Follow-up study of a Colombian family with a novel MEN1 variant and rare ACTH-producing pancreatic neuroendocrine carcinoma

Julián C. Riaño-Moreno (jcriano@cancer.gov.co)
Instituto Nacional de Cancerología
Angélica María González-Clavijo
Universidad Nacional de Colombia
William C. Torres-Jara
Instituto Nacional de Cancerología
Vilma L. Medina-Boada
Instituto Nacional de Cancerología
Alfredo Ernesto Romero-Rojas
Instituto Nacional de Cancerología
Isabella Vieda-Celemin
Universidad Nacional de Colombia
Jordan A. Avila-Moya
Universidad Nacional de Colombia
Johan A. Baron-Cardona
Universidad Nacional de Colombia
Juan P. Bravo-Patiño
Universidad Nacional de Colombia
Oscar S. Torres-Zambrano
Universidad Nacional de Colombia
Luis Felipe Fierro-Maya
Instituto Nacional de Cancerología

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Abstract

Purpose

This article reports on a 12-year follow-up of a Colombian family with a novel MEN1 gene variant (c.698dup, p.Met233IlefsTer4), identified through cascade genetic screening. The index case involved a rare type of tumor, an ACTH-secreting pancreatic neuroendocrine carcinoma.

Methods

The index case underwent *MEN1* testing after presenting with pancreatic neuroendocrine tumors and hyperparathyroidism. Cascade genetic screening of relatives revealed four additional carriers. Biochemical and imaging surveillance was conducted as per clinical guidelines.

Results

All affected family members first showed signs of primary hyperparathyroidism (PHPT) in their 20s to 50s. Notably, the index case developed a rare type of tumor known as ACTH-secreting pancreatic neuroendocrine carcinoma, which, to our knowledge, is the first instance reported in a MEN1-affected family. Due to proactive screening, pituitary neuroendocrine tumors (PitNETs) were identified as microadenomas in two carriers.

Conclusion

This study demonstrates the value of cascade screening for early diagnosis and tailored management in MEN1 families. It also reports a unique ACTH-producing pancreatic neuroendocrine carcinoma in MEN1. Systematic documentation of cases is critical to elucidating geographical and phenotypic variation and devising genotype-based management approaches.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome marked by a predisposition to endocrine and non-endocrine tumors with equal gender distribution and near-complete penetrance due to loss-of-function variants in the MEN1 gene [1]. Penetrance increases with age, reaching approximately 95% by age 40. MEN1 typically involves primary hyperparathyroidism (PHPT), pituitary neuroendocrine tumors (PitNETs), and gastroenteropancreatic (GEP) neuroendocrine tumors (NETs), but it can also present with carcinoids, adrenocortical tumors, and facial angiofibroma, among others.

Diagnosis is based on (i) two MEN1-associated tumors, (ii) one MEN1 tumor and a first-degree relative with a MEN1 variant, or (iii) identification of an asymptomatic carrier through cascade genetic screening. Clinical variability and the influence of other factors complicate diagnosis [2], highlighting the role of genetic testing in confirming MEN1 and identifying at-risk family members.

Molecular techniques, such as MEN1 gene sequencing, reveal pathogenic variants in 70–90% of cases, with about 10% arising de novo [3]. Cascade screening has shifted diagnosis to younger, often asymptomatic individuals, advancing early intervention [4, 5]. Although not mandatory, molecular testing is invaluable for precise risk assessment, targeted monitoring, counseling, reducing morbidity and mortality, and avoiding unnecessary tests in unaffected relatives [6]. Ongoing research into genotype-phenotype correlations in MEN1 families continues to refine our understanding of the syndrome.

In this study, we report on a 12-year follow-up of a Colombian family with a novel MEN1 variant: c.698dup, p.Met233IlefsTer4, affecting five relatives across three generations (Fig. 1a). The variant was first identified in an index case meeting MEN1 clinical criteria. Subsequent cascade genetic testing identified high-risk individuals. Our analysis examines the clinical impact, expressivity, and intrafamilial behavior of this variant, contributing to the genetic knowledge of MEN1. The study also demonstrates the benefits of cascade screening for improving clinical management, early detection, and outcomes in families at risk for MEN1-associated diseases.

Case presentation

Index case (III-2)

The index patient (III-2), a 24-year-old female, was diagnosed with hyperinsulinemic hypoglycemia in March 2009, following a year of symptoms such as asthenia, adynamia, syncopal episodes, and a seizure episode a month before diagnosis. An initial endoscopic ultrasound revealed a focal hypoechoic lesion with regular edges, measuring 18 mm at the junction of the head and body of the pancreas. A subsequent partial pancreatectomy and splenectomy performed a month post-diagnosis (April 2009) confirmed a multifocal, well-differentiated grade 1 NET (mitoses 0 per 2 mm^2 and Ki67 index 1%), along with immunohistochemical positivity for insulin (insulinoma) (Table 1, 2). No necrosis, vascular invasion, or extrapancreatic extension was observed. The pancreatic section edge was free of tumors, as well as the spleen. A tumor-free peripancreatic lymph node was reported. The patient remained asymptomatic for eight months. However, following this period, she experienced tonic-clonic seizures alongside hyperinsulinemic hypoglycemia. Abdominal imaging revealed a new pancreatic head lesion, and the patient underwent further surgery in our institution (Instituto Nacional de Cancerología, Bogotá D.C., Colombia) with residual pancreatectomy, duodenal resection, and peripancreatic soft tissue resection (May 2010). Pathological examination confirmed a well-differentiated, histological grade 1 NET in the pancreas, with tumor involvement found in two lymph nodes; one node was immunohistochemically positive for gastrin and adrenocorticotropic hormone (ACTH) (Table 1, 2). Within the same year, parathyroid hormone (PTH)-dependent hypercalcemia was diagnosed and managed surgically through subtotal parathyroidectomy and parathyroid reimplantation, with appropriate biochemical control.

Given the presence of multiple entero-pancreatic NETs and parathyroid adenomas, a clinical suspicion of MEN1 was generated. The patient was referred to a genetic service in July 2010, where MEN1 testing via Sanger sequencing revealed the variant MEN1: c.698dup, p.Met233IlefsTer4 (Fig. 1b) .

In 2011, the patient lost contact with our institution due to pregnancy but re-engaged in 2013, presenting with symptoms of hyperglycemia and severe hypokalemia. Further evaluations led to a diagnosis of ACTH-dependent ectopic Cushing's syndrome. Imaging revealed focal hepatic lesions in segment IV and pelvic bone compromise. The liver compromise was treated with a left hemihepatectomy. The pathological study confirmed liver and periportal lymph node metastases of neuroendocrine neoplasia with an increase in the histological grade and morphology of a poorly differentiated small cell neuroendocrine carcinoma (25 mitoses per 2 mm^2 and Ki67 index of 50%). Immunohistochemistry showed focal positivity for ACTH (10% of tumor cells) in both the liver lesion and metastatic nodes. External radiotherapy with fractionation of 300 cGy up to a total dose of 3,000 cGy in the pelvic field was done, and chemotherapy with etoposide/cisplatin was initiated with poor response. Disease progression occurred, which involved the liver, bones, and lungs, and the patient passed away five years after the initial diagnosis.

Material and methods

Molecular analysis of the MEN1 gene was performed at the Instituto Nacional de Cancerología (Bogotá D.C., Colombia). Sanger sequencing was applied to genomic DNA extracted from peripheral lymphocytes of the index case, targeting the entire coding sequence and exon-intron junctions. Nine exons were amplified using eight primer pairs (available upon request) and sequenced with the BigDye Terminator Cycle Sequencing Kit v3.1 on a 3500 Genetic Analyzer (Applied Biosystems/HITACHI, USA), following standard protocols. Electropherograms (Fig. 1b) were compared to reference sequences NG_008929.1 and NM_130799.2 using the SeqA v6.0 and SeqScape v3.0 software (Applied Biosystems, USA).

A novel 698 base pair (T) duplication in the MEN1 gene was identified, resulting in a significant frameshift variant designated as MEN1 (NM_000244): c.698dup, p.Met233IlefsTer4, confirmed via Sanger sequencing (Fig. 1b). This variant manifests as a frameshift variant in transcript NM_000244.3 (NCBI) and an alternative transcript, ENST00000377316.6 (Ensembl). It remains unreported in ClinVar, the French MEN1 database (http://www.umd.be/MEN1/), and other genomic variation databases (1000Genomes, ExAC, dbSNP, and HGMD). This variant represents a non-conservative change, transitioning from a hydrophobic to an essential amino acid (BLOSUM62=-2; Grantham distance = 126) in a highly conserved position within the protein domain.

Initially, in alignment with the American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification [7], the variant was classified as "likely pathogenic" based on the phenotype observed in the index case. This categorization was tentatively maintained under the PVS1 and PM2 criteria. However, after thoroughly examining the family's clinical and genetic history, we refined this classification to "pathogenic." This reclassification was reinforced by the PP1 (co-segregation with the disease among several affected family members) and PP4 criteria (the patient's phenotype or family medical history distinctly correlates with a disease characterized by a unique genetic cause).

Cascade genetic screening was performed on eight additional family members (Fig. 1a) across three generations from 2010 to 2022, utilizing Sanger sequencing on genomic DNA samples. In 2010, the

screening involved the daughters of the index case, identifying one carrier (IV-2) (Fig. 1d) .. The investigation then extended to her parents: the mother was tested in 2010, yielding a negative result, while the father (II-4) was tested in 2013 and identified as a carrier (Fig. 1c). In the same year, the paternal aunts of the index case were screened, all of whom tested negative. However, the fraternal sister of the index case was identified as a carrier. Following a marital separation, the father (II-4) remarried and fathered a son, who was tested in 2021, given the familial antecedents. The test confirmed him as a carrier of the MEN1 variant. Following the Endocrine Society's clinical practice guidelines [8], the identified carriers within this family underwent rigorous imaging and biochemical monitoring, as detailed in Tables 1 and 2.

Results

Patient II-4

During the cascade genetic screening, patient II-4, the father of the index case, was identified as a carrier on June 21, 2013, at the age of 48 years. He remained asymptomatic until the age of 55 years (2020) when he experienced dyspepsia and self-limited diarrhea. Subsequently, hypergastrinemia was documented. Upper digestive tract endoscopy revealed a nodular lesion in the duodenum; the histopathological analysis of an endoscopic biopsy confirmed the presence of well-differentiated, multifocal, grade I duodenal NETs (Table 1, 2). An abdominal magnetic resonance imaging (MRI) disclosed a lesion adjacent to the uncinate process without a compressive effect on the central pancreatic duct, another similar lesion adjacent to the third portion of the duodenum without a compressive effect, and an intramural lesion at the level of the second portion of the duodenum. The tumoral lesions were not deemed suitable for surgical intervention, and treatment with proton pump inhibitors and somatostatin analogs commenced with the response of stable disease for approximately one year. Disease progression was noted in January 2022. A multidisciplinary board proposed treatment with lutetium-177 (Lu-177) DOTATOC; the patient completed four cycles with a cumulative dose of 800 mCi in September 2022 with a response of stable disease six months after the last cycle.

In early 2021, PHPT was also documented, prompting a left lower parathyroidectomy in March of the same year. The histopathological analysis confirmed a parathyroid adenoma, and biochemical control was reached. As of the latest follow-up, no pituitary involvement has been documented.

Patient III-3

Patient III-3, the sister of the index case, was identified as a carrier in June 2013 at the age of 21 years. After detecting the variant, she began follow-up consultations with the endocrinology service of a different institution than the other family members. Three years later, a prolactin-secreting pituitary microadenoma was discovered, for which treatment with cabergoline was initiated, as well as PHPT, which was treated with right lower parathyroidectomy. Prolactin and calcium levels have remained controlled with the interventions.

In June 2020, an MRI of the sella turcica did not show the lesion. Because of that, the treatment was stopped with a recurrence of symptomatic hyperprolactinemia. Thus, it was decided to reassume the treatment with cabergoline, which remains ongoing. She is currently 31 years old, and up to date, no duodenal-pancreatic NETs have been documented.

Patient III-4

Patient III-4 was identified as a carrier in March 2022 at the age of 22 years and began follow-up consultations with endocrinology and genetic services. Eight months post-variant identification, screening investigations revealed a lobulated pituitary adenoma with dimensions of 9 x 9 x 9 mm. The biochemical assessment evidenced a growth hormone (GH) and prolactin excess. Within the same year, surgical intervention for the pituitary lesion was undertaken through a transsphenoidal approach. Pathological examination revealed a pituitary microadenoma with a focal expression of prolactin and growth hormone, exhibiting a proliferation index (Ki-67) of 3%. Post-surgical central hypocortisolism was diagnosed, and hydrocortisone supplementation was initiated. Persistently elevated insulin-like growth factor 1 (IGF-1) and GH levels were detected; consequently, somatostatin analog treatment was indicated.

Additionally, PHPT was diagnosed with parathyroid scan results indicative of a left lower parathyroid adenoma, and the patient is waiting for surgery of parathyroidectomy. At the last control, no duodenal-pancreatic NETs have been documented.

Patient IV-1

Patient IV-1, the daughter of the index case, was identified as a carrier in December 2010 at the age of 1 year. Currently, at the age of 14, she remains asymptomatic, and no tumors have been detected.

Table 1
Clinical and biochemical findings in family members with MEN1 during the follow-up

	III-2	II-4	III-3	III-4	IV-1
MEN1 Sanger sequencing	+	+	+	+	+
Age at diagnosis (years)	24	48	21	23	1
PHPT	+	+	+	+	ND
Age at diagnosis (years)	24	55	23	24	
PTH (pg/ml) (reference value)	93.29 ↑ (15–65)	156 ↑↑ (15–65)	122 ↑↑ (15–65)	156 ↑↑ (15–65)	44 (15–65)
Calcium (mg/dl) (reference value)	11.1 ↑ (8.4–10.2)	13 ↑ (8.4–10.2)	10.8 ↑ (8.4–10.2)	11.2 ↑ (8.4–10.2)	9.6 (8.4–10.2)
PitNEN	ND	ND	+	+	ND
Pituitary MRI	Normal	Normal	Pituitary Microadenoma	Pituitary Microadenoma	Normal
Age at diagnosis (years)			23	25	
Prolactin (ng/ml) (reference value)	26.47 (1.3–25)	23.3 (4.7–23.3)	153.6 ↑↑↑ (1.3–25)	133 ↑↑↑ (1.3–25)	17.2 (1.3–25)
IGF-1 (ng/ml) (reference value)	-	298 (135–449)	232.5 (116–358)	581 ↑↑↑ (116–358)	292 (286–660)

	III-2	II-4	III-3	III-4	IV-1
OGTT-induced GH nadir (ng/ml) (reference value)				1.51 ↑↑↑ (< 0.4)	
DP-NETs	+	+	ND	ND	ND
Age at diagnosis (years)	24	56			
Abdominal image findings	Pancreas tumor Liver metastases	Duodenal tumors Nodal metastases	Normal	Normal	Normal
Functional DP tumors	Hyperinsulinemic hypoglycemia (insulinoma) and ectopic Cushing´s syndrome*	Zollinger-Ellison syndrome (gastrinoma)			

Symbols used include: +, presence; (-): not available; -, absence; ND: Non-Diagnostic; *PHPT*, primary hyperparathyroidism; *PTH*, parathyroid hormone; *PitNEN*, pituitary neuroendocrine neoplasia; *MRI*, magnetic resonance imaging; *DP-NETs*, duodenal-pancreatic neuroendocrine tumors; *IGF-1*, insulin-like growth factor 1; *OGTT*, oral glucose tolerance test; *GH*, growth hormone; *DP*, duodenal-pancreatic. Images used include MRI images for all subjects except III-3 and IV-1 for whom abdominal ultrasonography was used as alternative. *Ectopic Cushing's syndrome caused by a pancreatic neuroendocrine carcinoma metastatic to liver. Empty cells indicate not apply. Data for member IV-1 derived from the most recent follow-up at the age of 12 years.

Table 2
Biochemical findings in patients with functional DP-NETs

	III-2	II-4
Insulinoma	+	
Insulin (uU/ml)	3.71	-
(Cut-off to diagnosis)	(> 3)	
Proinsulin (pmol/l)	34.9	-
(Cut-off to diagnosis)	(> 5)	
C-peptide (ng/ml)	1.12	-
(Cut-off to diagnosis)	(> 0.6)	
Glucose (mg/dl)	27	118
(Cut-off to diagnosis)	(< 55)	(< 55)
Gastrinoma	-	+
Gastrin (pg/ml)	-	> 1000
(Cut-off to diagnosis)		(> 125)
Ectopic Cushing's syndrome	+	-
ACTH (pg/ml)	78.95	-
(Cut-off to diagnosis)	(> 15)	
Cortisol DST (ug/dl)	120	-
(Cut-off to diagnosis)	(< 1.8)	

Symbols used include: +, presence; -, absence; *DP-NETs*, duodenal-pancreatic neuroendocrine tumors; *ACTH*, adrenocorticotropic hormone; *DST*, dexamethasone suppression test. Empty cells indicate either data not available or not applicable.

Discussion

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder with a global prevalence ranging from 1 to 10 per 100,000 individuals, with geographical incidence variations that may reflect the founder effect [9]. Despite its global presence, data on MEN1's prevalence in Colombia remains sparse. Our 12-year study documents the clinical trajectory of a Colombian family carrying a novel MEN1 germline variant: c.698dup. Notably, with 10% of MEN1 variant arising de novo [3], the origin of the variant in this family—whether inherited from individual I-1, who had gastric cancer or as a new variant in

individual II-4—is uncertain (Fig. 1a). The absence of this variant in existing databases and the lack of a Colombian MEN1 registry complicate the assessment of a potential founder effect, highlighting the need for comprehensive case tracking.

The MEN: c.698dup variant was initially detected in the index case upon the emergence of clinical symptoms. A follow-up cascade genetic screening was performed on eight high-risk family members, uncovering four more carriers of this variant. Given that MEN1 predominantly manifests through tumors in the parathyroid glands, anterior pituitary, and gastroenteropancreatic (GEP) axis, alongside possible tumors in other regions like the adrenocortical glands, lungs, and thymus [3], the early identification of this variant holds substantial value. The age-associated risk of MEN1 reveals that over 50% of individuals show clinical features by the age of 20 years and a staggering 95% by age 40 years.

PHPT is the most common initial presentation in MEN1, occurring in about 85% of patients, and often serves as the first sign of this disorder [10]. In the family we studied, everyone who clinically manifested the disease (III-2, II-4, III-3, and III-4) initially presented with PHPT, accompanied by varying degrees of hypercalcemia.

Pancreatic neuroendocrine tumors (pNETs) are common in MEN1, with a 40% incidence rate, typically as non-functional pancreatic neuroendocrine tumors (NF-pNETs). Contrary to this trend, our study documents two cases of functional NETs within the same family. The index patient was diagnosed with an insulinoma at 24 and developed an ACTH-producing pancreatic neuroendocrine carcinoma (NEC) at 29—patient II-4 presented with Zollinger-Ellison syndrome at 48 [11]. Meanwhile, patients III-3, III-4, and IV-1, aged 31, 24, and 14, respectively, remain asymptomatic under close clinical surveillance.

Insulinomas are the most common functional NETs, representing 7–31% of cases, with gastrinomas accounting for 5% [12]. These findings align with the presentations in the index case and patient II-4. Notably, the index case's second pancreatic tumor, causing ectopic ACTH secretion syndrome (EAS), is a novel finding in MEN1, as such carcinomas are typically associated with thymic NETs [13–17]. This is the first report of a family exhibiting an ACTH-producing pancreatic NEC, marking a distinctive finding within the landscape of MEN1 phenotypic expression.

The 2022 WHO classification differentiates neuroendocrine neoplasms into well-differentiated NETs and poorly differentiated NECs [18]. NETs are graded as G1, G2, or G3 based on mitotic rate and Ki-67 index, reflecting their proliferative activity. NECs, characterized by high-grade nuclear features, display a high mitotic count (often > 20 per 2 mm^2) and Ki-67 index (typically > 55%) and are associated with aggressive clinical behavior and poor prognosis [18, 19].

NECs are further classified into small cell (SCNECs) or large cell types (LCNECs), rarely linked to hormonal syndromes or somatostatin receptor expression. The case in question involves a functional ACTH-producing P-SCNEC, a rare entity in MEN1, adding to the spectrum of MEN1-NET phenotypic diversity.

The heterogeneity of pNETs encompasses variations in histopathological grade, hormone secretion, and genetic alterations. Notably, grade progression is more common in metachronous than synchronous metastases [20]. Current studies based on next-generation sequencing (NGS) interpretation have shown that tumor variant burden (TMB) in synchronous and metachronous metastatic samples (liver and lymph nodes) is sometimes different from that of the primary tumor (pancreas). Analysis of the clonal and subclonal architecture and genetic profile suggests that most metastatic subclones could be traced back to the initial tumor [21, 22].

PitNETs, or pituitary adenomas, are among the three primary tumors associated with MEN1, with a 30–50% prevalence in affected individuals [23]. Typically developing between the fourth and sixth decades of life, PitNETs are rare before age 20. Prolactinomas are the most common type of PitNET in MEN1, comprising 65% of cases, with somatotropinomas also being significant [24]. This pattern is reflected in the family described in our study. While PitNETs in MEN1 are predominantly macroadenomas (85%), with microadenomas less common (14%) [25], two family members (III-3 and III-4) in our report presented with microadenomas, primarily as prolactinomas, and in one case, with additional GH secretion, which is noted in 5% of PitNETs.

The occurrence of microadenomas in both cases is notable, deviating from the typical macroadenoma presentation in MEN1 [25]. This may be attributed to the early detection of PitNETs in these variant carriers, facilitated by proactive screening, rather than the emergence of clinical symptoms.

This family report exemplifies the clinical heterogeneity of MEN1 syndrome, yet a definitive genotype-phenotype correlation remains elusive. MEN1 is associated with a diverse range of over 20 endocrine and non-endocrine tumors, all linked to loss of heterozygosity (LOH) at chromosome 11q13, where the MEN1 gene resides. We report a new MEN1 germline variant: c.698dup, p.Met233IlefsTer4. The MEN1 gene product, menin, is a tumor suppressor protein with broad expression and four domains: the N-terminal, the middle Thumb, the Palm, and the C-terminal domains. The Thumb and Palm domains contain tetracopeptide repeats crucial for menin protein interactions (Fig. 2a) [26]. These interactions allow menin to regulate gene expression, cell cycle, DNA repair, and other molecular functions [27–29], highlighting its central role in cellular homeostasis.

We propose two molecular mechanisms to explain the pathogenicity of the novel MEN1 variant c.698dup, p.Met233IlefsTer4. The first mechanism concerns the variant's location, which likely causes a methionine-to-isoleucine substitution at position 233 and introduces a premature stop codon shortly after that. This change is expected to result in the loss of the critical palm and fingers domains of menin, disrupting its interaction with menin interaction proteins (MIPs) (Fig. 2b, 2c) [1]. These domains are pivotal for menin's role in various cancer-related pathways, which may contribute to MEN1 phenotype variations in this family. For instance, compromised interaction with FANCD2 could impair DNA repair via the Fanconi anemia pathway [30], while disrupted interaction with MLL1 has been associated with parathyroid adenomas [31]. Altered interactions with proteins such as JunD may affect their oncogenic or tumor-suppressing activities, potentially leading to gastrinomas [27, 32]. Additionally, the menin-PRMT5

interaction is crucial for pancreatic cell proliferation, and its disruption is linked to pancreatic neuroendocrine neoplasms (pNENs). In contrast, the loss of interaction with CHES1 is involved in aggressive pNETs [33, 34]. The menin-NF-kβ interaction also plays a role in suppressing hepatocellular tumors [35].

The second mechanism involves the complete loss of menin protein due to nonsense-mediated decay (NMD), a cellular process that degrades mRNA transcripts with premature stop codons (Fig. 2d) [36–38]. Truncated menin proteins are often undetectable in MEN1 patients, indicating that variants like c.698dup are likely targets for NMD [39]. While further functional studies are needed to confirm these mechanisms, the familial segregation and clinical manifestations provide strong evidence of this variant's pathogenicity.

A deeper understanding of the genetic and molecular consequences of MEN1 variants is essential for developing targeted treatments. For example, functional studies have shown that null menin variants disrupt the interaction with BRCA2, a necessary protein in DNA repair, suggesting that poly (ADP-ribose) polymerase (PARP) inhibitors could be a promising treatment for MEN1-related conditions [40].

Documenting novel MEN1 variants is pivotal for dissecting the diverse phenotypic spectrum associated with this syndrome. Investigating the precise molecular disruptions these variants induce enhances our comprehension of MEN1's pathogenic mechanisms. Such insights enrich our scientific understanding and pave the way for personalized therapeutic interventions that are attuned to the distinct genetic underpinnings of each patient's condition.

Conclusion

In conclusion, our study underscores the importance of comprehensive genetic screening in MEN1-affected families. By tracking a novel MEN1 variant in five carriers, we demonstrated how early genetic identification facilitates prompt intervention and prevention strategies, significantly mitigating the risk of severe morbidity and mortality in high-risk individuals. Our findings also reveal a unique presentation of MEN1 with a specific pancreatic NEC, contributing to the spectrum of MEN1 manifestations. Moreover, our proactive surveillance enabled the early detection of pituitary adenomas at a subclinical size, deviating from the typical clinical discovery at a more advanced stage.

This research highlights the imperative of investigating genotype-phenotype correlations in MEN1 and the influence of distinct genetic variants on disease progression. Such knowledge is essential for developing individualized treatment regimens, including the potential application of targeted therapies like PARP inhibitors. The systematic documentation and analysis of MEN1 cases are particularly crucial in regions like Colombia, where data is scarce. Our study offers valuable insights for improved diagnostic and therapeutic strategies and calls for increased research and reporting on MEN1 worldwide. Enhanced understanding and management of MEN1, particularly in underrepresented areas, will undoubtedly lead to better patient care and outcomes on an international scale.

Declarations

Ethics approval and consent to participate

Approval for this study was obtained from the Research Ethics Committee of the Instituto Nacional de Cancerología (Bogotá, D.C., Colombia). The procedures used in this research adhere to the tenets of the Declaration of Helsinki. All patients involved in the study provided their written informed consent to participate.

Statements and Declarations.

The authors declare that they have no conflict of interest in relation to this study. No external funding was received for conducting this study.

Author Contribution

Conceived and designed the research: JCR and AMG. Took samples: VLM. Literature search and data collection: IVC, JAA, JAB, JPB, OS. Analyzed the data: JCR, AMG, WCT, AER, LFF. Wrote the main manuscript text: JCR and AMG, Prepared figures 1 and 2: JCR and WCT. Prepared tables 1 and 2: AMG and LFF. All authors reviewed the manuscript.

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Figures

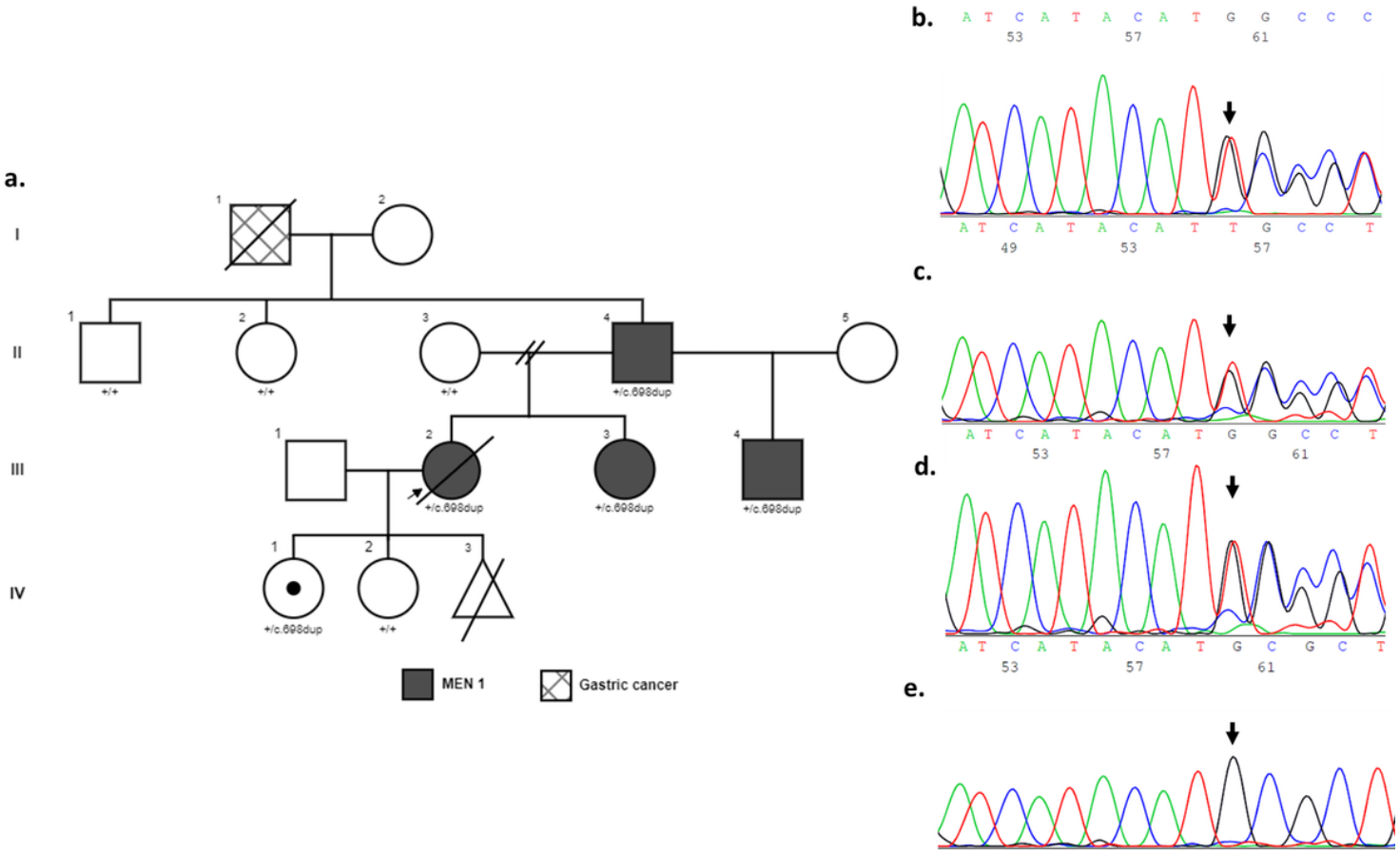

Figure 1

(a) Pedigree of the family affected by MEN1 spanning four generations, with the index patient indicated by an arrow. (b) Forward Sanger sequencing of the proband (III-2). (c) Sanger sequencing for the proband's father (II-4) displaying the frameshift mutation. (d) Sanger sequencing for the proband's daughter (IV-1) identifying her as a carrier of the frameshift variant. (e) Sanger sequencing for another of the proband's daughters (IV-2) revealing the site to be wild type.

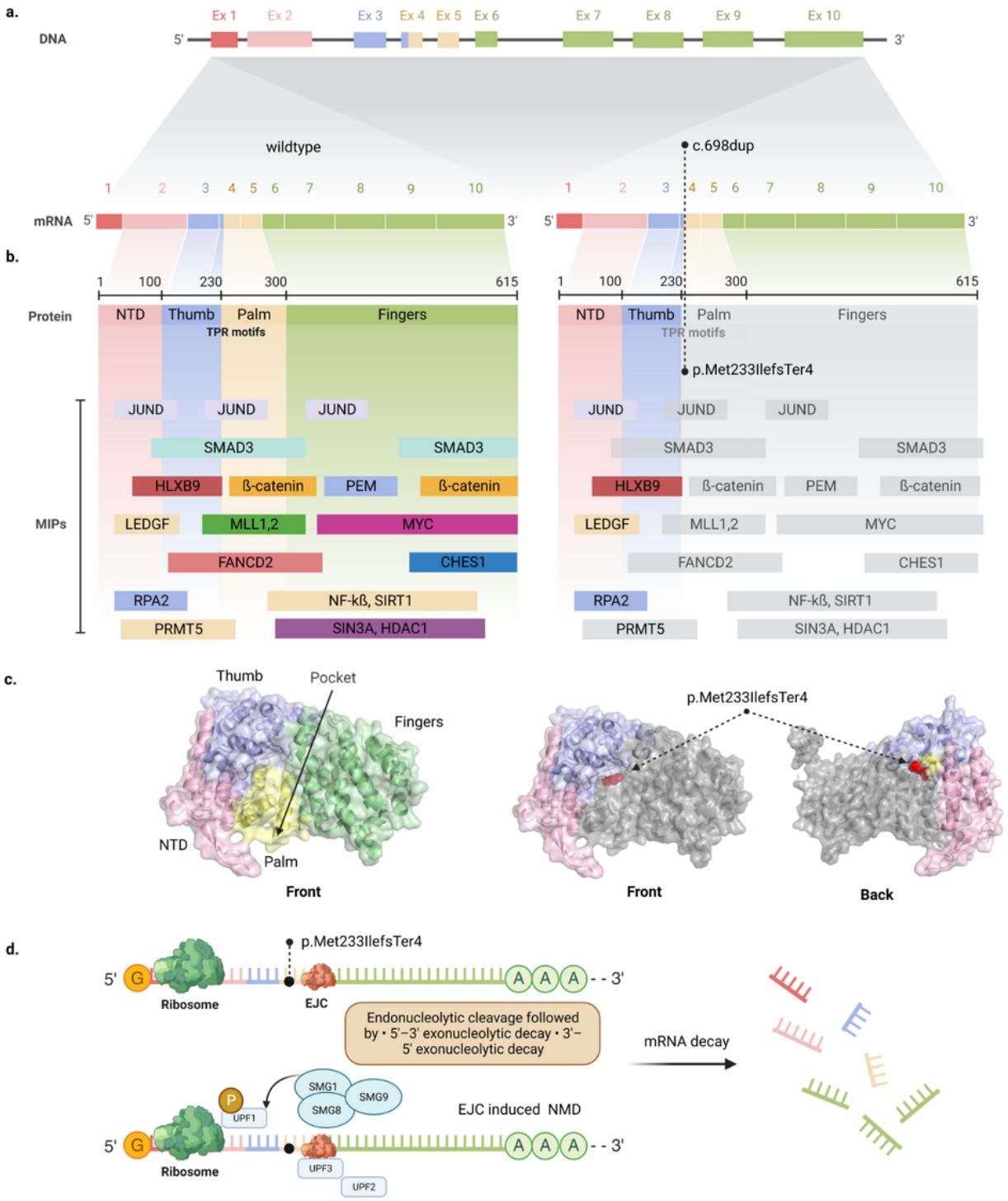

Figure 2

Menin translation and nonsense-mediated mRNA decay (NMD) pathway in MEN1 syndrome. (a) Normal menin translation: Schematic representation of the menin mRNA translation process, illustrating the intact exons and corresponding functional domains of the menin protein. The domains are color-coded for clear differentiation. (b) MEN1 variant-induced disruption: The introduction of a premature stop codon by the MEN1: c.698dup variant leads to a truncated menin protein, lacking the Palm and Fingers

domains. This truncation impedes the protein's ability to interact with menin interaction proteins (MIPs), which are crucial for its tumor suppressor functions. (c) Menin protein structure: The three-dimensional crystal structure of human menin (PDB ID: 3U84) is shown in a frontal view, with domains color-coded as follows: N-terminus domain in light pink, Thumb domain in light blue, Palm domain in pale yellow, and Fingers domain in pale green. The compromised domains in the MEN1: c.698dup variant are highlighted in gray, with the pivotal methionine (Met233) replaced by isoleucine in the variant marked in red. (d) NMD mechanism: Illustration of the NMD pathway activated by the MEN1: c.698dup variant. The exon-exon junction complex (EJCs), a component of the splicing machinery, detects the premature stop codon on the pre-mRNA. This detection recruits UPF1, initiating the formation of the translation termination complex (TTC) with UPF1 and the SMG1-SMG8-SMG9 kinase complex, along with eRF1-eRF3. UPF1-SMG1 binding to EJCs leads to the formation of the decay-inducing complex, where UPF1 is phosphorylated. This phosphorylation inhibits translation and promotes mRNA decay, with the involvement of various exo- and endonucleases. UPF1's ATPase and helicase activities are enhanced by interactions with UPF2 and UPF3X, other NMD factors. The figure also notes that NMD activation can occur independently of EJCs if the premature stop codon is significantly distant from the poly-A tail (not shown in the image).