Familial syndromes associated with neuroendocrine tumours

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Neuroendocrine tumours may be associated with familial syndromes. At least eight inherited syndromes predisposing to endocrine neoplasia have been identified. Two of these are considered to be major factors predisposing to benign and malignant endocrine tumours, designated multiple endocrine neoplasia type 1 and type 2 (MEN1 and MEN2). Five other autosomal dominant diseases show more heterogeneous clinical patterns, such as the Carney complex, hyperparathyroidism-jaw tumour syndrome, Von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1) and tuberous sclerosis. The molecular and cellular interactions underlying the development of most endocrine cells and related organs represent one of the more complex pathways not yet to be deciphered. Almost all endocrine cells are derived from the endoderm and neuroectoderm. It is suggested that within the first few weeks of human development there are complex interactions between, firstly, the major genes involved in the initiation of progenitor-cell differentiation, secondly, factors secreted by the surrounding mesenchyme, and thirdly, a series of genes controlling cell differentiation, proliferation and migration. Together these represent a formula for the harmonious development of endocrine glands and tissue.

Key words: neuroendocrine tumours, familial syndromes.

Introduction

In the last 20 years at least eight inherited syndromes predisposing to endocrine neoplasia have been identified. Two of these are considered to be major factors predisposing to benign and malignant endocrine tumours, and they have been designated multiple endocrine neoplasia type 1 and type 2 (MEN1 and MEN2) [1]. Five other autosomal dominant diseases show more heterogeneous clinical patterns, such as Carney complex, hyperparathyroidism-jaw tumour syndrome, Von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis [2, 3]. One striking clinical entity is familial isolated paraganglioma-phaeochromocytoma syndrome, which is caused by mutations in the mitochondrial enzyme succinate dehydrogenase (SDH). Finally, a very uncommon MEN-related disease, McCune-Albright syndrome, is defined by polyostotic fibrous dysplasia, 'cafe au lait' skin lesions, sexual precocity, and nodular hyperplasia or adenoma of endocrine glands.

The molecular and cellular interactions underlying the development of most endocrine cells and related organs represent one of the more complex pathways yet to be deciphered. Almost all endocrine cells are derived from the endoderm and neuroectoderm. It has been suggested that within the first few weeks of human development there are complex interactions between, firstly, the major genes involved in the initiation of progenitor-cell differentiation, secondly, factors secreted by the surrounding mesenchyme, and thirdly, a series of genes controlling cell differentiation, proliferation, and migration. Together these represent a formula for the harmonious development of endocrine glands and tissue.

To our knowledge, the only MEN-related gene that has been unambiguously shown to be involved in the embryological derivation of endocrine glands is the RET proto-oncogene, activating mutations of which predispose to MEN2 syndrome. RET encodes a transmembrane tyrosine kinase with an extracellular cadherin domain that is involved in calcium-dependent cell-cell interactions, and binding of glial cell-derived neurotrophic factor (GDNF) and derived molecules (e.g. neurturin, artemin, and persephin) [4]. RET expression is detected in all cranial ganglia, vagal neural crest cells (which colonise the entire gut), and subsequently all myenteric and submucous plexi, which later form the enteric nervous system [5, 6].

The situation is not so clear for MEN1, a genetic disease affecting tissues that originate from the endoderm. Some specific points may be of interest. The pancreas develops from the primitive foregut endoderm, which then differentiates into ductal, acinar, and endocrine cells [7, 8]. The protein encoded by MEN1, menin, is a pluripotent adapter factor that may interact with over 25 different proteins in the cell, all of which play a major role in various cellular and molecular pathways. From a practical point of view, it is important to link the relevant mutations with symptoms and diseases. Today we know what diseases are present in the described syndromes. Biochemistry and imaging allow prompt diagnosis. Early surgical treatment often results

Table 1. Familial syndromes associated with neuroendocrine tumours (genes and clinical symptoms)

Syndromes	Oncogenes and their role in disease development	Phenotypes – clinical features
MEN1 (Werner syndrome)	Menin – (tumour suppressor gene) controls the expression of inhibitors of the activity cyclin-dependent kinase p27Kipl and p181nk4c. The lack of menin activity results in down-regulation of p27Kipl and p181nk4c and leads to uncontrolled cell growth	primary hyperparathyroidism – 21% Zollinger–Ellison syndrome – 33% insulinoma – 17% VIP-oma – 35% pituitary tumours – 35% adrenocortical tumours – 25% thymic and/or bronchial tube endocrine tumours (foregut carcinoid tumours) – 10%
MEN2 (2a, 2b)	RET-oncogene encodes a receptor tyrosine kinase. RET presents two alternative isoforms – RET 9, RET 51. RET protein is a subunit of complex that binds growth factors of the glial-cell-derived neurotrophic factor (GDNF). Most MEN 2a mutations affect cysteine (634) in extracellular domain. Most MEN 2b patients carry the M918T mutation in intracellular tyrosine kinase domain	medullary thyroid carcinoma (MEN 2a and 2b) – 100% phaeochromocytoma (MEN 2a and 2b) – 50% primary hyperparathyroidism (MEN 2a) – 25% neuromas of the tongue ganglioneuromas of the intestine and a marfanoid habitus (MEN 2b) – 95%
Von Hippel-Lindau	VHL – gene responsible for creating the full length protein pVHL30 regulating cell cycle control, mRNA stability and activity of hypoxia-inducible gene expression	haemangioblastomas of central nervous system and retinae clear cell renal carcinoma phaeochromocytoma pancreatic cystic and/or endocrine tumours
Neurofibromatosis type 1 (Recklinghausen disease)	NF1 (suppressor gene) responsible for the expression of neurofibromin. Neurofibromin is homologous of proteins activating GTP-ase-dependent p21 Ras. Its importance lies in the tumour suppressing by regulating the activation of the Ras-dependent signal	cafe au lait macules of skin neurofibromas auxiliary or inguinal freckling optic glioma retinal Lisch nodules

in complete recovery. Patients with metastatic disease are treated with targeted therapy. Syndromes, their symptoms, and genetic factors are shown in Table 1.

MEN 1 syndrome

MENl (Werner syndrome) is an autosomal dominant disease characterised by multifocal endocrine tumours affecting the parathyroid glands, endocrine pancreas, anterior pituitary, cortical areas of the adrenal glands, and diffuse endocrine tissues in the thymus and bronchial tubes. The prevalence throughout the world is estimated to be 1 in 40 000 to 1 in 20 000. The prevalence has probably been underestimated because at initial diagnosis most patients only have a single endocrine lesion. MENl has a high penetrance and an equal sex distribution [9–11].

Clinical features

In MENl, primary hyperparathyroidism (pHPT) is the most common sign, seen in more than 90% of MENl patients. MENl-related parathyroid disease manifests as a multiglandular disease rather than as a solitary adenoma. Histological findings show hyperplasia of four (or more) glands, with a single or multiple adenoma/s, the chief cell being the predominant cell type. MENl parathyroid neoplasia remains benign and may be asymptomatic throughout the patient's life, causing only mild hypercalcaemia. To prevent the long-term complications of hypercalcaemia, particularly renal lithiasis, patients are treated with surgery: either a total parathyroidectomy with autotransplantation, or subtotal resection of three and a half

parathyroid glands with cryopreservation of the remaining gland [12–15]. Although a cure is not possible, there is no appreciable risk of malignant transformation. Recently, the calcimimetic cinacalcet has demonstrated control of PTH secretion in a MEN1 patient who refused surgery, but the broader indications of the compound are not yet defined. The second common manifestation in MEN1 is endocrine tumours of the duodenum and pancreas, which show highly variable clinical expression. Zollinger-Ellison syndrome is the most frequent clinical state related to gastrinomas, tumours that secrete gastrin. The resulting gastric acid hypersecretion leads to multiple peptic ulcers, reflux oesophagitis, and diarrhoea. Gastrinomas occur in 20–60% of MEN1 patients, and management of acid secretion by H+–K+ ATPase inhibitors has significantly reduced the risk of gastric bleeding or perforation. These tumours have a malignant evolution in 40–50% of cases [16–18]. Gastrinomas are most commonly located in the gastrinoma triangle, a term given to the region between the cystic and common bile duct, the junction of the second and third portions of the duodenum, and the junction of the neck and body of the pancreas; these tumours are typically multi-focal. Benign insulinomas are observed in a significant proportion of MEN1 patients and may affect young patients even after 1-3 years of atypical clinical symptoms (abdominal pain, diarrhoea). Malignant insulinomas are less frequent and may be present in 5–10% of cases. Less common MEN1-related tumours are glucagonomas, VIP-omas (vasoactive intestinal peptide secreting lesions) or somatostatinomas, which occur in around 5% of patients,

but these tumours are characterised by a high rate of malignant evolution (> 80%). Non-functioning pancreatic endocrine tumours may be in 20% patients. Surgical enucleation is indicated in cases where a hormonally active tumour – such as an insulinoma – can be specifically localised, or when a tumour exceeds 2 cm in size, as this appears to be associated with a higher risk of malignancy. Pituitary tumours represent the third component of the MEN 1 clinical triad and are the first clinical manifestation in 10–20% of cases. Such lesions affect 20–60% of MEN1 patients and are macroadenomas in more than 80% of cases [19–22]. Frequent secretion profiles are due to prolactinomas (around 60%), growth-hormone-secreting lesions (around 10–20%), or ACTH producing tumours (around 5%), but 15–30% of anterior pituitary adenomas in MEN1 are clinically silent with only in situ expression of single or multiple hormones. Lastly, thymic and bronchial neuroendocrine tumours affect 5–10% of MEN1 patients and, like duodenal and pancreatic tumours, they originate in the foregut. Thymic endocrine proliferations are observed exclusively in males and carry a poor prognosis [23–25]. They must be checked carefully by computed tomography (CT), magnetic resonance imaging (MRI), and somatostatin receptor scintigraphy for early surgery. Bronchial carcinoid tumours are less common in MEN1, occur predominantly in women, and also need curative resection [26, 27]. Cutaneous lesions are present in 40–80% of patients, mostly nodular lipomas, collagenomas, and multiple facial angiofibromas, the latter being histologically identical to those observed in patients with tuberous sclerosis [28, 29]. Other skin lesions observed are 'cafe au lait' macules, confetti-like hypopigmented macules, and gingival papules. In some families MEN1 co-segregates with primary malignant melanoma, which in rare cases may also affect the choroids [29]. This highlights a possible role for MEN1 gene alterations in a low-risk subgroup with melanoma predisposition [30]. Gastric tumours arising from enterochromaffin-like cells (ECLomas) in gastric fundus or body mucosa are observed in 5–10% of MEN1 patients, mainly those with Zollinger-Ellsion syndrome [31–33]. The diagnostic criteria for MEN1 are described in Table 2. Early surgical treatment in MEN1 provides opportunities for complete recovery. Pituitary microadenomas are operated neurosurgically. Macroadenomas are treated pharmacologically or by radiotherapy. In the case of parathyroid surgery, treatment is radical (total parathyroidectomy). Pancreatic neuroendocrine tumours are diagnosed in the stage of liver metastases. Primary lesions are surgically removed. Liver metastases are treated with somatostatin analogues. Radiofrequency ablation is an alternative method.

Genetic screening of the MEN1 locus and clinical implications

Germline and somatic mutations in the MEN1 gene do not cluster in hot spots, being spread over the entire coding (exon) and non-coding (intron) sequence. More than 400 different mutations have been described to date, and a limited number of these are derived from common ancestors in well-identified geographically clustered families [35–38]. Around 60% of germline mutations lead to a truncated protein, either by nonsense (around 40%) or frameshifts (around 20%). Thirty per cent of mutations are missense or in-frame deletions or insertions.

All mutations located in introns and some of the nucleotide substitutions inside exon sequences require reverse transcriptase PCR (RT-PCR) analysis of transcripts to identify splice defects. No functional tests for missense mutations have been established to date. It was recently suggested that almost all of the common amino-acid substitutions are rapidly degraded via the ubiquitin-proteasome pathway, thus suggesting that missense mutations lead to haploinsufficiency in the same way as truncating alterations [38–40].

Non-familial presentations of at least one or two MEN1-related endocrine tumours have been studied in different studies; it has been suggested that around 8% of patients with isolated pHPT and 6% of those affected by endocrine tumours of the pancreas harbour a MEN1 germline mutation when the disease occurs before the age of 50 years. Penetrance of MEN1 in gene-carriers is about 80% at age 50 years, and more than 10% of mutations arise *de novo* [41–44]. Several studies have suggested that genetic screening of MEN1 is not useful for patients who present with sporadic pituitary tumours or adrenal cortex lesions when the family history has been proven to be clearly negative.

MEN2 syndrome

Clinical features

MEN2 syndrome is an autosomal dominant disease predisposing in all cases to medullary thyroid carcinoma (MTC), with the coexistence of phaeochromocytoma

Table 2. Signs that may suggest MEN1 Syndrome

The following are the diagnostic criteria established during a consensus conference at the VII International Multiple Endocrine Neoplasia Workschop Gubbio, Italy 1999. Two or more of the following criteria in a single patient or in first, and/or second-degree relatives, may suggest the diagnosis of MEN1 and lead to a genetic analysis of the MEN1 gene

1. Primary hyperparathyroidism with multiglandular hyperplasia and/or adenoma, or recurrent primary hyperparathyroidism
2. Duodenal and/or pancreatic endocrine tumours both functional (gastrinoma, insulinoma, glucagonoma) or non-functional or multisecreting tumours, as proven by immunohistochemistry
3. Gastric enterochromaffin – like tumours
4. Anterior pituitary adenoma both functional (growth-hormone-secreting tumours or acromegaly, prolactinoma) or non-functional proven by immunohistochemistry
5. Adrenocortical tumours, both functional and non-functional
6. Thymic and bronchial tube endocrine tumours (foregut carcinoid tumours)

and pHPT in around 40–60% and 20–40% of patients, respectively. Three variants have been identified in MEN2A, MEN2B, and the familial isolated presentation of MTC (FMTC), all of which are allelic variants for the same predisposing gene: the RET proto-oncogene on chromosome 10 [45–48].

MEN2B is uncommon and is characterised by the onset of MTC at a very young age, with a relatively aggressive pattern and an absence of pHPT. Patients with MEN2B also show atypical lesions, such as neuromas of the tongue, ganglioneuromas of the intestine, and a marfanoid habitus.

The hereditary form of MTC may represent 25–30% of all MTCs, leading many clinicians and geneticists to suspect MEN2 in cases of MTC occurring before the age of 50 years. MTC is a cardinal lesion and may be diagnosed fortuitously in the evaluation of thyroid nodules. MEN2-related MTC occurs at a younger age (30–40 years) than the sporadic form (50–60 years) and is typically bilateral and multicentric. Another feature that distinguishes the familial and sporadic forms is the frequent presence of C-cell hyperplasia in MEN2-related MTC. Diagnosis is based on clinical examination, fine needle aspiration biopsy (FNAB), and basal and pentagastrin-stimulated calcitonin levels in blood, CT, and scintigraphy – 99mTc-methoxyisobutylisonitrile (99mTc-MIBI). General genetic tests based on RET mutations are performed routinely in each patient with MTC. Phaeochromocytoma is the second most common tumour in MEN2 and may occur as the first lesion to present in the course of the disease. Several reports have suggested that phaeochromocytoma may also occur after more than 10–20 years of follow-up in families initially diagnosed with familial MTC, indicating that patients with MTC, particularly those with a familial history, must be screened for adrenal medullary tumours. The most common symptoms of phaeochromocytoma are hypertension and signs related to adrenergic stimulation. Biochemically, phaeochromocytoma can be diagnosed by elevated levels of free catecholamines in a 24-hour urine test or more sensitively by the determination of plasma metanephrines. MEN2-related phaeochromocytoma may often occur as bilateral lesions. CT, MRI, and [131I]meta-iodobenzylguanidine (MIBG) scintigraphy will aid in diagnosis, which must be made before any operative procedure due to the high risk of acute hypertension and sudden death related to abnormal catecholamine secretion under stressful conditions [49–51].

The third most common disorder in MEN2 is pHPT, which has no clinical or histological specificity in MEN2 compared with MEN1 or sporadic situations. In the case of MEN2 total thyroidectomy is used. Medullary thyroid carcinoma occurs most frequently in this syndrome. In the case of pheochromocytoma, adrenalectomy is performed. Hyperparathyroidism is directed to total radical surgery. Tyrosine kinase inhibitors are applied in patients with metastatic medullary thyroid carcinoma. In some cases of pheochromocytoma, radioisotope therapy is used (131-I-MIBG).

Molecular genetics of MEN2 syndromes

Located near the centromere of chromosome 10, the RET (rearranged during transfection) gene spans 60 kb with 21 exons. It encodes a receptor tyrosine kinase (RTK). The extracellular part of RET contains four cadherin-like repeats, a calcium binding site and a cysteine-rich domain involved in RET protein dimerisation after the binding of a ligand. The intracellular part contains a typical tyrosine kinase domain. RET presents as two alternative isoforms of 1072 (RET9) and 1114 (RET51) amino acids.

The RET protein is a subunit of a multimolecular complex that binds growth factors of the glial cell-derived neurotrophic factor (GDNF) family. Four ligands have been characterised, GDNF, neurturin, artemin, and persephrin, which act on RET through four glycosylphosphatidylinositol anchored co-receptors and the GDNF family receptors-a (GFR-a) 1, 2, 3, and 4 [52–54]. The binding of ligands and GFR-a co-receptors brings together two RET molecules that then interact through the cysteine-rich domain. This triggers autophosphorylation and intracellular signalling.

A series of tyrosine molecules located in the RET intracellular domain are the autophosphorylation sites, which serve as docking sites for intracellular signalling proteins.

Activating point mutations of the RET proto-oncogene, both in the cysteine-rich and the tyrosine kinase domains, leads to MEN2 syndrome [55–57]. Most MEN2A and FMTC mutations affect cysteine residues in the extracellular cysteine-rich domain (exons 10 and 11). A common mutation found in over 80% of typical MEN2A patients is a missense mutation at amino acid 634, particularly C634R, whereas FMTC/MEN2A mutations are spread among the various cysteine molecules of this region [58, 59]. Patients with sporadic MTC also harbour somatic RET mutations in around 50% of cases, primarily at codons 768, 804, and 918. A MEN2B-like mutation in sporadic MTC might be related to a more aggressive course of the disease [60].

Endocrine tumours in von Hippel-Lindau syndrome

Clinical features

Von Hippel-Lindau syndrome (VHL) is an autosomal, dominantly inherited disease in which the most frequent tumours are retinal and central nervous system haemangioblastomas, clear cell renal carcinoma, phaeochromocytoma and pancreatic cystic and/or endocrine tumours [61–64]. The incidence has been estimated as 1 in 36,000 live births. Diagnostic criteria are mainly based on a confirmed family history and/or the occurrence of haemangioblastomas, tumours that are relatively uncommon in the general population.

Type 1 VHL is characterised by the presence of haemangioblastomas and clear cell renal carcinomas. Laparoscopic nephron-sparing surgery should be the approach for renal cell carcinomas less than 4 cm, otherwise radical nephrectomy is the treatment of choice. Patients with metastatic disease can be treated by chemotherapy or targeted agents (sunitinib, bevacizumab, everolimus) [65]. Patients with type 2 VHL disease also develop phaeochromocytomas. Familial isolated forms of phaeochromocytoma may be of interest and suggest VHL disease [66]. VHL-associated phaeochromocytomas

are multifocal, bilateral and may involve both adrenal and extra-adrenal chromaffin tissues. The mean age of diagnosis is 28 years, the youngest patient described being 5 years old. VHL phaeochromocytomas have been distinguished from those occurring in MEN2 by histological criteria: thick vascular tumour capsule, hyalinised stroma, and tumour cells mixed with a high density of small vessels and a lack of nuclear atypia. Tumours share a low catecholamine content, and this may be correlated with the frequent asymptomatic presentation (70–85%) of phaeochromocytoma in VHL patients. Low levels of phenylalanine-N-methyltransferase (PNMT) and tyrosine hydroxylase (TH) characterise VHL tumours when compared with MEN2-associated phaeochromocytoma [67, 68]. The prognosis is relatively good, and partial adrenalectomy is considered the gold standard of treatment to preserve, where possible, adrenal gland function. Around 5–20% of VHL patients may develop malignant disease, a local recurrence after surgery, and/or bilateral phaeochromocytoma. CT, MRI, or MIBG scanning can be utilised to diagnose phaeochromocytoma. Pancreatic cysts and tumours are observed in 20–75% of VHL patients. In one study, the systematic digestive tract screening of a large series of VHL patients showed pancreatic involvement in around 75% of VHL patients, including 91% with true cysts, 12% with serous cyst adenoma, 12% with neuroendocrine tumours, and 11% with combined lesions [69]. The neuroendocrine tumours in VHL patients are mostly non-functional – non-secreting.

Molecular genetics of Von Hippel-Lindau syndrome and clinical implications

Von Hippel-Lindau syndrome is caused by inactivating or missense mutations in the VHL gene located on chromosome 3p25-26. VHL consists of three exons with an open-reading frame of 639 nucleotides. Two alternative transcripts, characterised by the presence or absence of exon 2, characterise VHL protein isoforms I and II, both of which are expressed in most adult tissues and are developmentally regulated. The pVHL protein has been shown to influence several processes, including cell-cycle control, mRNA stability, and, mainly, the regulation of hypoxia-inducible gene expression [70–72].

All tumours characterising VHL syndrome are highly vascular and overexpress a large number of hypoxia-inducible genes and factors, such as vascular endothelial growth factor (VEGF) and its receptor (VEGFr). The pVHL protein has been implicated in many other cellular pathways, such as cell-cycle control, regulation of mRNA stability, and the metabolism and stability of fibronectin and microtubules inside the cell.

Other clinical correlations have been clearly shown for the type 2 VHL clinical variant, which exhibits a high risk of phaeochromocytoma. In contrast with the type 1 variant, in which the risk of adrenal medulla tumours is low and is characterised by truncating mutations [73–77]. A search for large germline deletions of the VHL gene must be routinely practiced, as these mutations may be seen in as many as 20–30% of VHL patients.

Endocrine tumours in neurofibromatosis type 1 syndrome

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1, Recklinghausen disease) is the most common familial disease predisposing to peripheral nervous system tumours, with a prevalence of 1 in 3000. The diagnostic criteria for NF1 are the presence of two or more of the following [78]:

• six or more 'cafe au lait' macules of significant size,
• two or more neurofibromas and/or one plexiform neurofibroma,
• auxiliary or inguinal freckling,
• optic glioma,
• two or more retinal Lisch nodules,
• osseous lesions such as sphenoidal dysplasia or pseudarthrosis,
• a first-degree relative with one or more of the previous lesions.

Two endocrine lesions, phaeochromocytoma, and/or gangliocytic paraganglioma may occur in 1–2% of NF1 patients and are symptomatic in around 50% of these cases. In addition, there may be duodenal or, rarely, gastric or pancreatic endocrine tumours, which label strongly with endocrine markers and may often express somatostatin [79]. These true somatostatinomas remain asymptomatic, in contrast with the sporadic forms of these rare tumours, which frequently display a multi-hormonal pattern. Nevertheless, more exhaustive clinical screening of NF1 patients might suggest that the frequency of adrenal and ectopic phaeochromocytoma has been underestimated, and may affect more than 6–9% of NF1 patients.

The NF1 gene is located at 17ql 1.2 and contains exons. The mutations are dominant and the well-documented function of the NF1-encoded protein, neurofibromin, is related to the NF1-GTPase activating protein (GAP) domain [80]. NF1 acts as a Ras-GTPase activating protein, a negative regulator that stimulates conversion of Ras-GTP to Ras-GDP. Close functional relationships may exist between neurofibromin and the tuberous sclerosis genes TSC1 and TSC2 through the mammalian target of rapamycin (mTOR) pathway, with NF1 acting as a negative regulator of mTOR [81]. Aberrant activation of mTOR depends on Ras and PI3-kinase, which inactivates the TSC2 gene product tuberin via an AKT-dependent pathway. Neurofibromin is rapidly degraded in response to growth factors and its re-expression is required to appropriately terminate the Ras signal under physiological conditions. The function of NF1 in the suppression of the mTOR signal in the absence of mitogenic stimuli may suggest that rapamycin derivatives are potential therapeutic agents in NF1-associated tumours [82]. Mutational analysis of the NF1 gene, covering 300 kb of genomic DNA and representing 11 kb of coding sequence, remains difficult, and around 50% of cases result from neomutations. Both loss of heterozygosity and neurofibromin expression have been observed in NFl-associated tumours. To date, extensive genetic screening of patients and families diagnosed as NF1 based on the previously described clinical criteria have an identified mutation in 20–60% of cases [83].

Tuberous sclerosis

Tuberous sclerosis (TSC) is a bigenic, autosomally dominant disorder characterised by benign hamartomas and low-grade neoplasms in multiple organs including the brain, heart, skin, kidney, lung, and pancreas. The two variants, TSC1 and TSC2, are related to inactivating mutations in one of the two growth suppressor genes; TSC1 on chromosome 9q34, which encodes hamartin; and TSC2 on chromosome 16p13, which encodes tuberin. Major clinical signs in tuberous sclerosis are epilepsy and mental retardation due to intracerebral proliferations, renal failure, skin hypopigmentation, and various other tumours. Malignant islet cell tumours have been described in 1–5% of patients. Depending on the gene mutated, immunohistochemical analysis of pancreatic tumours shows loss of hamartin or tuberin expression. As with NF1, rapamycin derivatives have been considered as potential drugs for the co-treatment of tuberous sclerosis-related lesions [84].

Familial isolated forms of endocrine tumours

Familial isolated hyperparathyroidism type 2 syndrome represents a rare and particular form of familial pHPT (FIHPT), which is also referenced as familial pHPT with multiple ossifying jaw fibromas. HRPT2 is an autosomal dominant disease, which mainly affects the parathyroid glands, either as an adenoma or carcinoma. Associated lesions in HRPT2 are: renal hamartomas, uterine polyps, and pancreatic neuroendocrine tumours [85].

Familial isolated forms of phaeochromocytoma and paraganglioma linked to SDH genes are particular familial diseases that are recognised recently through long-term studies focusing on patients and their relatives with adrenal and extra-adrenal paragangliomas (PGLs) or phaeochromocytomas without any evidence of VHL. Familial isolated forms of PGL and phaeochromocytoma have recently been linked to germline mutations – to three nuclear genes encoding subunits of the mitochondrial complex of succinate dehydrogenase (SDH) [86].

In conclusion, the identification of the major genes involved in predisposition to endocrine tumours has begun to provide some insights into the pathways involved in endocrine cell hyperplasia and tumour progression. The main processes include gene regulation by transcription factors, response to stress through the p53 pathway, regulation of DNA replication, and repair.

Finding the specific genes, and more importantly the key functions of the genes that are involved in endocrine tumour initiation, remain a challenge. Recognising familial endocrine tumour syndromes is an important way to understand not only genetic predisposition, but also tumour pathogenesis, and numerous animal models are now available both for biological research and the identification of pharmaceutical targets. In the last 15 years most of the syndromes that predispose to endocrine tumours have been identified and studied extensively, thus providing clinicians with important tools for the differential diagnosis of MEN disorders and guidelines for clinical follow-up and therapy [87, 88].

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