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Hereditary Paragangliomas

Margarita Raygada[a], **Barbara Pasini**[c], and **Constantine A. Stratakis**[b]

[a]Section on Clinical Genomics, Program Reproductive and Adult Endocrinology, National Institutes of Health, Bethesda, Md., USA

[b]Section on Endocrinology and Genetics, Program on Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md., USA

[c]Department of Genetics, Biology and Biochemistry, University of Turin, Turin, Italy

Abstract

Paragangliomas (PGL) and pheochromocytomas (PCC) are rare, usually benign tumors that originate from the neuroendocrine tissue along the paravertebral axis. Up to 35% of these tumors may be hereditary; they are associated with germline mutations in genes encoding subunits of the succinate dehydrogenase (SDH) enzyme complex in the context of the familial PGL syndromes, PGL1, 3 and 4 caused by mutations in the *SDHD*, *SDHC* and *SDHB* genes, respectively. Another familial PGL syndrome, PGL2, is caused by mutations in *SDHAF2*/*SDH5*, which encodes for a molecule that is an accessory to the function of the SDH enzyme and its SDHA subunit. Less frequently, mutations in the genes responsible for Von Hippel Lindau disease (VHL), multiple endocrine neoplasia type 2 (MEN2), and neurofibromatosis type 1 (NF1) are also found in patients with hereditary PGL and PCC. Recently mutations were found in the *SDHA* subunit in a limited number of patients with PGL and/or PCC. The *SDHB*, *SDHC* and *SDHD* gene mutations (but not *SDHA*) can also be found in patients with PGL and/or PCC and gastrointestinal stromal tumors (GISTs), also known as the Carney-Stratakis syndrome; *SDHB* mutations, in particular, may also predispose to thyroid and renal cancer, and possibly other tumors. A new gene was recently found to predispose to PGL and/or PCC when mutated is TMEM127. In this text, we provide an overview of the genetics of PGLs and related conditions with an emphasis on genetic risk assessment, prevention, and prognosis.

Historically, paragangliomas were thought of as benign tumors derived from specialized periocytes in the glomus complexes [1]; we now know that they originate from the chromaffin-negative glomus cells of the embryonic neural crest. These cells which migrated in close association with the autonomic nervous system ganglia are dispersed from the middle ear and the skull to the pelvic floor. Based on their anatomical distribution, and autonomic function, PGLs can be divided into two categories: (1) extra-adrenal tumors of the head and neck (HNPGLs) usually located at the carotid bifurcation, along the vagal

Constantine A. Stratakis, Section on Endocrinology and Genetics, Program on Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), 31 Center Drive, Bethesda, MD 20892-2425 (USA).

nerve, in the jugular foramen, or in the middle ear space, and (2) tumors located below the neck which are most commonly found in the adrenal medulla (pheochromocytoma; PCC), urinary bladder, and the upper mediastinum. The incidence of clinically significant PGLs in the general population is approximately 1:30,000 to 1:100,000; in most cases, there is high morbidity but mortality remains low; early screening for familial cases and intervention are essential for good prognosis.

All types of PGLs and PCCs can occur in both sporadic and hereditary forms; approximately 7–10 to 50% of cases of PGLs are familial or present as bilateral or multiple primary tumors thus suggesting a genetic predisposition [2–5]; the proportion of PGLs due to an inherited predisposition is close to 35% [6]. Hereditary syndromes associated with PGLs include Von Hippel Lindau disease (VHL), multiple endocrine neoplasia type 2 (MEN2), and neurofibromatosis type 1 (NF1) and the PGL syndromes (PGLs 1–4) and Carney-Stratakis syndrome or dyad. In NF1, adrenal PCCs occur in nearly 1% of patients [7, 8].

In general, extra-adrenal PGLs are associated with a greater risk of metastasis (23.9%) than adrenal PCCs (6.7%) [9–11]. Recent studies have identified an additional locus on chromosome 1p36 that also seems to predispose to PCCs (gene *KIF1Bβ*) [12, 13]. In 2000, mutations in the succinate dehyrogenase subunit D *(SDHD)* gene were found to be associated with hereditary PGLs [14]; this finding was followed by more mutations in SDH subunit genes that are also associated with hereditary PGLs. These are: three loci on chromosome 11 and 1, named PGL1 on 11q23 [15–18], PGL2 on 11q13.1 [19, 20] and PGL3 on 1q21–23 [21, 22]. Co-occurrence of both PGLs and PCCs is well documented in these syndromes [23]. *SDHD* (OMIM 602690) is responsible for PGL1 in familial PGLs [14], whereas two other subunits of this mitochondrial enzyme, *SDHC* (PGL3, OMIM 602413) and *SDHB* (PGL4, 1p36, OMIM 185470) are also associated with heritable PCC and/or PGL [24, 25]. The gene responsible for PGL2 was recently identified to be *SDHAF2* (also known as *SDH5*), encoding a protein necessary for flavination of the A subunit of the SDH enzyme, SDHA (PGL2, 11q13.1, OMIM 601650) [26].

The genetic predisposition to HNPGLs and adrenal/extra-adrenal PGLs caused by heterozygous mutations by SDHD, SDHC, and SDHB is transmitted in an autosomal dominant fashion with age-dependent and incomplete penetrance [24, 25]. Mutations in the *SDHD* gene show a parent-of-origin effect (transmitted mostly from the father) [4, 15]. Despite this pattern of inheritance, *SDHD* shows bi-allelic expression in normal tissues and neural crest derived cancers with no promoter hyper-methylation in neuroendocrine tissues and related tumours [27]. In 2009, Hao et al. [26] evaluated a previously reported large Dutch family with an autosomal-dominant pattern of PGLs; they identified a mutation (G- to -A transition at nucleotide 232 of exon 2) in the *SDHAF2* gene [26]. The pattern of inheritance seen in this family was suggestive of an SDHD-like inheritance. However, more studies are needed to elucidate the mechanism. More recently, mutations in SDHA were reported in a limited number of kindreds with PGL and/or PCC (see below).

Herited Predisposition to Paragangliomas: Epidemiology and Risk Assessment

In a recent report, we reviewed 95 studies of *SDH* germline mutations (57 in *SDHD*, 54 in *SDHB* and 13 in *SDHC*) in patients affected by tumours related to the 'PGL/PCC syndromes' [29]. This review included all published reports cited in the LOVD *SDH* gene databases by July 2008. For the purpose of the current chapter, we will focus primarily on epidemiology, management, risk assessment, and preventive measures.

Prevalence and Clinical Manifestations of PGL Syndromes

PGL syndromes involve either sympathetic paraganglia (mainly abdominal, adrenal or extra-adrenal) or parasympathetic organs in the head and neck region (mainly carotid bifurcation, the jugular bulb (the tympanic plexus on the promontory or the vagal nerve). Table 1 provides a summary of the prevalence of *SDHB*, *SDHD*, and *SDHC* mutations in sporadic cases of PGL, and table 2 provides a summary of SDHB, SDHC, and SDHD mutations in malignant tumors PGL-PCC. Sixty-one percent of *SDHD*-mutated index cases have a positive family history, while 69% of *SDHB* mutations carriers have an apparent negative family history. The few *SDHC* mutated cases described to date have a positive family history in 62.5% of the cases. Therefore, the prevalence of *SDHB* germline mutations among sporadic cases is somewhat higher than that one of *SDHD*. Very few sporadic cases have been reported with *SDHC* germline mutations (0.6%). The prevalence of *SDHAF2*/*SDH5* mutations has not been well described to date; only one study has been reported so far [26, 28]. In summary, the prevalence of *SDH* mutations is as follows: sporadic extra-adrenal tumours (29.4%), malignant tumours (42.4%, table 2) and pediatric cases (29%) with strong preponderance of *SDHB* mutations in all categories (RET, NF1, VHL, MEN, SDHC, SDHB, SDHD). *SDH* mutations seem less frequent than *RET* and *VHL* in bilateral or familial adrenal PCCs. Higher *SDH* mutations frequencies can be found in cases affected by HNPGLs outside the area of the Low Countries (Belgium, The Netherlands and some adjacent lands). The general prevalence of mutations among sporadic, multiple and familial HNPGLs is 19, 71.4 and 96.3%, respectively, with a strong predominance of *SDHD* germline mutations among multiple (71.4%) and familial cases (68.4%), in accordance to the overall higher penetrance of mutations of this genes.

We also reported on the analysis of the clinical manifestations of 689 published carriers of deleterious mutations in *SDHB* (264), *SDHC* (30) and *SDHD* (395) which led to the recognition of a genotype-phenotype correlation [see 29, for review] confirmed by other recent studies [30, 31]. In summary, median age at diagnosis of the first tumour is similar in *SDHB* and *SDHD* mutations carriers (32 and 33 years of age, respectively) and lower than that in *SDHC* mutation carriers (38 years). Approximately 25% of affected *SDHB* carriers have been diagnosed in the first and second decades of life while only 15% of *SDHD* mutation carriers and no *SDHC* mutation carriers have been diagnosed in the first decade of life. Multiple primary tumours are frequently observed in *SDHD* mutation carriers (79%, 167/211 with available information, 66.9% (87/130) while patients with *SDHB* and *SDHC* mutations have single tumours in 67 and 73% of the cases, respectively [30]. The most frequent phenotype associated with *SDHB* germline mutations is the development of extra-

adrenal PGL (53%, 140/264, [30]), mainly abdominal (including pelvis and retro-peritoneum) but also thoracic, mediastinal and cervical. Twenty percent of cases present with adrenal PCC alone or associated with PGL (52/264) and another 20% of cases develop only HNPGL (52/264). On the contrary, *SDHD*-affected carriers presented with only HNPGL, single or multiple, in 78% of cases (305/395[YUN1]) while adrenal PCC and/or extra-adrenal PGL are the sole manifestations in 8% (31/395) and 1% (1/395) of cases. Overall 98% of SDHD affected patients develop a HNPGL during follow-up [30]. Among the 30 *SDHC* affected carriers in our review, 87% (26/30) presented with HNPGL alone (87.5% 14/16) [30] while PGL and PCC occurred more rarely. Finally, the prevalence of multiple tumours among *SDHD* mutation carriers is 30–74 vs. 12–28% in *SDHB* carriers. The risk for malignant tumours in *SDHB* carriers is 34–37.5% (37.5%, 36/96 [30]) versus 0–8% in *SDHD* carriers (3.1%, 4/130 [30]). The risk for malignancy for each type of tumor is based on reported cases; many studies are still analysing data on newer cases and these associated risks may change as more cases are reported. Data about the penetrance of SDH mutations (i.e. the risk of developing a tumor for an asymptomatic carrier) can be derived from three major studies [31–33] dealing with a total of 482 (42 + 82 + 358) SDHB and 128 (35 + 30 + 63) SDHD mutation carriers. *SDHB* mutation carriers have a life time cancer risk of 76 with 50% penetrance by age 35–45 years while *SDHD* carriers who inherited the mutation from their father seem to have a life time cancer risk of 85–100% with penetrance of 50% by age 30–40 years. Considering the tumour location, all studies recognized a higher risk for extra-adrenal paragangliomas in *SDHB* mutation carriers, and a higher risk for HNPGLs in *SDHD* mutation carriers. The lifetime risk of developing a renal tumor is higher in SDHB carriers (14 vs. 8% in SDHD) and mutations in all three genes can be associated with gastrointestinal stromal tumors too.

Management of Patients with PGL

Genetic testing of the different mutations associated with PGLs should be done based on the clinical presentation, medical history, family history, and previous testing of relatives. Guidelines for stepwise testing have been recently published and include a detailed family history, tumor size, location, prior history of surgeries, and clinical presentation [32–36]. However, the efficacy of these approaches in preventing disease has not been validated. The approach for managing and counseling PGL patients should include several one-on-one in-person sessions. These meetings can be divided in two categories:

- Pre-test, to make sure that the person understands the implications of a positive test, and that he or she has enough and balanced information to be able to formulate a truly informed consent.
- Post-test, if the person decides to proceed with testing: description of diagnosis, prognosis, assessment of understanding of current treatment and/or management, explanation of recurrence risk, testing of relatives, future options (including prenatal diagnosis for younger patients), and coping with the results.

These sessions are aimed at exploring the impact of the diagnosis on both affected and unaffected family members, assisting families and individuals as they adjust to the diagnosis, and to always be non-directive. These measures are important because of the

uncertainty associated with these mutations and the inability to predict with accuracy the appearance and location of tumors, as well as their tendency to recur. The critical components of this process include ascertainment of medical and family history, determination and communication of risk (including risk of malignancy, assessment of risk perception, education regarding the genetics of PGL syndromes, and discussion of prevention and screening options). The prevention and screening options include urine, blood and imaging tests as indicated by the clinical presentation and the type of tumors. In addition to informed decision-making regarding genetic testing, primary outcomes of genetic counseling for PGL syndromes should include decreased worry, increased sense of control, and improved accuracy of risk perception. If left untreated, PGLs can result in significant clinical morbidity and mortality; early treatment and the identification of at risk individuals are thus imperative. The counseling approach highlighted above is aimed at improving adherence to screening recommendations, and thus decreasing morbidity and mortality.

The clinical manifestations of PGLs are broad and the majority of symptoms can mimic minor ailments (e.g. headaches, palpitations). Therefore, once a mutation has been identified individuals should be monitored closely with a lower threshold for further evaluation of symptoms by a physician. Many studies are on the way that will characterize further the genotype-phenotype correlations, with the hope that more specific guidelines can be generated for this patient population. More recently, mutations in SDHA were reported in a limited number of patients with PGL and/or PCC [37]. Additionally, a new gene was identified that predisposes to non-syndromic PGLs and/or PCC [38, 39]. The impact of these new discoveries in genetic risk counseling is currently unknown.

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Table 1

SDH germline mutations in series of sporadic or unselected patients with adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma

Tumor type	Number of cases	SDHB	SDHC	SDHD	References (population)
Sporadic PHEO-PGL	24	2 (8.3%)	0	0	Astuti et al., 2001 (English)
Sporadic PHEO-PGL 14 adrenal, 4 extra-adrenal	18	n.d.	n.d.	2 (11.1%)	Gimm et al., 2000 (German)
Sporadic PHEO-PGL	271	12 (4.4%)	n.d.	11 (4%)	Neumann et al., 2002 (German, Polish)
Adrenal	241	6 (2.5%)		7 (2.9%)	
Extra-adrenal	30	6 (20%)		4 (13.3%)	
Multiple tumours	26	0 (0%)		4 (15.4%)	
Sporadic PHEO-PGL	304	16 (5.3%)	neg	13 (4.3%)	Neumann et al., 2004 (German, Polish)
Sporadic PHEO-PGL	371	21 (5.7%)	0	21 (5.7%)	Schiavi et al., 2005 (German, Polish and other countries)
Sporadic PHEO-PGL including multiple tumors	947	59 (6.2%)	neg	25 (2.6%)	Erlic et al., 2009 (European-American)
Sporadic PHEO-PGL	84	8 (9.5%)	n.d.	0	Gimenez-Roqueplo et al., 2003 (French)
Adrenal	69	3 (4.3%)			
Adrenal benign	57	1 (1.7%)			
Adrenal malignant	12	2 (16.7)			
Extra-adrenal	15	5 (33.3%)			
Sporadic PHEO-PGL	258	18 (7%)	0	3 (1.2%)	Amar et al., 2005 (French)
Sporadic PGL >35 years, benign	40	6 (15%)	0	0	Burnichon et al., 2009 (French)
Sporadic PHEO-PGL	213	1/47 (2%)	n.d.	2/126 (1.6%)	Korpershoek et al., 2006 (Dutch)
Sporadic PHEO-PGL	18	0	0	0	Persu et al., 2008 (Belgian)
PHEO collected anonymously	35	1 (2.8%)	n.d.	2 (5.7%)	Cascòn et al., 2004 (Spanish)
Sporadic PHEO-PGL single tumors	119	12 (10%)	0	3 (2.2%)	Cascòn et al., 2009 (Spanish)
Adrenal	95	2 (2.1%)	0	0	
Extra-adrenal	24	10 (41.6%)	0	1 (4.2%)	

Data on the prevalence of *SDH* germline mutations in sporadic non-syndromic PHEOs/PGLs have been derived from 13 studies in which the family history was clearly indicated. n.d. = Analysis not done.

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Table 2

SDH germline mutations in series of malignant adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma

Tumor type	Number of cases	SDHB	SDHC	SDHD	References (population)
Malignant PHEO-PGL	44	13–18 (30–41%)	n.d.	n.d.	Brouwers et al., 2006 (NIH – USA) 5 cases with genetic variants
Adrenal	13	2 (15.4%)			
Extra-adrenal	29	16 (55.2%)			
Uncertain	2	0 (0%)			
Malignant PHEO-PGL	9	1 (11%)	n.d.	0	Isobe et al., 2007 (Japanese)
Adrenal	5	0			
Extra-adrenal	4	1 (25%)			
Malignant PHEO-PGL	28	6–7 (21–25%)	n.d.	1–2 (3.6–7%)	Klein et al., 2008 (USA) 2 cases with genetic variants
Adrenal	12	0		2 (16.7%)	
Extra-adrenal	16	7 (43.8)		0	
Malignant PHEO-PGL	88	20 (22.7%)	n.d.	1 (1.1%)	Erlic et al., 2009 (European-American)
Malignant PHEO-PGL	54	23 (42.6%)	n.d.	0	Amar et al., 2007 (French)
Syndromic	5	2 (40%)			
Sporadic	49	21 (42.8%)			
Adrenal	29	7 (24.1%)			
Extra-adrenal	25	16 (64%)			
Malignant PGL-HNPGL	49	36 (73.5%)	0 (0%)	4 (8.2%)	Burnichon et al., 2009 (French)
Thoracic, abdominal, pelvis	24	20 (83.3%)	0 (0%)	1 (4.1%)	
HNPGL	11	6 (54.5%)	0 (0%)	0 (0%)	
Multiple tumors	14	10 (71.4%)	0 (0%)	3 (21.4%)	
Malignant HNPGL	33	13 (39.4%)	0 (0%)	9 (27.3%)	Neumann et al., 2009 (55% German, 45% other countries)
Total malignant PHEO/PGLs	305	112/305 (36.7%)		15/261 (5.7%)	combined data

Data on the prevalence of *SDH* germline mutations among malignant PHEOs/PGLs have been derived from 7 studies giving a general frequency of 42.4% with a marked predominance of *SDHB* mutations. In two studies, together with deleterious mutations, n.d. = Analysis not done.