

# Tinnitus With Unexpected Spanish Roots: Head and Neck Paragangliomas Caused by SDHAF2 Mutation

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It is estimated that up to 40% of all head and neck paragangliomas (HNPGL) have a hereditary background with the most common mutations being found in the succinate dehydrogenase (SDH) genes. *SDHAF2* mutation leads to the rare paraganglioma syndrome 2. The authors present the case of a 15-year-old male patient with 2, non-secretory HNPGLs, presenting with left-sided, pulsatile tinnitus, and hearing loss. Imaging led to the suspicion of a jugulotympanic paraganglioma on the left, as well as a carotid body tumor on the right. After resection of the jugulotympanic tumor, histology confirmed the presence of a paraganglioma; immunohistochemistry furthermore suggested a loss of SDHB expression. Genetic testing revealed a rare germline, loss-of-function mutation in the *SDHAF2* gene, previously described to cause hereditary paraganglioma syndrome 2. Twenty months after the first operation, the patient underwent a resection of the right carotid body paraganglioma. Plasma-free metanephrines/catecholamines always remained within the reference range; the patient is under regular follow-up, and his relatives will be screened. Our findings emphasize the relevance of genetic testing in patients with HNPGL, also with negative family history, especially when the patients present at a young age and with multiple lesions.

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**Key Words:** pheochromocytoma/paraganglioma, hereditary tumor syndrome, SDHAF2, paraganglioma syndrome

Head and neck paragangliomas (HNPGL) are a subtype of pheochromocytoma/paraganglioma (Pheo/PGL) and originate from the extra-adrenal ganglia of the autonomic nervous system. In contrast to abdominal and thoracic Pheo/PGL, HNPGL are usually nonsecretory, exclusively have a parasympathetic origin, and only rarely metastasize [1]. The initial manifestation of HNPGL depends on the localization and the secretory pattern of the tumor. Tinnitus and hearing loss are typical for tympanic HNPGL and should prompt further evaluation.

Although HNPGL may occur as sporadic tumors, it is estimated that up to 50% of all Pheo/PGL have a hereditary background that may influence the therapeutic strategies, follow-up of affected patients, and screening of family members [2, 3]. The most common mutations are found in the succinate dehydrogenase (*SDH*) genes with the highest prevalence of mutations in *SDHD*, followed by *SDHB* and *SDHC* [1].

Abbreviations: FAD, Flavin adenine dinucleotide; HNPGL, head and neck paraganglioma; MRI, magnetic resonance imaging; PGL2, paraganglioma syndrome 2; Pheo/PDL, pheochromocytoma/paraganglioma

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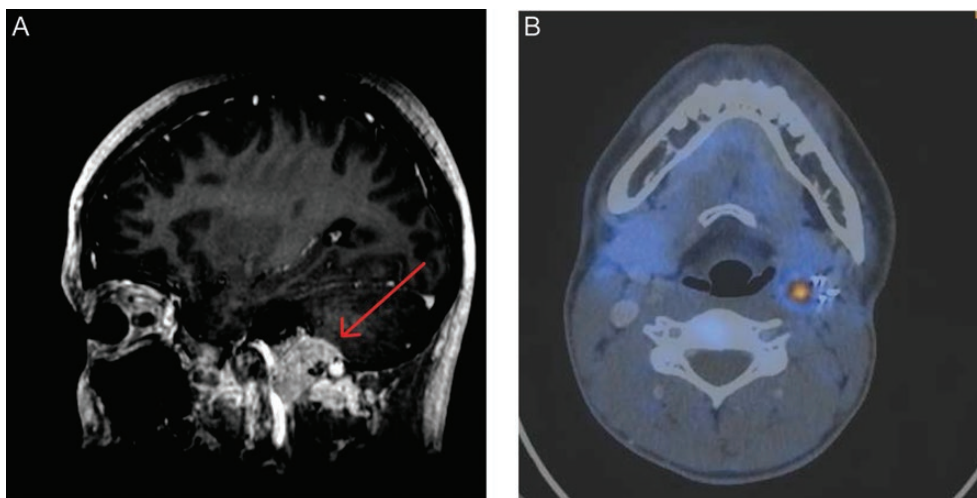
SDH is a membrane-bound, mitochondrial enzyme and part of the tricarboxylic acid cycle, as well as of the electron transport chain. It plays a key role in energy metabolism [4]. The enzymes of the tricarboxylic acid cycle in general are considered tumor suppressors, and mutations in the corresponding genes are associated with tumorigenesis in different tissues [5]. Several of the mutations associated with hereditary Pheo/PGL cause a disturbed cellular response to hypoxia, leading to a condition called pseudohypoxia. Interestingly also with actual, chronic hypoxia a high incidence of Pheo/PGL occurs. This association was observed in populations living in high-altitude regions, as well as in patients with cyanotic congenital heart disease. It suggests an etiological link between the cellular responses to hypoxia and the development of Pheo/PGL [6].

## 1. Case

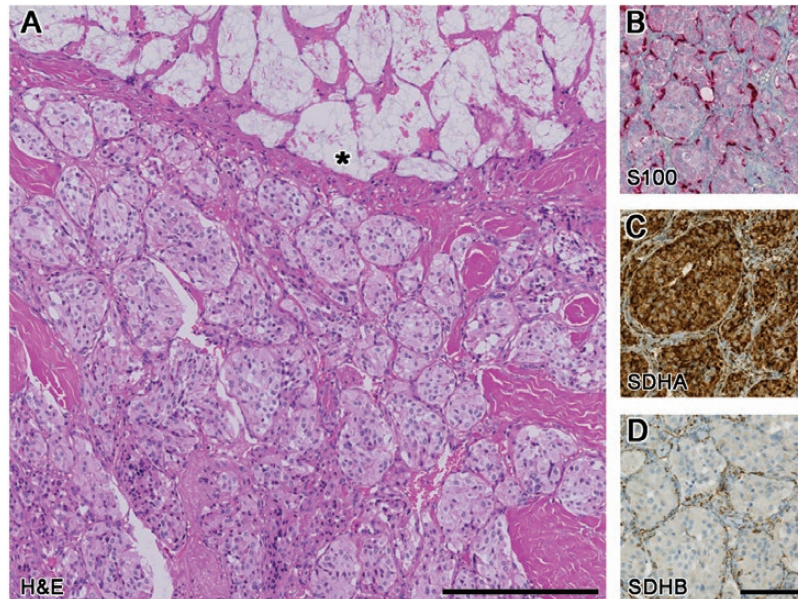
A 15-year-old male patient presented with a 4-month history of pulsatile tinnitus and hearing loss of the left ear. The patient was normotensive, did not report spells, and plasma-free metanephrines/catecholamines were not elevated. Family history was negative for tumors, the mother of the patient comes from Morocco, the father from Spain, and they are not consanguine.

Imaging by magnetic resonance imaging (MRI) and Ga<sup>68</sup>-DOTATATE-positron emission tomography-computed tomography (shown in Fig. 1) revealed a left-sided jugulotympanic tumor (33 × 34 mm, Fisch classification C2 De2 Di1), as well as a tumor of the right carotid body (12 × 15 mm). The jugulotympanic tumor was resected after prior embolization and the morphological suspicion of a paraganglioma was confirmed histologically. As shown in Fig. 2, immunohistochemistry revealed a loss of SDHB expression with positive staining for SDHA in neuroendocrine cells and S100 in sustentacular cells. The result of the immunohistochemistry, the young age of the patient, as well as the multiplicity of the lesions led to the hypothesis of a hereditary tumor syndrome, although family history was negative.

DNA from peripheral blood (leukocytes) was isolated and targeted next-generation sequencing of 27 (neuro-)endocrine tumor-related (including the *SDHx*) genes revealed no pathogenic mutation in the *SDHD* and *SDHC* genes but a germline mutation in the *SDHAF2* gene (NM\_017841.2; c.232G>A).



**Figure 1.** (A) Preoperative magnetic resonance imaging, T1-weighted postcontrast agent: mass lesion of the jugular foramen (33 × 34 mm) with extension to the middle ear, affecting the epi- and mesotympanum. (B) Postoperative Ga68DOTATATE-positron emission tomography-computed tomography: SSTR2-positive lesion of the right carotid body (12 × 15 mm, SUVmax 23.2).



**Figure 2.** (A) Overview of the paraganglioma (hematoxylin and eosin): sheets and nests of neuroendocrine cells (lower part) and foreign material (asterisk, upper part) from preceding embolization. (B) Immunohistochemistry with sustentacular cells entwisting the neuroendocrine cells, staining positive for S100. (C) Diffuse positivity for SDHA in the tumor cells. (D) Loss of SDHB expression in the tumor cells. Scale bar, 250  $\mu\text{m}$  (overview), 100  $\mu\text{m}$  (magnification).

Unfortunately, after the surgery the patient experienced a complete hearing loss on the left without further persistent deficits. The follow-up MRI after 15 and 20 months documented a stable size of the residual tumor on the left and of the carotid body tumor on the right. Plasma-free metanephrines/catecholamines remained within the reference range. Twenty months after the first operation, the patient underwent a resection of the right carotid body paraganglioma without any complications. The patient is under regular follow-up, and his relatives will be screened.

## 2. Discussion

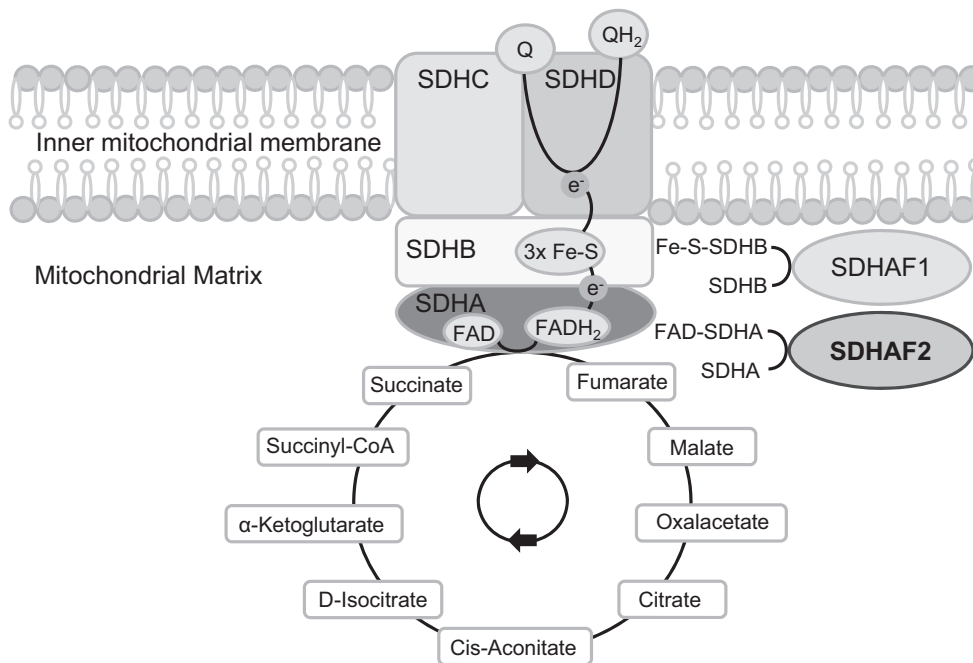
This young patient presented with 2 paragangliomas of the head and neck region without evidence of catecholamine excess. Immunohistochemical staining for SDHB was negative; this investigation is a reasonable first screening, as a loss of SDHB expression is seen in the case of any *SDHx* mutation, but not in other hereditary tumor syndromes [2]. He was found to have a germline, missense mutation of the *SDHAF2* gene on chromosome 11 in position 12.2 at site 232 with an exchange of guanine to adenine (11q12.2 c232 G>A). This mutation is known to cause a loss of SDHAF2 function, leading to the hereditary paraganglioma syndrome 2 (PGL2), first discovered in 1982 by van Baars et al. in a Dutch family with HNPGL. Up to now, it was only found in 1 other family in Spain. In 2009, Hao et al. succeeded in identifying the underlying gene mutation [4, 5, 7].

SDHAF2 is an evolutionary highly conserved cofactor of the SDH complex. As shown in Fig. 3, it inserts Flavin adenine dinucleotide (FAD) into SDHA, a step necessary for a fully functional and stable SDH complex [4, 8].

The inheritance of PGL2 is autosomal dominant with maternal imprinting, leading to tumorigenesis only by paternal transmission, rendering the recognition of a hereditary cause more difficult [5, 9]. Given the small number of reported patients with PGL2, we assume a connection to the Spanish descent of the patient and recommended genetic testing for his father and possibly affected relatives.

As in our case, patients with PGL2 usually present at a young age with multiple, benign, and nonsecretory HNPGL. Because of the benign nature of the tumors, the indication for surgery could be debated and a close follow-up might be chosen in some cases; in others, a radiation therapy might be an option if resection is not feasible without greater damage. In this patient, the tumors were threatening to cause complications because of their sheer size, so that an operative approach was chosen. The penetrance of tumorigenesis in affected individuals reaches 88% to 100% by the age of 50 years. So far, no pheochromocytomas, abdominal or thoracic paragangliomas, or malignant tumors have been observed [1].

Interestingly, it seems that the Spanish family was diagnosed with more tumors per patient than the original Dutch kindred. Table 1 summarizes the available patient data. Kunst et al. detected 24 tumors in 11 at-risk individuals in the Netherlands, whereas Bayley et al. found 11 tumors in 4 family members in Spain. In addition, the average age of onset was slightly younger in Spain (31 years) than in the Netherlands (33 years). Whether these discrepancies represent an actual difference, or whether they are caused by a screening bias, remains to be clarified [5, 9].



**Figure 3.** Structure of the SDH complex with 2 hydrophobic units: SDHC and SDHD, anchoring the complex within the inner mitochondrial membrane, and 2 hydrophilic proteins: SDHA and SDHB, forming the enzymatic active component of the complex. SDHAF1 and 2 insert iron sulfate (Fe-S) and FAD into SDHB and SDHA, respectively. To oxidate succinate to fumarate, 2 electrons are transferred from succinate to FAD, leading to FADH<sub>2</sub>. The electrons are then passed through the Fe-S clusters and reduce ubiquinone (Q) to ubiquinol (QH<sub>2</sub>) [8].

**Table 1. Overview on the Available Patient Data From the 2 Known PGL2 Families from the Netherlands and Spain, as Well as Our Patient [5,9]**

	Netherlands	Spain	Switzerland
Number of patients	11	4	1
Age at diagnosis (y)	33 (22–47)	31 (20–59)	15
Gender	50% female	75% female	100% male
Number of tumors	24	11	2
Localization	CBT (17), VT (4), JTT (3)	CBT (6), VT (2), JTT (2), TT (1)	CBT (1), JTT (1)

Abbreviations: CBT, carotid body tumor; JTT, jugulotympanic tumor; TT, thyroid tumor; VT, vagal tumor.



HNPGL in general are usually nonsecretory and mostly benign tumors and they occur in up to 50% in the context of a specific germline mutation [3].

Our findings emphasize the relevance of genetic testing in patients with HNPGL (independent of family history), especially in patients present at young age and with multiple lesions. Because of the high rate of hereditary Pheo/PGL, genetic testing is recommended for all patients with these tumors [3, 10]. Testing algorithms with serial analysis depending on clinical presentation and immunohistochemistry of the tumor tissue have been proposed in the past. Because of the high number of susceptibility genes and the better availability and feasibility of next-generation sequencing, the next-generation sequencing in the PPGL Study Group recently published a consensus statement recommending targeted gene panels with a basic, extended, or comprehensive gene panel [3]. Patients with a genetically proven paraganglioma syndrome should undergo regular clinical, laboratory, and radiological follow-up. According to the particular mutation and its specific tumor risk, the imaging modality and the examined body region can be adapted [1, 2, 6, 11]. Because there is only a small number of PGL2 patients, the recommendations for patients with *SDHD* mutation can be applied, for instance an MRI of the head and neck region every 18 months and 3 yearly an MRI scans from head to pelvis [12].

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## Additional Information

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