

**1° Meeting Italiano congiunto su FOP e POH  
20 – 21 Marzo 2009 Cerignola (FG)**

**Diagnosi molecolare nelle ossificazioni cutanee**

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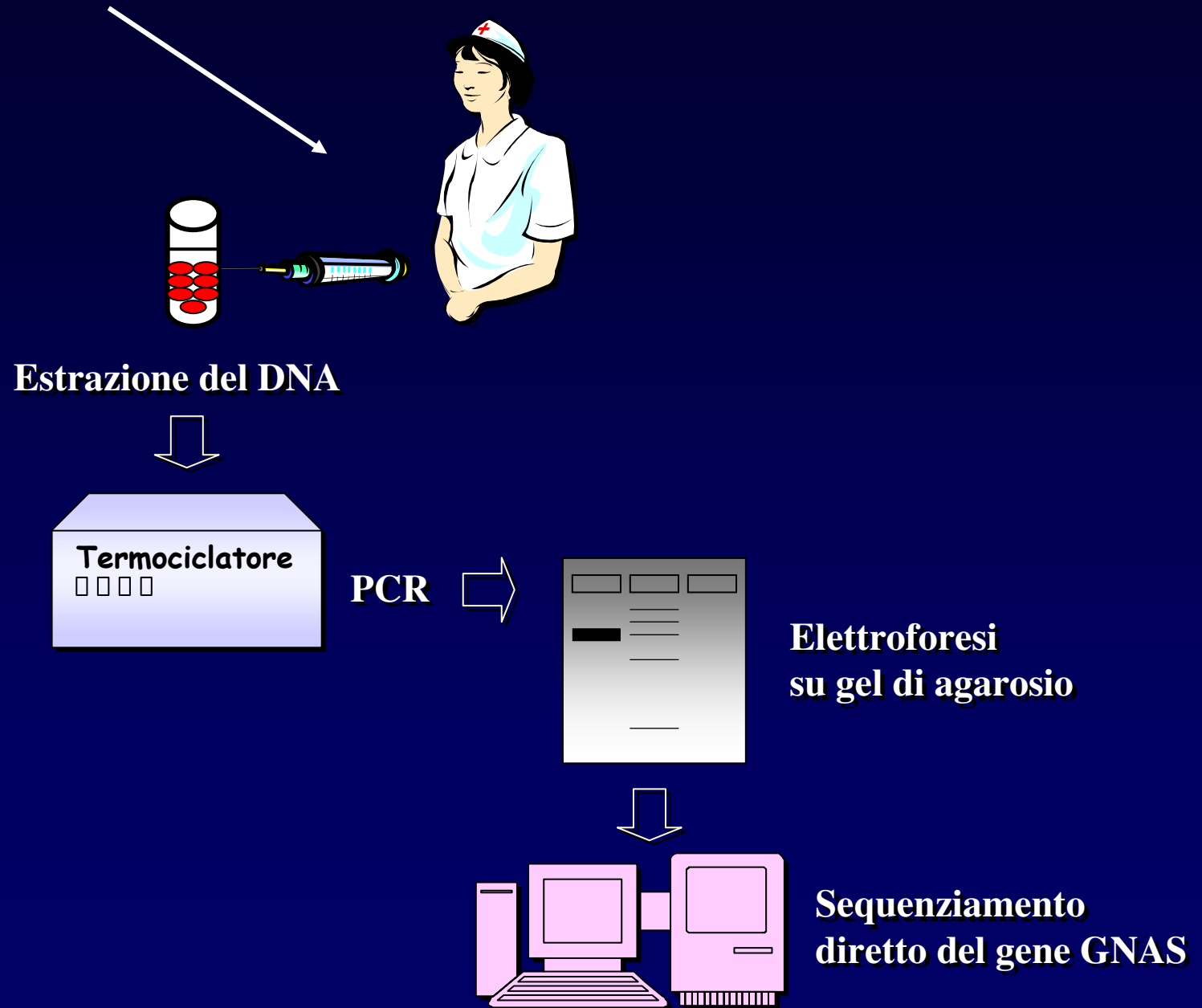
January 10, 2002

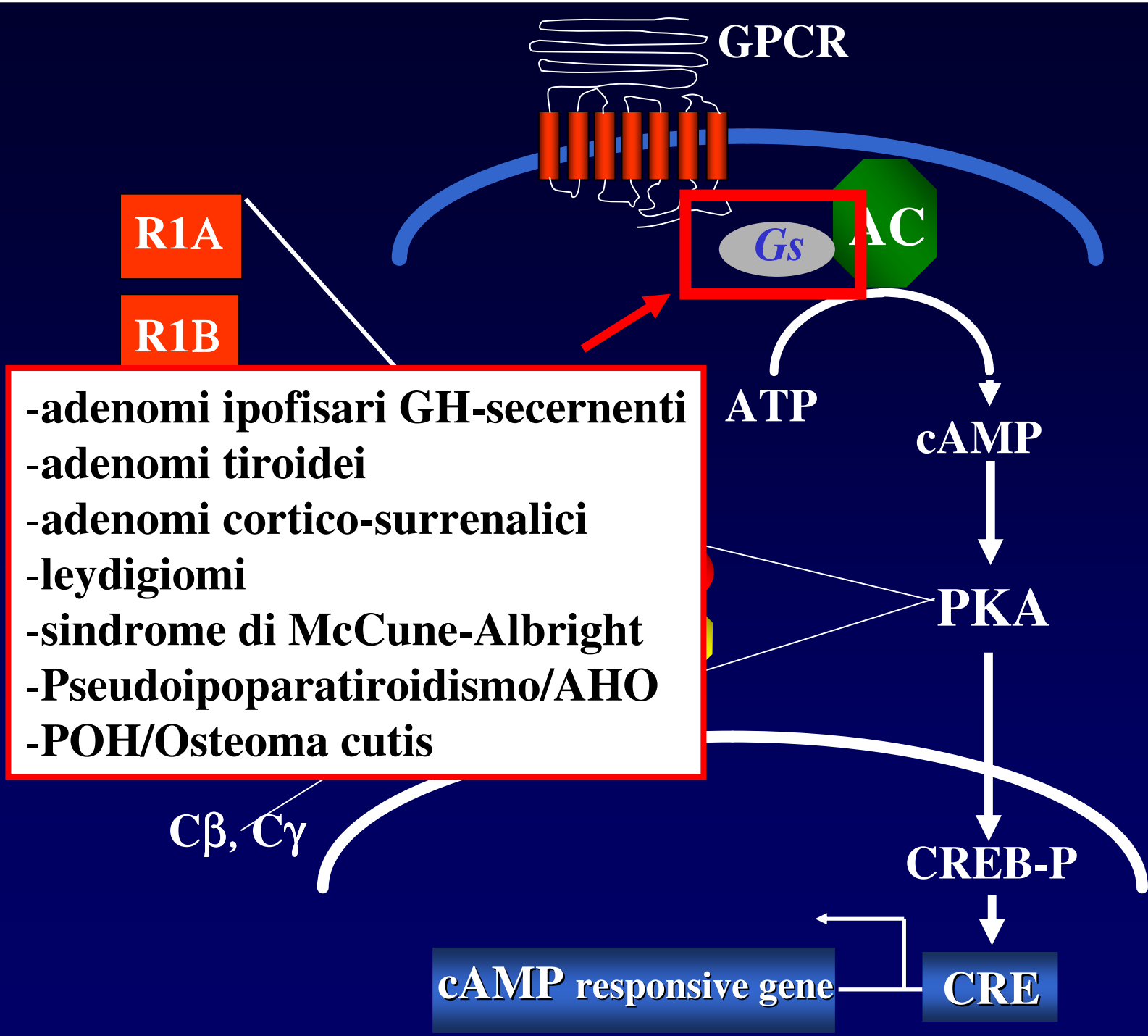
PATERNALLY INHERITED INACTIVATING MUTATIONS OF THE *GNAS1* GENE  
IN PROGRESSIVE OSSEOUS HETEROPLASIA

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.

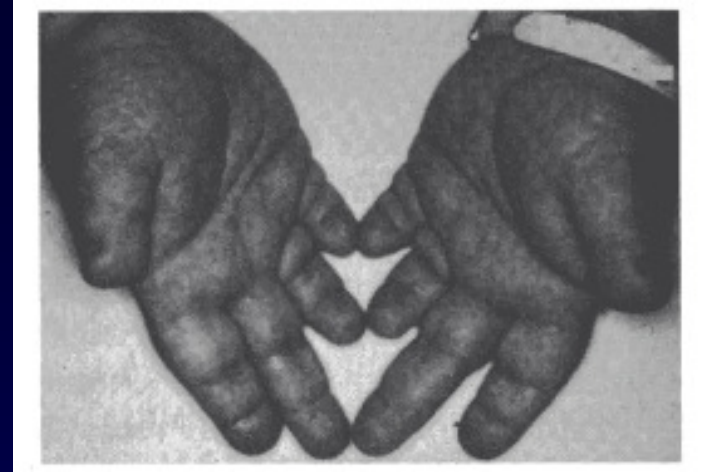
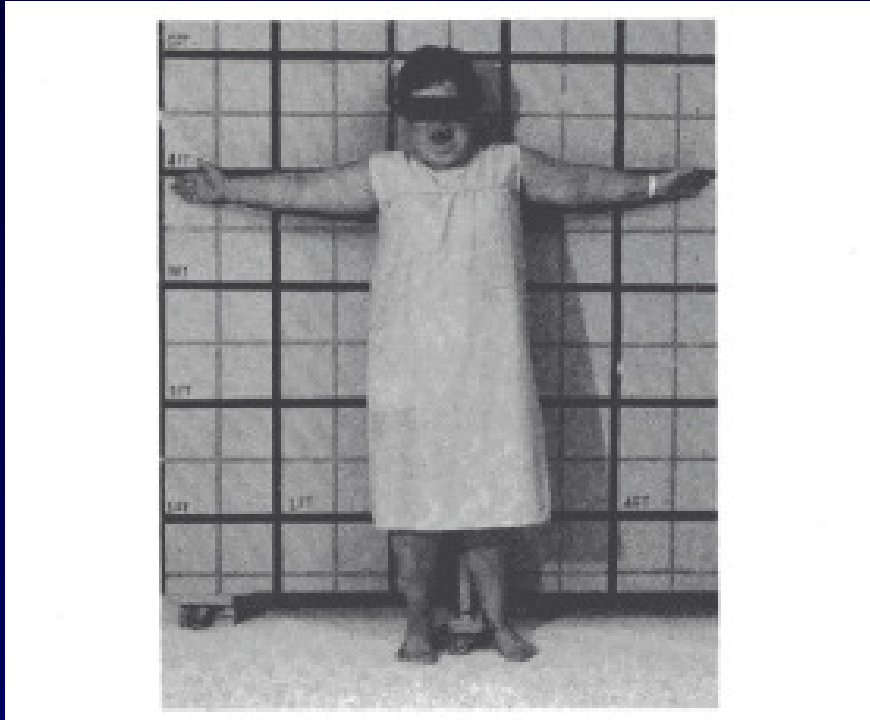
**Mutazione in eterozigosi nel gene *GNAS* in 13 su 18 famiglie**

# Paziente con sospetta POH/osteoma cutis

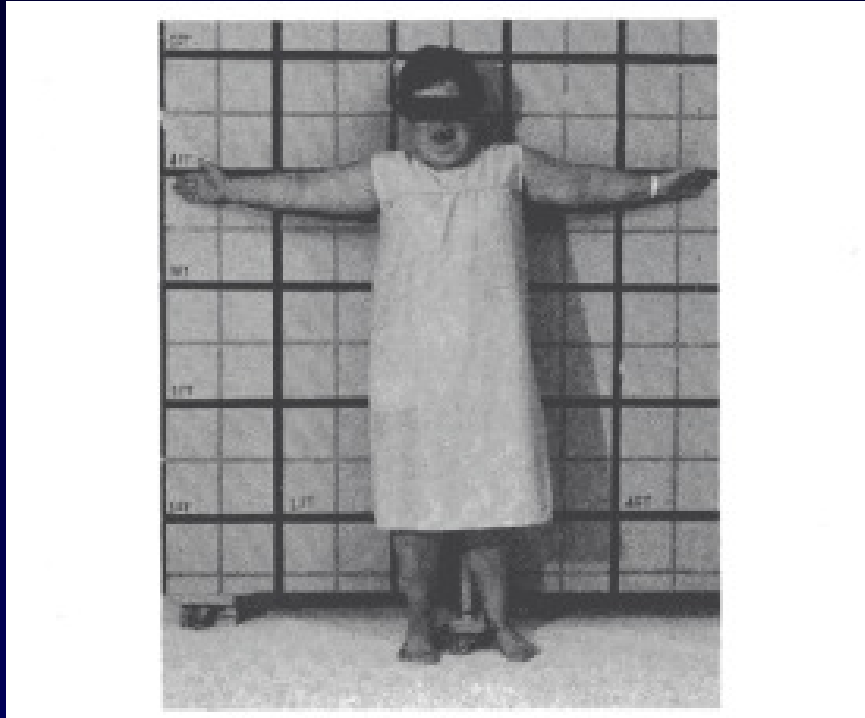




- adenomi ipofisari GH-secernenti
- adenomi tiroidei
- adenomi cortico-surrenalic
- leydigomi
- sindrome di McCune-Albright
- Pseudoipoparatiroidismo/AHO
- POH/Osteoma cutis



## **OSTEODISTROFIA DI ALBRIGHT (AHO)**



**Ipocalcemia**  
**Iperfosforemia**  
**PTH alto**

**TSH alto**  
**OT variabili**

**Ipogonadismo**



**PSEUDOIPOPARIETIROIDISMO**

# **OSTEODISTROFIA DI ALBRIGHT (AHO):**

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malattia genetica autosomica dominante caratterizzata da:

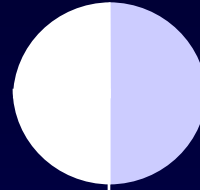
- bassa statura
- obesità
- faccia tondeggiante
- brachidattilia
- ossificazioni sottocutanee
- frequente ritardo mentale

Può presentarsi come:

- Associato a resistenza ormonale: PTH, TSH, Gn, GHRH  
    → **PSEUDOIPOPARIETIROIDISMO Ia (PHP Ia)**
- Difetto isolato  
    → **PSEUDOPSEUDOIPOPARIETIROIDISMO (PPHP)**

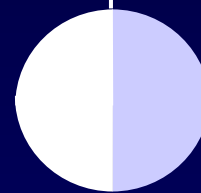
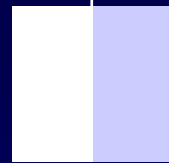
# FAMILY n. 5

**NOT  
AFFECTED**



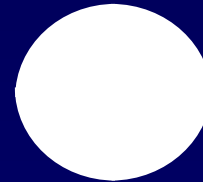
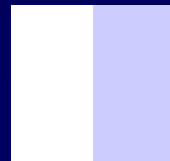
**AHO**  
**PTH: 41 pg/mL**  
**TSH: 2.5 mU/L**

**AHO**  
**PTH: 250 pg/mL**  
**TSH: 11 mU/L**



**AHO**  
**PTH: 198 pg/mL**  
**TSH: 7.8 mU/L**  
**Amenorrea**

**AHO**



***PROPOSITUS***

**NOT  
AFFECTED**



# Mutazioni *GNAS*

Materne

Paterne

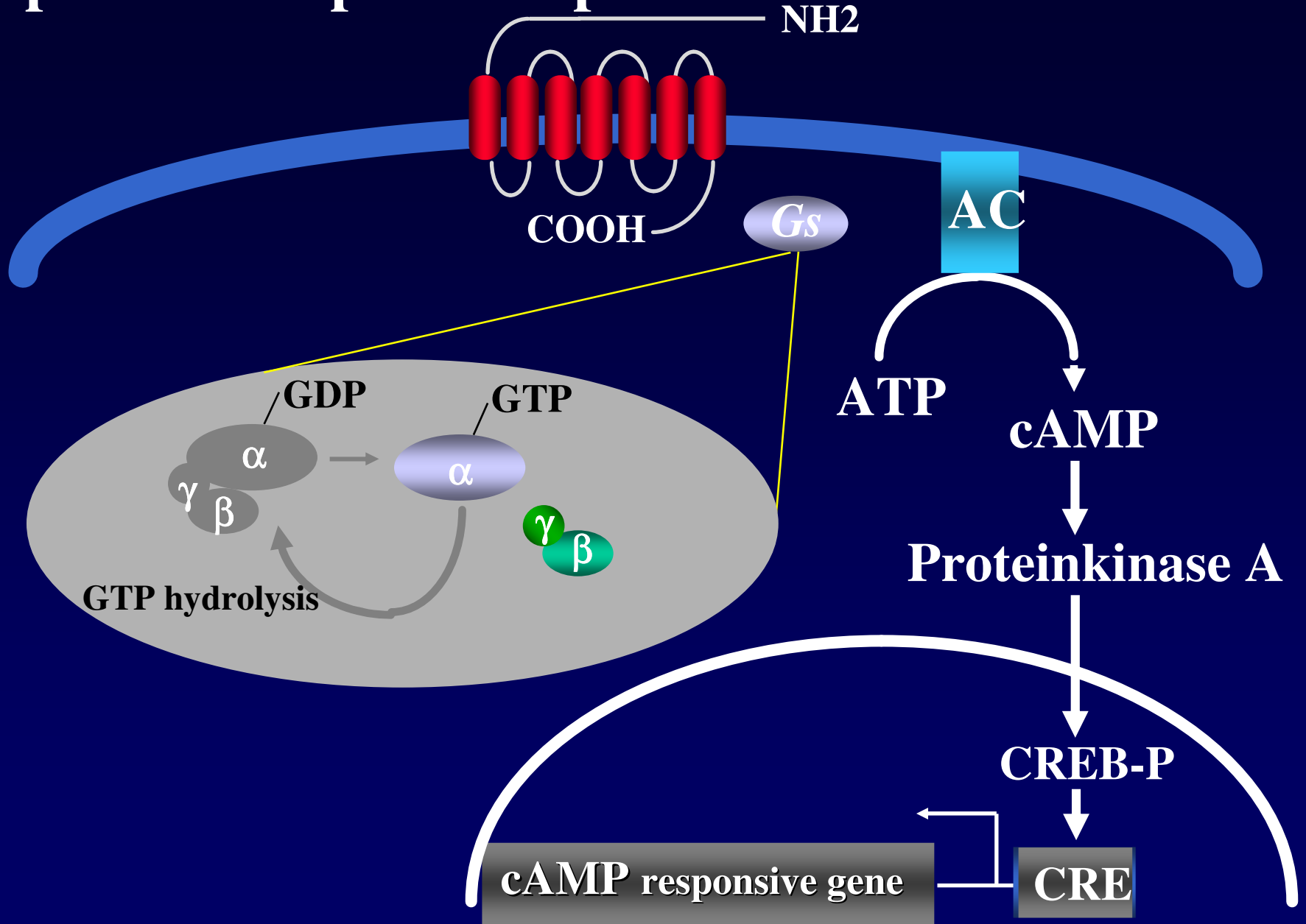
PHP-Ia

PPHP

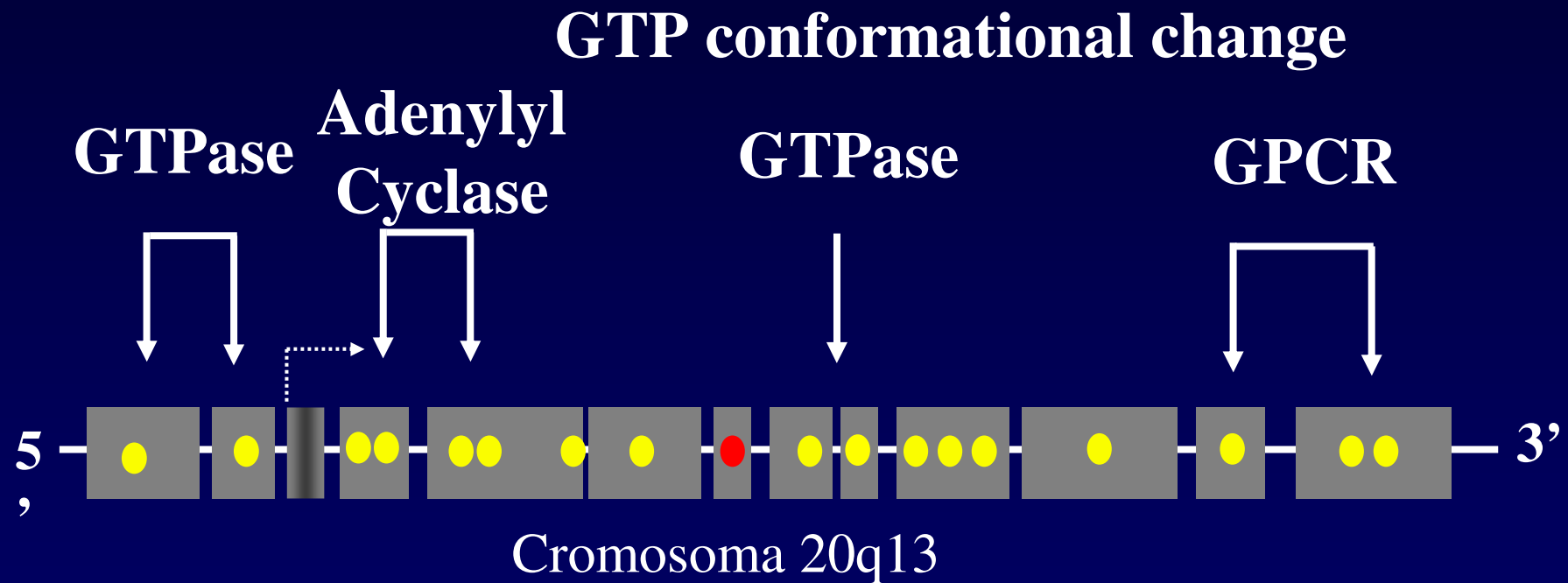
POH

OC

# G-protein coupled receptor



# Mutazioni inattivanti associate a AHO/PHP/POH



- **Inactivating mutations: insertions/deletions, nonsense & missense mutations > aberrant or instable mRNA > no Gs protein**
- **Mutational hot-spot (20%)**

# CLASSIFICAZIONE DI AHO e PHP

## Tipo I

Assente risposta di cAMP plasmatico ed urinario all'infusione di PTH

• PHP Ia

• PHP Ib

• PHP Ic

• PPHP

**GNAS**

## Tipo II

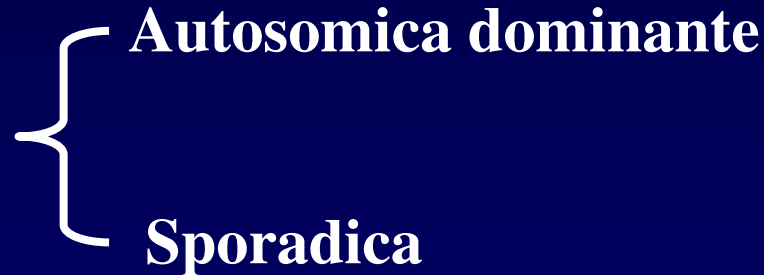
Presente risposta di cAMP plasmatico ed urinario all'infusione di PTH

• PHP II

# Pseudoipoparatiroidismo tipo Ib

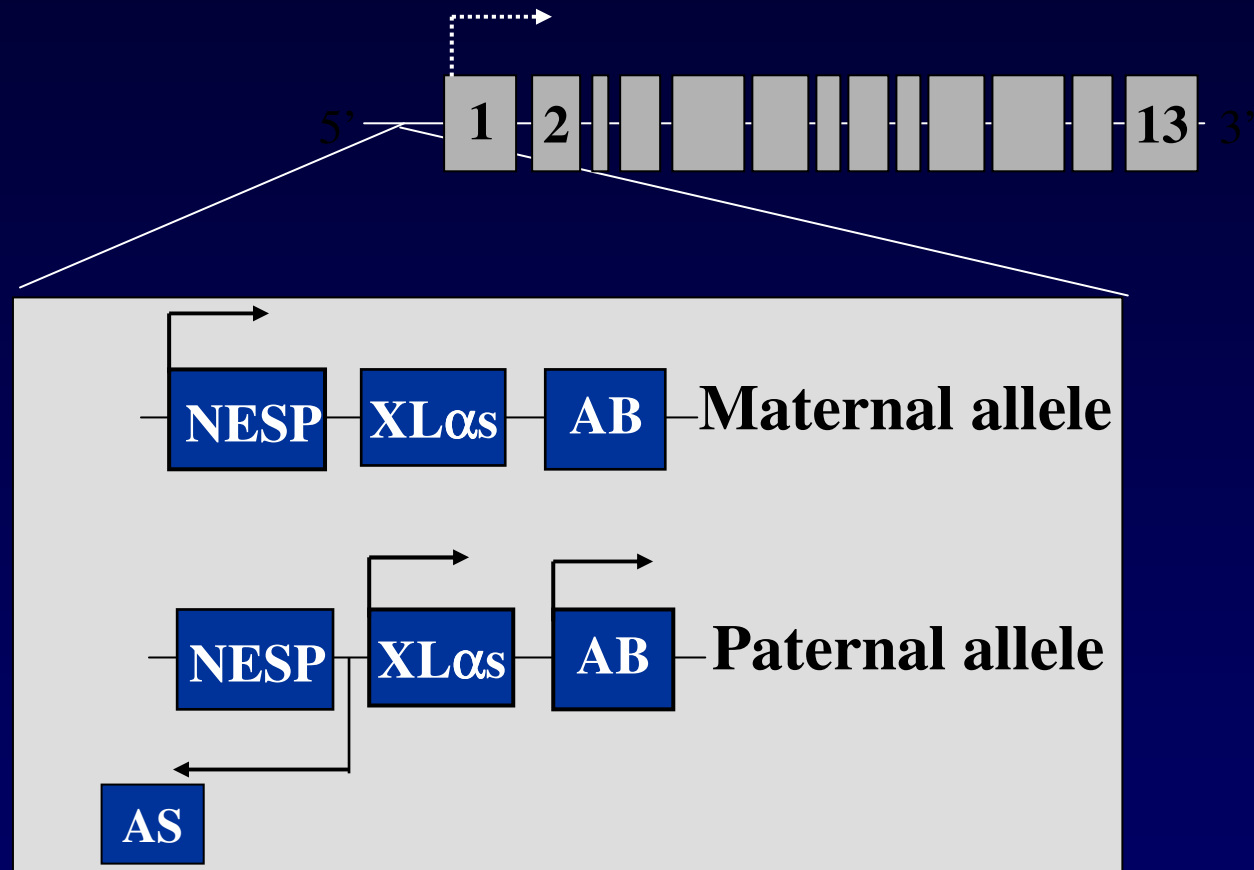
- Resistenza renale all'azione del PTH
- Nessuna altra resistenza ormonale (TSH?)
- Nessuna anomalia fisica
- Nessuna mutazione nel gene PTH-R
- Nessuna mutazione Gs alpha

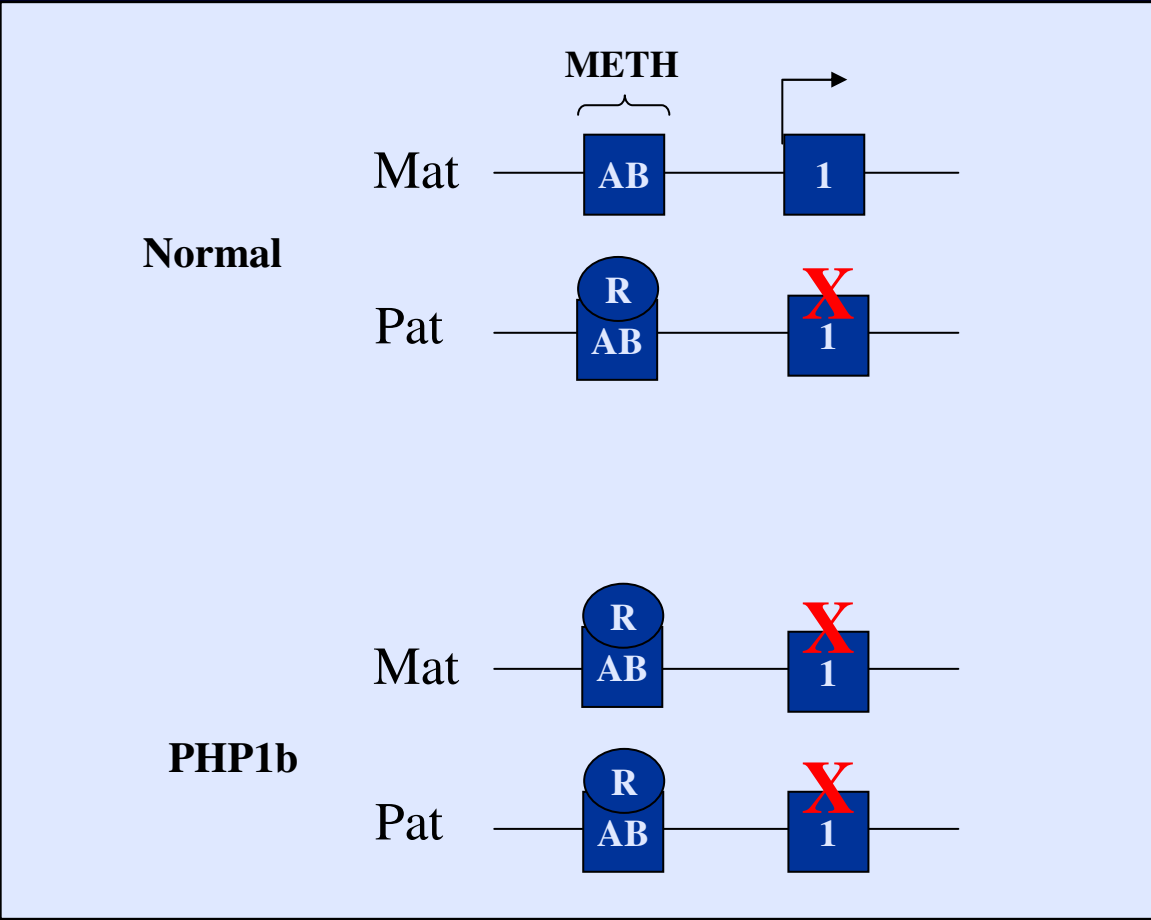
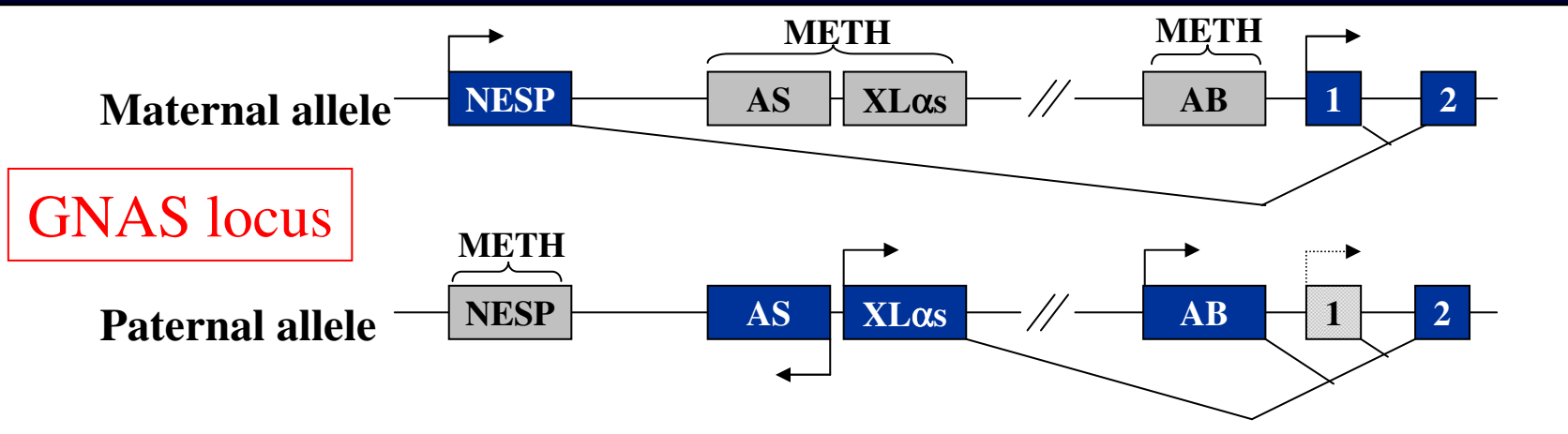
**2 FORME**



Alterazioni dell'imprinting del locus GNAS >  
Riduzione dell'espressione Gs $\alpha$   
(limitata ai tubuli prossimali renali?)

# GNAS LOCUS





## BRIEF REPORT

# Epigenetic Defects of *GNAS* in Patients with Pseudohypoparathyroidism and Mild Features of Albright's Hereditary Osteodystrophy

Guionan Pérez de Nanclares, Eduardo Fernández-Rebollo, Isortze Santín, Beatriz García-Cuartero, Sonia Gastambide, Edelmiro Menéndez, María José Morales, Manuel Pombo, José Ramón Bilbao, Francisco Barros, Nuria Zazo, Wieslke Ahrens, Harald Juppner, Olaf Hiort, Luis Castaño, and Murat Bostops

*J Clin Endocrinol Metab*, 2007

SPECIAL FEATURE

Clinical Case Seminar

## A Maternal Epimutation of *GNAS* Leads to Albright Osteodystrophy and Parathyroid Hormone Resistance

Virginie Mariot,<sup>\*</sup> Stéphanie Maupetit-Méhouas,<sup>\*</sup> Christiane Sinding, Marie-Laure Kottler, and Agnès Lingart

*J Clin Endocrinol Metab*, 2008



Table 1: Clinical characteristics and molecular analysis of patients included in the present study

Patient	Sex	Age years	Hormone resistances	AHO features	Abnormal methylation
1	F	9	PTH/TSH(msb)	Bc/RF	AB/AS/CL
2	M	22	PTH/TSH(msb)	Bc/SS/RF/Ob/SC/MR	AB/CL
3	F	22	PTH/TSH(msb)	Bc/SS/RF/Ob/SC/MR	AB/NESP/AS/CL
4	F	18	PTH/TSH	Bc/SS/RF/Ob/SC/MR	AB/NESP/AS/CL
5	F	15	PTH/TSH(msb)	Bc/SS/RF/Ob/SC/MR	AB/CL
6	F	4	PTH/TSH(msb)	SS/RF/Ob/SC/MR	AB/AS/CL
7	M	3	PTH/TSH	Bc/SS/RF/MR	AB/NESP/CL
8	M	3	PTH/TSH(msb)	Bc/SS/RF/Ob/MR	AB/NESP/CL
9	M	8	PTH/TSH	Bc/RF/Ob/SC/MR	AB/CL
10	M	12	PTH/TSH(msb)	SS/RF	AB/AS/CL
11	F	13	PTH/TSH(msb)	Bc/SS/RF	AB/CL
12	F	10	PTH/TSH	Bc/SS	AB/AS/CL
13	F	8	PTH/TSH	Bc/RF/Ob	AB/NESP/AS/CL
14	F	4	PTH/TSH(msb)	Bc/RF/Ob	AB/AS/CL
15	M	2	PTH/TSH	Bc/RF	AB/NESP/CL
16	M	13	PTH/TSH(msb)	Bc/SS/RF/Ob/SC	AB/NESP/AS/CL
17	F	15	PTH	Bc/RF/Ob/SC/MR	AB/AS
18	M	19	PTH	Bc/RF/Ob	AB/AS/CL
19	F	13	PTH	Bc/SS/RF/Ob/MR	AB/NESP/AS/CL
20	F	18	PTH/TSH(msb)	Bc/MR	AB/AS/CL
21	M	6	PTH/TSH(msb)	Bc/SS/RF/Ob	AB/AS
22	F	5	PTH/TSH(msb)	Bc/SS/RF/Ob/SC/MR	AB/AS
23	F	14	PTH	Bc/SS/RF/Ob/SC/MR	AB/NESP/AS
24	F	7	PTH	Bc/SS/RF/Ob	AB/AS
25	F	13	PTH/TSH	Bc/SS/RF/Ob/MR	No
26	F	2	PTH/TSH(msb)	Bc/RF/SC	No
27	F	12	PTH/TSH(msb)	Bc/SS/RF/Ob/SC	No
28	M	5	PTH/TSH(msb)	Bc/RF/Ob/SC/MR	No
29	F	1	PTH/TSH	Bc/RF/Ob/SC	No
30	F	13	PTH/TSH(msb)	Bc/SS/RF/Ob/SC	No
31	F	11	PTH/TSH	RF/MR	No
32	F	15	PTH/Ga	Bc/RF	No
33	F	30	PTH/TSH	Bc/SS/RF/Ob/SC/MR	No
34	F	10	PTH/TSH(msb)	Bc/SS/RF/Ob/SC	No
35	F	1	PTH	Bc/RF/SC	No
36	F	12	PTH/TSH(msb)	Bc/RF/SC	No
37	F	12	PTH	Bc/RF	No
38	F	23	PTH/TSH(msb)	Bc/RF	No
39	M	10	PTH	Bc/SS/RF/Ob/MR	No
40	M	22	PTH/TSH(msb)	Bc/SS/MR	No

40 patients with PHP-Ia and no mutation in *GNAS*:

24/40: abnormal pattern of methylation at *GNAS* locus

*Mantovani et al., submitted*

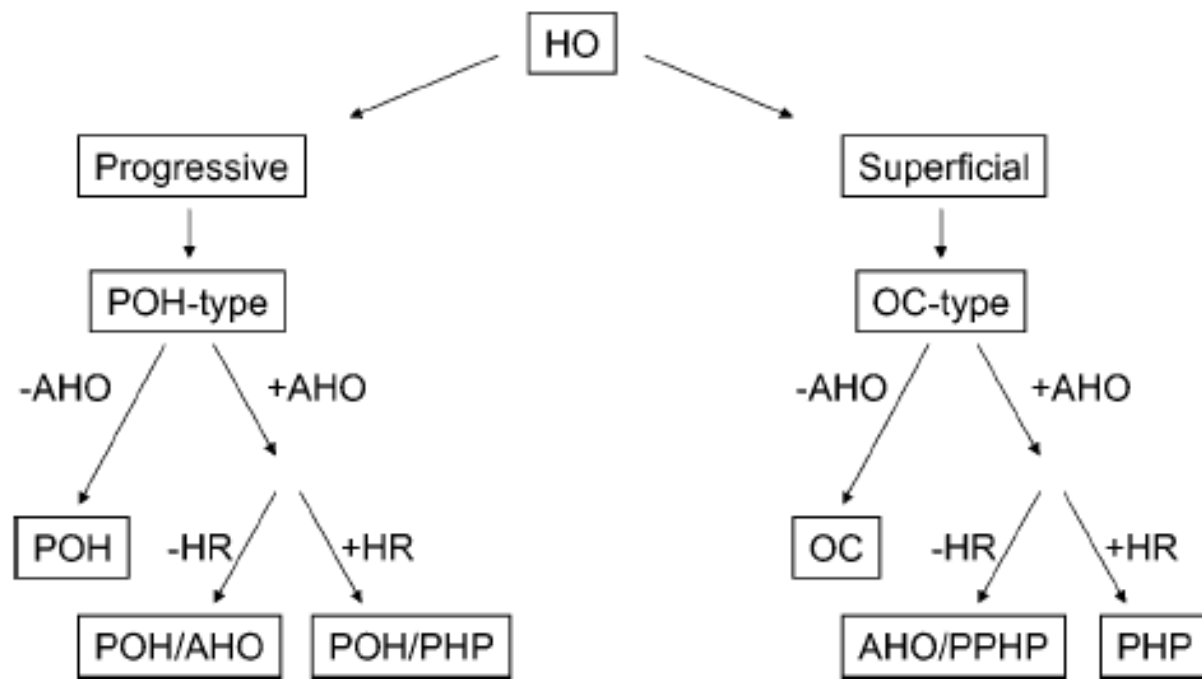
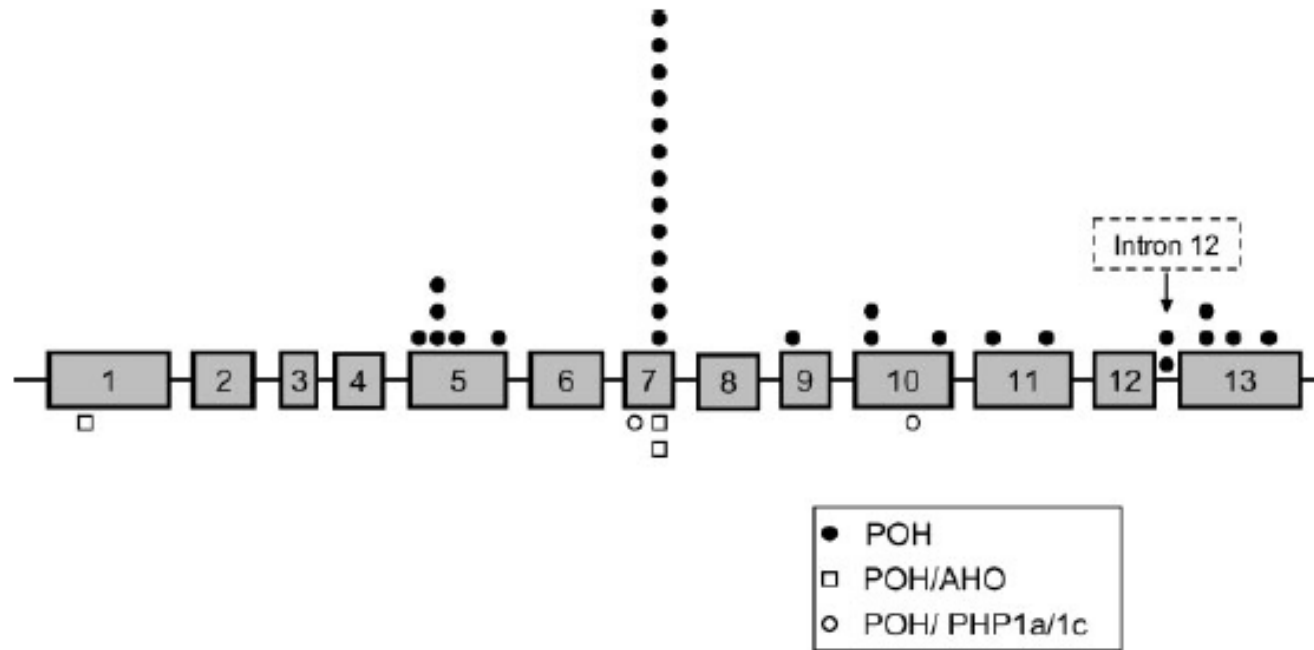
## Diagnostic and Mutational Spectrum of Progressive Osseous Heteroplasia (POH) and Other Forms of *GNAS*-Based Heterotopic Ossification

N.S. Adegbite,<sup>1</sup> M. Xu,<sup>1</sup> F.S. Kaplan,<sup>1,2</sup> E.M. Shore,<sup>1,3</sup> and R.J. Pignolo<sup>2\*</sup>

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

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

**N totale = 111**

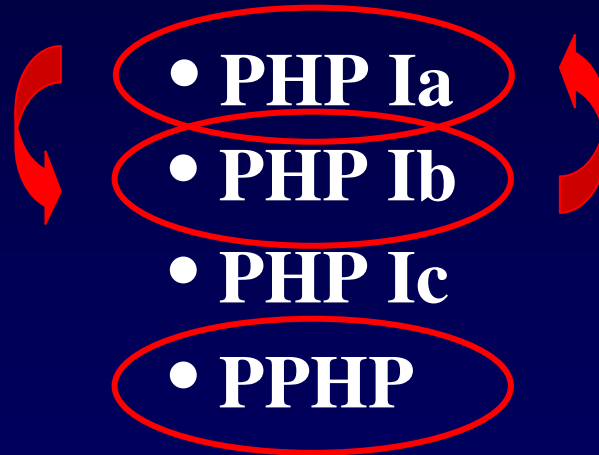


# CLASSIFICAZIONE DI AHO e PHP

## Tipo I

Assente risposta di cAMP plasmatico ed urinario all'infusione di PTH

**GNAS**



**AHO-like ???**

## Tipo II

Presente risposta di cAMP plasmatico ed urinario all'infusione di PTH

- PHP II

# Mutazioni/Alterazioni *GNAS*

