Familial endocrine tumours: phaeochromocytomas and extra-adrenal paragangliomas

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Abstract

About 30% of phaeochromocytomas (PCCs), sympathetic paragangliomas (sPGLs) and parasympathetic paragangliomas (pPGLs) are due to a familial syndrome. In half of these patients the presentation is syndromic or accompanied by a positive family history. However, over 10% of patients with clinically sporadic disease are still affected by an inheritable disease. Patients with multiple and/or bilateral tumours or disease onset at a young age are at an increased likelihood of such a syndrome and require genetic counselling and DNA testing. A genotype–phenotype correlation is emerging: multiple endocrine neoplasia type 2 (MEN-2) and von Hippel – Lindau disease-associated adrenal PCCs are often bilateral. Extra-adrenal (malignant) sPGLs are more typical in *SDHB* families. Multiple pPGLs (sometimes together with PCCs) occur in the setting of *SDHD* mutations, and *SDHC* families suffer from familial singular pPGLs. Some familial tumours also show typical histological features which should be looked for and reported by the pathologist. We review endocrine tumour syndromes with PCCs and/or PGLs, and summarize their genetic background and clinical and morphological features, and give recommendations for genetic testing.

Keywords genetics; multiple endocrine neoplasia type 2; neurofibromatosis type 1; paraganglioma; phaeochromocytoma; *SDHB*; *SDHC*; *SDHD*; tumour syndrome; von Hippel–Lindau disease

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Introduction

Phaeochromocytomas (PCCs) and paragangliomas (PGLs) are tumours of neural crest-derived cells, which are organized into so-called paraganglia and form part of the sympathetic and parasympathetic autonomous nervous system throughout the body. PCCs are defined as tumours that arise from chromaffin tissue in the adrenal medulla. Similar tumours may also arise outside the adrenal medulla in the vicinity of sympathetic ganglia or along visceral branches of sympathetic nerves; they are then called extra-adrenal sympathetic paragangliomas (sPGLs). PCCs and sPGLs exhibit similar histological features and biochemical profiles and may clinically become symptomatic due to overproduction of catecholamines.

Parasympathetic paragangliomas (pPGLs), which some clinicians unfortunately still refer to as 'glomus tumours' or 'chemodectomas', arise along cranial and thoracic branches of the glossopharyngeal and vagus nerve and are mostly located in the head and neck region. They are usually not functional and become clinically apparent by local symptoms.[1,2]

Histopathological diagnosis of PCCs and sPGLs is based upon the characteristic picture of so-called 'Zellballen', formed by nests of large uniform polygonal cells with granular amphophilic or basophilic cytoplasm and intense immunoreactivity for synaptophysin and chromogranin A. These cell nests are surrounded by sustentacular cells, which are non-neoplastic and only become evident after immunohistochemical staining with S-100.

Parasympathetic PGLs often exhibit a more pronounced 'Zellballen' pattern and a clearer or more eosinophilic cytoplasm than their sympathetic counterparts, but overlap exists between the two types of tumour.[1]

Malignancy of PCC and PGL is defined by the presence of metastases located at sites where paraganglionic tissue is not normally present, for example liver, bone or lymph node. Multifactorial scoring systems have been proposed to discriminate tumours that pose a significant risk of metastasis from those that do not.[3,4]

Recently it became clear that up to 30% of PCCs and PGLs occur in a familial setting and that syndromes exist in which both PCCs and PGLs may develop in the same family. Currently six different genes are known to be associated with hereditary syndromes encompassing PCCs and PGLs in their phenotype: *RET*, *VHL*, *NF1*, *SDHB*, *SDHC* and *SDHD*. The associated hereditary disorders of the above mentioned genes are multiple endocrine neoplasia (MEN) type 2A and 2B, von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1) and three newly recognized syndromes (PGL1, PGL3 and PGL4) in which inheritable PGLs or a combination of PCCs and PGLs occur in a familial setting (Table 1).

We review the different, above mentioned endocrine tumour syndromes and summarize their genetic background, clinical as well as morphological features, and give recommendations for genetic testing.

Multiple endocrine neoplasia

The term multiple endocrine neoplasia (MEN) encompasses genetically determined disorders with a predisposition to neoplastic endocrine lesions in two or more organs of the same patient.[5] Currently, two established well-described subtypes exist: MEN type 1 (MEN-1) and MEN type 2 (MEN-2).

Familial phaeochromocytomas and paragangliomas

Syndrome	PCC unilat	PCC bilat	PGL symp[a]	PGL para	Gene	Chromosome
MEN-2	+	++	–	–	*RET*	10q11.2
von Hippel-Lindau	+	++	(+)	–	*VHL*	3p25
von Recklingausen	+	(+)	–	–	*NF1*	17q11.2
PGL4	+	–	++[b]	+	*SDHB*	1p36
PGL3	–	–	–	+	*SDHC*	1q21
PGL1	(+)	–	(+)	++	*SDHD*	11q23

Unilat, unilateral; bilat, bilateral; para, parasympathtetic; (+), rare; symp, sympathetic and may secrete cathecholamines.

[a]'Extra-adrenal phaeochromocytoma'.
[b]Often malignant.

Table 1

The *MEN-1 syndrome* is characterized by the occurrence of pituitary adenomas, endocrine tumours of the pancreas/duodenum and parathyroid disease. Less common are endocrine tumours of the thymus, gastrointestinal tract and lungs. Furthermore, adrenocortical, lipomatous, skin lesions and ependymomas may also occur.[6] MEN-1 is caused by mutations of the *menin* tumour suppressor gene located on chromosome 11q13. The occurrence of PCC in this syndrome is very rare, with only a handful of patients described in the literature. However, the syndrome should be considered if a patient with a PCC also has other MEN-1-related tumours or a suggestive family history.[7]

The second type of multiple endocrine tumour syndrome is *MEN-2*, with an estimated incidence of 1.25–7.5 in 10,000,000 per year[8] and autosomal dominant inheritance (Table 2). It is historically subdivided into MEN-2A, MEN-2B and familial medullary thyroid carcinoma (FMTC). PCCs mainly occur in MEN-2A and MEN-2B but almost never in FMTC, which is characterized by the occurrence of medullary thyroid carcinoma (MTC) as the only manifestation of the disease.[9] MEN-2A is clinically defined by the presence of parathyroid hyperplasia, C-cell hyperplasia/MTC and PCC. The disease can manifest early in life, usually with MTC, but in 25% of cases, PCCs are the first manifestation of the disease. MEN-2B overlaps with the MEN-2A syndrome, with the exception of parathyroid hyperplasia. Striking in this syndrome is the occurrence of mucosal neuromas (leading to a peculiar facial appearance), intestinal ganglioneuromatosis, skeletal deformities and early onset of disease.[9]

Phenotypes of the multiple endocrine neoplasia type 2 syndrome

	PCC	MTC	Oral/intestinal ganglioneuromas	HPT
MEN-2A	+	+	–	+
MEN-2B	+	+	+	–
FMTC	–	+	–	–

FMTC, familial medullary thyroid carcinoma; HPT, hyperparathyroidism; MTC, medullary thyroid carcinoma; PCC, phaeochromocytoma.

Table 2

Since 1993 it has been well documented that activating germline mutations of the *RET* proto-oncogene, a tyrosine kinase located on chromosome 10q11, are responsible for all three subtypes of the MEN-2 syndrome. A variety of mutations have been described in different MEN-2 families with a clear genotype–phenotype correlation, allowing the prediction of disease phenotype, possible onset of disease and the risk for PCC development. This has led to recommendations concerning therapy and follow-up of gene carriers according to mutation type and location.[10,11]

In the MEN-2A subtype, mutations are mainly found in exons coding for the extracellular domain (exons 10 and 11) and 85% of mutations encompass codon 634. Only 10–15% of affected patients exhibit mutations of codons 609, 611, 618 and 620. Functional changes due to these mutations are dimerization of RET without the necessity of its ligand, with subsequent activation of the RET signalling pathway.[12]

Four mutations are associated with the MEN-2B phenotype, including point mutations at codons 918 and 883 (exons 16 and 15) and compound heterozygous mutations of V804M with Y806C and V804M with S904C. These mutations are located in the kinase domain of the receptor (coded by exon 16 of the *RET* gene, p.M918 T, in 95% of all cases) or close to it. The functional consequences of these mutations are diverse with loss of kinase inhibition, dimerization and autophosphorylation without substrate binding to the receptor, all leading to aberrant RET signalling.[13,14] Since the vast majority of mutations are located in exons 10, 11 and 16 of the *RET* gene and a few aberrations are known to occur in exons 13, 14 and 15, clinical genetic testing can usually be limited to the aforementioned exons.

It should be noted that family history alone is not sufficient to rule out the diagnosis of MEN-2, since de novo germline mutations occur. They account for about 10% of MEN-2A and up to 50% of MEN-2B patients. The presence of *RET* germline mutations in patients presenting with apparently sporadic PCC, however, is low (0.4%).[15]

MEN-2-associated PCCs are exclusively located in the adrenal medulla and are frequently multifocal and bilateral[9,16] (Figure 1a).