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Familial Pheochromocytomas and Paragangliomas

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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.

Key Terms

pheochromocytoma; paraganglioma; VHL; MEN2; NF1; SDHA; SDHB; SDHC; SDHD; SDHAF2; TMEM127; MAX; HIF2A; HRAS

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, Delgado Verdugo, Maharjan et al., 2013) and gain-of-function *HIF2α* mutations (Zhuang, Yang, Lorenzo et al., 2012). Approximately 35% of pheochromocytomas/paragangliomas are associated with an inherited mutation (Amar, Bertherat, Baudin et al., 2005, Gimenez-Roqueplo, Burnichon, Amar et al., 2008) and, as recently reported, approximately 14% of

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sporadic tumors demonstrate somatic mutations (Burnichon, Vescovo, Amar et al., 2011). 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), *HIF2 α* ; Cluster 2 = kinase receptor signaling and protein translation (*RET*, *NF1*, *TMEM127*, *MAX*) (Eisenhofer, Huynh, Pacak et al., 2004, Dahia, Ross, Wright et al., 2005, Lopez-Jimenez, Gomez-Lopez, Leandro-Garcia 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.

VHL

VHL encodes the von Hippel-Lindau protein, which functions as a regulator of hypoxia-inducible factor alpha (HIF α) – marking HIF α for degradation under normoxic conditions – and thereby controls blood vessel formation, energy metabolism, and apoptosis (Maxwell, Wiesener, Chang et al., 1999, Carmeliet, Dor, Herbert et al., 1998, Min, Yang, Ivan et al., 2002). Loss of function mutations in the *VHL* gene results in stabilization of HIF α 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, Yates, Harries et al., 1990, Choyke, Glenn, Walther 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, Kishida, Yao 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 around 30 years of age, though presentation of other *VHL*-related lesions often occurs much earlier. The biochemical make up of *VHL*-related pheochromocytomas is primarily solitary secretion of norepinephrine, related to a low, or no, expression of phenylethanolamine N-methyltransferase (PNMT) (Maher et al., 1990, Delman, Shapiro, Jonasch et al., 2006, Maher, Neumann and Richard, 2011, Lonser, Glenn, Walther et al., 2003, Eisenhofer, Lenders, Timmers et al., 2011).

RET Proto-Oncogene

The *RET proto-oncogene* encodes a tyrosine kinase transmembrane receptor that functions in the regulation of cell proliferation and apoptosis. Activating mutations of this proto-oncogene lead to the autosomal dominant syndrome known as multiple endocrine neoplasia type 2 (MEN 2)(Santoro, Carlomagno, Romano et al., 1995, Frank-Raue, Kratt, Hoppner et al., 1996). MEN2 syndrome has been well characterized and can be divided into three subgroups: MEN2A, MEN2B, and familial medullary thyroid carcinoma (not associated with pheochromocytoma/paraganglioma). MEN2A mutations are associated with a disulfide bond disruption causing active homodimers to increase tyrosine kinase activity. MEN2B mutations are known to alter the substrate specificity of *RET*(Santoro et al., 1995).

Clinically, MEN2A is associated with development of medullary thyroid carcinoma in all patients, a 50% risk for pheochromocytoma, and a 10–30% risk for development of hyperparathyroidism (Howe, Norton and Wells, 1993). MEN2B is associated with a nearly 100% risk of developing medullary thyroid carcinoma (earlier onset as compared to MEN2A), a 50% risk for development of pheochromocytoma, mucosal ganglioneuromas, and a marfanoid habitus (Brauckhoff, Machens, Hess et al., 2008, Wohllk, Schweizer, Erlic et al., 2010).

MEN2 associated pheochromocytomas are typically adrenal, often bilateral, and very infrequently associated with metastatic disease, translating to excellent prognosis in the majority of patients. MEN2B associated pheochromocytoma presenting in childhood, however, is associated with an increased risk of metastatic disease as compared to MEN2A and sporadic tumors (Pacak, Eisenhofer and Ilias, 2009). MEN2 related pheochromocytomas tend to be diagnosed between 30 and 40 years of age (Amar et al., 2005, Pacak et al., 2009, Mannelli, Castellano, Schiavi et al., 2009, Bryant, Farmer, Kessler et al., 2003, Lenders, Eisenhofer, Mannelli et al., 2005) and are typically associated with hypersecretion of epinephrine (Eisenhofer et al., 2011). In contrast to medullary thyroid carcinoma, which is the part of the MEN syndrome, there is no known specific genotype-phenotype correlation related to pheochromocytoma.

NF1

The *neurofibromatosis type 1* tumor suppressor gene encodes a protein that inhibits the RAS signaling cascade and the mTOR kinase pathway, and therefore controls cellular growth and differentiation (Johannessen, Reczek, James et al., 2005). Inactivating mutations of *NF1* lead to the autosomal dominant disorder von Recklinghausen's disease or neurofibromatosis type 1 (NF1). Genetic testing for *NF1* mutations is not commonly performed because of the large size of the gene, resulting in a high cost for testing, and because diagnosis can be made clinically. Clinical diagnosis is made when a patient has two or more of the following: six or more café-au-lait spots; two or more cutaneous neurofibromas or a plexiform neurofibroma; inguinal or axillary freckles; one or more optic nerve gliomas; dysplasia of sphenoid bone or pseudoarthrosis; two or more benign iris hamartomas (Lisch nodules); first degree relative

with NF1 (1988). Patients with NF1 are at risk for the development of various tumors including neurofibromas, medullary thyroid carcinoma, carcinoid tumors, parathyroid tumors, peripheral nerve sheath tumors, and pheochromocytomas (1988, Zoller, Rembeck, Oden et al., 1997).

Pheochromocytomas are rare in patients with NF1 with the literature reporting only approximately 1% of patients develop pheochromocytomas (Riccardi, 1991). When pheochromocytoma does occur in patients with NF1 it tends to be an adrenal tumor that preferentially secretes epinephrine similarly to those found in MEN syndrome. These tumors typically present in the patients 40s (in comparison to the dermal neurofibromas and other findings that can arise in childhood). Metastatic disease, although rare (similar to MEN syndrome), has been documented in patients with NF1 and pheochromocytoma (Eisenhofer et al., 2011, Mannelli et al., 2009, Bausch, Koschker, Fassnacht et al., 2006, Walther, Herring, Enquist et al., 1999).

SDHx: SDHA, SDHB, SDHC, SDHD

The succinate dehydrogenase complex is a mitochondrial enzyme complex made up of four subunits encoded by four genes: *SDHA*, *SDHB*, *SDHC*, *SDHD*. The SDHx complex participates in both the citric acid cycle and the electron transport chain and plays a key role in regulation of hypoxia inducible factor alpha (HIF α). HIF α activates a variety of target genes resulting in the regulation of apoptosis, angiogenesis, cellular proliferation, energy metabolism, and cellular migration (Favier and Gimenez-Roqueplo, 2010). Inactivating mutations of *SDHx* genes results in an accumulation of succinate and reactive oxygen free radicals, which can stabilize HIF α and thus activate the hypoxia dependent pathways.

The link between oxidative stress and pheochromocytoma/paraganglioma reaches back to the early 1970s. In 1973, Arias-Stella et al. described an association between high altitude and the presence of carotid body tumors (Arias-Stella and Valcarcel, 1973), which was also later correlated with *SDHB*-related head and neck paragangliomas by Cerecer-Gil et al. in 2010 (Cerecer-Gil, Figuera, Llamas et al., 2010). Another important discovery demonstrating the link between oxidative stress and pheochromocytoma/paraganglioma was the demonstration of multiple giant mitochondria and elevation of lactate dehydrogenase activity in an extra-adrenal paraganglioma (Cornog, Wilkinson, Arvan et al., 1970). Giant mitochondria were also later found in *SDHB*-related renal cell carcinoma (Housley, Lindsay, Young et al., 2010). In 1976 Watanabe et al. demonstrated decreased SDH activity and giant mitochondria in patients with adrenal pheochromocytoma (Watanabe, Burnstock, Jarrott et al., 1976). Heutink et al. later mapped the gene for hereditary head and neck paraganglioma to 11q (Heutink, van der Mey, Sandkuijl et al., 1992), and finally, in 2000, Baysal et al. discovered the first paraganglioma associated SDHx complex gene: *SDHD* (11q23) (Baysal, Ferrell, Willett-Brozick et al., 2000). All of these discoveries led to the hypothesis that HIF links mitochondrial dysfunction to development of pheochromocytoma/paraganglioma (King, Selak and Gottlieb, 2006). Mutations in all four genes of the SDHx complex are now known to be associated with the development of pheochromocytoma/paraganglioma though the clinical presentation varies significantly depending on which gene is mutated.

The link between *SDHA* mutations and pheochromocytoma/paragangliomas was long hypothesized but not proven until 2011. There is still very little data on the clinical features of *SDHA*-related pheochromocytoma/paraganglioma and it appears that *SDHA* mutations are not very common. From the data currently available, it appears that these tumors can present in a variety of ways throughout the lifespan. Burnichon et al. reported a case of a 32-year-old female with an extra-adrenal paraganglioma that secreted norepinephrine and normetanephrine (Burnichon, Briere, Libe et al., 2010). Korpershoek et al. later described 6

patients with *SDHA* mutations whose ages at presentation ranged from 27–77 years and who presented with an adrenal pheochromocytoma (1 patient), extra adrenal paragangliomas (3 patients), or head and neck paragangliomas (2 patients) (Korpershoek, Favier, Gaal et al., 2011). A recent study by Dwight et al. described a 30-year-old male patient with a *SDHA* mutation who presented with a non-secretory pituitary adenoma that demonstrated loss of *SDHA* protein expression, similar to that of the patients' mother who presented with an *SDHA*-related paraganglioma. This study suggests a potential role of *SDHA* mutations in the development of other tumors (Dwight, Mann, Benn et al., 2013). More studies are needed to elucidate the specific clinical presentation of *SDHA*-related pheochromocytoma/paranganglioma.

The clinical presentation of *SDHB*-related tumors has been much more widely studied and described. Primary tumors most commonly develop in extra-adrenal locations, though adrenal and head and neck primary tumors do occur. The mean age of diagnosis of *SDHB*-related pheochromocytoma/paranganglioma is 30 years of age though it ranges widely from 6 years to 77 years of age. Patients with *SDHB*-related pheochromocytomas/parangangliomas do not always present with the classic pheochromocytoma/paranganglioma symptoms (headache, palpitations, diaphoresis, hypertension) and instead present with symptoms related to mass effect, resulting in a delay in diagnosis that could affect prognostic outcome (Neumann, Pawlu, Peczkowska et al., 2004, Timmers, Kozupa, Eisenhofer et al., 2007, Timmers, Gimenez-Roqueplo, Mannelli et al., 2009, Ricketts, Forman, Rattenberry et al., 2010). When the tumor is secretory, *SDHB*-related pheochromocytomas/parangangliomas are likely to secrete dopamine and/or norepinephrine (Eisenhofer et al., 2011). Increased levels of methoxytyramine has also been associated with *SDHB*-related disease (Eisenhofer et al., 2011). *SDHB*-related pheochromocytoma/paranganglioma is associated with a high rate of malignancy (reported >30%) with some factors, such as primary tumor development in childhood, being associated with an increased risk for metastatic disease (Neumann et al., 2004, Timmers et al., 2007, Ricketts et al., 2010, King, Prodanov, Kantorovich et al., 2011, Brouwers, Eisenhofer, Tao et al., 2006). *SDHB* mutations are also known to be associated with an increased risk for development of other tumors such as renal cell carcinoma, gastrointestinal stromal tumors, breast cancer, and papillary thyroid cancer (Ricketts, Woodward, Killick et al., 2008, Pasini, McWhinney, Bei et al., 2008, Lee, Wang, Torbenson et al., 2010). With the associations of these tumors, *SDHx* related mutations may eventually be considered a metabolic syndrome of sorts. Other syndromes, such as Carney's triad and Carney-Stratakis dyad, have been described that include the presence of paragangliomas and cases have been associated with *SDHB*, *C* and *D* mutations (Stratakis and Carney, 2009). New syndromes, such as that recently described by Zhuang et al. (Zhuang et al., 2012) (discussed below) may demonstrate a greater link to oxidative stress, including mitochondrial dysfunction, to the development of several tumor types.

SDHC gene mutations are associated with head and neck paragangliomas. The typical age of presentation appears to be around 40–45 years of age. *SDHC*-related head and neck tumors are not associated with metastatic spread but can be multifocal. These tumors are not classically associated with catecholamine secretion. *SDHC*-related head and neck tumors are not associated with paternal transmission, unlike *SDHD*-related head and neck tumors (Schiavi, Boedeker, Bausch et al., 2005, Muller, Troidl and Niemann, 2005, Burnichon, Rohmer, Amar et al., 2009).

SDHD gene mutations predispose patients to development of head and neck paragangliomas. The tumors are often multifocal, bilateral, and recurrent but show a low rate of malignancy. Patients typically present with the tumor in their 30s (Neumann et al., 2004, Ricketts et al., 2010, Burnichon et al., 2009). Head and neck paragangliomas in general are typically thought to be non-secretory (silent) and while many *SDHD*-related

head and neck paragangliomas are silent, when the tumor does secrete catecholamines it typically secretes dopamine or norepinephrine (Eisenhofer et al., 2011). Interestingly, *SDHD* mutations exhibit maternal imprinting resulting in disease only with paternal transmission (Ricketts et al., 2010, Burnichon et al., 2009).

SDHAF2

SDHAF2 encodes the SDHAF2 protein, which is responsible for flavination of SDHA and thus proper functioning of the SDHA subunit (part of the mitochondrial SDHx complex) (Hao, Khalimonchuk, Schraders et al., 2009). Mutations in the *SDHAF2* gene result in the rare autosomal dominant syndrome known as familial paraganglioma syndrome 2. These mutations are very rare but when they do occur they predispose individuals to the development of head and neck paragangliomas. These tumors are often multiple and patients tend to present in their 30s. There currently is no indication that *SDHAF2* mutations predispose metastatic disease (Hao et al., 2009, Hensen, Siemers, Jansen et al., 2011, Bayley, Kunst, Cascon et al., 2010, van Baars, Cremers, van den Broek et al., 1982, Kunst, Rutten, de Monnik et al., 2011). Based on the current data, it appears that these mutations are paternally transmitted and have high penetrance (Bayley et al., 2010, Kunst et al., 2011).

TMEM127

TMEM127 is a tumor suppressor gene that encodes the TMEM-127 protein. The TMEM-127 protein has been highly conserved throughout evolution and is expressed in various normal tissues and cancer cell lines. Studies suggest TMEM127 is associated with cellular organelles such as the golgi, endosomes, and lysosomes and may play a role in protein trafficking. It has also been suggested that TMEM-127 acts to limit mTORC1 activation (Qin, Yao, King et al., 2010).

Given the recent discovery of *TMEM127* mutations predisposing to the development of pheochromocytomas/paragangliomas (Qin et al., 2010) more large studies are needed to elucidate the clinical presentation of pheochromocytoma/paraganglioma associated *TMEM127* mutations. The current literature suggests *TMEM127* mutations predispose to metanephrine producing adrenal pheochromocytomas in middle-aged individuals (around 40 years of life). In 2010, Qin et al. reported mutations in the *TMEM-127* gene in seven families, 16 patients, with pheochromocytoma (Qin et al., 2010). All 16 patients presented with adrenal pheochromocytomas, approximately 50% of which were bilateral. Following the discovery of a link between *TMEM127* mutations and pheochromocytoma several other investigators reported the presence *TMEM127* mutations in pheochromocytoma patients (Burnichon, Lepoutre-Lussey, Laffaire et al., 2011, Yao, Schiavi, Cascon et al., 2010, Neumann, Sullivan, Winter et al., 2011). Two studies (Burnichon et al., 2011, Yao et al., 2010) supported the findings of Qin et al., reporting patients presenting around age 40 with adrenal pheochromocytomas that most frequently produced and secreted metanephrine. A study by Neumann et al., however, reported the presence of *TMEM127* mutations in a patient with head and neck paragangliomas and another patient with an adrenal pheochromocytoma and an extra-adrenal paraganglioma (Neumann et al., 2011). Very little malignancy with *TMEM127* mutations has been reported (Qin et al., 2010, Burnichon et al., 2011, Yao et al., 2010, Neumann et al., 2011).

MAX

The *MAX* gene is a tumor suppressor gene that encodes for the MAX protein. MAX is involved in the MYC/MAX/MXD1 complex that is known to be involved in regulating cellular proliferation, differentiation and apoptosis. Mutation of *MAX* results in increased cellular proliferation and has been associated with development of pheochromocytomas

(Comino-Mendez, Gracia-Aznarez, Schiavi et al., 2011, Peczkowska, Kowalska, Sygut et al., 2013). The current belief is that MAX plays a pivotal role in repressing MYC expression and that in the absence of MAX MYC retains function (Cascon and Robledo, 2012).

Clinically, *MAX* mutations appear to be most commonly associated with adrenal pheochromocytomas and paternal transmission of *MAX* mutations has been suggested (Comino-Mendez et al., 2011). The 2011 Comino-Mendez et al. study, that presented the link between *MAX* mutations and pheochromocytoma for the first time, reported the presence of *MAX* mutations in 12 patients with adrenal pheochromocytomas (8 bilateral) (Comino-Mendez et al., 2011). Burnichon et al. presented clinical data for 19 patients found to have *MAX* mutations and reported all presented with adrenal pheochromocytomas at a mean age of 34 years; 13 had bilateral or multiple adrenal tumors, 3 patients had an additional extra-adrenal sympathetic paraganglioma, and 2 patients eventually developed metastatic disease. Overall these tumors may be more frequently metastatic than other hereditary pheochromocytomas/paragangliomas, except those with *SDHB/SDHD* mutations. Burnichon et al. also reported these tumors were associated mainly with normetanephrine secretion, though some metanephrine secretion was demonstrated, and the tumors had increased expression of PNMT (Burnichon, Cascon, Schiavi et al., 2012). Peczkowska et al. also described a patient who presented with a metanephrine and normetanephrine secreting adrenal pheochromocytoma at 36 years of age and who later developed a recurrence (Peczkowska et al., 2013). Based on these studies, *MAX* mutations appear to predispose to development of adrenal pheochromocytomas between 30 and 40 years of age with a mixed noradrenergic and adrenergic biochemical phenotype.

PHD2 and H-RAS

The association between *PHD2* and *HRAS* mutations with pheochromocytoma/paraganglioma have only been described in a limited number of patients thus far.

The product of the *PHD2* gene is a prolyl hydroxylase that is known to function in hydroxylation of HIF α and thus function in the cells response to hypoxia (Ivan, Haberberger, Gervasi et al., 2002). In 2008 Ladroue et al. described a patient with erythrocytosis and abdominal paragangliomas who was found to harbor a mutation in the *PHD2* gene (Ladroue, Carcenac, Leporrier et al., 2008). More studies are needed to further characterize the clinical presentation of *PHD2*-related pheochromocytomas/paragangliomas.

Constitutive RAS signaling is known to increase cell proliferation and induce tumor formation (Adari, Lowy, Willumsen et al., 1988) in several cancers but had not previously been related to the development of pheochromocytoma/paraganglioma. Genetic mutations of *NF1* and *RET* are known to affect RAS signaling and are associated with the development of pheochromocytoma/paraganglioma but a mutation to *RAS* itself predisposing to the development of these tumors was only recently described.

Crona et al. very recently described the presence of *H-RAS* mutations in a series of 4 male patients, 3 presenting with pheochromocytoma and 1 with an abdominal paraganglioma. The age of diagnosis of disease ranged from 31–76 and biochemical analysis demonstrated a noradrenergic plus adrenergic phenotype in the 3 patients with pheochromocytomas and no measured catecholamine secretion in the patient with an abdominal paraganglioma (patient reportedly presented with hypertensive crisis and died) (Crona et al., 2013). The discovery of this mutation presents a further link between RAS proteins and the development of pheochromocytoma/paraganglioma. This discovery also highlights the fact that there are still genetic mutations related to pheochromocytoma/paraganglioma yet to be discovered.

HIF2 α

Hypoxia-inducible factor is a protein composed of 2 subunits: the constitutively expressed HIF β subunit and the hypoxia dependent HIF α subunit (Wang, Jiang, Rue et al., 1995). In the presence of oxygen HIF α will be hydroxylated by prolyl hydroxylated domain protein 2. The von Hippel-Lindau tumor suppressor protein will then recruit an E3 ubiquitin-protein ligase that targets HIF α for degradation. Under hypoxic conditions HIF α hydroxylation is suppressed allowing it to heterodimerize with HIF β and induce various cellular activities including glycolysis, erythropoiesis, and angiogenesis (Kaelin and Ratcliffe, 2008, Hu, Wang, Chodosh et al., 2003, Iyer, Kotch, Agani et al., 1998). Carmeliet et al. demonstrated that HIF1 α deficiency stimulates cellular proliferation as opposed to hypoxic growth arrest (Carmeliet et al., 1998). Recently, gain-of-function *HIF2 α* mutations were discovered in several patients with paraganglioma and associated polycythemia (Zhuang et al., 2012) and *in vivo* and *in vitro* studies have been performed to support the oncogenic role *HIF2 α* in pheochromocytoma/paraganglioma (Toledo, Qin, Srikantan et al., 2013).

Several studies have recently been published describing the clinical presentation of paragangliomas developed in the setting of gain-of-function *HIF2 α* mutations. Pacak and Zhaung introduced a new syndrome involving four female patients with polycythemia, multiple duodenal somatostatinomas and multiple extra-adrenal paragangliomas. The women presented with extra-adrenal paragangliomas associated with elevated serum norepinephrine and normetanephrine at relatively young ages: 17 years of age, 18 years of age, 23 years of age, and 25 years of age (Zhuang et al., 2012, Pacak, Jochmanova, Prodanov et al., 2013). Favier et al. described a case of a 24-year-old female who presented with an adrenal pheochromocytoma and was found to have a somatic *HIF2 α* mutation (Favier, Buffet and Gimenez-Roqueplo, 2012). Taieb et al. recently described a case of a 25-year-old female with polycythemia who presented with adrenal and extra-adrenal paragangliomas and was found to have a gain-of-function *HIF2 α* mutation (Taieb, Yang, Delenne et al., 2013). Lorenzo et al. recently described a case of a 35-year-old male with polycythemia who presented with an extra-adrenal paraganglioma progressing to metastatic disease with an associated *HIF2 α* mutation (Lorenzo, Yang, Ng Tang Fui et al., 2013). Comino-Mendez et al. recently described 7 patients with *HIF2 α* mutations, 3 of whom presented with multiple paragangliomas and polycythemia, 1 of whom presented with multiple paragangliomas, 2 of whom presented with solitary pheochromocytomas, and 1 of whom presented with a solitary paraganglioma (Comino-Mendez, de Cubas, Bernal et al., 2013). These findings indicate that *HIF2 α* mutations may be present in the absence of polycythemia. Based on the current findings presented in the literature *HIF2 α* gain-of-function mutations appear to predispose to development of multiple extra-adrenal paragangliomas (multiple pheochromocytomas are much less common) and multiple duodenal somatostatinomas in females with polycythemia development either at birth or in early childhood.

The link between (pseudo) hypoxia and pheochromocytoma/paraganglioma has been long hypothesized but it was not until the discovery of the *VHL* mutation that a true association was made. Over the course of pheochromocytoma/paraganglioma research, several hereditary links to the hypoxic pathway and pheochromocytoma/paraganglioma have been made: *VHL*, *SDHx*, and now, *HIF2 α* . *RET* and *NF1* related tumors are also related to HIF dysfunction in a downstream fashion. While the importance of hypoxia in pheochromocytoma/paraganglioma development has long since been hypothesized we may just now be noticing its true impact. As research continues we could see a strong link between HIF and hereditary pheochromocytoma/paraganglioma and this link and knowledge of these pathways has a great potential to impact diagnosis, care, and, possibly, cure of patients.

Current Recommended Cost-Effective Genetic Screening

Triaging of genetic screening is extremely important both for guidance of patient care and to avoid excessive cost to any patient. With the advances in genetic screening, determining a patient's entire genome sequence may one day be cost effective but as of now we must rely on clinical presentation to determine which genetic test to perform first. In absence of a family history of a known mutation, determination of what genetic test to perform depends largely on the patient's clinical presentation (tumor location and biochemical phenotype) (Figure 1) and immunohistochemical evaluation for the presence of SDHB/A proteins.

Tumor Location

Adrenal pheochromocytomas are more commonly associated with *VHL* (Maher et al., 1990, Delman et al., 2006, Maher et al., 2011, Lonser et al., 2003), *RET* (Amar et al., 2005, Pacak et al., 2009, Bryant et al., 2003, Lenders et al., 2005), *NF1* (Bausch et al., 2006, Walther et al., 1999), *TMEM127* (Qin et al., 2010, Burnichon et al., 2011, Yao et al., 2010, Neumann et al., 2011), or *MAX* (Comino-Mendez et al., 2011, Peczkowska et al., 2013, Burnichon et al., 2012) gene mutations than with SDHx or *HIF2α* gene mutations (Mannelli et al., 2009). Extra-adrenal sympathetic paragangliomas are most commonly associated with *SDHB* mutations (Mannelli et al., 2009, Neumann et al., 2004, Timmers et al., 2007, Timmers et al., 2009, Ricketts et al., 2010, Burnichon et al., 2009). Head and neck paragangliomas are associated with *SDHD* (Neumann et al., 2004, Ricketts et al., 2010, Burnichon et al., 2009) (often multiple), *SDHC* (Schiavi et al., 2005, Muller et al., 2005, Burnichon et al., 2009), *SDHAF2*, and *SDHB* (Timmers et al., 2007, Timmers et al., 2009, Ricketts et al., 2010) gene mutations (Mannelli et al., 2009). *SDHAF2* mutations should be considered in patients with head and neck paragangliomas, who have a strong family history of head and neck tumors or present at a young age and are negative for other SDHx mutations (Hao et al., 2009, Hensen et al., 2011, Bayley et al., 2010, Kunst et al., 2011).

Biochemical Phenotype

A 2011 study by Eisenhofer et al. expertly helped elucidate the biochemical phenotype of pheochromocytomas/paragangliomas related to different genetic mutations. Eisenhofer et al. demonstrated a pattern of metanephrine secretion in *RET* and *NF1*-related pheochromocytomas, mainly normetanephrine secretion (some may have also elevated methoxytyramine) in *VHL*-related tumors, and methoxytyramine secretion (in about 70% of cases), with or without normetanephrine, has been associated with *SDHB*- and *SDHD*-related paragangliomas (Eisenhofer et al., 2011). To date, there is no large-scale study on biochemical phenotypes that includes *TMEM127*, *MAX*, and *HIF2α* mutations or *SDHB*-related adrenal pheochromocytomas. Nevertheless, current evidence from the literature suggests *TMEM127*-related pheochromocytomas are most commonly associated with metanephrine secretion (Burnichon et al., 2011, Yao et al., 2010), *MAX*-related pheochromocytomas are more commonly associated with mixed metanephrines and normetanephrine secretion (Burnichon et al., 2012), and *HIF2α*-related paragangliomas are associated with normetanephrine secretion (Zhuang et al., 2012, Pacak et al., 2013). More studies are needed to properly determine the biochemical phenotype, if any, associated with these genetic mutations but we expect that future studies will confirm the preliminary, but very well carried out, currently available studies.

Presentation

If these tumors are found without any syndromic or familial presentation we recommend that: metastatic tumors to be tested for *SDHB* mutations; multiple abdominal paragangliomas should be first tested for the presence of *SDHD* mutations; multiple/bilateral adrenal pheochromocytomas should be tested for *TMEM127* mutations; and multiple

paragangliomas associated with other neuroendocrine tumors, currently with somatostatinoma, should first be tested for *HIF2α* mutations.

Histology

Immunohistochemical (IHC) testing with SDHB can also help guide genetic testing. *RET*, *NF1*, and *VHL*-related pheochromocytomas/paragangliomas are associated with positive SDHB IHC while *SDHx*-related pheochromocytomas/paragangliomas are associated with negative SDHB staining (*SDHD*-related tumors can be weakly positive) (van Nederveen, Gaal, Favier et al., 2009, Gill, Benn, Chou et al., 2010). Negative IHC for SDHA has been correlated with the presence of an *SDHA* mutation (Korpershoek et al., 2011).

Implications

Knowledge of a patients' mutation status can be very important in guiding treatment and follow up care. As previously mentioned, many of the genetic mutations discussed are associated with tumors and findings other than pheochromocytoma/paraganglioma that need to be followed. Prophylactic thyroidectomy, for example, is recommended for patients with specific *RET* mutations (Moore, Appfelstaedt and Zaahl, 2007, Kloos, Eng, Evans et al., 2009). Certain genetic mutations are more likely to predispose to metastatic disease than others and must be followed accordingly. Patients with *SDHB* mutations should be followed closely by both biochemistry and serial imaging for development of metastatic disease, especially those who presented with their primary tumor at a young age. Multiple studies have shown that certain imaging modalities work better in certain subsets of patients, for example ¹⁸F-FDG PET imaging is recommended for follow up and screening of all *SDHB*-related metastatic tumors (Timmers, Kozupa, Chen et al., 2007) while ¹⁸F-FDOPA PET imaging may be most accurate for imaging of head and neck tumor regardless of their genetic status (King, Whatley, Alexopoulos et al., 2010, Gabriel, Blanchet, Sebag et al., 2012). Additionally, knowledge of the genetics of pheochromocytoma/paraganglioma has led to developments that have improved our understanding of the disease process as a whole. For example, the development of the mouse pheochromocytoma cell line (MPC) from NF1 (Powers, Evinger, Tsokas et al., 2000), and the more aggressive mouse tumor tissue (Martiniova, Lai, Elkahoul et al., 2009), have greatly improved and eased our ability to study pheochromocytoma signaling pathways as well as test new imaging modalities (Martiniova, Perera, Brouwers et al., 2011, Martiniova, Ohta, Guion et al., 2006, Martiniova, Cleary, Lai et al., 2012).

Recent advances in genetics have caused a shift from a tumor defined by the “rule of 10s” to a “10-gene tumor” and now to a tumor defined by a multitude of genetic mutations with various clinical presentations. The links between signaling pathways are becoming more apparent and, perhaps one day may lead to a discovery that all hereditary pheochromocytomas/paragangliomas associate with a common signaling pathway or molecule. Knowledge of these genetic mutations and associated clinical presentations greatly assists in patient care. Despite our current knowledge, there is still much to learn about this disease. There are likely more pheochromocytoma/paraganglioma related genes yet to be discovered, such as a gene associated with the large percentage of metastatic pheochromocytomas/paragangliomas that are currently considered sporadic. As more research is done and more associations are made our understanding of pheochromocytomas/paragangliomas may eventually evolve to the point of finding a cure or, at the very least, advancement of more efficacious and specific therapeutic options in the future.

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Highlights

- Pheochromocytomas and paragangliomas are now known to be associated with 13 susceptibility genes
- Genetic testing can be triaged based on the individual patients clinical presentation
- Knowledge of genetic mutations allows for individualized care
- Research on the molecular actions of these genes will lead to greater understanding of this disease

Figure 1. Algorithm for gene mutation testing in pheochromocytoma/paraganglioma based on clinical presentation and biochemical phenotype

As indicated by the algorithm, in any patient with a positive family history of a pheochromocytoma/paraganglioma predisposing mutation, that mutation should be tested first. In patients with clinical features indicative of a specific syndrome, the syndromic mutation should be tested first; except in the case of NF1 where the diagnosis is made based on clinical presentation alone. In patients with no family history and without a classic syndromic presentation, determination of which genetic test to perform first depends upon the biochemistry and tumor location. In cases where both normetanephrine and methoxytyramine or metanephrine are elevated use the testing guidance of the latter (methoxytyramine or metanephrine). The biochemical phenotype and most common tumor location for *SDHA*-related pheochromocytoma/paraganglioma has not yet been elucidated. Patients with head and neck tumor development at a young age with a strong family history of disease should be considered for *SDHA*F2 genetic testing. *Abbreviations:* HNP = head and neck paraganglioma. Adapted from Karasek et al.(Karasek, Shah, Frysak et al., 2013)

Table 1
Summary of the clinical presentations of pheochromocytoma/paraganglioma associated with various genetic mutations.

Gene	Age at Primary Diagnosis	Primary Tumor Location	Biochemical Phenotype	Metastatic Potential	Some Other Tumors and Important Findings
<i>VHL</i>	30s	Adrenal (bilateral)	NE or NE & DA	Low	Retinal hemangiomas, CNS hemangioblastomas, clear cell renal carcinoma
<i>RET</i>	30s	Adrenal (bilateral)	EPI or EPI & NE	Low	Medullary thyroid cancer, hyperparathyroidism, marfanoid habitus, mucosal ganglioneuromas
<i>NFI</i>	40s	Adrenal	EPI or EPI & NE	Low	Caf-au-lait spots, neurofibromas, medullary thyroid cancer, carcinoid tumors, peripheral nerve sheath tumors
<i>SDHA</i>	27–77	Head and neck, adrenal, extra-adrenal	?	?	Clear cell renal carcinoma, GIST, pituitary adenoma
<i>SDHB</i>	30s	Extra-adrenal	NE or DA or NE & DA or nonsecretory	High	Clear cell renal carcinoma, GIST, pituitary adenoma, breast and thyroid cancer (?), neuroblastoma pulmonary chondroma
<i>SDHC</i>	40s	Head and neck	NE or nonsecretory	Low	Clear cell renal carcinoma
<i>SDHD</i>	30s	Head and neck (bilateral, multifocal) or extra-adrenal	NE or DA or NE & DA or nonsecretory	Low	Clear cell renal carcinoma, GIST, pituitary adenoma, pulmonary chondroma
<i>SDHAF2</i>	30s	Head and neck (multiple)	?	Low	None Known
<i>TMEM127</i>	40s	Adrenal (bilateral)	EPI?	Low	None Known
<i>MAX</i>	30s	Adrenal (bilateral)	NE & EPI	Moderate	None Known
<i>HRA5</i>	31–76	Adrenal	NE or EPI	Low	None Known
<i>HIF2a</i>	17–35	Extra-adrenal	NE	Low	Polycythemia, somatostatinoma

Abbreviations: DA = dopamine, CNS = central nervous system, EPI = epinephrine, GIST = Gastrointestinal stromal tumor, NE = norepinephrine.