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A Novel *SDHB* Mutation Associated with Hereditary Head and Neck Paraganglioma

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Abstract

Objective—To describe a novel germline mutation in the succinate dehydrogenase subunit B (*SDHB*) gene.

Methods—The medical records of a patient with bilateral carotid body paragangliomas were reviewed.

Results—A 35-year-old woman with a family history of neck masses presented with bilateral carotid body paragangliomas. DNA sequencing revealed a previously unreported conservative substitution (Leu111Val) mutation in the *SDHB* gene.

Conclusions—The Leu111Val germline mutation of *SDHB* is likely associated with a phenotype of head and neck paragangliomas, and carriers would benefit from periodic screening for sympathetic paragangliomas.

Keywords

succinate dehydrogenase; paraganglioma; *SDHB*; PGL4

INTRODUCTION

Paraganglia are collections of neuroectoderm-derived, catecholamine-secreting cells that are part of the autonomic nervous system. In adulthood, they are highly vascular and serve mostly as chemoreceptors that detect and respond to stresses such as hypoxia and hypercarbia.¹ Tumors of this system are classified as paragangliomas (PG), with those occurring in the adrenal glands termed pheochromocytomas. While pheochromocytomas are typically catecholamine-secreting; PG found in the head and neck, most often around the carotid body, in the jugulotympanic region, or around the vagal nerve, are typically non-secreting.

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Hereditary syndromes associated with PG and pheochromocytomas are well known and include multiple endocrine neoplasia type 2, von Hippel-Lindau disease, and neurofibromatosis type 1 (Table I). Additionally, germline mutations in the succinate dehydrogenase (SDH) enzyme complex have been identified in individuals with PG and pheochromocytomas. SDH is an enzyme complex that is bound to the inner mitochondrial membrane and functions as part of both the Krebs' cycle and the oxidative phosphorylation chain. Mutations of genes that produce subunits of this complex cause the inherited PG syndromes (PGL): a mutation of *SDHD* confers susceptibility to PGL1, *SDHB* to PGL4, *SDHC* to PGL3, and *SDHAF2* (also known as *SDH5*) to PGL2. Other genes such as *TMEM127* and *KIF1B* have also been implicated in PG and pheochromocytoma susceptibility in a few families.²

Due to the surge in knowledge of the genetics of PG syndromes, genetic testing is now an area of intense interest. Patients with risk factors for a hereditary cause of their tumors, such as those with a family history of PG, onset of disease at an early age or those with multiple primary tumors, may be screened for mutations as may their families. It is crucial to expand upon currently known mutations in the literature so that we can better understand and interpret the significance of a given mutation. To advance the body of known mutations, we report a novel mutation of the *SDHB* gene in a patient with bilateral carotid body paragangliomas.

CASE

A 35-year-old female presented with a painless left-sided neck mass and was found on computerized tomography (CT) imaging to have a 3.1 cm homogeneously and brightly enhancing left carotid body tumor that splayed the internal and external carotid arteries (Figure 1A, 1B). Assessment of her family history revealed that her paternal grandmother had undergone multiple surgical resections of neck masses in her fourth decade of life (records were not available for review). Whole-body CT imaging excluded the presence of a thoracic, abdominal or pelvic paraganglioma, and both serum and 24-hour urine fractionated metanephrines were negative for hypersecretion. She underwent preoperative embolization, where note was made of a contralateral 1.0 mm carotid body tumor that was not detectable by axial imaging techniques. The following day, she underwent definitive surgical resection of the tumor, which appeared to be encasing the carotid bifurcation and was on the deep surface of the artery (Figure 1C). After careful dissection, the tumor was removed and pathologic evaluation revealed it to be a paraganglioma (Figure 1D). Biopsy of two regional lymph nodes did not reveal metastases. She tolerated the procedure well and did not suffer any vascular or neurologic injury.

Due to the early onset, bilateral nature of her disease and family history of head and neck tumors, genetic counseling and screening for mutations in the *SDHB*, *SDHD*, *SDHC*, *SDHAF2*, and *TMEM127* genes was done. DNA was extracted from peripheral white blood cells and genomic analysis was done using high resolution melting Light Scanner technology (Idaho Technology Inc., Salt Lake City, UT) and multiplex ligation-dependent probe amplification (MLPA), followed by sequencing. This analysis revealed that the patient had a previously-undescribed mutation in the *SDHB* gene, defined by a cytosine to guanine mutation at nucleotide 331 (Figure 2). This mutation resulted in the conservative substitution of valine in place of leucine at amino acid position 111 in the peptide chain (Leu111Val). After confirmation of an *SDHB* mutation and PGL4, the patient was advised by the genetics counseling team. The patient's father was advised to undergo genetic screening for the Leu111Val variant and full body imaging. His medical data is not available for review, but he has reportedly since developed multiple paravertebral lesions. The patient's young children were advised to undergo a yearly screening regimen consisting of neck ultrasound

and free plasma metanephrins, catecholamines, and chromogranin-A. These tests were negative, and they will continue to be followed.

DISCUSSION

In this report, we describe a novel germline mutation in the *SDHB* gene, mutations of which are known to cause the heritable PG syndrome PGL4. In this syndrome, patients are at significantly increased risk of developing head and neck and sympathetic PG and, occasionally, pheochromocytomas.

The *SDHB* gene is located on chromosome 1p36-1p35 and contains eight exons and a total open reading frame of 756 nucleotides. The gene codes for the iron sulfur protein in the succinate-ubiquinone oxidoreductase of the succinate dehydrogenase enzyme complex.² Mutations in this gene are autosomal dominant, and estimates of their penetrance vary widely (8–55% at age 40 and 30–100% at age 80).³ In a combined pheochromocytoma and paraganglioma registry in Europe, 5% of registrants had one of 15 different germline mutations in *SDHB*, most of them missense mutations.⁴ A mutation in *SDHB* tends to cause fewer head and neck PG than *SDHD* mutations, though malignant tumors and additional extraparaganglial malignancies such as renal cell carcinoma and possibly thyroid papillary carcinoma are more common in those with *SDHB* mutations.⁴ Furthermore, gastrointestinal stromal tumors may occur in association with PG due to *SDHB*, *SDHD*, or *SDHC* mutations (also known as the Carney-Stratakis dyad). Thus, a patient with a known *SDHB* mutation deserves full body screening for other tumors or malignancies.

Mutations in the *SDH* gene family are hypothesized to cause PG syndromes via two putative mechanisms: the first is by disrupting normal apoptotic pathways in paraganglionic cells – SDH activity is required for the proapoptotic activity of the prolyl hydroxylase EglN3, which is feedback inhibited by succinate.² With a poorly-functioning SDH enzyme complex, the accumulation of succinate inhibits EglN3, leading to cellular escape from apoptosis. The second mechanism is the dysregulation of hypoxia-induced factors (HIF), which produces a cellular response similar to that of hypoxia, stimulating paraganglial hypertrophy and hyperfunction. Mutations of SDH result in the inhibition of HIF-1 prolyl hydroxylase, which leads to stabilization of HIF-1 cofactor that can enter the nucleus and stimulate gene transcription⁵.

The mutation described in this report is a cytosine-to-guanine mutation at nucleotide 331 that changes the amino acid from leucine to valine at amino acid position 111 in exon 4 (Leu111Val). This mutation has not been described previously in the literature or the *SDHB* mutation database.⁶ At the time of this drafting, the database contains 24 other mutations in *SDHB* that contributed to carotid body PG, though most of those patients had other PG or pheochromocytomas as well. Because this patient presented with bilateral PG of the carotid body, we presume she has an underlying genetic susceptibility to PG, and we speculate that the Leu111Val mutation of *SDHB* is pathogenic. However, it is possible that Leu111Val could be a rare but benign polymorphism not associated with PG risk, and the real disease-causing mutation is not able to be identified with current techniques. Further molecular analysis will be necessary to determine the oncogenic impact of this mutation.

Due to the rarity of PG and their hereditary syndromes, optimal therapy is challenging to determine, particularly among those with multiple or bilateral tumors.⁷ Earlier identification of disease could improve outcomes. Therefore, genetic screening is crucial in patients at risk of PG syndromes to identify those who merit enrollment in an appropriate imaging-based screening program. We suggest that patients with features suggesting a heritable PG syndrome undergo screening for mutations in *SDHD*, *SDHB*, and *SDHC*. The most recently

described genes responsible for PG syndrome, *SDHAF2*, *TMEM127*, and *KIF1B* should also be considered if the more common mutations are absent and as genetic testing becomes available. However, counseling patients will be challenging due to the paucity of data regarding mutation detection rates, the possibility of variants of uncertain significance and unknown disease penetrance associated with these genes. It has been argued that patients with seemingly sporadic disease may also benefit from genetic testing, though clinical judgment based on presentation and family history is likely a superior method from a cost-benefit point of view.⁸ In general, patients with an apparently sporadic single tumor who have a young-onset (age of diagnosis less than 40 years) or malignant disease are good candidates for genetic testing. Due to the substantial differences in allele frequencies seen in the literature, it is important to be aware of the local genetic variability in order to best decide on screening parameters in the clinician's place of practice. Further research with population-linked data on allelic frequencies will elucidate the appropriate specific genetic screening that should be performed on patients with suspected familial PG syndromes.

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REFERENCES

1. Kupferman ME, Hanna EY. Paragangliomas of the head and neck. *Curr Oncol Rep*. 2008; 10:156–161. [PubMed: 18377829]
2. Opocher G, Schiavi F. Genetics of pheochromocytomas and paragangliomas. *Best Pract Res Clin Endocrinol Metab*. 2010; 24:943–956. [PubMed: 21115163]
3. Schiavi F, Milne RL, Anda E, et al. Are we overestimating the penetrance of mutations in *SDHB*? *Hum Mutat*. 2010; 31:761–762. [PubMed: 20513144]
4. Neumann HPH, Pawlu C, Peczkowska M, et al. Distinct clinical features of paraganglioma syndromes associated with *SDHB* and *SDHD* gene mutations. *JAMA*. 2004; 292:943–951. [PubMed: 15328326]
5. Cerecer-Gil NY, Figueroa LE, Llamas FJ, et al. Mutation of *SDHB* is a cause of hypoxia-related high-altitude paraganglioma. *Clin Cancer Res*. 2010; 16:4148–4154. [PubMed: 20592014]
6. Bayley J-P, Devilee P, Taschner PEM. The *SDH* mutation database: an online resource for succinate dehydrogenase sequence variants involved in pheochromocytoma, paraganglioma and mitochondrial complex II deficiency. *BMC Med Genet*. 2005; 6:39. [PubMed: 16288654]
7. Moskovic DJ, Smolarz JR, Stanley D, et al. Malignant head and neck paragangliomas: is there an optimal treatment strategy? *Head Neck Oncol*. 2010; 2:23. [PubMed: 20863367]
8. Jiménez C, Cote G, Arnold A, Gagel RF. Review: should patients with apparently sporadic pheochromocytomas or paragangliomas be screened for hereditary syndromes? *J Clin Endocrinol Metab*. 2006; 91:2851–2858. [PubMed: 16735498]

Figure 1.

(A) “Lyre sign” of carotid body tumor on pre-operative angiogram. (B) Three-dimensional reconstruction of left carotid body tumor from pre-operative angiogram. (C) Intraoperative photograph of left carotid body tumor. (D) Photograph of excised left carotid body tumor.

Figure 2.
Sequence of patient's *SDHB* gene, showing a cytosine (C) to guanine (G) mutation at the position marked by the red 'S' (substitution).

Table I

Syndromes associated with paragangliomas and pheochromocytomas

Syndrome	Causative gene	Gene product	Function of protein	Characteristic tumor associations
MEN 2	<i>RET</i>	RET	Tyrosine kinase receptor	Pheochromocytoma, medullary thyroid carcinoma
VHL	<i>VHL</i>	VHL	Ubiquitin ligase activity	Hemangioblastoma, renal cell carcinoma, pheochromocytoma
NF1	<i>NF1</i>	Neurofibromin	GTP hydrolysis and inactivation of Ras signal transduction pathway	Neurofibroma, optic glioma, pheochromocytoma
PGL1	<i>SDHD</i>	Succinate dehydrogenase complex subunit D	Transmembrane subunit of Complex II of mitochondrial respiratory chain	Parasympathetic paraganglioma, sympathetic paraganglioma, pheochromocytoma, GIST
PGL2	<i>SDHAF2</i>	Succinate dehydrogenase assembly factor 2	Assembly factor for Complex II of mitochondrial respiratory chain	Parasympathetic paraganglioma
PGL3	<i>SDHC</i>	Succinate dehydrogenase complex subunit C	Transmembrane subunit of Complex II of mitochondrial respiratory chain	Parasympathetic paraganglioma, GIST
PGL4	<i>SDHB</i>	Succinate dehydrogenase complex subunit B	Iron-sulfur catalytic component of Complex II of mitochondrial respiratory chain	Sympathetic paraganglioma, parasympathetic paraganglioma, pheochromocytoma, GIST, renal tumors

MEN2 = multiple endocrine neoplasia type 2; VHL = von Hippel-Lindau disease; NF1 = neurofibromatosis type 1; PGL = familial paraganglioma syndrome