5th F.O.P. Conference
24-26 Marzo, 2011 Roma

Mutazioni nel gene *GNAS* e ossificazioni eterotopiche

GNAS mutations and heterotopic ossifications

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Università di Milano

The NEW ENGLAND JOURNAL of MEDICINE

January 10, 2002

PATERNALLY INHERITED INACTIVATING MUTATIONS OF THE *GNAS1* GENE IN PROGRESSIVE OSSEOUS HETEROPLASIA

EILEEN M. SHORE, PH.D., JAIMO AHN, PH.D., SUZANNE JAN DE BEUR, M.D., MING LI, B.A., MEIQI XU, B.S., R.J. MCKINLAY GARDNER, M.B., MICHAEL A. ZASLOFF, M.D., PH.D., MICHAEL P. WHYTE, M.D., MICHAEL A. LEVINE, M.D., AND FREDERICK S. KAPLAN, M.D.

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

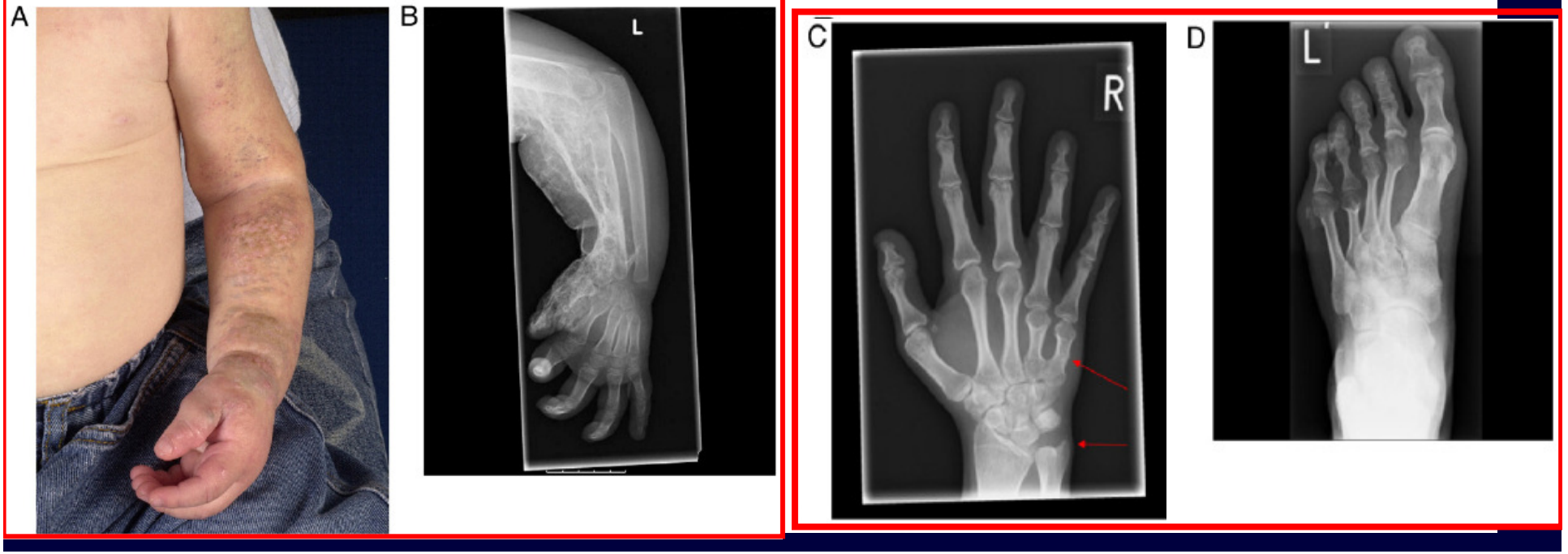
Case Report

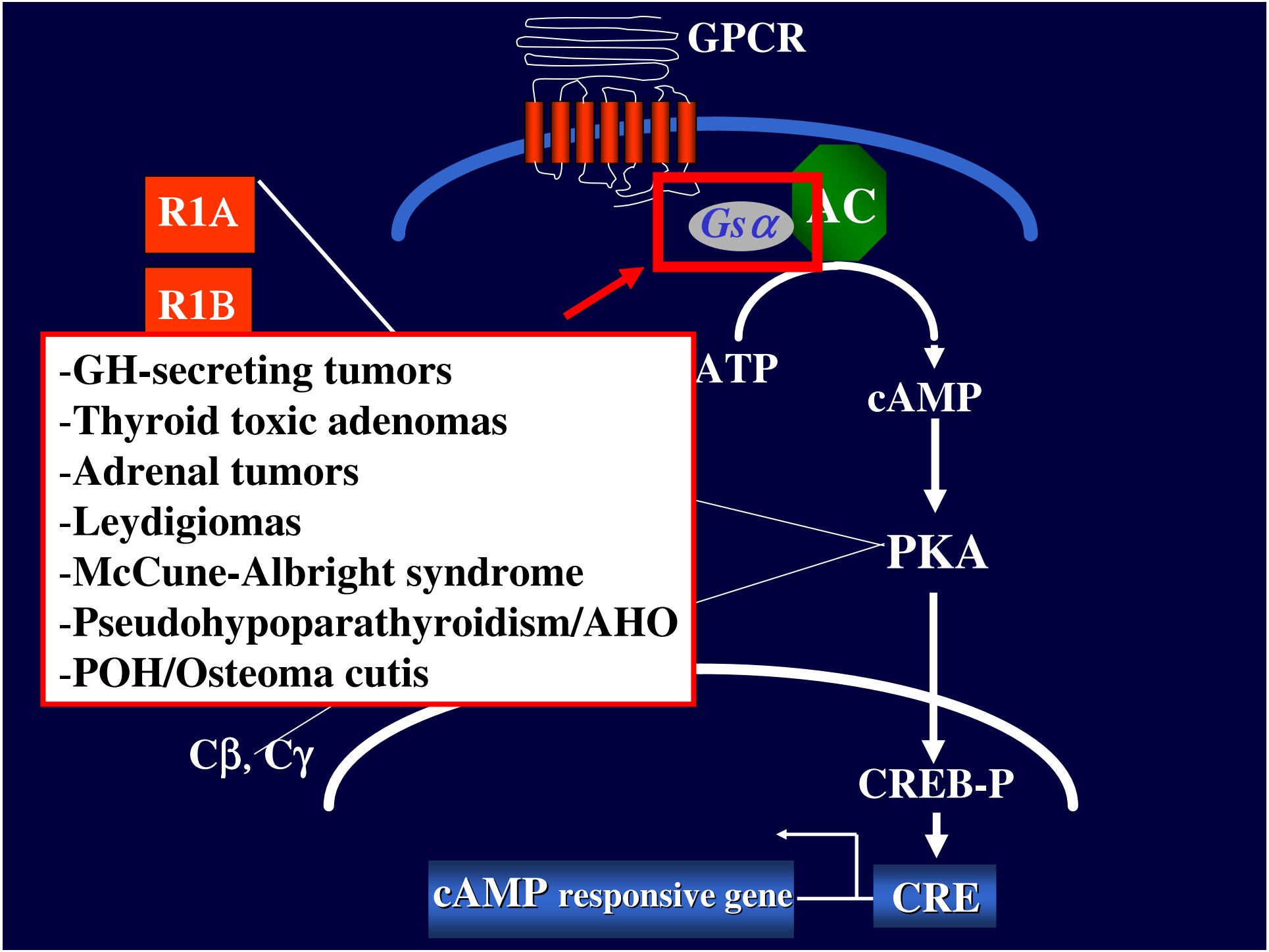
GNAS-associated disorders of cutaneous ossification: Two different clinical presentations

R.J. Schimmel [a,1], S.G.M.A. Pasmans [a,*,1], M. Xu [b], S.A.E. Stadhouders-Keet [c], E.M. Shore [d], F.S. Kaplan [e], N.M. Wulffraat [f]

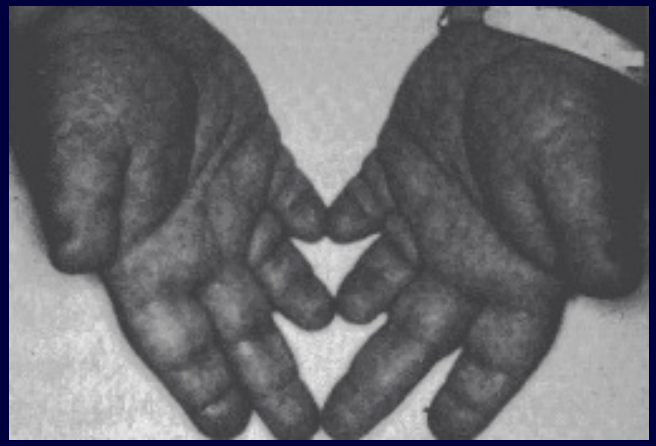
POH

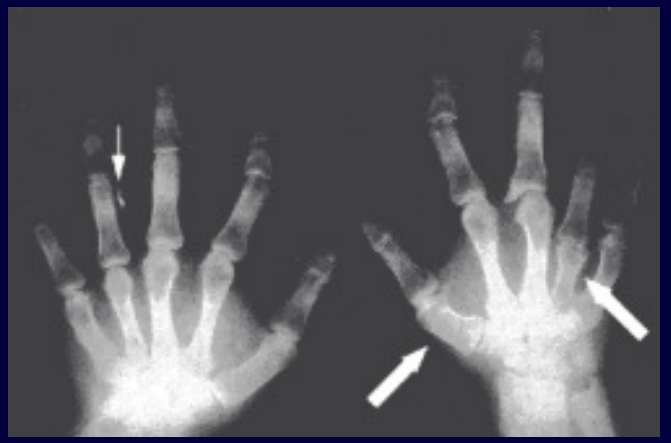
AHO




GPCR
R1A
R1B
-GH-secreting tumors
-Thyroid toxic adenomas
-Adrenal tumors
-Leydigiomas
-McCune-Albright syndrome
-Pseudohypoparathyroidism/AHO
-POH/Osteoma cutis
Gs α
AC
ATP
cAMP
PKA
Cβ, Cγ
CREB-P
cAMP responsive gene
CRE

ALBRIGHT'S HEREDITARY OSTEODYSTROPHY (AHO):





AHO

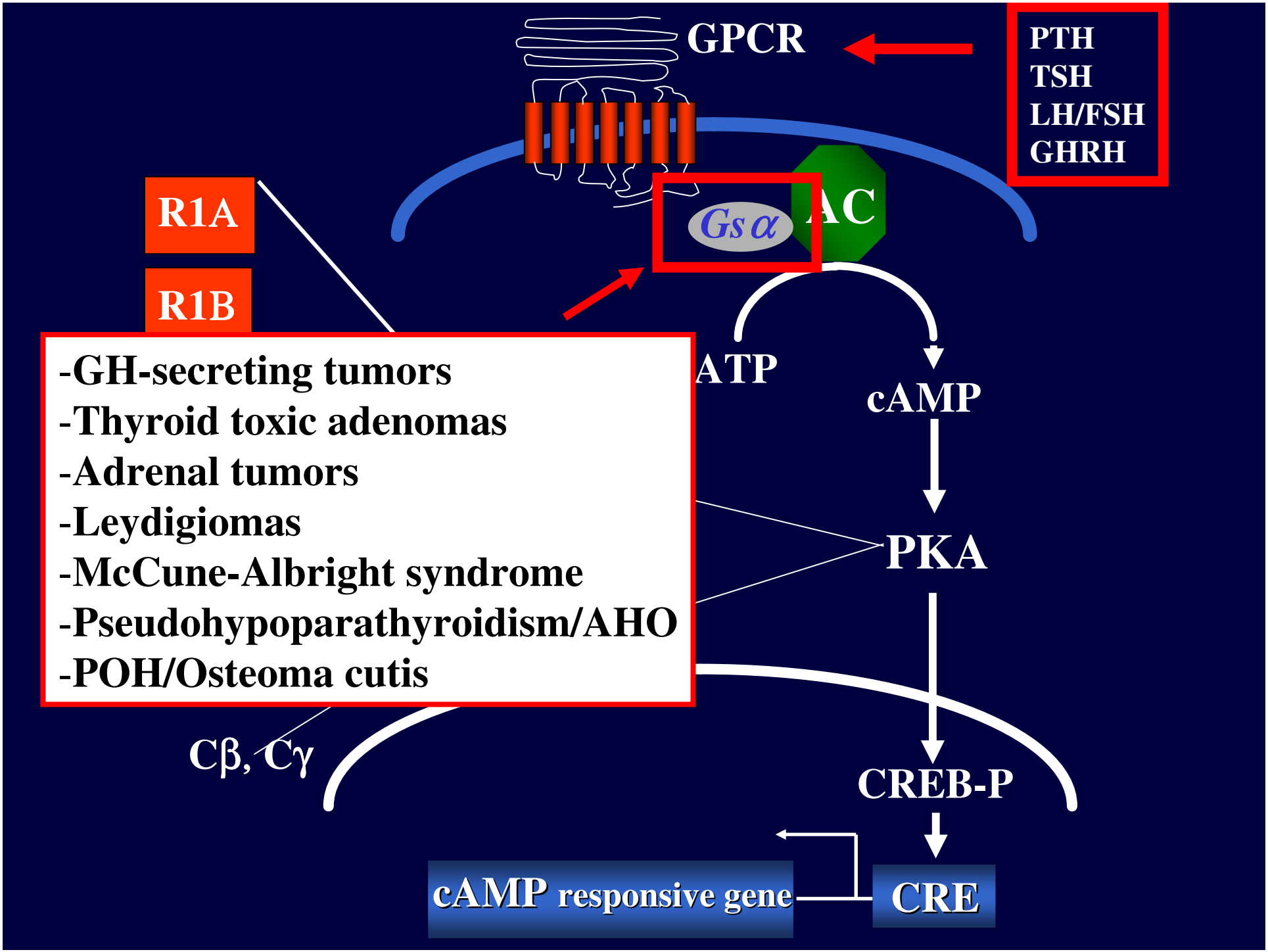
- short stature
- *obesity*
- rounded face
- brachydactyly
- subcutaneus ossifications
- mental retardation

Pseudohypoparathyroidism Ia (PHP-Ia)

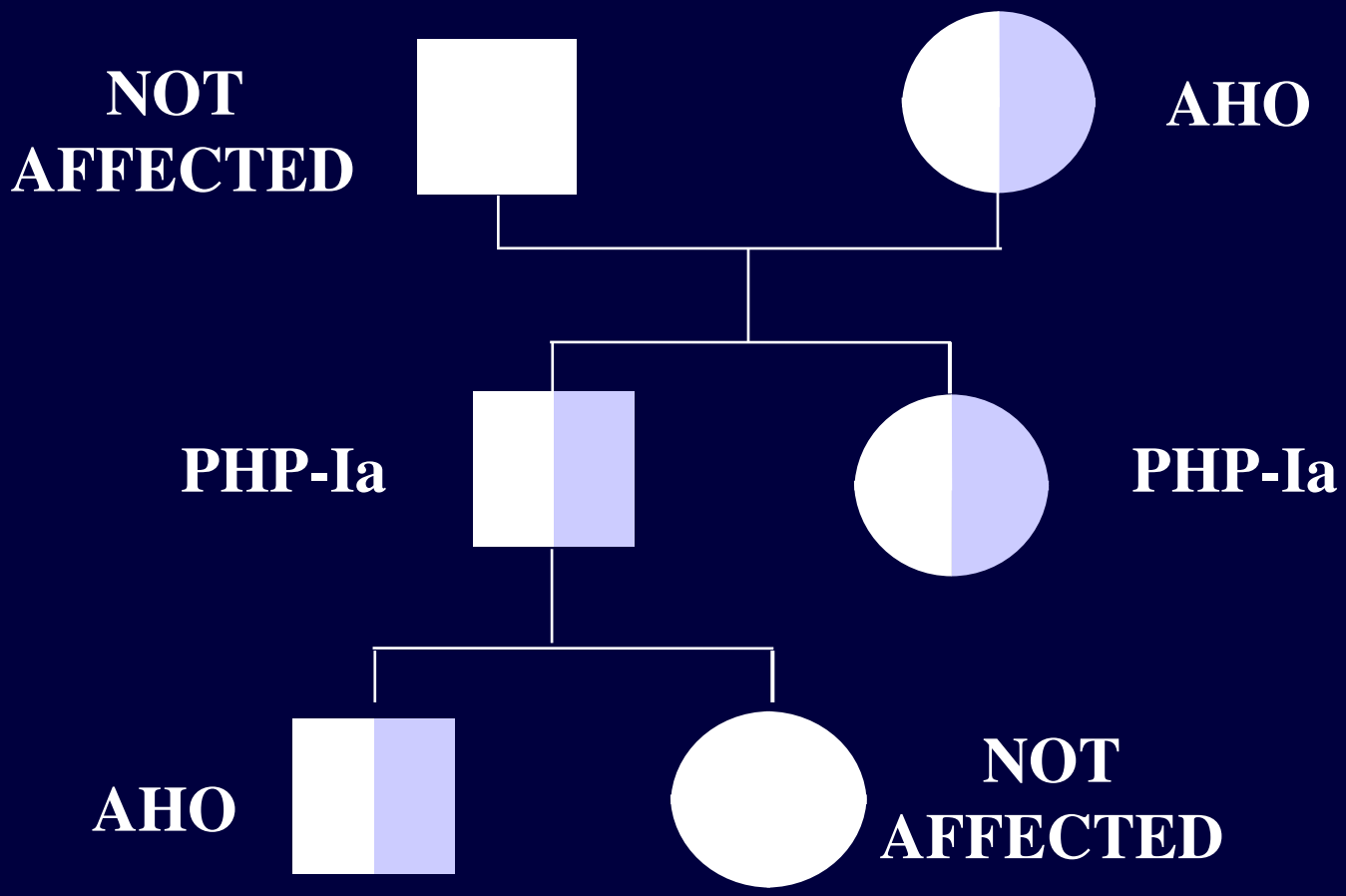
AHO

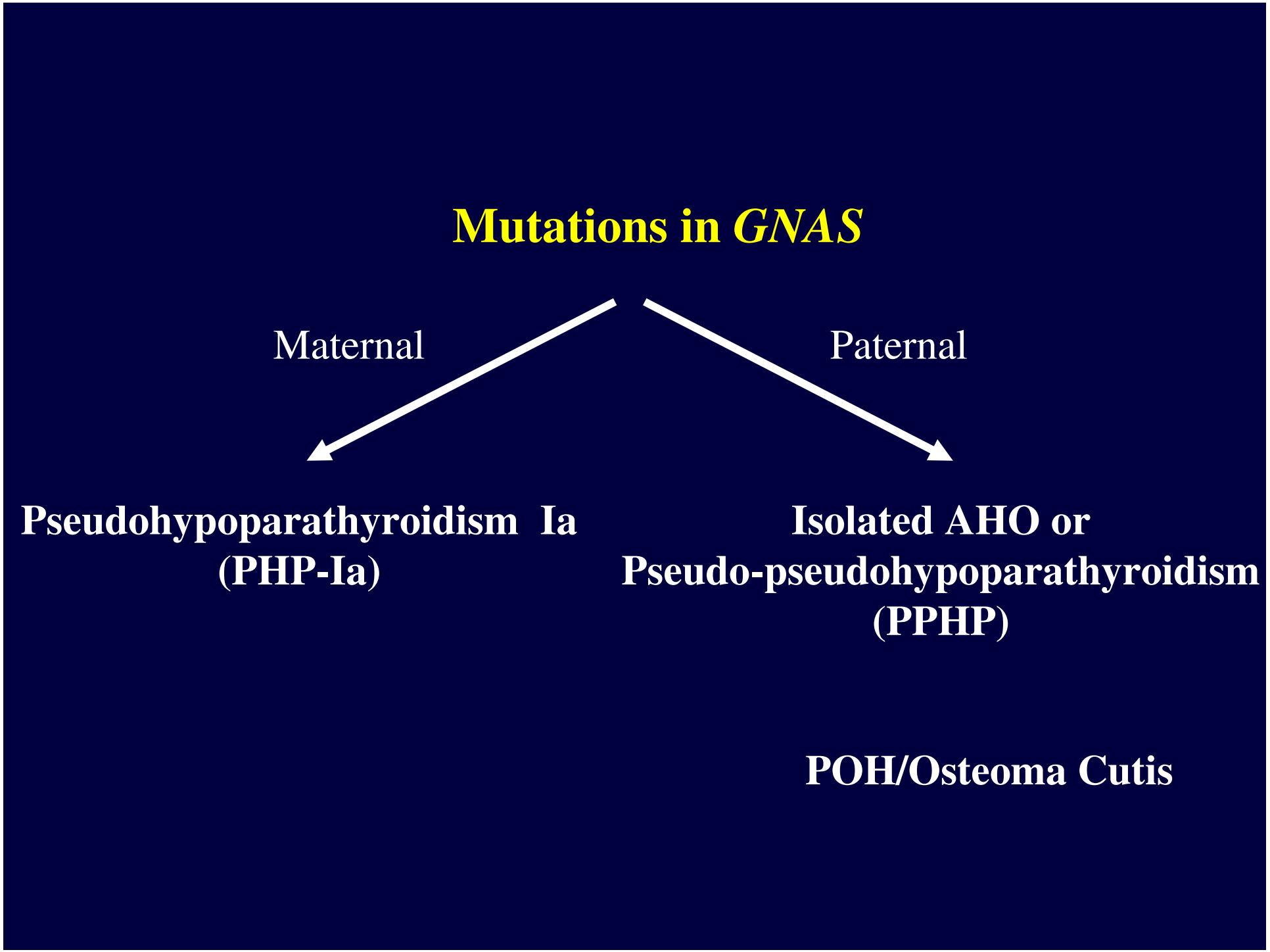
+

- resistance to PTH = hypocalcemia
- resistance to TSH = hypotiroidism
- resistance to gonadotropins = hypogonadism
- resistance to GHRH = GH deficit

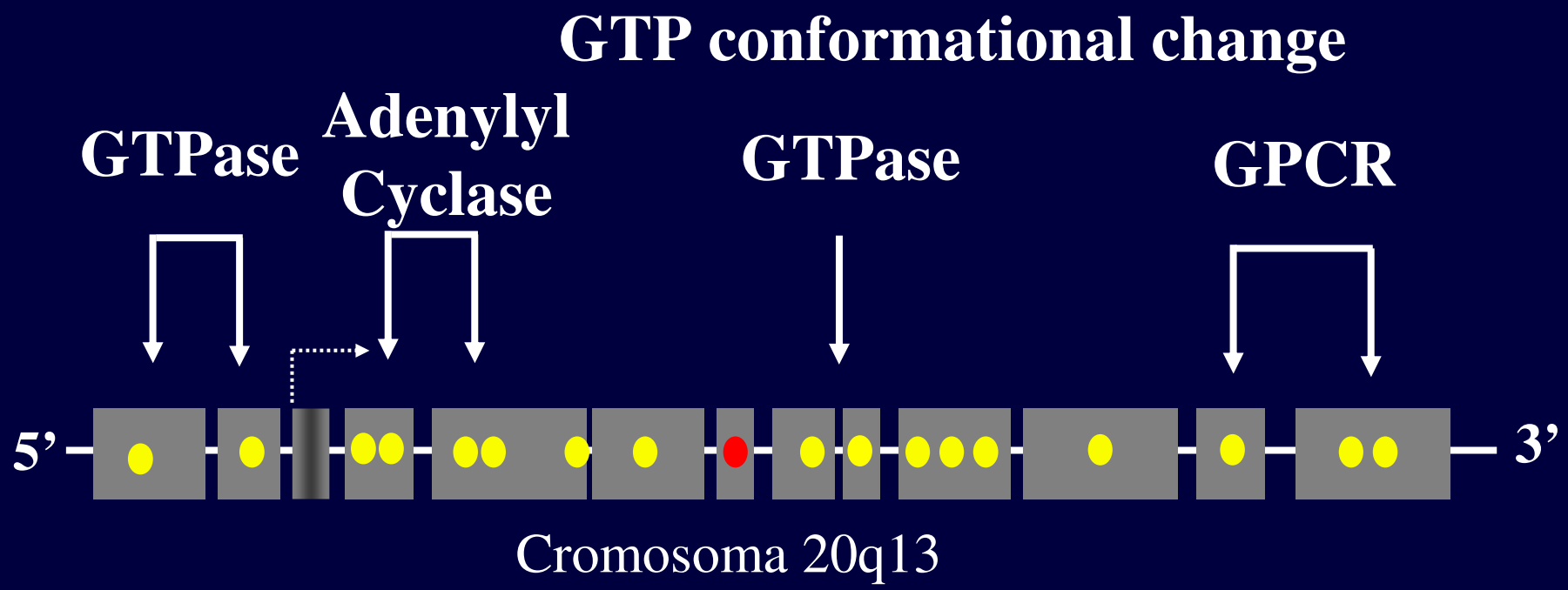

GPCR
PTH
TSH
LH/FSH
GHRH
R1A
R1B
Gsα
AC
ATP
cAMP
PKA
-GH-secreting tumors
-Thyroid toxic adenomas
-Adrenal tumors
-Leydigiomas
-McCune-Albright syndrome
-Pseudohypoparathyroidism/AHO
-POH/Osteoma cutis
Cβ, Cγ
CREB-P
cAMP responsive gene
CRE

FAMILY WITH AHO/PHP




Mutations in *GNAS*
Maternal
Paternal
Pseudohypoparathyroidism Ia (PHP-Ia)
Isolated AHO or Pseudo-pseudohypoparathyroidism (PPHP)
POH/Osteoma Cutis

Inactivating mutations associated withAHO/PHP/POH



- Inactivatingmutations > altered mRNA > no protein
- Hot-spot (20%)

CLASSIFICATION OF AHO e PHP

Type I — Absent plasmatic and urinary cAMP response to exogenous PTH

- PHP Ia
- PHP Ib
- PHP Ic
- PPHP

GNAS

Type II — Normal plasmatic and urinary cAMP response to exogenous PTH

- PHP II

Pseudohypoparathyroidism type Ib

- **Renal resistance to PTH**
- **No other hormone resistance (TSH?)**
- **No physical abnormalities**
- **No mutation in the PTH-R gene**
- **No mutation in GNAS**

2 FORMs { **Familial: autosomal dominant**

Sporadic

Alterations of imprinting at the GNAS gene
> Reduced expression of Gsα protein
(in selected tissues only)

J Clin Endocrinol Metab, Feb 2010

ORIGINAL ARTICLE

Endocrine Care

Pseudohypoparathyroidism and *GNAS* Epigenetic Defects: Clinical Evaluation of Albright Hereditary Osteodystrophy and Molecular Analysis in 40 Patients

Giovanna Mantovani,* Luisa de Sanctis,* Anna Maria Barbieri, Francesca M. Elli, Valentina Bollati, Valentina Vaira, Pamela Labarile, Sara Bondioni, Erika Peverelli, Andrea G. Lania, Paolo Beck-Peccoz, and Anna Spada

Patient	Sex	Age	Hormone Resistance	AHO features	Abnormal methylation	STX deletion
1	F	9	PTH/TSHs	Br/RF	AB/AS/XL	No
2	M	22	PTH/TSHs	Br/SS/RF/Ob/SO/MR	AB//XL	No
3	F	22	PTH/TSHs	Br/SS/RF/Ob/SO/MR	AB/NESP/AS/XL	No
4	F	18	PTH/TSH	Br/SS/RF/Ob/SO/MR	AB/NESP/AS/XL	No
5	F	15	PTH/TSHs	Br/SS/RF/Ob/SO/MR	AB/XL	No
6	F	4	PTH/TSHs	SS/RF/Ob/SO/MR	AB/AS/XL	No
7	M	3	PTH/TSH	Br/SS/RF/MR	AB/NESP/XL	No
8	M	3	PTH/TSHs	Br/SS/RF/Ob/MR	AB/NESP/XL	No
9	M	8	PTH/TSH	Br/RF/Ob/SO/MR	AB/XL	No
10	M	12	PTH/TSHs	SS/RF	AB/AS/XL	No
11	F	13	PTH/TSHs	Br/SS/RF	AB/XL	No
12	F	10	PTH/TSH	Br/SS	AB/AS/XL	No
13	F	8	PTH/TSH	Br/RF/Ob	AB/NESP/AS/XL	No
14	F	4	PTH/TSHs	Br/RF/Ob	AB/AS/XL	No
15	M	2	PTH/TSH	Br/RF	AB/NESP/XL	No
16	M	13	PTH/TSHs	Br/SS/RF/Ob/SO	AB/NESP/AS/XL	No
17	F	15	PTH	Br/RF/Ob/SO/MR	AB/AS	No
18	M	19	PTH	Br/RF/Ob	AB/AS/XL	No
19	F	13	PTH	Br/SS/RF/Ob/MR	AB/NESP/AS/XL	No
20	F	18	PTH/TSHs	Br/MR	AB/AS/XL	No
21	M	6	PTH/TSHs	Br/SS/RF/Ob	AB/AS	No
22	F	5	PTH/TSHs	Br/SS/RF/Ob/SO/MR	AB/AS	No
23	F	14	PTH	Br/SS/RF/Ob/SO/MR	AB/NESP/AS	No
24	F	7	PTH	Br/SS/RF/Ob	AB/AS	No
25	F	13	PTH/TSH	Br/SS/RF/Ob/MR	No	No
26	F	2	PTH/TSHs	Br/RF/SO	No	No
27	F	12	PTH/TSHs	Br/SS/RF/Ob/SO	No	No
28	M	5	PTH/TSHs	Br/RF/Ob/SO/MR	No	No
29	F	1	PTH/TSH	Br/RF/Ob/SO	No	No
30	F	13	PTH/TSHs	Br/SS/RF/Ob/SO	No	No
31	F	11	PTH/TSH	RF/MR	No	No
32	F	15	PTH/Gn	Br/RF	No	No
33	F	30	PTH/TSH	Br/SS/RF/Ob/SO/MR	No	No
34	F	10	PTH/TSHs	Br/SS/RF/Ob/SO	No	No
35	F	1	PTH	Br/RF/SO/MR	No	No
36	F	12	PTH/TSHs	Br/RF/SO	No	No
37	F	12	PTH	Br/RF	No	No
38	F	23	PTH/TSHs	Br/RF	No	No
39	M	10	PTH	Br/SS/RF/Ob/MR	No	No
40	M	22	PTH/TSHs	Br/SS/MR	No	No

CLASSIFICATION OF AHO e PHP

Type I — Absent plasmatic and urinary cAMP response to exogenous PTH

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- PHP Ic
- PPHP

GNAS

Type II — Normal plasmatic and urinary cAMP response to exogenous PTH

- PHP II

American Journal of Medical Genetics Part A 146A:1788–1796 (2008)

Diagnostic and Mutational Spectrum of Progressive Osseous Heteroplasia (POH) and Other Forms of *GNAS*-Based Heterotopic Ossification

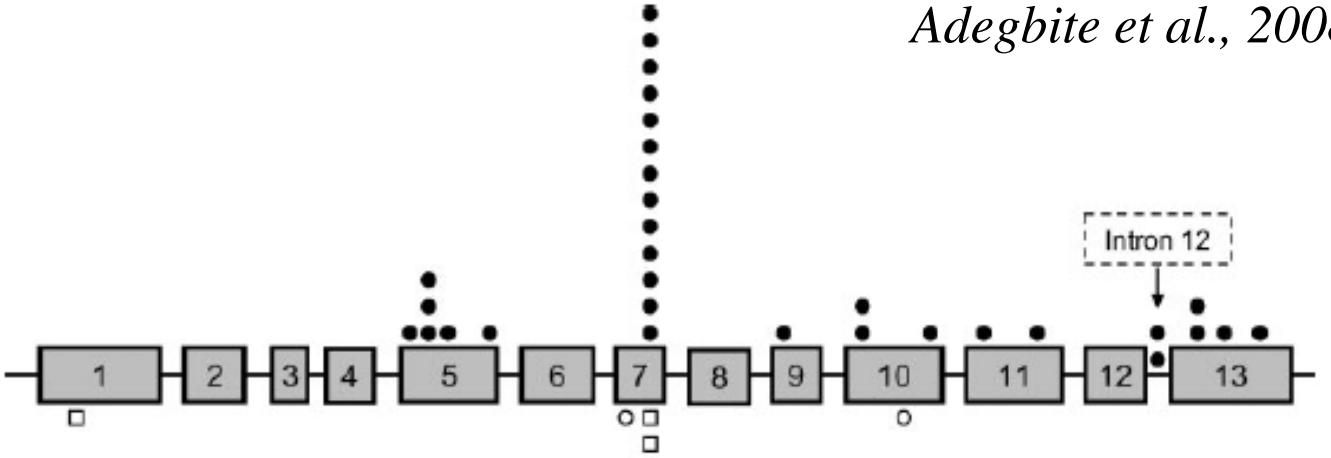
N.S. Adegbite,[1] M. Xu,[1] F.S. Kaplan,[1,2] E.M. Shore,[1,3] and R.J. Pignolo[2]*

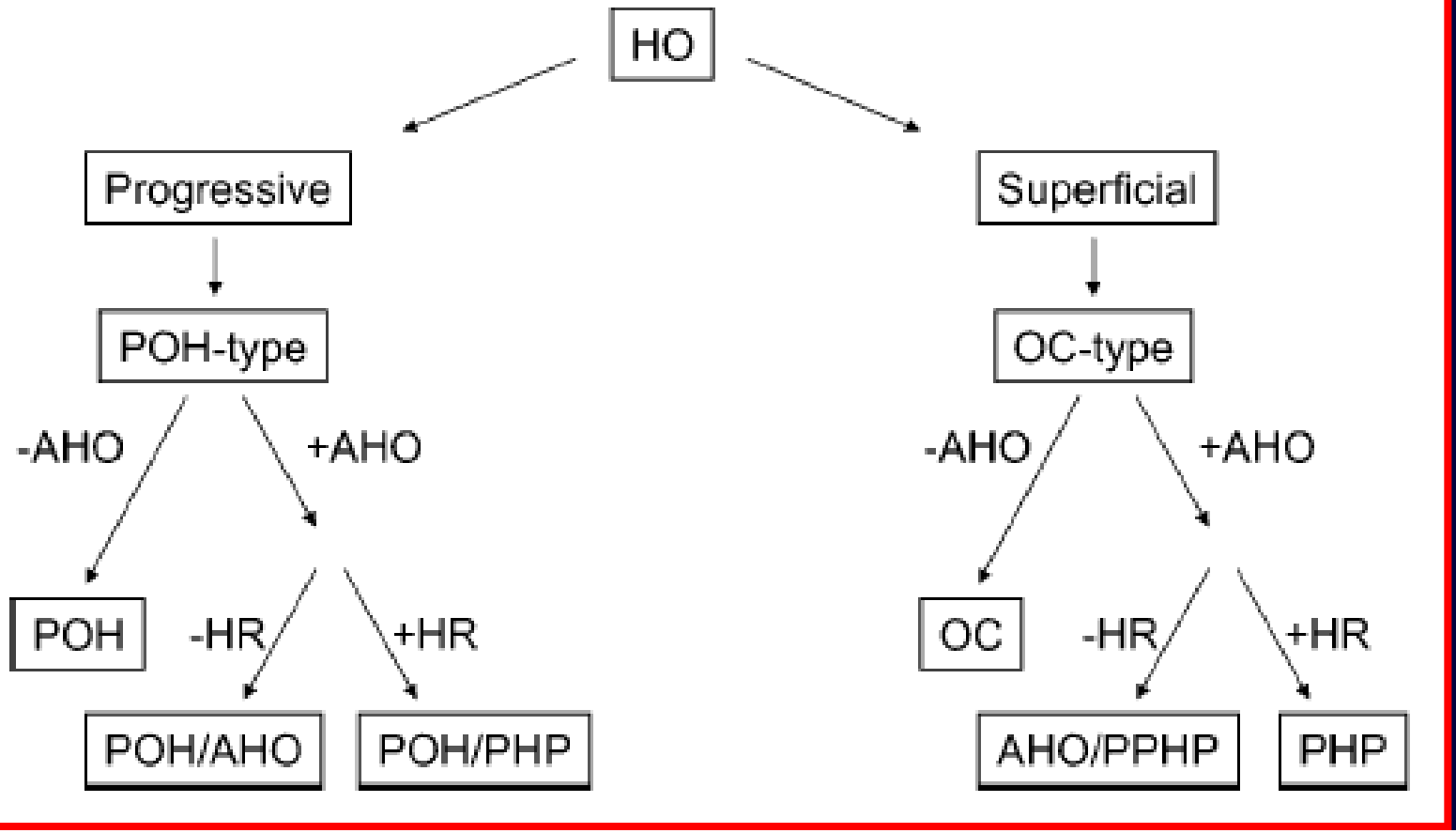
TABLE I. Clinical characteristics of POH and other *GNAS*-based disorders of superficial heterotopic ossification (HO)

Diagnosis	*n*	Superficial HO	Deep HO[a]	>2 AHO features[b]	PTH resistance[c]
POH	52	+	+	–	–
POH/AHO	6	+	+	+[d]	–
POH/PHP1a/1c	5	+	+	+[d]	+[d]
Osteoma cutis	26	+	–[d]	–	–
AHO	10	+	–[d]	+[d]	–
PHP1a/1c	12	+	–[d]	+[e]	+[d]

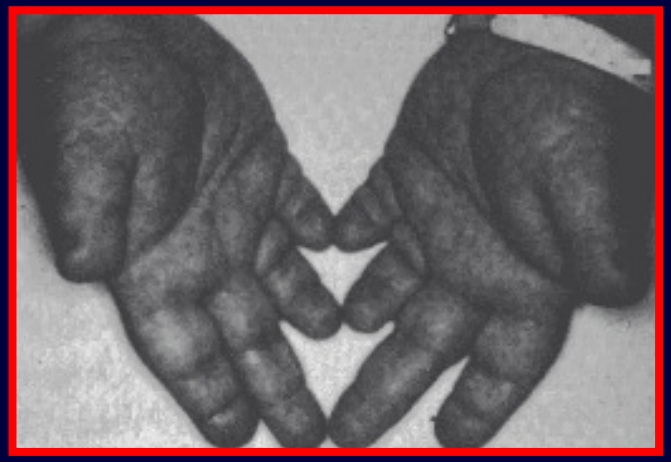
N total = 111

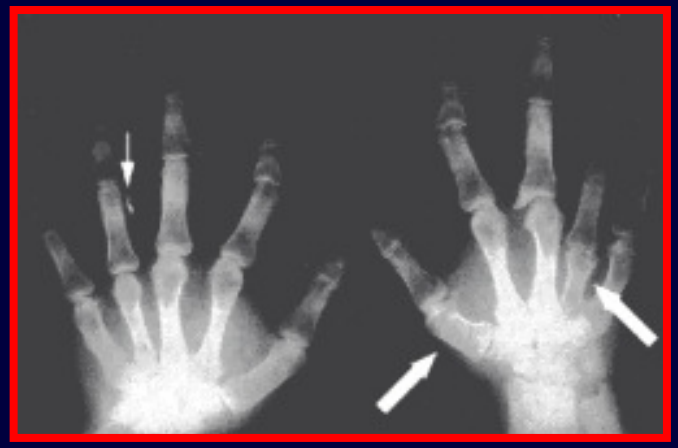
Adegbite et al., 2008

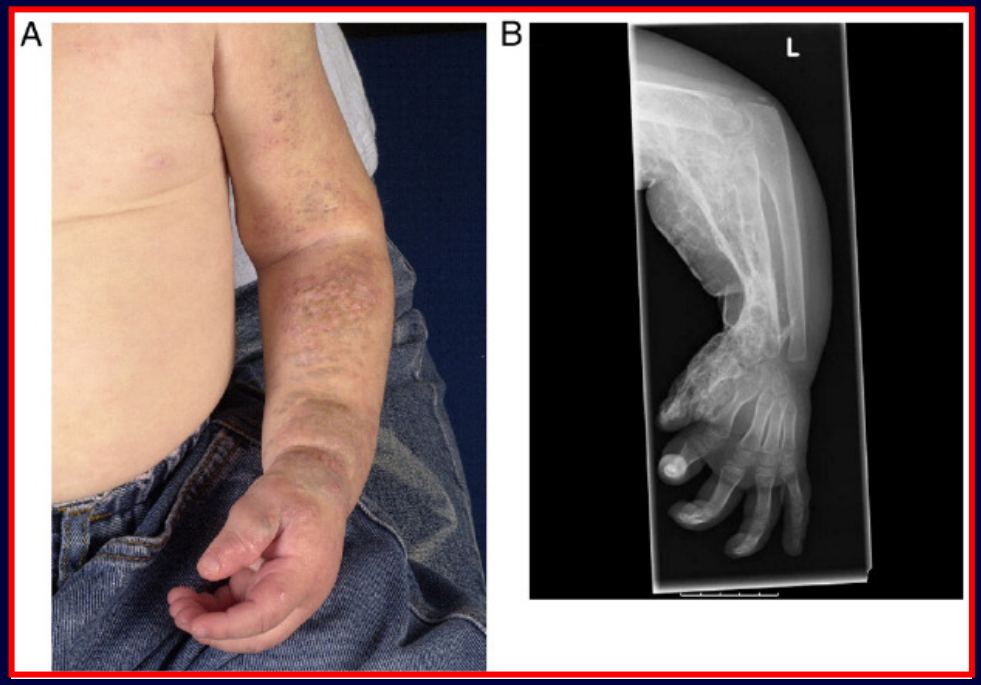




GNAS and ectopic ossifications





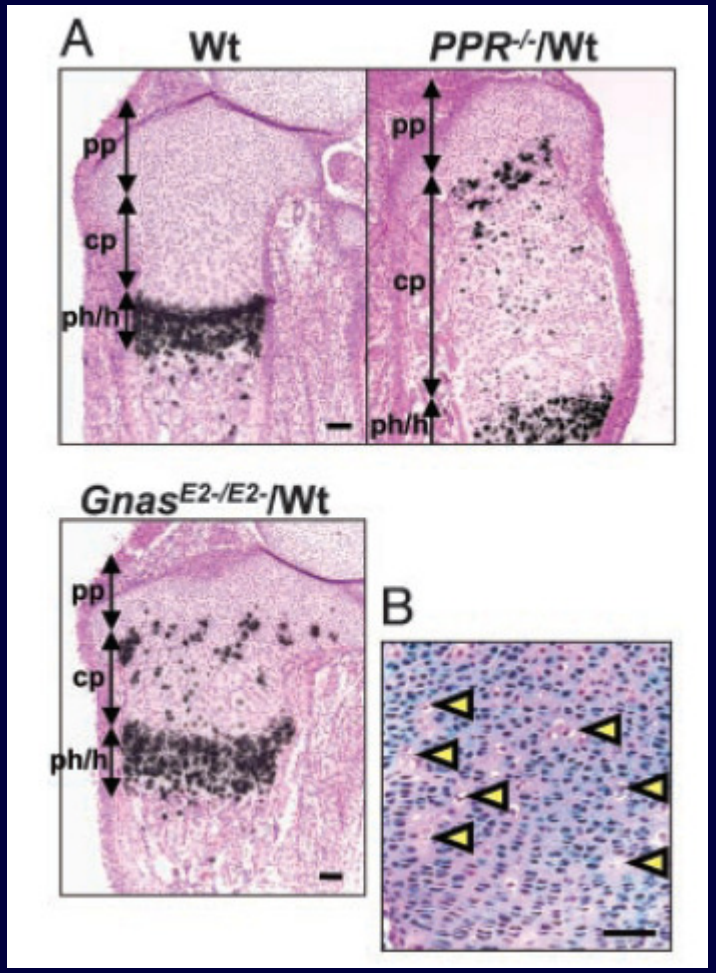


?

PNAS | October 12, 2004

Stimulatory G protein directly regulates hypertrophic differentiation of growth plate cartilage *in vivo*

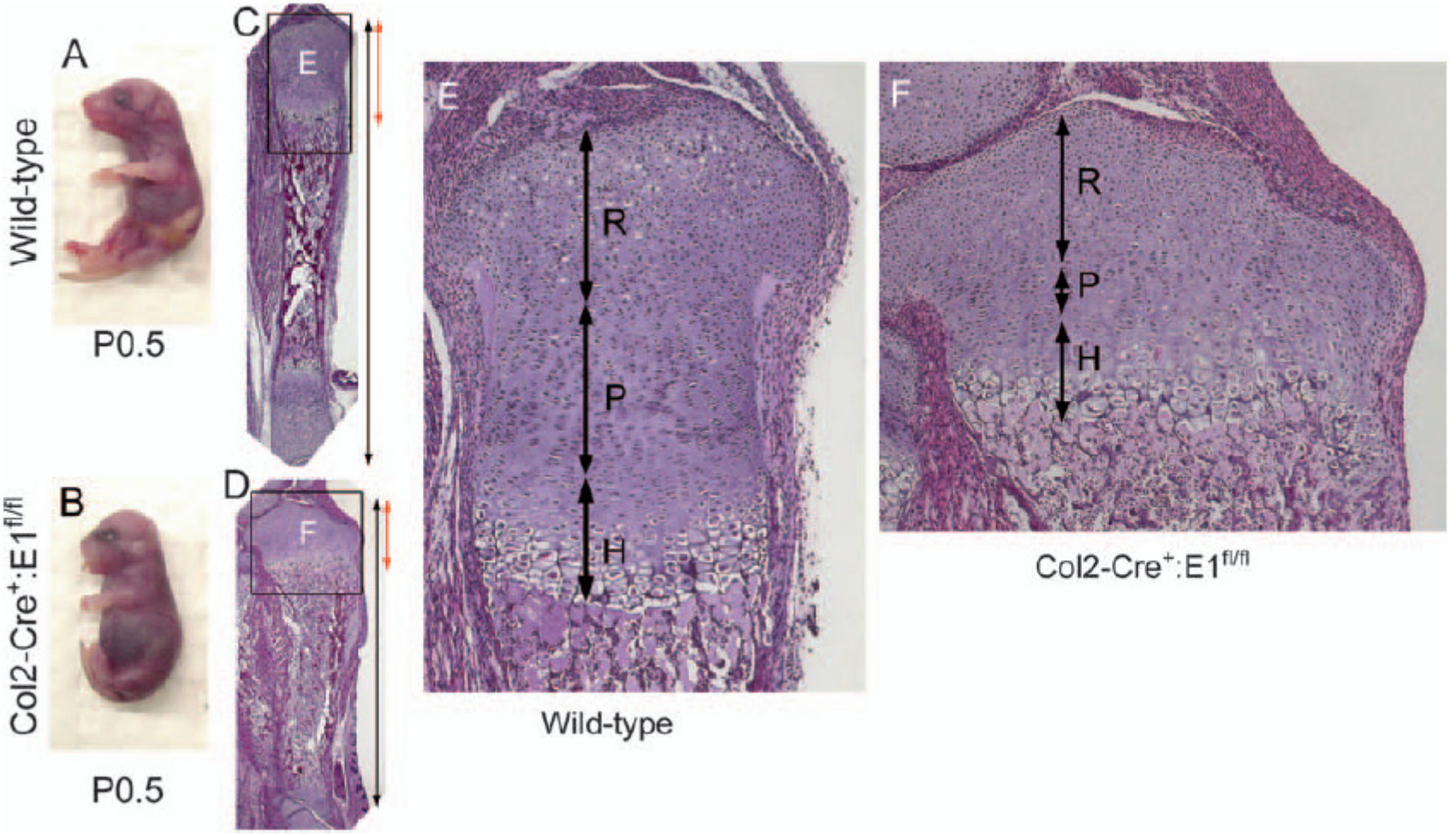
Murat Bastepe*, Lee S. Weinstein†, Naoshi Ogata‡, Hiroshi Kawaguchi‡, Harald Jüppner*, Henry M. Kronenberg*, and Ung-il Chung‡§



In condrocytes, the reduction of Gsα protein induces premature hypertrophic differentiation of the growth plate and, likely, premature bone formation with reduced long bones length

Chondrocyte-Specific Knockout of the G Protein $G_s\alpha$ Leads to Epiphyseal and Growth Plate Abnormalities and Ectopic Chondrocyte Formation

Akio Sakamoto,[1] Min Chen,[1] Tatsuya Kobayashi,[2] Henry M Kronenberg,[2] and Lee S Weinstein[1]



Chondrocyte-Specific Knockout of the G Protein $G_s\alpha$ Leads to Epiphyseal and Growth Plate Abnormalities and Ectopic Chondrocyte Formation

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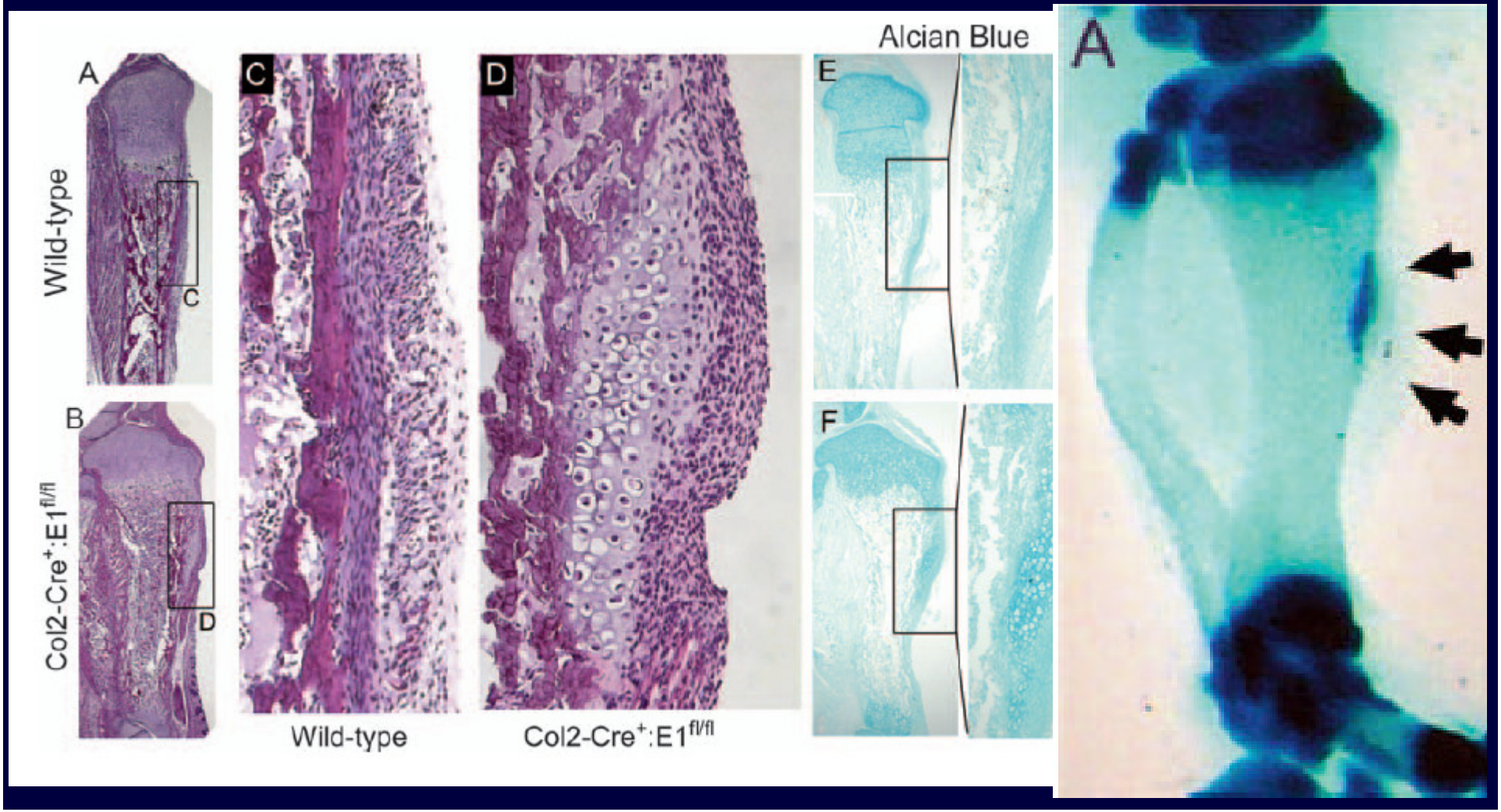
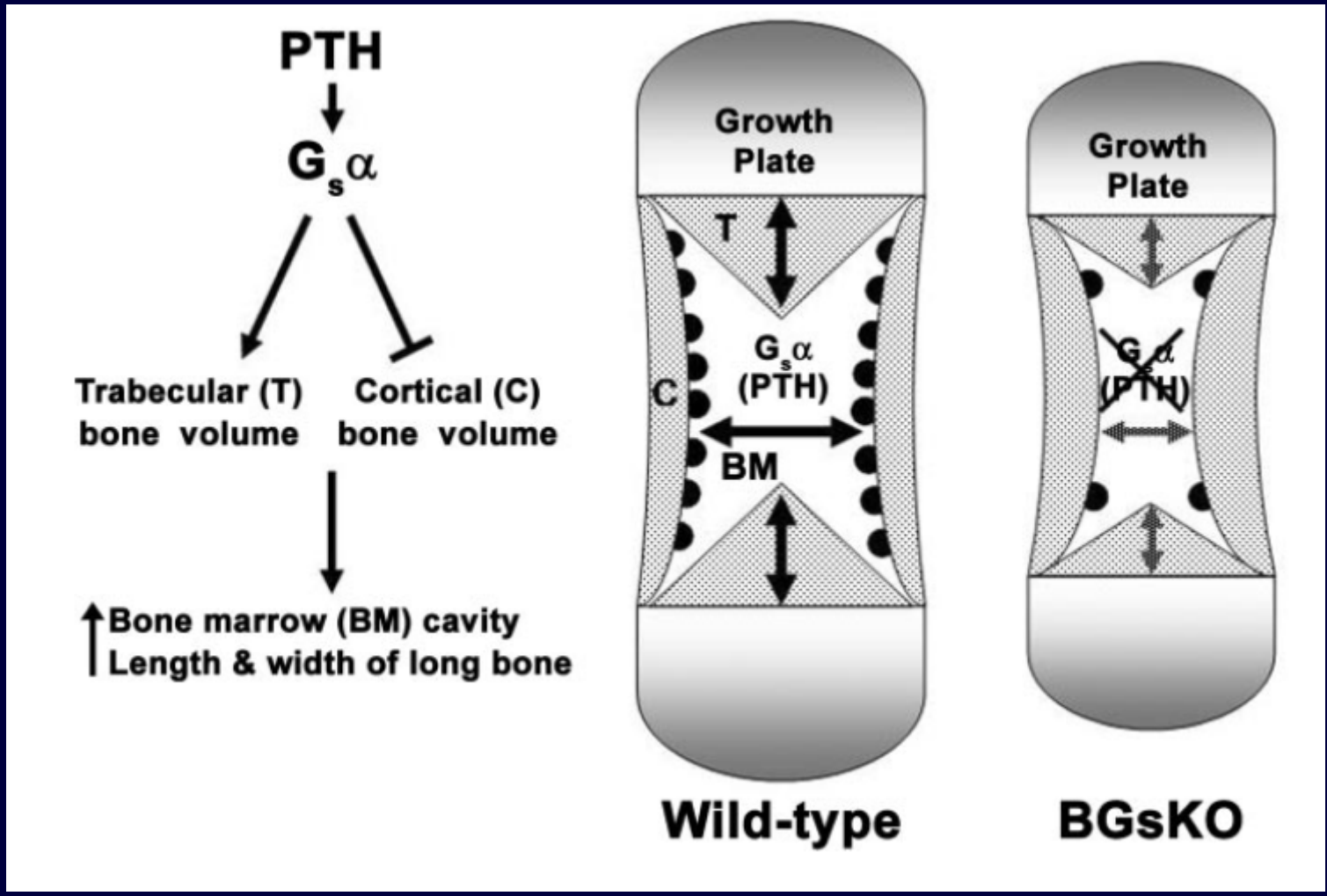


THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 280, No. 22, Issue of June 3, pp. 21369–21375, 2005
Printed in U.S.A.

Deficiency of the G-protein α-Subunit $G_s\alpha$ in Osteoblasts Leads to Differential Effects on Trabecular and Cortical Bone*



European Journal of Endocrinology (2011) **164** 295–301 ISSN 0804-4643

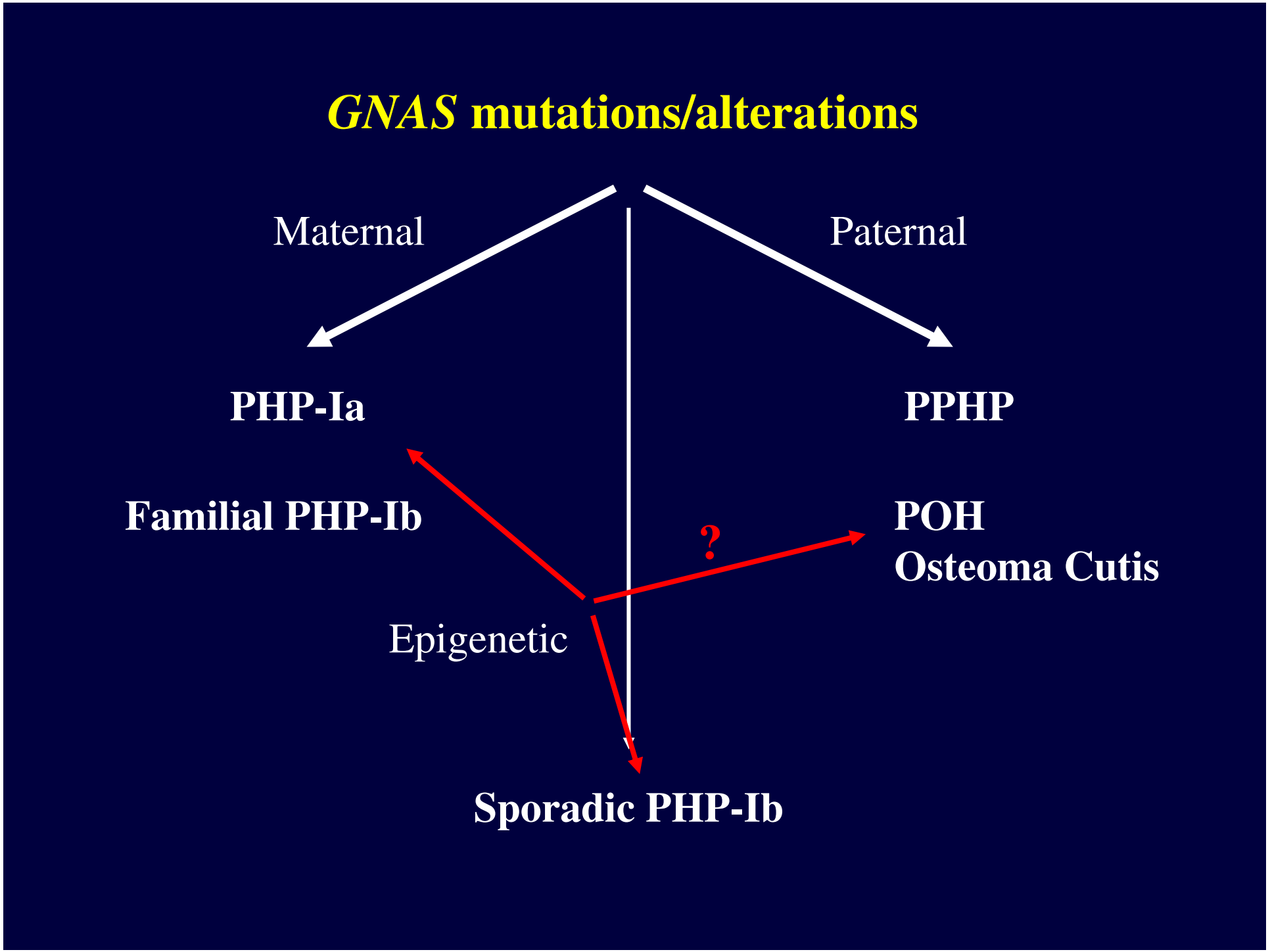
CASE REPORT

Osteosclerosis in two brothers with autosomal dominant pseudohypoparathyroidism type 1b: bone histomorphometric analysis

Anne Marie Sbrocchi, Frank Rauch[1], Margaret L Lawson, Stasia Hadjiyannakis, Sarah Lawrence, Murat Bastepe[2], Harald Jüppner[2] and Leanne Marie Ward

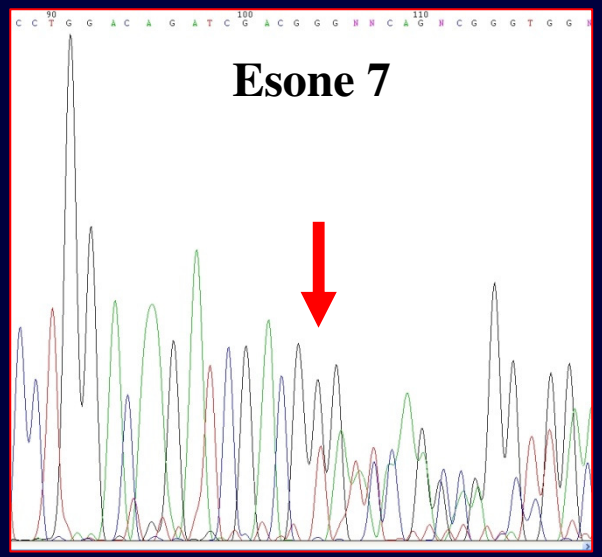
Table 2 Histomorphometric results in trans-iliac bone samples: structural parameters.

		Proband 1		Proband 2	
	Reference range[a]	Raw result	Percentage of age- and gender-matched mean	Raw result	Percentage of age- and gender-matched mean
Core width (μm)	8.2±1.6	13.3	162	8.4	102
Cortical width (μm)	1006±195	2429	241	2106	209
Cortical porosity (%)	6.6±5	7.2	128	10.8	220
Bone volume/tissue volume (%)	27.8±4.5	35.5	128	45.6	164
Trabecular number (/mm)	1.8±0.3	1.8	96	2	108
Trabecular thickness (μm)	153±24	203	132	230	150

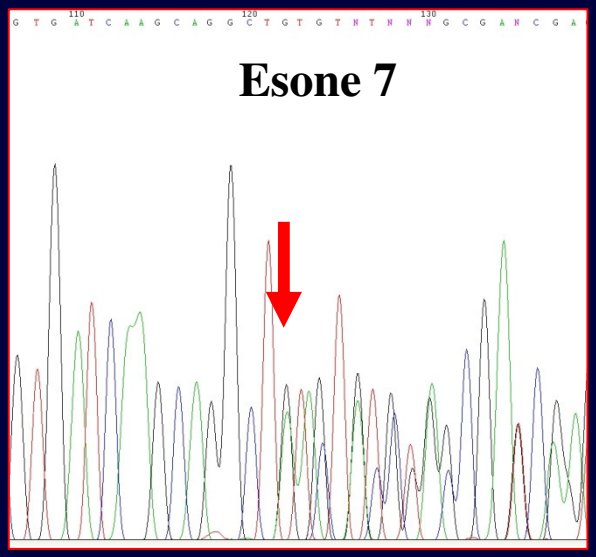

GNAS mutations/alterations
Maternal
Paternal
PHP-Ia
PPHP
Familial PHP-Ib
?
POH
Osteoma Cutis
Epigenetic
Sporadic PHP-Ib

POH/OC patients studied in our laboratory:

- 8 patients: 4M, 4F
- 5 OC, 3 POH, no apparent endocrine manifestation, 1 case with suspect AHO/PHP
- From: Milano (N=4), Modena (N=1), Roma (N=1), Mestre (N=1), Brescia (N=1)
- Age at diagnosis: 1 – 42 anni
- *GNAS* analyisis: 5 *de novo* mutations
- In 3 negative cases: no imprinting alteration



delT184



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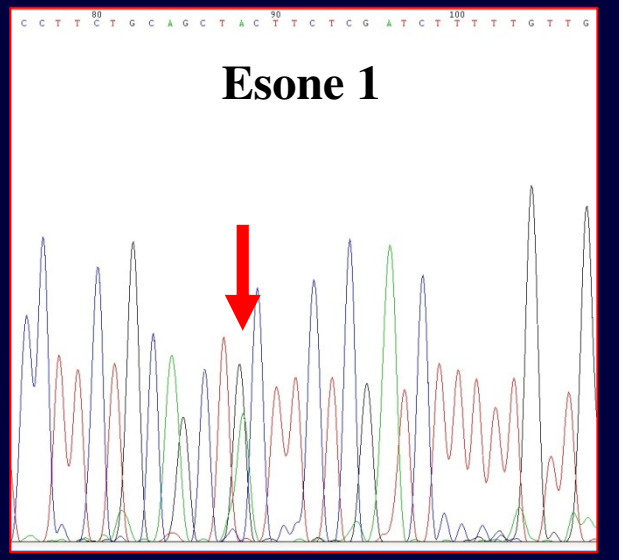
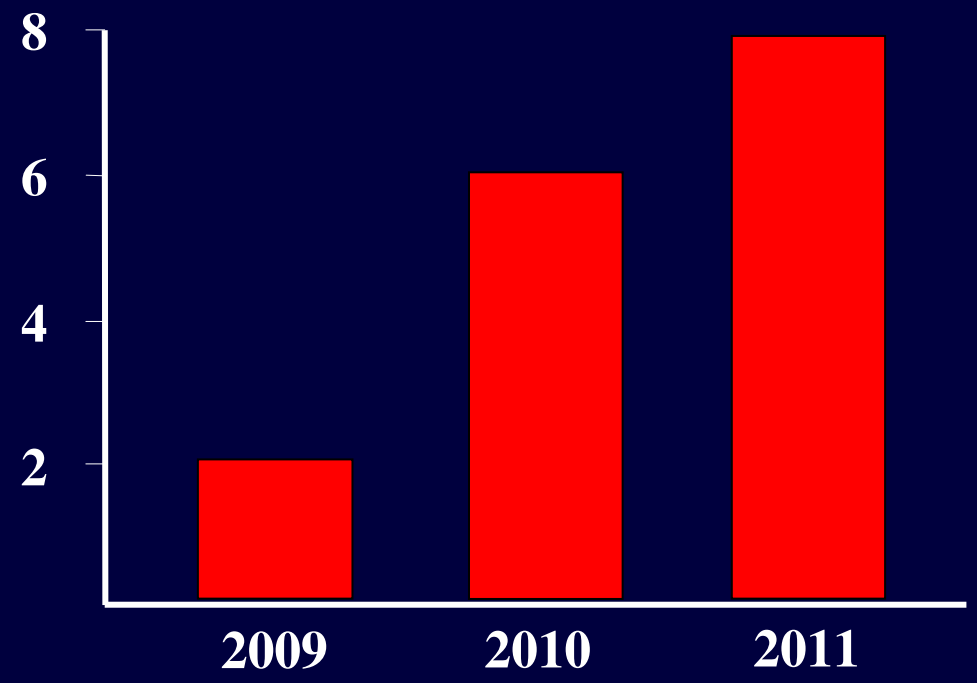


CAG→TAG, Gln29X

POH/OC patients studied in our laboratory:



Grazie a:

Unità di Endocrinologia
Fondazione IRCCS Ca' Granda
University of Milan

Francesca Elli
Andrea Lania
Erika Peverelli
Anna Maria Barbieri
Sara Bondioni
Paolo Beck-Peccoz

Anna Spada

Collaboratori esterni

Luisa de Sanctis (Torino)
Marco Cappa (Roma)
Aurora Rossodivita (Roma)
Mohamad Maghnie (Genova)
Mariangela Cisternino (Pavia)
Valeria Brunelli (Milano)
Giovanna Weber (Milano)
Roberto Bufo (Cerignola)
Paola Ferrari (Modena)

Agnès Linglart (Paris)