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Genetic Testing for Pheochromocytoma

David Karasek, M.D., Ph.D.¹, Zdenek Frysak, M.D., Ph.D.¹, and Karel Pacak, M.D., Ph.D., D.Sc.²

¹3rd Department of Internal Medicine, University Hospital Olomouc, I.P.Pavlova 6 Olomouc 77520, Czech Republic

²Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA

Abstract

Pheochromocytomas and paragangliomas (PHEOs/PGLs) are rare, usually sporadic, catecholamine-producing tumors. However, about 30% of these tumors have been identified of inherited origin. Up to date, nine genes have been confirmed to participate in PHEOs/PGLs tumorigenesis. Germline mutations used to be found in 100% of syndromic cases and in about 90% of patients with positive familial history. In non-syndromic patients with apparently sporadic tumors the frequency of genetic mutations has been recorded up to 27%. Nowadays, genetic testing is recommended for all patients with PHEOs/PGLs. Patients with syndromic lesions and/or positive family history should be tested for appertaining gene. Latest discoveries have shown that the proper order of tested genes in non-syndromic, non-familial cases could be based on histological evaluation, localization and biochemical phenotype of PHEOs/PGLs – the “rule of three”. Identification of gene mutation may lead to early diagnosis, treatment, regular surveillance and better prognosis for patients and their relatives.

Keywords

genetic testing; paraganglioma; pheochromocytoma; multiple endocrine neoplasia type 2; von Hippel-Lindau disease; neurofibromatosis type 1; succinate dehydrogenase complex genes; immunohistochemistry; catecholamines

Introduction

Although most pheochromocytomas (PHEOs) are sporadic, genetics in the development of these tumors is becoming more and more crucial these days. According to the latest discoveries, already nine genes play an important role in the pathogenesis of PHEOs. These genes include: REarranged during Transfection (*RET*) proto-oncogene, von Hippel-Lindau disease tumor suppressor gene (*VHL*), neurofibromatosis type 1 tumor suppressor gene (*NF1*), genes encoding four succinate dehydrogenase complex (SDH) subunits (*SDHx*; *i.e.*

Corresponding author: Karel Pacak, M.D., Ph.D., D.Sc., Chief, Section on Medical Neuroendocrinology, Professor of Medicine, Reproductive and Adult Endocrinology Program, NICHD, NIH, Building 10, CRC, 1-East, Room 1-3140, 10 Center Drive, MSC-1109, Bethesda, Maryland 20892-1109, karel@mail.nih.gov, Fax: 1-301-402-0884, Phone: 1-301-402-4594.

Other authors: David Karasek, M.D., Ph.D., ³rd Department of Internal Medicine, University Hospital Olomouc, I. P.Pavlova 6, Olomouc 77520, Czech Republic, david.karasek@fnol.cz, Fax: +420 585852526, Phone: +420 585855895

Zdenek Frysak, M.D., Ph.D., ³rd Department of Internal Medicine, University Hospital Olomouc, I.P.Pavlova 6, Olomouc 77520, Czech Republic, zdenek.frysak@fnol.cz, Fax: +420 585852526, Phone: +420 585854741

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SDHA, *SDHB*, *SDHC*, and *SDHD* genes), gene encoding the enzyme responsible for flavination of the *SDHA* subunit (*SDHAF2* or *SDH5* gene, for its yeast ortholog), and newly described tumor suppressor *TMEM127* gene [1-3,4•,5•,6•,7•]. Furthermore, although previously about 24% of sporadic PHEOs presented genetic mutations [8], nowadays this number is about 30% or more [3,9•,10,11•]. Finally, there are new data linking specific genotype of these tumors to the specific localization, typical biochemical phenotype or future clinical behavior (e.g. *SDHB* gene mutations are associated with extra-adrenal localization, overproduction of norepinephrine and of dopamine, and a high risk of malignancy) [12•,13•, Eisenhofer G, Pacak K, et al.; unpublished observations].

PHEOs are associated with the following familial syndromes: multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Lindau disease (VHL), von Recklinghausen's neurofibromatosis type 1 (NF 1) and familial paragangliomas (PGLs). Hereditary forms of PHEOs/PGLs can differ in age of diagnosis, localization, malignant potential and catecholamine phenotype – see table 1.

Familial syndromes associated with PHEOs/PGLs

Multiple endocrine neoplasia type 2

MEN 2 is an autosomal-dominant syndrome caused by activating germline mutations in the *RET* proto-oncogene located on chromosome 10q11.2, which encodes a transmembrane receptor tyrosine kinase involved in the regulation of cell proliferation and apoptosis [1,2,14]. This syndrome is usually divided into three subgroups: MEN 2A is characterized by medullary thyroid carcinoma (MTC) in 95%, PHEO in 50%, and hyperparathyroidism (caused by parathyroid hyperplasia/adenoma) in 15-30% of cases. MEN 2B is characterized by MTC in 100%, PHEO in 50% of cases, marfanoid habitus, and multiple mucosal ganglioneuromas. The third group is represented by familial MTC that occurs alone [1,14]. In most cases, MTC is the first presentation of MEN 2. Approximately 90% of MEN 2 cases are of the MEN 2A subtype [1,2,14-16]. More than 85% of patients with MEN 2A have mutations in codon 634, exon 11, and about 95% of MEN 2B cases are caused by a single missense mutation in codon 918, exon 16 of *RET* proto-oncogene [1,2,15,16].

In MEN 2 patients the PHEOs are usually of adrenal localization, benign and bilateral in more than 50% of patients [1,2,9•,10,17]. The frequency of malignant transformation is less than 5%, but children with MEN 2B-associated PHEOs have a higher risk of malignancy compared to those with MEN 2A or sporadic disease [15]. PHEOs are most commonly diagnosed between the age of 30 and 40 years [2,9•,10,15,17]. MEN 2-related tumors overexpress phenylethanolamine N-methyltransferase (the enzyme that converts norepinephrine to epinephrine), thus the biochemical phenotype is consistent with hypersecretion of epinephrine in large amounts, resulting in an early clinical phenotype characterized by attacks of palpitations, nervousness, anxiety, and headaches rather than more common patterns of hypertension to be seen in other hereditary tumors [17,18]. The increased plasma and urinary levels of catecholamine O-methylated metabolite of epinephrine – metanephrine in MEN 2 patients distinguish them from those with *VHL* and *SDHx* mutations [Eisenhofer G, Pacak, K et al.; unpublished observations].

Von Hippel-Lindau disease

VHL is an autosomal-dominant inherited syndrome with (VHL type 2) or without (VHL type 1) PHEOs [1,2,19]. VHL type 1 is the most common form with predisposition to develop retinal angiomas, central nervous system hemangioblastomas and clear cell renal carcinomas; there could be also other tumors: islet tumors of the pancreas, endolymphatic sac tumors, cysts and cystadenomas of the kidney, pancreas, epididymis, and broad ligament. VHL type 2 is characterized by a predisposition to develop PHEO: without renal

carcinoma, and with infrequent other VHL type 1 tumors – type 2A; or with all VHL type 1 tumors – type 2B; and or rarely without all VHL type 1 tumors – type 2C, developing PHEO alone, as apparently sporadic tumor [2,3,17,19-21]. VHL is caused by heterozygous germline mutations in the *VHL* tumor suppressor gene on chromosome 3p25.5. The gene encodes a VHL protein, which is involved in blood vessel formation by regulating activity of hypoxia inducible factor -1 alpha (HIF-1 α). Loss of VHL protein function predisposes the *VHL* carriers to both benign and malignant tumors in multiple organs [2,3,20,22]. More than 300 mutations of the *VHL* gene have been identified [1,21]. Approximately 20 % of families with VHL carry *de novo* mutations, highlighting the need for mutation analysis in patients with apparently sporadic PHEOs [21].

VHL catecholamine-producing tumors are most commonly intra-adrenal PHEOs, although rare extra-adrenal sympathetic PGLs, and parasympathetic head and neck PGLs use to be found too [9•,10,23,24•,25•]. PHEOs associated with VHL are more likely to be bilateral (up to 50%) and more than half of the VHL patients with PHEOs have multiple tumors [2,9•,10,23,24•]. VHL-associated PHEOs appear to undergo malignant transformation less frequently than sporadic PHEOs (< 5 % of patients) [2,17,22,24•]. PHEOs develop in 10%-20% of VHL patients with a mean age of presentation of 30 years [3,9•,10,15]. The biochemical profile of VHL patients differs from those with MEN 2 and NF 1. PHEOs in VHL mostly produce only norepinephrine due to a low expression of phenylethanolamine-N-methyltransferase [18]. So, VHL patients usually show solitary increases in plasma and urinary normetanephrine levels [Eisenhofer G, Pacak K, et al.; unpublished observations].

Neurofibromatosis type 1

NF 1 or von Recklinghausen's disease is an autosomal-dominant genetic disorder caused by inactivating mutations of a tumor suppressor *NF 1* gene being localized on chromosome 17q11.2. This large gene encodes a neurofibromin, which is a GTPase-activating protein involved in the inhibition of Ras activity, which controls cellular growth and differentiation. Up to 50% of NF 1 patients with identified germline mutations carry a *de novo* mutation [1,2,20]. PHEOs occur in 0.1%–5.7% of patients with NF 1 and in 20%–50% of NF 1 patients with hypertension [26,27]. The clinical diagnosis of NF 1 requires two of the following seven criteria: six or more café-au-lait spots; two or more cutaneous neurofibromas or a plexiform neurofibroma, inguinal, or axillary freckles; two or more benign iris hamartomas (Lish nodules); at least one optic-nerve glioma; dysplasia of sphenoid bone or pseudoarthrosis; and a first degree relative with NF 1, according to the preceding criteria [28]. In addition, a variety of tumors including MTC, carcinoid tumors of the duodenal wall, parathyroid tumors, peripheral nerve sheath tumors, and leukemia, particularly chronic myeloid leukemia have been described with higher frequency in NF 1 than in the general population [2,20].

In NF 1, the mean age of PHEO diagnosis is in the fifth decade (mean age 42 years), the same as in the general population [9•,10,27,29]. On occasion, NF 1 can be diagnosed concurrently with PHEO; however, the skin lesions typical of NF 1 usually lead to the diagnosis of NF 1 in childhood, whereas PHEOs is usually diagnosed in adulthood [26]. In most cases, PHEOs are benign and unilateral, followed by seldom bilateral PHEOs, and rare extra-adrenal sympathetic PGLs. Malignant PHEOs have been identified in up to 12% of cases, similar to the frequency of malignancy in the general population [2,9•,10,27,29]. NF 1-related PHEOs produce both epinephrine and norepinephrine. The increased plasma and urinary levels of metanephrine (indicating epinephrine overproduction) help to discriminate NF 1 patients from those with *VHL* and *SDHx* mutations [Eisenhofer G, Pacak K, et al.; unpublished observations].

Familial paragangliomas syndromes

Hereditary PGLs syndromes are caused by mutations in the genes encoding the SDH complex subunits [3,4•,30-32]. Inactivation of SDH is associated with the accumulation of succinate, increased oxygen free radical production and resulting in the stabilization of HIF-1 α [3,33]. It has been suggested that loss of SDH function mimics chronic hypoxia leading to cellular proliferation. In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, the most of malignant tumor cells instead rely on aerobic glycolysis, this phenomenon is termed “the Warburg effect” [34]. SDH enzyme complex consists of four subunits encoded by four *SDHx* genes – *SDHA*, *SDHB*, *SDHC*, and *SDHD* genes. Mutation of *SDHD* gene is responsible for PGL 1 syndrome. *SDHC* gene mutation is causative for PGL 3 syndrome and *SDHB* gene for PGL 4 syndrome. Succinate dehydrogenase complex assembly factor 2 (*SDHAF2*) encoded by *SDHAF2* gene (or *SDH5*, for its yeast ortholog) plays the main role in flavination of SDHA, that is necessary for correct function of this subunit. Loss of *SDHAF2* results in loss of SDHA subunit function and leads to reduction in stability of the whole SDH enzyme complex. Mutation of *SDHAF2* gene has been discovered to be responsible for PGL 2 syndrome [5•,6•].

PGL 1 is an autosomal-dominant syndrome characterized by familial parasympathetic head and neck PGLs, less frequently by sympathetic extra-adrenal PGLs and rare unilateral or bilateral PHEOs [3,9•,10,11•,29], caused by inactivating mutations in *SDHD* gene located on chromosome 11q23 [2,3,32]. The mean age of the diagnosis is about 35 years. *SDHD* mutation carriers should be observed especially for head and neck PGLs, often multifocal, sometimes recurrent and rarely malignant [3,9•,10,11•,29]. Family history in *SDHD* mutations patients could be inconclusive because of maternal genomic imprinting [3,20,35].

PGL 2 is a very rare autosomal-dominant syndrome defined by familial head and neck PGLs. No cases of PGL 2 syndrome presenting as PHEOs have been described yet. Hereditary transmission occurs exclusively in children of fathers carrying the gene, pointing to the importance of maternal imprinting [36]. The causative gene has been identified as *SDHAF2* gene [5•,6•]. The gene was mapped to chromosome 11q13.1 by genomic sequence analysis [5•].

PGL 3 is a rare autosomal-dominant syndrome linked to the mutations in *SDHC* gene, which is located on chromosome 1q21 [2,3,31]. It is characterized by benign and seldom multifocal head and neck PGLs [9•,10,36]. *SDHC* mutations were originally believed to be associated with parasympathetic head and neck PGLs only [2,36]. However, extra-adrenal sympathetic PGLs and PHEOs have been already reported [9•,11,37•]. No genomic imprinting use to be found in PGL 3 and PGL 4 [21,36].

PGL 4 is an autosomal-dominant syndrome characterized by sympathetic extra-adrenal PGLs, followed by intra-adrenal PHEOs and parasympathetic head and neck PGLs [3,9•,10,11•,29]. The syndrome is caused by inactivating mutations of the tumor suppressor *SDHB* gene located on chromosome 1p35-p36 [2,3,30]. An increased risk for renal cell carcinoma, gastrointestinal stromal tumors (GIST), breast and papillary thyroid carcinoma in *SDHB* mutation carriers may be expected [38•,39•,40,41]. The mean age at the moment of diagnosis of PGL 4 is approximately 30 years. Typically, *SDHB*-related PGLs originate in extra-adrenal locations (abdomen – Zuckerkandl organ, thorax – mediastinum, and pelvis), use to be often large, mostly solitary and have strong tendency for metastatic spread [9•,10,11•,29,41,42]. Diagnosis is frequently delayed due to an atypical clinical presentation. Symptoms are caused by tumor mass effect rather by catecholamine excess [12•,41,44]. *SDHB* gene mutations have been implicated as the most common cause in the pathogenesis of malignant PHEOs/PGLs in both children and adults [9•,10,11•,12•,13•,33,41,42].

Recently, *SDHB*-related PGLs have been observed to be malignant in about 38% of cases [11•]. Even if there is no previous history of familial syndrome related to PHEOs/PGLs, all patients with metastatic tumors should be considered for *SDHB* gene mutation testing. No clear genotype-phenotype correlations were detected for *SDHB* mutations. Genotype-phenotype correlations failed to distinguish differences in tumor size, location, malignant potency, aggressive behavior, hypersecretion of dopamine, and metastatic disease at presentation of *SDHB*-related PGLs between different mutations. Identical *SDHB* mutations of family members may result in tumors of variable localization and severity [33,42,43•, 44].

The predominant biochemical phenotype of *SDHB* and *SDHD* related PHEOs/PGLs consisted of dopamine hypersecretion alone or of both dopamine and norepinephrine hypersecretion (*SDHB*-related tumors) [12•]. Thus increased plasmatic levels of methoxytyramine (indicating dopamine hypersecretion) could discriminate patients with *SDHB* and *SDHD* mutations from those with *VHL*, *RET* and *NF 1* mutations [Eisenhofer G, Pacak K, et al.; unpublished observations].

Recently, immunohistochemistry staining for SHDB of removed tumors has been observed as a cost-effective approach for distinguish *SDHx* related PHEOs/PGLs (the negative staining due to absent of *SDHB*) from other forms (the positive staining for *MEN 2*, *VHL* and *NF1* due to present of *SDHB*) [45•,46•]. Completely absent staining is more commonly found with *SDHB* mutation, whereas weak diffuse staining often occurs with *SDHD* mutation [45•]. The sensitivity and specificity of the *SDHB* immunohistochemistry to detect the presence of *SDHx* mutation in the prospective series were 100% and 84%, respectively [46•].

New genes related to PHEOs/PGLs

Except above mentioned *SDHAF2* gene, the other two genes have been recently detected to be causative for familial PHEOs/PGLs. Previously, *SDHA* gene was thought to be associated only with a neurodegenerative disorder known as Leigh syndrome, but not with PHEOs/PGLs [3,20,21]. Now the specific mutation of *SDHA* linked with catecholamine-secreting abdominal PGL has been described. This mutation was present in 4.5% of a large series of PHEOs/PGLs [4•]. Recently, tumor suppressor gene *TMEM127* has been identified as a new PHEO susceptibility gene. This gene located on chromosome 2q11 encodes transmembrane protein 127 (TMEM 127), which dynamically associates with a subpopulation of vesicular organelles, Golgi complex and lysosomes, suggesting a subcompartmental-specific effect. Germline *TMEM127* mutation was detected in approximately 3% of sporadic-appearing PHEOs [7•].

Genetic testing approaches in clinical practice

Genetic testing in patients with known or suspected familial syndrome

There are two main reasons for genetic testing in these cases. First, the familial syndromes are associated with other malignant tumors, so an early diagnosis of the syndrome (confirmed by the genetic testing) may lead to regular surveillance and early treatment. Second, hereditary forms of PHEOs are often multiple, extra-adrenal, recurrent and sometimes malignant, so a strict follow-up is recommended for better prognosis of the patients [17]. This approach could extend to other family members with the similar benefits. Personal, family history and clinical examination are starting points before the assessing of an appropriate germline mutation. In case of positive family history or of evidence for specific features of above mentioned familial syndromes (see table 1 and table 2), targeted genetic testing should be performed (see figure 2). Germline mutations used to be found in 100% of syndromic patients [9•,47•] and in 41-64% of non-syndromic patients [9•,48•]

with positive familial history. Overall, about 90% of patients with positive familial history have a chance to find specific gene mutation [9••]. Whenever a specific germline mutation has been identified, screening for associated disorders should be performed in the patient. Moreover, genetic testing should be offered to patient's first degree relatives to ascertain the presence or absence of this gene mutation. Predictive testing helps to identify asymptomatic individuals at risk of developing the familial syndrome and early identification of such individuals allows targeted biochemical and radiological screening, which reduces morbidity and mortality [3,17,49].

Genetic testing in patients with non-familial, apparently sporadic PHEOs/PGLs

The majority of PHEOs/PGLs are usually sporadic tumors without known family history, or other symptoms of above mentioned familial syndromes. However, familial nature of the disease may not be recognized due to genomic imprinting, incomplete penetrance, *de novo* mutation, or incomplete familial history [2,36]. Previous studies displayed that a significant number (7.5-27.0%) of patients with apparently sporadic PHEOs/PGLs were carriers for germline mutations of genes associated with familial syndromes. The frequency of genetic mutations in non-familial PHEOs/PGLs without an obvious syndrome varied significantly (*VHL* 3.5%-11.1%, *RET* 0.4%-5.0%, *SDHD* 0.8%-10.0%, *SDHB* 1.5%-10.0%) and showed geographical differences [49]. Recently, two large studies have found the frequency of germline mutations in non-syndromic patients with negative family history about 18-19% [47••,48••]. But in the case of multiple or recurrent PHEOs/PGLs, the frequency has been estimated about 39% [9••].

These findings led to the recommendation that all patients with apparently sporadic PHEOs/PGLs should be screened for hereditary causes. Routine testing of all genes is expensive and time consuming, but the proper order of tested genes can reduce the financial expenses. In general the presence of a germline mutation is likely in patients with any of the following features: early onset (<45 years), bilateral, multifocal or extra-adrenal tumors (especially head and neck PGLs), recurrent or malignant disease [9••,36,47••,48••,49].

PHEOs associated with NF1 can be identified by a careful physical examination or positive family history, so the genetic testing for *NF1* gene is not necessary in principle. Other genes (*RET*, *VHL*, *SDHB*, *SDHD*, *SDHC*, rarely *SDHA*, *SDHAF2* and potentially *TMEM127*) remain to be involved for subsequent mutation analysis. Patients with positive personal history and/or presenting specific syndromic lesions (*i.e.* syndromic patients, see table 2) should be tested for correspondent genes. Decision-making for gene testing of nonsyndromic patients with sporadic PHEOs/PGLs could be based on histological evaluation, localization and catecholamine production of the tumor – see figure 1.

Histological evaluation of PHEOs/PGLs

Malignant PHEOs/PGLs, especially extra-adrenal PGLs, used to be associated mostly with *SDHB* germline mutations [10,11••,12••,13••,^{29,33},41,43•,44,48••]. On contrary, malignant tumors in *SDHD* or *SDHC* mutation carriers have been described rarely (in less than 5 % of cases) [3,10••,11••,29,33,41,44,48••]. Malignant NF 1-related PHEOs were identified with similar frequency of malignancy like sporadic PHEOs in the general population [2,9••,10••,27,29]. Like *VHL*-associated PHEOs, MEN 2-associated PHEOs appear to undergo malignant transformation less frequently than sporadic PHEOs, only children with MEN 2B-associated PHEOs have a higher risk of malignancy compared to those with MEN 2A [2,15,17,22,24••].

Immunohistochemistry staining for SDHB positivity could distinguish between *SDHx* related PHEOs/PGLs and other familial syndromes (MEN 2, VHL, NF 1), or true sporadic tumors with high sensitivity and specificity [45•,46•].

Tumor localization and biochemical phenotype

Identification of intra-adrenal PHEOs suggests mutation of either the *RET* or *VHL* gene, than followed by *NF 1*, *SDHB* and rarely by *SDHD* or very rarely by *SDHC* genes [1,2,9•, 10,11•, 17, 23, 25•, 27, 29, 37•]. If the biochemical profile shows elevated metanephrine values (indicating epinephrine overproduction), then *RET* should be tested first (NF 1 patients are usually diagnosed by clinical investigation). Tumors due to mutations of *VHL* and *SDHx* are not characterized by increase of epinephrine/metanephrine hypersecretion. Additional measurement of plasma methoxytyramine (indicating dopamine production) could discriminate patient with *SDHx* mutations from those with *VHL* mutations [Eisenhofer G, Pacak K, et al.; unpublished observations].

When extra-adrenal PGLs are diagnosed, the germline mutations in *SDHx* genes used to be are found most commonly [3,9•,10,11•,29,47•,48•], particularly in case of dopamine hypersecretion (detected by increased levels of methoxytyramine) [Eisenhofer G, Pacak K, et al.; unpublished observations]. *SDHx*- related parasympathetic head and neck PGLs are mostly associated with *SDHD* (especially multiple tumors) and less frequently with *SDHB* or *SDHC* mutations [3,4•,9•,10,11•,29,47•,48•]. In the case of negative testing for *SDHD*, *SDHB*, and *SDHC*, respectively, testing for *SDHAF2* gene mutation should be performed, especially in young age of diagnosis [6•]. If the tumors do not overproduce dopamine/methoxytyramine, thereafter the testing for *VHL* gene mutations should be made first, because parasympathetic head and neck PGLs are extremely rare in patients with MEN 2 or NF 1 [9•,10,25•,29,47•,48•].

Extra-adrenal sympathetic PGLs (in abdomen, thorax and pelvic localization) are usually related to *SDHB* (especially solitary, large tumors), less frequently to *SDHD*, rarely to *SDHC* and very rarely to *SDHA* mutations [9•,10,11•,37•,41,47•,48•]. *SDHB*-related tumors usually overproduce dopamine and norepinephrine (detected by increased plasmatic levels of methoxytyramine and normetanephrine, respectively). The increased levels of metanephrine (indicating epinephrine hypersecretion) are specific for MEN 2 (or NF 1) patients and could distinguish them from those with *VHL* and *SDHx* mutations. *VHL*-related tumors produce only norepinephrine/normetanephrine [Eisenhofer G, Pacak K, et al.; unpublished observations].

Conclusion

Now, it has been proved that about 30% or more of PHEOs/PGLs may be of inherited origin. Up to day, nine genes have been established to cause the familial PHEOs/PGLs. These tumors might be a part of the complex clinical syndromes or could be found alone as apparently sporadic neoplasmas. The clinical, histological and biochemical evaluation (the “rule of three”) could help with the decision-making for subsequent gene analysis. Genetic testing for appropriate germline mutation leads to the correct diagnosis and by this way to regular surveillance, early treatment and better prognosis for the patients with PHEOs/PGLs. This approach could extend to other family members with the similar benefit.

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pheochromocytomas and paragangliomas. *J Clin Endocrinol Metab.* 2007; 92:779–786. [PubMed: 17200167] . Twenty-nine patients with *SDHB*-related abdominal or thoracic PGL were included. Mean age at diagnosis was 33.7 $\pm$ 15.7 yr. Tumor-related pain was among the presenting symptoms in 54% of patients. Seventy-six percent had hypertension, and 90% lacked a family history of PGL. All primary tumors but one originated from extraadrenal locations. Mean $\pm$ sd tumor size was 7.8 $\pm$ 3.7 cm. Twenty eight percent presented with metastatic disease and all but one eventually developed metastases after 2.7 $\pm$ 4.1 yr. The biochemical phenotype was consistent with hypersecretion of both norepinephrine and dopamine in 46%, norepinephrine only in 41%, and dopamine only in 3%. No obvious genotype-phenotype correlations were identified.

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Figure 1. Flow chart for genetic testing

In patients with syndromic lesions and/or positive family history the appropriate specific gene should be tested. In non-syndromic patients with apparently sporadic tumors the immunohistochemistry staining for SDHB presentation could discriminate *SDHx*-related tumors (SDHB staining is negative, or weak diffuse positive for *SDHD* mutations) from others (SDHB staining is positive). In case of tumor malignancy the patient is probably carrier for *SDHB* mutation. If patient with intra-adrenal PHEO have increased levels of metanephrine (indicating hypersecretion of epinephrine), he is probably *RET* proto-oncogene carrier or suffers from NF 1, but this disease used to be diagnosed in previous clinical evaluation. *VHL*-related PHEOs produce only norepinephrine (detected by solitary increased normetanephrine levels). Presence of dopamine hypersecretion (detected by increased methoxytyramine levels) could distinguish *SDHx*-related PHEOs from other inherited forms. *SDHx*-related PHEOs are mostly associated with *SDHB*, less frequently with *SDHD* and very rarely with *SDHC* mutations. Sympathetic extra-adrenal PGLs of *SDHx* origin usually overproduce dopamine; *SDHB*-related tumors produce often norepinephrine and/or dopamine. The genetic testing should start with *SDHB* (especially in case of solitary large extra-adrenal tumors or of simultaneous extra-adrenal PGL and PHEO occurrence) prior than *SDHD* gene. Rarely *SDHC* and very rarely *SDHA* related extra-adrenal PGLs were described. Sympathetic extra-adrenal PGLs with epinephrine/metanephrine hypersecretion would be probably associated with *RET* mutations (NF 1 patients use to be clinically diagnosed before). Patients with solitary increased normetanephrine levels (indicating hypersecretion of norepinephrine) would have sympathetic extra-adrenal PGLs due to *VHL* mutations, or *SDHB* mutations. Parasympathetic head and neck PGLs are predominantly associated with *SDHx* mutations and may overproduce dopamine. The genetic testing should start with *SDHD* gene (especially in multiple tumors). Less frequently *SDHB* or *SDHC* mutations are related to these tumors. In case of absence of *SDHD*, *SDHB* and *SDHC* mutations, respectively, *SDHAF2* gene mutation should be tested, especially in young age of onset. *VHL*-related, head and neck PGLs are relatively rare and do not produce dopamine. *RET* or *NF 1* related head and neck PGLs are extremely rare.

Biochemical phenotype: dopaminergic: >10% of plasmatic methoxytyramine levels; adrenergic: >6% of plasmatic metanephrine levels, noradrenergic: everything else [Eisenhofer G, Pacak K, et al.; unpublished observations].

PHEOs = pheochromocytomas; sPGLs = sympathetic paragangliomas; pPGLs = parasympathetic paragangliomas; MEN 2 = multiple endocrine neoplasia type 2; *VHL* = von Hippel-Lindau disease; NF 1 = neurofibromatosis type 1; *SDHB* = succinate dehydrogenase subunit B; *RET* = Rearranged during transfection proto-oncogene; *VHL* = von Hippel-Lindau disease tumor suppressor gene; *NF 1* = neurofibromatosis type 1 tumor suppressor gene; *SDHx* = succinate dehydrogenase subunits genes; *SDHA* = succinate dehydrogenase subunit A gene; *SDHB* = succinate dehydrogenase subunit B gene; *SDHC* = succinate dehydrogenase subunit C gene; *SDHD* = succinate dehydrogenase subunit C gene; *SDHAF2* = succinate dehydrogenase complex assembly factor 2 gene.

Table 1

Main familial syndromes associated with pheochromocytomas and paragangliomas

Syndrome	MEN 2	VHL	NF 1	PGL 1	PGL 4
Gene	<i>RET</i>	<i>VHL</i>	<i>NF 1</i>	<i>SDHD</i>	<i>SDHB</i>
Mean age of diagnosis	30-40	20-40	40-50	30-40	20-40
Adrenal PHEOs	+++	++	+++	-/+	++
Bilateral PHEOs	+++	+++	+	-/+	-/+
Extra-adrenal sPGLs	-/+	+	-/+	+	+++
Head and neck pPGLs	-	-/+	-	+++	+
Biochemical profile	E/MN NE/NMN	NE/NMN	E/MN NE/NMN	DA/MT	DA/MT NE/NMN
Malignant	-/+	-/+	-/+	-/+	+++

PHEOs = pheochromocytomas; sPGLs = sympathetic paragangliomas; pPGLs = parasympathetic paragangliomas; MEN 2 = multiple endocrine neoplasia type 2; VHL = von Hippel-Lindau disease; NF 1 = neurofibromatosis type 1; PGL 1 = paraganglioma syndrome type 1; PGL 4 = paraganglioma syndrome type 4; RET = Rearranged during transfection proto-oncogene; VHL = von Hippel-Lindau disease tumor suppressor gene; NF 1 = neurofibromatosis type 1 tumor suppressor gene; SDHD = succinate dehydrogenase subunit D gene; SDHB = succinate dehydrogenase subunit B gene; E = epinephrine; NE = norepinephrine; MN = metanephrine; NMN = normetanephrine; DA = dopamine; MT = methoxytyramine

Table 2

Clinical features of familial PHEOs/PGLs

<p><u>Familial or personal history suspected from PHEOs:</u></p> <ul style="list-style-type: none"> • sudden death, especially at a young age • hypertensive crisis, stroke, heart attack or heart failure, especially at a young age • hypertensive reaction during instrumental intervention or anesthesia <p><u>MEN 2:</u> MEN 2A - MTC, hyperparathyroidism; MEN 2B - MTC, marfanoid habitus, mucosal ganglioneuromas</p> <p><u>VHL:</u> retinal angiomas, central nervous system hemangioblastomas, renal cell carcinomas, islet tumors of the pancreas, cysts and cystadenomas of the kidney, pancreas, epididymis</p> <p><u>NF 1:</u> café-au-lait spots, mucosal and cutaneous neurofibromas, inguinal, or axillary freckles, benign iris hamartomas (Lish nodules), optic-nerve glioma, dysplasia of sphenoid bone</p> <p><u>PGL 1,2,3:</u> usually benign, multiple head and neck tumors, with symptoms mainly related to their location, with maternal imprinting (only in PGL 1 and 2)</p> <p><u>PGL 4:</u> mostly extra-adrenal tumors (abdomen – Zuckerkandl organ, thorax and pelvis), with symptoms caused by large tumor mass effect rather by catecholamine excess, frequently malignant</p>

PHEOs = pheochromocytomas; PGLs = paragangliomas; MEN 2 = multiple endocrine neoplasia type 2; MTC = medullary thyroid carcinoma; VHL = von Hippel-Lindau disease; NF 1 = neurofibromatosis type 1; PGL 1,2,3 or 4 = paraganglioma syndrome type 1,2,3 or 4