The Clinical Phenotype of *SDHC*-Associated Hereditary Paraganglioma Syndrome (PGL3)

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Context: Mutations in the genes encoding subunits of the succinate dehydrogenase complex cause hereditary paraganglioma syndromes. Although the phenotypes associated with the more commonly mutated genes, *SDHB* and *SDHD,* are well described, less is known about *SDHC*-associated paragangliomas.

Objective: To describe functionality, penetrance, number of primary tumors, biological behavior, and location of paragangliomas associated with *SDHC* mutations.

Design: Families with an *SDHC* mutation were identified through a large cancer genetics registry. A retrospective chart review was conducted with a focus on patient and tumor characteristics. In addition, clinical reports on *SDHC*-related paragangliomas were identified in the medical literature to further define the phenotype and compare findings.

Setting: A cancer genetics clinic and registry at a tertiary referral center.

Patients: Eight index patients with *SDHC*-related paraganglioma were identified.

Results: Three of the eight index patients had mediastinal paraganglioma and four of the eight patients had more than one paraganglioma. Interestingly, the index patients were the only affected individuals in all families. When combining these index cases with reported cases in the medical literature, the mediastinum is the second most common location for *SDHC*-related paraganglioma (10% of all tumors), occurring in up to 13% of patients.

Conclusions: Our findings suggest that thoracic paragangliomas are common in patients with *SDHC* mutations, and imaging of this area should be included in surveillance of mutation carriers. In addition, the absence of paragangliomas among at-risk relatives of *SDHC* mutation carriers suggests a less penetrant phenotype as compared to *SDHB* and *SDHD* mutations. **(*J Clin Endocrinol Metab* 99: E1482–E1486, 2014)**

Paragangliomas (PGLs) and pheochromocytomas (PCs) are rare tumors arising from cells of the autonomic nervous system and adrenal medulla, respectively. PGLs can originate from parasympathetic and sympathetic paraganglia of the head and neck, thorax, abdomen, and pelvis. Most head and neck PGLs (HNPGLs) are parasympathetic in origin and do not secrete any catecholamines, whereas PCs and abdominal PGLs are of sympathetic origin and often secrete catecholamines. Only approximately 2% of PGLs occur in the thoracic cavity or mediastinum; however, these tumors often exhibit an aggressive phenotype (1).

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Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; GIST, gastrointestinal stromal tumor; HNPGL, head and neck PGL; MEN2, multiple endocrine neoplasia type 2; MIBG, (^{123}I)metaiodobenzylguanidine; NF1, neurofibromatosis type 1; PC, pheochromocytoma; PGL, paraganglioma; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease.

Over the last two decades, an increasing number of genetic predisposition syndromes associated with risk for PGL/PC have been identified. Location of tumors, family history, age at diagnosis, and biochemical phenotype can be used to prioritize targeted genetic diagnosis of an underlying syndrome. Tumors associated with von Hippel-Lindau disease (VHL), multiple endocrine neoplasia type 2 (MEN2), and neurofibromatosis type 1 (NF1) commonly occur in the adrenal gland. MEN2-associated PCs secrete epinephrine, and VHL-associated PCs predominantly secrete norepinephrine (2). All of these syndromes are associated with specific phenotypic characteristics, including predisposition to other tumors.

Several distinct familial PGL syndromes (PGL1–5) are caused by mutations in genes encoding subunits of succinate dehydrogenase (SDHx) itself or factors necessary for the correct assembly of the SDH complex. A recent multicenter retrospective study that included 20 French referral centers found that half of all PGL patients carry a mutation in one of these genes: *SDHB* (PGL4, 22%), *SDHC* (PGL3, 7%), or *SDHD* (PGL1, 29%) (3). With regard to clinical features, there is a significant overlap between the different subtypes of the hereditary PGL syndromes. *SDHB*-related tumors are preferentially found in the abdomen, but head and neck PGLs and PCs can occur as well. Most commonly, these tumors secrete norepinephrine or/and dopamine, but they can also be nonfunctional (2). *SDHD* mutations predispose commonly to non-catecholamine-secreting HNPGLs and less commonly to PCs or abdominal PGLs. In contrast, the phenotype caused by *SDHC* germline mutations is less well described. Most *SDHC*-associated PGLs have been reported to preferentially arise in the head and neck region, to be almost always benign, and rarely to be multifocal (4). Very few families have been described with mutations in *SDHA* (PGL5) or *SDHAF2* (PGL2), and the clinical characteristics of these syndromes are less well established (5, 6).

The classic syndromes, such as MEN2, VHL, and NF1, are associated with disease penetrance of close to 100%. The penetrance for PC specifically varies considerably with a risk of 50% for MEN2, 10–20% for VHL, and 5–10% for NF1 (7). Penetrance for PC and PGL among *SDHB* and *SDHD* mutation carriers is estimated to be approximately 80% by age 50 (8). *SDHD*-related tumors develop earlier in life than *SDHB*-related PGLs (3). Because *SDHC* mutations are less common, penetrance analysis has not been attempted due to the small number of patients described. In this study, we describe eight new cases of *SDHC*-related PGLs and their clinical phenotype.

Patients and Methods

Patients with *SDHC* mutations were identified in the Cancer Genetics Registry at the University of Michigan (HUM no. HUM00043430). All patients gave written informed consent to take part in the registry. Family histories were verified with medical records when available. DNA was isolated from peripheral blood, and *SDHC* mutation analysis was conducted as part of clinical care in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. The partial gene deletion was identified by a CLIA-certified laboratory using the SALSA MLPA P226 SDH probemix (MRC Holland). The SDHC reference sequence is NM_003001.3. The following patient characteristics were extracted by individual chart review: gender, age at diagnosis, tumor location, number of primary tumors, date of diagnosis and recurrence for any tumor, biochemical phenotype (plasma or urine catecholamines or metanephrines), mode of preoperative scans, and family history. Catecholamine levels were measured as part of clinical care in different CLIA-certified laboratories. The literature search included publications of *SDHC*-related PGLs from January 2000 to May 2012.

Results

Characteristics of *SDHC*-related PGL

Clinical characteristics are summarized in Table 1. The average age at diagnosis of our index patients was 29.3 years (range, 15–40 y), and median follow-up was 59 months (range, 10–364 mo). Half of these patients had multiple tumors, and three of the eight index patients had a mediastinal PGL. Two of the patients with a mediastinal PGL had elevated normetanephrine levels, whereas presurgical metanephrines were not documented in the third patient. None of the patients developed distant metastases, but two of the eight patients developed recurrent disease at the same site as the initial tumor (local recurrence) after 3 and 13 years, respectively. None of the presented cases reported any other family history of PGL or PC. The results of functional imaging were only available for three patients. A (^{123}I)metaiodobenzylguanidine (MIBG) scan was mildly positive in a thoracic PGL and negative in two HNPGLs. This is in accordance with prior reports of SDHx-related PGLs often being MIBG negative (9). One HNPGL was detected in a pentetreotide scan. Functional data regarding catecholamine secretion were available on six of the eight patients. All patients with thoracic PGL with available data had increased levels of normetanephrine, norepinephrine, and dopamine. Only one of the remaining four patients with HNPGL had the same biochemical pattern, whereas no elevated levels were detected in the other three patients. However, both functional imaging and biochemical evaluation were not complete in all patients, and information is limited to data extractable from the medical charts. Furthermore, different assays and laboratories were used, and methoxytyramine was not

Table 1. Clinical Characteristics

Case No.	Age, y	Sex	Secretion	Location	Multiple/ Single	Recurrent	Malignant	Functional Imaging		Mutation
								Positive	Negative	
1	40	Fe	NM (P&U), NE (P&U), D (U) positive M (P&U), E (P&U) negative	HN (glomus jugulare), T (posterior to ascending aorta)	Mu	No primary surgery yet	N	MIBG (mildly avid)	N/A	*c.20-?_180-?del*, partial gene deletion
2	31	Ma	NM, M, NE, E, D negative (P)	HN (carotid body, glomus vagale)	Mu	Y (15 y)	N	FDG-PET, pentetreotide scan	MIBG	*c.379C>T*, p.His127Tyr
3	33	Ma	N/A	HN (carotid body), T (aortopulmonary window)	Mu	N	N	N/A	N/A	*c.43C>T*, p.Arg15X
4	28	Ma	NM, M, NE, E negative (U)	HN (glomus jugulare, carotid body)	Mu	N	N	N/A	N/A	*c.20-?_180-?del*, partial gene deletion
5	30	Fe	N/A	HN (glomus jugulare)	Si	Y (3 y)	N	N/A	N/A	*c.397C>T*, p.Arg133X
6	15	Fe	NM, M negative (U)	HN (glomus jugulare)	Si	N/A, incomplete resection	N	N/A	N/A	*c.405 + 1G>C*, splice site mutation
7	32	Fe	NM, D, NE positive (P) M negative (P)	HN (carotid body)	Si	N	N	N/A	MIBG	*c.214C>G*, p.Arg72Gly
8	25	Fe	NM, NE, D positive (U) M, E negative (U)	T (subcarinal)	Si	N	N	N/A	N/A	*c.43C>T*, p.Arg15X

Abbreviations: FDG-PET, 2-deoxy-2-(^{18}F)fluoro-D-glucose positron emission tomography; pentetreotide scan, (^{111}In)indium-pentetreotide scintigraphy; M, metanephrine; NM, normetanephrine; D, dopamine; E, epinephrine; NE, norepinephrine; U, urine; P, plasma; Ma, male; Fe, female, Mu, multiple, Si, single; N/A, not available, HN, head and neck; T, thoracic; N, no; Y, yes.

measured. Of note, four of the five PGLs diagnosed in female patients were diagnosed during pregnancy (three initial diagnoses and one recurrence). One patient with a thoracic PGL presented with classical symptoms of diaphoresis, palpitation, and hypertension; a second patient was initially diagnosed with pregnancy-related hypertension; and a third patient was diagnosed due to intermittent growth of a neck tumor during pregnancy. The recurrence was found as an enlargement in the area of the initial tumor site.

Discussion

We present eight additional cases of *SDHC*-related PGLs (PGL3). In summary, *SDHC*-related PGLs were nonmetastatic, of low penetrance, and most commonly HNPGL or thoracic PGLs, and at least three of the eight patients showed elevated normetanephrine, norepinephrine, and dopamine levels. Although none of the tumors was metastatic, local recurrence after initial therapy was common, and half of our index cases had multiple PGLs.

The spectrum of mutations in our series encompassed partial deletions, missense, and nonsense mutations. We report two new mutations not previously described in patients with *SDHC*-associated PGL: a novel missense mutation (*c.214C>G*; p.Arg72Gly), and a splice site mutation (*c.405+1 G>C*). Both mutations affect highly conserved sites, and mutations of the same codon and splice junction have been described previously (10, 11). The *c.405+1G>C* mutation has been described in a patient with a gastrointestinal stromal tumor (GIST) (11). The nonsense mutations in case 3 (*c.43C>T*; p.Arg15X) and case 5 (*c.397C>T*; p.Arg133X) have been described in several patients (3, 12, 13). Partial gene deletion was found in two presumably unrelated patients (no recognizable relation over four generations), both of Yemenite ancestry, suggesting a founder mutation in this population. A description of the partial gene deletion (*c.20+?_180-?del*) can be found in Supplemental Figure 1. Similar partial gene deletions have been described (3). The *c.43C>T* mutation, identified in two apparently unrelated patients, was described in one patient with a concurrent GIST and was also found incidentally in a patient undergoing whole genome sequencing (12, 14). Zbuk et al (13) described a patient with the same *SDHC* mutation plus coexisting PTEN hamartoma tumor syndrome (Cowden disease). The missense mutation in case 2 (*c.379C>T*; p.His127Tyr) has been recently shown to abrogate SDHB immunohistochemistry and to cause PGL3 (15). The absence of any additional affected family members precluded segregation analysis to confirm the disease-causing nature of the reported mutations. Furthermore, the lack of tumors in first-degree relatives suggests a very low penetrance of PGL tumors in carriers of *SDHC* mutations.

A total of 54 patients with *SDHC*-related PGLs have been reported in the literature (Table 2). An initial description of 22 individuals with *SDHC*-related PGLs revealed only HNPGLs, without mediastinal or abdominal PGLs or PCs, and only two patients with multiple PGLs (4). A subsequent description of 16 mutation carriers found 14 HNPGLs, two functional mediastinal PGLs, and five patients with multiple tumors (3). Another study found multiple tumors at presentation in three of seven *SDHC* carriers (16). There are at least three case reports

Table 2. PC and PGL Phenotype in PGL3 Patients

Study	Year	No. of Patients	No. of Tumors	HNPGL	Thoracic	Abdomen	Adrenal	Single	Multiple	Malignant
Niemann et al (1, 2)	2000	5	6	5	0	0	0	4	1	1
Niemann et al (3)	2003	1	1	1	0	0	0	1	0	0
Bauters et al (4)	2003	2	2	1	1	0	0	2	0	0
Baysal et al (5)	2004	6	7	7	0	0	0	5	1	0
Schiavi et al (6)	2005	8	8	8	0	0	0	8	0	0
Bayley et al (7)	2006	1	1	1	0	0	0	1	0	0
Peczkowska et al (8)	2007	2	2	1	0	0	1	2	0	0
Zbuk et al (9)	2007	1	1	1	0	0	0	1	0	0
Lopez-Jiminez et al (10)	2008	1	1	1	0	0	0	1	0	0
Pasini et al (11)	2008	2	2	0	0	2	0	2	0	0
Burnichon et al (12)[a]	2009	16	21	18	3	0	0	11	5	0
Bayley et al (13)	2009	1	1	1	0	0	0	1	0	0
Papaspyrou et al (14)	2011	7	13	10	0	0	0	4	3	1
Illouz et al (15)	2012	1	1	0	1	0	0	1	0	0
Present study, Else et al	2012	8	12	9	3	0	0	4	4	0
Total n		62	79	64	8	2	1	48	14	2
Total %				81.0%[a]	10.1%[a]	2.5%[a]	1.3%[a]	77.4%[b]	22.6%[b]	2.5%[a]

Mean age, 38.4 years (51 available); catecholamine production of 34 available: 8 (23.5%) positive (1 adrenal, 4 thoracic, 3 HNPGL), and 26 (76.5%) negative (all HNPGL). References: please see supplemental material.

[a] Percent of all tumors.

[b] Percent of all patients.

(including one of case 3) of *SDHC*-related mediastinal PGL (Table 2, Ref. 21). When considering prior reports with findings from the patients presented in the current study, the prevalence of multiple tumors among PGL3 patients is 23%. The mediastinum is the second most common location for SDHC-associated PGL, with tumors reported in eight of 62 patients (13%), representing 10% of PGLs in these patients.

One study of 10 patients with mediastinal PGLs found an almost equal distribution of *SDHB* (six of 10) and *SDHD* (four of 10) mutations, seven of 10 tumors secreted catecholamines, and more than half were malignant (1). In contrast, the mediastinal *SDHC*-related PGLs in our study and the ones reported in the literature did not show an overt malignant phenotype, suggesting a difference in biological behavior depending on the underlying *SDHx* gene mutation. Overall, only two malignant *SDHC*-related paragangliomas have been reported: one with local lymph node metastasis, and one with distant metastases (Table 2). Interestingly, all tumors that occurred in the adrenal gland or thoracic cavity for which biochemical analysis was available secreted catecholamines (3, 17, 18). All nonfunctional *SDHC*-related tumors were HNPGLs. This observation underscores the general rule that a functional phenotype is mainly dependent on the site of origin, rather than the underlying mutation.

There are increasing numbers of reports regarding associations of tumors other than PGL with *SDHx* mutations. The association of GISTs in patients with *SDHx* mutations is well established (12). For *SDHC*-related PGLs, single case reports of patients with PGLs and breast cancer, sigmoid adenocarcinoma, thyroid tumor, adrenal incidentaloma, and pituitary macroadenoma have been described (17–20). We did not observe any GIST or renal cell cancer in the current series. Of note, case 2 in our series has two adrenal incidentalomas with imaging characteristics typical for lipid-rich adenomas, which screened negative for adrenocortical hormone production.

Most studies on *SDHC*-related PGLs, including the current one, suffer from their retrospective nature and often incomplete data availability. Hopefully, future large consortia will elucidate the full phenotype of *SDHC*-related PGLs more definitively. Furthermore, we cannot exclude a referral bias in our series. For example, patients with multiple PGLs may be more likely to be referred to the Cancer Genetics Clinic.

In conclusion, *SDHC* mutations appear to be associated with a lower disease penetrance of PGL/PC when compared with *SDHB* or *SDHD* mutations. Mediastinal and multiple PGLs might be more common in PGL3 than was appreciated in prior studies. Patients with *SDHC* mutations should undergo screening with biochemical evaluation and imaging. Furthermore, up to one in 10 patients with PGL3 may develop a mediastinal PGL, and imaging of this area should be considered for surveillance in individuals with *SDHC* mutations.

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