VARIABLE EXPRESSIVAL IN THREE GENERATIONS OF A COLOMBIAN FAMILY WITH MULTIPLE ENDOCRINE NEOPLASIA WITH MUTATION C.482G> A (P.GLY161ASP) IN THE MEN1 GENE

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INTRODUCTION

Multiple endocrine neoplasia (MEN1, OMIM: 171400) is a genetic disease caused by the germline mutation of the MEN1 gene, which encodes the menin protein. The absence of this tumor suppressor protein facilitates the development of neoplasms in some endocrine glands. This pathology is defined by the predominant presence of:

- Hyperparathyroidism due to parathyroid adenoma: 95% of the carriers of the gene mutation are under 40 years of age.
- Tumors of other endocrine glands: neuroendocrine tumors of the pancreas (gastrinoma, insulinoma), digestive tract, bronchi and thymus.
- Pituitary adenomas: prolactinomas and somattropinomas.
- Adrenal tumors: rarely pheochromocytomas.

DIAGNOSIS

1. **SPORADIC FORM** (No family predisposition to MEN1): coexistence of at least 2 of the 3 following disorders: primary hyperparathyroidism, pancreatic neuroendocrine tumors, pituitary adenomas.

2**. FAMILY FORM** (in families with known predisposition to MEN1): the diagnosis of a parathyroid tumor (or primary hyperparathyroidism), pituitary or pancreatic is sufficient.

The molecular diagnosis of the MEN1-causing mutation is essential for family genetic counseling, since it allows early treatment with which the natural course of the disease can be changed. Taking into account that 20-25% of patients with this pathology can present mutations that are still unknown, a negative result in the genetic analysis does not rule out the disease.

MATERIALS AND METHODS

Clinical analysis, mutational and sequencing report Sanger from gene MEN1 are reported to 6 patients with neoplasia within a large family 15 members (three generations), with 8 members affected.

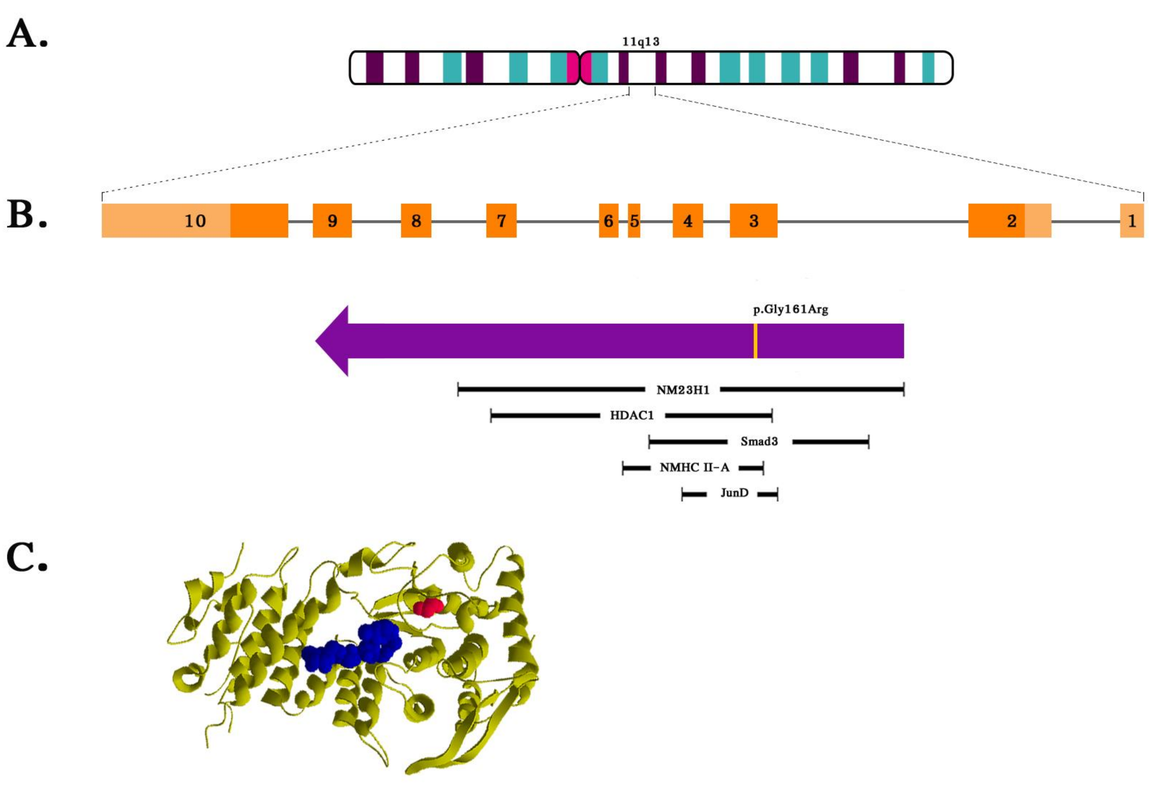

Figure 1: A. Chromosomal location of the MEN1 gene. B. Schematization of the mRNA and transcript of the MEN1 gene. The yellow line indicates the familiar mutation and the black bars indicate the regions of interaction with the proteins. C. Three-dimensional modeling of the menin protein (green) interacting with the JunD protein (blue). The mutation p.Gly161Arg is represented in red. Own image

OUTCOMES

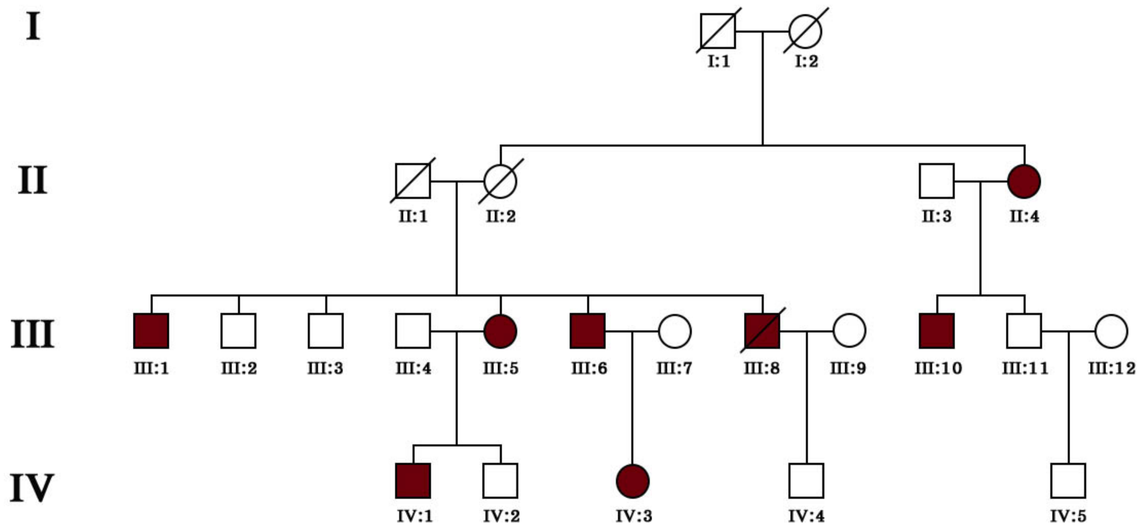

Figure 2: Familiogram of three generations affected with MEN1

	Gender	Age	First Tumor	Other Tumors				Mutation
				Hypophysis	Thymoma	Trachea or Lung	Pancreas	
II:4	F	75	Parathyroid					+
III:1	M	28	Parathyroid	Gh Prolactin			+	+
III:5	F	40	Parathyroid	Adenoma		+	+	+
III:6	M	46	ND		+			ND
III:8	M	44	ND		+			ND
III:10	M	53	Parathyroid					+
IV:1	M	10	Parathyroid	Prolactinoma				+
IV:3	F	9	Parathyroid					+

Table 1: Clinical characteristics of family with MEN1. F: female, M: male, ND: not available

DISCUSSION AND CONCLUSIONS

The 66% of the adults population debuted with parathyroid pathology. And the 100% of the children affected. The 33% of the adults showed thymoma.

The presence of the c.482G>A (p.Gly161Asp) mutation in MEN1 gene were confirmed by Sanger sequencing in all patients. Therefore, this family with hereditary multiple endocrine neoplasia demonstrate an autosomal dominant inheritance with complete penetrance and high expressivity and is recommend to look always for a parathyroid affection as the first demonstration in the carriers.

All the bioinformatic tools used to predict the mutation effect indicates that the substitution of glycine for aspartic acid at position 161 of MEN1, potentially affect protein structure and function since it is an aminoacid highly conserved between species and is located in a region of interaction with important proteins for the regulation of gene transcription and the progression of the cell cycle, which demonstrates the pathogenic potential of the variant. Although this mutation in MEN1 gene was previously reported by one single japanese family, it has not been described in Colombia.

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