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# Multiple Endocrine Neoplasia Type 4: A New Member of the MEN Family

## A systematic review

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### KEY WORDS

Multiple endocrine neoplasia type 4 – CDKN1B – parathyroid gland – pituitary gland

## ABSTRACT

**Objective:** Multiple endocrine neoplasia type 4 (MEN4) is caused by a *CDKN1B* germline mutation first described in 2006. Its estimated prevalence is less than 1/million. The aim of this study was to define the disease characteristics.

**Methods:** Systematic review according to the PRISMA 2020 criteria. MEDLINE® and Web of Science™ search from January 2006 to August 2022.

**Results:** Forty-eight symptomatic patients fulfilled the pre-defined eligibility criteria. Twenty-eight different *CDKN1B* variants, mostly missense (21/48, 44%) and frameshift mutations (17/48, 35%), were reported. The majority of patients were women (36/48, 75%). Men became symptomatic at a median age of 32.5 years (range 10-68, mean 33.7 ± 23), whereas the same event was recorded for women at a median age of 49.5 years (range 5-76, mean 44.8 ± 19.9) ( $p = 0.25$ ). The most frequently affected endocrine organ was the parathyroid gland (36/48, 75%; uniglandular disease 31/36, 86%), followed by the pituitary gland (21/48, 44%; hormone-secreting 16/21, 76%), the endocrine pancreas (7/48, 15%) and the thyroid gland (4/48, 8%). Tumours of the adrenal glands and thymus were found in three and two patients, respectively. The presenting first endocrine pathology concerned the parathyroid (27/48, 56%) and the pituitary gland (11/48, 23%). There were one (27/48, 56%), two (13/48, 27%), three (3/48, 6%), or four (5/48, 10%) syn- or metachronously affected endocrine organs in a single patient, respectively.

**Conclusion:** MEN4 is an extremely rare disease, which most frequently affects women around 50 years of age. Primary hyperparathyroidism as a uniglandular disease is the leading pathology.

## INTRODUCTION

Multiple endocrine neoplasia (MEN) is a rare group of autosomal dominant disorders with a wide spectrum of endocrine and non-endocrine manifestations (Table 1). Five different types of MEN have been described so far: MEN1, MEN2 (formerly MEN2A), MEN3 (formerly MEN2B), the recently identified MEN4 [1, 2, 3, 4] and MEN5 [5, 6]. The penetrance is varied and the phenotypic expression is heterogeneous, thereby leading to different manifestations of the syndrome even within members of the same family [2, 5, 7, 8].

The prevalence of MEN1 is estimated to lie between 1/10'000 and 1/30'000, whereas the prevalence of MEN2 is approximately 1/35'000 [9, 10] ([www.orpha.net](http://www.orpha.net), last access 1 September 2022). MEN3 is about 20 times less frequent than MEN2, which amounts to an estimated prevalence of 1/500'000 [11, 12]. The newly described MEN4 syndrome is extremely rare and its prevalence is probably less than 1/million ([www.orpha.net](http://www.orpha.net), last access 1 September 2022). MEN5 presents another very rare syndrome, the incidence of which has not yet been established [5].

MEN1 is the most frequent syndrome. The underlying germline mutation is a heterozygous loss-of-function of the tumour suppressor gene *MEN1*. Affected patients present with primary hyperparathyroidism (PHPT), functional or non-functional pancreatic neuroendocrine tumours (pNETs) and pituitary adenomas [13, 14]. However, about 10-30% of patients with a MEN1-like phenotype do not show any alterations of the *MEN1* gene [7, 15, 16].

In 2002, Fritz and co-workers first described an autosomal recessive MEN-like syndrome in the rat. Animals exhibiting the mutant phenotype spontaneously developed multiple neuroendocrine malignancies within the first year of life with a high penetrance. These included bilateral adrenal pheochromocytoma, multiple extra-adrenal pheochromocytomas, bilateral medullary thyroid cell neoplasia, bilateral parathyroid hyperplasia and pituitary adenoma. The appearance of these tumours was preceded by the development of bilateral juvenile cataracts. All animals tested negative for mutations of the *MEN1* and *RET* gene. The causative genetic defect initially remained unknown and the syndrome was termed MENX [17].

Eventually, in 2006, Pellegata and co-workers discovered the underlying mutation of this novel MEN syndrome [1]. The mutation was not only described in rats, but the first human case was reported. The syndrome is caused by an inactivating germline mutation of the cyclin-dependent kinase (CDK) inhibitor 1b gene (*CDKN1B*), a gene coding for the nuclear protein p27<sup>kip1</sup>, commonly referred to as p27 or KIP1. It is a putative tumour suppressor gene regulating cell cycle progression, notably the progression from the G1 to the S phase. Mutations of *CDKN1B* result in a truncated p27 protein, which is unstable and rapidly degraded [18, 19]. It exhibits a reduced binding capacity to interacting partners and its concentration within the nucleus is reduced [2]. Immunohistochemical staining of the tissue of affected patients often show a delocalization from the nucleus to the cytoplasm or they

completely fail to detect expression of the p27 protein [1, 18, 20, 21, 22, 23, 24, 25]. The incidence of *CDKN1B* mutations in patients with a MEN1-like phenotype, testing negative for the *MEN1* and the *RET* gene, is likely to be in the range of 1.5 to 3.7% [20, 21, 26]. The *CDKN1B* germline mutation has an autosomal dominant inheritance pattern in humans. In 2008, the novel human MENX syndrome, caused by the *CDKN1B* germline mutation, was renamed MEN4 during the 11<sup>th</sup> International Workshop on Multiple Endocrine Neoplasia in Delphi, Greece [4]. Up until 2017, only 19 cases of MEN4 had been reported in medical literature [2]. The clinical penetrance and precise tumour spectrum of MEN4 is still poorly defined.

The present study constitutes a systematic review of MEN4. A patient from our hospital was included.

## MATERIALS AND METHODS

### **Case presentation**

A 54 year-old woman from our hospital underwent medical therapy for macroprolactinoma, focused parathyroidectomy for primary hyperparathyroidism and total thyroidectomy for multifocal papillary thyroid carcinoma. The patient displayed a MEN1-like phenotype, however, no pathogenic MEN1 gene mutation was found. Genetic analysis identified a previously unreported variant in exon 1 of the *CDKN1B* gene (c.349C>T, p.P117S) [27] ([www.ncbi.nlm.nih.gov/clinvar/variation/493111](http://www.ncbi.nlm.nih.gov/clinvar/variation/493111), last access 1 September 2022). So far, it was classified as a variant of unknown clinical significance according to the standards and guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [28]. In the present clinical context, the diagnosis of MEN4 was established.

### **Systematic review**

A literature search (MEDLINE®, [www.PubMed.gov](http://www.PubMed.gov), Web of Science™) on MEN4 was carried out. A systematic review was performed in accordance with the PRISMA 2020 criteria [29]. Figure 1 provides the PRISMA flow chart [8, 30, 31, 32]. The search terms “MEN4”, “MENX” and “CDKN1B” were used. The full search strategy is shown in Table S1 (supporting information). All records from 1 January 2006 to 31 August 2022 were scrutinized. The start of the search predates the first description of MEN4 in humans. The last search update was performed on September 1, 2022. Additional records were identified from citation searching. After excluding duplicates, the records were screened by two reviewers independently (H.S., P.R.), according to the inclusion and exclusion criteria shown in Table S2 (supporting information). The two reviewers independently analyzed the remaining records, as full-text articles. Twenty studies were eventually included in the review. Data concerning phenotype and genotype of all published symptomatic cases of MEN4 patients, as well as of all asymptomatic carriers of the pathogenic *CDKN1B* mutations, were collected. The characteristics of the included studies are detailed in Table S3 (supporting information). Table A (supplemental online material) provides detailed information on the data retrieved. The collected data was cross-checked by the two assessors.

### **Statistical methods**

Data were captured on a spread sheet (Microsoft Excel®). Categorical data were presented as frequencies and percentages. Age was presented as median with range and mean  $\pm$  standard deviation (sd). Age was compared between asymptomatic carriers and symptomatic patients, female and male patients at first presentation and symptomatic female and symptomatic male patients with a Welch t-test (R Statistics, version 4.2.2)

## RESULTS

From 2006 to August 2022, 20 publications with 64 patients met the inclusion criteria [1, 15, 18, 20, 21, 22, 26, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45]. Including the patient from our hospital, 65 cases were available for further analysis. Table A (supplemental online material) provides detailed information on the published data.

There were 48 symptomatic patients (median age 43.5 years, range 5-76, mean  $42.2 \pm 20.8$ ) and 17 asymptomatic carriers (median age 47.5 years, range 16-76, mean  $49.3 \pm 17.8$ ) ( $p = 0.26$ ). All asymptomatic carriers were first-degree relatives of and shared the same pathogenic *CDKN1B* variants with the related symptomatic index patients. Twenty-four symptomatic patients were described as isolated sporadic cases. Whereas, the remaining 24 symptomatic patients were reported in families with at least two members carrying the same genetic variant. The latter 24 symptomatic patients were found in a total of 11 families. In each family a different *CDKN1B* variant was described. The median number of affected family members was three (range 2-13).

There were 47 women (47/65, 72%) and 16 men (16/65, 25%). In two instances, no gender information was available (2/65, 3%). The age at first presentation for symptomatic patients and the age at the time of diagnosis for asymptomatic carriers was provided for women in 35 instances (median 49 years, range 5-76, mean  $46.3 \pm 19.2$ ) and for men in 11 instances (median 34 years, range 10-70, mean  $36.9 \pm 22.2$ ) ( $p = 0.22$ ). There were 28 different *CDKN1B* variants. The majority were missense (29/65, 45%) and frameshift (22/65, 34%) alterations. To a lesser extent nonsense (8/65, 12%) and small deletions (6/65, 9%) were found. In one case report the underlying *CDKN1B* mutation was not specified (1/65, 2%). For further analysis, all asymptomatic carriers of a *CDKN1B* variant were excluded. Table 2 provides an overview of the remaining 48 symptomatic MEN4 patients with a proven underlying *CDKN1B* mutation.

The majority of patients were women (36/48, 75%). The median age for presentation of the first endocrine disorder was 43.5 years (range 5-76). Men became symptomatic at a median age of 32.5 years (range 10-68, mean  $33.7 \pm 23$ ), whereas the same event was recorded for women at a median age of 49.5 years (range 5-76, mean  $44.8 \pm 19.9$ ) ( $p = 0.25$ ). There were one (27/48, 56%), two (13/48, 27%), three (3/48, 6%), or four (5/48, 10%) syn- or metachronously affected endocrine organs in a single patient, respectively.

The most frequently affected endocrine organ was the parathyroid gland (75%), followed by the pituitary gland (44%), the endocrine pancreas (15%), the thyroid gland (8%), the adrenal gland (6%) and the thymus (4%).

Thirty-six patients presented with PHPT as the leading endocrine disorder (36/48, 75%). In five patients either multi-glandular (5/36, 14%) and/or recurrent disease (2/36, 6%) was diagnosed. Most patients were women (29/36, 81%) and the median age at diagnosis of PHPT was 51 years (range 15-74).

Twenty-one patients presented with an adenoma of the pituitary gland (21/48, 44%). The adenoma was non-functioning in five patients and hormone secreting in 16 patients (7x ACTH, 5x prolactin, 4x growth hormone). Ten patients presented with a pituitary microadenoma (<1 cm), five patients with a pituitary macroadenoma and in six instances the size of the adenoma was not specified. Most patients were women (16/21, 76%) and the median patient age at presentation was 39 years (range 5-79).

Nine patients (9/48, 19%) presented with gastroenteropancreatic neuroendocrine tumours (GEP-NET). There were four patients with a non-functional NET of the pancreas (1x metastatic, 1x non-metastatic, 2x non-metastatic multifocal), three patients with gastrinoma of the pancreas (Zollinger-Ellison syndrome, 2x metastatic, 1x non-metastatic) and two patients with a NET of the stomach (non-metastatic) and ileum (metastatic), respectively. Four patients presented with papillary thyroid carcinoma (4/48, 8%), of which three were multifocal. All patients were women and the median age was 57.5 years (range 55-64). There were three patients with tumours of the adrenal gland (1x bilateral nonfunctioning, 1x bilateral with suspicion of cyclic cortisol secretion, 1x unilateral with subclinical cortisol secretion) and two patients with tumours the thymus (1x thymic hyperplasia causing myasthenia gravis, 1x atypical carcinoid tumour causing ectopic Cushing's syndrome). Finally, one patient presented with a carcinoid tumor of the lungs (metastatic) and an angiomyolipoma of the kidney was found in two patients.

The presenting endocrine disease for each patient was reviewed. The leading first endocrine pathologies concerned the parathyroid (27/48, 56%) and the pituitary gland (11/48, 23%). In two instances the thymus was the presenting organ (2/48, 4%). In one patient each, the first affected organ was the thyroid gland, the stomach, the ileum and the pancreas (4/48, 8%). Finally, in four patients two or more endocrine organs were simultaneously diagnosed as being diseased (4/48, 8%).

## DISCUSSION

The 2022 WHO Classification of Tumors of the Endocrine Organs describes 15 syndromes associated with endocrine lesions and tumours [5]. Three new syndromes have been added to the last edition of 2017, namely MEN4, MEN5 and MAFA-related insulinomatosis. MEN syndromes now include five entities, MEN1-5.

### ***Clinical definition of MEN***

Patients with tumours of two or more endocrine organs fulfill the diagnostic criteria of MEN. Furthermore, a familial MEN is defined by the presence of an index patient and the identification of at least one first-degree relative with a tumor in one or more endocrine organs or tissues, known to be classically affected in MEN syndromes [26].

### ***Genetic definition of MEN***

There is an ever-expanding understanding of the genetic basis of diseases. This also holds true for MEN. MEN1 is caused by a germline mutation of the tumour suppressor gene *MEN1*, which is composed of ten exons encoding the 610 amino-acid protein menin [15]. A germline mutation of the proto-oncogene *RET* (rearranged in transfection), on the other hand, is responsible for the MEN2 and MEN3 syndromes. In contrast to MEN1, the type of *RET* mutation strongly correlates with its phenotype. Additionally, there is MEN4, which is the result of a germline mutation of a tumor suppressor gene called cyclin-dependent kinase (CDK) inhibitor 1b (*CDKN1B*). Finally, MEN5 is related to a germline mutation of a tumor suppressor gene named MYC-associated factor X (*MAX*) [6].

### ***The rationale for a systematic review***

Pellegata and co-workers described the first human case of *CDKN1B* related MEN4 in 2006 [1]. Since then, there has been a constant trickle of case reports only slowly increasing our understanding of this new entity.

In 2019, Frederiksen published a literature review on MEN4. They identified 30 mutation positive patients representing 16 different pathogenic *CDKN1B* variants. The authors added a further 13 mutation-positive members of a large Danish family to the list [34].

The present study is the first systematic review on MEN4 according to the PRISMA 2020 criteria [29]. We identified 65 individuals displaying 28 different pathogenic *CDKN1B* variants. There were 17 asymptomatic carriers of the mutation and 48 symptomatic patients with at least one endocrine disorder.

### ***Phenotypic similarities between MEN1 and MEN4***

There is substantial phenotypic overlap between MEN1 and MEN4. Prior to the identification of the underlying *CDKN1B* mutation in MEN4, most patients were probably misclassified as



MEN1. In 10-30% of clinical MEN1 cases, no variant of the more than 400 *MEN1* mutations can be found [15, 16]. Identifiable germline mutations of the *MEN1* gene can be found in approximately 80% of familial MEN1 syndromes, but only in about 30% of sporadic MEN1 syndromes [26]. The remainder of MEN1 patients, being negative for the *MEN1* mutation, are due to other still to be identified tumour-susceptibility gene mutations. Approximately 3% of patients displaying a MEN1-like phenotype but testing negative for *MEN1* mutations are reported to have mutations in the causative *CDKN1B* gene [1, 15, 18, 20, 21, 22, 26, 32, 33], reclassifying these patients as belonging to the MEN4 syndrome [32, 44].

### ***Clinical presentation of MEN1 and MEN4***

The phenotypic characteristics of MEN4 are still ill defined due to the limited number of published cases. The multitude of underlying genetic mutations may further contribute to clinical diversity. In fact, the present systematic review listed no less than 28 different *CDKN1B* variants in 48 symptomatic MEN4 patients.

Parathyroid adenomas are the most frequent tumours in both MEN1 and MEN4, with a prevalence of about 85% and 80%, respectively. In MEN1, PHPT manifests in early adulthood with an almost even gender distribution [3, 7, 8, 14]. In contrast, MEN4 not only displays a clear female predominance (81%), but also manifests about two decades later [1, 18, 20, 21, 22, 26, 33]. The median age of presentation of 51 years for women coincides with the hormonal changes of menopause, which have been implicated in the pathogenesis of PHPT by altering p27kip1 levels [18, 46]. PHPT in MEN1 is an overwhelmingly multiglandular disease with a high recurrence rate, even after routine subtotal (three-and-a-half) gland resection [3, 7, 8, 14]. In the present systematic review of MEN4, only a minority of patients presented with multiglandular (14%) or recurrent disease (6%). Simple excision of the single enlarged parathyroid gland (focused parathyroidectomy) might therefore be an appropriate surgical approach for MEN4 patients.

Pituitary adenomas are the second and third most frequent endocrine tumours in MEN4 and MEN1, respectively. For MEN1, this percentage amounts to 20% for clinically apparent adenomas and up to 40% if adenomas detected by hormonal testing or MRI screening are included [3, 7, 8, 14, 47]. With regards to MEN4, the present systematic review reported pituitary adenomas in 44% of patients. In MEN1 patients, the pituitary adenomas are mostly lactotroph, followed by somatotroph, corticotroph, gonadotroph as well as non-functioning. A similar hormonal distribution is found for MEN4 patients in the present systematic review. Pituitary adenomas in MEN1 are mostly macroadenomas (80%), whereas in MEN4 we report a 2 to 1 ratio in favor of pituitary microadenomas. In MEN1, pituitary adenomas display an aggressive biologic behavior. Normalization of the hormonal hypersecretion after treatment occurs in less than 50% of patients [3, 8, 9, 14, 47]. Given the paucity of data, no conclusion concerning treatment and treatment success in MEN 4 patients can be drawn.

Pancreatic islet cell and gastroduodenal neuroendocrine tumours are the second most common endocrine pathology in MEN1 [13]. They become manifest in 30% to 80% of patients. GEP-NETs often present with multifocality and a propensity to metastasize. Surgery is often extensive with a high risk of recurrence. Due to their malignant potential, they are the leading pathology determining the patient's outcome *quoad vitam* [13, 14, 34].

As for MEN4, the present systematic review found GEP-NETs in just 19% of patients. However, four out of nine patients presented with metastatic disease.

### ***Two different diagnostic pathways***

MEN syndromes are clinically defined by the affection of *two or more* endocrine organs in one specific individual. Such a cluster of endocrine diseases in a single person will eventually raise the suspicion of an underlying genetic mutation. A *positive family history* will further underline the need for genetic testing.

The *CDKN1B* mutation as a causative factor for MEN was first described in humans in 2006 [1]. Since then, genetic testing for the *CDKN1B* mutation was also performed for patient cohorts with just a *single* endocrine pathology and a *negative family history* [36, 37, 40, 42]. These are patients, who do not fulfill the clinical criteria for MEN syndromes. Such "screening" studies led to the identification of additional MEN4 patients, who were included in the present systematic review.

Costa-Guda et al. studied somatic mutations and germline sequence abnormalities in the *CDKN1B* gene in 86 patients with sporadic parathyroid adenomas [36]. Two germline mutations were identified. A similar study by Borsari et al. investigated 147 patients with sporadic parathyroid adenomas for *CDKN1B* gene mutations finding three pathologic germline variants [42]. Tichomirowa et al. performed a *CDKN1B* germline analysis in 124 *AIP* mutation-negative familial isolated pituitary adenoma (FIPA) kindreds [37]. Two *CDKN1B* germline mutation carriers were identified. Finally, Chasseloup et al. studied germline *CDKN1B* loss-of-function variants in mostly pediatric Cushing's disease patients with or without a MEN4 phenotype [40]. Five variants of interest were found.

### ***Genetic testing for CDKN1B mutations***

A distinction has to be made between patients clinically presenting with MEN and their asymptomatic relatives. All patients with the clinical diagnosis of MEN should be tested for mutations of the *MEN1* and *RET* genes, in accordance with the leading endocrine tumors. If negative, then testing of the *CDKN1B* and *MAX* genes should be considered (next generation sequencing). Genetic testing for asymptomatic relatives should be stratified according to the mutation found in the symptomatic index patient (Sanger sequencing). In general, genetic testing can be offered if it confers a substantial benefit to the asymptomatic carrier of the genetic alteration in terms of disease prevention or prognosis. As for MEN1,

such a benefit has only been shown with regard to prophylactic thymectomy for thymic NET [2, 14]. With regards to MEN2 and MEN3, the potential benefit of germline *RET* testing has been proven far greater. Prophylactic surgery for medullary thyroid carcinoma and pheochromocytoma provides a clear survival benefit to carriers of certain *RET* germline mutations [48]. Due to the paucity of data on MEN4 and MEN5, no guidelines currently exist with regard to genetic testing of asymptomatic relatives.

In general, genetic testing and counseling for MEN should be performed by an experienced and specially qualified team. The MEN syndromes are transmitted in an autosomal dominant fashion. Therefore, each sibling carries a 50% risk of having the mutation. A negative genetic test result will offer reassurance to those who do not carry the mutation and prevents unnecessary clinical, biochemical and radiological screenings [2]. A positive genetic test result, on the other hand, should ensure inclusion into a surveillance program according to the risk profile of the respective MEN syndrome.

### ***Strengths and weaknesses of the systematic review***

Despite the comprehensive literature search, only 48 symptomatic MEN4 patients were available for the final analysis. Due to the paucity of data, the results and conclusions drawn have to be interpreted with caution.

Firstly, it has to be noted that, of this whole collective, thirteen patients belong to one large Danish family (13/48, 27%). This relative preponderance of one single family may have led to a certain distortion of the data [34].

Secondly, some further bias may result from the fact that a quarter of all patients (12/48, 25%) were derived from large *CDKN1B* “screening” studies of populations with a single endocrine pathology and a negative family history [36, 37, 40, 42]. The inclusion of patients with a single endocrine neoplasm may have had an influence on the prevalence data concerning the respective endocrine pathologies.

Despite all the shortcomings, the present study allows for a more precise description of the phenotypic manifestations of MEN4. In particular, it enabled a more detailed elaboration of the clinical differences to the somewhat similar MEN1 syndrome. Eventually, it also provides a listing of the underlying genetic variants.

### ***Conclusions***

MEN4, first described in 2006, is still a very rare disease with only a few dozen cases reported in the literature. The underlying genetic alternations and the phenotypic manifestations are still poorly defined. Therefore, the establishment of evidence based management guidelines remains difficult. The present systematic review showed that MEN4 most frequently affects women around 50 years of age with uniglandular primary

hyperparathyroidism presenting as the leading pathology. A MEN4 registry and future larger scale systematic reviews are needed.

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## FIGURE LEGEND

### Figure 1

PRISMA flow chart for the literature search. MEN: multiple endocrine neoplasia

**Declaration of interest**

No conflict of interest.

**Funding**

The authors received no financial funding.

**Registration**

The study was not registered.

**Consent**

Written informed consent was obtained from the patient.

**Table 1**

## Multiple endocrine neoplasia (MEN) type 1-5

	<b>MEN1</b>	<b>MEN2</b>	<b>MEN3</b>	<b>MEN4</b>	<b>MEN5</b>
Alternative Nomenclature	Wermer syndrome	MEN2A Sipple syndrome	MEN2B Gorlin-Vickers / Williams-Pollock / Wagenmann-Froboese syndrome	---	---
OMIM®	#1311000	#171400	#162300	#610755	---
Gene	<i>MEN1</i>	<i>RET</i>		<i>CDKN1B</i>	<i>MAX</i>
Location	11q13.1	10q11.21		12p13.1	14q23.3
Inheritance	autosomal-dominant	autosomal-dominant		autosomal-dominant	autosomal-dominant
Encoded protein	Menin	RET		p27	MAX
Leading tumour (Prevalence %)	PHPT (85%)	Medullary thyroid cancer (95-100%)		PHPT (80%)	Pheochromocytoma
Further manifestations	pNET: gastrinoma, insulinoma (30-80%)	Pheochromocytoma (50%)		Pituitary adenoma (40%)  Thyroid cancer pNET: non-functional, gastrinoma Lung cancer Cervical cancer Testicular cancer	Paraganglioma Pituitary adenoma Ganglioneuroma Ganglioneuroblastoma PHPT
	Pituitary adenoma (30-50%)	PHPT (20-30%)  FMTC	Ganglioneuroma of the lips, tongue and colon Marfanoid habitus (95%)		

OMIM® Online Mendelian Inheritance in Man®  
*RET* rearranged in transfection (proto-oncogene)  
*CDKN1B* cyclin-dependent kinase (CDK) inhibitor 1b gene (tumor suppressor gene)  
*MAX* MYC-associated factor X (tumor suppressor gene)  
 PHPT primary hyperparathyroidism  
 pNET pancreatic neuroendocrine tumours  
 FMTC familial medullary thyroid cancer

**Table 2**Genotype and phenotype of published symptomatic cases of *CDKN1B* mutated MEN4

(In order of the year of publication, age at the time of presentation in parenthesis)

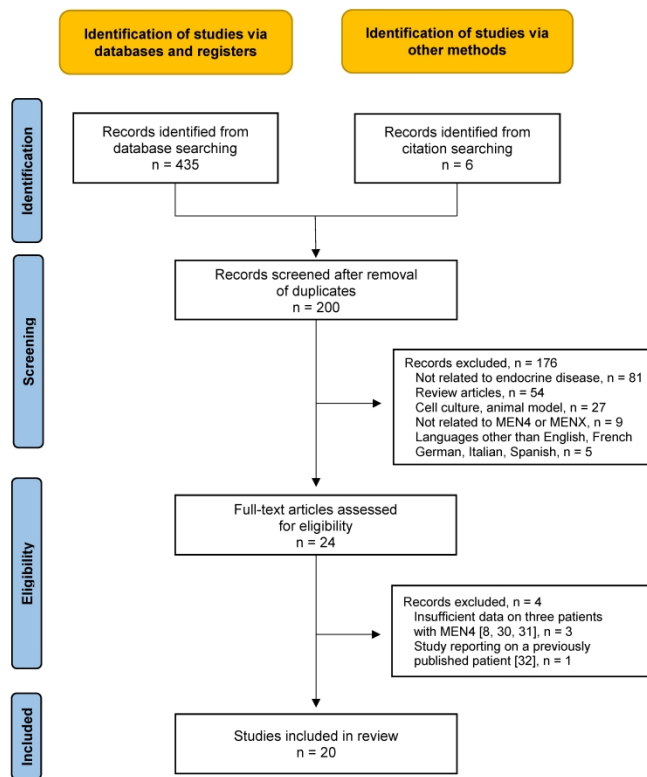
Ref.	M/F	Age*	Mutation	Type*	Parathyroid gland	Pituitary gland	Endocrine pancreas	Thyroid gland
1	F	30	c.G692A, p.W76*	NS	PHPT (46)	adenoma, GH (30)		
20	F	45	c.59_77dup19	FS	PHPT (47)	adenoma, ACTH (46)		
26	F	61	c.-7G>C	MS	PHPT (61)			
26	F	50	c.283c>T, p.P95S	MS	PHPT, mg (50)		gastrinoma, ZES (50)	
26	F	50	c.595T>C, p.*199Qext60	NS	PHPT, mg (50)			
26	F	66	c.595T>C, p.*199Qext60	NS	PHPT, ug (66)			
21	F	64	c.678C>T, p.P69L	MS	PHPT (67)	adenoma, nf (79)		papillary cancer (64)
36	M	68	c.25G>A, p.G9R	MS	PHPT (68)			
36	F	53	c.397C>A, p.P133T	MS	PHPT (53)			
15	F	42	c.163G>A, p.A55T	MS	PHPT (51)		gastrinoma, m, ZES (42)	
37	F	NA	c.286A>C, p.K96Q	MS		adenoma, PRL (NA)		
37	F	NA	c.356C>T, p.I119T	MS		adenoma, GH (NA)		
33	F	69	c.-32_-29delGAGA	SD	PHPT (74)			
22	F	62	c.-456_-453delCCTT	SD		adenoma, GH (62)	NET, nf (62)	
18	F	41	c.374_375delCT, p.S125*	FS	PHPT, mg, r (41, 50, 55)	hyperprolactinemia (56)	gastrinoma, m, ZES (50)	
38	F	15	c.378G>C, p.E126D	MS	PHPT (15)			
41	F	5	c.-29_-26delAGAG	SD		adenoma, GH (5)		
39	F	56	c.397C>A, p.P133T	MS	PHPT (56)			papillary cancer, mf (56)
42	M	38	c.-80C>7	MS	PHPT, mg (38)			
42	F	61	c.-29_-26delAGAG	SD	PHPT, ug (61)			
42	F*	49	c.397C>A, p.P133T	MS	PHPT, ug (49)			
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)			
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)		NET, nf (67)	
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)	adenoma, nf (66)		
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)			
34	M	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)	adenoma, nf (64)		
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)			
34	M	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)	adenoma, nf (46)		
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)			
34	F	36	c.121_122delTT, p.L41Nfs*83	FS	PHPT (36)	adenoma, ACTH (37)		

34	M	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)		
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)		
34	F	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)		
34	M	NA	c.121_122delTT, p.L41Nfs*83	FS	PHPT (NA)		
35	M	65	c.285dupC, p.K96Qfs*29	FS	PHPT, ug (65)		
40	M	11	c.407A>G, p.D136G	MS		adenoma, ACTH (11)	
40	F	9	c.376G>C, p.E126Q	MS		adenoma, ACTH (9)	
40	F	10	c.356T>C, p.I119T	MS		adenoma, ACTH (10)	
40	M	13	c.320delA, p.Q107Rfs*12	FS		adenoma, ACTH (12)	
40	M	10	c.-29_-26delAGAG	SD		adenoma, ACTH (10)	
45	F	35	c.281C>T, p.P94L	MS	PHPT (51)	hyperprolactinemia (NA)	papillary cancer, mf (55)
45	F	66	c.206C>T, p.P69L	MS	PHPT (66)	adenoma, nf (66)	
43	M	34	c.356T>C, p.I119T	MS			
43	F	76	c.482C>G, p.S161C	MS		NET, nf, mf, (NA)	
44	F	33	c.179G>A, p.Trp60*	NS	PHPT, mg, r (33, 45)	adenoma, PRL (39)	NET, nf, mf (47)
44	F	26	c.475G>A, p.D159N	MS	PHPT (26)		
44	M	31	c.374_375delCT, p.S125*	NS			
PC	F	54	c.349C>T, p.P117S	MS	PHPT (59)	adenoma, PRL (54)	papillary cancer, mf (59)

\* simultaneous MEN1 germline mutation: c.1621G>A, p.A541T

Ref.	reference	mg	multiglandular
M	male	ug	uniglandular
F	female	r	recurrent
Age*	age at the time of presentation of the first endocrine disease	GH	growth hormone
Type*	type of mutation	ACTH	adrenocorticotrop hormone
MS	missense mutation	PRL	prolactin
FS	frameshift mutation	nf	non-functioning
NS	nonsense mutation	mf	multifocal
SD	small deletion	ZES	Zollinger Ellison syndrome
NA	not available	m	metastatic
PC	present case	NET	neuroendocrine tumour
PHPT	primary hyperparathyroidism		

**Figure 1**  
PRISMA diagram for the systematic review



MEN multiple endocrine neoplasia

**Figure 1**  
PRISMA diagram for the systematic review

126x178mm (1000 x 1000 DPI)

**Table S1**Search syntax

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Database: MEDLINE® (www.PubMed.gov), Web of Science™

Search:	“MEN4”	182 hits
	“MENX”	136 hits
	“MEN4 and CDKN1B”	63 hits
	“MENX and CDKN1B”	54 hits
	Total	435 hits

Search period: 1 January 2006 to 31 August 2022

Last search update: 1 September 2022



**Table S2**Inclusion and exclusion criteria (screening and eligibility)

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- Inclusion criteria:
- MENX with CDKN1B mutation
  - MEN4 with CDKN1B mutation
  - Human study
  - All ages
  - All types of articles (original article, case series, case report, review article with case report, letter to the editor)
  - Publication in English, French, German, Italian, Spanish
  - Detailed case description of symptomatic patients.
- Data on the following three categories must be available:
- Gender (male/female)
  - Affected endocrine organs
  - Mutation (genotype)
- Exclusion criteria:
- Publication not related to MEN4 or MENX
  - Cell culture
  - Animal model
  - Review article
  - Publication in languages other than English, French, German, Italian, Spanish
  - Insufficient case description of symptomatic patients.
- No data on at least one of the following categories:
- Gender (male/female)
  - Affected endocrine organs
  - Mutation (genotype)

**Table S3**

## Characteristics of included studies

Study	Country	Year <sup>1</sup>	Study <sup>2</sup>	Study description	Symptomatic patients (n)
Pellegata et al. [1]	Germany	2006	OA	Case report, genetic analysis in rats and one patient	1
Georgitsi et al. [20]	Finland, multiple countries	2007	OA	Retrospective analysis of 37 suspected MEN1 and 69 acromegaly patients	1
Agarwal et al. [26]	USA	2009	OA	Retrospective analysis of 196 suspected MEN1 patients	4
Molatore et al [21]	Germany, Italy	2010	OA	Retrospective analysis of 27 suspected MEN1 patients	1
Costa-Guda et al [36]	USA, Germany	2011	OA	Retrospective analysis of 86 patients with sporadic parathyroid adenomas	2
Belar et al. [15]	Spain	2012	OA	Retrospective analysis of 79 suspected MEN1 patients	1
Tichomorowa et al. [37]	Belgium, multiple countries	2012	OA	Retrospective analysis of 124 <i>AIP</i> mutation-negative FIPA patients	2
Malanga et al. [33]	Italy, Spain	2012	OA	Retrospective analysis of 15 suspected MEN1 patients	1
Occhi et al. [22]	Italy, UK, Germany	2013	OA	Case report, genetic analysis	1
Tonelli et al. [18]	Italy	2014	CR	Case report, short review	1
Elston et al. [38]	New Zealand	2015	CR	Case report	1
Samburgaro et al. [41]	Italy, Germany	2015	CR	Case report, genetic analysis	1
Bugalho et al. [39]	Portugal	2016	CR	Case report	1
Borsari et al. [42]	Italy, Germany	2017	OA	Retrospective analysis of 147 patients with sporadic parathyroid adenomas	3
Frederiksen et al. [34]	Denmark, UK	2019	OA	Case series, short review	13
Brock et al. [35]	USA	2020	CR	Case report	1
Chasseloup et al. [40]	USA, multiple countries	2020	OA	Retrospective analysis of 211 pediatric patients with Cushing's disease	5
Chevalier et al. [45]	France	2020	L	Case report	2
Lavezzi et al. [43]	Italy	2022	CR	Case report, short review	2
Seabrook et al. [44]	Australia	2022	CR	Case report	3

Year <sup>1</sup>	year of publication
Study <sup>2</sup>	type of study
OA	original article
CR	case report
L	letter to the editor
<i>A/P</i>	aryl hydrocarbon receptor interacting protein gene
FIPA	familial isolated pituitary adenoma

Table A  
Supplemental online material

	A	B	C	D	E	F	G	H	I
1	First author	Year	Index patients / carriers	Index patient (IP) / relatives	Family	Mutation (original from publications)	Mutation (uniformly rewritten by Adamczyk)	Type of mutation	Gender
2	Pellegata et al. [1]	2006	Symptomatic index patient	IP	family 1	c.692G>A (p.W76X)	c.G692A, p.W76*	Nonsense	F
3	Pellegata et al. [1]	2006	Asymptomatic carrier	sister of IP	family 1	c.692G>A (p.W76X)	c.G692A, p.W76*	Nonsense	F
4	Pellegata et al. [1]	2006	Asymptomatic carrier	sister of IP	family 1	c.692G>A (p.W76X)	c.G692A, p.W76*	Nonsense	F
5	Pellegata et al. [1]	2006	Asymptomatic carrier	niece of IP	family 1	c.692G>A (p.W76X)	c.G692A, p.W76*	Nonsense	F
6	Georgitsi et al. [20]	2007	Symptomatic index patient	IP	-	c.59_77dup19 (fsK25)	c.59_77dup19, p.K25fs (in ClinVar p.S27fs)	Frameshift	F
7	Agarwal et al. [26]	2009	Symptomatic index patient	IP	family 2	p27ATG-7G>C	c.-7G>C	missense mutation in 5'UTR	F
8	Agarwal et al. [26]	2009	Asymptomatic carrier	daughter of IP	family 2	p27ATG-7G>C	c.-7G>C	missense mutation in 5'UTR	F
9	Agarwal et al. [26]	2009	Asymptomatic carrier	daughter of IP	family 2	p27ATG-7G>C	c.-7G>C	missense mutation in 5'UTR	F
10	Agarwal et al. [26]	2009	Symptomatic index patient	IP	-	p27P95S	c.283c>T, p.P95S	Missense	F
11	Agarwal et al. [26]	2009	Symptomatic index patient	twins	family 3	p27Stop>Q	c.595T>C, p.*199Qext60	Nonsense	F
12	Agarwal et al. [26]	2009	Symptomatic index patient	twins	family 3	p27Stop>Q	c.595T>C, p.*199Qext60	Nonsense	F
13	Molatore et al [21]	2010	Symptomatic index patient	IP	-	c.678C>T, (p.P69L)	c.678C>T, p.P69L	Missense	F
14	Costa-Guda et al [36]	2011	Symptomatic index patient	IP	-	c.25G>A (p.G9R), Gly9Arg	c.25G>A, p.G9R	Missense	M
15	Costa-Guda et al [36]	2011	Symptomatic index patient	IP	-	c.397C>A, p. Pro133Thr	c.397C>A, p.P133T	Missense	F
16	Belar et al. [15]	2012	Symptomatic index patient	IP	-	c.163G>A, (p.A55T)	c.163G>A, p.A55T	Missense	F
17	Tichomorowa et al. [37]	2012	Symptomatic index patient	IP	family 4	c.286A>C, (p.K96Q)	c.286A>C, p.K96Q	Missense	F
18	Tichomorowa et al. [37]	2012	Asymptomatic carrier	sister of IP	family 4	c.286A>C, (p.K96Q)	c.286A>C, p.K96Q	Missense	F
19	Tichomorowa et al. [37]	2012	Symptomatic index patient	IP	-	c.356T>C, (p.I119T)	c.356T>C, p.I119T	Missense	F
20	Malanga et al. [33]	2012	Symptomatic index patient	IP	-	c.-32_-29delGAGA in 5' UTR	c.-32_-29delGAGA	Small deletion in 5'UTR	F
21	Occhi et al. [22]	2013	Symptomatic index patient	IP	-	c.-456_-453delCCTT in 5' UTR	c.-456_-453delCCTT	Small deletion in 5'UTR	F
22	Tonelli et al. [18]	2014	Symptomatic index patient	IP	family 5	c.374_375delCT (p.S125X)	c.374_375delCT, p.S125*	Frameshift	F
23	Tonelli et al. [18]	2014	Asymptomatic carrier	son of IP	family 5	c.374_375delCT (p.S125X)	c.374_375delCT, p.S125*	Frameshift	M
24	Elston et al. [38]	2015	Symptomatic index patient	IP	family 6	c.378G>C, (p.E126D)	c.378G>C, p.E126D	Missense	F
25	Elston et al. [38]	2015	Asymptomatic carrier	mother of IP	family 6	c.378G>C, (p.E126D)	c.378G>C, p.E126D	Missense	F
26	Elston et al. [38]	2015	Asymptomatic carrier	maternal grandfather of IP	family 6	c.378G>C, (p.E126D)	c.378G>C, p.E126D	Missense	F
27	Samburgaro et al. [41]	2015	Symptomatic index patient	IP	family 7	c.-29_-26delAGAG	c.-29_-26delAGAG	Small deletion in 5'UTR	F
28	Samburgaro et al. [41]	2015	Asymptomatic carrier	mother of IP	family 7	c.-29_-26delAGAG	c.-29_-26delAGAG	Small deletion in 5'UTR	F
29	Bugalho and Domingues [39]	2016	Symptomatic index patient	IP	-	c.397C>A, Pro133Thr	c.397C>A, p.P133T	Missense	F
30	Borsari et al. [42]	2017	Symptomatic index patient	IP	-	c.-80C>7	c.-80C>7	missense mutation in 5'UTR	M
31	Borsari et al. [42]	2017	Symptomatic index patient	IP	-	c.-29_-26delAGAG	c.-29_-26delAGAG	Small deletion in 5'UTR	F
32	Borsari et al. [42]	2017	Symptomatic index patient	IP	-	p.P133T(c.397C>A)	c.397C>A, p.P133T	Missense	F
33	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F

Table A  
Supplemental online material

	A	B	C	D	E	F	G	H	I
34	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
35	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
36	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
37	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	M
38	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
39	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	M
40	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
41	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
42	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	M
43	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
44	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	F
45	Frederiksen et al. [34]	2019	Symptomatic index patient	IP	family 8	c.121_122delTT, p.Leu41Asnfs*83	c.121_122delTT, p.L41Nfs*83	Frameshift	M
46	Brock et al. [35]	2020	Symptomatic index patient	IP	-	c.285dupC, p.Lys96Glnfs*29	c.285dupC, p.K96Qfs*29	Frameshift	M
47	Chasseloup et al. [40]	2020	Symptomatic index patient	IP	-	c.407A>G, p.D136G	c.407A>G, p.D136G	Missense	M
48	Chasseloup et al. [40]	2020	Symptomatic index patient	IP	-	c.376G>C, p.E126Q	c.376G>C, p.E126Q	Missense	F
49	Chasseloup et al. [40]	2020	Symptomatic index patient	IP	-	c.356T>C, (p.I119T)	c.356T>C, p.I119T	Missense	F
50	Chasseloup et al. [40]	2020	Symptomatic index patient	IP	family 9	c.320delA, p.Q107Rfs*12	c.320delA, p.Q107Rfs*12	Frameshift	M
51	Chasseloup et al. [40]	2020	Asymptomatic carrier	mother of IP	family 9	c.320delA, p.Q107Rfs*12	c.320delA, p.Q107Rfs*12	Frameshift	F
52	Chasseloup et al. [40]	2020	Asymptomatic carrier	brother of IP	family 9	c.320delA, p.Q107Rfs*12	c.320delA, p.Q107Rfs*12	Frameshift	M
53	Chasseloup et al. [40]	2020	Asymptomatic carrier	child of IP	family 9	c.320delA, p.Q107Rfs*12	c.320delA, p.Q107Rfs*12	Frameshift	NA
54	Chasseloup et al. [40]	2020	Asymptomatic carrier	child of IP	family 9	c.320delA, p.Q107Rfs*12	c.320delA, p.Q107Rfs*12	Frameshift	NA
55	Chasseloup et al. [40]	2020	Symptomatic index patient	IP	-	c.-29_-26delAGAG	c.-29_-26delAGAG	Small deletion in 5'UTR	M
56	Chevalier et al. [45]	2020	Symptomatic index patient	IP	-	c.281C>T, p.(Pro94Leu)	c.281C>T, p.P94L	Missense	F
57	Chevalier et al. [45]	2020	Symptomatic index patient	IP	-	c.206C>T, p.(Pro69Leu)	c.206C>T, p.P69L	Missense	F
58	Lavezzi et al. [43]	2022	Symptomatic index patient	IP	family 10	p.I119T (c.356T>C)	c.356T>C, p.I119T	Missense	M
59	Lavezzi et al. [43]	2022	Asymptomatic carrier	brother of IP	family 10	p.I119T (c.356T>C)	c.356T>C, p.I119T	Missense	M
60	Lavezzi et al. [43]	2022	Asymptomatic carrier	father of IP	family 10	p.I119T (c.356T>C)	c.356T>C, p.I119T	Missense	M
61	Lavezzi et al. [43]	2022	Symptomatic index patient	IP	family 11	c.482C>G (p.S161C)	c.482C>G, p.S161C	Missense	F
62	Lavezzi et al. [43]	2022	Asymptomatic carrier	sister of IP	family 11	c.482C>G (p.S161C)	c.482C>G, p.S161C	Missense	F
63	Seabrook et al. [44]	2022	Symptomatic index patient	IP	-	c.179G>A, p.Trp60Ter	c.179G>A, p.Trp60*	Nonsense	F
64	Seabrook et al. [44]	2022	Symptomatic index patient	IP	-	c.475G>A, p.Asp159Asn	c.475G>A, p.D159N	Missense	F
65	Seabrook et al. [44]	2022	Symptomatic index patient	IP	-	c.374_375delCT (p.Ser125*)	c.374_375delCT, p.S125*	Nonsense	M
66	<b>Present case</b>	-	Symptomatic index patient	IP	-	p.Pro117Ser (c.349C>T)	c.349C>T, p.P117S	Missense	F

Table A  
Supplemental online material

	J	K	L
1	Age at first presentation	Parathyroid/ pituitary/endocrine pancreas/thyroid phenotype (neoplasms) (age at diagnosis)	Neoplasms of the parathyroid gland (age)
2	30	PHPT (46), GH-secreting invasive pituitary macroadenoma (30)	PHPT (46)
3	55		
4	44		
5	teenage girl, approx. 16		
6	45	PHPT (47), ACTH secreting pituitary adenoma -> cushing disease (46)	PHPT (47)
7	61	PHPT (61)	PHPT (61)
8	47		
9	48		
10	50	PHPT (50), multiglandular, Zollinger Ellison syndrome, masses in duodenum and tail of pancreas (50)	PHPT (50), multiglandular
11	50	PHPT (50), multiglandular	PHPT (50), multiglandular
12	66	PHPT (66), uniglandular	PHPT (66), uniglandular
13	64	PHPT (67), non-functioning pituitary microadenoma (79), papillary thyroid cancer (64)	PHPT (67)
14	68	PHPT (68)	PHPT (68)
15	53	PHPT (53)	PHPT (53)
16	42	PHPT (51), Zollinger-Ellison syndrome with gastrinoma and hepatic metastases (42)	PHPT (51)
17	NA	Prolactin secreting pituitary macroadenoma (NA)	
18	NA		
19	NA	GH secreting pituitary adenoma (NA)	
20	69	PHPT (74)	PHPT (74)
21	62	GH secreting pituitary adenoma (62), nonfunctional endocrine pancreatic neoplasm (62)	
22	41	PHPT (41, 50, 55), multiglandular and recurrent, dopamine agonist Tx for high prolactin levels (56), Zollinger-Ellison, pancreatic tumor (metastatic gastrinoma) (50)	PHPT (41, 50, 55), multiglandular and recurrent
23	35		
24	15	PHPT (15)	PHPT (15)
25	46		
26	74		
27	5	GH-secreting pituitaryadenoma (5)	
28	approx. 50		
29	56	PHPT (56), multifocal papillary thyroid carcinoma (56)	PHPT (56)
30	38	PHPT (38), multiglandular	PHPT (38), multiglandular
31	61	PHPT (61), uniglandular	PHPT (61), uniglandular
32	49	PHPT (49), uniglandular	PHPT (49), uniglandular
33	NA	PHPT (NA)	PHPT (NA)

Table A  
Supplemental online material

	J	K	L
34	NA	PHPT (NA), neuroendocrine tumor (carcinoid) in pancreas (67)	PHPT (NA)
35	NA	PHPT (NA), non-functioning pituitary microadenoma (66)	PHPT (NA)
36	NA	PHPT (NA)	PHPT (NA)
37	NA	PHPT (NA), non-functioning pituitary microadenoma (64)	PHPT (NA)
38	NA	PHPT (NA)	PHPT (NA)
39	NA	PHPT (NA), non-functioning pituitary macroadenoma (46)	PHPT (NA)
40	NA	PHPT (NA)	PHPT (NA)
41	36	PHPT (36), ACTH-producing pituitary microadenoma (37)	PHPT (36)
42	NA	PHPT (NA)	PHPT (NA)
43	NA	PHPT (NA)	PHPT (NA)
44	NA	PHPT (NA)	PHPT (NA)
45	NA	PHPT (NA)	PHPT (NA)
46	60ies, = 65	PHPT (65), uniglandular	PHPT (65), uniglandular
47	11	ACTH secreting pituitary microadenoma, 3 mm (11)	
48	9	ACTH secreting pituitary microadenoma, 5 mm (9)	
49	10	ACTH secreting pituitary microadenoma, 8 mm (10)	
50	12.5	ACTH secreting pituitary microadenoma. 4 mm (12)	
51	NA		
52	NA		
53	NA		
54	NA		
55	10	ACTH secreting pituitary microadenoma, 3 mm (10)	
56	35	PHPT (51), hyperprolactinemia, adenoma not detected at MRI (NA), multifocal papillary thyroid carcinoma (55)	PHPT (51)
57	66	PHPT (66), non-functioning pituitary macroadenoma (66)	PHPT (66)
58	34		
59	31		
60	70		
61	76	multifocal pancreatic G1-NET (NA)	
62	76		
63	33	PHPT (33, 45), multiglandular and recurrent, Prolactin secreting pituitary microadenoma (39), multifocal pancreatic NET (47)	PHPT (33, 45), multiglandular and recurrent
64	26	PHPT (26)	PHPT (26)
65	31		
66	54	PHPT (59), Prolactin secreting pituitary macroadenoma (54), multifocal papillary thyroid carcinoma (59)	PHPT (59)

Table A  
Supplemental online material

	M	N	O
1	Neoplasms of the pituitary gland (age)	Neoplasms of the endocrine pancreas (age)	Neoplasms of the thyroid gland (age)
2	GH-secreting invasive pituitary macroadenoma (30)		
3			
4			
5			
6	ACTH secreting pituitary adenoma -> cushing disease (46)		
7			
8			
9			
10		Zollinger Ellison syndrome, masses in duodenum and tail of pancreas (50)	
11			
12			
13	non-functioning pituitary microadenoma (79)		papillary thyroid cancer (64)
14			
15			
16		Zollinger-Ellison syndrome with gastrinoma and hepatic metastases (42)	
17	Prolactin secreting pituitary macroadenoma (NA)		
18			
19	GH secreting pituitary adenoma (NA)		
20			
21	GH secreting pituitary adenoma (62)	nonfunctional endocrine pancreatic neoplasm (62)	
22	dopamine agonist Tx for high prolactin levels (56)	Zollinger-Ellison, pancreatic tumor = metastatic gastrinoma (50)	
23			
24			
25			
26			
27	GH-secreting pituitary adenoma (5)		
28			
29			multifocal papillary thyroid carcinoma (56)
30			
31			
32			
33			



Table A  
Supplemental online material

	M	N	O
34		neuroendocrine tumor (carcinoid) in pancreas (67)	
35	non-functioning pituitary microadenoma (66)		
36			
37	non-functioning pituitary microadenoma (64)		
38			
39	non-functioning pituitary macroadenoma (46)		
40			
41	ACTH-producing pituitary microadenoma (37)		
42			
43			
44			
45			
46			
47	ACTH secreting pituitary microadenoma, 3 mm (11)		
48	ACTH secreting pituitary microadenoma, 5 mm (9)		
49	ACTH secreting pituitary microadenoma, 8 mm (10)		
50	ACTH secreting pituitary microadenoma, 4 mm (12)		
51			
52			
53			
54			
55	ACTH secreting pituitary microadenoma, 3 mm (10)		
56	Hyperprolactinemia, adenoma not detected at MRI (NA)		multifocal papillary thyroid carcinoma (55)
57	non-functioning pituitary macroadenoma (66)		
58			
59			
60			
61		multifocal pancreatic G1-NET (NA)	
62			
63	Prolactin secreting pituitary microadenoma (39)	multifocal pancreatic NET (47)	
64			
65			
66	Prolactin secreting pituitary macroadenoma (54)		multifocal papillary thyroid carcinoma (59)

Table A  
Supplemental online material

	P	Q
1	Neoplasms of the adrenal and thymus (age)	Various diseases (age)
2		
3		renal angiomyolipoma (55)
4		
5		
6		small-cell neuroendocrine cervical carcinoma (45), multiple sclerosis (46)
7	bilateral adrenal mass nonfunctioning (63)	uterine fibroids (NA)
8		
9		
10		
11		
12		
13		bronchial carcinoid tumor (67), diabetes mellitus type 2 (NA), subcutaneous epigastric lipoma (67)
14		
15		
16		
17		breast cancer (age 41)
18		
19		
20		gastric carcinoid tumor (69)
21		
22		Hashimoto/hypothyroidism (41), multiple G1 NET tumor of the duodenal wall (52), uterine fibroids (43)
23		
24		
25		
26		
27		
28		
29		Hürthle cell adenoma (56), uterine leiomyoma (NA), grade II cerebral meningioma (NA)
30		
31		
32		autoimmune hypothyroidism (NA), fibrocystic breast disease (NA)
33		benign lung tumor (NA)

Table A  
Supplemental online material

P	Q
34	hypothyroidism (NA)
35	
36	goiter (NA)
37	
38	breast cancer (diagnosis in autopsy, died age 77)
39	
40	hirsutism (NA)
41	polycystic ovarian syndrome (30)
42	
43	polycystic ovarian syndrome (NA)
44	
45	
46	neurofibromatosis type 1 (NA), prostate cancer with transition into metastatic small cell cancer (in his 60ies)
47	
48	
49	diabetes mellitus type 2 (NA), hypertension (NA)
50	Gilbert syndrome (NA), transient ischemic attack (NA), right hydrocele and left epididymal cyst(NA)
51	hypertension (NA), diabetes mellitus type 2 (NA), hypercholesterolemia (NA), colon adenocarcinoma (NA)
52	
53	
54	
55	
56	myasthenia gravis requiring thymectomy (12) breast cancer (37), ovarian serous cystadenoma (50), Sjögren syndrome (NA)
57	subclinical cortisol autonomous secretion by adrenal adenoma (NA) autoimmune thyroiditis (NA), Crohn's disease (56)
58	metastatic ileal G2-NET (metastases to LN and liver) (NA)
59	
60	
61	
62	
63	benign cortical adrenal adenoma (47)
64	polycystic ovarian syndrome (NA)
65	atypical thymic carcinoid tumor causing ectopic Cushing's syndrome (31) diabetes mellitus type 2 (31)
66	angiomyolipoma left kidney (59), multiple small subpleural nodules (59)

Table A  
Supplemental online material

	R
1	<b>Site of metastases of GEP-NET and lung NET</b>
2	
3	
4	
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6	
7	
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9	
10	pancreatic NET (gastrinoma): no metastases reported (no information on treatment/surgery)
11	
12	
13	lung NET: bilateral multiple lung metastases (patient underwent resection of the lung tumors)
14	
15	
16	pancreatic NET (gastrinoma): hepatic metastases (no information on treatment/surgery)
17	
18	
19	
20	gastric NET: no metastases reported (no information on treatment/surgery)
21	pancreatic NET (non-functional): no metastases reported (G1 tumor, no information on treatment/surgery)
22	pancreatic NET (gastrinoma): liver metastases (CT, MRI, OctreoScan/SSRS), surgery 2 years later: multifocal G1 NET of duodenal wall, N1 (1/33), intraoperative no liver metastases
23	
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Table A  
Supplemental online material

	R
34	pancreatic NET (non-functional): metastatic (site of metastases and treatment not reported)
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43	
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57	
58	ileal NET: multiple metastases to the lymph nodes, mesentery, and liver (G2 tumor, patient underwent ileal resection)
59	
60	
61	pancreatic NET (non-functional, multifocal): no metastases (G1 tumor, patient underwent pancreatic resection)
62	
63	pancreatic NET (non-functional, multifocal): no metastases (G1 tumor, patient underwent pancreatic resection)
64	
65	
66	

Table A  
Supplemental online material

S	
1	<b>Family history</b>
2	Father acromegaly, no mutation analysis (died). Brother died from hypertension (39) (pheochromocytoma not excluded), no mutation analysis done. Sister angiomyolipoma
3	Patient is sister of index patient. Son: testicular cancer (28)
4	Mother of asymptomatic carrier. Sister of index.
5	Daughter of asymptomatic carrier.
6	First-degree relatives free from MEN1 related lesions.
7	
8	
9	
10	Family not reachable
11	Monozygotic twin with PHPT (66), maternal aunt (52) and cousin (NA) with PHPT: genetically not tested.
12	Identical twin
13	
14	
15	
16	
17	Sister is carrier, asymptomatic
18	
19	Maternal aunt with acromegaly, not tested genetically
20	
21	
22	Two children not tested (35, 28), asymptomatic. 2 sisters + 1 brother: no symptoms. 1 sister: diabetes. 1 brother: hypertension + heart failure (67). 1 sister not tested (69)
23	
24	Mother (46), maternal grandfather (74): both mutation positive, no symptoms.
25	
26	
27	
28	
29	
30	
31	
32	Simultaneous MEN1 germline mutation: c. 1621G>A, Ala541Thr
33	

Table A  
Supplemental online material

	S
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46	First- and second-degree relative with clinical diagnosis of NF-1. Lymphangioliomyomatosis, thyroid cancer, bladder cancer, lymphoma, colon cancer, leukemia, prostate cancer
47	
48	Multiple family members with diabetes and hypertension.
49	
50	Mother: hypertension, diabetes mellitus type 2, deceased due to colon cancer, carrier of CDKN1b variant. Brother and 2 children: healthy carriers.
51	
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