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CLINICAL REPORT

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The recurrent p.(Pro540Ser) *MEN1* genetic variant should be considered nonpathogenic: A case report

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Abstract

Pheochromocytoma/paraganglioma (Pheo/PGL) associated with pituitary adenoma (PA) is rare in clinical practice, and a common pathogenic mechanism has been suggested owing to the germline pathogenic variants found in some cases. Our aim is to propose a reassignment for a recurrent *MEN1* genetic variant found in a 54-year-old male patient with bilateral pheochromocytoma and GH-secreting PA. Pheo/PGL genes study was carried out in DNA samples from Pheo as well as PA and no pathological variants or large deletions were detected. Additionally, a *MEN1* gene analysis was performed, and a heterozygous germline variant in exon 10: c.1618C>T; p.(Pro540Ser) was found. No *MEN1* gene deletions/duplications were detected. In evaluating a causal relationship between the c.1618C>T *MEN1* variant and both tumors, we took into account that missense variants are common pathogenic variants in *MEN1*, and the population frequency of this variant is too high to be considered pathogenic. His son (aged 38 and carrier) is asymptomatic, and computational analysis showed discrepancies. We propose that this recurrent variant, previously considered as likely pathogenic, subsequently as variant of uncertain significance, and likely benign should now be reclassified as benign.

KEYWORDS
acromegaly, multiple endocrine neoplasia type 1, p.(Pro540Ser) *MEN1* genetic variant, pheochromocytoma

1 | INTRODUCTION

Pheochromocytomas (Pheo) and paragangliomas (PGL) are rare neuroendocrine tumors arising from the adrenal gland and extradrenal paraganglia, respectively. Globally, up to 40% of patients with Pheo/PGL carry germline variants predisposing to genetic syndromes development. They include multiple endocrine neoplasia (MEN) 2A and MEN2B (*RET*), Von Hippel–Lindau (VHL), neurofibromatosis type 1 (NF1), and familial Pheo/PGL syndromes caused by pathological variants in *SDHx* (*SDHB*, *SDHA*, *SDHAF2*, *SDHC*, *SDHD*). Other less prevalent germline/mosaic variants can be found in genes like *TMEM127*, *MAX*, *EPAS1*, *MDH2*, *FH*, *HIF2A*, *KIF1B*, *PHD1/EGLN2*, *PHD2/EGLN1*, *GOT2*, *SLC25A11*, *BAP1*, and *DLST* among others (Cascón et al., 2019; Kavinga-Gunawardane & Grossman, 2017).

Acromegaly is mostly a sporadic disease almost always caused by a growth hormone (GH) secreting pituitary adenoma (PA). In some cases, acromegaly is part of a hereditary syndrome, of which MEN1 is the most common. MEN1 is an autosomal dominant disease caused by a germline pathogenic variant in *MEN1* (11q13) and is characterized by the presence of primary hyperparathyroidism (PHPT; almost all patients over 50 years of age), PA (around 50%), and gastrointestinal neuroendocrine tumors (30%–70%) (Thakker, 2014; Thakker et al., 2012). Less commonly, MEN1 is associated with other endocrine (adrenocortical and carcinoids) and nonendocrine (facial angiofibromas and collagenomas) neoplasms (Falchetti, 2017). Rarely, GH-secreting PA appears in other hereditary disorders such as McCune-Albright syndrome; Carney Complex; familial pituitary isolated adenoma syndrome, SDH familial syndromes, MEN4 syndrome,

and X-linked acrogigantism (Gadelha et al., 2017; Syro et al., 2015; Thakker, 2014; Thakker et al., 2012).

The coexistence of Pheo/PGL and GH-secreting PA has been described in few cases (Iversen, 1952; O'Toole et al., 2015). In the same vein, Pheo in patients with MEN1 is extremely rare, and most of them are not extensively studied (Dénes et al., 2015; O'Toole et al., 2015). In the present work, we describe a patient with bilateral Pheo and a GH producing PA who harbored a formerly considered likely pathogenic *MEN1* variant (Crépin et al., 2003; Cuny et al., 2013) and later as likely benign (Romanet et al., 2019). This patient was previously reported by us (Guerrero-Pérez et al., 2019), and herein, we detail the expanded study recently performed and suggest a new reclassification for this genetic variant.

2 | CLINICAL REPORT

A 54-year-old male with previous hyperlipidemia, diabetes mellitus, and long-term arterial hypertension (no hypertensive crisis) complained of erectile dysfunction. An abdominal ultrasound performed showed bilateral adrenal masses. The hormonal study showed that 24-h urinary catecholamines levels were 3488 nmol/24 h (normal range 116–699), metanephrines 7.5 μmol/24 h (normal range <6.6), and 4-hydroxi-3-mandelate 198 μmol/24 h (normal range 15–38). The CT scan and MRI revealed a 6 cm heterogeneous right adrenal mass and a 2 cm nodule in the left adrenal. Meta-iodobenzylguanidine scintography showed a bilateral uptake. A successful laparoscopic bilateral adrenalectomy was performed, and pathological evaluation was consistent with typical bilateral Pheo.

During follow-up, physical examination revealed features suggestive of acromegaly. Pituitary profile showed a serum insulin-like growth factor 1 of 46.4 nmol/L (normal range 8–32) and unsuppressed serum GH after an oral glucose tolerance test. Sellar MRI revealed an 8 mm right intra and infrasellar tumor. Subsequently, patient underwent a transphenoidal surgery achieving a complete tumor resection, and pathological evaluation showed a PA with positive immunostaining for GH (focally) and negative for other pituitary hormones. Twelve years after the initial diagnosis, there is no clinical or biochemical evidence of PHPT, neuroendocrine tumor, or other MEN1 related neoplasms.

2.1 | Pheo/PGL gene analysis

For the initial study of pheo/PGL genetic syndrome, DNA samples were obtained from Pheo and PA formalin-fixed paraffin-embedded (FFPE) tumor tissues with Covaris S2 System (Covaris, Woburn, MA, United States), according to the instructions provided by the manufacturer. The Agilent 2100 Bioanalyzer System (Agilent, Santa Clara, CA, United States) was used to assess the size and quantity of DNA fragments in FFPE DNA samples. The genetic test was performed applying a panel previously reported and designed to work with DNA from FFPE tumor tissues (Currás-Freixes et al., 2017), which included the *RET*, *VHL*, *NF1*, *MAX*, *TMEM127*, *SDHA*, *SDHB*, *SDHD*, *SDHC*, *SDHAF2*, *MDH2*, *FH*, *EPAS1*, and *HRAS* genes. DNA libraries were prepared according to the manufacturer's protocol, and samples were sequenced using the MiSeq platform (Illumina) with a paired-end mode using MiSeq Reagent Kit V3 (Illumina) and 300 cycles. Additionally, multiplex ligation-dependent probe amplification (MLPA, MRC-Holland) was applied to germline DNA in order to discard the presence of gross deletions in *SDHs/MAX* genes (SALSA MLPA probemix P226 SDH; SALSA MLPA Probemix P429 SDHA-MAX), *VHL* (SALSA MLPA Probemix P016 VHL), *FH* (SALSA MLPA Probemix P198 FH), *TMEM127*, and *MDH2* by multiplex PCR. No pathological variants or large deletions were detected when using these approaches. FFPE tumor slides were evaluated for SDHB-immunohistochemistry using anti-SDHB rabbit polyclonal antibody (Sigma-Aldrich Corp), as positive staining suggests the absence of a mutation in SDHs genes.

2.2 | *MEN1* genetic study

Since no causative genetic variants were found in the first genetic study, analysis of the *MEN1* gene (NM_130799.2) was performed using germline DNA, applying standardized PCR protocol in which coding regions of exons 2–10 were amplified. PCR products were sequenced by using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, United States) and purification with Millipore system (96 well plates Multiscreen PCRu96 & Montage seq96), followed by analysis with ABI Prism Genetic Analyzer 3130.xl (Applied Biosystems). Possible deletions/duplications were studied using MLPA (SALSA MLPA probemix P244 AIP-MEN1). After sequencing all the coding regions and boundaries of exons, we found a heterozygous germline variant in exon 10: c.1618C>T; p.(Pro540Ser). This variant had been previously described as likely pathogenic (Crépin et al., 2003; Cuny et al., 2013), and this led us to label this patient as MEN1 with an incomplete clinical expression. No deletions/duplications were found in the MEN1 MLPA analysis. The 38-year-old patients' son was studied, and the same variant was found. To date, after 6 years of follow-up, he has no symptoms of endocrine disease, and repeated biochemical analyses have ruled out PHPT.

In order to evaluate a causal relationship between the c.1618C>T *MEN1* variant and both tumors in our patient, we looked for the presence of loss of heterozygosity (LOH) in the Pheo and PA tumor tissues. We isolated genomic DNA from FFPE of both tissues as follows: 5 tissue sections of 10 μm of tumor-tissue were placed in 180 μl of ATL buffer (QIAmp DNA Minikit, QIAGEN) and 20 μl of Proteinase K/24 h at 56°C for 72 h without previous paraffin extraction. The rest of the process was performed according to the standard kit procedure. The amplification of exon 10 of *MEN1* gene where the c.1618C>T variant is located was performed using flanking primers 5′ GCCAGCACTGGACAAGGGCC3′ and 5′ CAAGCGGTCCGAAGT CCCCA 3′. After Sanger sequencing, Pheo showed LOH (Figure 1), but it was not present in the PA. This variant (rs745404679) presents a total allele frequency of 0.0001380 in gnomADv3, showing an allele

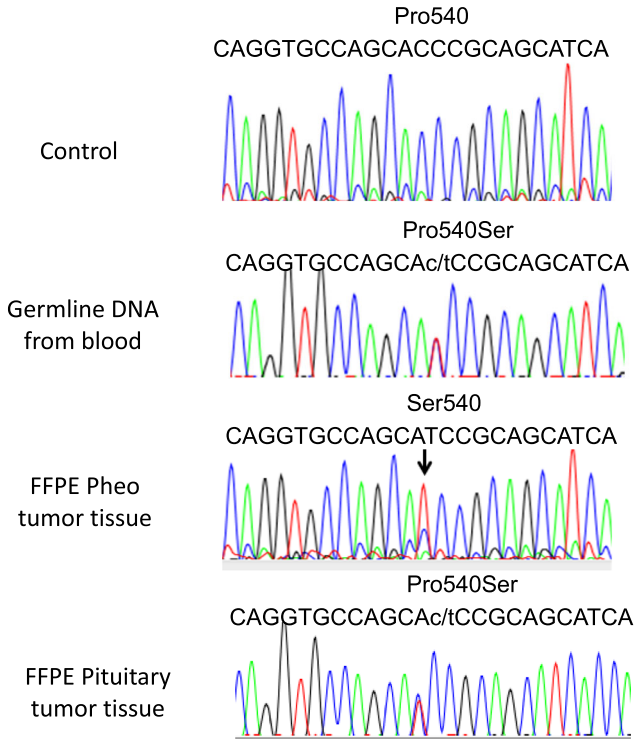

FIGURE 1 Loss of heterozygosity (LOH) analysis in pheochromocytoma and pituitary tumor. LOH is observed in pheochromocytoma but not in the pituitary tumor tissue [Color figure can be viewed at wileyonlinelibrary.com]

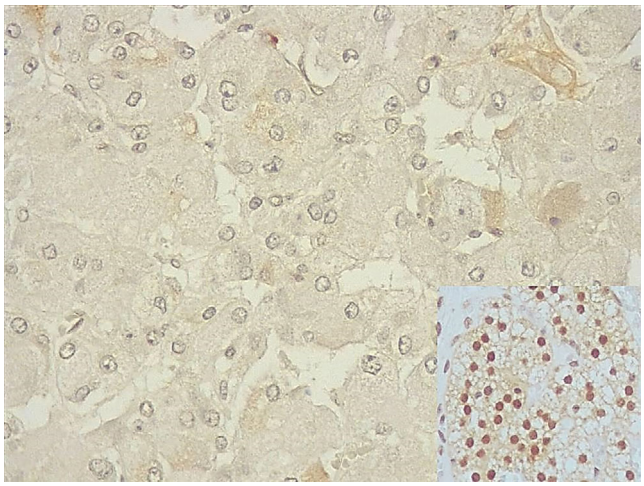

FIGURE 2 Menin staining shows loss of expression in neoplastic pheochromocytoma cells (immunoperoxidase, ×40), whereas retaining the expression in adrenal cortex is used as positive control [Color figure can be viewed at wileyonlinelibrary.com]

frequency of 0.0009813 in the Latin population. In ClinVar, this change is described in one case as likely benign and in eight cases as variant of uncertain significance (VUS). Multiple computational analysis showed discrepancies (e.g., GVGD, mutationtaster, and polyphen predicted pathogenicity but Provean predicted neutrality).

Immunostaining for menin was performed using menin antibody (recombinant Anti-Menin antibody [EPR3986]). Pheo and GH producing PA of patient were stained for menin using a rabbit polyclonalantimenin antibody (Abcam; ab2605, dilution 1:500), as previously described (Lodewijk et al., 2015). Normal adrenal cortex and Pheo from a patient with no known germline variant were used as a positive control (Figure 2).

3 | DISCUSSION

The prevalence of Pheo/PGL in general population is about 1 case per 2500–7000 people (Eisenhofer et al., 2013; Mazzaglia, 2012), and symptomatic PA is roughly 1 case per 1000–1300 people (Daly et al., 2006). GH-secreting PA is an even rarer tumor with an estimated prevalence around 3–7 cases per 100,000 people (Ribeiro-Oliveira & Barkan, 2012). Considering the statistical probability, the presence of both entities in the same patient should make the clinician strongly consider the possibility of hereditary disease. Some hypotheses have been proposed for this tumor association: Pheo/PGL predisposing variants might cause PAs and vice versa; two different variants are responsible for each tumor; an ectopic hormone secretion produced by Pheo/PGL mimics a PA or both tumors are caused by a novel gene pathologic variant (O'Toole et al., 2015).

Including the previous cases reported and their own cohort of patients studied with Pheo/PGL and PA, Dénes et al. found germline variants in *SDHA*, *SDHB*, *SDHC*, *SDHD*, *VHL*, *RET*, and *MEN1* genes (Dénes et al., 2015). They demonstrated LOH at *SDHB* locus in the PA samples and LOH at *MEN1* locus in the Pheo samples; suggesting the pathogenic role of these genes in developing these tumors (Dénes et al., 2015). Regarding two patients with *MEN1* variant, only one harbored acromegaly. He was a 27-year-old male patient with a mixed GH-PRL secreting macroadenoma, and a Pheo was detected 4 years later. The patient also had PHPT and a carcinoid tumor. In this case, a *MEN1* variant (c.1452delG; p.Thr557Ter) was found. Pheo showed LOH in the *MEN1* gene, and the menin staining of the Pheo tissue was negative. The second patient with *MEN1* variant was affected by Pheo, parathyroid hyperplasia, and pancreatic neuroendocrine tumor; but, in this case, there was no PA. They concluded that genes predisposing Pheo/PGL can rarely be associated to PA, whereas known genes cause PA as *MEN1* can be associated with Pheo/PGL (Dénes et al., 2015). A further four patients with PA associated to Pheo/PGL and *MEN1* variant have been described, although none had acromegaly (Dackwin et al., 1999; Jeong et al., 2014; Langer et al., 2002). In the review by O'Toole et al. (2015), they report 23 patients without identified variants but with suspicious features of family syndromes; 11 patients with acromegaly. Also, from 28 patients without identified variants or suspicious features (considered isolated cases), 11 patients had acromegaly.

The advent of high-throughput DNA and computing technologies in recent years have led to a dramatic increase of genetic variants identification. Many variants initially classified as pathogenic were

finally considered as VUS or benign after further analyses, which highlight the complexity of this issue.

According to the current ACMG rules, classification of variants fall into five categories based on criteria using several evidence types (e.g., population data, computational data, functional data, and segregation data): "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" (Romanet et al., 2019). The missense p.(Pro540Ser) in *MEN1* was initially described by Crépin et al. (2003) and later classified as likely pathogenic by Cuny et al. (2013). While using the ACMG guidelines and the Romanet's specific guides for *MEN1* variant evaluation, this variant was the subject of a new classification and was labeled as likely benign. In our patient, LOH affecting *MEN1* locus together with a menin negative staining was observed in the Pheo tissue. Meanwhile, LOH was not observed on the PA tissue (Figure 1), and the menin staining was inconclusive (data not shown). According to the classification guidelines for the interpretation of *MEN1* missense variants, this c.1618C>T variant includes the following items: PP2 (pathogenic missense variants in *MEN1* gene are a common cause of MEN1 disease), BS1 (frequency of this variant is 1.76 and 12.5 times too high to be considered pathogenic according to the total allele frequency and to the Latin population, respectively), BS4 (his son does not present biochemical or clinical features of MEN1), and BP4 supporting (multiple computational analysis shows discrepancies). The absence of LOH in PA is not helpful in the variant classification (Tanaka et al., 1998). LOH in 11q13 is frequent in Pheos, and its presence also does not contribute to the classification (Sun et al., 2006). It is also known that the rate of LOH increases with age in normal cells, and therefore, in this case, it does not necessary indicate a direct association.

In conclusion, even though PA and Pheo/PGL is a rare tumor association and a genetic syndrome should be suspected, we suggest that p.(Pro540Ser) genetic variant, formerly considered as likely pathogenic of MEN1, subsequently as a VUS, should be reclassified as a benign.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceived the study and wrote original draft: Carles Villabona and Josep Oriola. *Acquisition and curation data*: Teresa Serrano, Fernando Guerrero-Pérez, Nuria Valdés and Mariló Chiara. *Analysis and interpretation data*: Carles Villabona and Josep Oriola. *Critical revision of the manuscript*: Mercedes Robledo. All authors have read and agreed to publish the final version of the manuscript.

ETHICAL COMPLIANCE AND INFORMED CONSENT

The patient's confidential information was protected according to national normative. This manuscript has been approved for its publication by the Clinical Research Ethics Committee of Bellvitge University Hospital (PR134/21).

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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