# Familial endocrine tumours: pheochromocytomas and extra-adrenal paragangliomas – an update

Esther Korpershoek
Francien H van Nederveen
Paul Komminoth
Ronald R de Krijger

## Abstract

Pheochromocytomas (PCC) and paragangliomas (PGL) are tumours occurring in the adrenal medulla and in extra-adrenal paraganglia, respectively. They have long been associated with familial occurrence and several syndromes had been described in which PCC formed an important component, including multiple endocrine neoplasia type 2, von Hippel-Lindau disease and neurofibromatosis type 1. Since the beginning of this millennium, both by the elucidation of specific genes, such as the various succinate dehydrogenase genes, as well as by generic molecular biology approaches, such as The Cancer Genome Atlas (TCGA) initiative, it was shown that the frequency of germline mutations in candidate genes for PCC and PGL has increased to 35–40%. In addition, somatic mutations have been shown to be much more frequent than previously thought, such that now 60–65% of these tumours harbour either a germline or a somatic mutation. This review gives an overview of the various syndromes and the genes involved, concluding with recommendations for genetic testing in the current era of genome wide analysis.

**Keywords** genetics; MEN2; NF1; paraganglioma; pheochromocytoma; SDHB; SDHC; SDHD; tumour syndrome; VHL

***Esther Korpershoek*** *PhD, Department of Pathology, Erasmus MC University Medical Centre Rotterdam – Cancer Institute, Rotterdam, The Netherlands. Conflicts of interest: none declared.*

***Francien H van Nederveen*** *MD PhD, Laboratory for Pathology, PAL Dordrecht, Dordrecht, The Netherlands. Conflicts of interest: none declared.*

***Paul Komminoth*** *MD PhD, Institute of Pathology, Stadtspital Triemli, Zurich, Switzerland. Conflicts of interest: none declared.*

***Ronald R de Krijger*** *MD PhD, Department of Pathology, Reinier de Graaf Hospital, AD Delft, and Department of Pathology, University Medical Center Utrecht and Princess Maxima Center for Paediatric Oncology, Utrecht, The Netherlands. Conflicts of interest: none declared.*

## Introduction

Pheochromocytomas (PCC) are neuroendocrine tumours of the adrenal medulla, whereas paragangliomas (PGL) are their extra-adrenal counterparts. Paragangliomas may arise from the sympathetic and parasympathetic autonomous nervous system and thus have a wide range of anatomical sites where they may occur, including abdominal, thoracic and head and neck locations, as well as in viscera, such as the bladder, pancreas or thyroid. Both PCC and PGL arise from cells that have their origin in the neural crest and are characterized by overproduction of catecholamines, including epinephrine, norepinephrine and dopamine.

Histologically, PCC and PGL also are very similar, and display a nested growth pattern with so-called "Zellballen", which are surrounded by non-tumourous sustentacular cells. The tumour cells have ample granular cytoplasm, which is basophilic in PCC and more eosinophilic in PGL, although there is overlap and this criterion cannot be used for the distinction of the two groups. The nuclei vary in size and may show significant degrees of atypia, even in benign tumours. To date, no good distinction can be made on the basis of histology, or indeed any other modality, between PCC and PGL that behave aggressively and/or metastasize and those that do not. Several classification systems have been proposed, but so far these have not gained wide acceptance and all of them have certain limitations.[1,2] Meanwhile, the original definition for malignancy for PCC and PGL, namely the presence of metastases in places where chromaffin tissue does not normally occur, is still valid, although some have postulated that all PCC and PGL should be regarded as having malignant potential, although not always displaying it.[3]

The tumour cells can be recognized by immunohistochemistry for neuroendocrine markers, such as chromogranin A and synaptophysin, or for components of the catecholamine biosynthetic pathway, including tyrosine hydroxylase or aromatic L-amino acid decarboxylase. In addition, the sustentacular cells can be stained with S-100. PCC and PGL do at most display weak and focal staining for keratin markers, and are frequently negative, in contrast to neuroendocrine tumours from pancreas and digestive tract.

Until the year 2000, there was a rule of 10, in which one of the rules was that 10% of PCC and PGL had a familial background. However, with the detection of more susceptibility genes, it was shown that this part of the rule of 10 was no longer valid, and currently up to 35–40% of patients have germline mutations in one of 21 genes. As many of these genes have been found in only very low numbers of patients, this review concentrates on those susceptibility genes and related syndromes that have been characterized more extensively. These will include the traditional syndromes, such as multiple endocrine neoplasia type 2, Von Hippel-Lindau disease and neurofibromatosis type 1, the succinate dehydrogenase gene-related syndromes, and also the most recently discovered PCC and PGL susceptibility genes and syndromes.

## Multiple endocrine neoplasia

This term is used for disorders that are composed of a combination of predominantly endocrine tumours occurring in the same patient or family, with a distinct genetic inheritance

 

pattern. Traditionally, there were two forms of multiple endocrine neoplasia (MEN), type 1 and type 2, but this has been more recently expanded to encompass 4 types, including MEN3 (the former MEN2B) and MEN4. For the purpose of this review, only MEN1, MEN2, and MEN3 will be discussed, and the latter will be referred to as MEN2A and MEN2B.[4]

MEN1 syndrome is an autosomal dominant syndrome with a prevalence of 2–3 per 100,000, caused by mutations in the menin tumour-suppressor gene on chromosome 11q13.[5] The syndrome is characterized by the occurrence of tumours in the pituitary gland, parathyroid glands and by endocrine tumours in the pancreas. In addition, but less frequently, there are endocrine tumours in the thymus, gastrointestinal tract, lungs, and adrenal cortex. Non-endocrine tumours include angiofibromas, collagenomas and lipomas of the subcutis, ependymomas, meningiomas, and schwannomas of the central nervous system, and smooth muscle tumours, including both leiomyomas and leiomyosarcomas.[5] PCC have been reported very rarely in the context of MEN1, but less than a dozen cases has been described. However, it seems prudent to consider MEN1 syndrome in the clinical differential diagnosis in patients that have a PCC plus another endocrine tumour that is known to occur in the context of MEN1.

MEN2 syndrome is another autosomal dominant syndrome and is known for the combination of medullary thyroid carcinoma (MTC) in 100% of patients, with frequently multifocal and/or bilateral PCC in 50% of patients. The syndrome encompasses three subgroups: MEN2A, which has, apart from the abovementioned tumours, also a 25–30% rate of parathyroid disease, MEN2B (also termed MEN3), which does not have parathyroid disease, but instead is characterized by very early onset MTC in combination with mucosal neuromas (of tongue and lips), intestinal ganglioneuromatosis, and skeletal deformities,[4] and familiar MTC (FMTC), which is characterized by MTC as the only manifestation. MEN2 has an incidence of 1.25–7.5 per 10,000,000 per year and is caused by germline mutations in the RET proto-oncogene.[6] Point mutations occur at specific locations along the RET gene, including exons 8, 10, 11, and 13–16.[7] The mutations cause ligand-independent dimerization of the tyrosine kinase receptor or autophosphorylation in the absence of ligand binding. A strong genotype–phenotype correlation has been established, predicting the age of onset and aggressiveness of MTC and the presence or absence of PCC.

In the context of MEN2 only PCC have been described and PGL do not occur. PCC are frequently multifocal and bilateral.[8,9] While MTC are the most frequent presenting tumour in MEN2, PCC are the first manifestation of MEN2 in up to 25% of patients. The histology of such tumours is indistinguishable from sporadic cases of PCC, although multinodularity may provide a clue to a syndromic diagnosis. They may be accompanied by diffuse and/or nodular hyperplasia of the surrounding and contralateral adrenal medulla which represents a precursor for PCC. On microscopic examination, MEN2-associated PCCs show cells with enlarged and hyperchromatic nuclei, cytoplasmic hyaline globules and an increased mitotic index (Figure 1). A fibrous capsule surrounding the tumours is absent.

PCC in the context of MEN2 are generally benign with less than 5% of cases exhibiting malignant behaviour. As indicated in the introduction, there are no criteria by which such malignant behaviour could be expected. Molecular analysis of PCC and adrenal medullary hyperplasia has revealed that similar genetic abnormalities at similar frequencies, including loss of heterozygosity at 1p, 3p, and 3q, indicating that such small nodules should be regarded a small PCC.[10]

## Von Hippel-Lindau disease

Von Hippel-Lindau disease is an autosomal dominant disorder with an incidence of slightly less than 1 per 35,000.[11] It is caused by genetic abnormalities, including various types of mutations and larger deletions, in the VHL gene on chromosome 3p25. These abnormalities involve the entire gene and thus no targeted approach, such as in the RET gene, can be employed. As in MEN2 syndrome, there is a peculiar genotype–phenotype

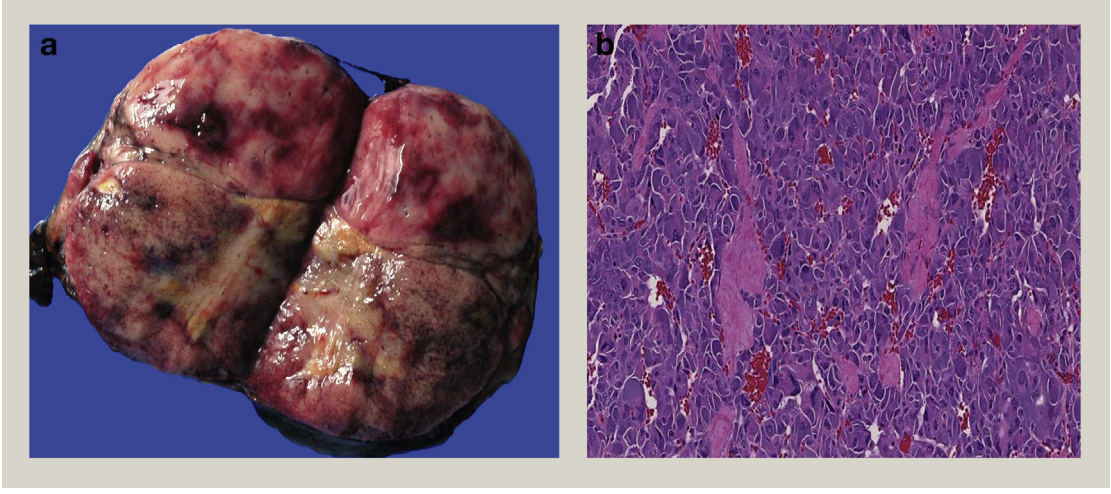


**Figure 1 (a)**: Macroscopy of adrenal tumours of a patient with MEN2A. Note the collision of two separate tumours. These tumours are different tumours, as proven by LOH analysis. MEN2-related pheochromocytomas often show medullary hyperplasia, which is a precursor of pheochromocytoma. **(b)**: Microscopy of a pheochromocytoma, with abundant basophilic cytoplasm, as frequently observed in patients with MEN2A syndrome.