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Chapter 1

Hereditary Neuroendocrine Tumor Syndromes

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Additional information is available at the end of the chapter

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1. Introduction

Neuroendocrine tumours (NETs) are rare and heterogeneous neoplasms with variable biological behaviour. The estimated incidence of NETs is about 1-5 cases/100,000/year. The most recent data show a progressive increase of the incidence in the last years and a high increase of their prevalence and survival [1]. NETs can be sporadic or can arise in complex hereditary endocrine disorders such as Multiple Endocrine Neoplasias (MENs), Familial Paragangliomatosis (FPGLs), Neurofibromatosis type 1 (NF1), von Hippel-Lindau Disease (VHL), Tuberous Sclerosis (TSC) [1]. It has been estimated that hereditary NETs occurrence varies with site of origin of the tumour, ranging 5 to 30% of cases [1]. Due to the recent advances in the knowledge of biology and genetics of NETs, these rates seems to be an underestimation and novel mutations of well known oncogenes or tumour suppressor genes as well as new genes and molecular pathways responsible for unknown syndromes are expected to be characterized.

Patients with hereditary NET syndromes inherit the susceptibility to develop multiple endocrine neoplasias which can be associated with non-endocrine tumours and/or non-tumour lesions. They are characterized by germline mutations usually inherited as an autosomal dominant disease according to the Knudson's "two-hits hypothesis" [2].

Compared to the sporadic forms, hereditary NETs generally present an earlier age at onset, multiple tumour localizations, higher secretory activity. Diagnosis is made around sixth decade of life in sporadic NETs while it is anticipated of about three decades in hereditary tumours [3]. The identification of hereditary NET syndromes is relevant to achieve a precocious diagnosis and this may be important to prevent severe complications and unfavourable outcome. For this reason, the genetic screening is nowadays a well established procedure in many tumor types allowing to reclassify as carrier of specific hereditary NET

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syndromes, a number of patients with an apparently sporadic tumours [4]. Some studies, focusing in particular on MEN type 1, highlighted that the genetic screening impacts on the management and clinical outcome of NETs, because it allows to detect tumours at an early stage or even before their development [5-7].

In spite of these recent advances, at now, clinical pictures of most of the hereditary NET syndromes are incomplete or not updated. In addition, follow-ups of these patients are not standardized. Furthermore, although in the last years it has been possible to identify a lot of genes and molecular pathways responsible for the development of hereditary NETs, many other molecular pathways responsible for apparently sporadic NETs or influencing the phenotype of well known hereditary NETs remain to be detected and characterized.

In summary, the genetic origin influences the natural history of NETs, however, natural history and clinical course of hereditary NETs is not well defined for most of the actually known hereditary NET syndromes and other syndromes remained to be discovered.

In this chapter two hereditary endocrine syndromes (Multiple Endocrine Neoplasias and Familial Paragangliomatosis) will be discussed.

2. Epidemiology and clinical characteristics

2.1. Multiple Endocrine Neoplasias

Multiple Endocrine Neoplasias (MENs) are rare hereditary autosomal dominant syndromes with complete penetrance and variable expressivity, characterized by the onset of various endocrine and non endocrine tumors with different localization. We distinguish the MEN type 1 (MEN1) and MEN type 2 (MEN2) that are two distinct syndromes.

2.1.1. MEN1

MEN1 or Wermer's Syndrome (OMIM #131100) is characterized by high penetrance (more than 95% of carriers develop disease within 50 years of age), variable inter- and intra-familial expressivity and genetic anticipation [3, 8]. It has been estimated that the prevalence of MEN1 is 2-3:100,000 individuals, with the same distribution between males and females [9]. MEN1 is characterized by the occurrence of tumors of the parathyroid glands, the anterior pituitary, the pancreatic islets and the adrenal glands, as well NETs in the foregut (thymic, bronchial and gastric carcinoids). Other non-endocrine tumors can associate in the skin (angiofibromas, lipomas, collagenomas) and in the central nervous system (ependimoma, meningioma) (Table 1). According to the MEN Consensus published in 2001, the clinical diagnosis of this syndrome is based on the concomitant occurrence of at least two of the three MEN1-related endocrine tumors (parathyroid adenoma, pituitary adenoma, duodenopancreatic-NET). Familial MEN1 is defined as at least one MEN1-related NET plus at least one first-degree relative with at least one of the three classical tumors or a known germline *MEN1* mutation [10].

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Endocrine tumors	**%**
Parathyroid glands	75-95
Pancreatic islets	55
Gastrinomas	45
Insulinomas	10
Non-functioning	10
Other (VIPomas, etc.)	2
Pituitary	47
PRLomas	30
Non-functioning	10
ACTHomas	1
GH-omas	3-6
Adrenal cortical	20
Foregut	18
Thymus	8
Lungs	8
Stomach	5
Non-endocrine tumors	
Skin	80
Angiofibromas	75
Collagenomas	5
Lipomas	30
Leiomyomas	5
CNS (meningiomas)	25

ACTH: adrenocorticotrophic hormone; CNS: central nervous system; GH: growth hormone; PRL: prolactin; VIP: vasoactive intestinal peptide.

Table 1. Endocrine and non-endocrine tumors associated to Multiple Endocrine Neoplasia type 1

Typically, NETs associated to MEN1 rise up two decades before the sporadic ones. They are generally benign; however, both duodeno-pancreatic NETs and carcinoids can be malignant.

Hyperparathyroidism, caused by parathyroid adenoma/hyperplasia, is often the first manifestation of MEN1. About 75-95% of MEN1 patients develop parathyroid adenomas [10]. Usually parathyroid adenomas are multiple and benign. The main clinical manifestations of primary hyperparathyroidism and the resulting hypercalcemia are represented by renal diseases (dehydration, hypercalciuria, nephrolithiasis and, in advanced cases, kidney failure), bone changes (early osteopenia/osteoporosis), neurological manifestations (drowsiness, depression, confusion), gastrointestinal disturbances (anorexia, constipation, nausea, vomiting) and cardiovascular alterations (hypertension, short QT-trait).

Laboratory investigation to detect primary hyperparathyroidism consist of measurement of (ionized) calcium, phosphate and parathyroid hormone in blood and the 24-hour calcium excretion in the urine. Bone densitometry can be used to detect bone mass reduction. Parathyroid adenomas can be localized by neck ultrasonography (US) and Tc-99m sestamibi scintigraphy (useful to detect also ectopic parathyroid glands).

Pancreatic endocrine tumors develop in about 55% of MEN1 patients [11]. Pancreatic tumor in the context of MEN1 is, generally, multicentric with considerable variability in size (micro-and macro-tumors) and clinical behavior (lesion localized, invasive or metastatic). Multicentric microadenomas are present in 90% of MEN1 patients [12]. It is common to detect functioning NETs associated with non-functioning NETs. The main locations of occurrence are represented by the pancreas in toto and the duodenal submucosa. In order of frequency, the duodeno-pancreatic NETs associated with the syndrome of gastrin hypersecretion are the most frequent and are responsible for the Zollinger-Ellison syndrome. Functioning syndromes and related symptoms are shown in Table 2.

Hormonal syndromes often occur late and may indicate metastases in 50% of MEN1 patients [13].

Laboratory investigation to detect duodeno-pancreatic NETs includes specific markers (such as gastrin, insulin, glucose, glucagon) and the aspecific marker cromogranin-A. Duodeno-pancreatic NETs can be detected by US and echo-endoscopy, magnetic resonance imaging (MRI), computed tomography (CT) and functional imaging techniques such as somatostain receptor scintigraphy.

Pituitary adenomas are found in about 50% of MEN1 patients and evidence of MEN1 is found in approximately 2.7% of patients with pituitary adenomas [10]. Pituitary tumors in MEN1, compared to sporadic tumors, are larger in size and more aggressive. Since childhood MEN1 subjects need to be evaluated for pituitary tumors [14].

The diagnosis of functioning pituitary adenoma is confirmed by determining a specific hormone excess on blood or urinary samples. Pituitary adenomas can be detect visually by MRI with gadolinium contrast.

Syndrome	Symptoms
Zollinger-Ellison syndrome (gastrin hypersecretion)	Pain or burning sensation in the abdomen
	Nausea
	Vomiting
	Diarrhea
	Fatigue
	Weakness
	Weight loss
Insulinoma syndrome	Anxiety
	Behavior changes
	Clouded vision
	Confusion
	Convulsions
	Dizziness
	Headache
	Hunger
	Loss of consciousness
	Rapid heart rate
	Sweating
	Tremor
	Weight gain
Verner-Morrison syndrome (VIP hypersecretion)	Abdominal pain and cramping
	Diarrhea (watery, and often in large amounts)
	Flushing or redness of the face
	Nausea
	Weight loss
Somatostatinoma syndrome	Mild diabetes mellitus
	Steatorrhoea
	Gall stones
Glucagonoma syndrome	Anemia
	Diarrhea
	Weight loss
	Necrolytic migratory erythema
	Diabetes mellitus

Table 2. Functioning syndromes and related symptoms associated to Multiple Endocrine Neoplasia type 1

2.1.2. MEN2

MEN2 or Sipple's Syndrome (OMIM #171400) is an autosomal dominant disease resulting from germline mutations of the RET proto-oncogene, with an estimated prevalence of 1:30,000 subjects [10]. It is divided in three clinical variants: a) MEN2A (medullary thyroid cancer, pheochromocytoma, primary hyperparathyroidism and cutaneous lichen amyloidosis or Hirschsprung disease); b) familial medullary thyroid cancer (FMTC); c) MEN2B (me-

dullary thyroid cancer, pheochromocytoma, mucosal and intestinal ganglioneuromatosis, marfanoid habitus) [10, 15, 16]. Although these variants have medullary thyroid cancer as a common denominator, they differ for the aggressiveness of this cancer, in a decreasing order MEN2B>MEN2A>FMTC [15]. In patients with FMTC, medullary thyroid cancer (MTC) is the only clinical manifestation. According to the "International RET Mutation Consostium", to make the diagnosis of FMTC is required the onset of medullary thyroid cancer (MTC) in at least four family members [17]. About 56% of cases belong to the subtype 2A, while the subtype 2B is the most aggressive with an elevated morbidity and mortality [15, 16, 18].

Plasma free metanephrines have the highest sensitivity and specificity for detecting pheochromocytoma. However, measurement of 24-hour urine catecholamines and metanephrines, and serum catecholamines are also frequently used [19, 20]. Imaging techniques include abdomen CT-scan and/or MRI. Functional imaging techniques include somatostatin receptor scintigraphy and metaiodobenzylguanidine (MIBG) scintigraphy.

2.2. Familial paragangliomatosis

Familial Paragangliomatosis (FPGLs) are hereditary syndromes of susceptibility to multiple neuroectodermal tumors characterized by high vascularisation and slow growth that arise from the medullar of adrenal glands (pheochromocytomas, PCCs) or from extra-adrenal ganglia (paragangliomas, PGLs).

PCCs and PGLs occur as sporadic tumors and in 10-50% of cases the tumors were associated with hereditary syndromes, mainly MEN2, von Hippel–Lindau disease (VHL), and neurofibromatosis type 1 (NF1) [21]. A small fraction is associated with other syndromes, including Carney triad, Carney–Stratakis syndrome, and, very rarely, MEN1.

There are four subtypes of FPGLs. PGLs can found in all three types of FPGL while phaeochromocytomas are very rare in the FPGL3 [22].

Hereditary PCCs/PGLs, in comparison to sporadic ones, arise more prematurely, can be bilateral or multifocal and can more frequently relapse.

About 10% of the PCCs/PGLs is malignant. FPGL4 is characterized by an increase chance of malignant paragangliomas; in this disorder, then, renal cell cancers and thyroid cancers can be found [22].

Pheochromocytomas and sympathetic paragangliomas result in hypersecretion of catecholamines, which can cause headache, palpitations, hypertension, tachycardia and excessive perspiration, as well as many other nonspecific symptoms. Although most pheochromocytomas and paragangliomas are benign, they can cause major morbidity and death due to uncontrolled hypertension precipitated by stressful events such as anesthesia and pregnancy. Parasympathetic paraganglioma are typically located within the head and neck and usually do not secrete excess catecholamines. They generally do not present symptomatically unless there is a mass effect causing a visible or palpable mass.

Laboratory tests include plasma free metanephrines, 24-hour urine catecholamines and metanephrines.

Imaging techniques include neck, skull base and abdomen/pelvis CT-scan and/or MRI. Functional imaging techniques include somatostatin rceptor scintigraphy and MIBG scintigraphy.

3. Genetic pathways and pathophysiology of mutations

The genetic origin influences the natural history of NETs. This is particularly evident in MEN1 where the diagnosis is made around the sixth decade of life in sporadic tumors while it is anticipated of about three decades in hereditary tumors [3, 10]. The identification of hereditary NET syndromes is relevant to achieve a precocious diagnosis of the tumors and this may be important to prevent severe complications and unfavourable outcome. In the last years, it has been possible to identify a number of genes and molecular pathways involved in the development of NETs. Of consequence, some patients with apparently sporadic tumor have been reclassified as carriers of hereditary NET with relevant implications on the clinical course of disease and quality of life.

3.1. Multiple Endocrine Neoplasias

3.1.1. MEN1

MEN1 is an autosomal dominant syndrome resulting from an inactivating germline mutation of the *MEN1* gene located on chromosome 11q13 [23].

Up to 80% of MEN1-associated tumors exhibit loss of heterozigosity (LOH) of 11q13, indicating that *MEN1* functions as a tumor suppressor gene.

Approximately 21% of sporadic pancreatic neuroendocrine tumors (PNETs) harbour mutations in *MEN1*, but there is substantial variation across different tumor subtypes. Whereas only 8% of insulinomas and non-functioning PNETs have identifiable MEN1 mutations, they are more frequent in gastrinomas [37%), VIPomas (44%) and glucagonomas (67%) [24-31].In contrast to the relatively low frequency of MEN1 mutations in sporadic PNETs, up to 68% display LOH at chromosome 11q13 [32].

This raises the possibility there may be other, yet to be identified, tumor suppressor genes on the long arm of chromosome 11. Similarly, LOH of chromosome 11 is present in up to 78% of gastrointestinal carcinoids, but the frequency of MEN1 mutations is much lower. Gortz et al. reported MEN1 mutations in 2/11 (18%) gastrointestinal carcinoids and 2/11 [18%) lung carcinoids [26] and Debelenko et al identified MEN1 mutations in 4/11 (36%) lung carcinoids [33]. The MEN1 gene product, menin, is a nuclear protein that binds to many transcription factors, including the AP1 component JunD. Upon binding to JunD, menin represses JunD-mediated transcription to inhibit cellular proliferation. Inactivating mutations of MEN1 disrupt the binding to JunD to enhance transcription and augment cellular proliferation [34, 35]. More recently, menin was also identified in a complex with the MLL histone methyltransferase that associates with regulatory elements in the promoters of the

cell cycle inhibitors p27KIP1 and p18Ink4c to methylate histone H3 and enhance gene transcription [36]. In mouse models, the absence of Men1 results in down-regulation of p27KIP1 and p18Ink4c and a phenotype resembling the MEN1 syndrome, including islet-cell hyperplasia [37, 38].

Of note, a similar phenotype was also observed in p27KIP1/p18Ink4c double-mutant mice suggesting that deregulation of the cell cycle may be the critical consequence of MEN1 mutations and a necessary feature of NET pathogenesis in general [39]. Recently, the telomerase (hTERT) gene was identified as a menin target gene. The end of chromosome in a cell, shorten after DNA replication. Eventually, after several cell divisions, the DNA loses its stability and the cell is subjected to apoptosis. Telomerase is an enzyme that maintains the length of the telomeres and is not expressed in normal cells, but it is active in stem cells and tumor cells. Menin is a suppressor of the expression of the telomerase gene. Possibly, inactivation of menin could lead to cell immortalization by telomerase expression, which could allow a cell to develop into a tumor cell [40].

In approximately 10-15% of patients with a clinical diagnosis of MEN1 is not possible to identify a known mutation, due to the presence of regulatory sequences inactivated. In such cases the genetic analysis of first-degree relatives of patients with apparently negative family history can be helpful in identifying possible new mutations [41].

3.1.2. MEN2

MEN2 is dominantly inherited, and its genetic cause, mutations of the REarranged during Transfection (RET) protooncogene, was first recognized nearly 20 years ago [10, 42-44].

Since then, the range of mutations identified, their potential for predicting clinical course, and the underlying functional effects have been explored. Detection of RET mutations in MEN2 represents a paradigm for genetically guided patient management, and genotype–phenotype correlations in this disease now inform recommended interventions, patient and family screening, and long-term follow-up [10, 45].

The RET proto-oncogene encodes a receptor tyrosine kinase that is required for the development of neural-crest derived cells, the urogenital system, and the central and peripheral nervous systems, notably the enteric nervous system [46, 47].

The RET protein has a large extracellular domain containing a cysteine-rich region and a series of cadherin homology domains, a transmembrane domain, and an intracellular tyrosine kinase domain, required for RET phosphorylation and downstream signalling [48, 49].

The RET kinase is structurally similar to other tyrosine kinases, sharing many conserved functional motifs and regulatory residues that have been shown to have importance for kinase enzyme function [50]. RET is activated by binding of a multi-protein ligand complex. RET binds a soluble ligand of the glial cell-line-derived neurotrophic factor (GDNF) family but also requires a co-receptor of the GDNF family receptors a (GFRa), which is tethered to the cell membrane via glycosylphosphatidylinositol linkage [51, 52]. Initially, GDNF binds to GFRa, and these complexes are then able to recruit RET to form heterohexamers that are

concentrated in regions of the cell membrane called lipid rafts These are membrane domains enriched in glycosylphosphatidylinositol-linked proteins and signaling molecules that provide a platform not only for enhanced cell signaling, but also for regulation of receptor kinase activity and down-regulation [53].

Activation of RET leads to stimulation of multiple downstream pathways, including mitogen-activated protein kinase and extracellular signal-regulated kinase, phosphoinositide 3-kinase and protein kinase B, signal transducer and activator of transcription 3, proto-oncogene tyrosine-protein kinase Src1, and focal adhesion kinase that promote cell growth, proliferation, survival, and/or differentiation [54, 55].

MEN2 is associated with point mutations of RET, predictably leading to its activation in the absence of ligands and co-receptors. Mutations are primarily amino acid substitutions affecting a very small number of RET codons in either the extracellular domain or within the kinase domain.

Mutations are dominant, requiring only a single mutant allele to confer the disease phenotype. MEN2 RET mutation occurrence [56-59] are available online (http://www.arup.utah.edu/database/MEN2/MEN2_welcome.php). Together, these data suggest strong overall themes as to functional effects of these mutations, but also as to their clinical significance.

Together, these data suggest strong overall themes as to functional effects of these mutations, but also as to their clinical significance. Strong associations of disease subtype, and also specific disease phenotypes, with individual RET mutations have made it possible to stratify risk of MEN2 by genotype [10, 45].

The management guidelines of the American Thyroid Association base the recommendations for initial diagnosis, therapeutic intervention, and long-term follow-up on patient genotype and the current understanding of the natural history of the disease associated with each RET mutation. Mutations of cysteine residues (primarily cysteines 609, 611, 618, 620, 630, and 634] in the RET extracellular domain account for the majority of MEN2A cases, and are also common in patients with FMTC. Intracellular kinase domain mutations are mainly associated with FMTC and MEN2B. Mutations in the intracellular codons 768, 790, 791, 804, and 891 underlie FMTC, and occur less commonly in patients with MEN2A [60] while specific mutations of codon 918 (M918T) or 883 (A883F) account for the vast majority of MEN2B cases, and are exclusive to the subtype [61].

In addition to association with disease subtype, significant correlations of specific mutations with disease features are reported. For example, RET codon 634 mutations carry a greater patient risk for pheochromocytoma and parathyroid hyperplasia [62-64] and are associated with a higher frequency of detection of MTC at the time of early thyroidectomy [65].

Variation in clinical presentation has even been observed with different codon 634 substitutions. The specific substitution of an arginine at codon 634 (C634R) is strongly associated with increased risk of parathyroid hyperplasia increased frequency of distant metastases, earlier onset of both lymph node and distant metastases, and bilaterality of pheochromocytoma [66, 67].

3.2. Hereditary pheochromocytoma/paraganglioma syndromes

During the last decade, mutations in the genes encoding different subunits of the succinate dehydrogenase (SDH) complex have been linked to familial PCC/PGL syndrome, and subsequent genetic screenings have revealed that about 30% of PCCs and PGLs are caused by hereditary mutations [68, 69]. In addition, several novel susceptibility genes, such as kinesin family member 1B (KIF1Bb) [70], EGL nine homolog 1, also termed PHD2 (EGLN1/PHD2) [71], transmembrane protein 127 (TMEM127) [72], and MYC-associated factor X (MAX) [73], have recently been added to the list. The predisposing genes that have been identified seem at a first glance to have entirely different functions but, in spite of this, malfunction of their different gene products can give rise to clinically and histologically undistinguishable tumors. Nevertheless, some clinical features may be quite different, e.g. patients with SDHB mutations have considerably higher risk of malignancy than many other PCC/PGL patients [74].

The feature of RET gene and MEN2 syndrome were previously described, we want to remember that activating RET mutations predispose to PCCs, which are often recurrent and bilateral, but typically have a low risk of malignancy.

Familial paragangliomatosis are associated to known germline mutations of the genes encoding subunits of succinate dehydrogenase (SDH).

SDH is a mitochondrial enzyme complex consisting of four subunits: SDHA, SDHB, SDHC, and SDHD, which are all encoded by the nuclear genome [75]. The enzyme, also known as mitochondrial complex II, is involved both in the tricarboxylic acid cycle, where it catalyzes the oxidation of succinate to fumarate, and in the respiratory electron transfer chain, where it transfers electrons to coenzyme Q. The gene SDHA is located on chromosome 5p15.33 and consists of 15 exons. It encodes a protein that functions as a part of the catalytic core and contains the binding site for succinate. The other part of the catalytic domain, which also forms an interface with the membrane anchor, is encoded by SDHB, a gene of eight exons located on chromosome 1p36.13. SDHC on chromosome 1q23.3 and SDHD on chromosome 11q23.1 contain six and four exons, respectively, and encode two hydrophobic proteins that anchor the complex to the mitochondrial inner membrane. The link between SDH and neuroendocrine tumors was first established in the year 2000, when germline mutations in SDHD were discovered in patients withfamilial PGLs [76]. SDHD mutations were subsequently found also in apparently sporadic PCCs [77] and PGLs [78] as well as in familial PCCs [79]. Shortly after, germline mutations were also identified in SDHB in both PCCs and PGLs [80]. SDHC mutations were reported in PGLs in 2000 [81] and were also recently found in PCCs [82]. During several years, homozygous and compound heterozygous mutations in the gene encoding the fourth subunit, SDHA, were associated with a rare early-onset.

Germline mutations in the SDHx genes give rise to familial PCC–PGL syndrome, sometimes only referred to as familial PGL. The syndrome can be divided into PGL1, PGL2, PGL3, and PGL4, which are caused by mutations in SDHD, SDHAF2, SDHC, and SDHB respectively. They are all inherited in an autosomal dominant manner but with varying penetrance.

SDHD is putatively maternally imprinted and PGL1 is thus only passed on to children by their father [83], although one exception of maternal transmission has been reported [84]. To date, PGL2 has also only been diagnosed in individuals with an affected father, suggesting a similar parent-of-origin-specific inheritance for SDHAF2 [85]. No specific PCC/PGL syndrome has yet been described for SDHA mutations, but they seem to have a low penetrance of PCC/PGL and do not seem to be associated with a familial presentation [86, 87]. The prevalence of PCC/PGL syndrome is unknown, but a summary of the cases reviewed here (about 13% of all PCC/PGL cases) gives an estimate of 1:50 000 to 1:20 000, the majority represented by PGL1 and PGL4. Apart from PCCs and PGLs, SDHB mutations have been associated with renal cell carcinoma [88]. One SDHD mutation carrier with a renal cell tumor has also been described, as well as a few cases of SDHB and SDHD patients with thyroid carcinoma [88, 89]. In addition, mutations in SDHB, SDHC, and SDHD can give rise to the Carney–Stratakis syndrome, characterized by the dyad of PGLs and gastrointestinal stromal tumors. Very recently, SDHA mutations were also reported in two patients with gastrointestinal stromal tumors but without PGLs [90].

SDHD mutations (PGL1) predispose most frequently to parasympathetic, often multifocal PGLs, but also to sympathetic PGLs and PCCs. Several national and multinational studies have gathered information about tumor characteristics in patients with PCC/PGL syndrome [69, 88-92].

4. New susceptibility genes in hereditary PCC/PGLs

4.1. Transmembrane protein 127(TMEM127)

TMEM127 is a gene of four exons located on 2q11.2, a locus identified as a PCC susceptibility locus in 2005 [93]. The transmembrane protein was recently revealed to function as a tumor suppressor, and germline mutations in TMEM127 were detected in PCCs [72]. Qin et al. also demonstrated that TMEM127 is a negative regulator of mechanistic target of rapamycin, formerly mammalian target of rapamycin (mTOR), thus linking a critical signalling pathway for cell proliferation and cell death to the initiation and development of PCC. Both missense and nonsense mutations in TMEM127 have been reported. LOH of the gene was detected in tumors of all tested mutation carriers, suggesting a classical two-hit model of inactivation.

So far, no specific syndrome has been described for TMEM127. Other tumors, including MTC, breast cancer, and myelodysplasia, have been identified in carriers of TMEM127 mutations, but a causal relationship between the tumors and the mutations remains to be established [94]. A clear family history in only a fourth of the patients suggests an incomplete penetrance, and in a single family, the penetrance of PCC was 64% by the age of 55 years [95].

Among 990 patients with PCC or PGL, negative for RET, VHL, and SDHB/C/D mutations, TMEM127 mutations were identified in 20 (2.0%) of the cases, all of which had PCC [95]. Another study revealed one additional PCC patient with a TMEM127 mutation [96]. No

TMEM127 mutations were detected in 129 sympathetic and 60 parasympathetic PGLs [93], but in a recent study, germline missense variants were detected in two out of 48 patients with multiple PGLs [97], one of which also displayed bilateral PCC. Summarizing the 23 reported patients, all but one (96%) had PCC and 39% had bilateral PCC.Two (9%) had PGL, of which one had sympathetic and the other multiple parasympathetic PGLs. The mean age at presentation was 43 years, and one patient (4%) displayed a malignant tumor.

4.2. MYC-associated factor X (MAX)

MAX is a gene of five exons, located on chromosome 14q23.3. It encodes a transcription factor, MAX, that belongs to the basic helix–loop–helix leucine zipper (bHLHZip) family and plays an important role in regulation of cell proliferation, differentiation, and death as a part of the MYC/MAX/MXD1 network [98]. Members of the MYC family are proto-oncoproteins and their expression correlates with growth and proliferation, whereas expression of MXD1 (also known as MAD) is associated with differentiation. Heterodimerization of MAX with MYC family members results in sequence-specific DNA-binding complexes that act as transcriptional activators. In contrast, heterodimers of MAX with MXD1 family member repress transcription of the same target genes by binding to the same consensus sequence and thus antagonize MYC–MAX function. Interestingly, PC12 cells, derived from a rat PCC, express only a mutant form of MAX incapable of dimerization, and a reintroduction of normal MAX in these cells resulted in a repressed transcription and inhibited growth [99]. This suggests that some tumors can grow in the absence of MYC–MAX dimers and may imply that MAX can function as a tumor suppressor. A tumor suppressor role of MAX was most recently confirmed when germline MAX mutations were discovered in PCC patients by next-generation exome sequencing [73]. The mutations were missense, nonsense, splice site, or altering the start codon, and immunohistochemical analysis confirmed the lack of full-length MAX in the tumors. LOH of 14q, caused either by uniparental disomy or by chromosomal loss, was seen in investigated tumors in agreement with classical tumor suppressor behaviour.

MAX mutations segregate with the disease in families with PCC [73], but no specific syndrome has been described yet. A paternal origin of the mutated allele in investigated cases, together with the absence of PCC in persons who inherited a mutated allele from their mother, may suggest a paternal transmission of disease similar to that of PGL1 (SDHD) and PGL2 (SDHAF2). MAX-associated PCCs and PGLs. Comino-Mendez et al. [73] reported 12 PCC patients with MAX mutations, of which three were discovered with exome sequencing and four were relatives of those. The remaining five were found in a subsequent screening of 59 PCC patients lacking mutations in other known susceptibility genes but suspected to have hereditary disease (due to bilateral tumors, early age of onset, and/or familial antecedents with the disease). Of the 12 patients, eight (67%) had bilateral PCC and the mean age at presentation was 32 years. Notably, 25% of the patients (38% of the probands) showed metastasis at diagnosis, suggesting that MAX mutations are associated with a high risk of malignancy. So far, no studies on PGLs have been reported.

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5. Therapy of hereditary NETs

5.1. Multiple Endocrine Neoplasias

5.1.1. MEN1

The therapeutic management of MEN1-related hyperparathyroidism, as the only curative therapy, is a surgical approach designed to remove all hyperfunctioning parathyroid tissue. This approach consists of the sub-total or total parathyroidectomy followed by autotransplantation of parathyroid tissue in a normal forearm. This approach is clearly different surgery for sporadic hyperparathyroidism. The main consequence of a radical intervention is a severe hypoparathyroidism, which requires treatment with high doses of calcium and vitamin D. This condition often leads to a difficulty in controlling the homeostasis of calcium and a reduced quality of life for the possible occurrence of gastro-intestinal disorders. It is not rare, in addition, the recurrence of hyperparathyroidism even after an apparently total parathyroidectomy. Studies are in progress to evaluate the efficacy of calcium-mimetic agents in the treatment of primary hyperparathyroidism in patients MEN1. Also somatostatin analogues, used in MEN1 subjects for the treatment of duodeno-pancreatic NETs, can have a role in reducing the levels calcium and PTH [6, 10, 100, 101]. The therapy of duodeno-pancreatic NETs in MEN1 patients varies depending on the type and number of tumors. Drug therapy involves the use of biologic therapy such as somatostatin analogues. For all pancreatic tumors MEN1-dependent, the standard surgical treatment involves the distal pancreatectomy combined with ultrasonography and intraoperative manual palpation. In the case of tumors located in the head of the pancreas a duodeno-cephalo-pancreatectomy second Whipple should be practiced. The treatment of choice of a solitary gastrinoma is enucleation. However, in MEN1patients gastrinomas are often multiple and/or metastatic and the role of surgery, in these cases, it is debated [6, 10].

Several studies are ongoing to evaluate the efficacy of new drugs such as tyrosine kinase and mTOR inhibitors for the treatment of metastatic pancreatic NETs.

The treatment of pituitary adenomas in MEN1 patients varies depending on the type of adenoma and is the same treatment applied to the sporadic counterpart. Finally, even in the case of a successful therapy, MEN1-related pituitary adenomas require a careful follow-up because these neoplasms can easily recur [6, 10].

At the moment there is no known preventive surgical approach that can significantly improve outcomes in MEN1 patients, with the exception of prophylactic thymectomy to prevent the occurrence of the rare thymic carcinoid tumor, a tumor frequently malignant and aggressive. This further supports the need to identify quite early the presence of malignancies, with a view to a better clinical management [10].

5.1.2. MEN2

The therapeutic strategy for MEN2 patients should be adapted to the clinical variant and the type of mutation in the *RET* gene according to the risk levels.

Subjects with the highest risk level have the most aggressive MTC and should have thyroidectomy with a central node dissection within the first six months of life and preferably within the first month of life. In subjects classified as risk 2 level, thyroidectomy with removal of the posterior capsule should be performed before the age of five years. For subjects with the lowest risk level (risk level 1) at this moment there are differing opinions on when thyroidectomy should be performed. According to some authors, in fact, total thyroidectomy with lymph node dissection of the central compartment should be practiced within the fifth year of life, according to others such intervention should be performed later, but within the tenth year of life. Other authors finally suggest to periodically perform the pentagastrin stimulation test for calcitonin and to perform the surgery at the first positive test. In all cases, if a pheochromocytoma is present, total thyroidectomy should be performed after surrenectomy to avoid a catecholaminergic crisis during the surgery [10].

Several studies are ongoing to evaluate the efficacy of new drugs such as tyrosine kinase inhibitors for the treatment of metastatic MTC.

The treatment of choice in unilateral pheochromocytoma in MEN2 is laparoscopic adrenalectomy [10].

The treatment for hyperparathyroidism in MEN2 includes the same surgical strategy as provided in other syndromes associated with multiple parathyroid adenomas [10].

5.2. Familial paragangliomatosis

The treatment of choice for FPGL is surgical removal of paraganglioma / pheochromocytoma, after preparation with α-and β-adrenergic blocking drugs in order to improve the perioperative hemodynamic stability. In the case of benign pheochromocytomas/paragangliomas the percentage of full resolution with surgery is approximately 100% [102]. Early intervention and timely manner helps to minimize the morbidity and mortality of this disease.For malignant pheochromocytomas/paragangliomas are available chemo- and radiotherapic approaches. Studies are in progress to evaluate the efficacy of tyrosine kinase inhibitors, such as sunitinib, for the treatment of malignancies. At the moment, there is no specific treatment prior to the onset of hereditary pheochromocytomas/paragangliomas [103, 104].

Early diagnosis and a periodic follow-up are the best approaches for the management and better outcome because of the possible malignant degeneration, especially in the forms associated with *SDHB* gene mutations [105].

6. Impact of genetic screening on natural history and clinical management

In the last years, the growing number of subjects with hereditary NET who is diagnosed at a pre-clinical stage is changing the clinical picture of these tumors. Until now the clinical features and natural history of hereditary NETs were based on data from patients with clinical

evidence of disease. With the identification of specific genes responsible for the development of hereditary NETs, more and more subjects are recognized to be carriers of NET-related gene mutations. Pre-clinical genetic screening in asymptomatic first-degree relatives of patients with hereditary NET syndromes leads to detect these neoplasias at an early stage, even when subjects are still asymptomatic.

The genetic risk assessment can provide crucial information on the patient's future risk for tumors and the assessed risk to their family members. An early genetic diagnosis in asymptomatic subjects is recommended to identify subjects at risk to develop one of the above mentioned hereditary NET syndromes as early as possible before the occurrence of clinical manifestations, in order to improve their long-term outcome and to ensure a survival and quality of life similar to that observed in the general population [5].

Since the screening for early symptoms starts, parents should be given counseling in the process of considering the test for their child. Support by a psychosocial worker may be a valuable part of the counseling.

Early detection of tumors in patients with hereditary NETs could encourage the use of cytostatic drugs for blocking the development of lesions in early stage or even in a pre-clinical phase, before that they are developed. Several studies are underway to demonstrate the anti-proliferative effect of these drugs.

7. Clinical, biochemical and instrumental monitoring of patients with hereditary NETs

Periodical evaluations in reference health centers are necessary in subjects with hereditary NETs in a pre-clinical phase (before the appearance of tumors), especially young subjects, to early detect tumors and prevent complications and risk of malignant transformation.

7.1. Multiple Endocrine Neoplasias

MEN1 patients and MEN1 carriers have to be monitored periodically.

The new guidelines for periodic clinical, biochemical and morphological monitoring of MEN1 patients is shown in Table 3 [106].

7.2. Familial paragangliomatosis

Patients with FPGL and SDHx carriers have to be monitored periodically to detect the presence of new lesions and to rule out a malignancy. Periodic clinical examination, laboratory tests measuring plasma free metanephrines, 24-hour urine catecholamines and metanephrines, imaging techniques including neck, skull base and abdomen/pelvis CT-scan and/or MRI and functional imaging techniques including somatostatin receptor scintigraphy and MIBG scintigraphy are mandatory in all patients with FPGL.

Tumor	Age to begin (yrs)	Biochemical tests annually	Imaging tests (time interval)
Parathyroid adenoma	8	Calcium, PTH	-
Gastrinoma	20	Gastrin	-
Insulinoma	5	Glucose, insulin	-
Other enteropancreatic NETs	10	CgA, PP, VIP, glucagon	MRI, CT or EUS (annually)
Anterior pituitary	5	PRL, IGF-1	MRI (every 3 yrs)
Foregut carcinoid	20	-	CT or MRI (every 1-2 yrs)

PTH: parathyroid hormone; CgA: chromogranin-A; PP: pancreatic polypeptide; VIP: vasoactive intestinal peptide; PRL: prolactin; IGF-1: insulin-like growth factor 1; MRI: magnetic resonance imaging; CT: computed tomography; EUS: echoendoscopy ultrasonography.

Table 3. Periodic clinical, biochemical and morphological monitoring of MEN1 patients

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