SDHA mutated paragangliomas may be at high risk of metastasis

Dear Editor,

We report the clinical outcomes of eleven patients with succinate dehydrogenase subunit A (*SDHA*) germline mutations from three UK tertiary referral centres to highlight a more diverse and expanding clinical spectrum of associated phenotypes. We suggest that *SDHA* paraganglioma-related disease is not a low-risk condition as first described. Of our six index cases, two developed metastatic disease and a further one had local vascular invasion. One patient developed multiple metachronous disease. Therefore, we believe these patients, like those with *SDHB* and *SDHD* mutations, should be part of a surveillance programme.

Paraganglioma (PGL)-associated mutations in *SDHA* have only been reported in a small number of patients worldwide. There is controversy over the necessity for surveillance screening in these patients, compared to *SDHB* and *SDHD*, as penetrance is thought to be lower (Benn *et al.* 2015) and variants exist with uncertain pathogenicity. Initial reports associated *SDHA* with autosomal recessive causes of juvenile encephalopathy (Leigh syndrome) (Bourgeron *et al.* 1995) and homozygous mutations in *SDHA* cause severe neurological dysfunction and cardiomyopathy (Renkema *et al.* 2015). *SDHA* mutations have now been associated with phaeochromocytoma and paraganglioma (PPGL) formation in an autosomal dominant manner. *SDHA* mutations account for only 3% of cases of familial PGL cases, with presumed low penetrance (Korpershoek *et al.* 2011) and therefore very little data on clinical features of *SDHA*-related PPGL exist.

Six index cases were originally diagnosed between 1973 and 2011 and had histologically proven PPGL, who subsequently underwent genetic testing during the course of their follow-up and were confirmed to have an underlying *SDHA* germline mutation. We performed a retrospective analysis of their notes and describe their clinical outcomes. From these six index cases, cascade genetic testing occurred and identified five further asymptomatic carriers of *SDHA* mutations. All patients are now being followed up in specialised endocrine clinics and are undergoing annual screening, including annual clinical and biochemical assessment and cross-sectional imaging, although the frequency and modality of imaging differs between centres. To predict the pathogenicity of the DNA variants, the missense variants were investigated *in silico* using PloyPhen2 and SIFT.

Table 1 provides a detailed summary of the patients described.

The six index patients originally presented were aged 18, 34, 36, 46, 47 and 68 years. Five patients presented with a single lesion at diagnosis: intrathyroidal PGL, mediastinal PGL, phaeochromocytoma and two extra-adrenal PGLs. One patient (patient 3) presented with two synchronous lesions: she had a 3-methoxytyramine (3MT)-secreting carotid body tumour and a noradrenaline-secreting thoracic PGL. All patients underwent surgical resection of the primary tumours. Two patients developed recurrence in the surgical bed and both patients went on to develop metastatic disease 16 and 37 years later (patients 8 and 9). One of these two patients (patient 8) also developed an additional five metachronous lesions 7–10 years after original diagnosis. These two cases are described in more detail.

Patient 8 presented aged 46 years with headaches and malignant hypertension (210/130 mmHg). Urinary noradrenaline was very raised (Table 1) and imaging confirmed a 5 cm para-adrenal PGL, which was subsequently resected. He developed a symptomatic recurrence one year later, which was surgically resected. Eight years after his original diagnosis, he presented with symptoms of catecholamine excess and four new lesions were identified and resected. On surveillance imaging three years later, a new non-secretory lesion was identified. Surgical resection was undertaken one year subsequently due to increasing PGL size and plasma catecholamine levels. He remained well with no evidence of further disease on imaging until five years later when rising noradrenaline levels were noted and uptake in the left adrenal bed and in the vertebral body of L4 was

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Table 1 The demographic details of each patient showing the mutation type, specific tumour details, treatment given and other clinical information.

Pt. No.	Mutation	Age at diagnosis/ starting screening (years) and gender	Diagnosis	Years of original diagnosis	Size (mm)	Treatment	Biochemistry	Other clinical information	PMH, FH
1 Index	c.91C>T exon 2	36F	Intrathyroidal PGL			Open surgical resection and radiotherapy 60 Gy 30#	Not tested pre-operatively	Initially thought to be chemodectoma of thyroid	
		50	Right breast DCIS	14	100	B/L mastectomies and right axillary clearance	Negative	BRCA1/2 negative	
		52	DCIS right axilla	16	16	25/3/2014 – redo axillary clearance and radiotherapy 50 Gy in 25#	Negative		
2 Carrier		22F	No tumours				Negative		
3 Index	c.1338delA exon 10	28F	Neck mass biopsied					Biopsied and told indeterminate lesion	
			MI					Troponin positive	MI, depression, IBS
		47	Mediastinal PGL		56	MIBG and open surgical resection	Urine NMA 15,607 nmol/day	Trop –ve, had angio – unobstructed	
							Urine 3MT 17,169 nmol/day	Biopsy showed brown fat only	
		47	Right carotid body tumour		35	Embolisation, followed by open surgical resection	Urine NMA 1159 nmol/day	Urine NMA normalised following resection of mediastinal lesion	
							Urine 3MT 6837 nmol/day		
4 Carrier		21F	No tumour				Negative		
5 Carrier		20F	No tumour				Negative		
6 Carrier		25M	No tumour				Negative		
7 Index	c.1753C>T exon 7	34F	Mediastinal PGL			Open surgical resection		Initially diagnosed as NHL – underwent 6 months chemo. Left vocal cord palsy after 1st operation	
			PHPT	30	15	Open surgical resection	Negative	SDH immunostain positive	Strong FH of breast carcinoma
8 Index	c.923G>T exon 8	46M	Left para-adrenal PGL	1993	50	Open surgical resection	Positive		1 son awaiting genetic testing – no tumours
		47	Recurrence aortoiliac junction	1	70	Open surgical resection		Urethral stricture requiring nephrectomy	
		55	PGL above bifurcation between IVC and aorta	8	15	All 4 open surgical resection	Urine NA 4080 nmol/day Plasma NA 41.9 nmol/L		
		55	Left retro aortic PGL	8	20				
		55	Left para-aortic region above diaphragm	8	12				
		55	Retrocaval PGL	8.5	34		Plasma NA >70 nmol/L		
							Plasma AD 3.04 nmol/L		
		58	Left retrocrural region	11	24		Negative		
		59	Increase in size of above PGL	12	30	Open surgical resection	Urine NA 880 nmol/day		
							Urine AD negative		
		63	Lesion in left adrenal bed	16	14		Urine NA 1309 nmol/day	MIBG negative	
		63	L4 metastatic deposit	16	16	EBRT 50 Gy 25# over 35 days			
		64	L4 deposit increase in size	17	30	Cyber-knife 14 Gy 1#		Progressive spine lesion	
9 Index	c.91C>T exon 2	18F	Right PCC			Open surgical resection + nephrectomy			Perforated peptic ulcer, aged 14 years Chronic autoimmune hepatitis, aged 21 years
		54	Recurrent right PCC in surgical bed	36			Urine NA 1030 nmol/day Urine/plasma AD negative		Steroid induced diabetes mellitus
			Metastatic disease to sacrum, T10+ para-aortic LN	36	24 (LN)	Octreotide LAR monthly	Plasma NMA 1.57 nmol/L		Grandmother – breast carcinoma
		55	Left adrenal nodule Paracaval LN	37 37	14 15	Laparoscopicadrenalectomy and LN clearance	Plasma NMA 2.31 nmol/L	MIBG avid	Father – hypertensive stroke

10 Carrier	c.91C>T	29F	No tumour					Negative				
11 Index	c.91 C>T exon 2	68M	Retroperitoneal (aortic bifurcation) PGL		110	Open surgical resection and pre-operative embolisation		Negative		Metastatic potential (vascular invasion)		Prostate carcinoma
		73	Macroprolactinoma		5	13	Cabergoline			Tumour reduction demonstrated on MRI after 6 months treatment		Sister has breast carcinoma Mother – bladder carcinoma Daughter – macroprolactinoma 3 children awaiting genetic testing – no tumours

3MT, 3-methoxytyramine (urine <2500 nmol/day); AD, adrenaline (urine <144 nmol/day, plasma <4 nmol/L); LN, lymph nodes; MA, metadrenaline (urine <2000 nmol/day, plasma <5.10 pmol/L); NA, noradrenaline (normal range urine <814 nmol/day, plasma <5.67 nmol/L); NHL, non-Hodgkins lymphoma; NMA, normetadrenaline (urine <4440 nmol/day, plasma <1180 pmol/L); PCC, phaeochromocytoma; PGL, paraganglioma; PHPT, primary hyperparathyroidism.

demonstrated on FDG PET. A bone biopsy confirmed a metastatic deposit and he underwent external beam radiotherapy (50 Gy 25#), followed by cyber-knife radiotherapy (14 Gy 1#) when this lesion doubled in size. His metanephrines have remained normal since his radiotherapy six years ago, and the bone lesions have stabilised in size.

Patient 9 presented aged 18 years with a symptomatic phaeochromocytoma in 1973. She underwent an adrenalectomy and nephrectomy, and remained asymptomatic for 36 years until experiencing episodes of hot flushes, hypertension and haematuria. Imaging revealed a lesion in the para-aortic region and metanephrine levels were raised (Table 1). ^{68}Ga DOTATATE PET scan identified metastatic disease in the sacrum and T10 vertebral body with lymph node involvement and she was commenced on Octreotide LAR 30 mg monthly. Most recent surveillance imaging (MRI and MIBG) shows no disease progression, and she has normal biochemistry.

The five asymptomatic carriers identified through cascade screening have not had any tumours identified in surveillance imaging and all have negative biochemistry. They have had a total of 17 years of surveillance. Additionally, patient 8 has one adult son who has been undergoing clinical and radiological screening with no tumours identified to date, but has not yet undergone genetic testing. Patient 11 has three children and one sister (who has breast carcinoma) who are awaiting genetic testing, but have no history of PPGL.

The six index cases described here presented with a variety of clinical manifestations extending the known phenotypic spectrum in *SDHA* disease.

Little is known about PGL-associated disease in carriers of an *SDHA* mutation. Table 2 shows the 26 cases reported in the literature with 14 different *SDHA* mutations (Burnichon *et al.* 2010, 2012, Korpershoek *et al.* 2011, Dwight *et al.* 2013, Welander *et al.* 2013, Papathomas *et al.* 2015, von Dobschuetz *et al.* 2015, Casey *et al.* 2017). These patients presented aged 12–62 years. Unlike in *SDHB* and *SDHD*, in the described combined cases, there is no obvious predilection to any specific body site.

PGLs occurring in the thyroid gland are extremely rare. A recent evaluation of the ENSAT registry identified only five cases of thyroid PGL (prevalence 0.5%). Four of these patients were subsequently found to have *SDH* germline mutations (von Dobschuetz *et al.* 2015). Interestingly, two of these four patients carried a *SDHA* mutation, but both

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Table 2 Details of the 26 patients with *SDHA* mutations who developed phaeochromocytoma or paraganglioma, previously reported in the literature.

Reference	*SDHA* mutation	Age (years)	Gender	Clinical presentation
Burnichon *et al.* (2010)	c.1765C>T	32	F	Abdominal PGL
Korpershoek *et al.* (2011)	c.91C>T	48	F	Phaeochromocytoma
		41	M	Bladder PGL with local LN spread
		55	F	Thoracic PGL
		33	F	Vagal PGL
		45	M	CBT
		27	M	Abdominal PGL
Welander *et al.* (2013)	c.223C>T	20	F	Abdominal PGL
Dwight *et al.* (2013)	c.1873C>T	46	F	CBT*
von Dobschuetz *et al.* (2015)	c.394T>C	36	F	Thyroid PGL
	c.1799G>A	37	F	Thyroid PGL
Papathomas *et al.* (2015)	c.1534C>T	23	M	Abdo PGL with malignant LN spread
	c.1766G>A	24	M	Phaeochromocytoma
	c.1765C>T	31	F	Abdo PGL
	c.1753C>T	19	F	Phaeochromocytoma
Casey *et al.* (2017)	c.91C>T	56	M	HNPGL
		33	M	Abdo PGL
		45	M	Abdo PGL
		15	F	PCC
	c.923C>T	43	M	Malignant thoracic PGL
		52	M	Bilateral HNPGL+PCC
	c.1753C>T	34	F	PGL
	c.1273G>A	62	M	Abdo PGL+PCC
	c.133G>A	36	M	Thoracic PGL
	c.136A>G	12	F	Abdo PGL
	c.1338delA	48	F	HNPGL

*Son had a pituitary adenoma.
Abdo, abdominal; CBT, carotid body tumour; HNPGL, head and neck paraganglioma; LN, lymph node; PCC, phaeochromocytoma; PGL, paraganglioma.

mutations were different to the one our patient carried. Similar to our patient, both were female and presented at similar ages (36 and 37 years), with no family history of PGL.

Recognised associations of *SDHA* mutations include gastrointestinal stromal tumours (GIST) (Papathomas *et al.* 2014) and *SDHA* variants have been described in three patients with pituitary adenomas, although SDHA deficiency was only demonstrated in one tumour by immunohistochemistry (IHC) and loss of heterozygosity (LoH) was not demonstrated (Dwight *et al.* 2013, O'Toole *et al.* 2015). To date, only one case of *SDHA*-deficient renal carcinoma has been reported (Yakirevich *et al.* 2015). Additional findings in our cohort included: bilateral breast carcinoma 14 years after PGL diagnosis (patient 1). Patient 11's PGL was discovered incidentally during staging imaging for his prostate carcinoma, and he was subsequently found to have a macroprolactinoma. His daughter also has a microprolactinoma, although is awaiting genetic testing.

Two out of six of our index patients have developed distant metastatic PPGLs. Time to disseminated disease was 16 and 37 years, and occurred following development of recurrent disease, suggesting a long duration of disease before onset of metastases.

A cautious approach must be used before ascribing definite pathogenicity to newly identified mutations. Table 3 combines the evidence that suggests pathogenicity for each of the described mutations. SDHA immunohistochemistry (IHC) was performed on tissue that was available. One sample (patient 8) demonstrated positive SDHA IHC. It has previously been described that SDHA IHC maybe positive in the presence of a definitive mutation, but on rare occasions, there is disparity between molecular genetic aberrations of a tumour suppressor gene and retention of protein expression (Miettinen *et al.* 2013, Evenepoel *et al.* 2015, Papathomas *et al.* 2015). It has been hypothesised that this may be due to the second hit in the *SDHx* gene in the tumour tissue resulting in an inactive SDH complex with preservation of antigenicity (Papathomas *et al.* 2015).

The mutation carried by this patient (patient 8) had the most aggressive phenotype in our cohort. A recently reported metastatic case carried the same *SDHA* mutation (Casey *et al.* 2017). Casey and coworkers went on to

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Table 3 Investigations of pathogenicity for mutation variants.

Pt. No.	Mutation	Type	*In silico* analysis	Immunochemistry analysis	EXAC database population frequency	Published reports on pathogenicity
1	c.91C>T exon 2	Frameshift	ExPASy translate tool – premature stop codon resulting in a truncated protein	PGL tissue unavailable for analysis. Breast tissue immunopositive for SDHA and SDHB	0.2 per 1000 individuals (South Asian population). 0.3% of Dutch controls	Korpershoek *et al.* (2011) Casey *et al.* (2017)
3	c.1338delA exon 10	Frameshift	ExPASy translate tool: premature stop codon resulting in a truncated protein	PGL immunonegative for SDHA	<1 per 1000 individuals 1.499E-05	Casey *et al.* (2017)
7	c.1753C>T exon 7	Missense	PolyPhen2 programme with a score of 1.000 (damaging)	PGL immunonegative for SDHA	<1 per 1000 individuals	Korpershoek *et al.* (2011)
			SIFT programme, with a score of 0.00 (deleterious)	Parathyroid tissue immunopositive for SDHA	0.0000248	Casey *et al.* (2017) Papathomas *et al.* (2015)
8	c.923C>T exon 8	Missense	PolyPhen2 programme with a score of 1.000 (damaging)	PGL tissue unavailable for analysis	Not reported	Casey *et al.* (2017)
			SIFT programme, with a score of 0.00 (deleterious)	Tissue specimen from bone biopsy immunopositive for SDHA and heterogenous SDHB immunochemistry. Not enough tissue available for LoH analysis		
9	c.91C>T exon 2	Frameshift	ExPASY translate tool – premature stop codon resulting in a truncated protein	PGL tissue unavailable for analysis	0.2 per 1000 individuals	Korpershoek *et al.* (2011) Casey *et al.* (2017)
11	c.91C>T exon 2	Frameshift	ExPASY translate tool – premature stop codon resulting in a truncated protein	PGL tissue unavailable for analysis	0.2 per 1000 individuals	Korpershoek *et al* (2011) Casey *et al.* (2017)

In silico analyses were performed on each missense mutation using programmes SIFT and PolyPhen2 in order to predict pathogenicity of the DNA variants. The mutations were classified as probably damaging by PolyPhen2 programme with a score of 1.000 (scores 0.0–1.00, with the most damaging at 1.000), (sensitivity 0.00; specificity 1.00) and classified as deleterious by SIFT programme with a score of 0.00 (scores 0.0–1.0, with the most damaging at 0.0). Column five shows immunohistochemistry analysis of tissue (where available). Column six shows population frequency from the EXAC database and references for where mutations have been previously published are shown in the last column.

perform structural analysis of the effects of this mutation (using DUET scoring) and predicted that it would cause mild destabilisation of the protein promoter region and part of the substrate-binding region and therefore likely to affect protein stability. This may explain the positive protein expression seen in patient 8.

The patients we report highlight a more diverse and expanding clinical spectrum of *SDHA*-associated phenotypes. Of our six index cases, two developed metastatic disease and a further one had local vascular invasion. There are three previous reported metastatic cases in the literature (Table 2) with three different *SDHA* mutations. Interestingly, the two metastatic cases we report each carry one of these mutations (Korpershoek *et al.* 2011, Papathomas *et al.* 2015, Casey *et al.* 2017). With five of the 32 reported cases developing metastatic disease, we suggest that *SDHA*-related disease is therefore not seen as a low-risk condition.

We believe, with the current uncertainty about pathogenicity and penetrance, these patients should be part of a surveillance programme to monitor for metachronous and metastatic disease. Very few familial

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cases have been reported and none of our asymptomatic carriers have developed tumours. This raises questions about cascade genetic screening and subsequent clinical surveillance. However, given the recognition of aggressive behaviour in *SDHA*, we believe these relatives should be monitored in surveillance programmes until the full phenotype and penetrance are established.

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