CASE REPORT

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DIAGNOSIS AND MANAGEMENT OF HEREDITARY PARAGANGLIOMA SYNDROME DUE TO THE F933>X67 SDHD MUTATION

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Abstract: *Background*. The hereditary paraganglioma syndromes (PGLs) are autosomal dominant conditions with an increased risk for tumors of the sympathetic and parasympathetic neuroendocrine systems. The recognition of patients with hereditary PGL and identification of the responsible gene are important for the management of index patients and family members.

Methods. We present the clinical, radiological, biochemical, and family history findings of a 15-year-old boy patient with a glomus vagale versus glomus jugulare tumor.

Results. Evaluation of the family history and the patient's history led to the identification of a familial succinate dehydrogenase subunit D (SDHD) gene mutation (F933>X67), consistent with a diagnosis of hereditary PGL1. Although this family had all head and neck tumors, this SDHD mutation has previously been described in a family with primarily functional pheochromocytomas.

Conclusions. This case report highlights the variable expressivity of a single mutation in SDHD, (F933>X67). Careful and comprehensive screening is warranted for individuals at risk. ©2008 Wiley Periodicals, Inc. *Head Neck* **31:** 689–694, 2009

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The hereditary paraganglioma syndromes (PGLs) are autosomal dominant conditions associated with an increased risk for the development of tumors of the sympathetic and parasympathetic neuroendocrine systems. The sympathetic paraganglioma can produce excess catecholamines and most frequently involve the adrenal medulla (adrenal pheochromocytomas), but can also occur elsewhere in the abdomen or thorax (extraadrenal pheochromocytomas). The parasympathetic paraganglioma are typically hormonally silent and occur in the head and neck (also called glomus tumors). The most frequent type of head and neck paraganglioma is the carotid body tumor, followed by the glomus jugulare and glomus tympanicum tumors.[1,2]

The majority of all paraganglioma occur sporadically; however, at least 25% appear to occur because of an inherited risk.[3–5] Hormonally active

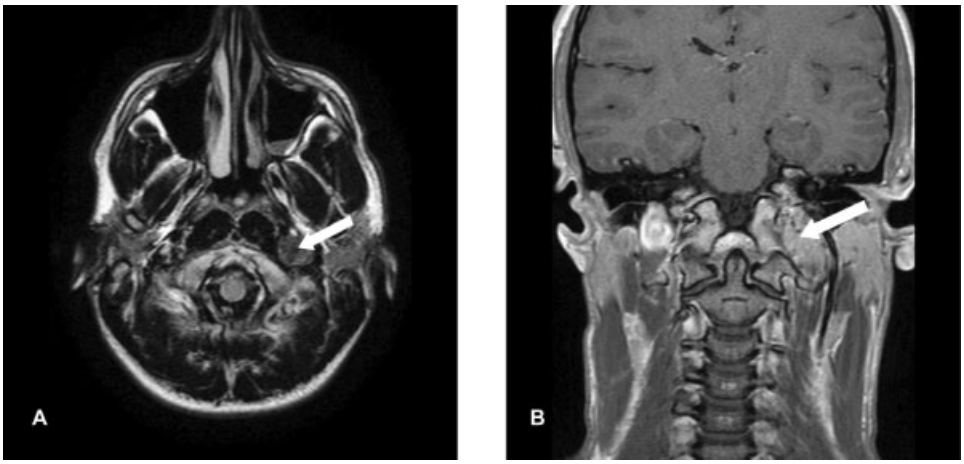

FIGURE 1. MR image, axial (**A**) and coronal (**B**) views, shows mass in the left carotid sheath extending up to the skull base, compatible with a paraganglioma, likely a glomus vagale tumor.

intraabdominal (adrenal or extraadrenal) and thoracic pheochromocytomas are recognized components of a number of autosomal dominant syndromes, including von Hippel-Lindau syndrome, multiple endocrine neoplasia type 2, and neurofibromatosis type 1.[6–8] Head and neck paraganglioma is not typically associated with the aforementioned conditions, but it is a salient feature of the hereditary PGLs, including PGL1, PGL2, PGL3, and PGL4 which occur due to inherited mutations in 1 of several genes that encode subunits of the succinate dehydrogenase complex. Specifically, mutations of the succinate dehydrogenase subunit D (SDHD) gene, succinate dehydrogenase subunit B (SDHB) gene, and succinate dehydrogenase subunit C (SDHC) gene are responsible for PGL1, PGL4, and PGL3, respectively.[9–11] The PGL2 gene at 11q13 has yet to be identified.[12]

The phenotype and inheritance of the hereditary PGLs are variable, in part dependent upon the gene involved. A population-based study examining SDHD and SDHB in unrelated patients with abdominal or thoracic pheochromocytomas or head and neck paraganglioma without syndromic features revealed that head and neck paraganglioma are more prevalent among carriers of SDHD mutations (79%) compared with SDHB mutation carriers (31%). In contrast, intraabdominal extraadrenal tumors were more prevalent in SDHB mutation carriers (50%) than in SDHD mutation carriers (21%), and malignant tumors were only observed in SDHB mutation carriers (34%). SDHD mutation carriers were more likely to present with multiple tumors than were SHDB mutation carriers.[13] Based on a limited number of families reported in the literature, germline mutations of the SDHC gene appear to be predominantly associated with head and neck paraganglioma that are typically benign and seldom multifocal.[14] However, a recent report described a norepinephrine-secreting abdominal paraganglioma in a 15-year-old with a novel nonsense SDHC mutation, suggesting the possibility of a wider clinical spectrum than originally suspected for SHDC mutation carriers.[15]

The hereditary PGLs are inherited in an autosomal dominant pattern. However, the inheritance of the condition due to SDHD gene mutations is complicated by a parent of origin effect. Specifically, studies of multiple families reveal that, with rare exceptions, only individuals who inherit an SDHD mutation from a male are at risk to develop paraganglioma.[16–18] However, all individuals who inherit the mutation have a 50% chance of passing the mutation on to their children. The molecular mechanism of the maternal imprinting in PGL1 is unclear. Unlike other genes that exhibit imprinting, SDHD exhibits biallelic expression in several tissues.[9] It has been suggested that a paternally imprinted gene at 11p15 acts in synergy with SDHD mutations during tumorigenesis.[19]

We report a case of hereditary PGL due to a mutation of the SDHD gene. The phenotype of this family is distinct from a previously described, presumably unrelated, family with the same mutation. The recognition of patients with hereditary PGL and identification of the responsible gene are important for the management of index patients and for the provision of appropriate genetic counseling and care of at-risk family mem-

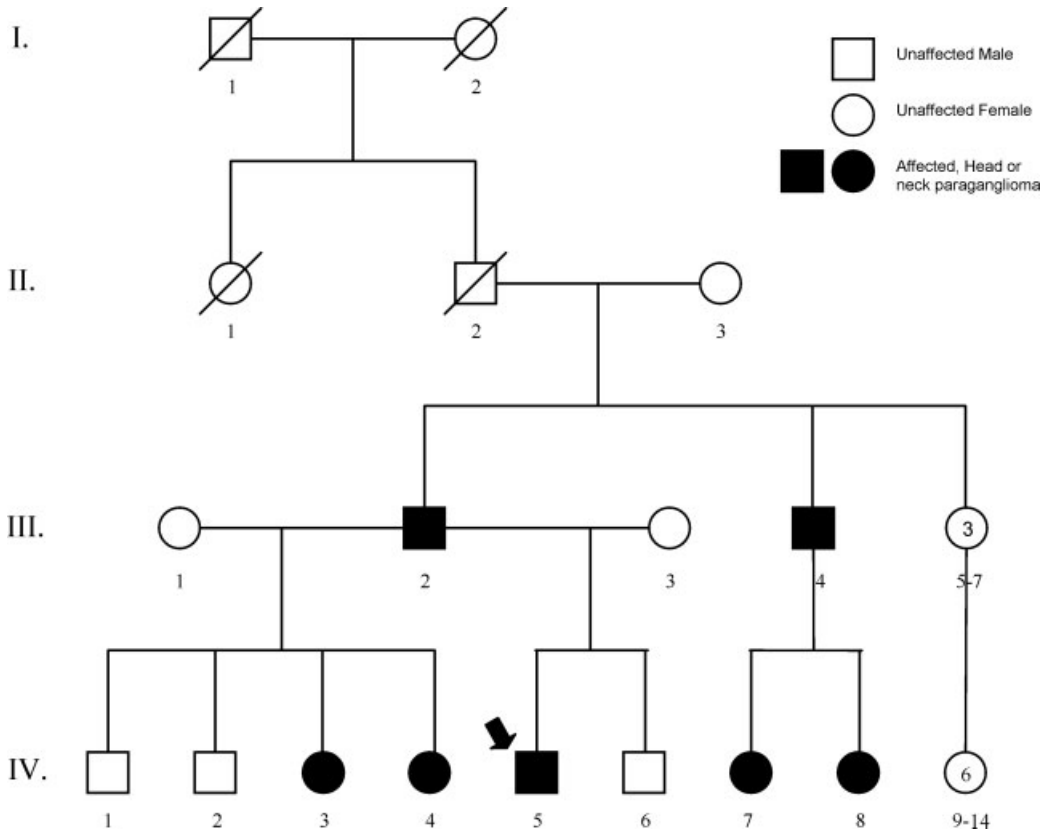

FIGURE 2. Family pedigree. Index patient is denoted with an arrow.

bers. Written assent/consent was obtained from the patient and family participants on an IRB-approved protocol at the University of Michigan.

CASE REPORT

A 15-year-old boy patient was seen with clinical depression, attention deficit disorder, and a family history of head and neck paraganglioma. His review of systems was noted for severe depression requiring recent hospitalization, attention deficit disorder, occasional postural presyncope, occasional left-sided nonpulsatile tinnitus, and occasional right-sided nonpulsatile tinnitus. Vertigo, dysphagia, odynophagia, dysphonia, and otalgia were not evident. Indirect mirror examination of the hypopharynx and larynx revealed bilaterally mobile true vocal cords. The patient reported a waxing and waning 2-year history of thick phlegm in his throat as well as nonseasonal rhinorrhea. An MRI at an outside institution revealed a heterogeneous enhancing 1.7 cm $\times$ 2 cm mass in the left jugular fossa interpreted as consistent with a glomus vagale versus glomus jugulare tumor. Repeat imaging at our institution in the form of MRI and CT showed the lesion to be a 2.2 cm $\times$ 1.6 cm tumor high in the left neck near the skull base, most likely a glomus vagale tumor. Additional studies performed at that time included normal plasma metanephrines and normetanephrines. Repeat imaging studies performed 1 year later revealed the mass to be stable in size, appearance, and contrast enhancement (Figures 1A and 1B). Surgical resection of the tumor was discussed with the family but was not pursued because of the patient's continued psychiatric instability and lack of change or symptoms in the lesion.

Family History. The patient's family history was noted for multiple head and neck paraganglioma (Figure 2 and Table 1). At age 54, the index patient's father (III, 2) had a large left vagal paraganglioma extending to the skull base and a left carotid body tumor surgically resected. He also had a small right jugulare versus high vagale paraganglioma that was not resected and had been stable for 5 years. His plasma metanephrines and normetanephrines were normal. The index patient's brother (IV, 6) was asymptomatic and had an unremarkable screening MRI of the head

Table 1. Genetic and clinical information from index patient and affected relatives.

ID Number	SDHD F933>X67	Tumors/Screening	Age first tumor identified
I, 1	Not tested	''Brain tumor''	Unknown
III, 2	Not tested, obligate carrier	Multiple head and neck paragangliomas	54 y
IV, 1	Not tested	Normal head and neck MRI	N/A
IV, 3	Not tested	Carotid body tumor	Unknown
IV, 4	Positive	Carotid body tumor, glomus vagale	31
IV, 5	Positive	Glomus vagale versus jugulare tumor	15 y
IV, 6	Positive	Normal head and neck MRI	N/A
IV, 7	Not tested	Carotid body tumor	Unknown
IV, 8	Not tested	Carotid body tumor	Unknown

and neck at age 14. The index patient's 2 paternal half sisters (IV, 3 and 4) were both reported to have carotid body tumors. One of these paternal half sisters (IV, 4) had a 2.0 cm $\times$ 3.0 cm left carotid body tumor excised at age 31 and a left 3.5 cm vagale paraganglioma resected at age 36. Her plasma metanephrine and normetanephrine studies were normal. The index patient's 2 paternal half brothers (IV, 1 and 2) were asymptomatic, although only 1 had imaging studies performed. The index patient's paternal uncle (III, 4) had a history of bilateral carotid body tumors and his 2 daughters (IV, 7 and 8) each had carotid body tumors. The index patient's paternal grandmother (II, 2) died at age 65 with a history of diabetes mellitus and no known history of paragangliomas. The index patient's father's paternal grandmother (I, 2) was deceased with a reported history of a brain tumor. Confirmation of the brain tumor diagnosis was unavailable.

Genetic Testing. After genetic counseling and obtaining the index patient's assent and his mother's consent for genetic testing, genetic testing was performed on a blood sample from the index patient at the Children's Hospital of Philadelphia. Sequencing of all coding regions and adjacent noncoding areas of the SDHD gene was performed and revealed a heterozygous deletion of 2 bases (del TC) at nucleotides 94 to 95 in exon 2. This mutation results in the shift of the translational frame of the encoded mRNA at amino acid position 33 to a premature stop codon at position 67 (F933>X67). This mutation has been reported previously in patients with familial pheochromocytoma.[20] With their informed consent, sequence analysis of exon 2 of the SDHD gene was performed in the index patient's full brother and 1 of his half sisters. Both were found to carry the mutation previously described in the index patient.

DISCUSSION

Hereditary PGL1 results from germline mutations of the SDHD gene. Review of the index patient's medical history and family history made SDHD the gene most likely responsible for the tumors in this family. Specifically, there were multiple individuals with head and neck paragangliomas, with most affected individuals seen with multiple tumors. Furthermore, the pedigree was consistent with a parent of origin effect such that all affected individuals appeared to have inherited the putative mutation from a father. Genetic testing for SDHD was offered to confirm our strong clinical suspicion of PGL1 and also to allow for the eventual identification of other gene mutation carriers in the family who could benefit from screening for paragangliomas.

The SDHD mutation identified in the index patient (F933>X67) is predicted to produce a truncated protein of 66 amino acids, which lacks the transmembrane, signal, and haem-binding domains.[20] As expected, the patient's paternal half sister who had multiple head and neck paraganglioma was also found to carry this mutation. The identification of the causative gene mutation in the family allowed for genetic counseling and genetic testing of at-risk relatives including the index patient's full brother who was found to carry the mutation.

Although the phenotype in our family was consistent with what has been described in the literature for SDHD gene mutations in general, it is quite discordant from a case report of another family with the same F933>X67 mutation of the SDHD gene. The previously reported family with this mutation was characterized primarily by

Table 2. Proposed guidelines for screening asymptomatic carriers of SDHD mutation carriers and at-risk relatives.

Examination	Age to begin	Frequency
Careful history, physical exam and blood pressure measurement	5 y	Annual
Plasma metanephrine and normetanephrine measurement	10 y	Annual
Abdominal MRI	10 y	Biennial
Head and neck MRI	10 y	Biennial

early-onset pheochromocytomas, rather than head and neck paraganglioma.[20] This family contained 5 affected individuals, including 1 with a unilateral adrenal pheochromocytoma at age 19, 1 with a paraaortic pheochromocytoma at age 18, 1 with bilateral adrenal pheochromocytomas at age 23, 1 with a unilateral pheochromocytoma at age 13, and 1 with 2 carotid body tumors in her 60s.

Given the variability in phenotype associated with this mutation, it is likely that other factors, possibly genetic or environmental, contribute to the penetrance and variable expressivity of this condition. In fact, a recent study described an Italian founder mutation (Q109X) in 6 families with wide variability in the age of onset; clinical presentation; and number, site, and secreting properties of the tumors.[21] In addition, recent reports have shown that SDHD mutations can be associated with malignant paragangliomas,[22,23] albeit less frequently than SDHB mutations.

The variability in age of onset, site, hormonal activity, malignant potential, and number of primary tumors that can occur in SDHD mutation carriers poses challenges for screening and management. One proposed "minimal" monitoring program includes yearly history, physical examination, blood pressure measurement, and biochemical screening and biennial (every other year) imaging by CT or MRI beginning at age 10.[24] Our preference is for MRI screening to reduce excessive radiation exposure. Furthermore, we recommend yearly physical examination, history, and blood pressure measurement beginning in early childhood (Table 2).

CONCLUSIONS

This case report highlights the variable expressivity of a single mutation in SDHD (F933>X67) in families with hereditary paraganglioma (PGL1). Clues to the diagnosis in the family included multiple affected individuals, early onset, multiple primary tumors, and a recognizable pattern of inheritance demonstrating a parent of origin effect. Careful and comprehensive screening is warranted for individuals at risk, which can accurately be predicted using genetic testing and counseling based on the parent of origin. Just as importantly, complicated and expensive screening can be avoided in those who are not at risk. However, as is evident within this family, uptake of genetic counseling and genetic testing is not uniform.

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