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Case Report

Case Report

SDHB-Associated Paraganglioma Syndrome in Africa—A Need for Greater Genetic Testing

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Abbreviations: CT, computed tomography; MEN, multiple endocrine neoplasia; NF1, neurofibromatosis type 1; PCC, pheochromocytoma; PGL, paraganglioma; PPGL, pheochromocytoma/paraganglioma; SDH, succinate dehydrogenase; SDHB, succinate dehydrogenase subunit B; VHL, von Hippel-Lindau.

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Abstract

A germline mutation is identified in almost 40% of pheochromocytoma/paraganglioma (PPGL) syndromes. Genetic testing and counseling are essential for the management of index cases as well as presymptomatic identification and preemptive management of affected family members. Mutations in the genes encoding the mitochondrial enzyme succinate dehydrogenase (SDH) are well described in patients with hereditary PPGL. Among patients of African ancestry, the prevalence, phenotype, germline mutation spectrum, and penetrance of *SDH* mutations is poorly characterized. We describe a multifocal paraganglioma in a young African male with an underlying missense succinate dehydrogenase subunit B (*SDHB*) mutation and a history of 3 first-degree relatives who died at young ages from suspected cardiovascular causes. The same *SDHB* mutation, Class V variant c.724C>A p.(Arg242Ser), was detected in one of his asymptomatic siblings. As there are limited data describing hereditary PPGL syndromes in Africa, this report of an *SDHB*-associated PPGL is a notable contribution to the literature in this growing field. Due to the noteworthy clinical implications of PPGL mutations, this work highlights the existing need for broader genetic screening among African patients with PPGL despite the limited healthcare resources available in this region.

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Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare neuroendocrine tumors, collectively termed pheochromocytoma/paraganglioma (PPGL). PCCs are derived from the adrenal medulla while PGLs originate from extra-adrenal paraganglia [1, 2]. Clinical presentation is based on their site of origin, as PCCs and sympathetic PGLs present with adrenergic symptoms, compared with parasympathetic PGLs, which are typically silent and present due to mass effects [2, 3].

In contrast to the classic maxim stating that 10% of PPGL are bilateral, extra-adrenal, malignant, and familial, it is now estimated that a third to half of all PPGL are heritable [4, 5]. The susceptibility to develop a PPGL is an established component of several genetic syndromes, including neurofibromatosis type 1 (NF1), von-Hippel-Lindau (VHL) syndrome, and multiple endocrine neoplasia (MEN) types 2A and 2B. Most cases of hereditary paraganglioma are accounted for by mutations in the *NF1*, *VHL*, *RET*, and succinate dehydrogenase (*SDH*) genes encoding components of the SDH enzyme [4]. In addition, new mutations in genes such as Kinesin family member 1B (*KIF1Bβ*), Egl nine homolog 1 (*EGLN1*), prolyl hydroxylase domain-containing protein 2 (*PHD2*), transmembrane protein 127 (*TMEM127*) and Myc-associated factor-X (*MAX*) may also result in PPGL [2].

The global incidence of PPGL is estimated as 2 to 8 persons per million with a population prevalence of 0.05% to 0.1% [6]. Recently, incidental diagnosis due to the more widespread use of cross-sectional imaging and family screening for germline mutations has contributed to a greater incidence of PPGLs [1, 6, 7]. Unfortunately, incidence and prevalence data on PPGL from sub-Saharan Africa are lacking, with just 3 South African case series of 60, 54, and 35 patients, respectively, reported in the literature. Genetic mutational analysis was seldom performed in these studies and the diagnosis of a genetic syndrome was based on clinical criteria alone in almost all cases [8-10]. Genetic mutational analysis was performed in just 2 South African case studies of patients with PPGL. The first was in a patient with MEN type 2A and the second in 2 cases of VHL syndrome [11].

An additional recent retrospective laboratory-based study from Cape Town re-examined 52 archived histopathological PPGL specimens utilizing a commercially available succinate dehydrogenase subunit B (SDHB) immunohistochemical stain. Loss of SDHB staining was present in 19 specimens (36%), suggesting the presence of *SDHB*-associated PPGL in these cases [12]. The prevalence noted in this study is similar to that reported globally and serves to illustrate that many cases of heritable PPGL likely remain undetected in sub-Saharan Africa [13, 14]. The paucity of reports from sub-Saharan Africa may be attributed to the limited health care resources and the lack of availability of genetic testing in the region [7-9, 11]. The lack of PPGL data from patients of African ancestry also extends to *SDH*-associated PPGLs and to date there is just a single reported case of an *SDHB*-associated PPGL, confirmed by genetic mutational analysis, in a patient from Southern Africa [15]. Here we report a family from Africa with confirmed *SDHB*-associated PPGL, further illustrating that *SDH*-associated PPGL is prevalent within the region and that greater genetic testing is necessary to identify such cases.

Case Description

A 34-year-old man presented to the endocrinology clinic with a 2-year history of sustained hypertension associated with the classic triad of hyperhidrosis, headaches, and palpitations. In view of the classic presenting symptoms and hypertension at a young age, a PPGL was suspected, and the 24-hour urine specimen confirmed the diagnosis with elevated measured fractionated normetanephrines (Table 1).

A computed tomography (CT) scan of the abdomen showed an intra-abdominal paraganglioma (Fig. 1) and neck CT showed a carotid body mass. Both lesions were radio-avid on a [^{68}Gallium]-DOTATATE-positron emission tomography (PET)-CT (Fig. 2). There were no features to suggest metastatic disease.

Family history was notable with early-unexpected cardiovascular deaths of his father, age 42 years, and 2 younger brothers at the ages of 13 years and 14 years, respectively. Based on the early age of his clinical presentation, a strong family history of unexplained early deaths, predominant norepinephrine secretion, and multifocal tumors on imaging, genetic testing was requested.

A comprehensive genomic analysis was performed by whole genome sequencing at an international accredited commercial laboratory. A Class V pathological *SDHB* missense variant, c.724C>A p.(Arg242Ser), was identified, confirming a familial paraganglioma 4 (PGL4) syndrome.

A 2-staged surgery was planned. The first stage, laparoscopic surgery for the removal of the intra-abdominal PGL was successful (Fig. 3A). However, following the second

Table 1. Laboratory results

	Test	Result	Reference range
Urine (HPLC)	24-hour urine normetanephrines	35 807	480-2424 nmol/24 hours
	Normetanephrine: creatinine	3270	28-158 nmol/mmol creatinine
	24-hour urine metanephrines	689	264-1729 nmol/24 hours
	Metanephrine:creatinine	63	15-89 nmol/mmol creatinine
Bloods	Chromogranin A	2765	0.0-8.4 ng/mL
	Blood urea nitrogen	4.2	2.1-7.1 mmol/L
	Creatinine	99	64-104 umol/L
	Calcium	2.4	2.15-2.50 mmol/L
	Magnesium	0.83	0.63-1.05 mmol/L
	Phosphate	0.93	0.78-1.42 mmol/L
	White cell count	5.69	3.92-10.4 × 10^9/L
	Hemoglobin	15.1	13.4-17.5 g/dL
	Hematocrit	0.463	0.39-0.51 L/L
	Mean cell volume	91.6	83.1-101.6 fL
	Platelet count	287	171-388 × 10^9/L

Abbreviation: HPLC, high-performance liquid chromatography

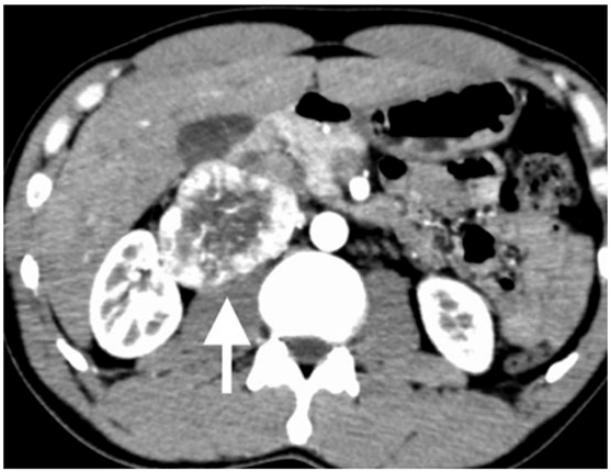

Figure 1. Computed tomography scan of the abdomen. A, cross-sectional view of the paraganglioma measuring 5.9 × 3.6 × 6.6 cm located anterior to the right kidney and separate from the right adrenal gland (arrow).

surgery, for removal of the left carotid body tumor, (Fig. 3B), the patient died due to postoperative complications from an associated carotid artery injury.

Histopathological examination of both tissue specimens revealed features in keeping with a PPGL. The tumors showed nests of cells with neuroendocrine morphology, surrounding sustentacular cells and delicate branching vasculature. The tumors had a typical Zellballen appearance (nests of cells) (Fig. 4A). The intra-abdominal tumor showed areas suspicious for capsular breach. Immunohistochemistry showed positive

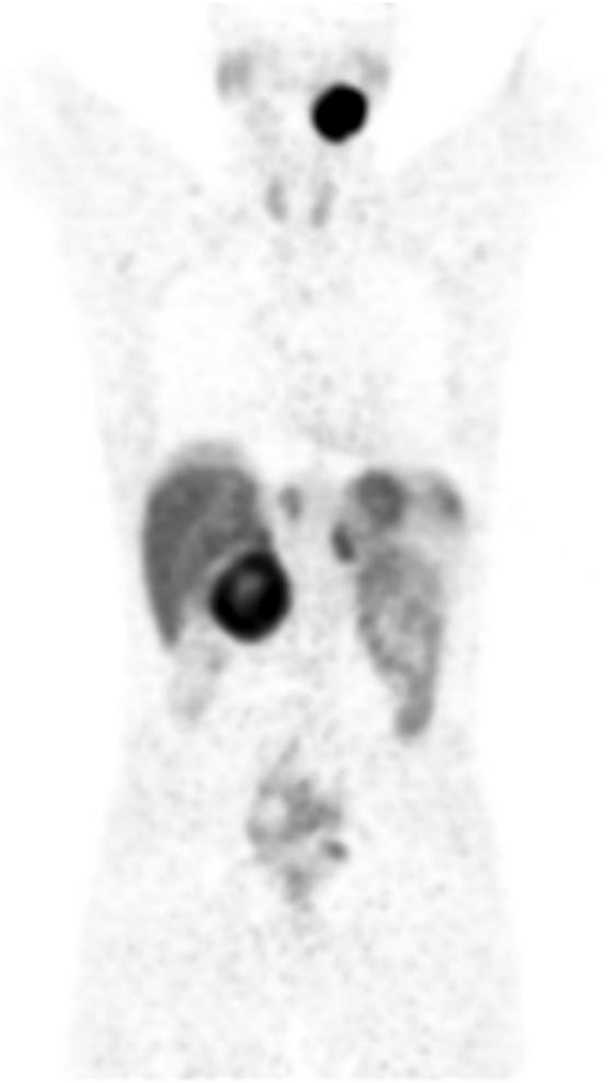

Figure 2. [^{68}Ga]-DOTATATE–positron emission tomography scan showing evidence of gallium-68 avid masses in the left carotid body and abdomen. No evidence of distal, nodal, or visceral metastasis.

staining of chromogranin and synaptophysin in tumor cells, with S100 highlighting sustentacular cells. The Ki-67 proliferation index was 1% and 3% for the intra-abdominal and carotid body tumors, respectively. SDHB immunohistochemistry showed a weak blush staining of tumor cells, interpreted as negative in comparison to the internal control of strong granular staining in surrounding endothelial cells (Fig. 4B).

Genetic counseling was provided and predictive testing was performed on first-degree relatives. The same *SDHB* mutation was detected in his youngest sister (Fig. 5). His 16-week-old son will be offered presymptomatic genetic counseling and testing at age 6 to 8 years as suggested by current recommendations [16]. Informed consent was provided by the index patient and all relatives who underwent genetic testing.

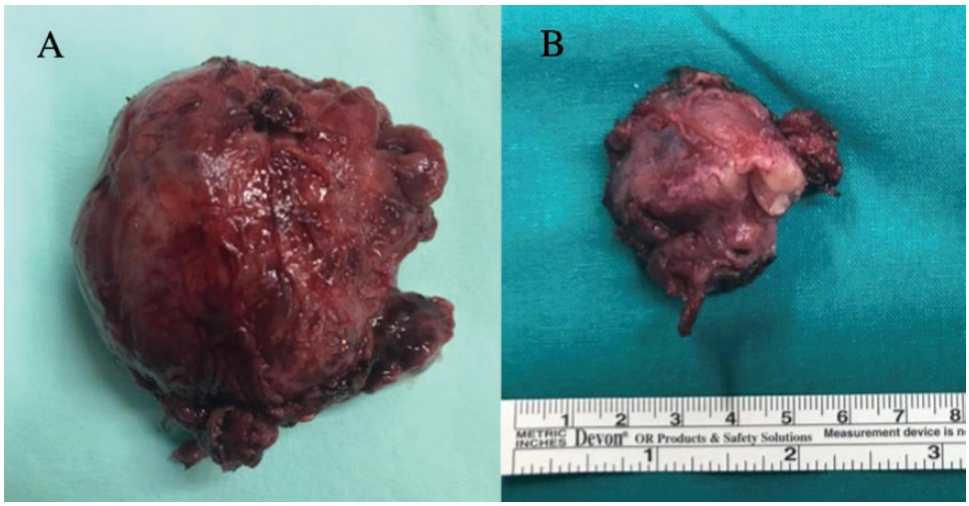

Figure 3. A, Intra-abdominal paraganglioma: a well circumscribed mass of 28 g covered with fibro-adipose tissue measuring 6.5 × 5.0 × 3.5cm. B, Left carotid body tumor: single unoriented portion of fibro-adipose tissue with a weight of 20 g and measuring 3.4 × 3.3 × 3.2cm.

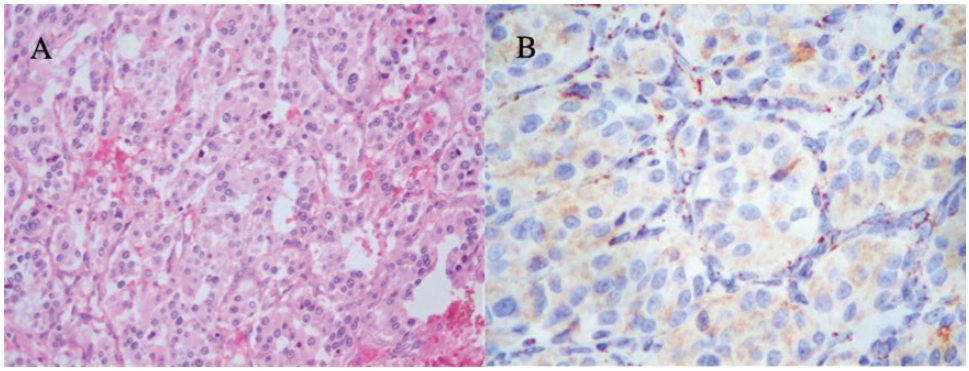

Figure 4. A, Microscopy: hematoxylin and eosin stain (200×) showing nests of neuroendocrine cells imparting a "Zellballen" appearance. B, SDHB immunohistochemistry (400×) showing weak blush staining in tumor cells, interpreted as negative.

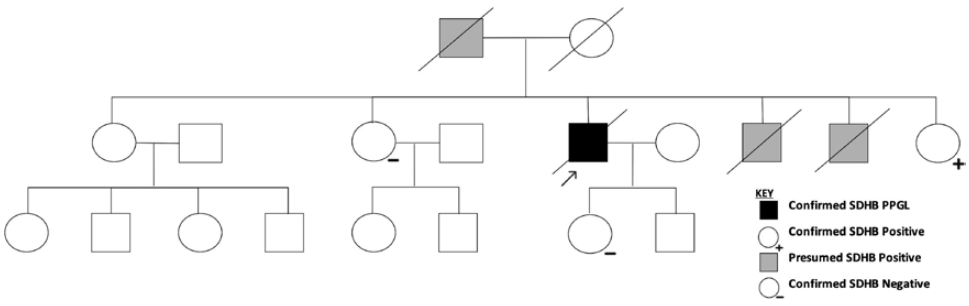

Figure 5. Pedigree illustrating SDHB-positive family. Abbreviation: PPGL, pheochromocytoma/paraganglioma.

Discussion

Our patient presented with an *SDHB* missense variant c.724C>A with an amino acid change of arginine to serine at position 242. The arginine residue is highly conserved and there is a moderate physicochemical difference between arginine and serine. This specific mutation is a known pathogenic Class V *SDHB* variant [17, 18]. Following family screening, the same mutation was detected in his younger sister. Additionally, the early cardiovascular mortality in 3 first-degree relatives is suggestive of the possible presence of an underlying *SDHB* mutation and consequent PGL4 syndrome in these family members.

There is a considerable lack of data describing PPGL-associated genetic mutations among the sub-Saharan

African population. The 2001 National Cancer Database report on malignant paragangliomas of the head and neck found that just 7 of 59 patients with head and neck paragangliomas were of African American ancestry, and just 1 of 598 patients from the 2007 European-American Head and Neck Paraganglioma registry was of African ancestry [19, 20]. Three South African case series report 15 of 149 patients (10%) with hereditary PPGL. Of these, 8 were associated with VHL (4 of whom were a father, a son, and 2 daughters from the same family), 3 with NF1, and 4 more with MEN 2A syndrome (1 who was diagnosed solely on clinical grounds) [8-10]. Genetic mutational analysis was performed in just 3 of these cases: 2 with VHL (missense mutation [c. 256C>T] and missense mutation [c. 499C>T]) and 1 with MEN 2A (missense mutation [c.634 exon 11]) [9, 11]. None of the cases included in these case series were associated with *SDH* mutations and to date there is just a single case report of a 23-year-old male from sub-Saharan Africa with an abdominal *SDHB*-associated extra-adrenal PGL reported in the literature; however, the specific mutation was not described [8, 9, 15]. The lack of data describing specific mutations in the African region is likely due to the paucity of genetic analysis rather than novel mutations of existing PPGL phenotypes.

Genetic testing is important to identify pathogenic germline mutations that may influence both the phenotypic presentation and the malignancy risk and prognosis of the index case. This has implications for the approach to further investigations and the subsequent individualized definitive therapeutic management approach. For example, *SDHB*-associated PPGL have a unique phenotypic presentation with a greater proportion of intra-abdominal, thoracic, and pelvic PGLs, with head and neck tumors less common [21, 22]. Furthermore, in a third of cases, multifocal disease is present [3]. *SDHB*-related PGLs confer a higher risk of malignancy and poorer prognosis [23, 24]. Moreover, susceptibility to renal cell carcinoma, papillary thyroid tumors, neuroblastomas, pituitary neoplasms, and gastrointestinal stromal tumors are also increased with *SDHB* mutations [1, 25]. Furthermore, presymptomatic genetic screening of first-degree relatives is vital to identify family members at risk for current or future clinical disease. Family members who test negative can be reassured that they do not require surveillance. Those who test positive require regular clinical, biochemical, and radiological screening [26, 27].

Genetic testing in Africa is fraught with numerous challenges. A lack of infrastructure, not enough skilled personnel, and limited healthcare resources all contribute to scarcely available facilities with the necessary expertise to reliably perform genetic testing and analysis. Moreover, variants of unknown significance are more likely to be detected in persons of African ancestry due to both the lack of data among normal persons and the genetic diversity across the African continent [28]. Despite these limitations, our case clearly emphasizes the need to improve the availability of genetic testing across the continent to expand the epidemiological knowledge of hereditary PPGL. This would improve clinical outcomes in both patients with hereditary PPGL and in family members who carry pathogenic mutations.

Presently, it is recommended that all patients with PPGL undergo genetic testing regardless of age of presentation [26]. However, in low-resource settings with limited access to genetic testing, although desirable, this approach may not be feasible. In the study from Cape Town that re-stained PPGL specimens with a commercial SDHB stain, those with loss of SDHB staining were of younger age, (26 years vs 50.5 years old [$P < 0.001$]), PPGLs were more likely located in extra-adrenal areas compared with within the adrenal medulla, and 47.4% of all extra-adrenal PPGLs demonstrated loss of SDHB staining compared with just 7.1% of adrenal PPGLs [12]. Considering these data, in low-resource settings it may be most cost-effective to offer genetic testing to those at highest risk of a hereditary PPGL based on clinical presentation. Such clinical scenarios include all patients with PGL regardless of age, bilateral PCC, unilateral PCC if younger than 60 years, multifocal or malignant disease, clinical features of a PPGL-associated clinical syndrome, and a family history of PPGL.

Conclusion

Due to a lack of genetic testing, there is a paucity of data describing hereditary PPGL in people of African ancestry. We report a sub-Saharan African family with proven *SDHB*-associated PPGL due to the *SDHB* missense variant c.724C>A. Further studies are needed to clarify the prevalence, phenotypic presentation, penetrance, and prognosis of hereditary PPGL in patients from Africa. In order to do so, greater access to genetic testing among African patients with PPGL is required to expand the knowledge of contributory germline mutations to hereditary PPGLs among this population group.

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Consent and Ethics Approval: The patient gave verbal and written consent for this case report prior to his demise. Ethics approval was granted from the Human Research Ethics Committee (Medical) from the University of the Witwatersrand (M200699) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Additional Information

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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