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Higher risk of phaeochromocytoma/paraganglioma (Phaeo-Pgl) in SDHD than SDHB carriers – an Australian cohort study

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Phaeochromocytomas (PCC) and paragangliomas (PGL) are neuroendocrine tumours arising from the adrenal medulla or the sympathetic and parasympathetic chains respectively. Phaeochromocytomas may secrete noradrenaline and adrenaline alone or in combination, sympathetic paragangliomas found in the thorax and abdomen can secrete noradrenaline while parasympathetic paragangliomas of the head and neck are predominantly non-secretory. Up to 50% of PCC/PGLs can have an underlying germline driver mutation[1]. Of these, mutations in the genes encoding the subunits (SDHA, SDHB, SDHC, SDHD & SDHAF2) of the enzyme succinate dehydrogenase (SDHx), a tumour-suppressor gene, are the commonest[1]. Carriers of SDHx mutations are at increased risk of developing PCC/PGL and other tumours such as renal cancer, gastrointestinal stromal tumours, and pituitary adenoma[2, 3], and need lifelong surveillance. However, opinions remain divided regarding the most appropriate surveillance strategy[4-6]. The aim of this study is to describe the outcomes of a cohort of SDHx mutation carriers followed at a tertiary Australian hospital, incorporating annual clinical review with plasma/urine metanephrines and biennial MRI imaging from skull base to pelvis. Tumours detected on screening which did not require immediate intervention were followed with annual imaging. All (n=50, including index cases) SDHx patients attending our clinic from 2007 to May 2017 were included. A retrospective review of medical records was conducted following ethics approval. Median follow-up was 4.0 (range 1 – 10) years. Data was analysed using

student's t-test or Fisher's exact test (Microsoft Excel) and presented as mean ± standard deviation or number (percentage). P-value of <0.05 was considered significant.

There were 13 (26%) index cases (n=10 SDHB and n=3 SDHD) and 37 mutation-positive relatives (n=22 SDHB, n=9 SDHD and n=6 SDHC) in our cohort. Patient characteristics and tumour details are described in Table 1. The mean age at first presentation of the index cases was 33.5±16.5 years for SDHB and 49.3±17.2 years for SDHD patients respectively (p=ns). The mean age at last follow-up of the combined groups (index cases + mutation positive relatives) was 40.1±16.2, 49.5±17.9 and 55.8±16.8 years and the oldest unaffected carrier was 66, 63 and 46 years for SDHB, SDHC, and SDHD respectively. The mean follow-up period was 3.9±3.0 years for SDHB, 2.8±1.2years for SDHC and 6.4±2.6 years for SDHD patients respectively. During surveillance, 2 index patients (1 SDHB and 1 SDHD) developed additional tumours, both head and neck paragangliomas (HNPGL). Of the 37 mutation-positive relatives, 8 (22%, 7 SDHD and 1 SDHC) had tumours on initial imaging and 5 (13%, all SDHD) developed additional tumours. All of the non-index SDHB carriers remained unaffected at last follow-up.

In the 10 index SDHB subgroup, a total of 12 tumours (8 HNPGL, 2 sympathetic paragangliomas (sPGL), 1 phaeochromocytoma and 1 renal cell carcinoma) were present at diagnosis. One patient developed a new HNPGL 11 years following initial

presentation. Two patients had metastatic disease on their 1st scan (one primary abdominal PGL and one HNPGL) and another with a large PCC represented 5 years later with metastatic disease.

In the SDHD group, 3 index patients had six tumours at diagnosis (all HNPGL). Of the mutation-positive relatives 7 out of 9 (77.8%) had 14 tumours (12 HNPGL, 2 sPGL, 4 with synchronous lesions) on the initial scan and five developed additional tumours (5 HNPGL, 2 sPGL, two with multifocal lesions) during surveillance. The majority of mutation-positive relatives with tumours were from one kindred with c.274G>T (p.Asp92Tyr) Dutch founder mutation in the SDHD gene[7].

In the SDHC group, (all mutation-positive relatives), one had a HNPGL on initial surveillance. None developed tumours during follow-up.

A total of seven (one SDHB and six SDHD patients) patients developed new tumours during surveillance (Table 2). One SDHD patient developed a liver lesion, which was positive on ^{68}Ga-Dotatate imaging, most likely a metastasis. Among those with new tumours, one had mildly elevated plasma normetanephrine (HNPGL), two had mildly elevated methoxytyramine (one patient with HNPGL and sPGL, another with sPGL and liver metastasis) and four (3 HNPGL, 1 sPGL) had normal biochemistry when diagnosed with new tumour. Importantly of the three SDHB carriers who had metastatic disease only one (sPGL) had elevated normetanephrine when diagnosed

with metastases whilst another (PCC) had elevated normetanephrine approximately 18 months later. One SDHB patient (HNPGL) with metastases has normal biochemistry several years into follow-up.

Seventeen patients with local disease underwent intervention – eight had surgery, three received radiotherapy, six received both). Seven tumours were monitored with annual imaging (6 HNPGL, 1 sPGL). Of the four patients with malignant disease one is being monitored for disease progression, two were treated with peptide receptor radionuclide treatment (PRRT, ^{177}Lutetium dotatate) and one with multiple modalities including PRRT, Sunitinib, chemotherapy and radiotherapy. This patient (SDHB) subsequently died.

Overall, adherence to the surveillance protocol was suboptimal with only 45% of patients having annual biochemistry and 67% undergoing biennial MRIs.

To our knowledge this is the first single centre Australian study describing the surveillance outcomes of SDHx carriers, which adds to a multicentre study published 12 years ago (ref 5). Twenty-one patients (42%) had disease manifestation at last follow-up. Whilst SDHB mutations predominate, disease featured most commonly in SDHD carriers (31% vs. 83%, $p<0.05$, Fisher's Exact test) who had multifocal tumours with the majority discovered through screening. Additionally, this cohort is notable for the higher prevalence of tumours in the non-index SDHD compared to the

non-index SDHB mutation-positive relatives (77% vs. 0%, P<0.05). Unrecognised metastatic disease was rare in mutation-positive relatives of index SDHB cases. Three SDHB and one SDHD patient developed malignant disease and one died from disease progression in our cohort. Of those with malignant disease two had metastases at first visit and two developed metastases 5 and 7 years later.

Most evidence-based guidelines for surveillance in SDHx carriers, are based on small retrospective studies and given the rarity, large prospective studies are unlikely to be feasible. The Australian national guideline (EVIQ)[8, 9] recommends screening of SDHx carriers from 5 years of age with annual examination and biochemistry and biennial MRI imaging from 10 years. MRI is chosen over other modalities because it lacks radiation exposure[10]. A recent study recommended that surveillance for SDHB-related HNPGL begin at age 27.1 years and be repeated 3-yearly[4]. In this study the optimum surveillance for sPGL and PCC could not be assessed due to insufficient numbers, however 4 of 9 patients in their cohort had sPGLs before 20 years of age suggesting that screening had to start at an earlier age. In agreement with this, in our cohort the youngest age for sPGL was 14 (SDHB) and 17 (SDHD) years.

Some studies reporting the highest penetrance estimates[11] included index patients which overestimates penetrance[2]. Establishing penetrance after exclusion of index patients was not feasible in our study due to the low number of patients and events in our cohort. However, our observation that none of the mutation-positive SDHB

relatives developed tumours suggests that penetrance in SDHB may be lower than initially reported[11, 12]. Our study also confirms that HNPGL are indolent tumours[13]. Therefore, active surveillance with annual imaging is an acceptable strategy for asymptomatic HNPGLs which remain stable. However, one SDHB positive patient with a large HNPGL in our cohort developed metastatic disease highlighting that these tumours may have malignant potential. HNPGLs were the most common tumours in SDHD carriers, however three patients developed sPGL and two were younger than 25 years, underscoring the importance of screening for sPGL in this group. SDHC mutations are infrequent in patients with PGLs often presenting as sporadic tumours[14] similar to our cohort with only one of six carriers affected by disease. One SDHB patient presented with distant metastases five years after initial therapy, emphasising the importance of educating patients about the risks of late metastases and need for life-long surveillance.

Non-adherence to screening was common, which may reflect poor acceptance of the surveillance protocol. Adoption of rapid sequence, non-contrast MRI imaging which shortens scanning time (25 to 30 minutes versus 75 minutes for conventional MRI at our institution) [15, 16], may lessen the burden of surveillance on our patients. Rapid-sequence full-body MRI protocols have been examined for staging in other cancers, and preliminary reports support its use for screening SDHx mutation carriers without compromising results[15, 16].

Our study has several limitations. It is retrospective, which potentially introduces some bias. The cohort was small and follow-up was relatively short precluding any conclusion on penetrance. Metanephrine measurements were not available in all patients. MRI techniques evolved with time, which could have underestimated disease prevalence in the early years. However, all images were reviewed independently of the imaging reports at our multidisciplinary meeting, similar to what occurs in real-world practice. We did not use functional imaging routinely for surveillance. Although the superiority of ^{68}Ga-Dotatate imaging over conventional CT/MRI in detecting PCC/PGL is established (lesion based sensitivities of 93-96% for ^{68}Ga-Dotatate PET/CT versus 76-81% for conventional CT/MRI imaging [17, 18]), future studies will need to address its use in surveillance of asymptomatic carriers without compromising safety. The retrospective nature also predisposes to selection bias for the management approaches, however, a prospective randomised study may not be possible given the rarity of the disease. Non-adherence was common, which may be due to unrecognised financial and psychological burden on carriers which we did not evaluate. Despite these limitations, we believe our results provide useful information regarding SDHx carriers in Australia, a rare cohort. Our finding that not all patients had abnormal biochemistry at tumour detection including metastases has clinical relevance and underscores that imaging as well as biochemistry is integral during follow-up.

In conclusion, our study confirms that MRI is useful in the surveillance of SDHx patients for tumours, and that SDHD mutations are highly penetrant but are rarely malignant whilst SDHB mutations are of lower penetrance but are associated with a higher risk of malignancy. Current screening practices, although effective, were poorly adhered to by our patients. Therefore, studies addressing the optimal frequency and modality of imaging are warranted to develop evidence-based guidelines that address surveillance practices in this population. In the interim, our results add to the available literature and aid decision-making.

Conflict of interest: The authors have no conflict of interest to declare.

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Abstract

Carriers of SDHx mutations are at risk of developing phaeochromocytomas, catecholamine secreting extra-adrenal paragangliomas and non-secretory head and neck paragangliomas and require lifelong surveillance. There is no current consensus on the optimal surveillance strategy. This study describes the outcomes of a cohort of 50 SDHx mutation carriers followed at a tertiary Australian hospital using a surveillance protocol involving annual clinical review with plasma/urine metanephrines and biennial MRI imaging from skull base to pelvis.

Table 1. Patient and tumour characteristics.

	Proband			Non-Proband		
	SDHB	**SDHD**	**SDHC**	**SDHB**	**SDHD**	**SDHC**
No. of patients	10	3	0	22	9	6
Sex (F/M)	5/5	1/2	-	14/8	3/6	5/1
Age (mean, yrs)	39.0	51.0	-	36.3	40.4	53
Patients with tumour (n,%)	10	3	0	0, 0%	7, 77.8%	1, 16.7%
Age at first tumour (mean, yrs)	33.5	49.3	-	N/A	-[†]	70
Patients with new tumour on follow-up (n, %)	1, 10%	1, 33.3%	-	0, 0%	5, 55.5%	0, 0%
Metastases (n, %)	3[‡], 30%	0, 0%		0, 0%	1, 11%	0, 0%
Tumour type (number of tumour[§])						
Head and neck PGL	8	6	-	-	17	1
Abdominal PGL	2	0	-	-	3	0
Thoracic/mediastinal PGL	0	0	-	-	1	0
Phaeochromocytoma	1	0	-	-	0	0
Renal cell carcinoma	1	0	-	-	-	0

[†] Unable to calculate due to incomplete data

[‡] Two index patients had widespread metastases on initial scan, and one developed metastases 5 years after initial treatment

[§] Bilateral tumours are counted as two tumours

PGL = paraganglioma, N/A = not applicable

Table 2. Patients diagnosed with new tumour on surveillance.

Mutation	**Proband**	**Tumour type**	**No. of years following initial tumour**	**Plasma metanephrine**	**Plasma normetanephrine**	**Plasma 3-methoxytyramine**
SDHB	Yes	HNPGL	11	Normal	Normal	Normal
SDHD	Yes	HNPGL	3	Normal	High (1.4xULN)	Normal
SDHD	No	HNPGL	16	Normal	Normal	Normal
SDHD	No	HNPGL	3	Normal	Normal	Normal
SDHD	No	Mediastinal paraganglioma and liver metastasis	7	Normal	Normal	High (1.2xULN)
SDHD	No	HNPGL and abdominal PGL	1	Normal	Normal	High (1.35xULN)
SDHD	No	Abdominal PGL	>15	Normal	Normal	N/A

HNPGL = head and neck paraganglioma

PGL = paraganglioma

ULN = upper limit of normal

N/A = not available