Virchows Arch (2007) 451 (Suppl 1):S29–S38
DOI 10.1007/s00428-007-0450-3

REVIEW AND PERSPECTIVE

Hereditary neuroendocrine tumors of the gastroenteropancreatic system

Martin Anlauf · Nele Garbrecht · Juliane Bauersfeld · Anja Schmitt · Tobias Henopp · Paul Komminoth · Philipp U. Heitz · Aurel Perren · Günter Klöppel

Received: 11 June 2007 / Accepted: 11 June 2007 / Published online: 8 August 2007

Abstract Approximately 5–10% of neuroendocrine tumors (NETs) of the gastroenteropancreatic system (GEP) have a hereditary background. The known inherited syndromes include multiple endocrine neoplasia type 1, neurofibromatosis type 1, von Hippel–Lindau disease, and the tuberous sclerosis complex. This review discusses for each of these syndromes the: (1) involved genes and specific types of mutations, (2) disease prevalence and penetrance, (3) affected neuroendocrine tissues and related clinical syndromes, (4) special morphological features of NETs and their putative precursor lesions. In addition, GEP-NETs clustering in individual families or associated with other malignancies without known genetic background are discussed.

Keywords Neuroendocrine tumors · Pancreas · Gut · Hereditary syndromes · Multiple endocrine neoplasia type 1 · Neurofibromatosis · Tuberous sclerosis complex · von Hippel–Lindau disease · Gastrinoma · Insulinoma

M. Anlauf (✉) · N. Garbrecht · J. Bauersfeld · T. Henopp · G. Klöppel
Department of Pathology, University of Kiel,
Michaelisstr. 11,
24105 Kiel, Germany
e-mail: manlauf@path.uni-kiel.de

A. Schmitt · P. U. Heitz · A. Perren
Department of Pathology, University Hospital Zürich,
Zurich, Switzerland

P. Komminoth
Institute of Pathology, Triemli Spital,
Zurich, Switzerland

A. Perren
Department of Pathology, Munich University of Technology,
Munich, Germany

Introduction

Hereditary cancer susceptibility is more frequent and variable in tumors of endocrine organs than in any other category of human neoplasms. Often, a variety of endocrine and nonendocrine tissues are involved, resulting in complex clinical syndromes.

In the digestive tract, approximately 5–10% of neuroendocrine tumors (NETs) have a hereditary background. Inherited tumor syndromes include multiple endocrine neoplasia type 1 (MEN1), neurofibromatosis type 1 (NF1), von Hippel–Lindau disease (VHL), and the tuberous sclerosis complex (TSC). In this article, we focus for each of these syndromes on: (1) the involved genes and specific types of mutations, (2) the disease prevalence and penetrance, (3) the affected neuroendocrine tissues and the related clinical syndromes, and (4) the morphological features of the respective NETs and their putative precursor lesions. In addition, suspected hereditary backgrounds [e.g., association with other malignancies, familial clustering of gastroenteropancreatic system (GEP)-NETs] are discussed.

Multiple endocrine neoplasia type 1

MEN1 is an autosomal-dominant disorder characterized by multifocal endocrine tumors affecting the anterior pituitary, parathyroids, stomach, duodenum, pancreas, adrenal cortex, thymus, and lungs. In addition, various uncommon tumoral lesions may occur in the skin, central nervous system, and soft tissues [12, 57].

The *MEN1* gene is localized on chromosome 11q13 and consists of 10 exons spanning approximately 9 kb of genomic sequence and encoding a 68-kDa protein of 610 amino acids, named menin [12, 15, 57] (Table 1). Menin is

Table 1 Genetic and clinicopathological features of MEN1 and NF1

	MEN1	NF1
Function	Tumor suppressor gene	Tumor suppressor gene
Chromosomal location	11q13	17q11.2
Gene structure	10 exons (~9 kb)	>50 exons (~300 kb)
Protein	Menin (610 amino acids)	Neurofibromin (2,818 amino acids)
Mode of inheritance	Autosomal-dominant (10% de novo)	Autosomal-dominant
Prevalence	~1:20,000–1:40,000	~1:2,000–1:5,000
Penetrance	>95% (at age 50)	~100% (in childhood)
Diagnosis	According to WHO clinical criteria (genetic testing of family members recommended)	According to WHO clinical criteria (genetic testing not recommended)
Intestinal tract		
NETs	Multiple duodenal gastrinomas	Duodenal NETs (somatostatin)
Penetrance	20–60%	~1%
Functional activity	Zollinger–Ellison syndrome	No
Malignancy	Early metastases	~20% metastases
Pancreas		
NETs	Macrotumors and microadenomatosis	Somatostatin/insulin-producing NETs or functionally active insulinomas (case reports)
Penetrance	30–70% (>90% microadenomas)	
Functional activity	Nonfunctioning>insulinoma>PETs with ectopic hormone production	
Malignancy	<10% metastases	<20% metastases
Other GEP tumors	ECL cell tumors (associated with ZES)	GIST (often multiple)
	Esophageal leiomyomas (rare)	Neurofibroma
Tumors or endocrine hyperfunction outside the GEP	Primary hyperparathyroidism, anterior pituitary adenoma, adrenocortical tumor, thymic and bronchial NET, cutaneous lipoma and angiofibroma	*Cafe au lait* macules, neurofibroma, plexiform neurofibroma, MPNST, pheochromocytoma, optic/brain stem gliomas, bone lesions, renal artery stenosis, congenital glaucoma

NETs Neuroendocrine tumors, *GEP* gastroenteropancreatic system, *MEN1* multiple endocrine neoplasia type 1, *WdNEC* well-differentiated neuroendocrine carcinoma (defined by presence of lymph node metastases or infiltrative growth in the outer smooth muscle layers), *ECL* enterochromaffin-like, *PETs* pancreatic endocrine tumors, *ZES* Zollinger–Ellison syndrome, *NF1* neurofibromatosis type 1, *GIST* gastrointestinal stroma tumor, *MPNST* malignant peripheral nerve sheath tumor

a cell cycle-regulated nuclear protein. Menin is assumed to play an important role in pathways controlling cell growth and differentiation during embryogenesis and postnatal life. To date, menin has been shown to interact with numerous proteins involved in regulation of transcription, DNA replication, mitosis, apoptosis, genome integrity, growth factor signaling pathways, and extracellular matrix organization [12, 57]. However, it remains still unresolved why *MEN1* mutations affect primarily endocrine tissues.

The prevalence of the MEN1 syndrome has been estimated to be between 1:20,000 and 1:40,000. In approximately 10% of patients, MEN1 germline mutations arise de novo without any family history [8, 12, 15] (Table 1). The *MEN1* germline mutations are found spread over the entire exonic and intronic sequences and are not clustered in hotspots. Approximately 60% are truncating mutations, either frameshift (~40%) or nonsense (~20%) mutations; 20% are missense mutations; 10% are in-frame deletions or insertions, and about 10% are intronic and splice-site mutations. Large germline deletions encompassing the whole *MEN1* locus have also been detected [12, 14, 15]. A stringent genotype/phenotype relation correlation could not be demonstrated. Among patients meeting the clinical criteria of a MEN1 syndrome, approximately 10% have no identifiable mutations [43]. Most MEN1-associated tumors show somatic loss of the wild-type allele (loss of heterozygosity; LOH) on chromosome 11q13, consistent with the role of *MEN1* as a tumor suppressor gene [6, 26, 54, 66].

Twenty to 60% of MEN1 patients suffer from a Zollinger–Ellison syndrome (ZES), characterized by elevated fasting gastrin serum levels, a positive secretin stimulation test, and clinical symptoms such as recurrent peptic ulcer disease, gastroesophageal reflux disease, and occasionally, diarrhea [44, 87]. The gastrinomas observed in MEN1 are almost exclusively localized in the duodenum (Table 1). They are multiple and are associated with multifocal gastrin cell hyperplasia and tiny gastrin-producing microtumors. Despite their small size of 0.3 to 5 mm, the gastrinomas tend to metastasize to regional lymph nodes [3, 4, 67]. In addition, the duodenum harbors multiple tiny somatostatin cell neoplasms and multifocal somatostatin cell hyperplasia [6] (Fig. 1). Recently, molecular studies have

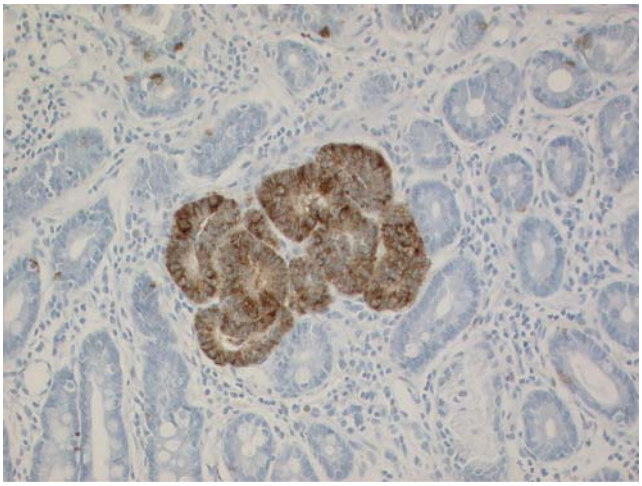

Fig. 1 Linear hyperplasia of somatostatin cells in the duodenal mucosa of a MEN1 patient with ZES

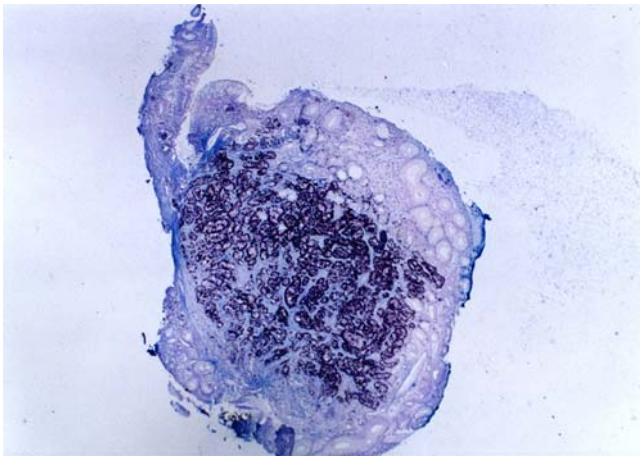

Fig. 3 Polypectomy specimen showing a small benign ECL cell tumor in a MEN1 patient with ZES (immunostaining for the vesicular monoamine transporter 2)

allowed the separation from hyperplastic and neoplastic lesions. LOH of the *MEN1* locus was found in approximately 50% of MEN1-associated duodenal NETs [6]. Allelic loss was detected in tumors as small as 300 μm (gastrin) and 400 μm (somatostatin) in diameter, which therefore represent true neoplasms. In contrast, hyperplastic gastrin and somatostatin cells lacked LOH on chromosome 11q13. These findings suggested that although the hyperplastic cells were hyperproliferative and carried the *MEN1* germline mutation, they had not yet assumed the neoplastic genotype characterized by the loss of the *MEN1* wild-type allele.

In addition to duodenal NETs, MEN1 patients with ZES may show multiple gastric NETs of the enterochromaffin-like (ECL) cells (Fig. 2). These tumors occur in a hypertrophic oxyntic mucosa and are associated with an ECL cell hyperplasia, which can be visualized using antisera against the ECL cell-specific marker vesicular monoamine transporter 2 [25] (Fig. 3). They are probably induced by both the MEN1 germline mutation and the trophic effect of hypergastrinemia. Metastases of these ECL cell tumors are rare, and tumor-related deaths are the exception [9, 10, 12].

Pancreatic NETs lead to symptoms in 30–75% of MEN1 patients [12] and up to 10% of all pancreatic NETs may be associated with a MEN1 syndrome [57]. In a recent study on surgical specimens of the pancreas from MEN1 patients in more than 90% of the cases, numerous microadenomas (i.e., up to 5 mm in diameter) were found [5], a condition that has been called pancreatic microadenomatosis. Although this finding is a hallmark for MEN1, it is not MEN1 specific, as recently, pancreatic microadenomatosis characterized by multiple glucagon-producing or multiple insulin-producing microadenomas was described in several patients who had no evidence of MEN1 or any other known hereditary syndrome [5].

In MEN1 patients, the pancreatic microadenomas are typically multihormonal and are often associated with one or more macrotumors (diameter >5 mm; Fig. 4) [12, 42,

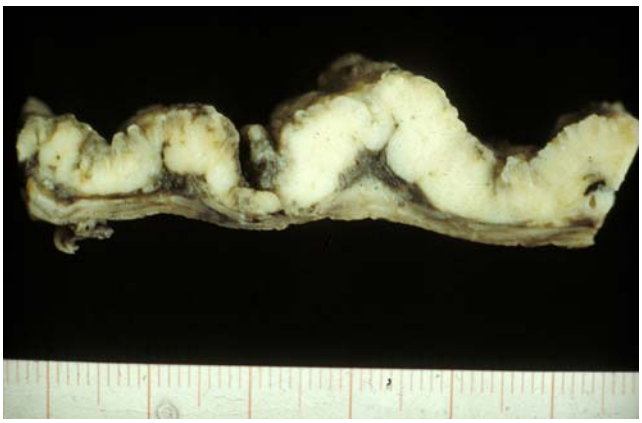

Fig. 2 Cut surface of a gastric specimen from a MEN1 patient with ZES, showing multiple small tumors in the mucosa and submucosa

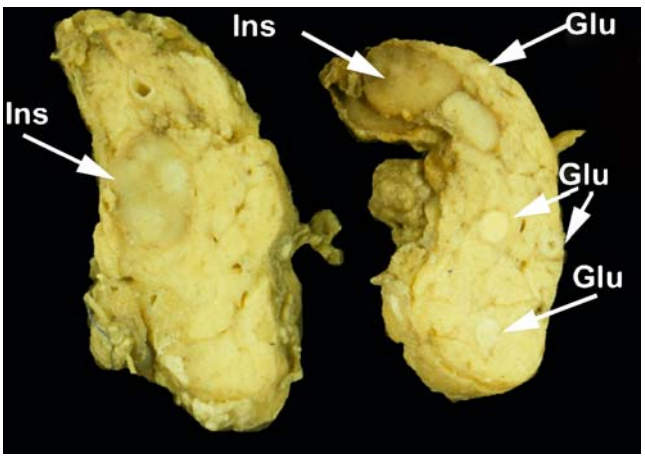

Fig. 4 Pancreatic specimen from a MEN1 patient showing two insulin-positive (*Ins*) macrotumors and four glucagon-positive (*Glu*) microadenomas

77]. The microadenomas in MEN1 are characterized, irrespective of their size (i.e., less than 200 μm), by the following features: (1) frequent expression of glucagon and/or pancreatic polypeptide, (2) trabecular growth pattern, and (3) a distinct stromal component [5, 42, 77]. Their neoplastic nature was demonstrated by LOH of the MEN1 gene [66, 82]. The MEN1-associated macrotumors (≥5 mm) also frequently express glucagon and pancreatic polypeptide or, rarely, somatostatin. In all these cases, the patients do not have a hormonal syndrome. However, if one of the macrotumors produces insulin, the patient presents with a hyperinsulinemic hypoglycemia syndrome. This is seen in approximately 10–25% of the cases. Only exceptionally, there are macrotumors that express hormones such as gastrin, vasoactive intestinal polypeptide, or growth hormone releasing hormone, which then may give rise to the respective hormonal syndromes. Regarding MEN1 patients with ZES, this implies that, with all likelihood, the source of hypergastrinemia is not a pancreatic gastrinoma but multiple duodenal gastrinomas.

Recently, forerunners of microadenomas were identified in the MEN1 pancreas, which have been called monohormononal islet-like endocrine cell clusters [66]. In addition, single irregularly shaped and enlarged islets with an increased number of glucagon cells were found. However, in contrast to the monohormononal islet-like endocrine cell clusters, the cells of the glucagon-cell-rich islets show retention of heterozygosity of the *MEN1* gene and are therefore still nonneoplastic in nature.

In summary, the MEN1 syndrome is characterized by multiple endocrine duodenal and pancreatic NETs expressing several peptide hormones, but preferentially either gastrin or somatostatin (duodenum) or glucagon or pancreatic polypeptide (pancreas). The duodenal NETs are associated with multifocal gastrin and somatostatin cell hyperplasia that can be considered precursor lesions. In the pancreas, the islets with hyperplastic glucagon cells are probably the precursors from which microadenomas evolve. Similar precursor changes have so far not been observed in the usually solitary nonhereditary NETs [6].

Neurofibromatosis type 1

NF1 (i.e., von Recklinghausen disease) shows an autosomal-dominant inheritance and a high penetrance: In almost all patients, there is sufficient evidence of the disorder to allow diagnosis in childhood [27]. The condition is characterized by neurofibromas, *Café au lait* patches of the skin, and bone dysplasia. Neurofibromas occur widely throughout the body, but affect mainly the skin. Other tumors are optic nerve and brain stem gliomas, pheochromocytomas, and malignant nerve sheath tumors [27] (Table 1). Gastroenteropancreatic NETs are rare and occur in 1% of the NF1 patients. They typically arise in the duodenum [23].

The *NF1* gene is localized on chromosome 17q11.2 and consists of more than 50 exons spanning approximately 300 kb of genomic sequence and encoding a 327-kDa protein of 2,818 amino acids, called neurofibromin [81]. Neurofibromin acts as a negative regulator of the ras-related G-proteins by increasing Ras GTPase activity, and thereby, functions at multiple levels: transcription, cell proliferation, cytoskeletal microtubule assembly. Mice that are homozygous for an NF1 mutation fail to develop the normal structure of heart and various neuroectodermal tissues and die in utero [27, 86]. Neurofibromin has been referred to as a tumor suppressor, as malignant peripheral nerve sheath tumors in NF1 patients display LOH of the NF1 gene [27].

Mutation screening is costly and not recommended clinically because of the size of the gene (50 exons) and the fact that the clinical manifestations are so characteristic. Mutations have been identified throughout the *NF1* gene; most mutations are protein-truncating mutations, consisting of nonsense, frameshift, and splice-site mutations. Five to 10% of patients have large deletions, often involving the whole gene, that are easily detectable by fluorescence in situ hybridization [36]. Large deletions of the NF1 gene have been correlated with a greater neurofibroma burden, as well as dysmorphic features, greater mental retardation, and a higher risk of developing malignant peripheral nerve sheath tumors [27]. Except for large deletions, genotype–phenotype correlations have not been described.

Our knowledge about the incidence, histopathology, biology, and functional activity of NF1-associated intestinal NETs is based on reports of single cases or small series of patients and reviews [22, 23, 75, 76]. Most of the GEP-NETs arise in the ampullary region of the duodenum and show glandular structures containing PAS-positive psammoma bodies. Immunohistochemically, they consistently express somatostatin and synaptophysin, but rarely chromogranin A. An association with the so-called somatostatinoma syndrome [i.e., markedly elevated somatostatin levels in the plasma and/or tumor, diabetes mellitus of recent onset, hypochlorhydria, gallbladder disease (cholelithiasis), diarrhea and steatorrhea, anemia, and weight loss] [24] has yet not been described. The clinical symptoms are caused by the site of the tumors, i.e., the ampulla, and lead to obstructive jaundice, intestinal obstruction, and/or bleeding. In our series of 82 duodenal NETs, we identified 15 somatostatin-producing NETs (SOM-NETs), 3 of them associated with the NF1 syndrome (Fig. 5). None of these tumors was associated with a somatostatinoma syndrome. Therefore, the high rate of NF1-associated SOM-NETs reviewed by Soga and Yakuwa [74] could not be confirmed in our series. Precursor lesions of NF1-associated SOM-NETs have not been identified. NF1-associated SOM-NETs

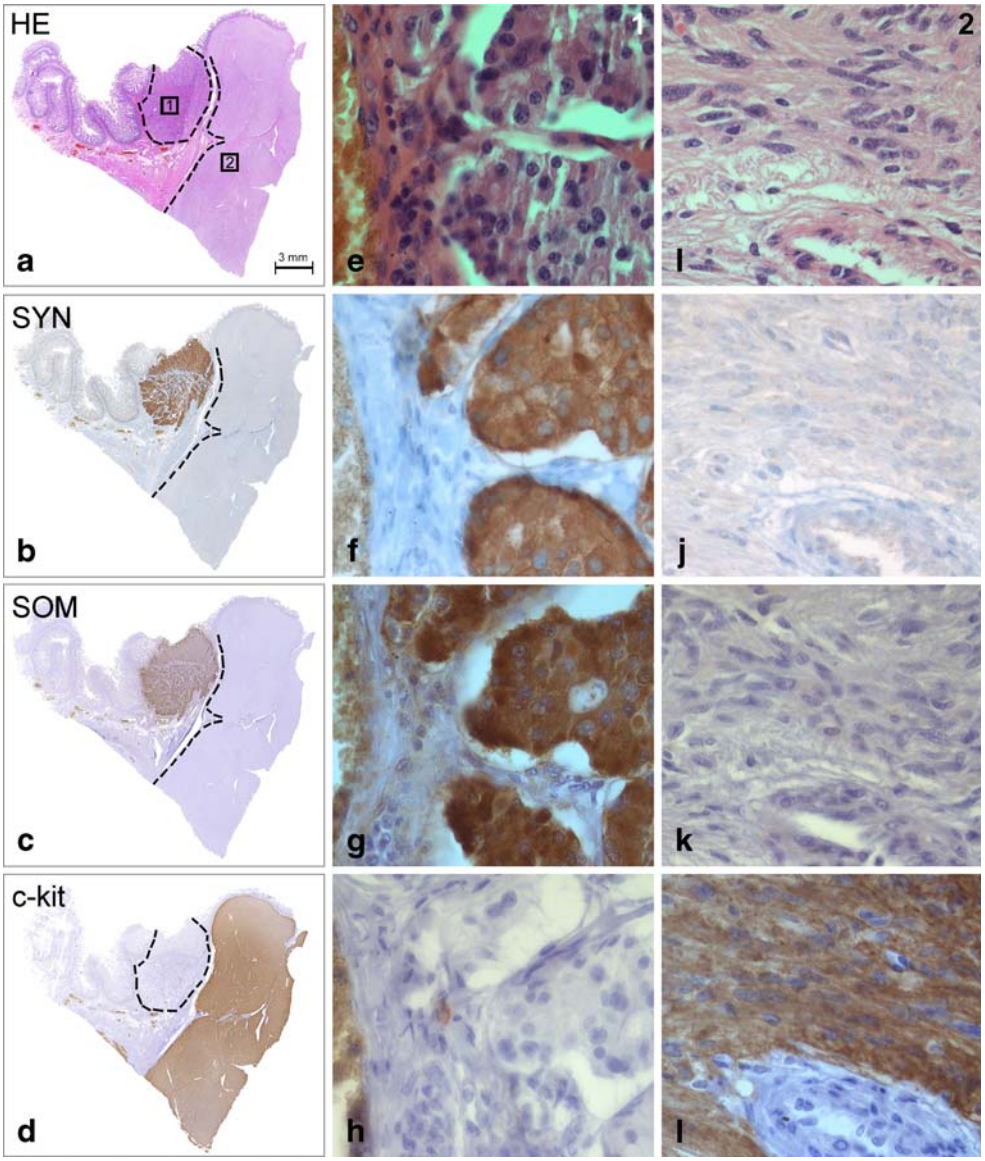

Fig. 5 Simultaneous occurrences of SOM-NET and GIST in a patient with the NF1 syndrome. Whole section scan (**a**–**d**) and high magnification of the SOM-NET (**e**–**h**) showing strong immunoreactivity for synaptophysin (*SYN*, **f**) and somatostatin (*SOM*, **g**) but not for c-kit (**h**). High magnification of the GIST (**i**–**l**) showing absence of synaptophysin (**j**) and somatostatin (**k**) but strong expression of the c-kit antigen (**l**)

may be associated with gastrointestinal stroma tumors (Fig. 5). In addition, gangliocytic paragangliomas and ampullary adenocarcinomas have been reported; however, it remains unclear whether these tumors are coincidental or due to the NF1 germline mutations.

Metastases have been described in 27% of SOM-NETs, mainly to the lymph nodes. They appear to be less aggressive than their sporadically occurring duodenal and pancreatic counterparts [35]. A tumor size of more than 2 cm and infiltration of the outer smooth muscle layers increase the risk of metastases ([76] and personal observations). In addition, a few cases of pancreatic NETs have been described in patients with the NF1 syndrome. These were somatostatin-producing NETs or insulinomas [29, 73, 74]. In our series of 541 non-MEN1-associated pancreatic NETs, we identified 19 somatostatin-producing NETs, none of them associated with NF1, and 162 insulinomas, one of them in a patient with NF1. In this patient, the tumor was proven to lack expression of the wild-type NF1 allele, providing strong evidence that there is indeed a close relationship between NF1 and the development of this insulinoma [65].

von Hippel–Lindau syndrome

VHL is a dominantly inherited familial cancer syndrome caused by germline mutations in the *VHL* tumor suppressor gene. VHL disease shows marked phenotypic variability and age-dependent penetrance [55, 84] (Table 2).

The VHL gene is localized on chromosome 3p25 and consists of three exons encoding two VHL transcripts. The major transcript (isoform I) represents all three exons, whereas exon 2 is absent from isoform II. They encode two

Table 2 Genetic and clinicopathological features of VHL and TSC

	VHL	TSC
Function	Tumor suppressor gene	Tumor suppressor gene
Chromosomal location	3p25	TSC1 9q34 TSC2 16p13.3
Gene structure	3 exons	TSC1 23 exons TSC2 42 exons
Protein	pVHL30 (~28–30 kDa) pVHL19 (~18–19 kDa)	TSC1 Hamartin (~140 kDa) TSC2 Tuberin (~200 kDa)
Mode of inheritance	Autosomal-dominant (~20% de novo)	Autosomal-dominant (~two thirds de novo)
Prevalence	~1:36,000	~1:10,000
Penetrance	~50% (at age 50) >95% (at age 60)	~100%
Diagnosis	According to WHO clinical criteria (genetic testing recommended)	According to clinical and radiological criteria
Intestinal tract		
NETs	Not described	Not described
Penetrance		
Functional activity		
Malignancy		
Pancreas		
NETs	Clear cell type	Insulin->somatostatin-producing
Penetrance	5–17%	<1%
Functional activity	Nonfunctioning	Insulinoma
Malignancy	10–20% metastases	n.d.
Other GEP tumors	Pancreatic microcystic adenoma or benign serous cysts	Hamartomatous rectal poyps
Tumors/lesions or endocrine hyperfunction outside the GEP	Pheochromocytoma, parasympathetic paraganglioma, renal cell carcinoma (clear cell), CNS hemangioblastoma, retinal angioma, papillary cystadenoma epididymis, papillary cystadenoma mesosalpinx, endolymphatic sac tumor, capillary hemangioblastoma and cysts at various locations, hyperparathyroidism	Hamartomatous tubers in cerebral cortex and subependymal nodules, giant cell astrocytomas, ocular retinal astrocytic hamartoma, cardiac rhabdomyoma, angiomyolipomas (kidney/liver), hypopigmented skin macules, shagreen patches, ungual and gingival fibromas, multiple renal cysts, pulmonary lymphangioleiomyomatosis, bone cysts

NETs Neuroendocrine tumors, *GEP* gastroenteropancreatic system, *VHL* von Hippel–Lindau syndrome, *CNS* central nervous system, *TBC* tuberous sclerosis complex, *n.d.* not enough data

gene products: a full-length 213-amino-acid protein (pVHL30; ~28–30 kDa) and a shorter protein (pVHL19; ~18–19 kDa). The *VHL* gene product has multiple functions, the best characterized of which is the role of pVHL in regulating proteolytic degradation of the subunits of the HIF transcription factors. In addition, there is strong evidence that pVHL targets other proteins for polyubiquination [18, 48, 53, 55]. VHL-associated tumors such as renal clear cell carcinoma, hemangioblastoma, and pheochromocytoma are highly vascular and overexpress a wide range of hypoxia-inducible mRNAs, including vascular endothelial growth factor (VEGF) and VEGF receptor. A variety of VHL mutations have been described. Large genomic deletions account for up to 40% of all mutations, and the rest are divided approximately equally between intragenic missense mutations and protein-truncating mutations (nonsense, frameshift insertions and deletions, splice-site mutations). Germline VHL mutations have been characterized in >500 patients and have provided a wealth of data for genotype–phenotype correlations. VHL mutations may cause (1) VHL diseases, (2) isolated familial pheochromocytoma (VHL disease type 2C), and (3) autosomal recessively inherited polycythemia due to homozygous missense mutations [17, 19, 55, 69, 84].

Although pancreatic involvement in VHL is very common (50–77%), the majority of lesions are cysts. These are rarely of clinical significance, and impairment of pancreatic function is uncommon. Hemangioblastoma occurs rarely in the pancreas of VHL patients [34, 55, 62].

The prevalence of pancreatic NETs in VHL patients has been reported at frequencies of 5–17%. VHL-associated NETs are usually confined to the pancreas and show a solid, trabecular, and/or glandular architecture. In approximately 30–50% of VHL patients, the tumors are multiple. Most of them reveal clear-cell cytology. Immunohistochemically, they are positive for general neuroendocrine

markers (chromogranin A and synaptophysin). A minor subset of tumor cells may be immunoreactive for pancreatic polypeptide, glucagon, somatostatin, or insulin. Clinically, however, almost all of the tumors are functionally inactive and are usually detected by routine radiological assessment of the abdomen in VHL patients [1, 51, 52, 54, 55]. Almost all VHL-related pancreatic NETs reveal LOH of the VHL gene locus on chromosome 3p25, supporting the concept that the VHL gene product acts as a tumor suppressor [54]. Although VHL-related tumors are often multifocal, precursor lesions were not identified in a systematic analysis of 14 patients [54]. VHL-related pancreatic NETs grow slowly. As with other NETs, the risk of malignancy seems to be directly proportional to the diameter of the tumor. In the largest reported series of 30 patients, the median size of the tumor in patients with no metastases was 2 cm (n=25) compared to 5 cm for those with metastases (n=5) [51].

Tuberous sclerosis complex

Tuberous sclerosis is an autosomal-dominant genetic disorder with a prevalence of 1:10,000 and a disease penetrance of approximately 100%. TSC is a multisystem disorder exhibiting a wide range of manifestations characterized by hamartomatous lesions in the brain, skin, eyes, heart, lungs, and kidneys (Table 2). Epilepsy, mental retardation, and autism are often present. A few cases of pancreatic NETs have been described in patients with TSC. TSC is caused by inactivating mutations in either the *TSC1* gene at 9q34 or the *TSC2* gene at 16p13.3 encoding the proteins hamartin (~140 kDa) and tuberin (~200 kDa), which form a complex that affects cell growth, differentiation, and proliferation [70, 71, 78, 85] (Table 2). The diagnosis of TSC is usually based on the clinical and radiological findings. Two thirds of the cases result from new dominant mutations. Clinical manifestations may vary, but there is no well-documented report on nonpenetrance.

The TSC1/TSC2 dimer mediates a key step in the phosphoinositide 3-kinase signaling pathway. Thereby, the TSC1/TSC2 complex is involved in the regulation of the activity of mTOR, a master controller of protein translation, integrating information on growth stimuli, cellular energy levels, nutrient availability, hypoxia, and cell growth [47, 49, 68, 79].

Mutations of the TSC1 and TSC2 genes were detected throughout the genes, with some clustering but no striking hotspots, and include inactivating nonsense, frameshift, and splice-site mutations. For TSC2, additionally in-frame deletions and large deletions involving the adjacent PKD1 gene have been reported. Somatic mosaicism occurs in a minority of patients with TSC and seems to be associated with a milder phenotype. Several studies showed that sporadic TSC2 mutations tend to be associated with a more severe phenotype than sporadic mutations of the TSC1 gene [20, 39, 46, 50]. Among patients meeting the clinical criteria of TSC, 15–20% have no identifiable mutations. These persons generally have milder clinical disease [20, 72]. Somatic mutations often involving large deletions spanning the gene (LOH) account for the majority of tumors occurring in TSC, following Knudsen's two-hit paradigm for tumor suppressor genes [30, 31, 85].

Pancreatic NETs have rarely been described in adults with TSC [21, 28, 33, 38, 41, 80]. In a case report analyzing a 6-year-old child with a de novo mutation of the TSC2 gene, who suffered from an endocrinologically silent malignant pancreatic NET, 16p13 LOH and absence of tuberin protein expression from the tumor were demonstrated [28]. These findings provide evidence for a role of tuberin in the pathogenesis of pancreatic NETs. Based on the small series of reported cases, pancreatic TSC-associated pancreatic NETs are insulinomas or endocrinologically silent. Some of them are malignant. Interestingly, in a postmortem series of nine TSC patients, one 21-year-old woman was found to have an incidental nonfunctioning pancreatic NET in association with multiple endocrine adenomas of the pituitary gland, adrenal, and parathyroid glands [38].

GEP-NETs with suspected hereditary background

Data regarding an association of GEP-NETs with other malignancies are limited. In the older literature, several studies indicated that patients with intestinal NETs are at increased risk for developing another primary malignancy [11, 45, 61]. Chen et al. [16] postulated that intestinal adenocarcinomas and intestinal NETs might have common endogenous or environmental risk factors. Kothari and Mangla [45] found that 36% of patients with ileal NETs (carcinoids) had an associated malignancy. However, these results could not be confirmed by two large population studies that included 1,029 and 245 patients from Denmark and the USA, respectively, and failed to confirm a general excess cancer risk in patients with GEP-NETs [7, 83].

Case reports described ileal and rectal NETs in first-degree relatives without any evidence of a known inherited disease [2, 56, 60, 64]. These observations were also confirmed in a large study including 245 patients with intestinal NETs in which 3.7% of patients had at least one first-degree relative with the same malignancy [7]. This rate was found to be much higher than age-adjusted incidence rates for intestinal endocrine tumors (p<0.00001 small bowel; p=0.008 large intestine). The findings of this study were confirmed by a nationwide epidemiological study from Sweden including 1,933 offspring and 4,713 parents with endocrine tumors at various sites [37]. Similar findings

were reported in four families suffering from lung NETs [63]. None of these studies identified environmental risk factors, which suggests a genetic background for the familial clustering of intestinal NETs that remains to be analyzed in detail.

Further clustering of intestinal NETs was very well established in patients with inflammatory bowel disease [13, 32, 58]. In addition, some case reports described GEP-NETs in patients suffering from familial adenomatous polyposis [40, 59]. However, for both conditions, it remains to be clarified whether and how a hereditary predisposition exists.

Acknowledgment This paper was supported by Hensel Stiftung, Kiel, Germany (F370011; MA and GK), Swiss National Foundation (SNF 31-108257; AP and PK). Nele Garbrecht and Tobias Henopp have a fellowship sponsored by Ipsen GmbH, Ettlingen, and Hensel-Stiftung, Kiel, Germany.

Conflict of interest statement We declare that we have no conflict of interest.

References

1. Alexakis N, Connor S, Ghaneh P, Lombard M, Smart HL, Evans J, Hughes M, Garvey CJ, Vora J, Vinjamuri S, Sutton R, Neoptolemos JP (2004) Hereditary pancreatic endocrine tumours. Pancreatology 4:417–433
2. Anderson RE (1966) A familial instance of appendiceal carcinoid. Am J Surg 111:738–740
3. Anlauf M, Perren A, Meyer CL, Schmid S, Saremaslani P, Kruse ML, Weihe E, Komminoth P, Heitz PU, Klöppel G (2005) Precursor lesions in patients with multiple endocrine neoplasia type 1-associated duodenal gastrinomas. Gastroenterology 128:1187–1198
4. Anlauf M, Garbrecht N, Henopp T, Schmitt A, Schlenger R, Raffel A, Krausch M, Gimm O, Eisenberger CF, Knoefel WT, Dralle H, Komminoth P, Heitz PU, Perren A, Klöppel G (2006) Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. World J Gastroenterol 12:5440–5446
5. Anlauf M, Schlenger R, Perren A, Bauersfeld J, Koch CA, Dralle H, Raffel A, Knoefel WT, Weihe E, Ruszniewski P, Couvelard A, Komminoth P, Heitz PU, Klöppel G (2006) Microadenomatosis of the endocrine pancreas in patients with and without the multiple endocrine neoplasia type 1 syndrome. Am J Surg Pathol 30: 560–574
6. Anlauf M, Perren A, Henopp T, Rudolph T, Garbrecht N, Schmitt A, Raffel A, Gimm O, Weihe E, Knoefel WT, Dralle H, Heitz PU, Komminoth P, Klöppel G (2007) Allelic deletion of the *MEN1* gene in duodenal gastrin and somatostatin cell neoplasms and their precursor lesions. Gut 56:637–644
7. Babovic-Vuksanovic D, Constantinou CL, Rubin J, Rowland CM, Schaid DJ, Karnes PS (1999) Familial occurrence of carcinoid tumors and association with other malignant neoplasms. Cancer Epidemiol Biomark Prev 8:715–719
8. Bassett JH, Forbes SA, Pannett AA, Lloyd SE, Christie PT, Wooding C, Harding B, Besser GM, Edwards CR, Monson JP, Sampson J, Wass JA, Wheeler MH, Thakker RV (1998) Characterization of mutations in patients with multiple endocrine neoplasia type 1. Am J Hum Genet 62:232–244
9. Bordi C, D'Adda T, Azzoni C, Ferraro G (1998) Pathogenesis of ECL cell tumors in humans. Yale J Biol Med 71:273–284
10. Bordi C, Corleto VD, Azzoni C, Pizzi S, Ferraro G, Gibril F, Delle FG, Jensen RT (2001) The antral mucosa as a new site for endocrine tumors in multiple endocrine neoplasia type 1 and Zollinger–Ellison syndromes. J Clin Endocrinol Metab 86: 2236–2242
11. Brown NK, Smith MP (1973) Neoplastic diathesis of patients with carcinoid. Report of a case with four other neoplasms. Cancer 32:216–222
12. Calender A, Morrison CD, Komminoth P, Scoazec JY, Sweet KM, Teh BT (2004) Multiple endocrine neoplasia type 1. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds) Pathology and genetics: tumours of endocrine organs. WHO classification of tumors. IARC, Lyon, pp 218–227
13. Camp ER, Hochwald SN, Liu C (2004) FAP with concurrent duodenal adenomatous polyposis and carcinoid tumor. J Surg Oncol 87:187–190
14. Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, Debelenko LV, Zhuang Z, Lubensky IA, Liotta LA, Crabtree JS, Wang Y, Roe BA, Weisemann J, Boguski MS, Agarwal SK, Kester MB, Kim YS, Heppner C, Dong Q, Spiegel AM, Burns AL, Marx SJ (1997) Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 276:404–407
15. Chandrasekharappa SC, Teh B (2001) Clinical and molecular aspects of multiple endocrine neoplasia type 1. In: Dahia PLM, Eng C (eds) Genetic disorders of endocrine neoplasia. Karger, Basel, pp 50–80
16. Chen CC, Neugut AI, Rotterdam H (1994) Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomark Prev 3:205–207
17. Chen F, Kishida T, Yao M, Hustad T, Glavac D, Dean M, Gnarra JR, Orcutt ML, Duh FM, Glenn G (1995) Germline mutations in the von Hippel–Lindau disease tumor suppressor gene: correlations with phenotype. Human Mutat 5:66–75
18. Cockman ME, Masson N, Mole DR, Jaakkola P, Chang GW, Clifford SC, Maher ER, Pugh CW, Ratcliffe PJ, Maxwell PH (2000) Hypoxia inducible factor-alpha binding and ubiquitylation by the von Hippel–Lindau tumor suppressor protein. J Biol Chem 275:25733–25741
19. Crossey PA, Richards FM, Foster K, Green JS, Prowse A, Latif F, Lerman MI, Zbar B, Affara NA, Ferguson-Smith MA (1994) Identification of intragenic mutations in the von Hippel–Lindau disease tumour suppressor gene and correlation with disease phenotype. Hum Mol Genet 3:1303–1308
20. Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J, Choy YS, Reeve MP, Thiele E, Egelhoff JC, Kasprzyk-Obara J, Domanska-Pakiela D, Kwiatkowski DJ (2001) Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet 68:64–80
21. Davoren PM, Epstein MT (1992) Insulinoma complicating tuberous sclerosis. J Neurol Neurosurg Psychiatry 55:1209
22. Dayal Y, Doos WG, O'Brien MJ, Nunnemacher G, DeLellis RA, Wolfe HJ (1983) Psammomatous somatostatinomas of the duodenum. Am J Surg Pathol 7:653–665
23. Dayal Y, Tallberg KA, Nunnemacher G, DeLellis RA, Wolfe HJ (1986) Duodenal carcinoids in patients with and without neurofibromatosis. A comparative study. Am J Surg Pathol 10:348–357
24. Dayal Y, Öberg K, Perren A, Komminoth P (2004) Somatostatinoma. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds) Pathology and genetics: tumours of endocrine organs. WHO classification of tumors. IARC, Lyon, pp 189–190
25. Eissele R, Anlauf M, Schäfer MKH, Eiden LE, Arnold R, Weihe E (1999) Expression of vesicular monoamine transporters in

endocrine hyperplasia and endocrine tumors of the oxyntic stomach. Digestion 60:428–439
26. Emmert-Buck MR, Lubensky IA, Dong Q, Manickam P, Guru SC, Kester MB, Olufemi SE, Agarwal S, Burns AL, Spiegel AM, Collins FS, Marx SJ, Zhuang Z, Liotta LA, Chandrasekharappa SC, Debelenko LV (1997) Localization of the multiple endocrine neoplasia type I (MEN1) gene based on tumor loss of heterozygosity analysis. Cancer Res 57:1855–1858
27. Evans DGR, Komminoth P, Scheithauer BW, Peltonen J (2004) Neurofibromatosis type 1. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds) Pathology and genetics: tumours of endocrine organs. WHO classification of tumors. IARC, Lyon, pp 243–248
28. Francalanci P, Diomedi-Camassei F, Purificato C, Santorelli FM, Giannotti A, Dominici C, Inserra A, Boldrini R (2003) Malignant pancreatic endocrine tumor in a child with tuberous sclerosis. Am J Surg Pathol 27:1386–1389
29. Fujisawa T, Osuga T, Maeda M, Sakamoto N, Maeda T, Sakaguchi K, Onishi Y, Toyoda M, Maeda H, Miyamoto K, Kawaraya N, Kusumoto C, Nishigami T (2002) Malignant endocrine tumor of the pancreas associated with von Recklinghausen's disease. J Gastroenterol 37:59–67
30. Green AJ, Johnson PH, Yates JR (1994) The tuberous sclerosis gene on chromosome 9q34 acts as a growth suppressor. Hum Mol Genet 3:1833–1834
31. Green AJ, Smith M, Yates JR (1994) Loss of heterozygosity on chromosome 16p13.3 in hamartomas from tuberous sclerosis patients. Nat Genet 6:193–196
32. Greenstein AJ, Balasubramanian S, Harpaz N, Rizwan M, Sachar DB (1997) Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature. Am J Gastroenterol 92:682–685
33. Gutman A, Leffkowitz M (1959) Tuberous sclerosis associated with spontaneous hypoglycaemia. Br Med J 2:1065–1068
34. Hammel PR, Vilgrain V, Terris B, Penfornis A, Sauvanet A, Correas JM, Chauveau D, Balian A, Beigelman C, O'Toole D, Bernades P, Ruszniewski P, Richard S (2000) Pancreatic involvement in von Hippel–Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel–Lindau. Gastroenterology 119:1087–1095
35. Hamy A, Heymann MF, Bodic J, Visset J, le Borgne J, Leneel JC, Le Bodic MF (2001) Duodenal somatostatinoma. Anatomic/clinical study of 12 operated cases. Ann Chir 126:221–226 (article in French)
36. Han SS, Cooper DN, Upadhyaya MN (2001) Evaluation of denaturing high performance liquid chromatography (DHPLC) for the mutational analysis of the neurofibromatosis type 1 (NF1) gene. Hum Genet 109:487–497
37. Hemminki K, Li X (2001) Familial carcinoid tumors and subsequent cancers: a nation-wide epidemiologic study from Sweden. Int J Cancer 94:444–448
38. Ilgren EB, Westmoreland D (1984) Tuberous sclerosis: unusual associations in four cases. J Clin Pathol 37:272–278
39. Jones AC, Shyamsundar MM, Thomas MW, Maynard J, Idziaszczyk S, Tomkins S, Sampson JR, Cheadle JP (1999) Comprehensive mutation analysis of TSC1 and TSC2-and phenotypic correlations in 150 families with tuberous sclerosis. Am J Hum Genet 64:1305–1315
40. July LV, Northcott KA, Yoshida EM, Carr DM, Owen DA (1999) Coexisting carcinoid tumors in familial adenomatous polyposis-associated upper intestinal adenomas. Am J Gastroenterol 94:1091–1094
41. Kim H, Kerr A, Morehouse H (1995) The association between tuberous sclerosis and insulinoma. AJNR Am J Neuroradiol 16:1543–1544
42. Klöppel G, Willemer S, Stamm B, Häcki WH, Heitz PU (1986) Pancreatic lesions and hormonal profile of pancreatic tumors in multiple endocrine neoplasia type I. An immunocytochemical study of nine patients. Cancer 57:1824–1832
43. Komminoth P (1997) Multiple endocrine neoplasia type 1 and 2. 1997 diagnostic guidelines and molecular pathology. Pathologe 18:286–300 (article in German)
44. Komminoth P, Perren A, Öberg K, Rindi G, Bordi C, Klöppel G, Heitz PU (2004) Gastrinoma. In: DeLellis RA, Lloyd R, Heitz PU, Eng C (eds) Pathology and genetics: tumours of endocrine organs. WHO classification of tumors. IARC, Lyon, pp 191–194
45. Kothari T, Mangla JC (1981) Malignant tumors associated with carcinoid tumors of the gastrointestinal tract. J Clin Gastroenterol 3(Suppl 1):43–46
46. Kwiatkowska J, Wigowska-Sowinska J, Napierala D, Slomski R, Kwiatkowski DJ (1999) Mosaicism in tuberous sclerosis as a potential cause of the failure of molecular diagnosis. N Engl J Med 340:703–707
47. Kwiatkowski DJ, Manning BD (2005) Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways. Hum Mol Genet 14(Spec No. 2):R251–R258
48. Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, Stackhouse T, Kuzmin I, Modi W, Geil L (1993) Identification of the von Hippel–Lindau disease tumor suppressor gene. Science 260:1317–1320
49. Lee L, Sudentas P, Donohue B, Asrican K, Worku A, Walker V, Sun Y, Schmidt K, Albert MS, El Hashemite N, Lader AS, Onda H, Zhang H, Kwiatkowski DJ, Dabora SL (2005) Efficacy of a rapamycin analog (CCI-779) and IFN-gamma in tuberous sclerosis mouse models. Genes Chromosomes Cancer 42:213–227
50. Lewis JC, Thomas HV, Murphy KC, Sampson JR (2004) Genotype and psychological phenotype in tuberous sclerosis. J Med Genet 41:203–207
51. Libutti SK, Choyke PL, Bartlett DL, Vargas H, Walther M, Lubensky I, Glenn G, Linehan WM, Alexander HR (1998) Pancreatic neuroendocrine tumors associated with von Hippel Lindau disease: diagnostic and management recommendations. Surgery 124:1153–1159
52. Libutti SK, Choyke PL, Alexander HR, Glenn G, Bartlett DL, Zbar B, Lubensky I, McKee SA, Maher ER, Linehan WM, Walther MM (2000) Clinical and genetic analysis of patients with pancreatic neuroendocrine tumors associated with von Hippel–Lindau disease. Surgery 128:1022–1027
53. Lonergan KM, Iliopoulos O, Ohh M, Kamura T, Conaway RC, Conaway JW, Kaelin WG Jr (1998) Regulation of hypoxia-inducible mRNAs by the von Hippel–Lindau tumor suppressor protein requires binding to complexes containing elongins B/C and Cul2. Mol Cell Biol 18:732–741
54. Lubensky IA, Pack S, Ault D, Vortmeyer AO, Libutti SK, Choyke PL, Walther MM, Linehan WM, Zhuang Z (1998) Multiple neuroendocrine tumors of the pancreas in von Hippel–Lindau disease patients: histopathological and molecular genetic analysis. Am J Pathol 153:223–231
55. Maher ER, Nathanson K, Komminoth P, Neumann HPH, Plate KH, Bohling T, Schneider K (2004) Von Hippel–Lindau syndrome (VHL). In: DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds) Pathology and genetics: tumours of endocrine organs. WHO classification of tumors. IARC, Lyon, pp 230–237
56. Maroy B (1997) Similar rectal carcinoid tumors of two siblings with curative endoscopic snare resection. J Clin Gastroenterol 24:124–125
57. Marx SJ, Simonds WF (2005) Hereditary hormone excess: genes, molecular pathways, and syndromes. Endocr Rev 26:615–661
58. Matsumoto T, Jo Y, Mibu R, Hirahashi M, Yao T, Iida M (2003) Multiple microcarcinoids in a patient with long standing ulcerative colitis. J Clin Pathol 56:963–965
59. Miquel C, Sabourin JC, Elias D, Grandjouan S, Viguier J, Ducreux M, Duvillard P, Praz F (2004) An appendix carcinoid

tumor in a patient with hereditary nonpolyposis colorectal cancer. Hum Pathol 35:1564–1567
60. Moertel CG, Dockerty MB (1973) Familial occurrence of metastasizing carcinoid tumors. Ann Intern Med 78:389–390
61. Moertel CG, Sauer WG, Dockerty MB, Baggenstoss AH (1961) Life history of the carcinoid tumor of the small intestine. Cancer 14:901–912
62. Neumann HP, Dinkel E, Brambs H, Wimmer B, Friedburg H, Volk B, Sigmund G, Riegler P, Haag K, Schollmeyer P et al (1991) Pancreatic lesions in the von Hippel–Lindau syndrome. Gastroenterology 101:465–471
63. Oliveira AM, Tazelaar HD, Wentzlaff KA, Kosugi NS, Hai N, Benson A, Miller DL, Yang P (2001) Familial pulmonary carcinoid tumors. Cancer 91:2104–2109
64. Pal T, Liede A, Mitchell M, Calender A, Narod SA (2001) Intestinal carcinoid tumours in a father and daughter. Can J Gastroenterol 15:405–409
65. Perren A, Wiesli P, Schmid S, Montani M, Schmitt A, Schmid C, Moch H, Komminoth P (2006) Pancreatic endocrine tumors are a rare manifestation of the neurofibromatosis type 1 phenotype: molecular analysis of a malignant insulinoma in a NF-1 patient. Am J Surg Pathol 30:1047–1051
66. Perren A, Anlauf M, Henopp T, Rudolph T, Schmitt A, Raffel A, Gimm O, Weihe E, Knoefel WT, Dralle H, Heitz PU, Komminoth P, Klöppel G (2007) Multiple endocrine neoplasia type 1: loss of one *MEN1* allele in tumors and monohormonal endocrine cell clusters, but not in islet hyperplasia of the pancreas. A combined FISH and immunofluorescence study. J Clin Endocrinol Metab 92:1118–1128
67. Pipeleers-Marichal M, Somers G, Willems G, Foulis A, Imrie C, Bishop AE, Polak JM, Häcki WH, Stamm B, Heitz PU, Klöppel G (1990) Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger–Ellison syndrome. N Engl J Med 322:723–727
68. Plank TL, Yeung RS, Henske EP (1998) Hamartin, the product of the tuberous sclerosis 1 (TSC1) gene, interacts with tuberin and appears to be localized to cytoplasmic vesicles. Cancer Res 58:4766–4770
69. Richards FM, Schofield PN, Fleming S, Maher ER (1996) Expression of the von Hippel–Lindau disease tumour suppressor gene during human embryogenesis. Hum Mol Genet 5:639–644
70. Roach ES, Gomez MR, Northrup H (1998) Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 13:624–628
71. Roach ES, DiMario FJ, Kandt RS, Northrup H (1999) Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. J Child Neurol 14:401–407
72. Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, Zonnenberg B, Verhoef S, Halley D, van den OA (2005) Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype–phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. Eur J Hum Genet 13:731–741
73. Saurenmann P, Binswanger R, Maurer R, Stamm B, Hegglin J (1987) Somatostatin-producing endocrine pancreatic tumor in Recklinghausen's neurofibromatosis. Case report and literature review. Schweiz Med Wochenschr 117:1134–1139 (article in German)
74. Soga J, Yakuwa Y (1999) Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. J Exp Clin Cancer Res 18:13–22
75. Stamm B, Hedinger CE, Saremaslani P (1986) Duodenal and ampullary carcinoid tumors. A report of 12 cases with pathological characteristics, polypeptide content and relation to the MEN 1 syndrome and von Recklingshausen's disease (neurofibromatosis). Virchows Arch [A] Pathol Anat 408:475–489
76. Tanaka S, Yamasaki S, Matsushita H, Ozawa Y, Kurosaki A, Takeuchi K, Hoshihara Y, Doi T, Watanabe G, Kawaminami K (2000) Duodenal somatostatinoma: a case report and review of 31 cases with special reference to the relationship between tumor size and metastasis. Pathol Int 50:146–152
77. Thompson NW, Lloyd RV, Nishiyama RH, Vinik AI, Strodel WE, Allo MD, Eckhauser FE, Talpos G, Mervak T (1984) MEN 1 pancreas: a histological and immunohistochemical study. World J Surg 8:561–574
78. van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, Lindhout D, van den OA, Halley D, Young J, Burley M, Jeremiah S, Woodward K, Nahmias J, Fox M, Ekong R, Osborne J, Wolfe J, Povey S, Snell RG, Cheadle JP, Jones AC, Tachataki M, Ravine D, Sampson JR, Reeve MP, Richardson P, Wilmer F, Munro C, Hawkins TL, Sepp T, Ali JB, Ward S, Green AJ, Yates JR, Kwiatkowska J, Henske EP, Short MP, Haines JH, Jozwiak S, Kwiatkowski DJ (1997) Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science 277:805–808
79. van Slegtenhorst M, Nellist M, Nagelkerken B, Cheadle J, Snell R, van den OA, Reuser A, Sampson J, Halley D, van der SP (1998) Interaction between hamartin and tuberin, the TSC1 and TSC2 gene products. Hum Mol Genet 7:1053–1057
80. Verhoef S, Diemen-Steenvoorde R, Akkersdijk WL, Bax NM, Ariyurek Y, Hermans CJ, van Nieuwenhuizen O, Nikkels PG, Lindhout D, Halley DJ, Lips K, van den Ouweland AM (1999) Malignant pancreatic tumour within the spectrum of tuberous sclerosis complex in childhood. Eur J Pediatr 158:284–287
81. Viskochil D, Buchberg AM, Xu G, Cawthon RM, Stevens J, Wolff RK, Culver M, Carey JC, Copeland NG, Jenkins NA (1990) Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. Cell 62:187–192
82. Vortmeyer AO, Huang S, Lubensky I, Zhuang Z (2004) Non-islet origin of pancreatic islet cell tumors. J Clin Endocrinol Metab 89:1934–1938
83. Westergaard T, Frisch M, Melbye M (1995) Carcinoid tumors in Denmark 1978–1989 and the risk of subsequent cancers. A population-based study. Cancer 76:106–109
84. Woodward ER, Maher ER (2006) von Hippel–Lindau disease and endocrine tumour susceptibility. Endocr Relat Cancer 13:415–425
85. Yates JR (2006) Tuberous sclerosis. Eur J Hum Genet 14:1065–1073
86. Yla-Outinen H, Aaltonen V, Bjorkstrand AS, Hirvonen O, Lakkakorpi J, Vaha-Kreula M, Laato M, Peltonen J (1998) Upregulation of tumor suppressor protein neurofibromin in normal human wound healing and in vitro evidence for platelet derived growth factor (PDGF) and transforming growth factor-beta1 (TGF-beta1) elicited increase in neurofibromin mRNA steady-state levels in dermal fibroblasts. J Invest Dermatol 110:232–237
87. Zollinger RM, Ellison EH (1955) Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 142:709–723