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ORIGINAL ARTICLE

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SDHx-related pheochromocytoma/paraganglioma – genetic, clinical, and treatment outcomes in a series of 30 patients from a single center

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Abstract

Purpose Germline mutations in the four genes that encode the succinate dehydrogenase complex (*SDHx*) are a risk factor for developing pheochromocytomas and/or paragangliomas. The precise genotype–phenotype correlations are still uncertain and the most common *SDHx* genetic defects in the Portuguese population are poorly described. The objectives of our study were to characterize the genetic alterations, clinical features, and treatment outcomes of a cohort of *SDHx*-related pheochromocytomas and/or paragangliomas patients.

Methods Single center, retrospective analysis based on the presence of a *SDHx* mutation in cases diagnosed from 1986 until October 2016.

Results Thirty cases were included. The mean age at diagnosis was 36.8 years (±15.4 years) and 53.3% were females. Remission was observed in 33.3% and stable disease (including partial responses) in 53.0%. *SDHC* and *SDHD* patients were prone to develop single and multiple head and neck paragangliomas, respectively. *SDHB* patients carried an increased risk of malignancy. Deletions in *SDHB* exon-1 and in *SDHD* exon-4 were the most common genetic findings. *SDHB* patients and head and neck paragangliomas had the worse prognosis, the former related to malignancy, and the latter to cranial nerve deficits, unresectable disease, and multimodality interventions. Peptide receptor radionuclide therapy and radioactive iodine MIBG therapy proved to be ineffective. Radiotherapy represented a good alternative in unresectable head and neck paragangliomas and in bone metastases.

Conclusion This single center study is the most complete Portuguese cohort in the literature and helps to understand the behavior of tumors based on their genotype and anatomical location.

Keywords Paraganglioma · Pheochromocytoma · Succinate Dehydrogenase · Germ-line Mutation · Adrenal Glands · Paraganglia

Introduction

Paragangliomas and pheochromocytomas (PPGLs) are neuroendocrine tumors derived from the parasympathetic or sympathetic nervous system. They can be either functional or non-functional. Pheochromocytomas (Pheo) arise from the adrenal medulla and paragangliomas (PGLs) from the extra-adrenal paraganglia [1–5]. PGLs arising from head and neck (HNPGL) are usually derived from parasympathetic paraganglia and are non-functional. This contrasts with thoraco-abdominal-pelvic PGLs (TAPPGL), that are usually derived from the sympathetic ganglia, and together with Pheo, are typically functional active, producing an excess of catecholamines [1, 5–7].

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PPGLs can be either sporadic or familial. Germline mutations in predisposition genes are now found in up to 40% of all PPGLs [1, 7]. Familial cases may be associated with specific syndromes such as multiple endocrine neoplasias (MEN) type 2 (*RET* mutation), Von Hippel Lindau (VHL) (*VHL* mutation), neurofibromatosis type 1 (NF1) (*NF1* mutation) and familial PGL/pheochromocytoma [mutations in succinate dehydrogenase complex (*SDHx*)] [2, 6, 8]. Mutations in other genes such as those encoding fumarate hydratase (FH), transmembrane protein 127 (TMEM127) and MYC-associated factor X (MAX) are also associated with familial PPGLs [8–11]. Novel genes are continuously being added to this list.

Germline mutations in *SDHx* are responsible for up to 30% of the cases [2, 7, 12, 13]. Four distinct syndromes – PGL1–4 – are related to mutations in the different S*DHx* subunits, but the precise genotype–phenotype correlation is still uncertain [2, 3]. The most common *SDHx* genetic defects in the Portuguese population are not completely described.

Despite the majority of PPGLs cases being benign, 10–20% of the cases can be malignant. There are some germline variants (like those affecting the *SDHB* subunit) and particular anatomic locations (such as TAPPGLs) that are linked to malignancy [1, 4, 13–15].

Our general objective was to characterize the clinical features and genotype-phenotype associations in a group of *SDHx*-mutated PPGL patients. Our specific objectives were to study the most frequent genetic alterations, to characterize the clinical features and to study treatment outcomes in *SDHx*-mutated PPGL patients.

Material and methods

A retrospective analysis of all germline *SDHx*-mutated PPGL cases followed in our center was performed. The cases were retrieved from *SDHx* genetic tests performed at our institution between 1986 and October 2016. Genetic tests were performed using Sanger sequencing or next-generation sequencing (NGS) for the detection of missense and indel mutations, and multiplex ligation-probe amplification (MLPA) for the detection of large deletions and insertions.

Information was gathered based on clinical records, laboratory results, imaging exams, pathology reports, and genetic tests results.

Confidentiality was kept throughout the study and all patients or representatives signed informed consent. This study was approved by our center's ethics committee and conducted in accordance with the Declaration of Helsinki. The authors have followed the protocols of their center on the publication of data.

Clinical status and treatment outcomes at last follow-up visit were established using the Response Evaluation Criteria in Solid Tumors (RECIST). Excessive catecholamine secretion was assumed when more than two-fold of total and/or fractioned urinary metanephrines, and/or total and/or fractioned urinary catecholamines and/or urinary vanillylmandelic acid was observed. Multifocality and not metastases was assumed when tumors were located at usual PGL sites. Malignancy or metastatic potential was defined by the presence of metastases or a gross invasion of adjacent structures.

Data management and statistical analysis were performed using Excel Software Microsoft® and SPSS 23 IBM®. Categorical variables were compared using Chi-square and Exact F statistic tests. Numeric variables were compared using the Mann–Whitney statistic test.

Results

Thirty-one cases were first investigated but one case was excluded due to an early loss to follow-up. Therefore, 30 patients were included in the study for further analysis.

Clinical and genetic characterization

Clinical and genetic characteristics of the PPGLs patients included in the study are presented in Table 1.

At presentation, 96.7% (29/30) of the patients had symptoms, mainly hypertension or a cervical mass.

Excessive catecholamine secretion was detected in 33.3% (10/30) of the patients, unknown or undetermined in 10% (3/30) and doubtful in 6.7% (2/30). Catecholamine secretion was within the normal range in 50% (15/30).

There was no difference between age at diagnosis according to the affected *SDHx* subunit ($p = 0.15$).

Anatomical distribution

Anatomical distribution was assessed in 86.7% ($n = 26$) of the cases by computed tomography (CT) scan, in 63.3% ($n = 19$) by magnetic resonance imaging (MRI) and in 50% ($n = 15$) by both imaging modalities. All patients that performed MRI had HNPGL, except for two who had abdominal PGL (one was a 15 years-old male and the other a female in reproductive age). Octreoscan was performed in 50% ($n = 15$) of the patients, metaiodobenzylguanidine (MIBG) scan in 30% ($n = 9$), 68Gallium-DOTANOC positron emission tomography/computed tomography

Table 1 Clinical and genetic characteristics of PPGLs patients

	Total	*SDHB*	*SDHC*	*SDHD*	*p*
Number % (*n*)	100 (30)	60 (18)	10 (3)	30 (9)	
Gender (M/F) % (*n*)	46.7/53.3 (14/16)	50/50 (9/9)	33.3/66.7 (1/2)	33.3/66.7 (3/6)	0.860
Age at diagnosis (years)					
Mean ± SD	36.1 ± 16.0	34.3 ± 18.5	52.3 ± 10.6	34.3 ± 8.3	0.150
Range	4–71	4–71	41–62	25–47	
Follow-up time (months)					
Median (IQR)	89.5 (116)	96.5 (124.8)	70	83 (106)	0.447
Range	2–365	11–365	27–185	2–173	
Common presenting symptoms % (*n*)					
Hypertension	43.3 (13)	55.6 (10)	0 (0)	33.3 (3)	0.163
Cervical mass	36.7 (11)	33.3 (6)	66.7 (2)	33.3 (3)	0.536
Neurological deficit	23.3 (7)	22.2 (4)	33.3 (1)	22.2 (2)	0.914
Paroxysm	23.3 (7)	33.3 (6)	0 (0)	11.1 (1)	0.275
Pain	20.0 (6)	11.1 (2)	0 (0)	44.4 (4)	0.089
Incidental	3.3 (1)	5.6 (1)	0 (0)	0 (0)	0.717
Size (mm)					
Median (IQR)	47.5 (32)	52.5 (37.3)	60	41.5 (22)	0.417
Range	14–160	14–160	52–70	24–110	
Location of tumor *n**					
HNPGL	21	9	3	9	0.016¥
TAPPGL	7	6	0	1	0.275
Adrenal	5	5	0	0	0.145
Catecolamine secretion % (*n*)					
High	33.3 (10)	50. 0 (9)	0 (0)	11.1 (1)	0.062
Normal	50.0 (15)	38.9 (7)	33.3 (1)	77.8 (7)	0.145
Doubtful	6.7 (2)	5.6 (1)	33.3 (1)	0 (0)	0.137
Unknown/Undetermined	10.0 (3)	5.6 (1)	33.3 (1)	11.1 (1)	0.342

M male, *F* female, *SD* standard deviation, *IQR* interquartile range, *SDHx* succinate dehydrogenase complex, *HNPGL* head and neck paraganglioma, *TAPPGL* thoraco-abdominal-pelvic paraganglioma

*Some patients had tumors in more than one location

¥Statistical significance was considered when $p < 0.05$

Table 2 Sensitivity of nuclear medicine exams in evaluating primary lesions

Nuclear medicine method	Sensitivity in primary lesions (positive/tested)	Comments
^{111}In-Octreoscan	93.3% (14/15)	The false negative case was an HNPGL
^{68}Ga-DOTANOC	100% (8/8)	
^{123}MIBG	50% (5/10)	All false negative cases were HNPGL
^{18}FDG-PET	100% (2/2)	Both cases were malignant PPGLs

^{111}In indium-111, *HNPGL* head and neck paraganglioma, *^{68}Ga* gallium-68, *^{123}MIBG* metaiodobenzylguanidine, *^{18}FDG-PET* 18F-fluoro-deoxy-glucose positron emission tomography, *PPGLs* paragangliomas and pheochromocytomas

(68Ga-DOTANOC PET/CT) in 26.7% ($n = 8$) and 18F-fluoro-deoxy-glucose PET/CT (FDG-PET/CT) in 6.7% ($n = 2$).

Table 2 shows the sensitivity of each nuclear medicine exam in evaluating primary lesions.

As for the HNPGL, 57% (12/21) of the patients had a carotid PGL, 33% (7/21) a jugulotympanic PGL and 29% (6/21) a vagal PGL (some patients had HNPGL in more than one location). The majority of TAPPGLs were in the abdomen in 57.1% (4/7), followed by mediastinum in 28.6% (2/7) and pelvis in 14.3% (1/7).

Table 3 SDHx distribution of PPGL cases by anatomical location, catecholamine secretion, malignancy, and multifocality

SDHx	*B*	*D*	*C*
Number	18	9	3
Multiple	3¥	5¥	
Malignant	8□	1□	
Catecholamine secretion	9*	1*	
HNPGL	9	9	3
Multiple	1	5	
Malignant	3	1	
Catecholamine secretion	2	1	
TAPPGL	6	1	
Multiple	2	1	
Malignant	4	1	
Catecholamine secretion	5	1	
Pheochromocytoma	5		
Bilateral	0		
Malignant	3		
Catecholamine secretion	4		

Note: Digits in cells refer to the number of patients affected by each lesion type. Empty cells mean zero. Some patients had tumors in more than one location

SDHx succinate dehydrogenase complex, *HNPGL* head and neck paraganglioma, *TAPPGL* thoraco-abdominal-pelvic paraganglioma

¥Exact F test = 0.054

□Exact F test = 0.062

*Exact F test = 0.057

Statistical significance was considered when $p < 0.05$

Concerning multifocality, 16.7% (3/18) of *SDHB*, 55.6% (5/9) of *SDHD* and 0% (0/3) of *SDHC* affected patients showed a multifocal PPGL.

Table 3 shows an overview of the *SDHx* distribution of PPGL cases by anatomical site, catecholamine secretion, malignancy, and multifocality rates.

Malignancy

From all patients studied, 30% (9/30) were considered malignant. HNPLGs were malignant in 19% (4/21), TAPPGLs in 83% (5/6) and Pheo in 60% (3/5) of the cases. Metastatic *SDHB* patients involved bone in 75% (6/8), lung in 62.5% (5/8), liver in 50% (4/8), lymph nodes in 37.5% (3/8) and kidney in 12.5% (1/8) of the cases. As for the metastatic *SDHD* patient, he had bone, lung and liver metastases. Two patients with bone metastases developed pathological fractures and spinal cord compression. For metastases control, surgery was performed in two patients and radiotherapy in four.

Genetic findings

A positive family history of *SDHx*-related PPGL was present in 20% (6/30) of the patients.

The most frequent genetic findings in this population were *SDHB* exon-1 deletions, affecting 26.7% (8/30) patients, followed by *SDHD* exon-4 deletions, affecting 16.7% (5/30) patients. No direct familial relationship was found between PPGL patients.

All the identified mutations are listed in Table 4.

Associated tumors

Five patients had benign thyroid nodules (two with *SDHB* germline mutations and three with *SDHD)*, two patients had papillary thyroid cancer (one case was *SDHB* germline mutated and also had intestinal polyposis—and the other had a *SDHD* germline mutation), one had breast cancer and multiple myeloma (*SDHB* mutated), one had adrenal adenoma (*SDHC* germline mutation) and one had a uterine myoma (*SDHB* mutated).

Treatment outcomes

Surgery was performed in 80% (24/30) of the patients. Seven primary PGL lesions from six patients were not submitted to surgery (five carotid HNPGL, one thoracic and one pelvic PGL). One patient with a nonfunctioning bilateral carotid HNPGL was not submitted to surgery or any other intervention and was selected for watchful waiting. He showed stable disease during follow-up. There was a complete resection (R0) rate in 60% (3/5) of the Pheo, 50% (3/6) of the TAPPGL and in 33.3% (7/21) of the HNPGL. After R0 surgeries all patients achieved remission, except two, who were metastatic *ab initio*. All patients with R1 and R2 surgeries have persistence of disease except one who had a R1 surgery and is in remission.

Pre-surgical vascular embolization was performed in 43.3% (13/30) of the patients (11 HNPGL, one TAPPGL and in hepatic metastases of one patient), with a success rate (defined by post-embolization angiographic vascularization pattern) of 46.2% (6/13).

As for reoperations, 23.3% (7/30) of patients needed more than one surgery and 10% (3/30) of patients needed three surgeries. The causes for multiple surgeries were multiple PGLs in three patients, local relapses in three (all *SDHB* mutated) and distant metastases in the other three.

Radiotherapy was used in 40% (12/30) of the patients, intensity-modulated radiotherapy (IMRT) in 36.7% (11/30) and Gamma Knife in 3.3% (1/30). Radiotherapy was used in eight HNPGL, five bone metastases, one pelvic PGL and one lung metastasis. All lesions treated with radiotherapy showed stability or partial response, and none progressed during a median follow-up of 26 months (minimum 7.6; maximum 125).

Two patients were treated with 177Lutethium peptide receptor radionuclide therapy (177-Lu-PRRT) and other

Table 4 Germline mutations of *SDHB, SDHC*, and *SDHD* found among the 30 PPGL patients studied

Gene	Exon/Intron	Patient number	Variant description	Consequence	Clinical presentation
SDHB	Exon 1 [21]	P3	c.8 C > G (p.Ala3Gly)	Missense (clinical meaning not known; some evidence that might be benign in PPGL)	F, 32 years, Pheo in remission, PTC and intestinal polyposis
	Exon 1 [7, 22]	P10	c.49 A > G (p.Thr17Ala)	Missense	F, 26 years, progressive, metastatic, non-functional HNPGL, breast cancer and multiple myeloma
	Exon 1 [16, 22, 23]	P1 P6 P8 P9 P11 P13 P29 P30	NG_012340.1 (NM_003000.2): c.(?_1-173)_(1-87_109)del	Deletion of exon 1*	F, 24 years, Pheo with PR F, 20 years, persistent, functional abdominal PGL M, 15 years, functional abdominal PGL, in remission F, 46 years, non-functional HNPGL with PR, thyroid nodule M, 45 years, non-functional HNPGL with PR M, 13 years, non-functional HNPGL, in remission F, 45 years, non-functional HNPGL in remission F, 67 years, metastatic thoracic PGL, uterine myoma
	Exon 2 [7, 22]	P2 P7	c.127 G > C (p.Ala43Pro)	Missense	M, 8 years, persistent malignant Pheo M, 23 years, functional, metastatic abdominal PGL
	Exon 3 [7, 23]	P4	c.268 C > T (p.Arg90X)	Stop gain	M, 29 years, persistent, metastatic Pheo and pelvic PGL
	Exon 4 [7, 23]	P24	IVS4 + 1 G > A	Splice site donor (aberrant splicing)	F, 71 years, persistent non-functional HNPGL, thyroid nodule
	Exon 7 [7, 22, 23]	P5	c.725 G > A (p.Arg242His)	Missense	M, 35 years, progressive, metastatic Pheo and thoracic PGL
	Exon 7 [7, 23]	P12	c.761 C > T (p.Pro254Leu)	Missense	F, 56 years, non-functional HNPGL in remission
	Exon 7 [22]	P14	c.721 T > G (pTyr241Asp)	Missense	M, 29 years, non-functional, metastatic, multiple and progressive HNPGL
	Intron 4	P23	IVS4-14insCTT	Splice site acceptor (might result in aberrant splicing; never described previously, clinical meaning unknown)	M, 40 years, functional HNPGL in remission
SDHC	Exon 1 [7, 22, 23]	P17 P16	c.2 T > A (p.Met1?)	Start loss	F, 54 years, non-functional HNPGL with PR M, 62 years, non-functional HNPGL in remission and adrenal adenoma
	Intron 2	P15	IVS2 + 27	(Never described previously, clinical meaning unknown)	F, 41 years, non-functional HNPGL in remission
SDHD	Exon 1 [7]	P19	c.15 G > A (p.Trp5X)	Stop gain	F, 34 years, persistent, non-functional, multiple HNPGL, thyroid nodule
	Exon 2 [24]	P21	c.158 C > T (p.Pro53Leu)	Missense (clinical meaning unknown)	F, 47 years, non-functional HNPGL in remission, PTC
	Exon 3 [23]	P28	c.274 G > T (p.Asp92Tyr)	Missense	M, 28 years, metastatic, functional and multiple HNPGL and abdominal PGL in progression
	Exon 4 [22, 23]	P18	c.411delT (p.Leu139PhefsX29)	Frameshift	M, 19 years, non-functional, persistent and multiple HNPGL

Table 4 (continued)

Gene	Exon/Intron	Patient number	Variant description	Consequence	Clinical presentation
		P25			M, 37 years, non-functional HNPGL with PR
		P26			F, 32 years, non-functional HNPGL with PR
	Exon 4 [7, 22, 23]	P22	c.341_342delAT (p.Tyr114CysfsX76)	Frameshift	F, 38 years, non-functional HNPGL in remission, thyroid nodule
		P27			M, 37 years, non-functional, multiple HNPGL with PR
	Exon 4 [7]	P20	IVS3-2A > C	Splice site acceptor (aberrant splicing)	F, 37 years, non-functional, multiple HNPGL with PR, thyroid nodule

Note: P1, P4, and P16 had also an SDHC variant in intron 2 IVS2+27 which has never been described previously and the clinical meaning is unknown

SDHx succinate dehydrogenase complex, *cDNA* complementary DNA, *P* patient; *PPGL* paragangliomas and pheochromocytomas, *F* female, *Pheo* pheochromocytoma, *PTC* papillary thyroid cancer, *HNPGL* head and neck paraganglioma, *PGL* paraganglioma, *M* male, *PR* partial response

*The two probes from the MLPA kit (SALSA®MLPA®Probemix P226-D1 SDH, MRC Holland) that were used to detect alterations in exon 1 of the *SDHB* gene were deleted. One of these probes encompasses 59 bp before exon 1

two patients with 131-MIBG. All these patients had distant metastases and progressed after treatment.

After all treatment modalities, complete remission was observed in 33.3%, stable disease/partial response in 53.3% and disease progression in 13.3% of the patients. During follow-up, one disease-related death occurred, and significant disease and treatment-related morbidities were observed in 66.6% of the cases.

Table 5 shows the correlation between SDHx mutated subunit and treatment outcomes.

The most frequent complication was permanent cranial nerve deficit, found in 13 patients (61.9%) of the HNPGL, from which 9 were surgery-related. Pathologic bone fractures occurred in three patients, and nephrectomy and surgery-related gastrointestinal ischemia/bleeding occurred in two patients each. The other complications found in one patient each were pelvic neurological deficit, chronic bicytopenia related to 131-MIBG treatment, renal vein thrombosis, surgery-related pneumothorax and surgery-related abdominal abscess.

Discussion

In this study, we have characterized the clinical features and genotype-phenotype associations in germline *SDHx*-mutated PPGL cases followed in our center and we describe the largest series of Portuguese patients with *SDHx* related PPGL.

In our cohort, women were more frequently affected than men, which contrasts to previous publications [6, 16]. This difference may be justified by the small number of patients included in these studies.

There was no significant difference between age at diagnosis according to the affected *SDHx* subunit. There is some controversy in the literature regarding this issue since some series [3, 6], but not others [7], report a later onset of disease in *SDHB* mutated patients.

Germline mutations in *SDHD* and *SDHC* were more likely to develop HNPG (all cases in both groups) than *SDHB* affected patients who were more prone to develop TAPPGL and Pheo. This is in accordance with previous publications [2–7, 13, 17].

We also confirmed that patients with *SDHD* mutation are more likely to develop multifocal PPGLs, whereas *SDHB* and *SDHC* mutated patients are more likely to have a unifocal disease [2–4, 7, 13].

The percentage of *SDHB* mutated PPGL with catecholamine secretion was lower than we expected, perhaps because half of them were HNPGL, which are usually non-functional tumors [2]. The routine measurement of 3-Methoxytyramine could have identified additional secretory PGLs, but this test is not routinely available in our center [7, 14].

Table 5 Outcomes of various treatment modalities

Type of treatment	Response			
	Total % (*n*)	*SDHB* % (*n*)	*SDHC* % (*n*)	*SDHD* % (*n*)
All	CR 33.3 (10/30) SD and PR 53.3 (16/30) PD 13.3 (4/30)	CR 33.3 (6/18) SD and PR 50.0 (9/18) PD 16.7 (3/18)	CR 66.7 (2/3) SD and PR 33.3 (1/3)	CR 22.2 (2/9) SD and PR 66.7 (6/9) PD 11.1 (1/9)
Surgery	CR 41.7 (10/24) SD and PR 45.8 (11/24) PD 12.5 (3/24)	CR 35.3 (6/17) SD and PR 47.1 (8/17) PD 17.6 (3/17)	SD and PR 100.0 (3/3)	CR 50.0(2/4) SD and PR 50.0 (2/4)
RT	SD 41.7 (5/12) PR 58.3 (7/12)	SD 66.7 (4/6) PR 33.3 (2/6)	PR 100.0 (2/2)	SD 25.0 (1/4) PR 75.0 (3/4)
177-Lu-PRRT	PD 100 (2/2)	PD 100 (1/1)		PD 100.0 (1/1)
131-MIBG	SD 50.0 (1/2) PD 50.0 (1/2)	SD 50.0 (1/2) PD 50.0 (1/2)		

SDHx succinate dehydrogenase complex, *CR* complete remission, *SD* stable disease, *PR* partial response, *PD* progression of disease; *RT* Radiotherapy, *177-Lu-PRRT* 177Lutethium peptide receptor radionuclide therapy, *131-MIBG* Metaiodobenzylguanidine

SDHC mutated patients had non-functional HNPGL, which is in agreement with other publications [7].

We also confirm that *SDHB* mutations were the most frequently associated with malignancy, followed by *SDHD* mutations [1–7, 13, 14, 17, 18].

In agreement with previous publications, the majority of our patients did not have a family history of PPGL. This can be justified by the incomplete penetrance of these mutations, maternal imprinting of *SDHD* subunit mutations, the possibility of *de novo* mutations and limited access to specialized health care in the ancestral as suggested by others [3, 7].

The most common genetic alteration was a 15678 bp deletion in exon-1 of *SDHB* described in northern Portuguese, Galician and Brazilian patients. This highlights the possible founder effect of this mutation in the Portuguese population [4, 16, 17].

Two patients showed the *SDHB* mutation in exon-2 c.127 G > C (p.Ala43Pro), also described in some French patients [6, 17, 19].

One patient of Dutch origin had a *SDHD* mutation in exon 3 c.274 G > T, p.Asp92Tyr which is a founder mutation in the Netherlands, responsible for 68% of the cases of hereditary PPGLs in that country [2, 6, 17, 20].

It has been described that patients with *SDHx* mutations are prone to develop other tumors, such as gastrointestinal stromal tumors, renal carcinomas or pituitary adenomas which were not observed in our cohort [7, 17]. Two of our patients had a papillary thyroid carcinoma and another a breast cancer and a multiple myeloma.

Despite the elevated malignancy rate documented in our study, there was only one death, which can be justified by the slow progression rate of these tumors [4, 14].

Systemic treatment of PPGLs with MIBG and PRRT were disappointing since the four patients submitted to these treatment modalities showed progressive disease after therapy.

SDHB patients and HNPGLs had the worse prognosis, the first related to malignancy, and the latter to cranial nerve deficits, unresectable disease, and multimodality interventions.

Due to the limited number of cases, it is difficult to retrieve major conclusions about the efficacy of different treatment modalities, when analyzed regarding the subtype of SDHx subunit affected. Nevertheless, it is clear that progressive disease after surgery was more common in *SDHB* patients.

Conclusion

This single center study is the most complete Portuguese cohort in the literature and helps to understand the behavior of tumors based on their genotype and anatomical location.

Data availability

The data that support the findings of this study is available upon request from the corresponding author. Due to privacy restrictions it is not publicly available.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by our center's ethic committee and complies with the Declaration of Helsinki.

Informed consent Confidentiality was kept throughout the study and all patients or representatives signed an informed consent authorizing genetic testing and analysis of the results after full explanation of the purpose and nature of all procedures used.

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