Ann. Endocrinol., 2005 ; 66, 3 : 178-185
© Masson, Paris, 2005

Genetic Testing for Pheochromocytoma-associated Syndromes

Chr. Pawlu[1], B. Bausch[1], N. Reisch[2], H.P.H. Neumann[1]

(1) Department of Nephrology and Hypertension, Albert-Ludwigs-Universität, Freiburg, Germany,
(2) Department of Endocrinology, Medizinische Klinik Innenstadt, Ludwig-Maximilians- Universität, München, Germany.

Reprint request: H.P.H. Neumann, address above.
e-mail : neumann@medizin.ukl.uni-freiburg.de

Tests génétiques des syndromes des phéochromocytomes

Chr. Pawlu, B. Bausch, N. Reisch, H. P.H. Neumann

Ann. Endocrinol., 2005 ; 66, 3 : 178-185

Les phéochromocytomes et paragangliomes correspondent à des tumeurs du système nerveux autonome. Différents syndromes sont associés à la présence de phéochromocytomes et de paragangliomes : les néoplasies endocriniennes multiples de type 2 (NEM2, gène de susceptibilité : *RET*), la maladie de von Hippel-Lindau (VHL, gène de susceptibilité : *VHL*), le neurofibromatose 1 (NF1), et les syndromes paraganglionnaires de type 1, 3, et 4 (gènes de susceptibilité : SDH gènes des sous unités D, C et B de la succinate déshydrogénase). La prévalence et la présentation clinique des phéochromocytomes et des paraganglionomes sont différentes pour chacun de ces syndromes. L'analyse des mutations des gènes de susceptibilité de ces syndromes chez les patients ayant une phéochromocytome ou une paragangliome peut contribuer à l'évaluation du risque de tumeurs multiples et de l'apparition d'une phéochromocytome maligne ou d'une autre tumeur maligne. Nous présentons une revue des progrès de caractérisation clinique et de tests génétiques pour ces syndromes. À partir des caractéritiques des tumeurs et des données de prévalence, nous précisons les tests génétiques recommandés chez les patients ayant une phéochromocytome ou une paragangliome.

Mots-clés : Phéochromocytomes, paragangliomes, maladie de von Hippel-Lindau, néoplasies endocriniennes multiples, neurofibromatose, gènes de la succinate déshydrogénase, syndromes PGL.

Genetic Testing for Pheochromocytoma-associated Syndromes

Pheochromocytoma and paraganglioma are tumors of the autonomic nervous system. Various syndromes have been found to be associated with the development of pheochromocytomas and paragangliomas: multiple endocrine neoplasia type 2 (MEN 2, susceptibility gene: *RET*), von Hippel-Lindau disease (VHL, susceptibility gene: *VHL*), neurofibromatosis 1 (NF 1), and paraganglioma syndromes type 1, 3, and 4 (susceptibility genes: succinate dehydrogenase gene, SDH, subunits D, C and B, respectively). Prevalence and clinical features of pheochromocytomas and paragangliomas are different for each of these syndromes. Mutational analysis of the susceptibility genes of these syndromes in patients presenting with pheochromocytoma or paraganglioma may help to judge the risks of multifocality of the tumor as well as development of malignant pheochromocytoma or of other malignant tumors. Here we review the recent progress in clinical characterization and genetic testing for these syndromes. Based on tumor characteristics and prevalence data we give recommendations for an efficient genetic testing procedure in patients presenting with pheochromocytomas and paragangliomas.

Key words: Pheochromocytoma, paraganglioma, von Hippel-Lindau disease, multiple endocrine neoplasia, neurofibromatosis, succinate deshydrogenase gene, PGL syndromes.

INTRODUCTION

In recent years we and others have provided with details of pheochromocytoma patients and their possible risks for other tumors forming syndromes of genetic origin [1-5]. This has challenged the long established view that sporadic pheochromocytoma and paraganglioma reach a fraction of up to 90 per cent of these diseases. Today we know that likely at least each fourth case is associated with hereditable mutations in one out of just a few genes. Among these the best known syndrome is multiple endocrine neoplasia type 2 (MEN 2). In the past decade von Hippel-Lindau disease (VHL) has attracted much interest. For neurofibromatosis type 1 (NF 1) associated pheochromocytoma only a few reports exist. In recent years families with paraganglioma of the head and neck area have been subjected to genetic studies and form the complex of paraganglioma syndromes (PGL) with several subtypes. In this review we present a condensed description of all these syndromes and their genetic causes.

DEFINITION OF PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Pheochromocytoma and paraganglioma are tumors of the autonomic nervous system with an estimated

yearly incidence of 1:300000 [3, 6]. Tumors originating from the autonomous nervous system are named pheochromocytoma and paraganglioma. Although the terminology is divergent, for clinical purposes we and others use the terms as follows: pheochromocytoma refers to tumor location in the adrenal glands as well as in extraadrenal abdominal and in thoracic locations. The term paraganglioma refers to tumors in the head and neck area. Following this definition, most pheochromocytomas are endocrinologically active, whereas head and neck paragangliomas (HNPs) tend to be non-functioning.

To date it is still difficult to predict the clinical behavior of pheochromocytomas and paragangliomas. For the patient, however, it is of utmost importance whether at some stage of the disease malignancy has to be expected or not, whether multifocal tumors have to be taken into account or not and whether functioning or non-functioning neoplasias are likely.

A major progress in the characterization of these diseases and in the differentiation between distinct syndromes was the introduction of molecular-biological methods as standard diagnostic procedure in these patients. By now, based on a number of studies, predictions of the further progress of the disease are possible even in individual cases in which the syndrome is genetically clearly identified.

Given the costs of a detailed investigation of the candidate genes that may cause hereditary pheochromocytoma or paraganglioma, mutation analysis should start with the genes that are more likely affected than others in the respective patient. Therefore it may be valuable to define a diagnostic pathway based on tumor location and clinical features.

MEN 2 AND *RET* GENE

Two syndromes caused by mutations in two different gene loci are referred to as multiple endocrine neoplasias (MEN) [7]. MEN 1 is caused by mutations in the MEN 1 gene (11q13) and characterized clinically by tumors of the parathyroid, by entero-pancreatic tumors, and pituitary tumors. Whereas the adrenal cortex is also affected in up to 20 per cent of the cases, pheochromocytomas are extremely rare in MEN 1 patients (<1 per cent) [8]. MEN 2, on the other hand, is characterized by medullary thyroid carcinoma, pheochromocytoma, and parathyroid tumors. In up to 25 per cent of the cases, pheochromocytoma is diagnosed before medullary thyroid carcinoma is apparent [9]. MEN 2 is caused by mutations in the *RET*-protooncogene on chromosome 10q11.2, which encodes a transmembrane receptor tyrosine-kinase. There is good evidence for phenotype-genotype correlations in MEN 2 syndrome, i.e. the location of the mutation defines which of three subtypes develops: MEN 2A, MEN 2B, or familiar medullary thyroid carcinoma (FMTC). MEN 2A seems to be associated preferentially with mutations in the cysteine-rich extracellular domain of the RET protein, which allow the formation of pathological dimers. Codon 634 is affected in 85 per cent of the cases. Mutations in the intracellular tyrosin-kinase domain of RET (most often M918T), however, are found in MEN 2B [8, 10]. Pheochromocytomas have been found in both MEN 2A and MEN 2B patients. The vast majority are adrenal pheochromocytomas, other locations and head and neck paragangliomas are very rare *(table I)*. Codon 634 mutations seem to favor early development of pheochromocytomas. No pheochromocytomas, however, have been described so far in MEN 2 patients with mutations in the codons 609, 768, V804M, and 891 [8], which are usually found in patients with FMTC. Patients who present with pheochromocytoma as first symptom will thus benefit from early diagnosis of MEN 2 by DNA-based testing and subsequent total thyroidectomy even before expressing medullary thyroid carcinoma. As a standard procedure mutational analysis of *c-ret* is performed to dectect mutations in the codons 609, 611, 618, 620, 634, 768, 804, and 918 [11].

VHL AND *VHL* GENE

Patients with von-Hippel-Lindau disease (VHL) are at risk for retinal angiomas, hemangioblastomas of the brain and of the spinal cord, pheochromocytomas, renal cysts, renal clear cell carcinomas, pancreatic cysts, islet cell carcinomas, epididymal cystadenomas, and endolymphatic sac tumors of the inner ear. VHL is an autosomal dominant syndrome with an incidence of one in 39000 births per year [5, 12]. Clinically one can distinguish VHL patients from families with low risk (type 1) and with high risk of pheochromocytoma (type 2). In the second case, occurrence of renal cancer then defines a type 2A, other than type 2B. Sometimes a type 2C, defined by isolated pheochromocytoma, is defined as a distinct subtype [13]. These subtypes are based on substantial genotype-phenotype correlations [12, 14]. More than 400 different VHL mutations are known so far. Approximately 43 per cent of the VHL type 2 families have a mutation in codon 167 of the *VHL* gene. In general, missense mutations in the *VHL* gene seem to favor type 2 of the disease [15]. Mutations of the codons 595 and 695 seem to be associated with a young age of onset in pheochromocytomas [15].

The *VHL* gene contains three exons and is located on chromosome 3p25. *VHL* is a tumor suppressor gene that encodes a protein expressed in most tissues. It is

Download English Version:

https://daneshyari.com/en/article/9236070

Download Persian Version:

https://daneshyari.com/article/9236070

Daneshyari.com