

First-positive surveillance screening in an asymptomatic *SDHA* germline mutation carrier

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Summary

At least 40% of pheochromocytomas and paraganglioma's (PPGLs) are associated with an underlying genetic mutation. The understanding of the genetic landscape of these tumours has rapidly evolved, with 18 associated genes now identified. Among these, mutations in the subunits of succinate dehydrogenase complex (*SDH*) are the most common, causing around half of familial PPGL cases. Occurrence of PPGLs in carriers of *SDHB*, *SDHC* and *SDHD* subunit mutations has been long reported, but it is only recently that variants in the *SDHA* subunit have been linked to PPGL formation. Previously documented cases have, to our knowledge, only been found in isolated cases where pathogenic *SDHA* variants were identified retrospectively. We report the case of an asymptomatic suspected carotid body tumour found during surveillance screening in a 72-year-old female who is a known carrier of a germline *SDHA* pathogenic variant. To our knowledge, this is the first screen that detected PPGL found in a previously identified *SDHA* pathogenic variant carrier, during surveillance imaging. This finding supports the use of cascade genetic testing and surveillance screening in all carriers of a pathogenic *SDHA* variant.

Learning points:

- *SDH* mutations are important causes of PPGL disease.
- *SDHA* is much rarer compared to *SDHB* and *SDHD* mutations.
- Pathogenicity and penetrance are yet to be fully determined in cases of *SDHA*-related PPGL.
- Surveillance screening should be used for *SDHA* PPGL cases to identify recurrence, metastasis or metachronous disease.
- Surveillance screening for *SDH*-related disease should be performed in identified carriers of a pathogenic *SDHA* variant.

Background

Succinate dehydrogenase (*SDH*), also known as mitochondrial complex II, plays an important role in both the Krebs cycle and the electron transport chain, catalysing the oxidation of succinate to fumarate and the reduction of ubiquinone to ubiquinol respectively (1). Mutations in genes that encode this complex have been associated with familial paraganglioma syndromes since

2000 (2). Mutations in *SDHA* subunit, however, have only more recently been linked to causing paraganglioma disease (3). All the cases described in *SDHA* mutation carriers have occurred in symptomatic index cases, following which the genetic variant was identified (4). We report the first case of a paraganglioma being identified in an asymptomatic *SDHA* mutation carrier on their first

surveillance screening, which highlights the importance that asymptomatic relatives should undergo surveillance screening.

Case presentation

A 72-year-old female was referred to the endocrinology service following the identification of a pathogenic germline variant in the *SDHA* gene (c.91C>T, p.Arg31*) as part of a genetic panel for cardiomyopathy. She originally presented to the cardiology services 6 years previously due to exertional dyspnoea and palpitations and was diagnosed with hypertrophic cardiomyopathy. She was lost to follow-up but re-presented in 2017 with worsening dyspnoea, palpitations and ankle oedema. At this time, she was found to be normotensive (BP 120/80 mmHg, HR 64 bpm regular). During echocardiography, septal hypertrophy was observed but no left ventricular outflow tract obstruction was noted. Ejection fraction was estimated to be above 55%. At this time a 218 gene cardiomyopathy genetic panel was performed, which included the *SDHA* gene due to reports of neonatal isolated dilated cardiomyopathy in certain *SDHA* variants (5). The pathogenic variant in the *SDHA* gene was subsequently identified, with all other genetic mutations negative.

Her past medical history included bronchiectasis, hypertension (treated with 150 mg Irbesartan), hypothyroidism (replacement with 100 µg levothyroxine) and hyperparathyroidism. Family history was significant for breast cancer and hypercalcaemia. There was no personal or family history of pheochromocytoma or paraganglioma (PPGL), gastrointestinal stromal tumours or pituitary adenoma. A 4-generation pedigree is shown in Fig. 1.

Investigation

At our unit we run a specialist family *SDH* clinic, where patients are reviewed annually (in family groups if desired). On identification of an *SDH* mutation all patients are reviewed in clinic and biochemistry is sent (plasma or 24 h urine metanephrines). All patients undergo an initial surveillance scan involving non-contrast MRI from skull base (with one cut through the pituitary) to pelvis.

On review she reported no additional symptoms of catecholamine excess. She was normotensive (BP: 134/62 mmHg, HR: 78 bpm) on 150 mg Irbesartan. Urinary metanephrines were within the reference range – metanephrine: 795 nmol/24 h (<2000 nmol/24 h), normetanephrine: 1681 nmol/24 h (<4400 nmol/24 h) and 3-methoxytyramine: 950 nmol/24 h (<2500 nmol/24 h).

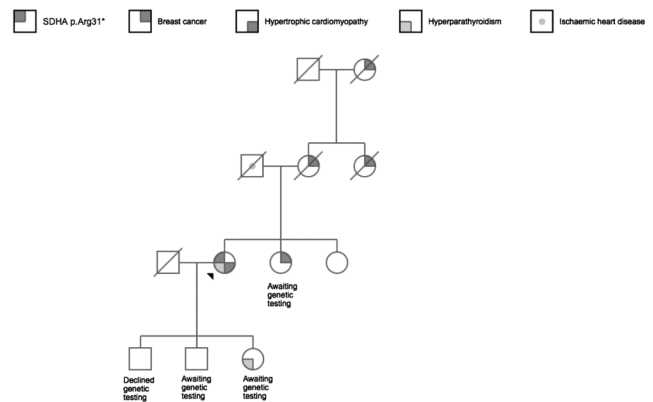


Figure 1
Four-generation pedigree showing *SDHA* status, family history of neoplasia, endocrine disorders and cardiovascular disease.

A non-contrast MRI (Fig. 2) revealed a heterogenous 3 × 3.6 cm lesion at the left carotid bifurcation, splaying the internal and external carotid arteries. The lesion was determined by expert radiologists to be consistent with a carotid body paraganglioma. No other *SDH*-related lesions were identified on complete surveillance imaging.

Treatment

Due to the patients' comorbidities of cardiomyopathy and the identified lesion being non-secretory, a decision was made for active surveillance. She underwent an interval MRI at 6-month follow-up. This MRI revealed an unchanged appearance of the suspected paraganglioma. Plasma metanephrines were also performed and were within the reference range (metanephrine: – 152.9 pmol/L (<510), normetanephrine: – 291.5 pmol/L (<1180),

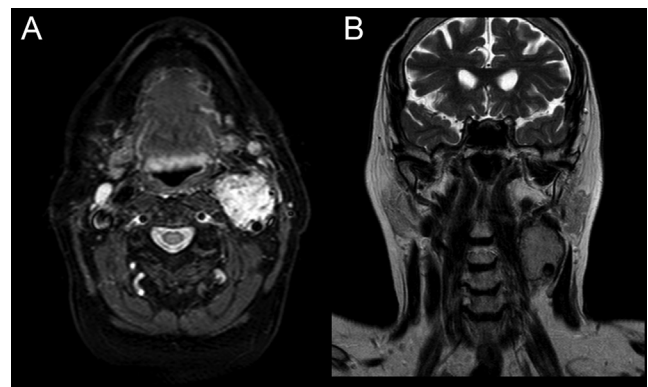


Figure 2
Head and neck surveillance MRI. (A) Axial image showing the 3 × 3.6 cm left carotid body paraganglioma, with typical MRI characteristics. An enlarged lymph node at the 1b nodal station can also be seen. (B) T2-weighted sagittal image highlighting the lesion.



3-methoxytyramine: – <75 pmol/L (<180)). She will undergo a further surveillance MRI at a 1-year interval from the preceding scan. In the interim, she is undergoing assessment and optimisation by the cardiology team.

Outcome and follow-up

The patients' children have been advised to undergo genetic screening to test for *SDHA* carrier status. If positive for the pathogenic variant, they will be entered into our *SDH* screening programme.

Discussion

It is now widely accepted that patients who carry *SDHB*, *SDHC* and *SDHD* pathogenic variants should undergo surveillance screening (6). The modality and frequency of this surveillance however is still controversial. The aim of surveillance programmes is for early identification of tumours, recurrence and metastases to allow timely intervention. As genetic testing is becoming more accessible, cascade genetic testing is leading to the identification of increasing numbers of asymptomatic familial carriers. These asymptomatic individuals should also be entered into surveillance screening programmes to allow early detection of PPGLs and other associated neoplasms (7).

SDHA mutations are less common than *SDHB* and *SDHD* mutations and therefore there are fewer reported cases and a limited understanding of the best surveillance for these individuals. Mutations in the *SDHA* gene were first associated with autosomal recessive inheritance of the mitochondrial disease Leigh syndrome (juvenile encephalopathy) (8), and more recently, with severe neurological dysfunction and cardiomyopathy (9). These rare cases of cardiomyopathy due to *SDHA* mutations occur in infancy with a high mortality due to congestive heart failure (5). As an autosomal dominant inherited tumour suppressor gene, *SDHA* mutations were only proven to be associated with inherited familial PGL syndromes in 2010 (3). *SDHA* mutations were originally estimated to be found in just 3% of all familial PPGL cases (10), but this is now thought to be higher, at 7.6% (11). Penetrance figures are thought to be lower for *SDHA* mutation carriers compared to *SDHB* and *SDHD* (12), but the actual penetrance figures are unknown. Ninety-five cases of PPGL in *SDHA* carriers have now been reported in the literature (3, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22). These were all symptomatic index cases. Of these cases, 49% were found to occur in the head and neck region (HNPGL), 20%

were pheochromocytoma (PCC) and 31% sympathetic extra-adrenal PGLs (abdominal, pelvic, thoracic regions). Thirteen of these cases (13.7%) were malignant. From these cases, subsequent to diagnosis five patients reported a positive family history of a single affected relative with possible *SDHA*-related tumour (one HNPGL, one GIST, two renal cell carcinoma, one pituitary adenoma) (11, 14, 22). None of these relatives were known to carry an *SDHA* mutation before diagnosis.

In the reported cases in the literature, there were 39 different germline loss-of-function or missense mutations identified (4). The most common of which was c.91C>T, p.Arg31*, the same mutation identified in our patient. The allele frequency of this pathogenic variant in a Dutch control population was reported as 0.3%, compared to 3% of patients with an apparently sporadic PCC/PGL (10). The ExAC database (exac.broadinstitute.org/about) cite an allele frequency of 0.026% in a European, non-Finnish control population, compared to 0.041% reported by the gnomAD database (gnomad.broadinstitute.org/about). This is a surprisingly high frequency for the small number of reported cases of *SDHA*-related PPGL and suggests a low penetrance for this pathogenic variant. In our patient, as the tumour has not been surgically resected, we were unable to perform further analysis on the tumour tissue to confirm the pathogenicity of this mutation variant in the development of this PGL, and therefore, the possibility remains that the development of this PGL may be unrelated to the discovered *SDHA* germline variant. However, given that there is increasing evidence that surgical resection is no longer the ideal first-line treatment for HNPGLs, this is impossible to prove. Previous reports have shown this *SDHA* variant to be pathogenic, with *in silico* analysis suggesting a truncated protein is produced, with loss of protein function demonstrated by negative staining with SDHA immunohistochemistry (10, 20, 21). Another paper used performed metabolic analysis on a PGL from a patient with the same mutation variant as our patient using MRI spectroscopy and identified a succinate peak in the tumour tissue, again providing supporting evidence to the pathogenicity of this mutation variant (23). Therefore, working in what we believe to be best clinical practice for the patient, we are undertaking clinical management on the assumption that the PGL is caused by this mutation variant.

Mutations in the *SDHA* gene are rare causes of cardiomyopathy, and the authors are surprised that the *SDHA* gene is included in the panel test. However, secretory PPGLs are recognised as more common causes of cardiomyopathy and a more practical approach would



be to screen for PPGLs with a single plasma or urine metanephrine measurement in patients with unexplained cardiomyopathies (24, 25).

To our knowledge, we report the first case of a surveillance screen detected PPGL to be found in an asymptomatic individual with previously identified *SDHA* mutation status. Previous literature has debated the need for surveillance screening in *SDHA* carriers due to estimated low penetrance rates (4). However, it appears that all PPGLs can have malignant potential and therefore surveillance is important. In several cases where malignancy has been reported there has been a long lag time from primary tumour to the development of malignancy (20, 21, 22). Although the true penetrance rates are unknown in *SDHA* mutation carriers, especially for specific mutation variants, as per *SDHB* and *SDHD* carriers, accurate penetrance rates can only be established through long-term follow-up of asymptomatic carriers, and perhaps subsequent surveillance protocols need to be adapted to be more personalised taking into account factors such as the specific mutation variant, other relevant comorbidities (e.g. cardiomyopathy in this case) and patient personal preference for screening.

We believe therefore that this case highlights the potential importance of at least an initial surveillance screening in all newly identified *SDHA* mutation carriers.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for the publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement

G W and N T contributed equally to the writing of the case report. S A A is the physician in charge of the patient's care and edited the case report.

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