XIX Corso di Aggiornamento Post-Specialistico in Endocrinologia, Diabetologia ed Endocrinologia Ginecologica

III SESSIONE - IPOFISI

Patogenesi e inquadramento dell'eccesso di GH

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Pathogenesis of GH excess

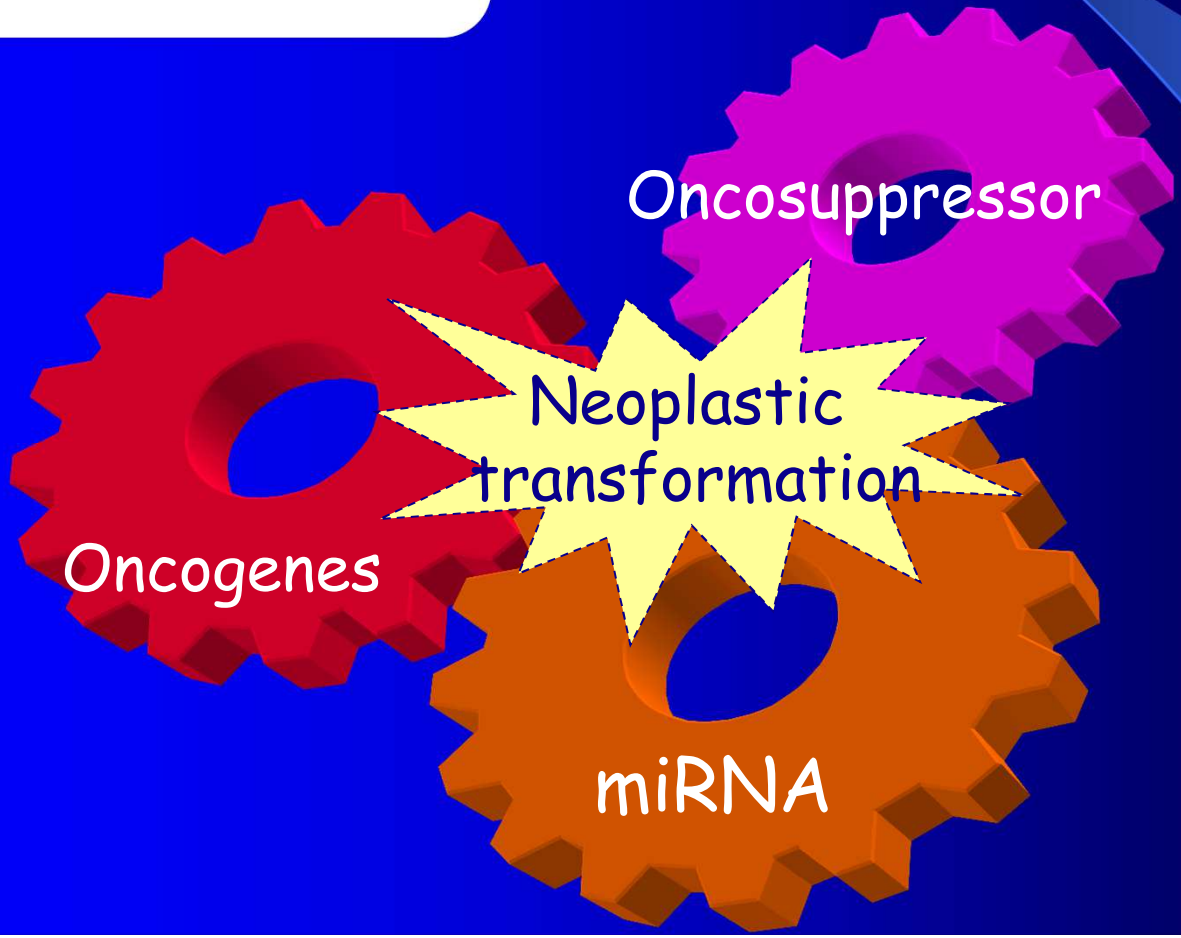
Pathogenesis

GH secreting pituitary adenomas

- sporadic
- familial
  - Associated with other endocrine abnormalities
  - Isolated disorder

Pathogenesis of GH excess

GH secreting pituitary adenomas → sporadic



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Pathogenesis of GH excess

GH secreting pituitary adenomas → familial

Familial syndrome	Responsible gene	Clinical characteristics	Other endocrine abnormalities	Non-endocrine abnormalities
FIPA	*AIP* in 20% Unknown in the majority of cases	Young patients (<40 years old at diagnosis) Usually macroadenomas, with extrasellar extension Less frequently controlled by surgery or SSA	None	None
MEN type 1	*MEN1* (*menin*) 11q13 in 75–80% *CDKN1B* in a minority		Pancreatic neuroendocrine tumors Parathyroid adenomas	
McCune–Albright syndrome	*GNAS* 20 q13		Precocious puberty Thyrotoxicosis Cushing's syndrome	Polyostotic fibrous bone dysplasia Café-au-lait skin pigmentation
Carney complex	*PRKAR1A* 17q22–24		Primary pigmented nodular adrenocortical disease (PPNAD) Thyroid nodules (benign/malignant)	Myxomas Skin pigmentation Gonadal tumors

Capatina et al. J Endocrinol 2015: 226, T141–T160

Pathogenesis of GH excess

Conditions with germline mutations

- MEN1
- FIPA
- SDHx
- MAS
- MEN4
- Carney Complex

Pathogenesis of GH excess

Familial Isolated Pituitary Adenomas: FIPA

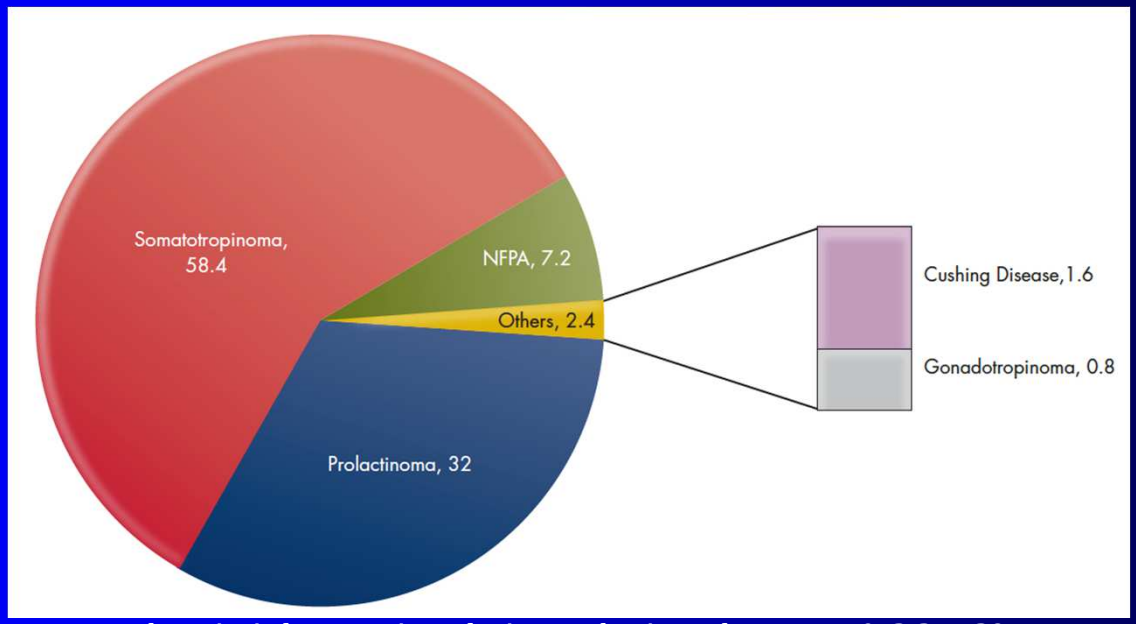
pituitary adenomas occuring in a familial setting without MEN1 or Carney complex mutations, including somatotropinomas, prolactinomas, and nonsecreting pituitary adenomas

Pathogenesis of GH excess

FIPA

30 homogeneous tumor phenotype

- 14 prolactinoma
- 12 somatotropinoma
- 2 NFA
- 2 Cushing's



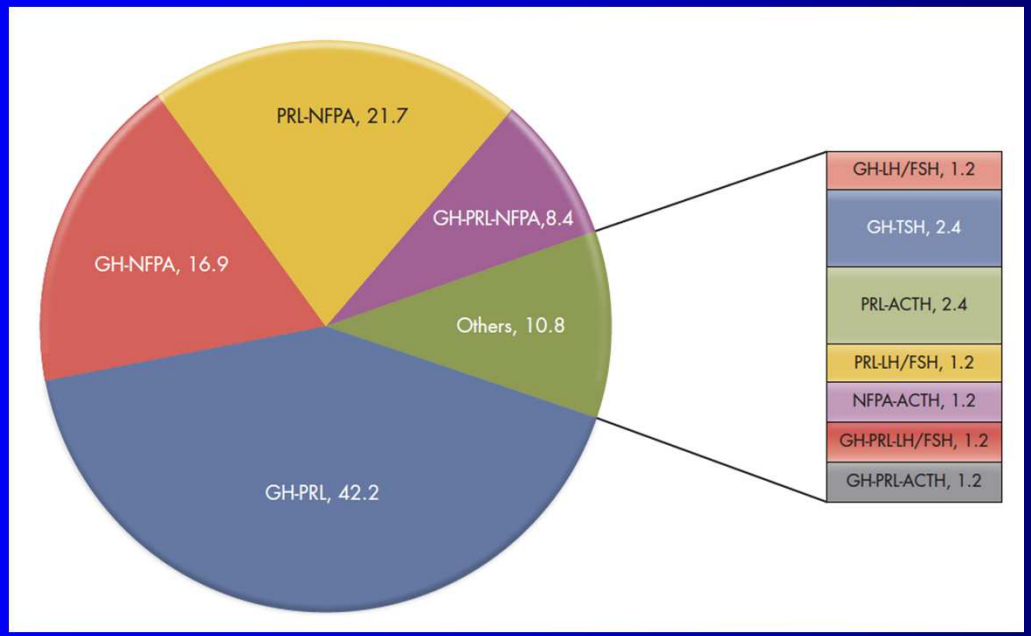
Beckers A, Aaltonen LA, Daly AF, Karhu A. Endocr Rev. 2013;34:239-77

Pathogenesis of GH excess

FIPA

34 heterogeneous phenotype families
up to 3 different tumour types possible
at least one PRLoma/GHoma per family

J Clin Endocrinol Metab. 2006 Sep;91(9):3316-23



Beckers A, Aaltonen LA, Daly AF, Karhu A. Endocr Rev. 2013;34:239-77

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Pathogenesis of GH excess

FIPA

vs Sporadic

FIPA younger at diagnosis

FIPA PRLomas and NFA more frequently invasive

Subgroups

Multigenerational FIPA families adenomas diagnosed earlier in 2nd generation (30) *vs* 1st generation (50)

Homogeneous somatotropinomas younger at diagnosis, more frequent extension *vs* heterogeneous somatotropinomas

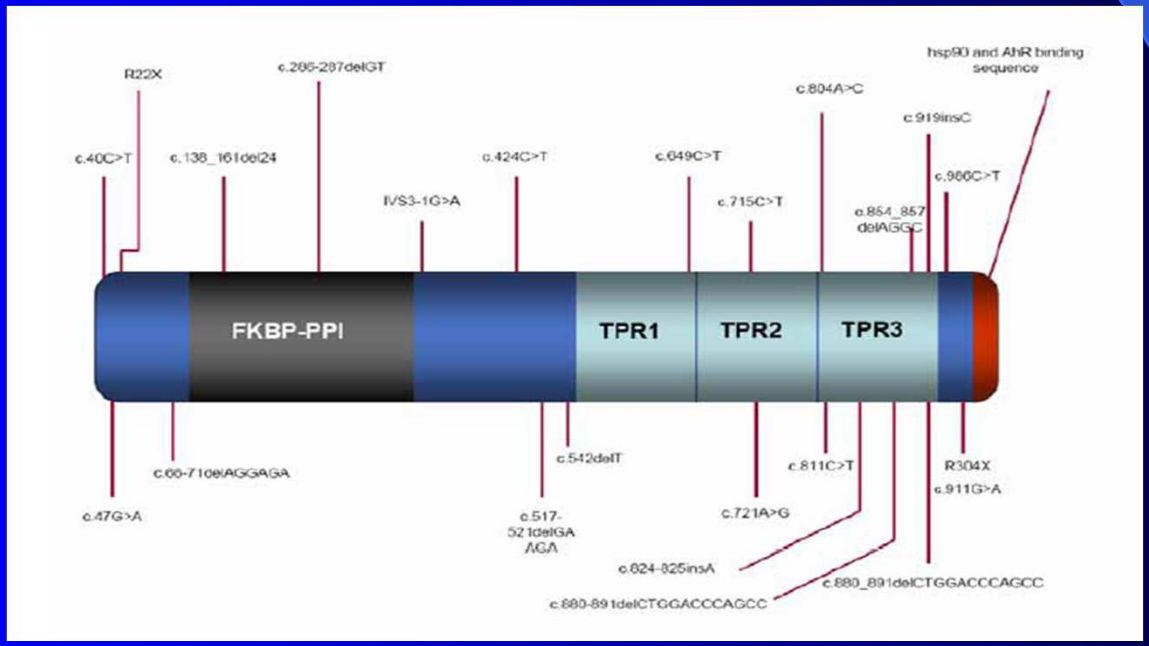
Pathogenesis of GH excess

AIP

Pituitary Adenoma Predisposition Caused by Germline Mutations in the *AIP* Gene

Outi Vierimaa,[1*] Marianthi Georgitsi,[3*] Rainer Lehtonen,[3] Pia Vahteristo,[3] Antti Kokko,[3] Anniina Raitila,[3] Karoliina Tuppurainen,[4] Tapani M. L. Ebeling,[2] Pasi I. Salmela,[2] Ralf Paschke,[5] Sadi Gündogdu,[6] Ernesto De Menis,[7] Markus J. Mäkinen,[4] Virpi Launonen,[3] Auli Karhu,[3] Lauri A. Aaltonen[3]†

Science, May 2006



Beckers and Daly. Eur J Endocrinol 2007

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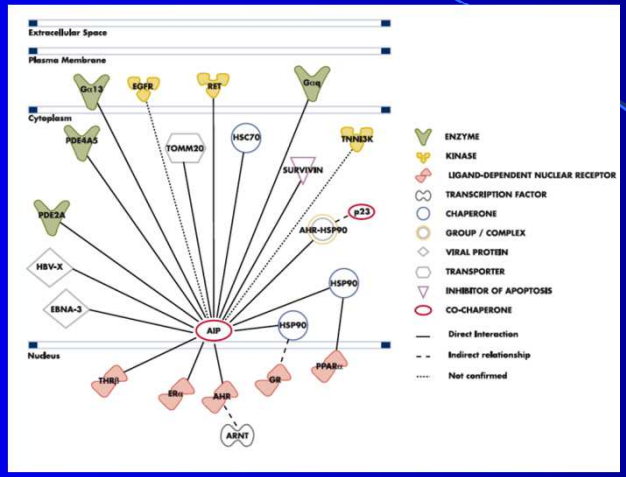
Pathogenesis of GH excess

AIP



Beckers et al. Endocr Rev. 2013;34:239-77

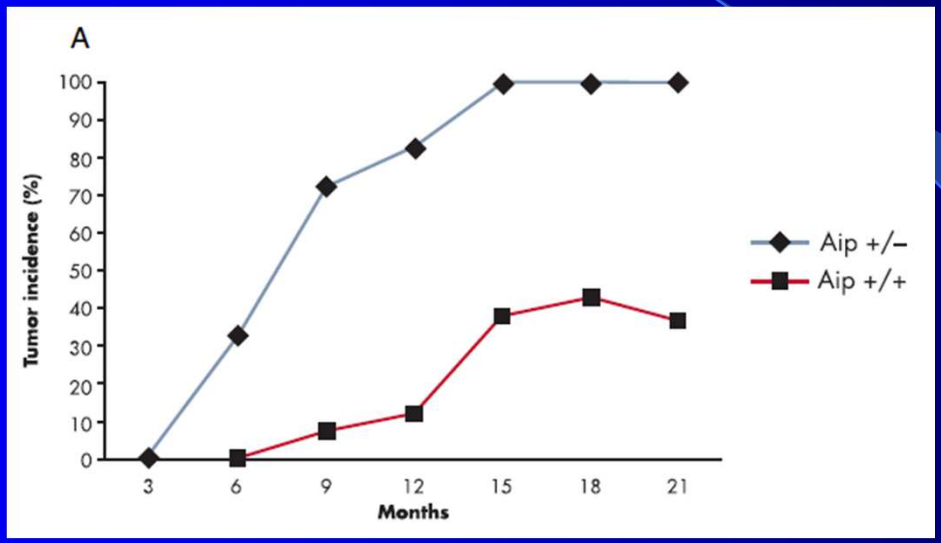
AIP's interacting partner	Possible role
PDE4A5	Increased cAMP; pro-proliferative, therefore, unlikely
PDE2A	Reduced cAMP; anti-proliferative
Survivin	Increases survivin's stability, inhibiting apoptosis, therefore, unlikely
RET	Prevents RET's interaction with surviving thus reducing its proto-oncogenic effect
Integrins	Stability of cell–extracellular matrix adhesion; convergence of cell cycle pathways at cell surface

Lloyd et al. Endocrine 2013

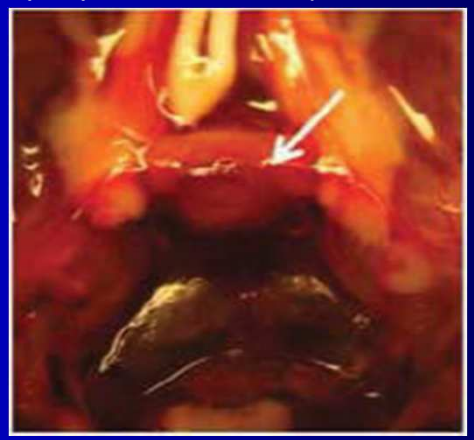
Pathogenesis of GH excess

AIP

Animal model



AIP mutated animals develop pituitary adenomas



Beckers et al. Endocr Rev. 2013;34:239-77

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Pathogenesis of GH excess

AIP

In humans

- 70 mutations (215 patients)
- R304X : 35 patients
- Q14X : 19 patients (only Finnish origin)
- R304Q : 10 patients
- R271W : 10 patients
- several variants (R16H?)

Beckers et al. Endocr Rev. 2013;34:239-77

Pathogenesis of GH excess

Prevalence of *AIP* mutations

Barlier A et al., JCEM 2007	105 Patients with sporadic adenoma	0%
Stratakis CA et al., Clin Genet 2010	76 pediatric Cushing's	1,3%
Cazabat L et al., EJE 2007	154 patients with GH secreting pituitary adenomas	3%
Daly AF et al., JCEM 2007	158 patients (FIPA)	15%
Tichomirova MA et al. EJE 2011	163 patients macroadenoma and <30 yr	11.7% < 30yr 20% <18 yr
Stratakis CA et al., Clin Genet 2010	11 pediatric FIPA	27,2%
Rostomyan L et al., Endocrine Abstracts, 2013	113 patients with pituitary gigantism	33%

Pathogenesis of GH excess

AIP

ORIGINAL ARTICLE

Endocrine Care

Clinical Characteristics and Therapeutic Responses in Patients with Germ-Line *AIP* Mutations and Pituitary Adenomas: An International Collaborative Study

AIM

determine the clinical characteristics
responses to therapy

in pts with AIP^{mut}-and
pituitary adenomas

with particular interest to somatotropinomas

Daly et al. J Clin Endocrinol Metab 2010 ;95:E373-83.

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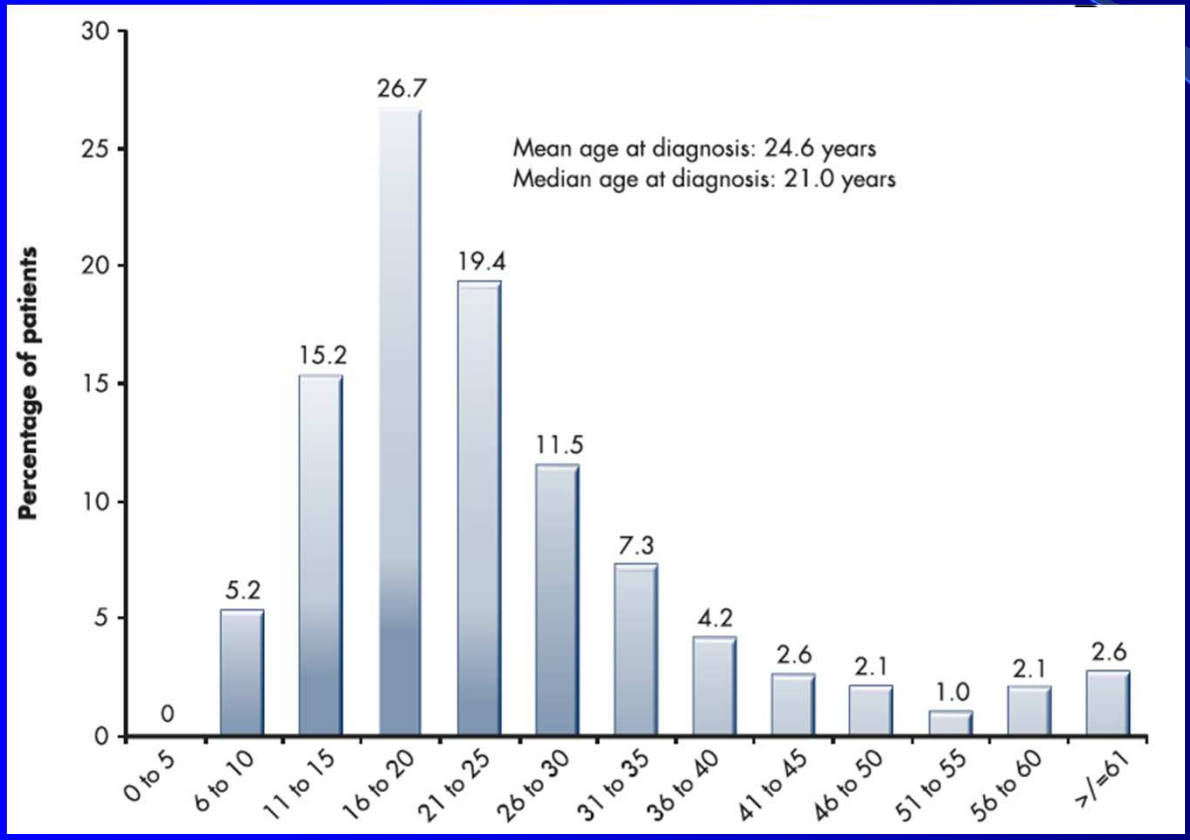
Pathogenesis of GH excess

AIP^{mut} Pituitary Adenomas

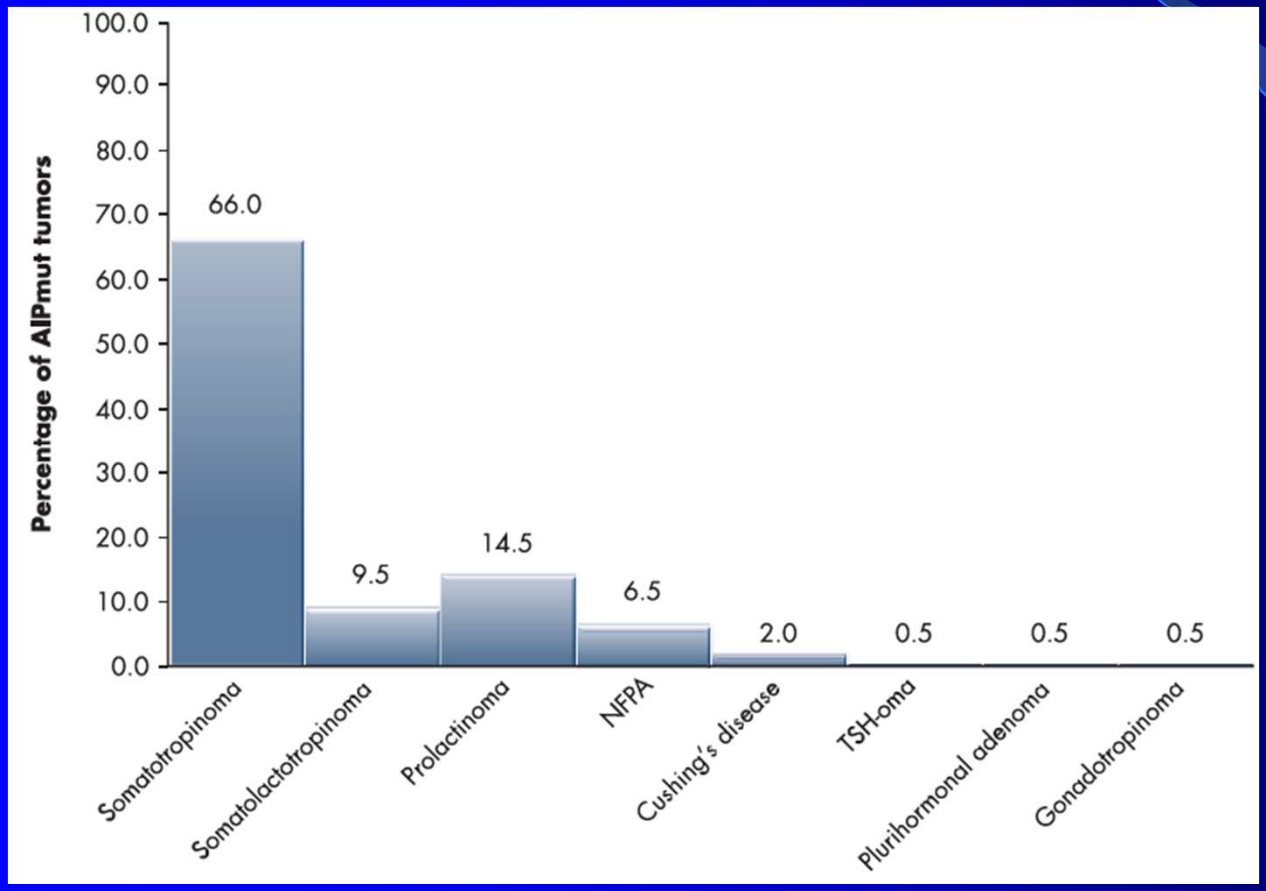


Beckers et al. Endocr Rev. 2013;34:239-77

Younger age at presentation

Pathogenesis of GH excess

AIP^{mut} Pituitary Adenomas



All tumor types represented

Beckers et al. Endocr Rev. 2013;34:239-77

Pathogenesis of GH excess

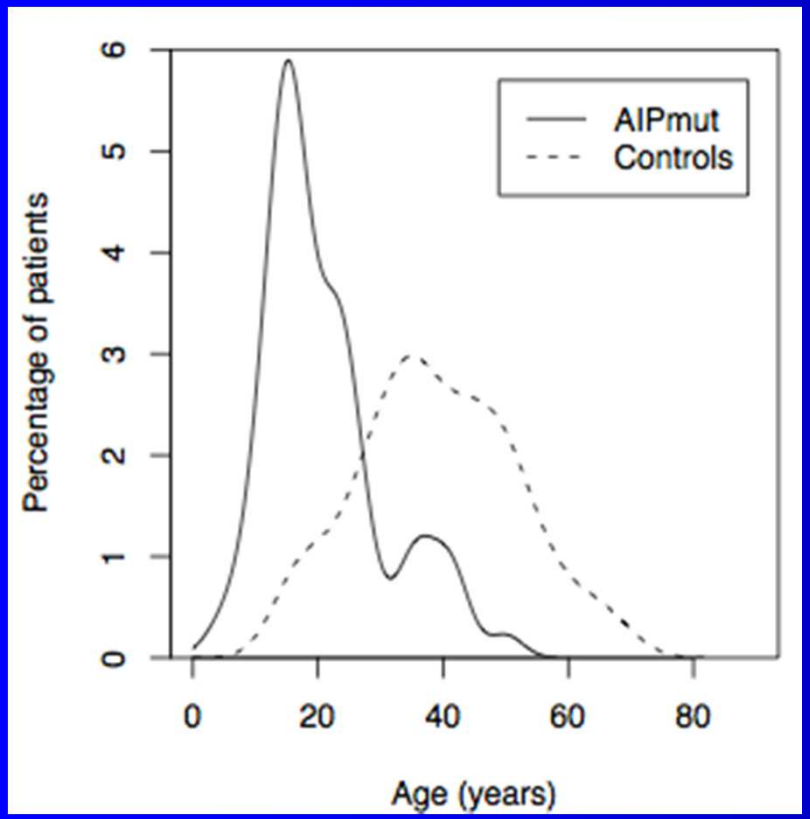
Clinical characteristics of *AIP*^{mut} Pituitary Adenomas

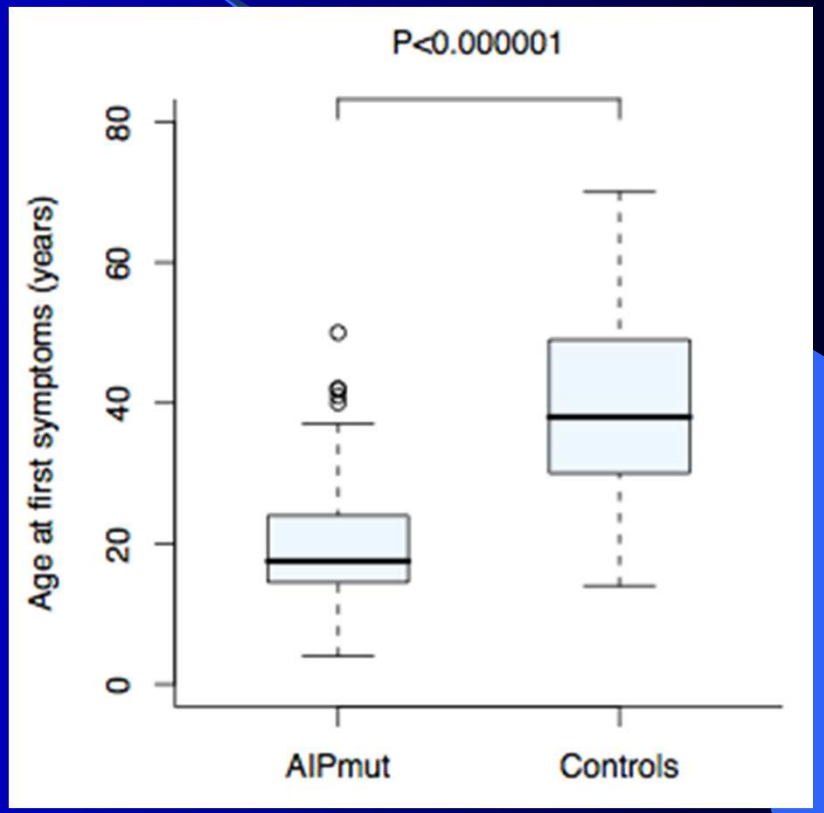
	All (n=96)	GH-oma (n=75)	PRL-oma (n=13)	NFA (n=7)	TSH-oma (n=1)
Sex (% male)	61M/35F (63.6%)	46M/29F (61.3%)	10M/3F (76.9%)	4M/3F (57.1%)	1M/0F (100%)
Age at diagnosis (yr)	23.0 (8.0-74.0)	22.5 (8.0-60.0)	22.0 (12.0-39.0)	31.0 (12-74)	39.0
Age at first symptoms (yr)	18.0 (4.0-67.0)	17.8 (4.0-50.0)	18.0 (12.0-39.0)	31.0 (12-74)	39.0
Delay in diagnosis (yr)	2.0 (0.0-19.0)	2.0 (0.0-19.0)	0.0 (0.0-6.0)	0.0 (0.0-7.0)	0.0
Maximum tumor diameter (mm)	25.0 (6.0-85.0)	22.5 (7.0-60.0)	31.0 (6.0-85.0)	27.5 (14-35)	30.0
Macroadenoma (%)	93.3%	93.1%	92.3%	100%	100%
Extrasellar extension (%)	79.5%	65.1%	91.7%	85.7%	0.0%
Invasion (%)	56.3%	51.7%	69.2%	57.1%	0.0%

Daly et al. J Clin Endocrinol Metab 2010 ;95:E373-83.

Pathogenesis of GH excess

AIP^{mut} acromegaly: Age at First Symptoms



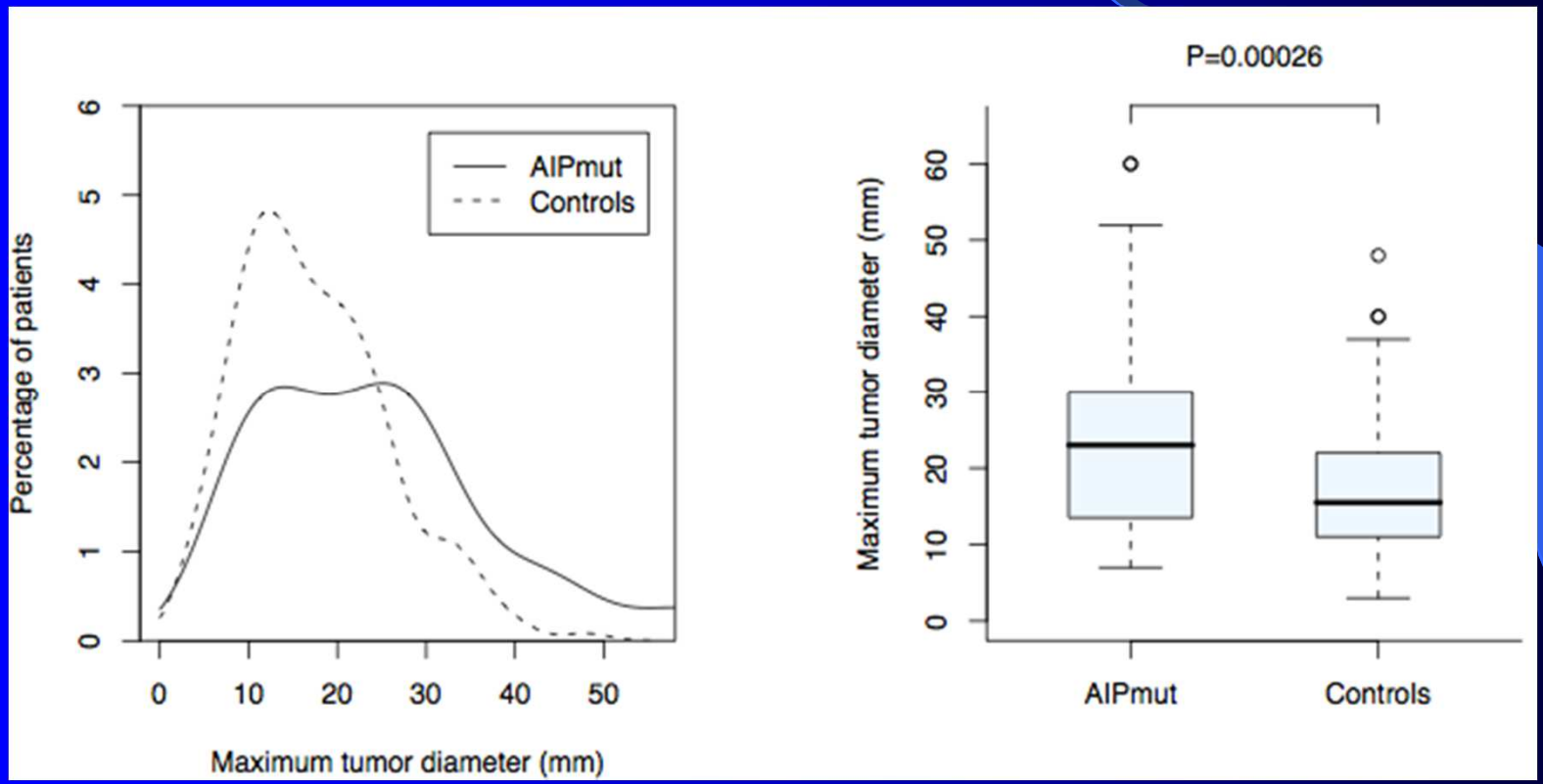


Younger age at first symptoms

Daly et al. J Clin Endocrinol Metab 2010 ;95:E373-83.

Pathogenesis of GH excess

AIP^{mut} acromegaly: Max Tumor Diameter

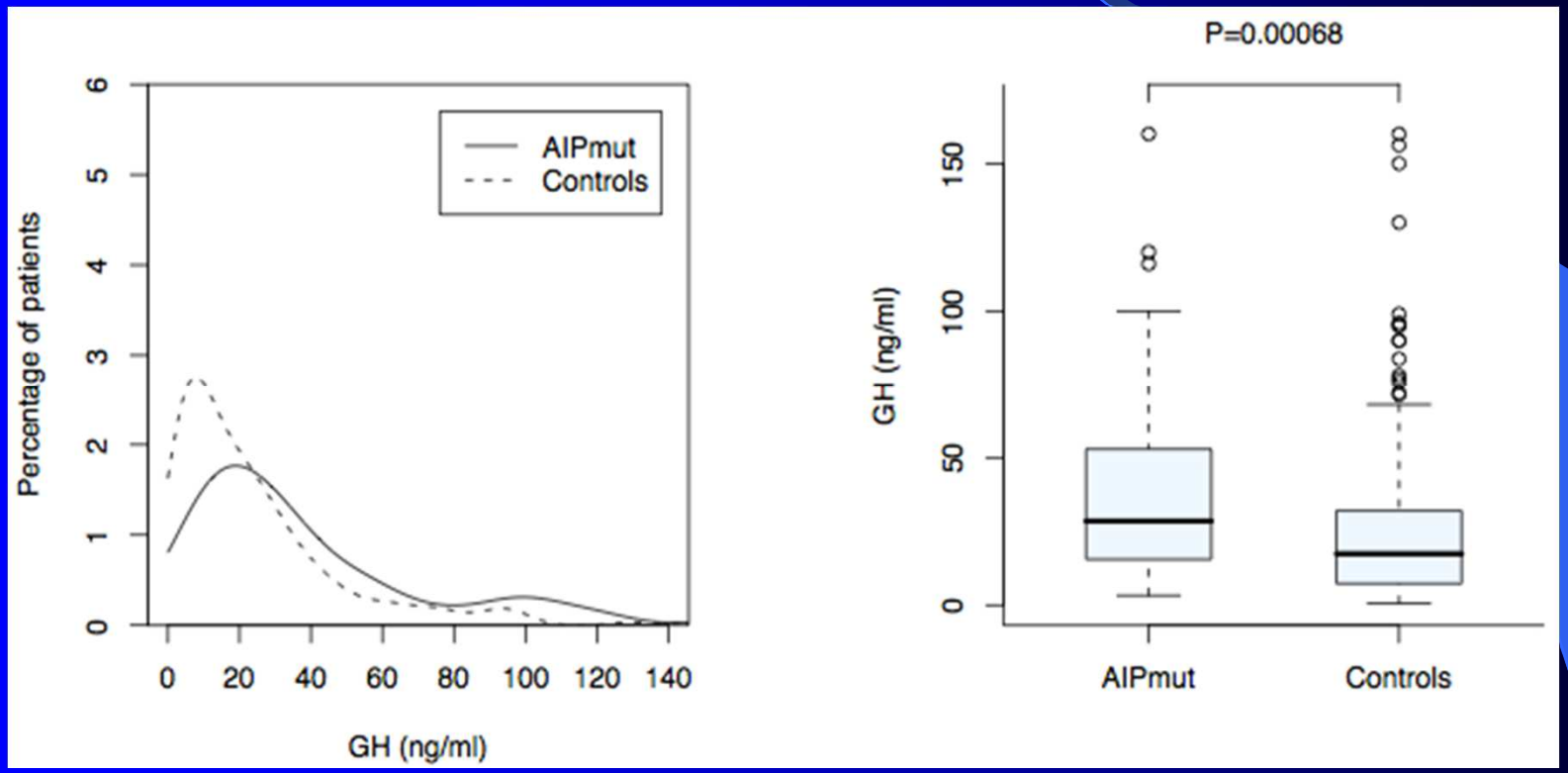


Greater tumor diameter

Daly et al. J Clin Endocrinol Metab 2010 ;95:E373-83.

Pathogenesis of GH excess

AIP^{mut} acromegaly: GH Secretion



More robust GH secretion

Daly et al. J Clin Endocrinol Metab 2010 ;95:E373-83.

Pathogenesis of GH excess

Treatment of *AIP*^{mut} Somatotropinomas

	AIP^{mut} (n=71)	Control (n=232)	*P* value
Disease control (%) *	70.4	80.5	0.06
Re-operation (%)	21.9	5.5	0.00069
Use of radiotherapy (%)	41.4	24.7	0.15
SA-induced reduction in GH (%) (n=38)	40	75	0.00037
SA-induced reduction in IGF-I (%) (n=38)	47.4	56	0.028
SA-induced tumor shrinkage (%) (n=38)	0	41.4	0.000001

More difficult to treat

Daly et al. J Clin Endocrinol Metab 2010 ;95:E373-83.

Pathogenesis of GH excess

At risk groups for *AIP*mut

0-4% of unselected sporadic adenomas

~30% gigantism

AIPmut

15-20% FIPA

11% of sporadic macroadenomas <30yr

9-20% children with pituitary adenomas

Beckers et al. Endocr Rev. 2013;34:239-77

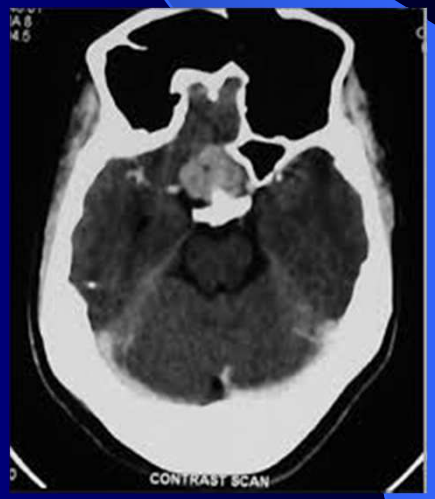
Pathogenesis of GH excess

DB

Birth weight: 3600 g

5 yrs and 3 mo
height 129 cm

6 yrs
height 135 cm



DIAGNOSIS

Pathogenesis of GH excess

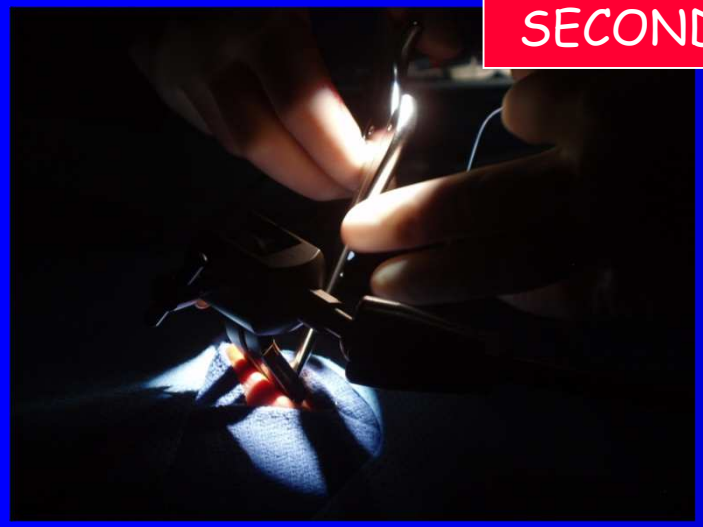
DB

6 yrs
FIRST SURGERY

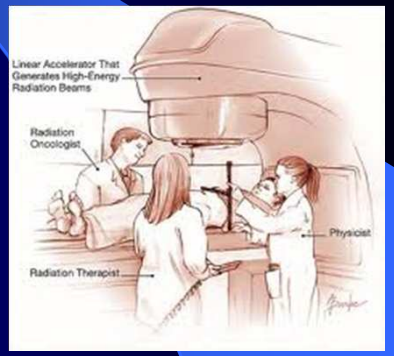
Pituitary adenoma with prevalent GH staining

Persistent disease

7 yrs
SECOND SURGERY



Biochemically persistent disease



8 yrs
external radiotherapy

Biochemically persistent disease

Pathogenesis of GH excess

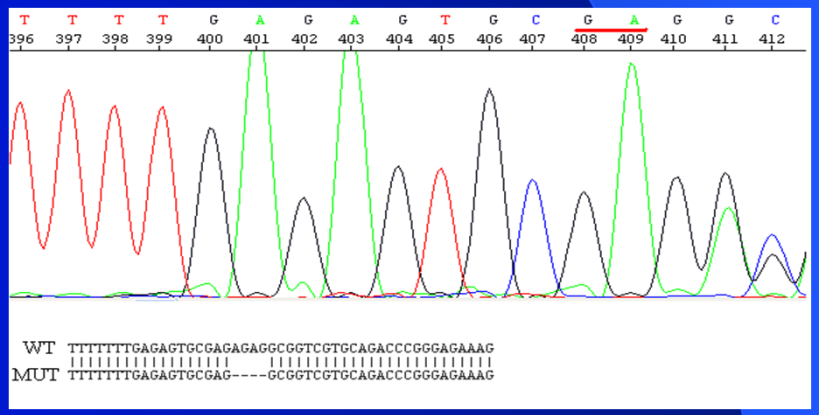
DB

Biochemically persistent disease

→ Medical therapy → Satisfactory control

AIP mutation ?

Final height: 166 cm
Oligo-amenorrhea
Central hypothyroidism



Pathogenesis of GH excess

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara

Arcispedale S.Anna
DIP. MEDICO SPECIALISTICO
UO ENDOCRINOLOGIA

EN-05 (39) AMB. ENDOCR. SEZ.ENDOCR. - CONA

3012194805
REFERTO

A0212251
CODICE U.O.

20.08.2012
DATA ACCETTAZIONE

PAZIENTE ESTERNO
PROVENIENZA

DATI ANAGRAFICI DEL PAZIENTE

NOME E COGNOME

F
SESSO

LUOGO E DATA DI NASCITA

CODICE FISCALE

INDIRIZZO

TELEFONO

PRESTAZIONI EROGATE
ANAL.MUTAZ. DNA(ELETTROFORESI)
ANAL.SEGMENTI DNA MED.SEQUENZIAMENTO
ESTR.DNA O RNA DA SANG.PER-TESS-COLT.CELL-VILLI C-
ANAL.MUTAZ. DNA(ELETTROFORESI)
ANAL.SEGMENTI DNA MED.SEQUENZIAMENTO
ANAL.MUTAZ. DNA(ELETTROFORESI)
ANAL.MUTAZ. DNA(ELETTROFORESI)
ANAL.MUTAZ. DNA(ELETTROFORESI)

REFERTO

OGGETTO: Esito dell'analisi genetica della Sig.ra per la ricerca di mutazioni germinali nel gene AIP.

La Sig.ra ha eseguito una analisi genetica al fine di accertare la presenza o meno di una mutazione germinale a carico del gene AIP in quanto riscontrata affetta da adenoma ipofisario.
Previo consenso della paziente è stato effettuato un prelievo di 20 ml di sangue venoso periferico per lo studio mutazionale. L'analisi genetica, effettuata sul DNA costituzionale estratto dai linfociti del sangue venoso periferico della Sig.ra , è stata eseguita mediante amplificazione per PCR (Polimerase Chain Reaction) con primers specifici, seguita da sequenziamento automatico del DNA (dall'esone 1 all'esone 6).

Risultati:
L'analisi genetica eseguita sul DNA costituzionale della Sig.ra , nelle condizioni sopra descritte, ha rilevato la presenza di:
- un polimorfismo in omozigosi in posizione 228 nell'esone 5 del gene AIP (isoforma 1, CCDS8168), che determina la sostituzione di un aminoacido Glicina in un aminoacido Lisina (Gln228Lys;CAG/AAG), privo di significato patologico;
- un polimorfismo in omozigosi in posizione 307 (isoforma 1, CCDS8168) dell'esone 6, che determina la sostituzione di un aminoacido Glicina in un aminoacido Arginina (Gln307Arg; CAG/CGG), di significato clinico imprecisato.

Il Medico
MARIA CHIARA ZATELLI

REFERTO

- un polimorfismo in omozigosi in posizione 228 nell'esone 5 del gene AIP (isoforma 1, CCDS8168), che determina la sostituzione di un aminoacido Glicina in un aminoacido Lisina (Gln228Lys;CAG/AAG), privo di significato patologico;

- un polimorfismo in omozigosi in posizione 307 (isoforma 1, CCDS8168) dell'esone 6, che determina la sostituzione di un aminoacido Glicina in un aminoacido Arginina (Gln307Arg; CAG/CGG), di significato clinico imprecisato

Pathogenesis of GH excess

Conditions with germline mutations

Pathogenesis of GH excess

MEN4

Table 1. Clinical and molecular characteristics of the identified *CDKN1B*/p27 variants

CDKN1B mutation	Clinical phenotype of proband	Relative affected	Mutation description	CDKN1B status in the tumor	Localization of p27 mutant	Reference
W76X	1°HPT, GH-pituitary tumor	2	truncated protein	no LOH	cytoplasm	[10]
K25fs	1°HPT, ACTH-pituitary tumor, carcinoid tumor of uterine cervix	0	frameshift longer protein	LOH		[11]
ATG–7G>C	1°HPT (1 parathyroid tumor) bilateral adrenal mass nonfunctioning	0	reduction in protein expression *in vitro*	no LOH		[12]
P95S	1°HPT (2 parathyroid tumors), ZES	0	reduced binding of the mutant protein with Grb2	ND		[12]
Stop>Q	1°HPT (3 parathyroid tumors)	3	longer protein, very unstable	ND		[12]
P69L	1°HPT, bronchial carcinoids, papillary thyroid carcinoma, pituitary macroadenoma and bilateral multiple lung metastasis	ND	unstable protein, impared CDK2 binding	ND	nuclear/ cytoplasmic	[13]

1°HPT = Primary hyperparathyroidism; ZES = Zollinger-Ellison syndrome; LOH = loss of heterozygosity; ND = not determined.

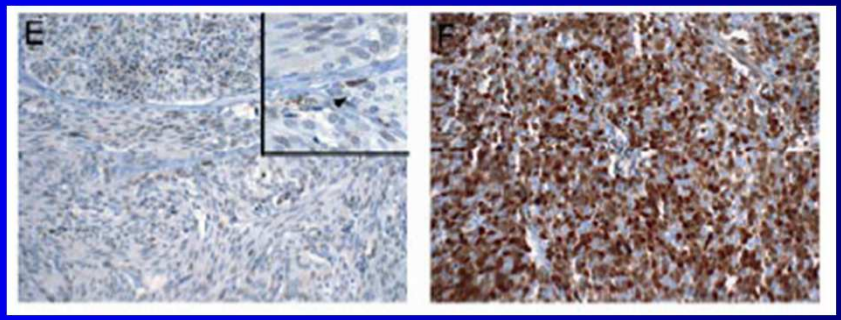
Marinoni et al. Neuroendocrinology 2011;93:19–28

Pathogenesis of GH excess

MEN4

P69L	1°HPT, bronchial carcinoids, papillary thyroid carcinoma, pituitary macroadenoma and bilateral multiple lung metastasis	ND	unstable protein, impared CDK2 binding	ND	nuclear/ cytoplasmic	[13]

bronchial carcinoid



P69L mutation-positive patient sporadic patient (wild-type p27)

Loss of p27 protein in tumors of affected patients

Molatore et al. Human Mutation 2010 Mutation in Brief 31: E1825-E1835

Pathogenesis of GH excess

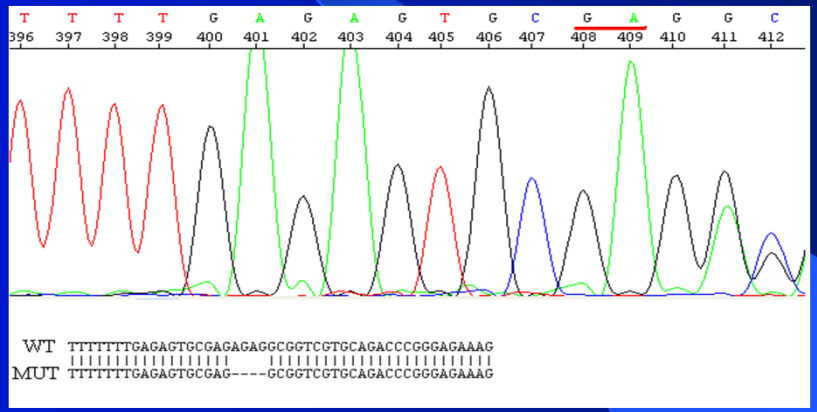
MEN4

p27 is a new tumor susceptibility gene for multiple neuroendocrine tumors

Marinoni et al. Neuroendocrinology 2011;93:19–28

Pathogenesis of GH excess

MEN4



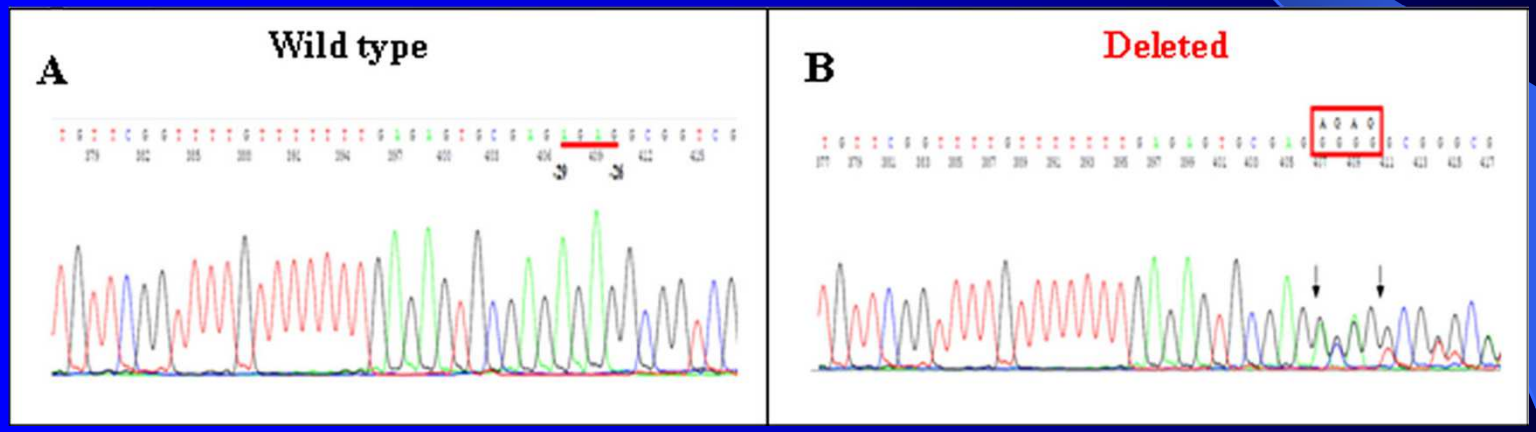
p27
mutation ?

Pathogenesis of GH excess

MEN4

Wild type

Deleted



Deletion in the CDKN1B 5'-UTR region
(c.-29_-26delAGAG)

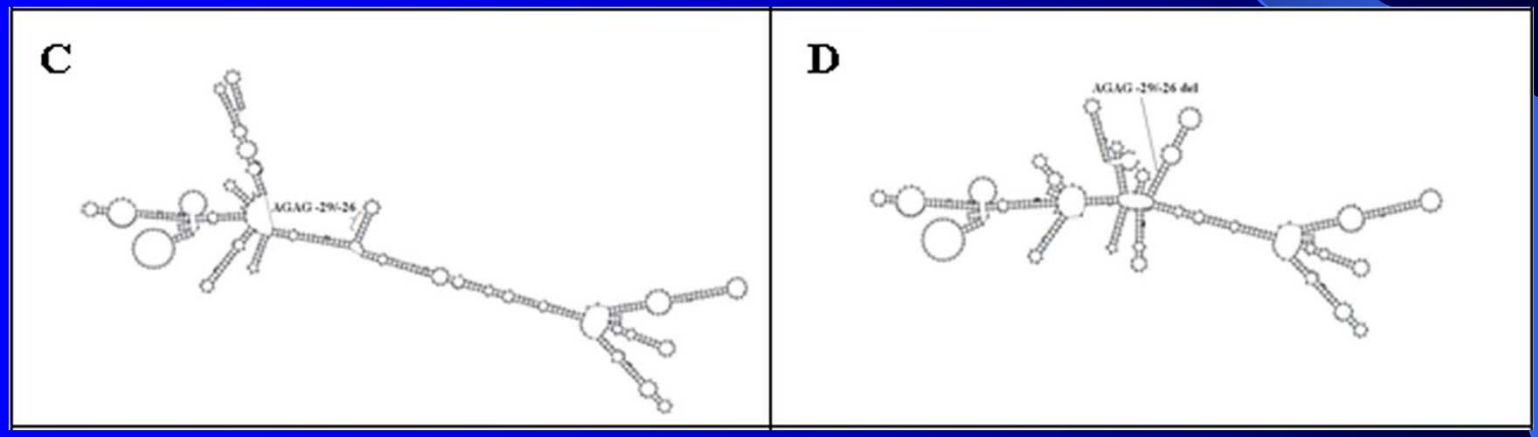
Sambugaro…, Zatelli MC Endocrine. 2015 ;49:58-64

Pathogenesis of GH excess

MEN4

Wild type

Deleted



Predicted secondary structure of the 5'-UTR (-575/-1) CDKN1B mRNA

www.rna.tbi.univie.ac.at/cgi-bin/RNAfold.cgi

Sambugaro…, Zatelli MC Endocrine. 2015 ;49:58-64

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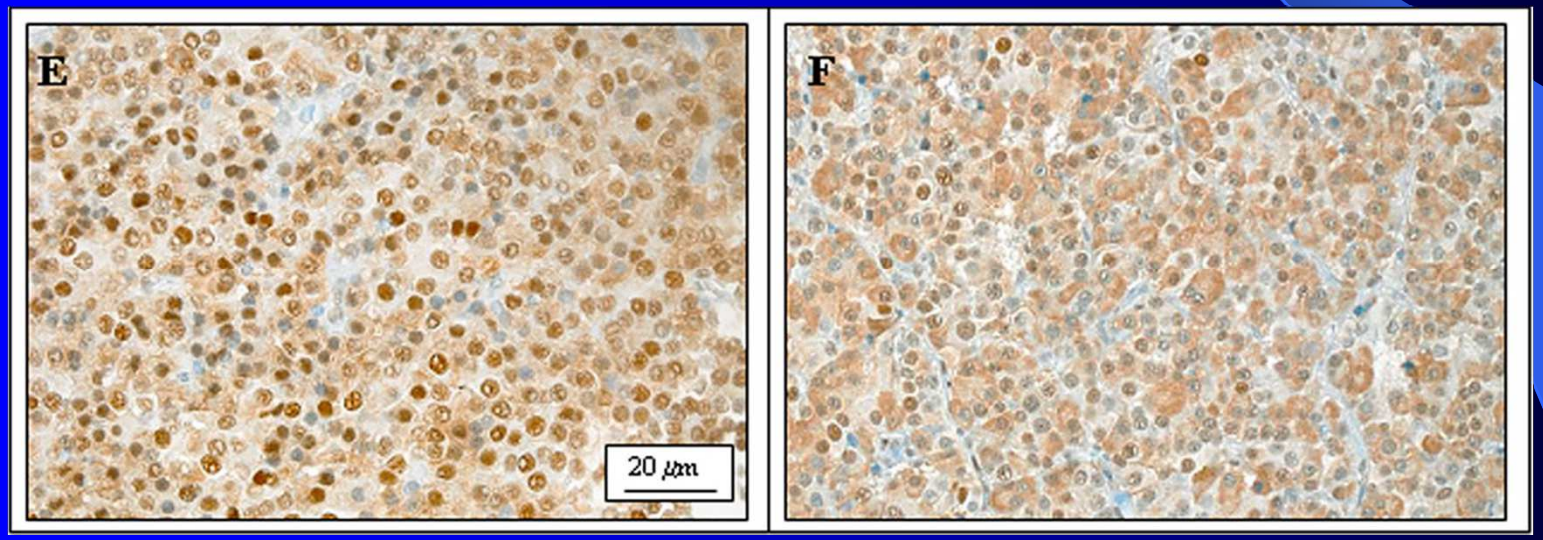
Pathogenesis of GH excess

MEN4

Wild type

Deleted



Immunohistochemical staining for p27Kip1

Sambugaro…, Zatelli MC Endocrine. 2015 ;49:58-64

Pathogenesis of GH excess

These findings indicate that the identification of functional alterations of newly discovered genetic derangements need to be fully characterized and always correlated with the clinical manifestations. However, the presence of other mutations (somatic or germ line) cannot be excluded, possibly contributing to the development of an aggressive and early onset acromegaly in our patient.

Sambugaro…, Zatelli MC Endocrine. 2015 ;49:58-64

Pathogenesis of GH excess

Conditions with germline mutations

Pathogenesis of GH excess

Others?

Endocrine
DOI 10.1007/s12020-015-0645-3

CrossMark

EDITORIAL

A giant? Think of genetics: growth hormone-producing adenomas in the young are almost always the result of genetic defects

Constantine A. Stratakis[1]

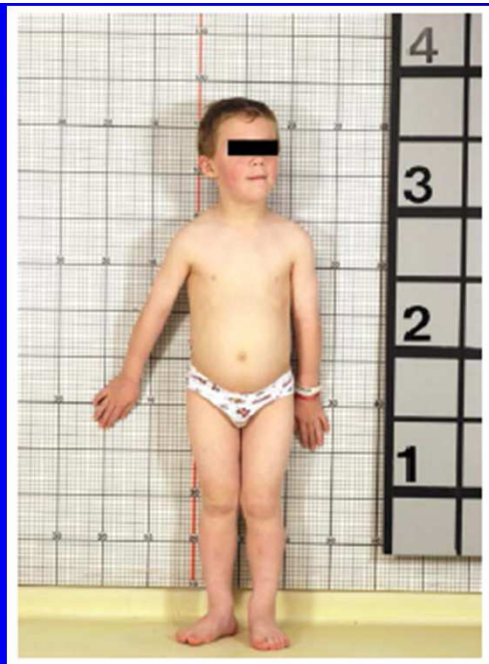
Pathogenesis of GH excess

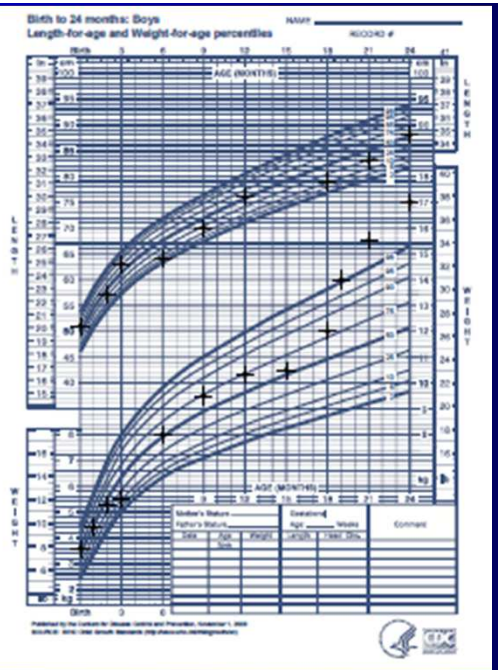
Other!!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gigantism and Acromegaly Due to Xq26 Microduplications and *GPR101* Mutation





Pathogenesis of GH excess

X-LAG

X-linked acrogigantism

pediatric disorder

"adult" acromegaly

Xq26.3 genomic duplication

GPR101 duplication

early-onset gigantism

recurrent GPR101 mutation

Trivellin et al. N Engl J Med 2014; 371:25

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Pathogenesis of GH excess

Table 1. Clinical Characteristics of 43 Patients with Gigantism with and without Xq26.3 Microduplications.

Characteristic	Xq26.3 Microduplication (N=14)	No Xq26.3 Microduplication (N=29)	P Value
Female sex — no. (%)	10 (71)	7 (24)	0.007
Median age at onset of rapid growth (range) — yr	1.0 (0.5 to 2.0)	16.0 (5.0 to 18.0)	<0.001
Median age at diagnosis (range) — yr	3 (1 to 22)	21 (5 to 34)	<0.001
Median height at diagnosis (range) — cm	116 (99 to 175)	187 (171 to 209)	<0.001
Median standard-deviation score for height at diagnosis (range)	+3.8 (+1.9 to +7.1)	+3.3 (+2.1 to +5.8)	0.45
Elevated levels of growth hormone and insulin-like growth factor 1 at diagnosis — no. (%)	14 (100)	29 (100)	1.00
No suppression of growth hormone during oral glucose-tolerance test — no. (%)	14 (100)	29 (100)	1.00
Median factor increase in insulin-like growth factor 1 at diagnosis (range) — multiple of ULN	4.4 (2.4 to 5.2)	2.1 (1.4 to 5.3)	0.005
Elevated prolactin level at diagnosis — no. (%)	13 (93)	6 (21)	<0.001
Median maximum tumor diameter (range) — mm	16 (10 to 39)	20 (9 to 41)	0.16
Adenoma or hyperplasia — no. (%)†			
Both adenoma and hyperplasia	2 (14)	0	
Adenoma only	10 (71)	29 (100)	—
Hyperplasia only	1 (7)	0	
Type of syndrome — no. (%)			
Sporadic	9 (64)	29 (100)	—
Familial	5 (36)‡	0	
Siblings with normal growth — no./total no. (%)	9/11 (82)	29/29 (100)	—

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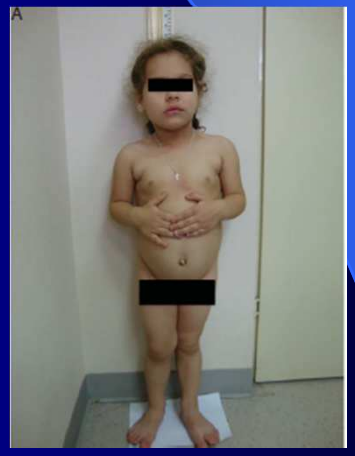
Pathogenesis of GH excess

Research | A Beckers, M B Lodish et al. | X-linked acrogigantism syndrome | 22:3 | 353–367

X-linked acrogigantism syndrome: clinical profile and therapeutic responses

- early and rapid growth (2–3 months of age)
- median height and weight > +3.9 SDS
- increased overall body size
- acromegalic symptoms
- increased appetite
- marked GH/IGF1 hypersecretion (usually also prolactin)
- pituitary macroadenoma or hyperplasia

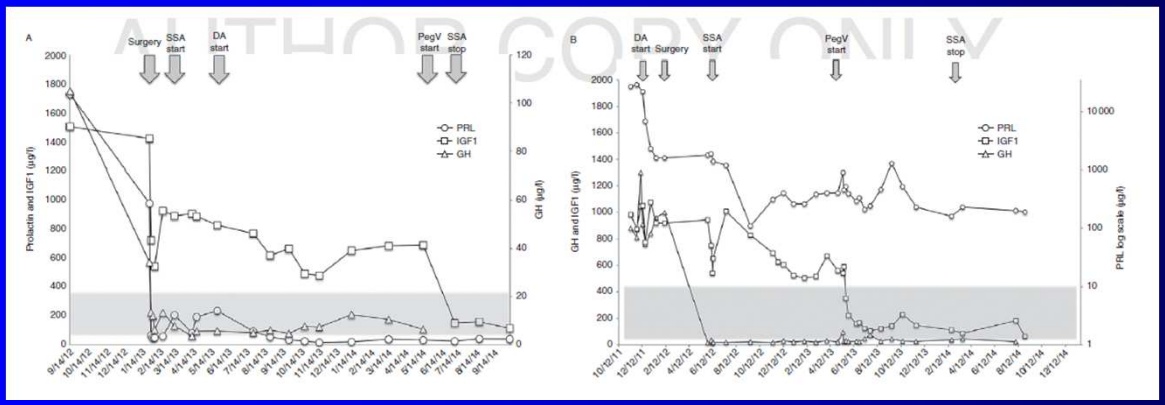


Pathogenesis of GH excess

Research | A Beckers, M B Lodish et al. | X-linked acrogigantism syndrome | 22:3 | 353–367

X-linked acrogigantism syndrome: clinical profile and therapeutic responses

- extensive anterior pituitary resection ➔ frequent postoperative hypopituitarism
- lack of control with somatostatin analogs despite SSTR2 expression
- postoperative adjuvant pegvisomant ➔ control of IGF1



Beckers et al. Endocrine-Related Cancer (2015) 22, 353–367

EFE 2015

Pathogenesis of GH excess

X-LAG

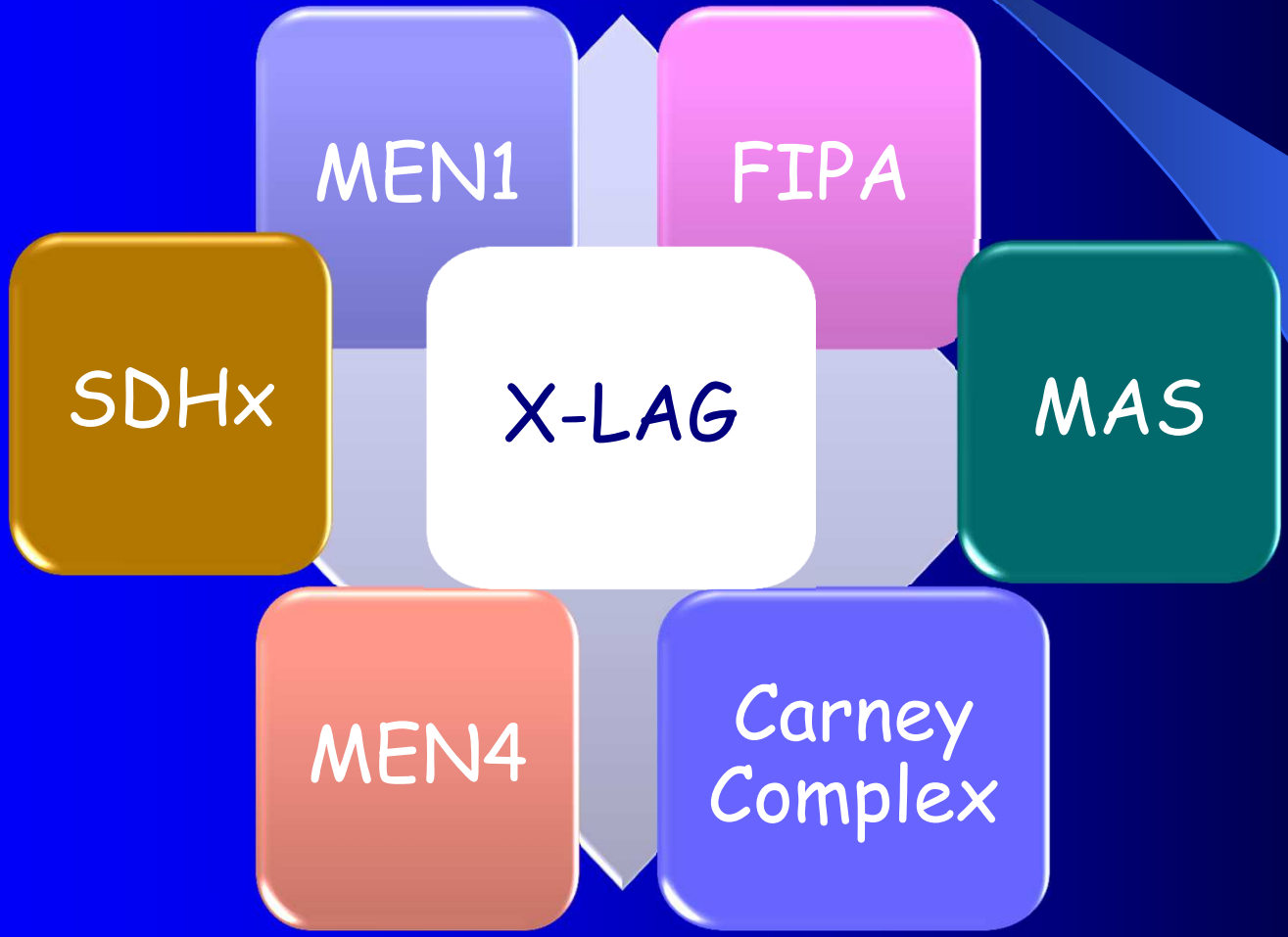
new infant-onset gigantism syndrome

with a severe clinical phenotype

and a challenging disease management

Pathogenesis of GH excess

Conditions with germline mutations

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FAMILY MATTERS
ANGEL PAGAN SALUTES THE JOYS OF FATHERHOOD

THANKS

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