showed a trend toward more frequent occurrence in deceased patients (Ito et al. 2013). Others did not find any relation between genotype and the course of dpNETs (Lairmore et al. 2000, Kouvaraki et al. 2002).

Molecular background of MEN1

Menin

The MEN1 gene product, menin, is highly conserved from nematodes and fruit flies to humans. Interestingly, the gene is absent in organisms like yeast and Caenorhabditis elegans. It is predominantly a nuclear protein, which is ubiquitously expressed in both endocrine and nonendocrine organs (Guru et al. 1998, Stewart et al. 1998, Ikeo et al. 2000). It has been challenging to elucidate its biological function, as menin lacks enzymatic activity and initially no homologous domains to other proteins were found. Abolition of menin during mouse embryogenesis is lethal at mid gestation and results in defects in neural tube, liver, and heart (Bertolino et al. 2003a). Its function is tissue-specific, sometimes showing opposite effects between different organs. Many interacting proteins involved in gene transcription and various signaling pathways have been identified (Matkar et al. 2013). Recently, the crystal structure of menin has been
endocrine-related cancer

GLI1 and JUND, with opposite effects on gene transcription (Huang et al. 2012). Further evidence supports a role for menin in DNA repair, through association with replication protein A2 (RPA2; Sukhodolets et al. 2003) and Fanconi anemia complementation group D2 protein (FANCD2; Jin et al. 2003). Subsequent functional experiments characterized menin both as an activator and a repressor of gene transcription. Growing evidence indicates that menin is involved in epigenetic regulation of gene transcription as menin has been shown to be part of chromatin-modifying protein complexes (Box 2). However, it is important to note that most studies focusing on menin interaction partners and its function were conducted in nonendocrine cell lines (Table 2).

Menin as an epigenetic repressor of gene transcription

Menin associates with proteins in removing acetylation marks from histones (Gobl et al. 1999, Kim et al. 2003). These histone deacetylases (HDACs) form complexes with menin through the general co-repressor mSin3A (Kim et al. 2003; Fig. 2A). Deacetylation of histones at promoters of target genes is associated with downregulation of gene transcription. GAST (gastrin) was identified as a potential target of menin/mSin3A/HDAC complexes (Mensah-Osman et al. 2011).

Recently, menin was shown to interact directly with protein arginine methyltransferase 5 (PRMT5), resulting in repression of the Hedgehog signaling pathway through increasing PRMT5-mediated dimethylation of arginine 3 on histone 4 (H4R3me2) at the GAS1 and GLI1 promoter (Gurung et al. 2013a,b; Fig. 2B). The Hedgehog signaling pathway is involved in various biological processes including (neuroendocrine) tumorigenesis (McMillan & Matsui 2012). Menin can be recruited to the promoter of the homeobox gene GBX2 through interaction with the histone lysine methyltransferase SUV39H1. This interaction induced H3K9 trimethylation at the gene promoter, providing the repressive chromatin environment for downregulation of GBX2 transcription (Yang et al. 2013; Fig. 2C).

Menin as an epigenetic activator of gene transcription

Menin stably associates with MLL1 and MLL2 (KMT2B)-containing protein complexes (Hughes et al. 2004, Yokoyama et al. 2004). The functional domain in MLL protein family members is the so-called SET domain that harbors histone methyltransferase activity for trimethylation toward lysine 4 of histone 3 (H3K4me3; Ruthenburg et al. 2007). H3K4me3 is associated with activation of gene transcription (Santos-Rosa et al. 2002, Guenther et al. 2007). MLL translocations leading to MLL1-fusion proteins are frequently seen in mixed lineage leukemia (Krivtsov & Armstrong 2007). In contrast to other menin interactors, the menin–MLL1/2 interactions are rather stable and have been detected in several cellular systems (Hughes et al. 2004, Yokoyama et al. 2004). The menin–MLL1/2 complexes induce trimethylation on H3K4, and menin disease-derived mutants fail to recruit histone methyltransferase activity (Hughes et al. 2004). Genome-wide analysis showed menin occupancy on promoters of many active genes, which is often accompanied with MLL1 or MLL2 and H3K4me3 (Saccheri et al. 2006, Agarwal & Jothi 2012). Menin–MLL1/2 complexes are positive regulators of several target genes, including genes of the HOX cluster (Hughes et al. 2004, Yokoyama et al. 2004).
and cyclin-dependent kinase (CDK) inhibitor genes (Milne et al. 2005) (Fig. 3A). HOX genes are characterized by a conserved DNA sequence, the homeobox. They encode homeodomain-containing TFs, which are essential in cell differentiation and the body plan during embryogenesis. Several HOX genes are identified as direct menin–MLL1/2 targets, such as HOXA9, Hoxc6, and Hoxc8 (Hughes et al. 2004, Yokoyama et al. 2004, Huang

<table>
<thead>
<tr>
<th>Reference</th>
<th>Protein complex</th>
<th>Cell type (origin)</th>
<th>Menin level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. (2012)</td>
<td>Menin–MLL1/2</td>
<td>Recombinant protein</td>
<td>Endogenous</td>
</tr>
<tr>
<td>van Nuland et al. (2013))</td>
<td>Menin–JUND</td>
<td>293T (human embryonic kidney)</td>
<td>Endogenous</td>
</tr>
<tr>
<td>Gobl et al. (1999)</td>
<td>Menin–JUND</td>
<td>Recombinant protein</td>
<td>Endogenous, overexpressed</td>
</tr>
<tr>
<td>Huang et al. (2012)</td>
<td>Menin–JUND</td>
<td>Recombinant protein</td>
<td>In vitro</td>
</tr>
<tr>
<td>Heppner et al. (2001)</td>
<td>Menin–NfkB</td>
<td>Cos7 (monkey kidney)</td>
<td>Overexpressed</td>
</tr>
<tr>
<td>Dreijerink et al. (2006)</td>
<td>Menin–ERα</td>
<td>CRC (human colorectal cancer)</td>
<td>Endogenous, overexpressed</td>
</tr>
<tr>
<td>Dreijerink et al. (2009)</td>
<td>Menin–PPARγ</td>
<td>Recombinant protein</td>
<td>In vitro</td>
</tr>
<tr>
<td>Gurung et al. (2013b)</td>
<td>Menin–PRMT5</td>
<td>293 (human embryonic kidney)</td>
<td>Overexpressed</td>
</tr>
<tr>
<td>Yang et al. (2013)</td>
<td>Menin–SUV39H1</td>
<td>293T (human embryonic kidney)</td>
<td>Endogenous, overexpressed</td>
</tr>
<tr>
<td>Shi et al. (2013)</td>
<td>Menin–Hlbx9</td>
<td>MIN6 (mouse insulinoma)</td>
<td>Endogenous, overexpressed</td>
</tr>
</tbody>
</table>

This table summarizes studies referred to in this review.

Figure 1
Chromatin structure and histone modifications. DNA is wrapped around octamers of histones into nucleosomes. Chromatin state is influenced by post-translational modifications of histone tails. These modifications are associated with chromatin accessibility for the effector proteins such as transcription factors and lead to an active or a repressed chromatin state. For simplicity, not all histone tails are represented in this figure. Adapted from the National Institutes of Health Common Fund Website, source: http://commonfund.nih.gov/epigenomics/figure.aspx, with permission.
et al. (2012). It was shown in pancreatic islet-like endocrine cells that HOX gene expression is regulated by menin through H3K4 methylation (Agarwal & Jothi 2012). Menin–MLL1 complexes stimulate the expression of CDKN1B and CDKN2C genes encoding p27Kip1 and p18Ink4c proteins respectively. Loss of function of menin or MLL1 resulted in downregulation of p27Kip1 and p18Ink4c and displayed effects on cell growth (Milne et al. 2005). p27Kip1 and p18Ink4c belong to two distinct families of CDK inhibitors which regulate cell-cycle progression (Besson et al. 2008). Reduced expression of these proteins...
contributes to tumor development in various tissues (Malumbres & Barbacid 2001).

**Recruitment of menin–chromatin modifying protein complexes to target genes**

Proteins can be recruited to gene promoters through specific interactions with DNA sequence-specific TFs. Menin stably interacts with the DNA sequence-specific TF JUND (Agarwal et al. 1999, Huang et al. 2012; Fig. 2A). Several MEN1-derived missense mutants failed to bind JUND efficiently in vitro and their repressive effect on transcription was lost (Agarwal et al. 1999). Interactions between menin and other TFs are less stable than menin–JUND interactions. Menin can be tethered to DNA through the nuclear receptor (NR) for estrogen ERz, the NR peroxisome-proliferator-activated receptor γ (PPARγ), and the vitamin D3 receptor (Dreijerink et al. 2006, 2009; Fig. 3B). NRs have the ability to bind DNA directly and translate changes in hormone levels into alterations in gene transcription. Transcriptional activation through menin–NR interactions is associated with H3K4me3 upregulation (Dreijerink et al. 2006, 2009). Furthermore, menin–MLL1/2 complexes are transcriptional co-activators of the Wnt-signaling pathway. Together with the TF CTNNB1 (β-catenin), the menin–MLL2 complex was shown to be recruited to the enhancer of the oncogene c-Myc (Sierra et al. 2006; Fig. 3C). Menin interacts and regulates NFKB1 (NF-κB) TFs (Heppner et al. 2001). Transforming growth factor β (TGFβ) signaling causes inhibition of proliferation in various cell types. Menin interacts with the TGFβ-regulated TF SMAD3. Inactivation of menin in pituitary cells disrupted SMAD3 binding to DNA, thereby blocking TGFβ signaling (Kaji et al. 2001). Recently, TF Hlx9β was shown to be a menin interaction partner specifically in mouse β-cells and to be involved in the regulation of β-cell proliferation rate and expression of insulin-modulating genes (Shi et al. 2013).

Besides DNA sequence-specific TF-mediated recruitment of menin–MLL1/2 complexes to target genes, interactions with chromatin-binding protein PC4 and SFRS1 interacting protein 1 (PSIP1) (also known as LEDGF/p75) are important for tethering these complexes to target genes. The transcription co-activator PSIP1 co-localizes with menin–MLL1 complexes at specific menin target genes, including HOXA9, CDKN1B, and CDKN2C (Yokoyama & Cleary 2008, Huang et al. 2012). The association of several menin mutants with PSIP1 was disrupted, resulting in reduced transcription of HOXA9 (Yokoyama & Cleary 2008).

**Contribution of menin loss to NET development**

Several studies have addressed the role of MEN1 in endocrine pancreatic cell function and proliferation. Absence of MEN1 does not seem to affect the initial pancreatic differentiation process from embryonic stem cells in vitro (Agarwal & Jothi 2012). β-cell specific disruption of MEN1 leads to the formation of insulinomas (Bertolino et al. 2003b, Crabtree et al. 2003, Biondi et al. 2004). α-cell-specific knockout of MEN1 was found to lead to transdifferentiation into insulin-producing cells and subsequent insulinoma development (Lu et al. 2010). Disturbance in epigenetic regulation of gene transcription is thought to contribute to MEN1-associated tumorigenesis. The most convincing evidence supporting this mechanism was reported recently (Lin et al. 2011). Mice with β-cell-specific knockout of MEN1 showed reduced tumor formation and increased survival in combination with gene knockout of the retinoblastoma-binding protein 2 (RBP2 also known as JARID1A, KDM5A), which is a histone demethylase for H3K4me2/3. This indicates that compensation of the loss of H3K4 trimethylation mark on certain target genes may restore the function of menin in pancreatic tumors. Identification of relevant menin target genes could provide further insights into the development of MEN1-related tumors. Currently, it is not clear how the tumor-suppressing roles of menin in cultured cells are related to suppression of MEN1-associated tumor development. HOX genes are important for the development of endocrine organs (Manley & Capecchi 1998). Comparison of HOX gene expression profiles in MEN1-associated parathyroid tumors and nonfamilial parathyroid tumors revealed differently expressed genes between these groups. This indicates a role for HOX genes in MEN1-associated parathyroid tumor development (Shen et al. 2008). This has not been shown for other NETs. Several animal studies support that menin target genes CDKN1B and CDKN2C are involved in endocrine tumorigenesis. p27kip1 or p18ink4c-deficient mice develop pituitary tumors and hyperplasia in multiple organs, including the thymus, without elevation in GH levels (Fero et al. 1996, Kiyokawa et al. 1996, Nakayama et al. 1996, Franklin et al. 1998). Strikingly, mice lacking both p27kip1 and p18ink4c developed hyperplasia and/or tumors predominantly in endocrine organs including the pancreas and duodenum. The tumor spectrum seen in these mice showed a remarkable overlap with the tumor spectrum seen in MEN1 patients (Franklin et al. 2000). Inactivating germline mutations in CDKN1B have been identified in patients with a MEN-like phenotype.
Although, hyperparathyroidism and pituitary tumors are the most commonly described manifestations (Pellegata et al. 2006, Georgitsi et al. 2007), pNETs have also been described in association with CDKN1B mutations (Agarwal et al. 2009, Occhi et al. 2013). Based on these studies, a role for p27kip1 and p18ink4c in MEN1-related tumor development seems reasonable. Menin–MLL1/2 complexes inhibit proliferation of pancreatic islet cells in mice by promoting H3K4me3 and transcription of p27kip1 and p18ink4c (Karnik et al. 2005). Interestingly, p18ink4c and menin collaborate in repressing development and growth rate of mouse pNETs. This synergetic effect was not observed with p27kip1 (Bai et al. 2007). Studies focusing on p27kip1 protein and mRNA expression in pNETs from MEN1 patients show conflicting results (Milne et al. 2005, Lindberg et al. 2008, Occhi et al. 2013).

### Tissue selectivity in MEN1-related tumorigenesis

Regarding the ubiquitous expression of menin, it is difficult to explain the tissue selectivity of tumorigenesis in MEN1 patients. Unfortunately, most studies focusing on menin interaction partners and its target genes are performed in nonendocrine cell lines (Table 2 and Supplementary Table 1, see section on supplementary data given at the end of this article). Menin acts as a tumor suppressor in endocrine organs, but it is an essential oncogenic cofactor in leukemogenesis (Yokoyama et al. 2005, Yokoyama & Cleary 2008). Understanding the predominance for endocrine tumor development resulting from MEN1 loss might help to develop targeted therapies for MEN1 patients. Several factors have been suggested as potential important players in the tissue selectivity of this endocrine tumor syndrome (Gracanin et al. 2009). Tissues may differ in their ability and requirement to compensate for the loss of one MEN1 allele (Gracanin et al. 2009). Physiological regulation of menin levels in response to increased insulin was shown to be important in adaptive β-cell proliferation during pregnancy in mice (Karnik et al. 2007). Intriguingly, mice with liver-specific loss of menin did not develop tumors (Scacheri et al. 2004). The expression levels of menin in lymphoblastic cell lines derived from MEN1 patients did not differ from healthy controls (Wautot et al. 2000) and downregulation of menin could activate the MEN1 promoter in a compensatory manner in nonendocrine cell lines (Zablewska et al. 2003). However, it has been suggested that menin haploinsufficiency through loss of one Men1 allele contributes to pNET development in mice (Crabtree et al. 2003, Lejonklou et al. 2012). In regard to tissue-specific regulation of menin expression, microRNAs are interesting candidates for further evaluation (Gracanin et al. 2009, Luzi & Brandi 2011). Menin interaction partners might be involved in the tissue-specific tumor formation in MEN1. For example, the TF HLXB9 was shown to be a β-cell-specific menin interaction partner (Shi et al. 2013). NRs are also potential candidates as they have tissue-specific functions.

### Implications for further research

Although in the past decade significant progress has been made in understanding menin function, many questions remain. Its tumor-suppressive role in endocrine organs is not well understood and elucidation of underlying biology should be an important focus for future studies. Regarding the observed tissue selectivity in MEN1-related tumorigenesis, it is important to study menin–protein interactions and target genes in endocrine cell lines specifically. To date, most studies addressing menin interactions and target genes were performed in nonendocrine cell lines. Not only basic research projects but also translational studies in unbiased MEN1 patient cohorts are needed. These studies should clarify which molecular pathways involving menin actually contribute to MEN1 NET tumorigenesis and are clinically relevant. With regard to novel therapeutic strategies, the involvement of altered epigenetic regulation of gene expression resulting in MEN1 tumorigenesis is an interesting candidate for further evaluation. The development of compounds that interfere with epigenetic regulation of gene transcription has gained a lot of attention recently and such drugs have shown to have therapeutic potential in cancer treatment (Dawson & Kouzarides 2012). These findings highlight the importance of better insights into MEN1 tumorigenesis for the improvement of MEN1 patient care.

From a clinical point of view, identifying natural course and prognostic factors has been hampered by the rarity of the disease and generally low number of events regarding distant metastases and disease-related mortality. Therefore, it is important to follow large unselected cohorts over a long period of time, by national or even international collaboration.

When comparing natural history of MEN1-related NETs with their sporadic counterparts, insulinomas in MEN1 seem to be more aggressive, while natural history in MEN1-related gastrinomas seems to be similar to sporadic gastrinomas. Data on NF-pNETs and thoracic NETs are insufficient to permit comparisons. However, currently...
available evidence does not support MEN1-related NETs to be more indolent than sporadic NETs.

Among MEN1-related NETs, thNETs occur with low frequency and show a remarkable gender difference. Compared with other NETs, their prognosis is poor. These different epidemiologic and natural history characteristics cannot be explained with the currently available evidence and warrants further research.

Pulmonary carcinoids and NF-pNETs in MEN1 share the fact that they are more common than previously thought. Identification of these NETs will further increase in the coming decade due to increased sensitivity of imaging techniques and standardized screening. As little is known about the natural history of small NETs in MEN1, clinical significance of these findings remains to be determined. To assist clinical decision-making in this respect, studies with a long-term follow-up in unselected patient cohorts are needed.

All dpNETs are potentially malignant and dpNETs are the most important determinant of long-term survival in MEN1 patients. Although the estimated 10-year survival rate is 75%, it is important to remember that MEN1-patients are usually in their thirties when these tumors develop. Moreover, unless a total duodenopancreatectomy is performed, MEN1 patients are always at risk for developing new dpNETs and subsequent malignant transformation. This means that a satisfactory 10-year survival rate does not automatically equal normal life expectancy. Although, the percentage of MEN1 patients with dpNETs that develop distant metastases is small, prognosis is poor in this group. At present, apart from tumor size, there are no known clinical or tumor characteristics that reliably predict the development of distant metastases. This means that the impact of therapeutic interventions has to be weighed against the overall change of distant metastases and disease-related mortality. Identification of additional clinical and molecular prognostic factors in MEN1-related dpNETs should therefore be an important research focus. Factors known to be of prognostic value in sporadic dpNETs should be validated in MEN1 and new prognostic indicators sought for. These efforts should lead to early identification of tumors with an aggressive phenotype and subsequent individualized patient care based on risk stratification.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-13-0482.

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