Molecular and Cellular Endocrinology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Familial pheochromocytomas and paragangliomas

Kathryn S. King, Karel Pacak *

Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Pheochromocytoma
Paraganglioma
VHL
MEN2
NF1
SDHA

ABSTRACT

Pheochromocytomas and paragangliomas are neural crest cell tumors of the adrenal medulla and parasympathetic/sympathetic ganglia, respectively, that are often associated with catecholamine production. Genetic research over the years has led to our current understanding of the association 13 susceptibility genes with the development of these tumors. Most of the susceptibility genes are now associated with specific clinical presentations, biochemical makeup, tumor location, and associated neoplasms. Recent scientific advances have highlighted the role of somatic mutations in the development of pheochromocytoma/paraganglioma as well as the usefulness of immunohistochemistry in triaging genetic testing. We can now approach genetic testing in pheochromocytoma/paraganglioma patients in a very organized scientific way allowing for the reduction of both the financial and emotional burden on the patient. The discovery of genetic predispositions to the development of pheochromocytoma/paraganglioma not only facilitates better understanding of these tumors but will also lead to improved diagnosis and treatment of this disease.

Contents

* Corresponding author. Address: Section on Medical Neuroendocrinology, Program in Reproductive and Adult Endocrinology, NICHD, NIH, Building 10, CRC, 1-East, Room 1-3140, 10 Center Drive, MSC-1109, Bethesda, MD 20892-1109, USA. Tel.: +1 301 402 4594; fax: +1 301 402 0884.
E-mail address: karel@mail.nih.gov (K. Pacak).

0303-7207/$ - see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.mce.2013.07.032

Please cite this article in press as: King, K.S., Pacak, K. Familial pheochromocytomas and paragangliomas. Molecular and Cellular Endocrinology (2013), http://dx.doi.org/10.1016/j.mce.2013.07.032

1. Introduction

Our understanding of the genetic basis of pheochromocytomas/paragangliomas (tumors of neural crest origin typically associated with catecholamine secretion) is rapidly increasing. We have moved from the "10% tumor" to the "10 gene tumor" to our current understanding of 13 susceptibility genes: the von Hippel-Lindau (*VHL*) gene; the *RET* gene in multiple endocrine neoplasia type 2 (*MEN2*); the neurofibromatosis type 1 (*NF-1*) gene associated with von Recklinghausen's disease; mutations of the A, B, C, and D subunits of the mitochondrial succinate dehydrogenase complex (*SDH*); the *SDHAF2* gene; *TMEM127* gene mutations; *MAX* gene mutations; *PHD2;* and the recently described: *H-RAS* (Crona et al., 2013) and gain-of-function *HIF2α* mutations (Zhuang et al., 2012). Approximately 35% of pheochromocytomas/paragangliomas are associated with an inherited mutation (Amar et al., 2005; Gimenez-Roqueplo et al., 2008) and, as recently reported, approximately 14% of sporadic tumors demonstrate somatic mutations (Burnichon et al., 2011a). As research has advanced, we have become more and more aware of the role that genetics play in the pathogenesis of pheochromocytomas/paragangliomas. Greater understanding of the genetic background will allow for further advancements in diagnostic and treatment options for pheochromocytoma/paraganglioma patients as well as continue the move towards individualized patient care.

While knowledge of an individual patients' mutation is extremely helpful in personalizing care, clustering of the different genetic mutations may help guide advances in diagnostic approaches and discoveries of new therapeutic opportunities. Currently, pheochromocytoma/paraganglioma predisposing genetic mutations are most commonly clustered based on transcriptomes: Cluster 1 = hypoxic transcriptional signature (*SDH* genes = 1A and *VHL* gene = 1B), *HIF2α*; Cluster 2 = kinase receptor signaling and protein translation (*RET*, *NF1*, *TMEM127*, *MAX*) (Eisenhofer et al., 2004; Dahia et al., 2005; Lopez-Jimenez et al., 2010). Several large clinical pheochromocytoma/paraganglioma studies have helped elucidate the clinical presentation of these tumors associated with different genetic mutations. Here we will discuss the 13 genes that are currently known to be associated with pheochromocytoma/paraganglioma and the clinical presentation associated with these specific genetic defects. We will also provide a recommendation on how to approach genetic testing for pheochromocytoma/paraganglioma patients based on clinical presentations, gene-specific biochemical phenotypes, and specific tumor locations. Approaching genetic testing using an individual patients' clinical presentation is considered cost-effective, timely and valuable for early and effective treatment of patients with hereditary pheochromocytoma/paraganglioma (see Table 1).

2. VHL

VHL encodes the von Hippel-Lindau protein, which functions as a regulator of hypoxia-inducible factor alpha (HIFα) – marking HIFα for degradation under normoxic conditions – and thereby controls blood vessel formation, energy metabolism, and apoptosis (Maxwell et al., 1999; Carmeliet et al., 1998; Min et al., 2002). Loss of function mutations in the *VHL* gene results in stabilization of HIFα leading to downstream transcription of cellular proliferation genes and to von Hippel-Lindau disease. von Hippel Lindau is an autosomal dominant syndrome characterized by development of various benign and malignant tumors including pheochromocytomas and, rarely, paragangliomas.

von Hippel-Lindau (VHL) disease was first described over 100 years ago and since that time the clinical features of this disease have been extensively studied. VHL is characterized by predisposition to a variety of tumors including hemangioblastomas, retinal angiomas, clear cell renal carcinoma, pheochromocytoma, pancreatic tumors, epididymal cystadenomas, and cysts of the kidney and pancreas (Maher et al., 1990; Choyke et al., 1995). VHL is clinically broken down into VHL type 1, which is not associated with pheochromocytomas/paragangliomas, and VHL type 2, which is associated with pheochromocytomas/paragangliomas (Chen et al., 1995). VHL type 2 is further broken down into type 2A, which does not have a predisposition for clear cell renal carcinoma; type 2B, which is essentially type 1 (retinal angiomas, central nervous system hemangioblastomas, clear cell renal carcinoma, cysts of kidney and/or pancreas) with pheochromocytoma/paraganglioma; and type 2C, which is pheochromocytoma/paraganglioma without other VHL associated lesions (Maher et al., 1990).

The adrenal medulla is the most common location of *VHL*-related pheochromocytoma though sympathetic and parasympathetic tumors have been described. *VHL*-related pheochromocytomas are often bilateral and can be multiple but metastatic disease rarely occurs thus, these tumors have an overall good prognosis. Patients typically present with pheochromocytoma around 30 years of age, though presentation of other *VHL*-related lesions

Table 1
Summary of the clinical presentations of pheochromocytoma/paraganglioma associated with various genetic mutations. *Abbreviations:* DA = dopamine, CNS = central nervous system, EPI = epinephrine, GIST = Gastrointestinal stromal tumor, NE = norepinephrine ? = not enough data is available to determine this clinical parameter.

Gene	Age at primary diagnosis	Primary tumor location	Biochemical phenotype	Metastatic potential	Some other tumors and important findings
VHL	30s	Adrenal (bilateral)	NE or NE and DA	Low	Retinal hemangiomas, CNS hemangioblastomas, clear cell renal carcinoma
RET	30s	Adrenal (bilateral)	EPI or EPI and NE	Low	Medullary thyroid cancer, hyperparathyroidism, marphanoid habitus, mucosal ganglioneuromas
NF1	40s	Adrenal	EPI or EPI and NE	Low	Café-au-lait spots, neurofibromas, medullary thyroid cancer, carcinoid tumors, peripheral nerve sheath tumors
SDHA	27–77	Head and neck, adrenal, extra-adrenal	?	?	Clear cell renal carcinoma, GIST, pituitary adenoma
SDHB	30s	Extra-adrenal	NE or DA or NE and DA or nonsecretory	High	Clear cell renal carcinoma, GIST, pituitary adenoma,breast and thyroid cancer (?), neuroblastoma pulmonary chondroma
SDHC	40s	Head and neck	NE or nonsecretory	Low	Clear cell renal carcinoma
SDHD	30s	Head and neck (bilateral, multifocal) or extra-adrenal	NE or DA or NE and DA or nonsecretory	Low	Clear cell renal carcinoma, GIST, pituitary adenoma, pulmonary chondroma
SDHAF2	30s	Head and neck (multiple)	?	Low	None known
TMEM127	40s	Adrenal (bilateral)	EPI?	Low	None known
MAX	30s	Adrenal (bilateral)	NE and EPI	Moderate	None known
HRAS	31–76	Adrenal	NE or EPI	Low	None known
HIF2α	17–35	Extra-adrenal	NE	Low	Polycythemia, somatostatinoma

Please cite this article in press as: King, K.S., Pacak, K. Familial pheochromocytomas and paragangliomas. Molecular and Cellular Endocrinology (2013), http://dx.doi.org/10.1016/j.mce.2013.07.032