2° Convegno interregionale AME
- Emilia Romagna
- Friuli Venezia Giulia
- Lombardia
- Trentino Alto Adige
- Veneto

Tumori dell' Ipofisi: fra Certezze e Criticità

Bologna, 10 Maggio 2014

Forme familiari: quando pensarci e come studiarle

Ernesto De Menis
Dipartimento Medicina Clinica
Ospedale Generale – Montebelluna

Forme familiari: quando pensarci

2014

PREVALENZA

3-5 % di tutti i tumori

PROGNOSI SOGGETTO

- tumore
- altri tumori (morbidità - mortalità)

IDENTIFICAZIONE FAMILIARI

AWARENESS: SEMPRE

Tumori ipofisari
+ altri tumori endocrini
± tumori non endocrini
± altre manifestazioni cliniche

MEN 1
MEN 4 (CDKIs)

Carney's Complex

SDH

(McCune-Albright)

SOLAMENTE Tumori Ipofisari

IFS/PAP

FIPA

Adenomi Ipofisari nella MEN1

Adenoma ipofisario "sporadico" rischio di MENI 0 – 4.8%

17% dei pazienti con MEN I esordisce con adenoma ipof.

(significativamente più giovani di PHP)

concomitante seconda neoplasia endocrina 27%	*successiva seconda* neoplasia endocrina dopo 9±8 aa

(Verlos, J Clin Endocrinol Metab 87:453,2002)

SCREENING MEN 1 in adenomi ipof. apparentemente sporadici ?

Clinical Endocrinology (2008) 69, 621–627 doi: 10.1111/j.1365-2265.

ORIGINAL ARTICLE

***Aryl hydrocarbon receptor interacting protein* (*AIP*) gene mutation analysis in children and adolescents with sporadic pituitary adenomas**

Clin Genet. 2010 November ; 78(5): 457–463. doi:10.1111/j.1399-0004.2010.01406.x.

The role of germline *AIP*, *MEN1*, *PRKAR1A*, *CDKN1B* and *CDKN2C* mutations in a large cohort of children and adolescents with pituitary adenomas

European Journal of Endocrinology (2013) 168 533–541

CLINICAL STUDY

Genetic analysis in young patients with sporadic pituitary macroadenomas: besides AIP don't forget MEN1 genetic analysis

37 adenomi vari		
AIP	2.7%	1/37
MEN1	0%	0/37
Tot	2.7%	

	74 ACTH	6 GH/PRL
AIP	3.7%	3/80
MEN1	0%	0/80
Tot	3.7%	

	< 30 aa	<18 aa
	174	46
AIP	8.6%	15.2%
MEN1	3.4%	6.5%
TOT	12%	21.7%

Clinical Practice Guidelines ***(Brandi, 2002; Thakker, 2012)***

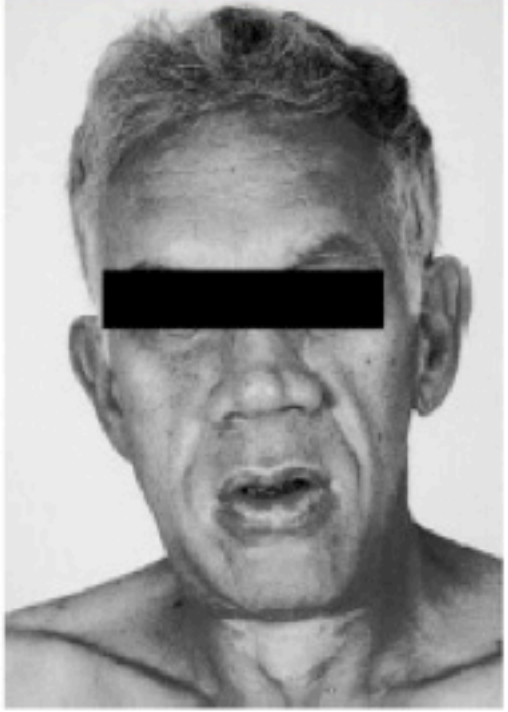
NO specific recommandation

PITUITARY in Carney Complex (CNC)

PROTEIN KINASE A (PKA) TYPE 1A REGULATORY (R1α) SUBUNIT

PRKAR1A - 17q22-24

- frequent mild elevation of GH, IGF-1 and PRL (in up to 75% of cases)
- biochemical acromegaly is often unmasked by abnormal OGTT or paradoxical response to TRH
- pituitary somatomammotroph hyperplasia in >80%

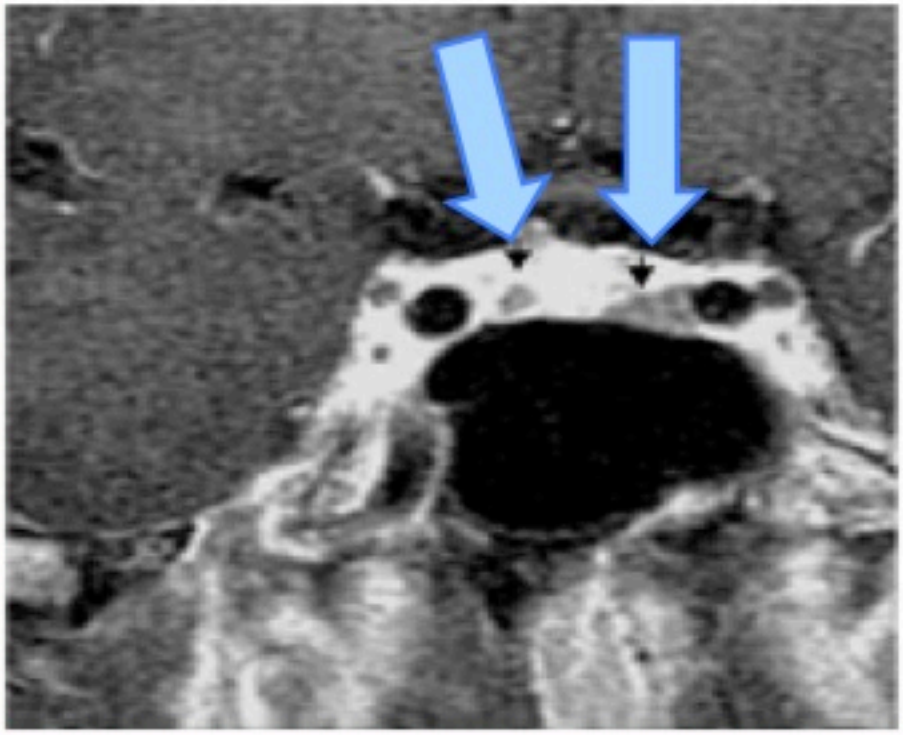


Watson JC et al. J. Neurosurg, 2000
Pack SD et al J Clin Endocrinol Metab. 2000
Raff SB et al J Ped Endocrinol Metab 2000
Boikos SA, Stratakis CA Pituitary 2006

However…..

Clinically evident **acromegaly** or **significant hyperprolactinemia** are relatively infrequent manifestations of CNC

- <10% somatomammotropic pituitary tumors
- do not appear until the second or third decad of life



multiple microadenomas

…The pituitary was removed almost entirely because *multiple* small *tumors* were identified in the background of *hyperplasia*…

Boikos & Stratakis, Pituitary 2006

PROTEIN KINASE A (PKA)

PRKAR1A

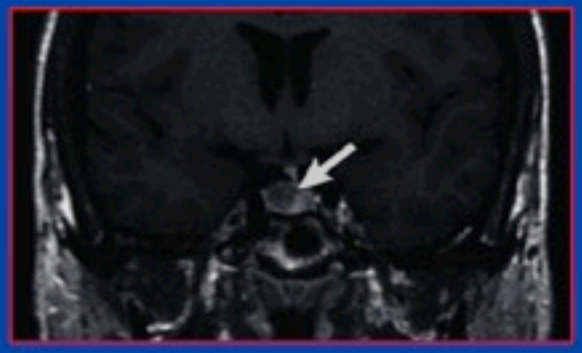
- Protein Kinase A (PKA) Regulatory Subunit 1alfa (R1α)

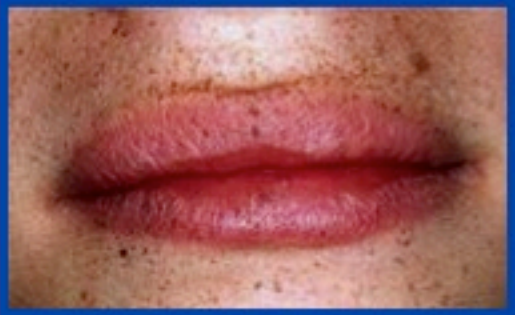
PRKACA

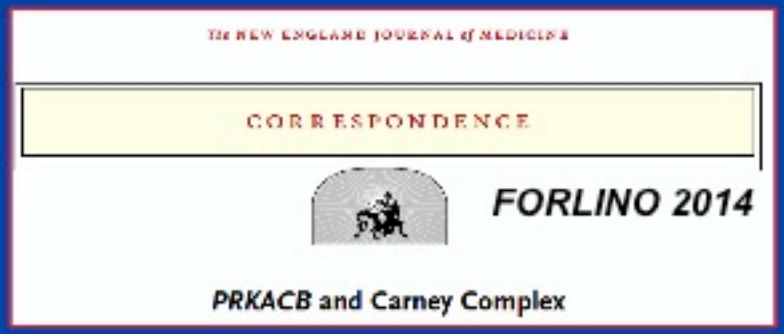
- Protein Kinase A (PKA) Catalytic subunit alpha (Cα)

PRKACB

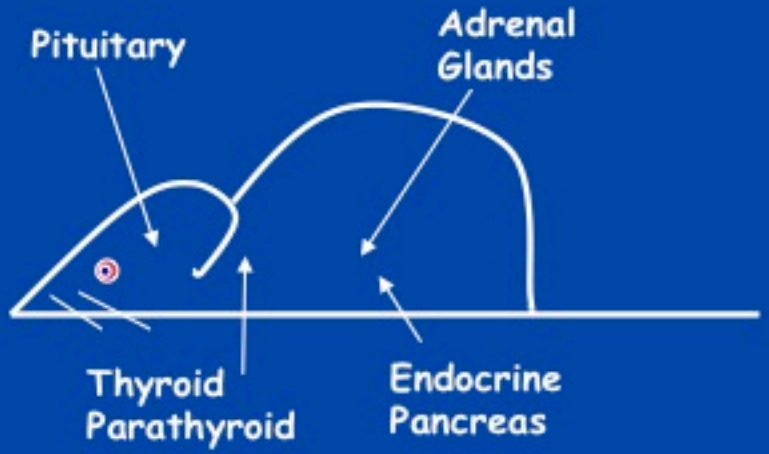
- Protein Kinase A (PKA) Catalytic subunit beta (Cβ)







MENX syndrome MEN 4



Phenotype of affected rats overlaps with both MEN1 and MEN2 human syndromes. Autosomal recessive, high penetrance

Fritz A et al. Cancer Res 2002;

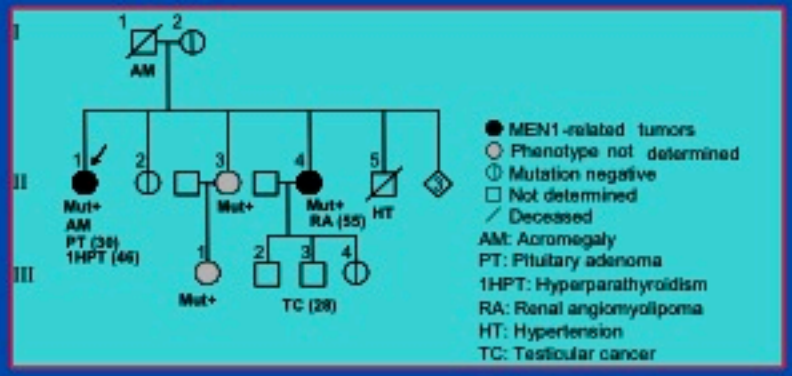
Mutations in p27 (CDKN1B/P27KIP .....) cause multiple endocrine neoplasias in rat and humans

Pellegata N. et al. PNAS, 2006

Germ-line mutations in p27^{Kip1} cause a multiple endocrine neoplasia syndrome in rats and humans

Natalia S. Pellegata*†, Leticia Quintanilla-Martinez*, Heide Siggelkow‡, Elenore Samson*, Karin Bink*, Heinz Höfler*§, Falko Fend§, Jochen Graw¶, and Michael J. Atkinson*

PNAS 2006



The Journal of Clinical Endocrinology & Metabolism

BRIEF REPORT

Germline *CDKN1B*/p27^{Kip1} Mutation in Multiple Endocrine Neoplasia

Marianthi Georgitsi,* Anniina Raitila,* Auli Karhu, Rob B. van der Luijt, Cora M. Aalfs, Timo Sane, Outi Vierimaa, Markus J. Mäkinen, Karoliina Tuppurainen, Ralph Paschke, Oliver Gimm, Christian A. Koch, Sadi Gündogdu, Anneke Lucassen, Marc Tischkowitz, Louise Izatt, Simon Aylwin, Gul Bano, Shirley Hodgson, Ernesto De Menis, Virpi Launonen, Pia Vahteristo, and Lauri A. Aaltonen

50 sporadic pituitary adenomas/19 FIPA

35 MEN1-LIKE negative MEN 1 gene

Neuroendocrine tumor of the cervix

ACTH-secreting adenoma

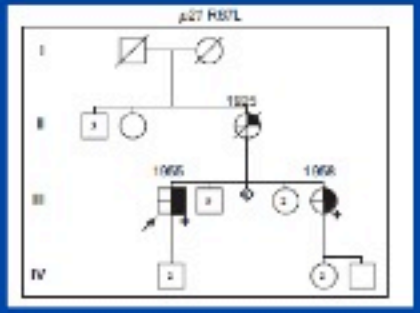
Primary hyperparathyroidism

Rare Germline Mutations in Cyclin-Dependent Kinase Inhibitor Genes in Multiple Endocrine Neoplasia Type 1 and Related States

Sunita K. Agarwal, Carmen M. Mateo, and Stephen J. Marx

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

JCEM 2009



196 pazienti indagati per MEN 1-LIKE

CDKI (7 genes)

7 heterozigous mutations (4%)

3 p27 (1.5%)

2 p15 (1%)

1 p18 (0.5%)

1 p21 (0.5%)

PITUITARY TUMORS and PHEO/PGLs

22 cases (Karbonits End. Societ 2012): 8 mutazioni
3 SDHB
1 caso SDHC
1 caso SDHA
1 caso VHL
1 caso MEN 2

Succinate Dehydrogenase (SDH) D Subunit (*SDHD*) Inactivation in a Growth-Hormone-Producing Pituitary Tumor: A New Association for SDH?

JCEM 2012

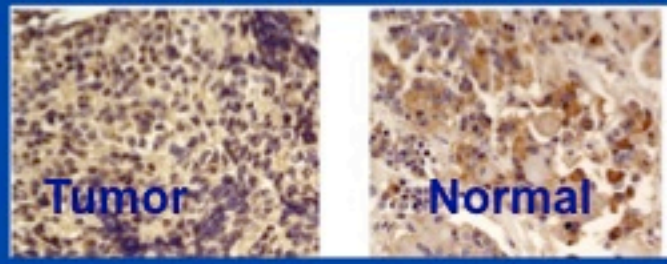
Paraskevi Xekouki, Karel Pacak, Madson Almeida, Christopher A. Wassif, Pierre Rustin, Maria Nesterova, Maria de la Luz Sierra, Joey Matro, Evan Ball, Monalisa Azevedo, Anelia Horvath, Charalampos Lyssikatos, Martha Quezado, Nicholas Patronas, Barbara Ferrando, Barbara Pasini, Aristides Lytras, George Tolis, and Constantine A. Stratakis

Familial *SDHA* Mutation Associated With Pituitary Adenoma and Pheochromocytoma/Paraganglioma

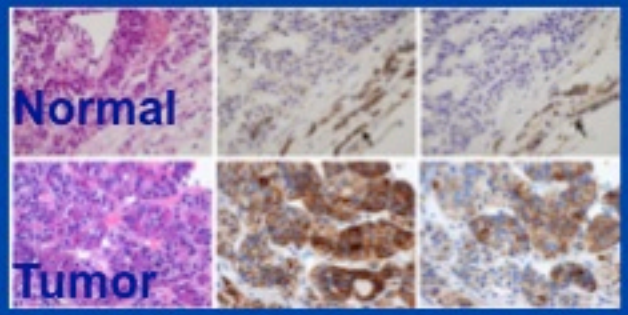
JCEM 2013

Trisha Dwight,* Kirsty Mann,* Diana E. Benn, Bruce G. Robinson, Penny McKelvie, Anthony J. Gill, Ingrid Winship, and Roderick J. Clifton-Bligh

LOH ipofisaria



ICH: SDHD



ICH: SDHA e D

Familial Isolated Pituitary Adenomas (FIPA)

Daly A.F. J Clin Endocrinol Metabol, 2006

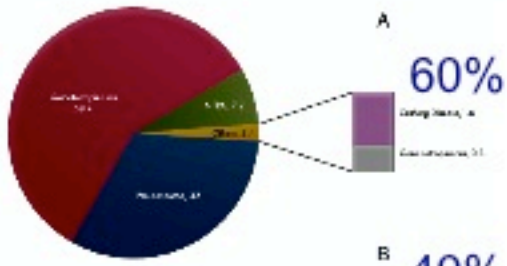
64 families
138 affected pts.

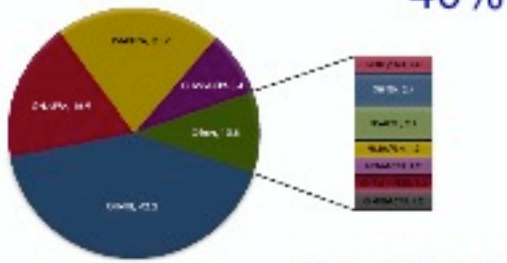
1.9-3.2% dei casi

30 homogeneous → 14 PRL, 12 GH, 2 NS, 2 ACTH

34 heterogeneous → At least one PRL or GH

PRL 40 % <
GH 34% >
NS 20%
ACTH 6%

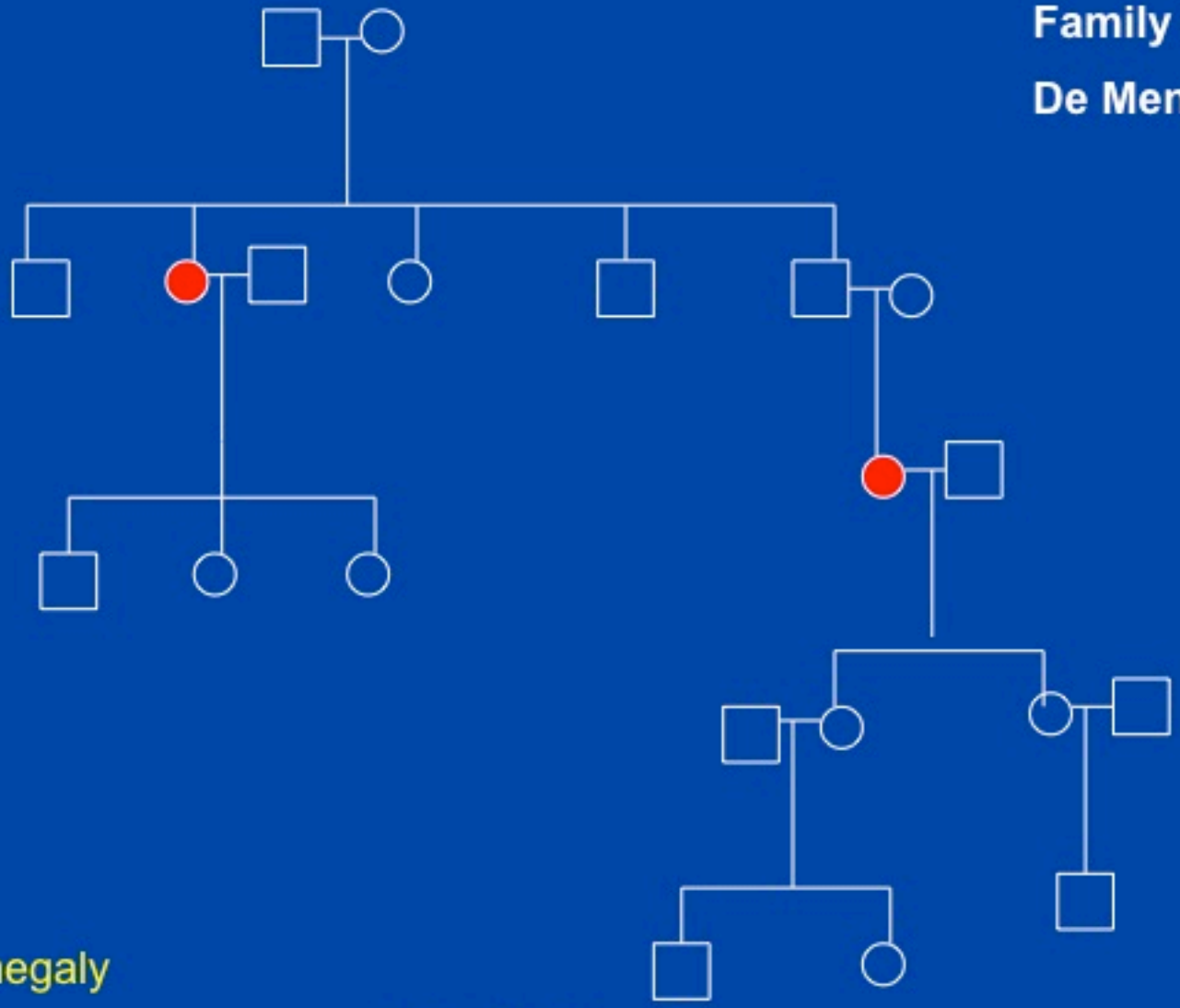




Beckers 2013

Family C.

De Menis, unpub.

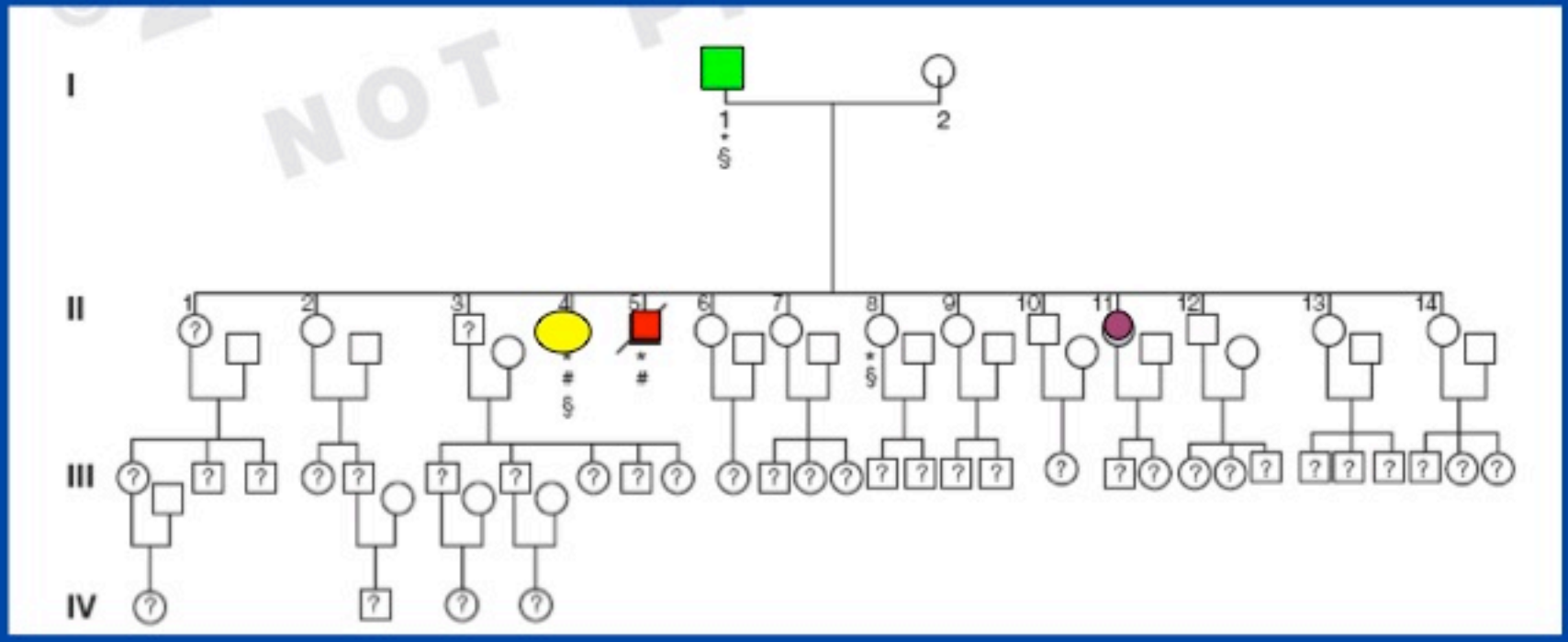


Acromegaly

FIPA

Homogeneous phenotype

Raverot, 2007



Acromegaly
Gonadotropinoma
Prolactinoma

Asymptomatic microadenoma

FIPA

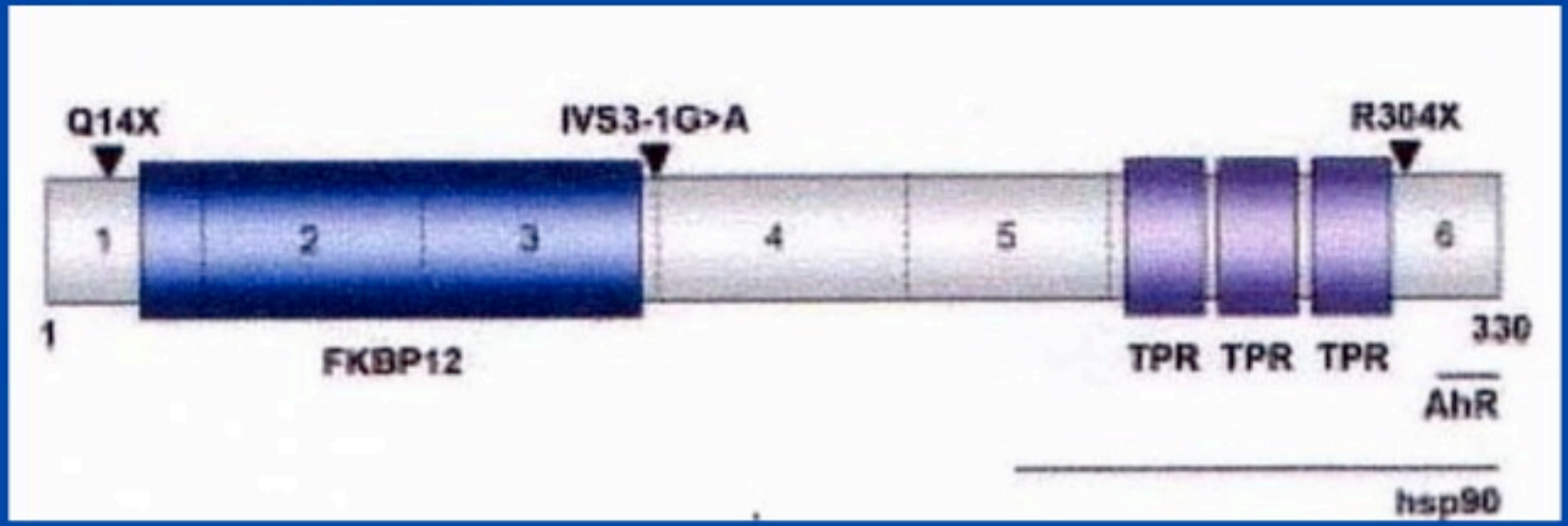
Heterogeneous phenotype

Aryl Hydrocarbon Receptor Interacting Protein - AIP - (XAP2, ARA9)

1996 Interaction and inhibition of hepatitis B virus X protein

Kuzhandaivelu N. Nucleic Acid Res. 24, 4741-4750, 1996

330-aminoacid protein; 37 Kd.



1997 Complex AIP - AHR - hsp90

Carver LA. J Biol- Chem.272:11452-11456,1997

GERMLINE AIP MUTATIONS

OMOGENEOUS FIPA (specially IFS) 23% (36%)

HETEROGENEOUS FIPA 20%

AGE young

VOLUME macro

SUBTYPE GH/PRL

THERAPY RESPONSE bad

CONCLUSIONI

Le forme familiari di adenomi ipofisari sono **più frequenti** di quanto ritenuto in passato

E' accettata l'esistenza di forme familiari di adenomi ipofisari isolati (**FIPA**)

AIP è responsabile di una parte di FIPA, soprattutto della forma omogenea di adenomi GH-secernenti (IFS), ma esistono sicuramente altri geni ancora sconosciuti. La **penetranza** di queste forme familiari non è ancora definita, ma è relativamente bassa, giustificando l'esistenza di una base ereditaria anche in adenomi apparentemente sporadici

AWARENESS DEL CLINICO (1)

Accurata anamnesi familiare

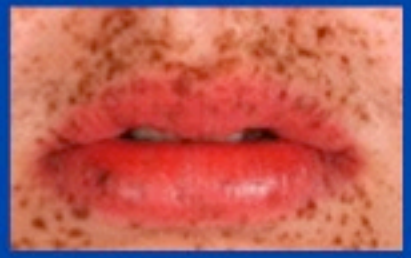
- neoplasie endocrine (anche nei non first degree)
- neoplasie non classificate
- sintomi (calcolosi renale, ulcera peptica..)

Accurata anamnesi personale

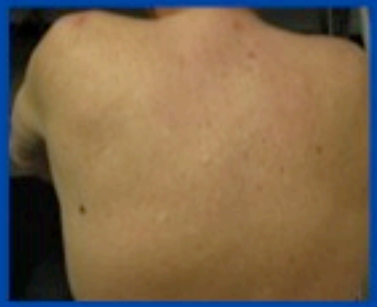
- calcolosi renale, ulcera peptica
- tumori endocrini
- tumori non endocrini

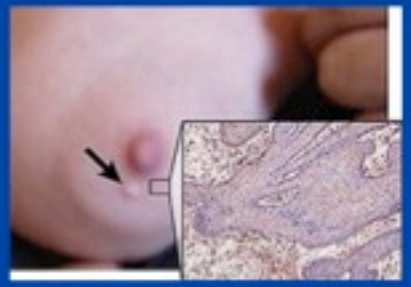
AWARENESS DEL CLINICO (2)

Accurato esame obiettivo (CCN; MEN; SDH)



- cute-mucose





- altri organi

- pressione arteriosa

Calcemia in tutti i pazienti con adenoma ipofisario ?

Solo 27% dei pz. con MEN1 che esordiscono con adenoma ipofisario hanno contemporanea evidenza di un' altra neoplasia endocrina

Calcemia ricontrollata periodicamente ?

AWARENESS DEL CLINICO (3)

Famiglia con FIPA: obbligatoria analisi genetica di AIP

Presenza di mutazioni di AIP

→ analisi genetica familiari primo grado
→ negativa → STOP
→ positiva → *screening* ormonale e di *imaging*

Presenza di adenoma → usuale gestione
Assenza di adenoma → rivalutazione clinica periodica

Assenza di mutazioni di AIP

→ esame clinico, eventualmente ormonale e di *imaging*, familiari → Presenza di adenoma → usuale gestione
Assenza di adenoma → rivalutazione clinica periodica

De Menis E. Sartorato P.

Endocrinologo 2013