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Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing

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Abstract

Background—Pheochromocytomas (PCC) and paragangliomas (PGL) are neuroendocrine tumors which, although rare, are an important cause of secondary hypertension because of the high morbidity and mortality. PCC/PGL are still thought of as the “tumor of tens” with 10% being hereditary; however, recent population based studies suggest that up to 32% of patients have a germline mutation in one of the known common susceptibility genes (including *NF1, VHL, RET, SDHB, SDHD*, *SDHC*). Despite this, most patients in the United States are not referred for clinical genetic testing by their physicians. We aimed to examine the mutation prevalence in a clinic-based population in the United States.

Methods—We performed a retrospective chart review of 139 consecutive patients with PCC/PGL from the Medical Genetics clinic at the Hospital of the University of Pennsylvania from January 2004 through February 2012.

Results—We found a 41% overall mutation detection rate. Twenty-six percent of the cohort had a mutation in the *SDHB* or *SDHD* genes. Of patients with at least one PGL tumor outside the adrenal gland, 53% had an identified mutation.

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Conflict of Interest

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Conclusion—Forty-one percent of the cohort had a heritable mutation and the most commonly mutated gene was *SDHB*, which carries the highest risk of malignancy. These data, together with American Society of Clinical Oncology guidelines suggesting that genetic testing be performed if the risk of a hereditable mutation is at least 10% or if it will affect medical management, strongly suggest that all patients with PCC/PGL need clinical genetic testing.

Introduction

Tumors of the autonomic nervous system which develop from chromaffin cells are called pheochromocytomas and paragangliomas (PCC/PGL), depending on whether they arise from the adrenal medulla or from extra adrenal sites, respectively. The estimated incidence is 2–8 per million with the peak age of occurrence in the third to fifth decade of life.[1] Although they are rare and often benign tumors, high morbidity and mortality can occur related to mass effect and the biochemical burden of high circulating catecholamines, leading to secondary hypertension, stroke and even death. The excessive catecholamine production can cause hemodynamic instability peri-operatively, including hypertensive crisis with induction of anesthesia and manipulation of the tumor itself, and hypotension and shock immediately after surgical resection of the tumor due to the acute withdrawal of catecholamines.[2, 3] Therefore, current management guidelines recommend that patients be pre-treated prior to surgical procedures with regimens usually including an alpha blockade.[4]

The historic “dogma of ten” for pheochromocytomas (10% are malignant, 10% are hereditary, 10% are extra-adrenal) has been shown to be inaccurate.[5, 6] In fact, approximately one-fourth of tumors are malignant with metastasis occurring even 20 years after removal of the primary tumor and with only a 50% five year survival rate.[7] The majority of PCC/PGL still are thought to be sporadic; however, with the identification of novel susceptibility genes over the last decade, multiple studies suggest that 24–32% of PCC/PGL cases have a hereditary germline mutation.[8–10] Therefore, given the clinical implications, these tumors, and any genetic predisposition to them, are important to recognize and diagnose early to prevent the associated morbidity and mortality. Despite these newer data, clinical genetic testing is not routinely offered by physicians in the United States (US) for patients with PCC/PGL.

Currently, there are ten known PCC/PGL susceptibility genes. Mutations in three genes causing well characterized cancer susceptibility syndromes have an increased risk of developing PCC/PGL including *VHL* (von Hippel Lindau, vHL), *NF1* (Neurofibromatosis Type 1, NF1), and *RET* (Multiple Endocrine Neoplasia Type 2, MEN 2).[5] These patients usually have other clinical characteristics of the associated syndromes, vHL, MEN 2A/B or NF1, at time of presentation. Mutations in any of the succinate dehydrogenase (SDH) complex subunit genes (*SDHA, SDHB, SDHC, SDHD)* and one of the complex cofactors, *SDHAF2*, (or *SDH5*), can lead to PCC/PGL with variable penetrance.[11–20] Germline mutations in *SDHB* are associated with extra-adrenal tumors and a higher rate of malignancy (31–71%) than the other known susceptibility genes.[8, 20–26] In fact, the identification of a germline *SDHB* mutation is the only reliable predictor of malignancy, again emphasizing the importance of knowing the germline genetic mutation. In addition, patients with germline

mutations in any of the *SDHx* genes have increased susceptibility for multiple primary tumors.[16, 24, 27, 28] More recently identified susceptibility genes are *TMEM127* and *MAX*,[29–33] and the associated clinical spectra are still being evaluated.

Despite the high rate of hereditary mutations known to be associated with PCC/PGL and the correlation of *SDHB* mutations with the development of malignant disease, many physicians in the US do not routinely refer affected patients for genetic counseling and testing as part of their clinical care. Our objective was to determine the prevalence of mutations in a US hospital based cohort, which would be generalizable to other centers, in order to determine the frequency of inherited mutations and make recommendations regarding testing in this population regarding the importance of clinical genetic testing.

Methods

A retrospective chart review was performed of patients referred for evaluation to the Medical Genetics clinic associated with the Neuroendocrine Tumor Center at the Hospital of the University of Pennsylvania (HUP) from January 2004 through February 2012. IRB approval for the retrospective chart review was obtained through the University of Pennsylvania. The clinical practice at HUP is to offer referral to Medical Genetics for genetic counseling and testing to all patients with PCC/PGL seen in the Neuroendocrine Tumor Center. All patients in the cohort had at least one PCC/PGL based on pathologic diagnosis. PCC refers to tumors within the adrenal gland. We defined PGL to refer to all tumors outside the adrenal gland, dividing them into head and neck PGL (HNPGL) and extra-adrenal PGL. Extra-adrenal PGLs are defined as tumors found in the abdomen/pelvis or thorax but not in the adrenal gland nor head and neck.

All genetic testing was done in a clinical setting and screening was done in a step-wise manner based on clinical presentation (Figure 1). The diagnosis of Neurofibromatosis type 1 (NF1) was based on the standard clinical diagnostic criteria.[34] All other diagnoses (vHL, MEN 2, or paraganglioma syndromes) were based on mutation detection in the associated genes (*VHL, RET, SDHx*, respectively) using direct sequencing and deletion/duplication studies done through clinical laboratory testing. This cohort was not tested for mutations in *SDHA, SDHAF2, TMEM127* or *MAX* as they were not widely available for clinical testing during the majority of the study period. Patients with clinical syndromes suggestive of vHL or MEN 2 were first screened for *VHL* or *RET* mutations, respectively. Patients with HNPGL had sequential testing beginning with *SDHD* mutation screening. Patients with extra-adrenal PGL in the torso had sequential testing beginning with *SDHB* mutation screening. Patients with biochemical profiles suggestive of particular gene mutations were tested for those genes first (i.e. metanephrine or dopamine/methoxytyramine predominance are associated with *RET* or *SDHB* mutations, respectively).[35–37] Once a positive mutation was found, no further genes were tested. Thus, each patient in the cohort did not necessarily have complete genetic testing for all six genes investigated. To be included in this cohort, they had to have at least one gene sequenced. Of note, the current genetic testing landscape allows for more cost efficient testing through S*DHx* panels or even PCC/PGL panels (testing nine of the ten susceptibility genes excluding *SDHA).* These panels may have been used for some patients towards the end of the study period when available.

Since late 2010, immunohistochemical staining for the SDHB protein on the clinical pathologic specimen became available at our institution after studies found an association between weak or absent staining with the presence of a mutation in SDHB or related protein subunits.[38, 39] If strong SDHB staining was found, this might suggest no need for *SDHB* mutation testing. However, because HUP is a large referral center for PCC/PGL and because of the clinical implications of having a germline mutation in a PCC/PGL susceptibility gene, it is our practice at HUP to perform clinical genetic testing on all patients with PCC/PGL. Therefore, during the study period, SDHB IHC results did not impact the clinical genetic testing algorithm.

Statistical analysis

Age is presented as mean age (SD) unless otherwise stated. A two-tailed T-Test was used for comparison of two groups. One way ANOVA for independent samples along with a Bonferroni test was used for comparison between multiple groups. P values less than 0.05 were considered to indicate statistical significance.

Results

Our retrospective review identified 139 consecutive patients diagnosed with PCC/PGL who were seen at the Medical Genetics Clinic between January 2004 and February 2012. Patients were excluded if they either declined genetic testing or ultimately had testing done through another institution with results not available for our review (N=14) or if they already had relatives included in the cohort (N=14). One additional patient had results still pending at the time of analysis and close of the study. In total, 110 unrelated subjects were included who had clinical genetic testing for at least one of the known susceptibility genes.

Table 1 shows the clinical characteristic of the 110 patient cohort. Twenty-five patients had only extra-adrenal PGL; 55 patients had only adrenal based PCCs; and 22 patients had only HNPGL. Twenty-four patients had multiple tumors, and six of them had bilateral adrenal PCC. There was no statistically significant difference in the ages of patients with tumors in each location (data not shown). Only 26% of patients (29/110) had a known family history of PCC/PGL or associated clinical syndrome (MEN 2A, NF1 or vHL).

Forty-five patients (41%) had an identified mutation in a known susceptibility gene (Table 2). Table 2 shows the distribution of mutations based on PCC/PGL location, and Supplemental Table 1 lists the specific mutations identified. The mutation detection rate was higher in patients with only PGLs (47%) when compared to patients with only adrenal based PCCs (29%). In patients who either had a positive family history of PCC/PGL or an associated clinical syndrome based on evaluation by a Medical Geneticist, the mutation detection rate was 90%. It was 23% for those with no known family history. No patients in the cohort had an identified *SDHC* mutation (data not shown). Nineteen patients had *SDHB* mutations; 15 of those had at least one extra-adrenal PGL, while the other four patients had only HNPGLs. Ten patients had *SDHD* mutations; all of them had at least one HNPGL.

Of the 55 patients with only adrenal based PCCs, 39 (71%) had no identifiable mutation in those genes examined (Table 2). The remaining 16 patients (or 29%) had a mutation in the

VHL or *RET* genes or had a clinical diagnosis of NF1. The six patients with bilateral adrenal PCC, all had either *RET* or *VHL* mutations. Of the 25 patients with only extra-adrenal PGL, 48% had an identified mutation, all in the *SDHB* gene. Of the 22 patients with only HNPGL, 45% had an identified mutation, all in one of the *SDHx* genes. Of the 55 patients with at least one tumor outside the adrenal gland, 29 of them (or 53%) had an identified mutation. Twenty of 24 patients (83%) with multiple primary tumors had an identified germline mutation.

Twenty-four patients (22%) had malignant disease, as defined by the standard pathologic diagnosis of chromaffin tissue found in areas where it is not normally present.[1] Interestingly, only ten of those patients (42%) had an identifiable mutation, all in the *SDHB* gene.

Table 3 shows that the mean age at initial diagnosis was significantly different when grouped by germline mutation ($p<0.001$). Patients with any identified germline mutation were younger at diagnosis than those without an identified mutation [30.44 (13.37) vs. 45.35 (14.99) years; p value<0.001]. Specifically, patients with *SDHB* and *VHL* mutations were initially diagnosed with PCC/PGL at a younger age than those without an identified mutation (Table 3). In addition, patients with only extra-adrenal PGL who had an identified germline mutation were significantly younger than those without an identified mutation [25.67 (11.81) vs 44.17 (17.10) years; p value=0.006].

Discussion

PCC/PGLs are more commonly associated with an inherited mutation than any other cancer type. Our data confirm a high mutation detection rate of 41% in PCC/PGL susceptibility genes in a Neuroendocrine Tumor Center. Patients with identified mutations were younger at time of initial diagnosis and were more likely to have at least one PGL. The most common mutations found were in the *SDHB* gene. The American Society of Clinical Oncology (ASCO) guidelines recommend genetic testing for any patient with over a 10% prior probability of carrying an inherited cancer susceptibility mutation;[40] however, this is not routinely done for PCC/PGL patients in the US. The specific inherited mutation in patients with PCC/PGL impacts surveillance and monitoring for tumor recurrence, additional primary tumors and malignancy. Furthermore, identifying that a mutation is carried in the family is important for screening unaffected individuals, given the overall life-time risk of developing PCC/PGL can be above 80% depending on the mutated gene.[20, 24] Our data emphasize the need for education of physicians in the US that all patients with PCC/PGL should be referred for genetic testing.

Our mutation prevalence data for specific populations are comparable with published population based studies.[8, 41, 42] Burnichon *et al.* found that 54.4% of patients with PGL had a germline mutation in *SDHD, SDHB* or *SDHC* regardless of the family history,[41] comparable to our 47% mutation detection rate for patients with PGL only. Cascon *et al.* and Mannelli *et al.* examined patients with both PCC and PGL, and found that 79.2% and 91.2%, respectively, of probands with a positive family history of PCC/PGL had a mutation

in one of the major susceptibility genes.[8, 42] We found a 90% mutation detection rate in patients with PCC/PGL who had a positive family history.

Our study has selection bias, which could increase our detection rates, as this cohort was selected by outpatient office visits to Medical Genetics, who were specifically referred for genetic testing. However, it is important to note that previous work from international consortiums with most patients from Europe have shown similar mutation detection rates between population based and referral based studies.[9, 20, 43] Moreover, it is notable that only 26% patients had a known family history of PCC/PGL or associated clinical syndrome. Therefore, most patients represented sporadic cases and still, 23% of these (19/81) had an identifiable germline mutation. This finding supports the notion that the penetrance of disease in mutation carriers is not 100%,[24, 44] and hence, the absence of a family history should not deter physicians from referring for clinical genetic testing. It also is important to recognize that a positive family history may be more difficult to ascertain for tumors caused by genes which have a parent of origin effect, such as *SDHD* and *SDHAF2*, as tumors may appear to skip several generations. Of note, ascertainment bias may play a role in the higher than usual rate of NF1 patients in this cohort, as we are a referral clinic for this disorder.

Despite the selection bias in our cohort, the reported prevalence of hereditary mutations in our study may, in fact, be underestimated. Our study used retrospective data from clinical genetic testing rather than performing comprehensive mutation screening on all the known susceptibility genes, as has been done in the larger aforementioned population based studies.[8, 9, 20, 41, 42] Many of our patients were not evaluated for mutations in all six susceptibility genes, as genetic testing was performed in a step-wise and stratified manner based on the clinical scenario using genotype/phenotype based correlations to improve cost-efficiency. While perhaps less comprehensive, our data are more generalizable to the practice of academic institutions. Furthermore, we could not test for mutations in the more recently identified susceptibility genes as clinical genetic testing was not offered during the study period. However, mutations in these genes, *SDHAF2*, *TMEM127*, and *MAX*, appear to account for a very small percentage of identifiable mutations and it is unlikely that their inclusion would significantly alter our detection rate.[16, 18, 29–32]

There are several perceived barriers that prevent physicians from recommending clinical genetic testing for patients with PCC/PGL. One barrier is the misconception that most medical insurances will not cover the cost of genetic consultation or genetic testing. However, genetic consultation is covered at a rate equal to other specialists and the vast majority of insurance plans cover medically necessary genetic testing. In our experience, very few patients have significant, if any, out of pocket expense associated with their decision to pursue genetic testing when following insurance plan guidelines regarding pre-certification. Another barrier is a lack of awareness or understanding about the utility of genetic testing for this indication, both on the part of referring physicians and the patients. In other words, a physician may not know what to do with the positive or negative results. Geneticists and genetic counselors are trained to discuss these issues and can serve as a resource when considering the benefits, limitations and the clinical implications of genetic testing. They can also serve as resources to discuss other possible concerns of patients and

physicians, such as the commonly cited fear of insurance discrimination when testing family members who are currently asymptomatic for a known familial mutation.

In summary, our study found that 41% of all patients with PCC/PGL seen in a US based academic institution have a mutation in a known susceptibility gene. Current ASCO guidelines suggest that genetic testing be done in the setting in which it will influence medical management [45] and prior ASCO guidelines suggested that it be done for any patient with a 10% risk of having a heritable mutation in a cancer susceptibility gene.[40] Thus, based on both sets of guidelines, our data suggest that all patients with PCC/PGL should be referred for clinical genetic testing. Knowledge of the heritable mutation has important implications for surveillance and monitoring of patients and their family members, and should become part of routine care for patients with PCC/PGL in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Synopsis

Knowing the heritable mutation for patients with PCC/PGL has important implications for surveillance for that patient and their family members. We found a 41% mutation detection rate in patients with PCC/PGL, suggesting that genetic testing should become part of routine care.

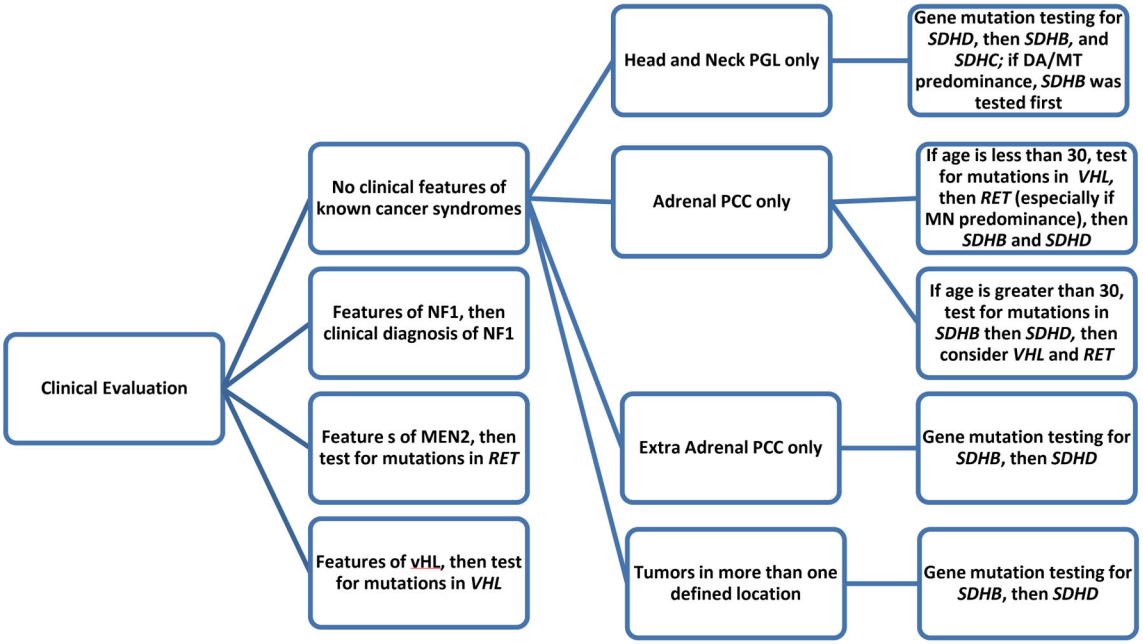

Figure 1.

Clinical Genetic Testing Algorithm. Clinical genetic testing was performed in a step wise manner based on clinical assessment by a medical geneticist. Deviations from this general algorithm could occur based on individualized patient care. During the majority of the study period, a PCC/PGL panel of gene testing and individual testing for *SDHAF2*, *TMEM127* and *MAX* was not readily available. Immunohistochemistry for SDHB also was not widely available during most of the study period and did not play a role in the testing algorithm. DA/MT – dopamine/methoxytyramine; MN – metanephrine

Table 1

Clinical characteristics of PCC/PGL cohort

Total population; N	110
Gender (males/females)	55/55
Age at first diagnosis; years	
Mean (SD)	38.98 (16.28)
median	41
range	7 to 72
Hypertension; N (%)	69 (62)
Positive family history; N (%)	29 (26)
Metastatic disease; N (%)	24 (22)
Location of tumors	
Adrenal only; N (%)	55 (50)
Extra-adrenal only; N (%)	25 (23)
Head and neck only; N (%)	22 (20)
Tumors in more than one defined location; N (%)	8 (7)

Table 2

Characteristics of mutation groups in PCC/PGL cohort

Diagnosis	***SDHB*** **N (%)**	***SDHD*** **N (%)**	***VHL*** **N (%)**	***RET*** **N (%)**	***NF1*** **N (%)**	**Mutation** **N (%)**	**NMI**[a] **N (%)**
Patients	19 (17)	10 (9)	6 (5)	3 (3)	7 (6)	45/110 (41)	65/110 (59)
Location of tumors							
Adrenal only	0	0	6	3	7	16/55 (29)	39/55 (71)
Extra-adrenal only	12	0	0	0	0	12/25 (48)	13/25 (52)
Head and neck only	4	6	0	0	0	10/22 (45)	12/22 (55)
Tumors in more than one defined location	3	4	0	0	0	7/8 (88)	1/8 (13)
Patients with multiple tumors	7	7	4	2	0	20/24 (83)	4/24 (17)
Patients with single adrenal tumor and no FHx	0	0	0	0	5	5/44 (11)	39/44 (89)
Patients with no FHX	7	4	2	1	5	19/81 (23)	--
Patients with FHX	12	6	4	2	2	26/29 (90)	--
Patients with metastatic disease	10	0	0	0	0	10/24 (42)	14/24 (58)

[a] NMI, no mutation identified

Table 3

Mean age at diagnosis for different mutation groups within PCC/PGL cohort

Mutation	N	Age at diagnosis, mean (SD)	p value[a]
no mutation identified	63[b]	45.35 (14.99)	
SDHB	19	26.42 (10.20)	<0.001
SDHD	10	31.90 (13.96)	0.063
VHL	6	18.00 (8.53)	<0.001
RET	3	39.00 (12.53)	1.000
NF1	7	46.29 (7.36)	1.000

[a] compared to the group with no mutation identified

[b] two patients dropped from analysis due to no documented age at first PCC/PGL diagnosis