OUR EXPERIENCE IN THE EVALUATION CRITERIA USED FOR THE GENETIC STUDY OF PATIENTS SUSPECTED OF BEING AFFECTED BY MULTIPLE ENDOCRINE NEOPLASIA TYPE1 AND MUTATIONAL SPECTRUM

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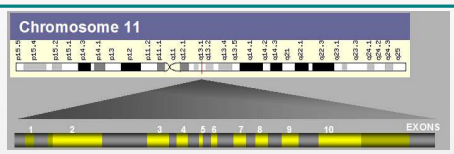
INTRODUCTION

The autosomal dominant Multiple Endocrine Neoplasia Type 1 **(MEN1)**, characterized by parathyroid hyperplasia **(PH)**, neuroendocrine digestive tumours **(NET)** and pituitary adenomas **(PA)**, is due to mutations in the tumor suppressor gene *MEN1* (11q13.1) encoding a 610-amino acid protein, menin. Guidelines recommend *MEN1* mutational analysis in index cases with two or more MEN1-associated tumors, in 1st degree relatives of mutation carriers and if clinical data suggest MEN1.



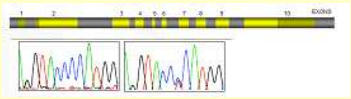
AIM

To compare our results in *MEN1* genetic analysis from patients referred by Spanish endocrinologists and geneticists from 1997 to 2013 with the inclusion criteria from MEN1 guidelines in order to improve our insight on mutations and phenotype spectrum

PATIENTS AND METHODS

164 index-cases, 117 females and 47 males from 13 hospitals in Spain *(decission to study was taken by referring centers)*

Coding regions and intron-exon boundaries of the *MEN1* gene were analyzed



When no mutation was thus found, MLPA was performed.

In negative cases, we analyzed:

- *CDKN1B*/P27 (MEN4) in MEN1-like
- *AIP* gene (FIPA) in PA
- *CaSR* & *AP2S1* in PH

RESULTS

164 index-cases: 117 female and 47 male (R:2.4)

108

***No MEN1* mutations**

➥ **106: no findings**

➥ **1 *CaSR* and 1 *AP2S1*** *(familiar PH)*

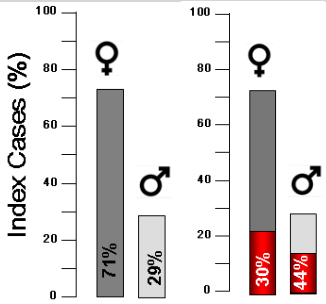
56

***MEN1* mutations**

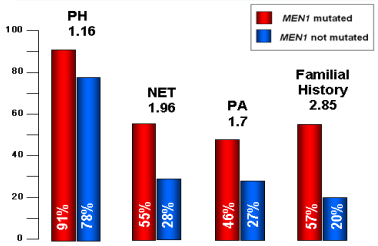
➥ ♀ **35/115 (30%)**

➥ ♂ **21/47 (44%)**

(cases are better selected in males than in females



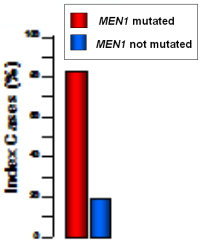
Clinical spectrum of index cases



RELATIONSHIP OF Nº OF MEN1-RELATED TUMORS AND FAMILY HISTORY (FH) WITH PRESENCE OF *MEN1* MUTATIONS

INDEX CASES WITH 3 MEN1-RELATED TUMORS

PH + NET + PA (N=11)	Nº	FH	No FH
Mutated MEN1	9	6	3
Non mutated MEN1	2	0	2



INDEX CASES WITH 2 MEN1-RELATED TUMORS

PH + PA (N=38)	Nº	FH	No FH
Mutated MEN1	14	10	4*
Non mutated MEN1	24	1	23#

Sex distribution:
*2 females, 2 males
#21 females, 2 males

PH + NET(N=27)	Nº	FH	No FH
Mutated MEN1	19	8	11
Non mutated MEN1	8	1	7

NET + PA (N=2)	Nº	FH	No FH
Mutated MEN1	0	0	0
Non mutated MEN1	2	0	2

INDEX CASES WITH 1 MEN1-RELATED TUMORS

PH (N=58)	Nº	FH	No FH
Mutated MEN1 (15%)	9	7#	2*
Non mutated MEN1	49	17	32

Age at diagnosis:
* *29, 56 years*
# *<50 years*
All 9 cases are **females**

NET (N=22)	Nº	FH	No FH
Mutated MEN1 (18%)	4	2	2
Non mutated MEN1	18	1	17

PA (n=4)	Nº	FH	No FH
Mutated MEN1 (25%)	1	1	0
Non mutated MEN1	3	2	1

MEN1 MISSENSE MUTATIONS IN FAMILIAL PH AND RELATED WITH NUMBER OF MEN1 TUMORS: *no association was observed (p value=0.72)*

MUTATIONS	Familial PH	3 tumors	2 tumors	1 tumor
missense	2	4	10	5
truncated	5	5	23	9
TOTAL	7	9	33	14

CONCLUSIONS

- Our data support clinical current referral criteria for *MEN1* molecular genetic testing
- The probability of finding a *MEN1* mutation in a patient is positively correlated with the presence of family history and the number of MEN1-related tumors (NET)
- Cases that present only one tumor + family history, or even one tumor if this is a NET, should be analysed.
- According to our results missense mutations are not associated with familial hyperparathyroidism or milder phenotype.

REFERENCES:

Thakker RV et al. Clinical practice guidelines for multiple endocrine neoplasia type ! (MEN1). J Clin Endocrinol Metab. 2012; 97:2990