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Germline genetic variants in young-onset sporadic pituitary macroadenomas: A multigene panel analysis

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ABSTRACT

Mutations in several genes have been associated with familial forms of pituitary adenomas. Sporadic pituitary adenomas (i.e. with no family history or coexistent endocrine tumours) are also occasionally found to result from germline mutations in these genes, especially in young patients with larger tumours. The aim of this study was to determine the frequency of germline mutations in patients with young-onset sporadic pituitary macroadenomas. A cohort of 225 Portuguese patients with sporadic pituitary macroadenomas diagnosed before the age of 40 years was studied by whole exome sequencing (WES) followed by the analysis of a virtual panel of 29 genes that have been associated with predisposition to pituitary adenomas. Pathogenic and likely pathogenic variants were identified in 16 (7.1 %) of patients. The affected genes were *AIP* (n = 4), *PMS2* (n = 4), *MEN1* (n = 2), *VHL* (n = 2), *CDH23* (n = 1), *MSH2* (n = 1), *SDHB* (n = 1), and *TP53* (n = 1). In patients diagnosed under the ages of 30 and 18 years, the frequency of pathogenic and likely pathogenic variants increased to 9.0 % and 12.0 %, respectively. This is so far the largest multigene analysis of patients with young-onset sporadic pituitary macroadenomas. We confirmed the *AIP* as the most frequently involved gene, but also uncovered rarer genetic causes of pituitary adenomas. The results may contribute to a better understanding of the genetic landscape of these tumours and help to decide which genes to include in the genetic screening of patients with young-onset pituitary macroadenomas.

Introduction

Most pituitary adenomas occur sporadically and are often attributed to acquired somatic and epigenetic mutations [1]. However, a subset of cases arises within a familial context, either as familial isolated pituitary adenomas (FIPA) or as part of syndromic diseases [2]. Tumours within familial settings tend to be more aggressive, manifesting at a younger age, with larger sizes, increased invasiveness, and resistance to standard treatments [3]. Germline mutations in several genes have been identified in individuals with sporadic and syndromic pituitary adenomas [4–6]. Identifying these genetic alterations is not only crucial for accurate diagnosis and personalized treatment, but also provides valuable insights into the molecular pathways disrupted in these tumours [7].

While sporadic cases traditionally lack a clear hereditary component, several studies have shown that a variable proportion of these cases harbour germline mutations [8]. The most extensively studied gene is *AIP*, which was first associated with FIPA [9], but later found to be mutated in many apparently sporadic cases, particularly among patients of younger ages and with larger tumours [10].

We recently screened a cohort of patients diagnosed with

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young-onset sporadic pituitary macroadenomas for *AIP* mutations [11]. This revealed the presence of *AIP* mutations in 1.8 %, 3.4 % and 5.0 % of patients diagnosed under the ages of 40, 30 and 18 years, respectively [11]. Building upon this, we have now expanded the genetic screening to 29 genes that have so far been associated with germline or mosaic mutations in familial isolated or syndromic pituitary adenomas.

Materials and methods

Subjects

This was a follow-up study of a Portuguese multicentre cohort that had been previously studied by conventional (Sanger) sequencing of the *AIP* gene [11]. A total of 225 patients were available for this study. Inclusion criteria were patients with macroadenomas (tumour greater diameter $\geq$ 1 cm) diagnosed under the age of 40 years. Exclusion criteria were patients with a family history of pituitary adenomas (i.e. affected first or second-degree family member) or with a personal history of additional tumours or other manifestations that would suggest a syndromic form of pituitary adenoma. Mean age ($\pm$ standard deviation) at diagnosis was 29.1 $\pm$ 7.3 years, 122 patients were under 30 years at diagnosis, and 25 patients were under 18 years at diagnosis. Gender distribution was 116 (51.6 %) females and 109 (48.4 %) males. Tumour classification was based on histological examination or, in the case of prolactinomas, by clinical, hormonal and radiological examination. Eighty-one (36.0 %) patients had prolactinomas, 62 (27.6 %) had somatotrophinomas, 37 (16.4 %) had non-functioning pituitary adenomas, 16 (7.1 %) had mixed-secreting pituitary adenomas, 15 (6.7 %) had corticotrophinomas, seven (3.1 %) had gonadotrophinomas, one (0.4 %) had a thyrotrophinoma, and six (2.7 %) had adenomas with undetermined histology. The study was approved by the Ethics Committee of the Faculty of Health Sciences, University of Beira Interior (Ref: CE-UBI-Pj-2018–027 and CE-FCS-2011–003) and written informed consent was obtained from all subjects.

Whole exome sequencing (WES) and virtual gene panel

Genomic deoxyribonucleic acid (DNA) was extracted from the peripheral blood leukocytes of each patient and used for WES analysis according to previously described methods [12]. A virtual gene panel was created, consisting of 29 genes in which germline or mosaic mutations have been reported in patients with familial isolated or syndromic pituitary adenomas, or that have been suggested as candidate genes for these disorders [4–6], namely *AIP* (NM_003977.3), *CABLES1* (NM_001100619.2), *CDH23* (NM_022124.5), *CDKN1A* (NM_078467.3), *CDKN1B* (NM_004064.4), *CDKN2B* (NM_004936.4), *CDKN2C* (NM_001262.3), *DICER1* (NM_177438.3), *GNAS* (NM_000516.7), *GPR101* (NM_054021.1), *MAX* (NM_002382), *MEN1* (NM_130799.2), *MLH1* (NM_000249.4), *MSH2* (NM_000251.3), *MSH6* (NM_000179.3), *NF1* (NM_000267.3), *PMS2* (NM_000535.7), *PRKACA* (NM_002730.4), *PRKACB* (NM_182948.4), *PRKAR1A* (NM_002734.5), *RET* (NM_020975.4), *SDHA* (NM_004168.3), *SDHAF2* (NM_017841.2), *SDHB* (NM_003000.3), *SDHC* (NM_003001.5), *SDHD* (NM_003002.3), *TP53* (NM_000546.6), *USP8* (NM_005154.5), and *VHL* (NM_000551.3).

Interpretation of genetic variants

Genetic variants were filtered according to the following cumulative criteria: 1) Location in one of the 29 genes previously implicated in pituitary adenomas; 2) Location in coding transcripts used by the Human Genome Mutation Database (HGMD) [13]; 3) Location in coding exons or up to ten nucleotides adjacent to the coding exons; and 4) Population allele frequency less than 0.001 in the Genome Aggregation Database (gnomAD) and 1000 Genomes database [14]. The variants selected by these criteria were classified as benign (B), likely benign (LB), variant of uncertain significance (VUS), likely pathogenic (LP) or pathogenic (P), according to American College of Medical Genetics and Genomics (ACMG) criteria [15] and ClinGen recommendations [16], using a web-based variant interpretation tool (Franklin by Genoox, reference hg19, https://franklin.genoox.com/, accessed on November 14th, 2024). Filtered variants were screened in an in-house database of 298 Portuguese control individuals to assess the possibility of variants being population-specific common polymorphisms. For simplicity, throughout the article we used the term "mutation" interchangeably with the terms "pathogenic" and "likely pathogenic" variants.

Validation of genetic variants by Sanger sequencing

Variants classified as P and LP were confirmed by conventional Sanger sequencing. The exon sequences containing each variant were amplified by polymerase chain reaction (PCR) using primers targeting flanking intronic regions. For *PMS2* variants, to avoid potential interference from the homologous *PMS2CL* pseudogene, the forward primer was anchored in exon 10, which is not shared by the pseudogene. The amplified fragments were then sequenced using a semi-automated DNA sequencer (STAB VIDA, Caparica, Portugal; and ABI 3730XL, Applied Biosystems; Thermo Fisher Scientific, Waltham, MA, USA).

Results

Rare sequence variants identified in the 29 analysed genes

A total of 154 (141 different) rare sequence variants (population allele frequency < 0.001) were identified in 25 of the 29 analysed genes and included three P, 13 LP (11 different), 63 VUS (56 different), 64 LB (61 different) and 11 B (10 different) (Supplementary Data 1). All rare sequence variants were identified in the heterozygous state.

Pathogenic (P) and likely pathogenic (LP) variants

P and LP variants were identified in 16 (7.1 %) patients with young-onset sporadic pituitary macroadenomas. These consisted of four *AIP* variants (previously reported by us [11]) (p.Ser53ThrfsTer36, p.Arg81Ter, p.Leu115TrpfsTer41, and p.Glu246Ter), four *PMS2* variants (three patients with p.Asn335Ser, and one with p.Asp486GlufsTer109), two *MEN1* variants (p.Trp183Ter, and p.Arg314_Asp315del), two *VHL* variants (p.Lys196Glu, and p.Glu52Ter), one *CDH23* variant (p.Glu2520Lys), one *MSH2* variant (p.Arg524His), one *SDHB* variant (p.Ile127Leu), and one *TP53* variant (p.Arg282Gln) (Table 1 and Fig. 1).

Prevalence of pathogenic (P) and likely pathogenic (LP) variants according to age of diagnosis and gender

The prevalence of P and LP variants was higher in patients with younger ages at diagnosis. The prevalence of these variants in patients diagnosed up until the age of 40, 30 and 18 years was 7.1 % (16/225), 9.0 % (11/122), and 12.0 % (3/25), respectively. The prevalence of P and LP variants was similar in females (7.8 %; 9/116) and males (6.4 %; 7/109).

Clinical characteristics of patients with pathogenic (P) and likely pathogenic (LP) variants

The clinical details of the 16 patients with identified P and LP variants are available in the Supplementary Data 2. Patients had no personal history of additional tumours or other syndromic features at the time of inclusion in the study. Family history was collected, but additional family members were unavailable for clinical and genetic screening. Two patients with *MEN1* P and LP variants were found to have hyperparathyroidism during or after undertaking the genetic studies.

Table 1
Clinical and genetic characteristics of 16 patients with pathogenic (P) and likely pathogenic (LP) variants.

Gene (transcript)	Patient number (id)	Sex	Age at diagnosis (yr)	Type of adenoma (hormones produced)	Size of adenoma (mm)	Variant (nucleotide change, protein change) (a)	Effect	Allele frequency in GnomAD	Allele frequency in Portuguese controls	ACMG classification (criteria) (b)	Previous report of the variant
AIP (NM_003977.3)	1 (8215)	F	20	GH	20	c.158_165delGCCGGGCT, p.Ser53ThrfsTer36	Frameshift deletion	0	0	LP (PVS1, PM2)	(11)*
	2 (7879)	M	22	GH	26	c.241C>T, p.Arg81Ter	Nonsense	0	0	P (PVS1, PS4, PM2, PP5)	[55] (11)*
	3 (7329)	M	14	GH/PRL	14	c.343delC, p.Leu115TrpfsTer41	Frameshift deletion	0	0	LP (PVS1, PM2)	[56] (11)*
	4 (7632)	F	25	GH	28	c.736G>T, p.Glu246Ter	Nonsense	0	0	LP (PVS1, PM2)	(11)*
CDH23 (NM_022124.5)	5 (7791)	M	23	GH	25	c.7558G>A, p.Glu2520Lys	Missense	0	0	LP (PS4, PM2, PP3, PP5)	(34)
MEN1 (NM_130799.2)	6 (7850)	M	32	GH/PRL	60	c.548G>A, p.Trp183Ter	Nonsense	0	0	P (PVS1, PS4, PM2, PP5)	(26)
	7 (7971)	F	22	GH/PRL/TSH	40	c.940_945delCGGGAT, p.Arg314_Asp315del	In-frame deletion	0	0	LP (PM2, PM4)	None
MSH2 (NM_000251.3)	8 (7642)	F	20	PRL	>10	c.1571G>A, p.Arg524His	Missense	0.000011	0.002342	LP (PM1, PM2, PM5, PP3)	(37)
PMS2 (NM_000535.7)	9 (8072)	M	37	GH	>10	c.1004A>G, p.Asn335Ser	Missense	0.000273	0	LP (PM2, PP3, BP6)	(24)
	10 (8094)	F	40	PRL	31	c.1004A>G, p.Asn335Ser	Missense	0.000273	0	LP (PM2, PP3, BP6)	(24)
	11 (8095)	F	33	Non-functioning	40	c.1004A>G, p.Asn335Ser	Missense	0.000273	0	LP (PM2, PP3, BP6)	(24)
	12 (7648)	M	25	PRL	>20	c.1458delC, p.Asp486GlufsTer109	Frameshift deletion	0	0	LP (PVS1, PM2)	None
SDHB (NM_003000.3)	13 (7887)	F	21	PRL	20	c.379A>C, p.Ile127Leu	Missense	0.000004	0	LP (PM1, PM2, PM5, PP2, PP3)	(41)
TP53 (NM_000546.6)	14 (8079)	F	36	ACTH	14	c.845G>A, p.Arg282Gln	Missense	0.000004	0	LP (PM1, PM2, PM5, PP3, PP5, BS3,)	(47)
VHL (NM_000551.3)	15 (6906)	F	17	PRL	>10	c.154G>T, p.Glu52Ter	Nonsense	0.000018	0	LP (PVS1, PM2)	(30)
	16 (7792)	M	18	TSH	10	c.586A>G, p.Lys196Glu	Missense	0	0	P (PM1, PM2, PM3, PP2, PP3, PP5)	(31)

id, identification; F, female; M, male; yr, years; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone; mm, millimeters; GnomAD, Genome Aggregation Database (v2.1.1). (a) All variants were heterozygous. (b) American College of Medical Genetics and Genomics (ACMG) classification of variants (P, pathogenic; LP, likely pathogenic) was based on the evidence for pathogenicity (very strong (PVS1), strong (PS1-4), moderate (PM1–6), or supporting (PP1–5)) or benign impact [stand-alone (BA), strong (BS1-4), or supporting (BP1-7)]. ACMG classifications were based on the web-based variant interpretation tool Franklin (Genoox Ltd, https://franklin.genoox.com/), accessed on November 14th, 2024. * Publication by the authors that included the same patient.

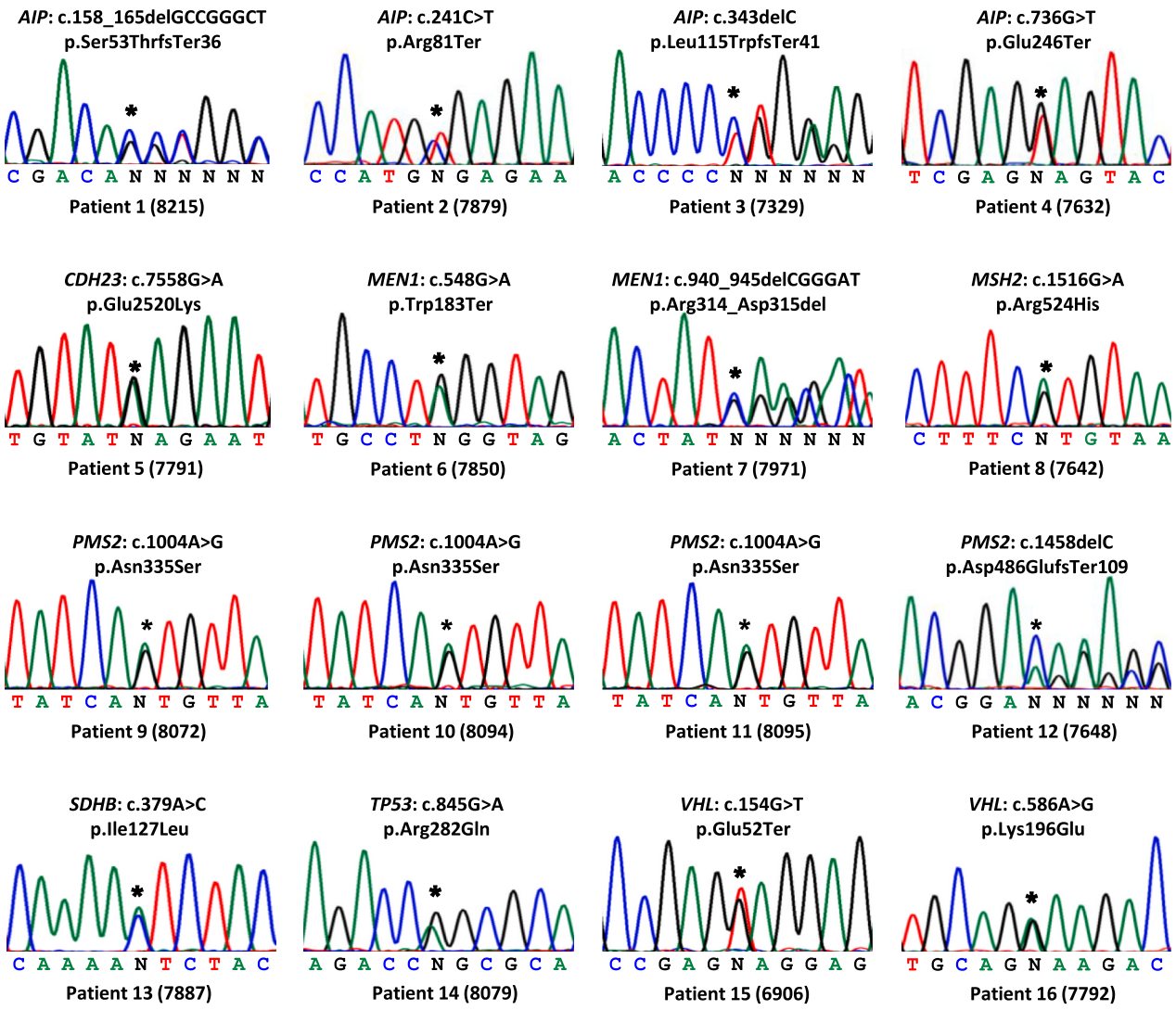

Fig. 1. Germline pathogenic (P) and likely pathogenic (LP) variants identified in patients. The Sanger sequencing chromatograms are presented for each heterozygous variant (indicated by an asterisk) and surrounding nucleotides. Chromatograms representing heterozygous deletions (Patients 1, 3, 7 and 12) show unequal peaks after the beginning of the deletion (asterisk) due to the simultaneous reading of both alleles.

Discussion

Our analysis of 225 patients with young-onset sporadic pituitary macroadenomas showed that 16 (7.1 %) patients had germline P and LP variants in genes that are associated with familial forms of pituitary adenomas. These variants involved the *AIP* (1.8 % of patients), *PMS2* (1.8 %), *MEN1* (0.9 %), *VHL* (0.9 %), *CDH23* (0.4 %), *MSH2* (0.4 %), *SDHB* (0.4 %), and *TP53* (0.4 %) genes.

The *AIP* gene is associated with FIPA (9), but has also been extensively studied in patients with sporadic pituitary adenomas. The prevalence of *AIP* germline mutations in patients with sporadic pituitary macroadenomas under the age of 40 has been reported to vary from 0 % to 18 % [11], depending of the country of origin, clinical characteristics of the cohort, and criteria used for the classification of genetic variants. We found four (1.8 %) patients with *AIP* P and LP variants, which were frameshift (p.Ser53ThrfsTer36, and p.Leu115TrpfsTer41) and nonsense (p.Arg81Ter, and p.Glu246Ter) variants expected to lead to a premature stop codon and to the formation of a shorter protein or to nonsense-mediated decay [17]. These *AIP* variants were all found in patients with GH-secreting adenomas, in agreement with the higher prevalence of *AIP* mutations in this tumour type [18]. These results confirm the results of our previous Sanger sequencing of the *AIP* gene in this cohort of patients [11].

The *PMS2* gene is associated with Lynch syndrome [19], which is characterised by the occurrence of a variety of tumours that include colorectal, endometrial, ovarian and gastric cancers [20]. Although some cases of aggressive pituitary tumours have been reported in patients with Lynch syndrome [21–23], the prevalence of *PMS2* mutations in sporadic pituitary adenomas has never been reported before. We found four (1.8 %) patients with *PMS2* LP variants, with no other apparent manifestations of Lynch syndrome. These consisted of a previously reported [24] missense variant (p.Asn335Ser) that was identified in three unrelated patients, diagnosed with a somatotrophinoma, prolactinoma and non-functioning pituitary adenoma, and a novel frameshift variant (p.Asp486GlufsTer109) in a patient with a prolactinoma. Thus, our study suggests that the *PMS2* gene has a more important role in pituitary tumorigenesis than previously acknowledged.

The *MEN1* gene is associated with the multiple endocrine neoplasia type 1 (MEN1) syndrome, which is characterised by the occurrence of parathyroid, pancreatic and pituitary tumours [25,26]. *MEN1* mutations are occasionally found in patients with pituitary adenomas without other MEN1 manifestations. A previous study identified *MEN1* mutations in 3.4 % of patients with sporadic pituitary macroadenomas diagnosed before the age of 30 [27]. Our study found two (0.9 %)

patients with *MEN1* P and LP variants, which consisted of a previously reported [26] nonsense variant (p.Trp183Ter) and a novel in-frame deletion (p.Arg314_Asp315del). Both patients had mixed GH-secreting adenomas. It is interesting to note that although there were no other apparent manifestations of the MEN1 syndrome at the time of the diagnosis of the pituitary adenoma, both patients were eventually found to have hyperparathyroidism during or after undertaking the genetic studies.

The *VHL* gene is associated with the Von Hippel–Lindau (VHL) syndrome, which is characterised by tumours in several organs, such as retinal and central nervous system haemangioblastomas, pheochromocytomas and clear-cell renal carcinomas [28]. Pituitary adenomas have also been described in patients with the VHL syndrome [29]. However, the prevalence of *VHL* mutations in sporadic pituitary adenomas has not been reported. We found two (0.9 %) patients with *VHL* P and LP variants, with no other apparent manifestations of the VHL syndrome. These consisted of a previously reported [30] nonsense variant (p.Glu52Ter) in a patient with a prolactinoma and a previously reported [31] missense variant (p.Lys196Glu) in a patient with a thyrotrophinoma. The latter variant was previously reported in homozygosity in a patient with autosomal recessive congenital erythrocytosis, but with no evidence of the VHL syndrome [31].

The *CDH23* gene is associated with the autosomal recessive Usher syndrome, which is characterized by congenital deafness [32]. However, a study by Zhang et al. [33] demonstrated the presence of *CDH23* heterozygous mutations in 33 % and 12 % of familial and isolated pituitary adenomas, respectively. So far, these results have not been independently confirmed. Furthermore, there have been no reports of a higher incidence of pituitary adenomas in patients with Usher syndrome or in their heterozygous relatives. We found one (0.4 %) patient with a GH-secreting adenoma and a previously reported [34] *CDH23* missense LP variant (p.Glu2520Lys). Thus, ours is the second study to associate *CDH23* with pituitary adenomas.

The *MSH2* gene is also associated with Lynch syndrome [35,36] and some affected patients have been reported to have aggressive pituitary adenomas [21–23]. We found one (0.4 %) patient with a previously reported [37] *MSH2* missense LP variant (p.Arg524His), who had a prolactinoma with no other apparent manifestations of Lynch syndrome.

The *SDHB* gene is associated with paragangliomas and pheochromocytomas [38]. Pituitary adenomas occasionally occur in association with these (3PA, Phaeochromocytoma, Paraganglioma and Pituitary adenoma association) [39]. However, the prevalence of *SDHB* mutations in sporadic pituitary adenomas is unknown. A French study of 263 patients with sporadic pituitary adenomas revealed two mutations in the *SDHA* gene, one in the *SDHC* gene, but none in *SDHB* [40]. We found one (0.4 %) patient with a previously reported [41] *SDHB* missense LP variant (p.Ile127Leu), who had a prolactinoma without any other syndromic manifestations.

The *TP53* gene is considered the most mutated tumour suppressor gene in human cancers [42]. Germline mutations in this gene are associated with the Li-Fraumeni syndrome, which predisposes to soft tissue sarcomas, osteosarcoma, breast cancer, leukaemia, and adrenocortical carcinoma [43]. Although somatic mutations in *TP53* have been reported in pituitary adenomas [44], germline mutations have only rarely been observed in patients with these tumours [45,46]. Nevertheless, in our study, we found one (0.4 %) patient with a previously reported [47] *TP53* germline missense LP variant (p.Arg282Gln), who had a corticotrophinoma without any other syndromic manifestations.

The variants described above were classified as P or LP following stringent ACMG criteria [15,16]. However, interpretation and application of these criteria can vary across laboratories. Differences may arise in the definition of mutational hotspots, the use of in-silico prediction tools, or the population frequency cut-offs for classifying variants [48]. For example, six of our variants are listed in the ClinVar database [49] as VUS (*MSH2* p.Arg524His; *SDHB* p.Ile127Leu; and *VHL* p.Glu52Ter) or with conflicting classifications (*PMS2* p.Asn335Ser; *TP53* p.Arg282Gln; and *VHL* p.Lys196Glu), despite having been previously reported as disease-causing [24,30,31,37,41,47]. We used the Franklin automated variant classification software (https://franklin.genoox.com), which has been demonstrated to have 94.5 % sensitivity and 96.6 % specificity in identifying P and LP variants [48]. While this provides a high level of confidence in our findings, our results should still be viewed with caution, especially in the absence of confirmatory functional and familial segregation studies, as well as the lack of additional syndromic manifestations in patients carrying these variants.

None of the patients in our study had coexistent tumours, syndromic features, or a family history that would typically raise suspicion of a germline mutation. The identification of germline P and LP variants in these patients, despite the absence of such indicators, was unexpected but could be explained by several factors. First, family history was self-reported, and may have been inaccurate or incomplete. Second, the absence of other affected family members could be due to incomplete penetrance of the mutation or to the presence of a *de novo* mutation. Third, other syndromic manifestations may have been missed during clinical screening or absent due to variable expression of the mutation. This occurred in two of our patients with *MEN1* P and LP variants, who were only found to have additional tumours and/or affected family members during or after genetic testing. These findings suggest that patients with young-onset pituitary macroadenomas should undergo comprehensive genetic screening, regardless of the presence of syndromic features or family history.

Previous studies of sporadic pituitary adenomas have mainly focused on the *AIP* gene, as this is the most commonly mutated gene in such cases [8]. Only three other studies performed gene panel analyses in patients with sporadic pituitary adenomas, but with a limited number of genes ($\leq$ 9) that did not include for example the *VHL, PMS2* or *CDH23* genes [40,50,51]. Nevertheless, these studies were able to identify pathogenic variants in 3.8 % to 10 % of patients with young-onset sporadic pituitary adenomas. In our study, we analysed the largest panel of genes so far in patients with sporadic pituitary adenomas. We confirmed the *AIP* as the most frequently involved gene in these patients, but also uncovered rarer genetic causes of pituitary adenomas. Altogether, germline P and LP variants were present in 7.1 % of our patients diagnosed with sporadic macroadenomas under the age of 40 years. However, this proportion increased to 9.0 % and 12.0 %, in patients diagnosed under the ages of 30 and 18 years, respectively. This is in agreement with the general observation that tumours arising in younger ages are more likely to have a genetic cause [52].

The existence of subsets of patients at higher risk of harbouring germline mutations has led to recommendations for *AIP* and *MEN1* mutation testing in patients with sporadic pituitary macroadenomas diagnosed under the age of 30 [10,27] or 40 years [53]. More recently, guidelines for the genetic testing of children have been proposed [52]. However, there are currently no recommendations for additional genetic testing of sporadic pituitary adenomas in adults that have been shown to be *AIP* and *MEN1* mutation-negative. Our study suggests that testing such patients for a wider gene panel may uncover further cases of genetically-determined pituitary adenomas. Importantly, our identification of patients with germline mutations will improve their clinical management, allow the screening of additional syndromic manifestations, and allow the identification of additional affected family members that can be screened for the disorder [6].

Our study has some limitations. First, we did not investigate copy number variants or mutations in non-coding genomic regions. Second, we did not screen for mutations in genes beyond those currently associated with pituitary adenomas. Third, we found a large number of VUS, for which there is currently insufficient evidence for an association with the disorder, but that may need reclassification over time [54]. Fourth, confirmatory functional and familial segregation studies were not performed for the identified variants. Finally, tumour DNA was not available to investigate somatic genetic alterations, namely loss-of-heterozygosity of the affected genes.

In conclusion, we found a prevalence of 7.1 % germline P and LP variants in patients with young-onset pituitary macroadenomas. These include variants in the *AIP*, *MEN1*, *MSH2*, *PMS2*, *SDHB*, *TP53* and *VHL* genes and the first independent confirmation of a variant in the *CDH23* gene. Our results may contribute to a better understanding of the genetic landscape of these tumours and help to decide which genes to include in the genetic screening of patients with young-onset pituitary macroadenomas.

CRediT authorship contribution statement

Leonor M. Gaspar: Writing – original draft, Investigation, Formal analysis, Data curation. **Catarina I. Gonçalves:** Writing – original draft, Investigation, Formal analysis, Data curation. **Ema L. Nobre:** Writing – review & editing, Resources. **Fernando Fonseca:** Writing – review & editing, Resources. **Cláudia Amaral:** Writing – review & editing, Resources. **João S. Duarte:** Writing – review & editing, Resources. **Luísa Raimundo:** Writing – review & editing, Resources. **Catarina Saraiva:** Writing – review & editing, Resources. **Luísa Cortez:** Writing – review & editing, Resources. **Olinda Marques:** Writing – review & editing, Resources. **Manuel C. Lemos:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2025.100389.

Data availability

The data from this study are available from the corresponding author on reasonable request.

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