ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Pheochromocytoma and Paraganglioma: Incidence and Comparative Analysis Between Familial and Sporadic Cases in a Portuguese Single Center

Feocromocitoma e Paraganglioma: Incidência e Análise Comparativa entre Casos Familiares e Esporádicos de um Centro Português

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Acta Med Port 2026 May;39(5):344-348 ▪ https://doi.org/10.20344/amp.24192

ABSTRACT

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors, with an estimated incidence rate of two to eight cases per million people, and one of the highest heritability rates among neoplasms, with a genetic cause identified in approximately 40% of cases. This study analyzed cases diagnosed within the referral area of Unidade Local de Saúde de Braga between 2004 and 2024, aiming to estimate incidence, characterize the population, and compare sporadic and familial pheochromocytomas and paragangliomas. A total of 85 patients were identified, corresponding to 87 cases, with an average annual incidence of 5.3 cases per million between 2012 and 2024 and a rising trend over the study period. Genetic testing was performed in 61 patients, revealing 43 sporadic and 20 familial cases. The age at diagnosis was significantly lower in familial cases (43.4 ± 12.7 years; $p < 0.001$). Metastatic disease occurred only in patients with familial pheochromocytomas and paragangliomas, four and six years after diagnosis, while recurrences were observed exclusively in sporadic cases, with a median of seven years after complete remission. These findings highlight the importance of genetic testing and long-term follow-up in patients with pheochromocytoma and paraganglioma, given the risk of metastasis and recurrence even several years after the initial diagnosis.

Keywords: Neuroendocrine Tumors/epidemiology; Paraganglioma/diagnosis; Paraganglioma/epidemiology; Pheochromocytoma/diagnosis; Pheochromocytoma/epidemiology

RESUMO

Os feocromocitomas e paragangliomas são tumores neuroendócrinos raros, com uma incidência estimada entre dois e oito casos por milhão de pessoas, e uma das maiores taxas de hereditabilidade entre as neoplasias com causa genética, identificada em cerca de 40% dos casos. Este estudo analisou os casos diagnosticados na área de referenciação da Unidade Local de Saúde de Braga entre 2004 e 2024, com o objetivo de estimar a incidência, caracterizar a população e comparar feocromocitomas e paragangliomas esporádicos e familiares. Foram identificados 85 doentes (87 casos), com uma incidência média anual de 5,3 casos por milhão entre 2012 e 2024, e tendência crescente ao longo deste período. O estudo genético foi realizado em 61 doentes, tendo revelado 43 casos esporádicos e 20 familiares. A idade no momento do diagnóstico foi significativamente inferior nos casos familiares (43,4 ± 12,7 anos; $p < 0,001$). A metastização ocorreu apenas em doentes com feocromocitomas e paragangliomas familiares, quatro e seis anos após o diagnóstico, enquanto as recidivas ocorreram exclusivamente nos casos esporádicos, com mediana de sete anos após remissão completa. Estes resultados reforçam a importância do estudo genético e do seguimento destes doentes a longo prazo, dado o risco de metastização e recidiva, mesmo vários anos após o diagnóstico inicial.

Palavras-chave: Feocromocitomas/diagnóstico; Feocromocitomas/epidemiologia; Paragangliomas/diagnóstico; Paragangliomas/epidemiologia; Tumores Neuroendócrinos/epidemiologia

Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors originating from chromaffin cells of the adrenal medulla or the sympathetic/parasympathetic paraganglia.[1] While many secrete catecholamines, responsible for classical clinical manifestations,[1,2] others are non-secretory and detected due to mass effect or as incidental imaging findings.[3]

Pheochromocytomas and paragangliomas have the highest known heritability among neoplasms, with up to 40% linked to germline mutations in susceptibility genes. Genetic testing is recommended for all PPGL patients and for first-degree relatives of mutation carriers,[4-6] as it distinguishes sporadic from familial forms. Sporadic PPGL typically appear later in life, are larger, and show lower metastatic and recurrence risk. Conversely, familial cases present earlier, often with smaller, multiple, and/or bilateral tumors, with greater recurrence and metastatic potential.[6-8]

The low global incidence of PPGL, estimated at two to eight cases per million people per year, combined with its highly variable natural history, poses significant diagnostic challenges.[1] In Portugal, epidemiological, clinical and genetic data on PPGL remain scarce. This study aimed to estimate PPGL incidence within the Unidade Local de Saúde de Braga (ULS Braga) referral area, characterize this population, and investigate potential differences between sporadic and familial cases.

An observational, retrospective study was conducted, including patients diagnosed with PPGL between 2004 and 2024, with at least one consultation at ULS Braga. In patients with more than one tumor, subsequent tumors were considered new cases only when deemed unrelated to the preceding lesion.

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Recebido/*Received*: 05/11/2025 - **Aceite/*Accepted*:** 10/02/2026 - **Publicado/*Published*:** 04/05/2026

Each case was classified as sporadic or familial according to the genetic test result. Genetic testing was performed using next-generation sequencing and included the following genes: *RET, MEN1, CDKN1B, EGLN1, FH, GDNF, KIF1B, VHL, SDHA, SDHAF2, SDHB, SDHC, SDHD, NF1, MAX, TMEM17,* and *PRKAR1A*.

To estimate incidence, cases diagnosed between 2012 and 2024 were analyzed, as electronic medical records ensured greater data reliability. All cases were included for descriptive analysis, while comparative analyses were restricted to patients who underwent genetic testing.

Collected variables included sociodemographic data, clinical presentation, tumor characteristics, treatment and outcomes. Informed consent was not obtained, in accordance with Article 31 of Law No. 58/2019 of 8 August, which implemented the General Data Protection Regulation, published in *Diário da República*, No. 151/2019, Series I, of 8 August 2019.

Pheochromocytomas and paragangliomas were classified as familial if pathogenic variants were detected. Outcomes were assessed by the response evaluation criteria in solid tumors and biochemical findings. The presence of metastasis was assessed, as well as recurrence, defined as a new lesion at the same site following complete remission of the primary tumor. Vital status and cause of death were also documented.

Statistical analyses were performed using IBM SPSS® 29.0. Annual incidence was calculated as the number of new PPGL cases per year divided by the population at risk.[9] The mean annual incidence (2012 - 2024) was derived as a weighted mean of yearly incidence. Incidence trends were analyzed using a linear trend line. Categorical variables were expressed as absolute and relative frequencies, and continuous variables as mean ± standard deviation or as median (interquartile range), depending on distribution. Group comparisons were performed using Student's *t*-test, Mann-Whitney test, Pearson's chi-square test, or Fisher-Freeman-Halton exact test, as appropriate. Confounding variables were evaluated through regression models and tumor location was identified as a confounder for tumor size, being included through analysis of covariance with bootstrapping.

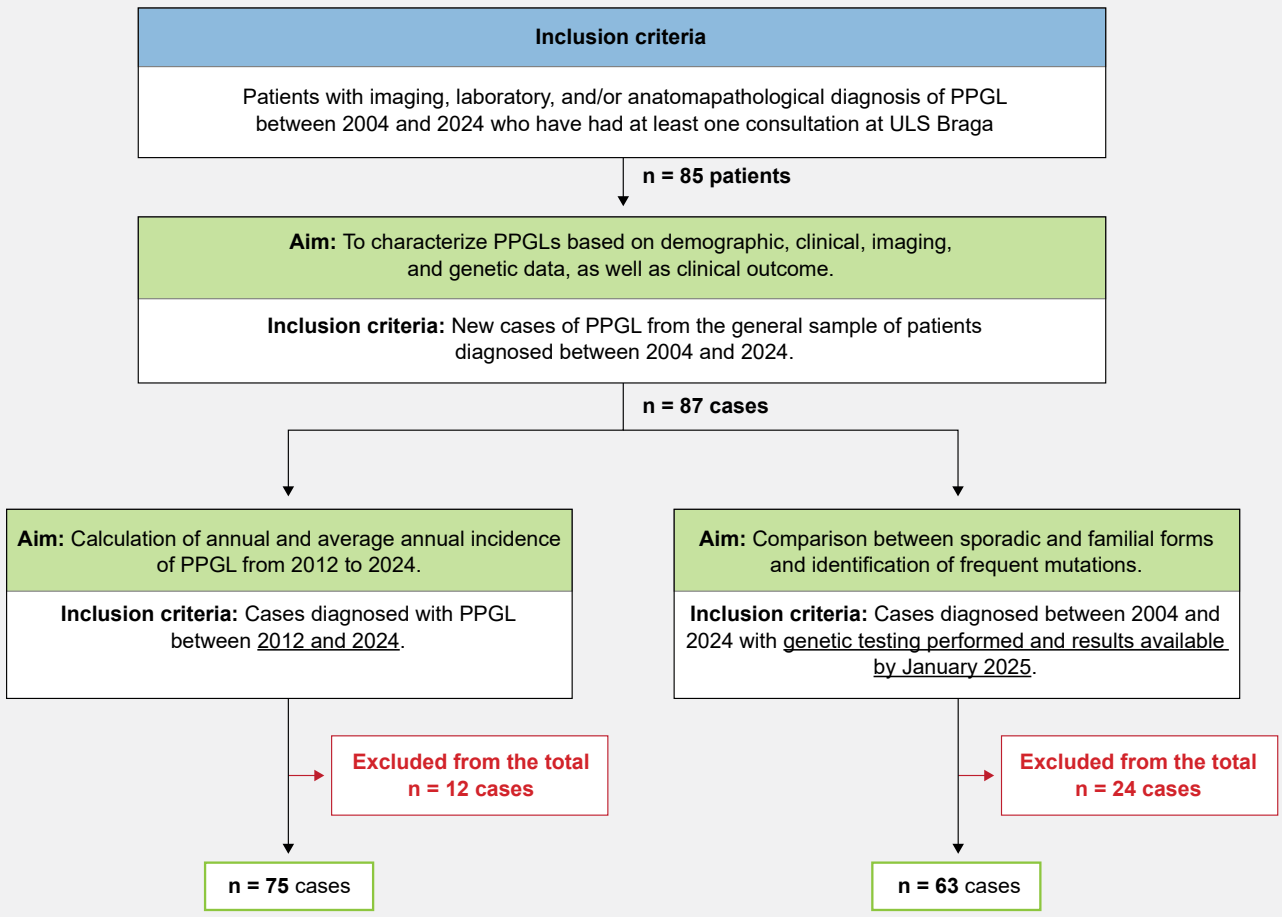

Figure 1 – Flowchart of the study design, definition of inclusion criteria, and subsamples for the different objectives

Statistical significance was defined as $p < 0.05$. Based on a 95% CI, 5% margin of error, and effect size of 0.5, the sample size for adequate statistical power was 260 cases.

A total of 85 patients were identified, with a mean follow-up of 5.7 ± 4.4 years. Two patients had two distinct tumors, totaling 87 PPGL cases. Of these, 75 were included in incidence analysis, and 63 in group comparisons (Fig. 1).

The mean annual incidence of PPGL was 5.3 cases per million people, ranging from 1.9 (2019/2020) to 10.9 (2023). Linear trend analysis revealed an annual increase of 0.41 cases per million.

The mean age at diagnosis was 54.3 years (ranging from 21 to 85 years), with 66.7% female patients. Most tumors were extra-adrenal, particularly of the head and neck (76.9%). Diagnosis was most often established based on symptoms (60.9%), followed by incidentaloma investigation (Table 1).

Sixty-one patients underwent genetic testing, of whom 42 (68.9%) were classified as sporadic and 19 (31.1%) as familial.

Mutations in the *SDHB* gene were the most frequent (11 patients), followed by *NF1* (three patients), *VHL* (two patients), and *RET, SDHD*, and *TMEM127* (one patient each). Familial cases were diagnosed at a significantly younger age, with no significant differences found regarding sex, clinical presentation, tumor size, or location. Multifocality was more frequent in familial PPGL, and both metastatic cases occurred in this group, four and six years after diagnosis (Table 1).

Three patients had a first-degree family history. In one of these cases, genetic testing identified a *SDHB* mutation, also detected in three additional family members.

Among 75 treated patients, 73 underwent curative-intent surgery, one received stereotactic radiotherapy, and one medical therapy. Reasons for absence of therapy included a decision for active surveillance in non-secretory PPGL and death prior to surgery. Complete remission occurred in 59 patients, while 16 had stable disease. Three recurrences occurred after a median of seven years, two in sporadic cases (Table 1). No significant differences were found in treatment or outcomes. At data collection, 80 patients were alive, with five deaths unrelated to the PPGL.

The identified mean annual incidence rate, and its upward trend, are consistent with published data.[1] The 2020 decline likely reflects the impact of COVID-19 pandemic on healthcare access, delaying diagnostic procedures. The overall rise may reflect both a true increase in disease occurrence and improvements in diagnostic accuracy, with greater imaging availability, adoption of metanephrine screening, and systematic monitoring of genetically predisposed individuals.[3,10]

Although genetic testing is currently recommended for all PPGL patients,[6] 28.2% of individuals in this cohort were not tested, all managed outside the Endocrinology department. This underscores the importance of referral to specialized multidisciplinary care. Among tested patients, 31.1% had familial PPGL, which aligns with the reported hereditary basis.[5]

The only significant difference between groups was younger age at diagnosis in familial cases, likely reflecting both earlier onset and detection through screening of at-risk individuals. Contrary to some reports, no significant differences were observed regarding tumor size, focality, metastases, or recurrences.[6-8] Interestingly, most recurrences were identified in sporadic cases. Although possibly attributable to the small sample size, undetected mutations not included in the genetic panel, limitations in variant interpretation, or acquired somatic alterations cannot be excluded.[5]

Finally, the relatively late onset of metastases and recurrence highlights the need for lifelong follow-up.

Study limitations include the small sample size, retrospective design, and potential underestimation of incidence, as patients treated outside ULS Braga may not have been captured. Nonetheless, this is, to our knowledge, the first Portuguese study to estimate PPGL incidence and compare familial and sporadic forms, covering a 20-year period. It provides valuable preliminary data to support future multicenter research.

Our findings highlight the heterogeneity of PPGL, underlining the need for systematic genetic testing and lifelong follow-up.

PREVIOUS AWARDS AND PRESENTATIONS

This study was conducted and presented within the scope of the MinhoMD 2 project at the Universidade do Minho Medical School, by the student Natacha Nair Freitas Paixão, during the 2024/2025 academic year.

ACKNOWLEDGMENTS

OpenAI® – ChatGPT was used to improve the clarity and fluency of the text. The model was not used to generate scientific content, interpret results, or formulate conclusions. After using this tool/service, the content was reviewed and edited by the authors, who assume full responsibility for the content.

The authors would like to thank the Director of the Department of Endocrinology, Olinda Marques, for granting permission to conduct this study within the department. They also wish to express their gratitude to the Universidade do Minho Medical School, particularly Jorge Diogo Silva and Sílvia Santos for their assistance with data analysis, and Gil Castro and Joana Palha for their support in data interpretation.

Table 1 – Characterization and comparison between groups (sociodemographic, clinical data, treatment and outcomes data)

	Total sample	n	Sporadic PPGL	n	Familial PPGL	n	*p*-value
Age at diagnosis, years, M ± SD	54.3 ± 15.13	87	57.4 ± 15.1	43	43.4 ± 12.7	20	**< 0.001**
Sex, n (%)		87		43		20	0.985
Female	58 (66.7)		30 (69.8)		14 (70.0)		
Male	29 (33.3)		13 (30.2)		6 (30.0)		
History of PPGL in a first-degree relative, n (%)		87		43		20	0.234
Yes	3 (3.4)		1 (2.3)		2 (10.0)		
No	84 (96.6)		42 (97.7)		18 (90.0)		
Clinical presentation, n (%)		87		43		20	0.169
Incidentaloma	32 (36.8)		14 (32.6)		6 (30.0)		
Screening in asymptomatic carriers	2 (2.3)		0		2 (10.0)		
Symptoms	53 (60.9)		29 (67.4)		12 (60.0)		
Young-onset hypertension	3 (5.7)		0		2 (16.7)		
Resistant hypertension	4 (7.5)		1 (3.4)		2 (16.7)		
Paroxysms	12 (22.6)		5 (17.2)		4 (33.3)		
Mass effect	29 (54.7)		15 (51.7)		4 (33.3)		
Other[a]	11 (20.8)		9 (31.0)		2 (16.7)		
Secretory phenotype, n (%)		64		39		15	
Adrenergic	22 (34.4)		12 (30.8)		5 (33.3)		
Noradrenergic	14 (21.9)		8 (20.5)		3 (20.0)		
Dopaminergic	2 (3.1)		2 (5.1)		0		
Non-secretory	26 (40.6)		17 (43.6)		7 (46.7)		
Location, n (%)		87		43		20	0.972
Adrenal	35 (40.2)		17 (39.5)		8 (37.5)		
Extra-adrenal	52 (59.8)		26 (60.5)		12 (60.0)		
Focality, n (%)		87		43		20	0.090
Unifocal	70 (80.5)		42 (97.7)		17 (85.0)		
Multifocal	17 (19.5)		1 (2.3)		3 (15.0)		
Size, mm, median (IQR)	33.0 (23.5)	81	35.0 (24.0)	43	27.5 (19.3)	20	0.060
Metastases, n (%)		87		43		20	0.097
Yes	2 (2.3)		0		2 (10.0)		
No	85 (97.7)		43 (100.0)		18 (90.0)		
Treatment, n (%)		86		43		20	
Yes	75 (87.2)		35 (81.4)		18 (90.0)		
No	11 (12.8)		8 (18.6)		2 (10.0)		
Status after treatment, n (%)		75		35		18	0.482
Complete remission	59 (72.0)		26 (74.3)		12 (66.7)		
Stable disease	16 (28.0)		9 (25.7)		6 (33.3)		
Recurrence, n (%)		59		26		12	0.543
Yes	3 (5.1)[b]		2 (7.7)		0		
No	56 (94.9)		24 (92.3)		12 (100.0)		
Vital status, n (%)		85		43		20	1.000
Alive	80 (94.1)		41 (95.3)		20 (100.0)		
Deceased	5 (5.9)		2 (4.7)		0		

a: Cervical swelling, abdominal pain, cardiac manifestations, hypertensive crisis.
b: One without genetic test.
IQR: interquartile range; M: mean; mm: millimeter; n: absolute frequency; SD: standard deviation; %: relative frequency.

AUTHOR CONTRIBUTIONS

PCB: Data analysis and interpretation, drafting of the manuscript.

NP: Study design, data collection, analysis and interpretation, critical review of the manuscript.

DBD: Study design, data analysis and interpretation, critical review of the manuscript.

All authors approved the final version of the manuscript and are accountable for the accuracy and integrity of the work.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY AND AVAILABILITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication. No additional data is available.

CONFLICTS OF INTEREST

PCB received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Academia PNA; received support for attending meetings and/or travel from Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo.

All other authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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