Grotte de Lascaux

Luciano Cavallo
Maria Felicia Faienza
Clinica Pediatrica
"B. Trambusti"
Dip. di Biomedicina
dell'Età Evolutiva
Università di Bari

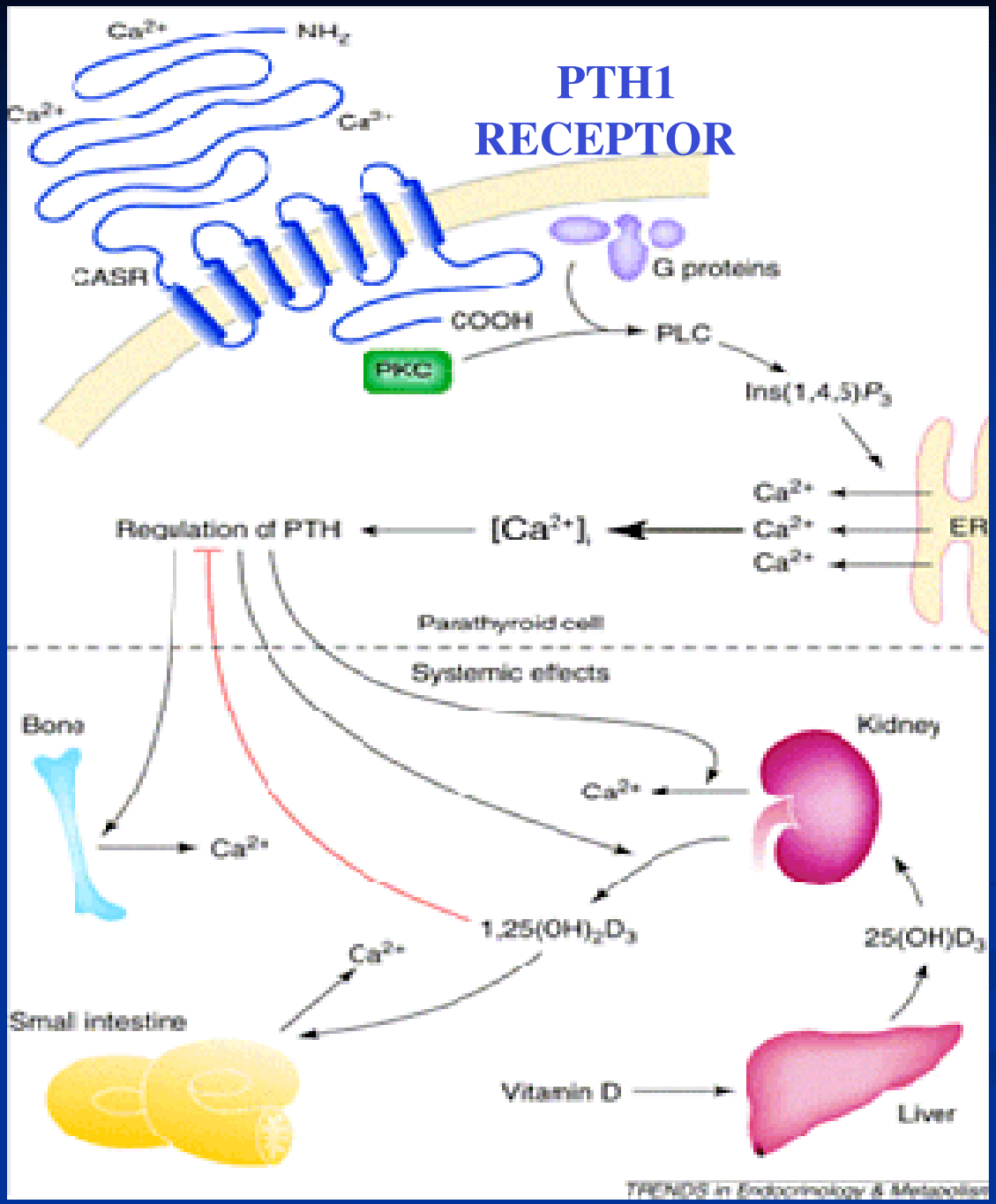
PSEUDO HYPOPARATHYROIDISM

PSEUDOHYPOPARATHYROIDISM

Pseudohypoparathyroidism (PHP) is a heterogeneous group of genetic disorders whose common feature is parathyroid hormone resistance (PTH)

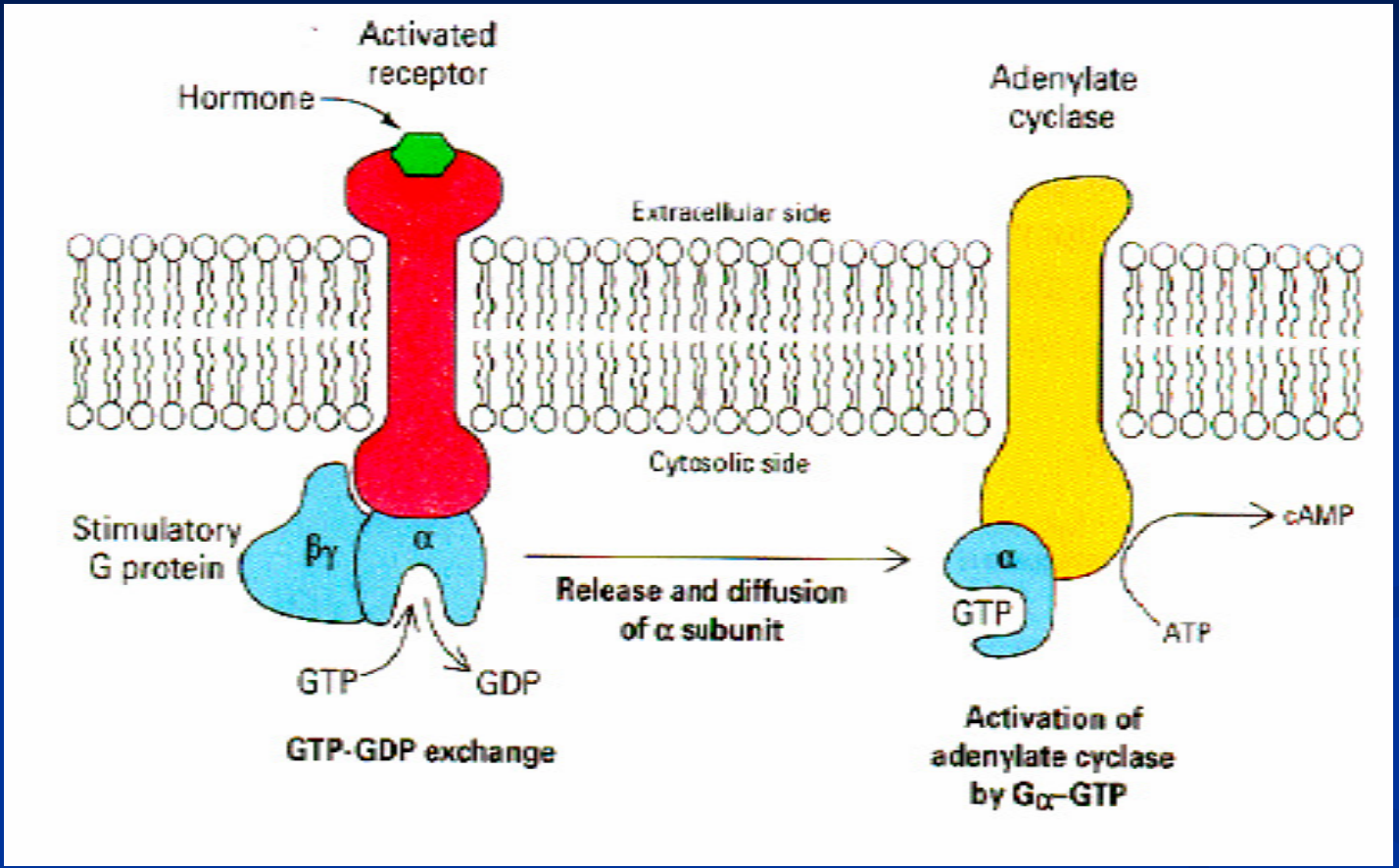
Biochemical features:

- **Hypocalcemia**
- **Hyperphosphatemia**
- **Increased serum concentration of PTH**
- **Decreased serum concentration of 1,25-dihydroxy vitamin D3**



Il recettore di tipo 1 del PTH è prevalentemente espresso a livello renale e sugli osteoblasti e il suo meccanismo di azione è mediato dalla proteina Gs-alfa

Gs-α protein action



La subunità alfa della proteina Gs è un mediatore del messaggio di alcuni ormoni proteici (PTH, TSH, FSH/LH, GHRH, ecc.) dalla membrana cellulare al 2° messaggero (AMPc).

Quando l'ormone si lega al recettore di membrana, la proteina Gs si attiva: la subunità **α** si scinde dalle subunità **ß-γ**, quindi si lega al GTP e scatena una cascata di eventi che porta all'attivazione dell'adenilciclasi.

Questa, a sua volta, determina la formazione dell' **AMPc**, 2° messaggero del messaggio ormonale, che permette quindi l'effetto dell'ormone

Hormones using cAMP as a second messenger

Calcitonin
Chorionic gonadotropin
Corticotropin
Epinephrine
Follicle-stimulating hormone
Glucagon
Lipotropin
Luteinizing hormone
Growth Hormone Releasing Hormone
Melanocyte-stimulating hormone
Norepinephrine
Parathyroid hormone
Thyroid-stimulating hormone
Vasopressin

Classification of PHP

ACCORDING TO DIFFERENT PHENOTYPES AND PATHOGENESIS

- PHP Ia: segni dismorfici della AHO, resistenza al PTH, resistenza ormonale multipla (TSH, LH/FSH, GHRH) **e** ridotta escrezione urinaria di AMPc dopo infusione di PTH

  ridotta attività della proteina Gs-alfa

- PHP Ib: non segni di AHO, resistenza al PTH e in alcuni casi ad altri ormoni

  normale espressione della proteina Gs-alfa

- PHP Ic: segni di AHO, resistenza ormonale multipla ma, a differenza del tipo Ia

  normale attività della proteina Gs-alfa, alterazione del legame del PTH col recettore

- PHP II: resistenza al PTH e ridotta risposta fosfaturica alla somministrazione di PTH con normale escrezione di AMPc urinario

- PseudoPHP: solo fenotipo Albright, non resistenza al PTH ed altri ormoni

  normale attività della proteina Gs-alfa

Albright's hereditary osteodystrophy (AHO)

Albright's hereditary osteodystrophy (AHO) is a complex genetic disorder (AD) characterized by multiple dysmorphic features

short stature

obesity

round face and short neck

brachydactyly

(shortened fourth and fifth metacarpals or metatarsals)

heterotopic ossifications, osteoma cutis

mental retardation

intracranial calcification

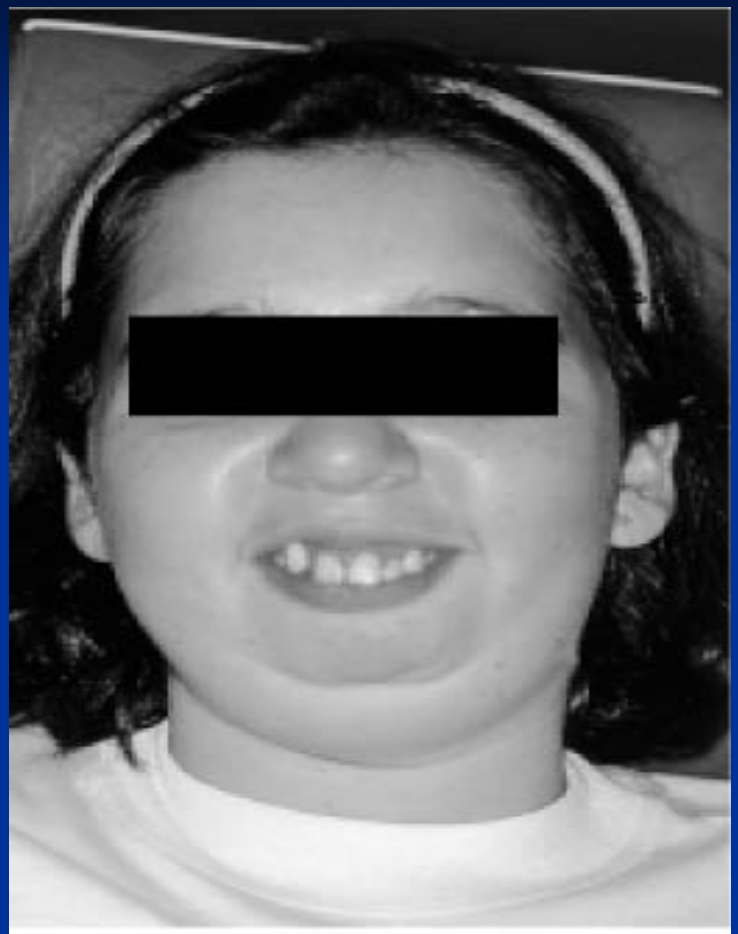
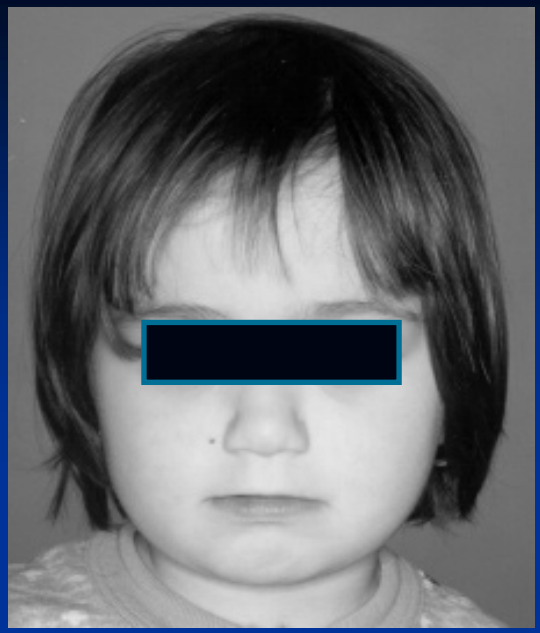
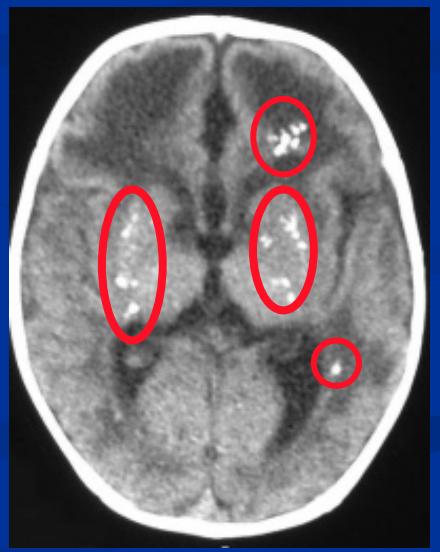
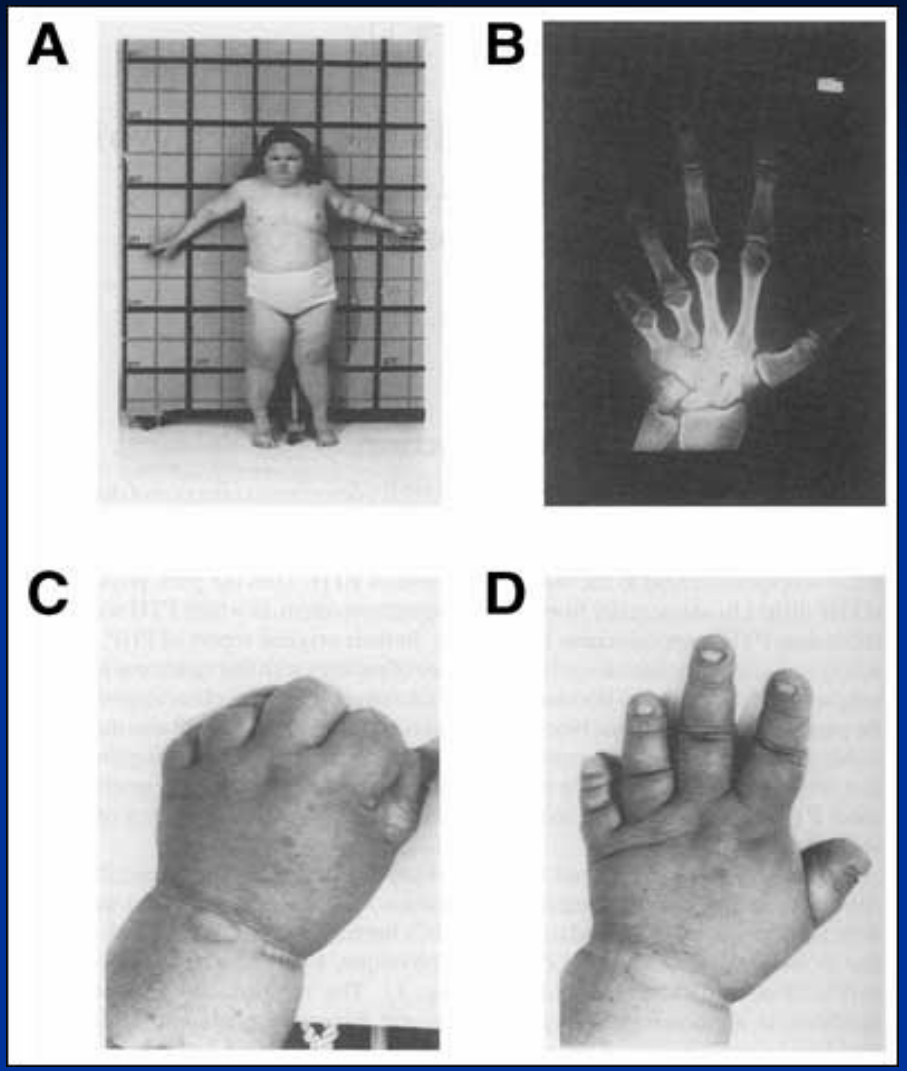
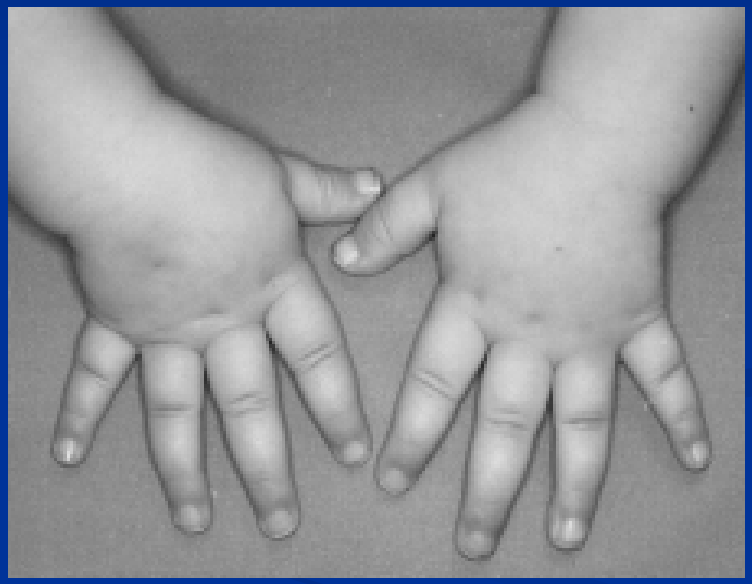


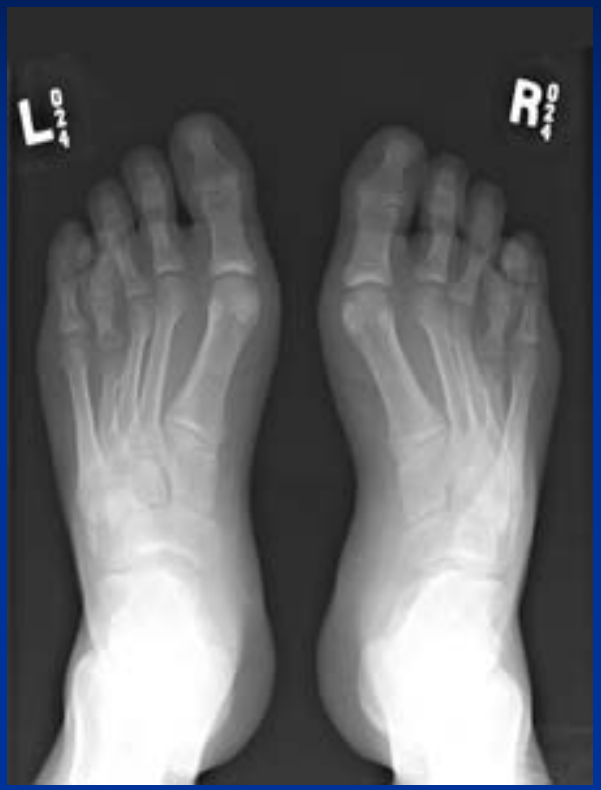
Figure 1 - Patient with Albright hereditary osteodystrophy. Round face, low nasal bridge, and short neck.

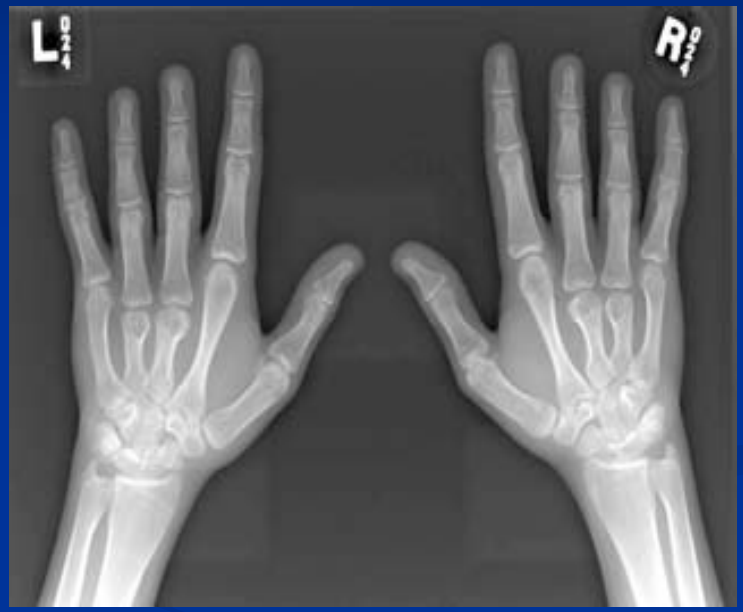


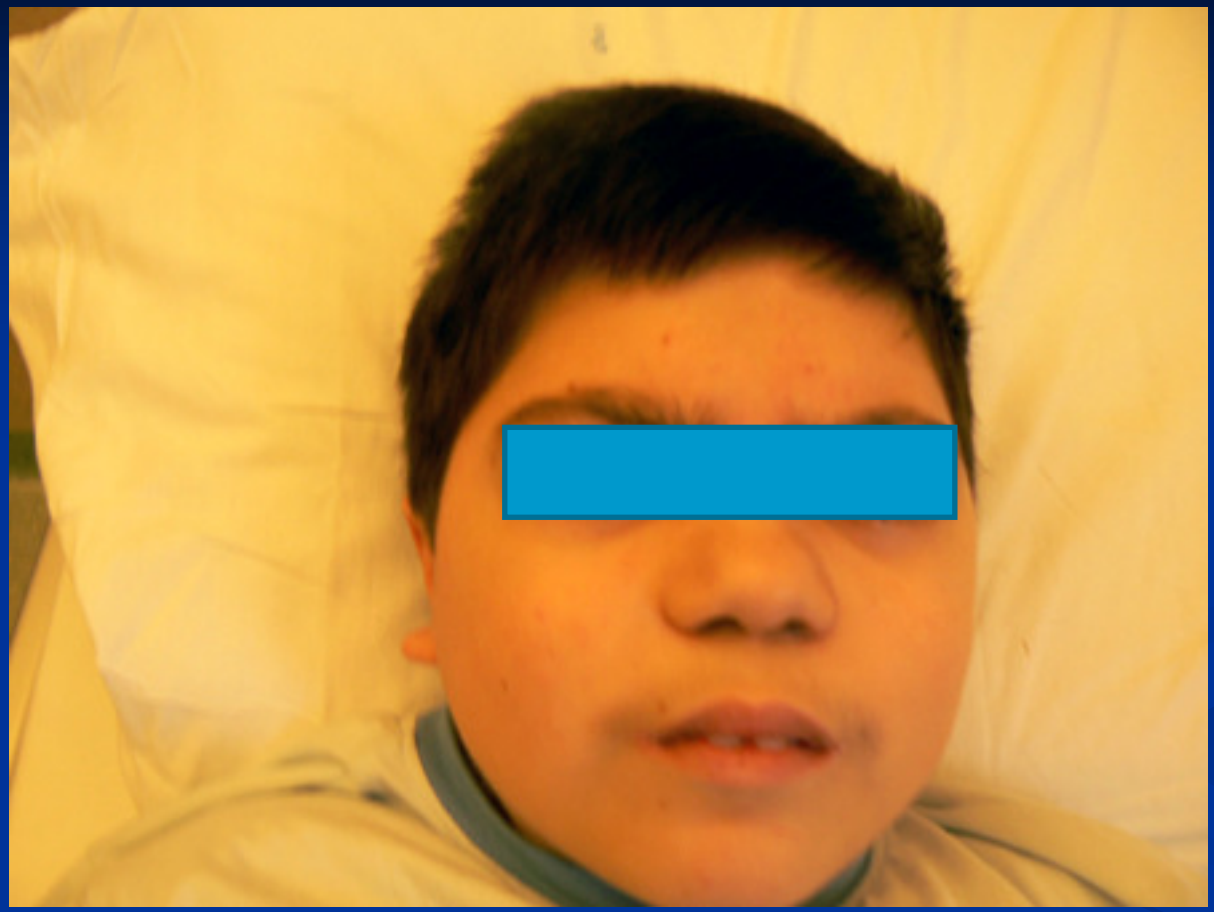



A
B
C
D

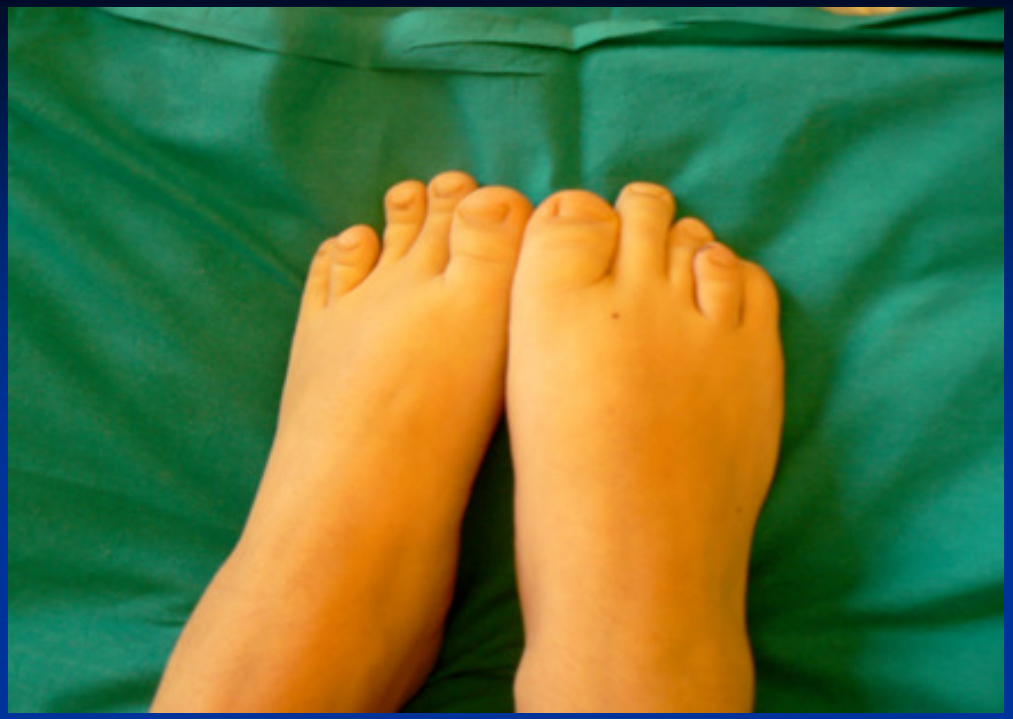


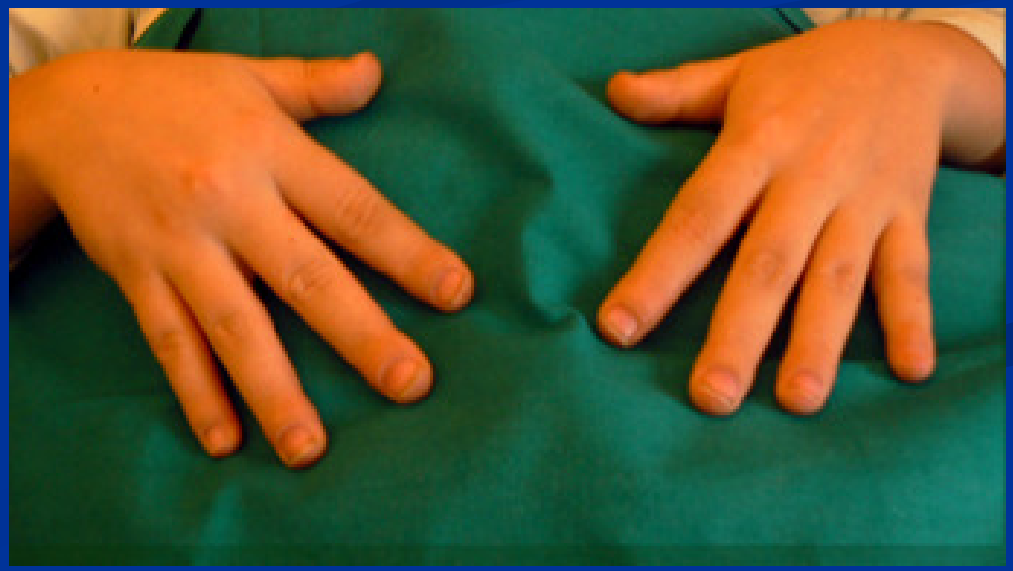

L
R


L
R



CA	11 yrs
BA	10 yrs
Weight	38 kg (>75°)
Height	126.8 cm (< 3°)





- **PTH 934 pg/ml** (nv 12-72)
- **Total Calcium 7.5 mg/dl** (nv 8.6-10.2)
- **Phosphate 8.4 mg/dl** (nv 4-6.5)

- **TSH 12.8 µU/ml**
- **GH** ITT test peak **3.7 ng/ml**
  Arginine test peak **2 ng/ml**

Molecular analysis of *GNAS1*
heterozygous nonsense mutation
(Arg-> stop codon) Q35X Ex1

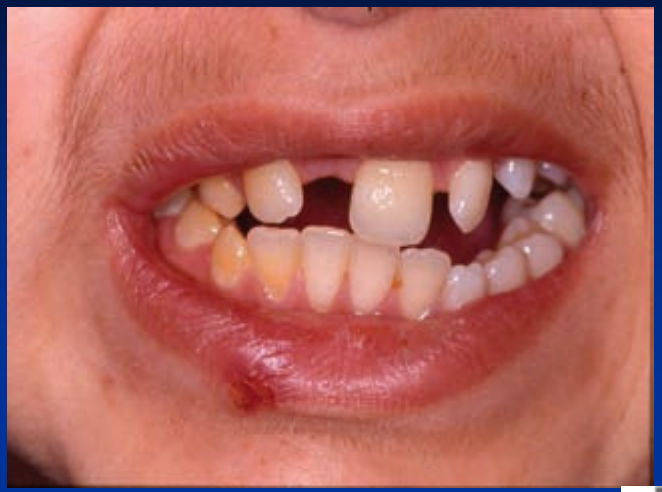
maternal trasmission

↓

PHP Ia

Signs of hypocalcemia

- Seizures
- Tetany
- Cataracts
- Dental abnormalities: delayed eruption, enamel hypoplasia, apical blunting hypodontia, pulp calcification



Patient with severe trismus straining to show maximum opening of his mouth limited by bony ankylosis of the temporo-mandibular joint

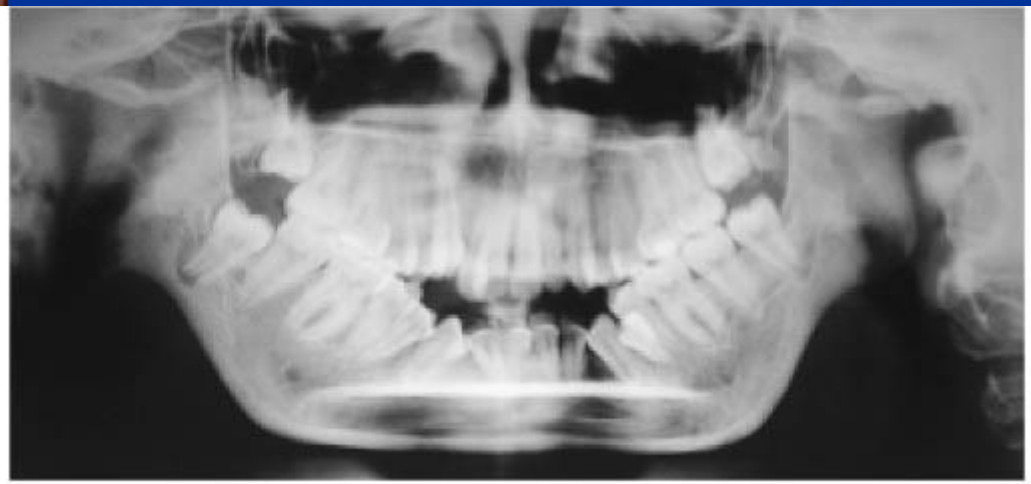


Figure 5 - Panoramic radiograph showing lack of anodontia, unaltered chronology of tooth eruption, and crowded teeth.

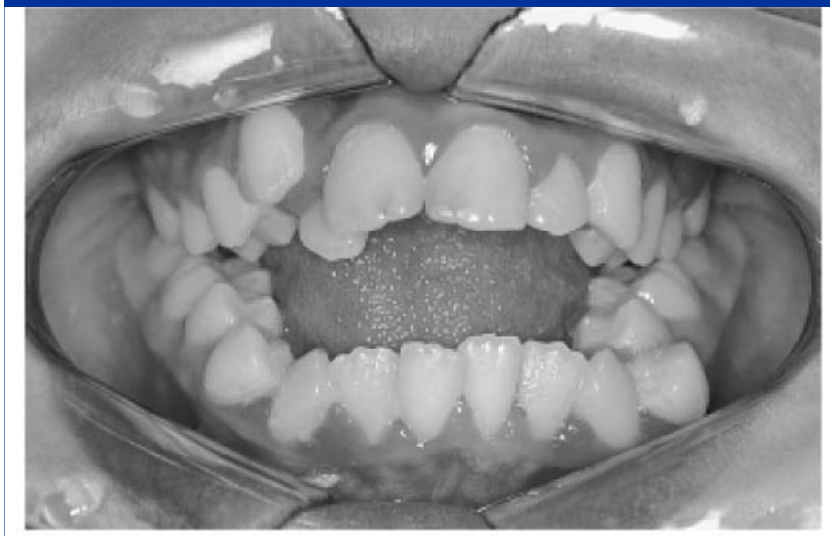
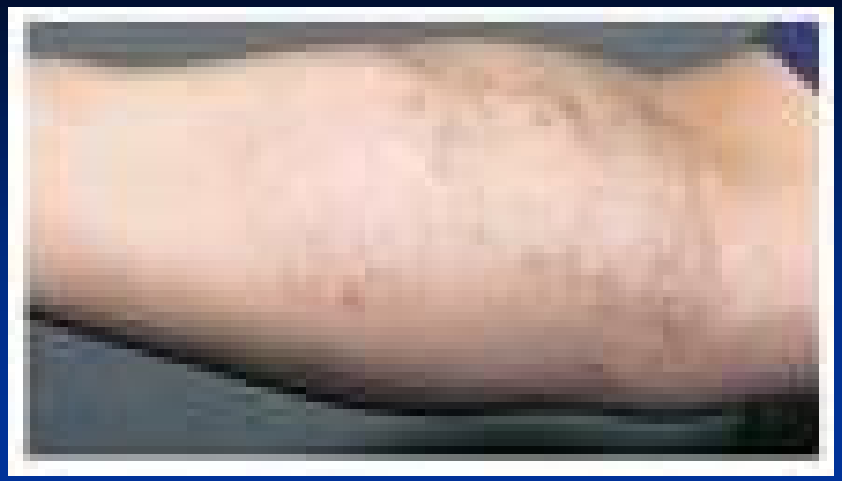
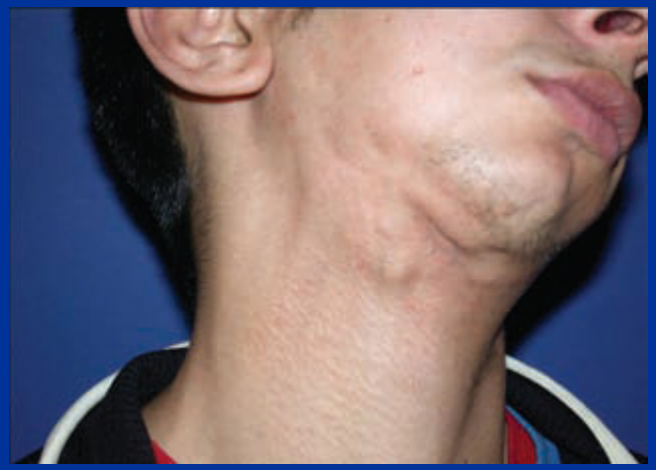


Figure 6 - Clinical intrabuccal exam showing calculus, accumulation of bacterial plaque and areas of spontaneous bleeding at the anterior superior and inferior region.

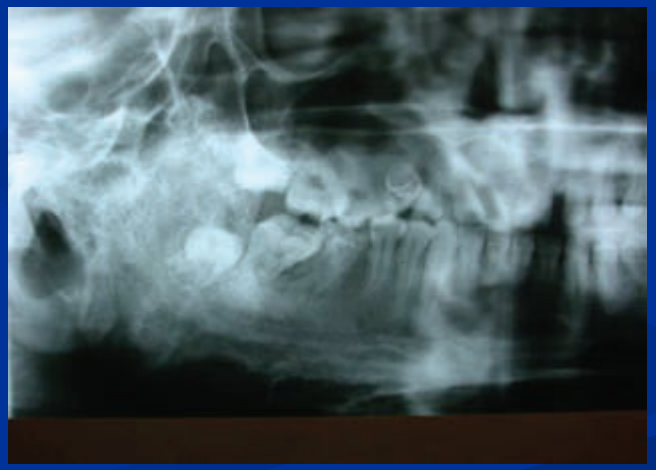


Heterotopic ossification often follows an inflammatory phase characterized by local swelling, pain, erythema and variable joint restriction that may include ankylosis, although it may also be asymptomatic

Palpable masses are present in the later stages



Extensive subcutaneous calcification in the right submandibular region and neck



Panoramic radiograph with visible calcification of the right cheek

DuVal MG, Davidson S, Ho A et al. JCDA 2007; 63:845-850

Pathogenesis of heterotopic ossification

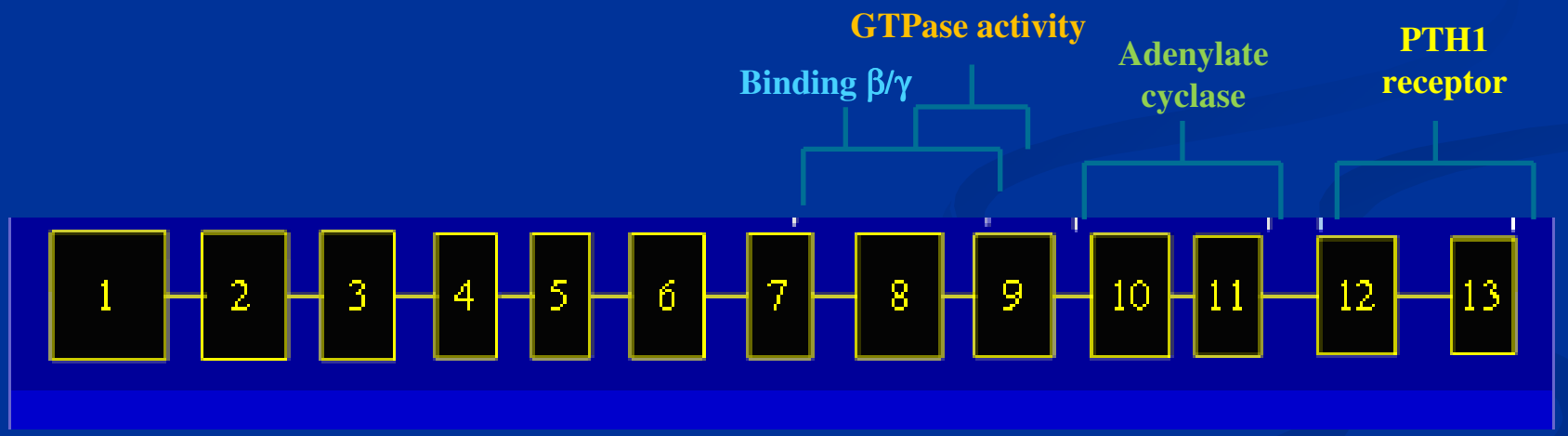
- Inflammatory factors resulting from denervated tissues
- Disrupted calcium homoeostasis
- Immobilization
- Prolonged pressure on periarticular structures
- Microtrauma
- Vascular stasis
- Hypoxia
- Hyperthermia
- Genetic factors

Vanden Bossche L, Vanderstraeten G. Heterotopic ossification: a review.
J Rehabil Med 2005; 37(3):129–136

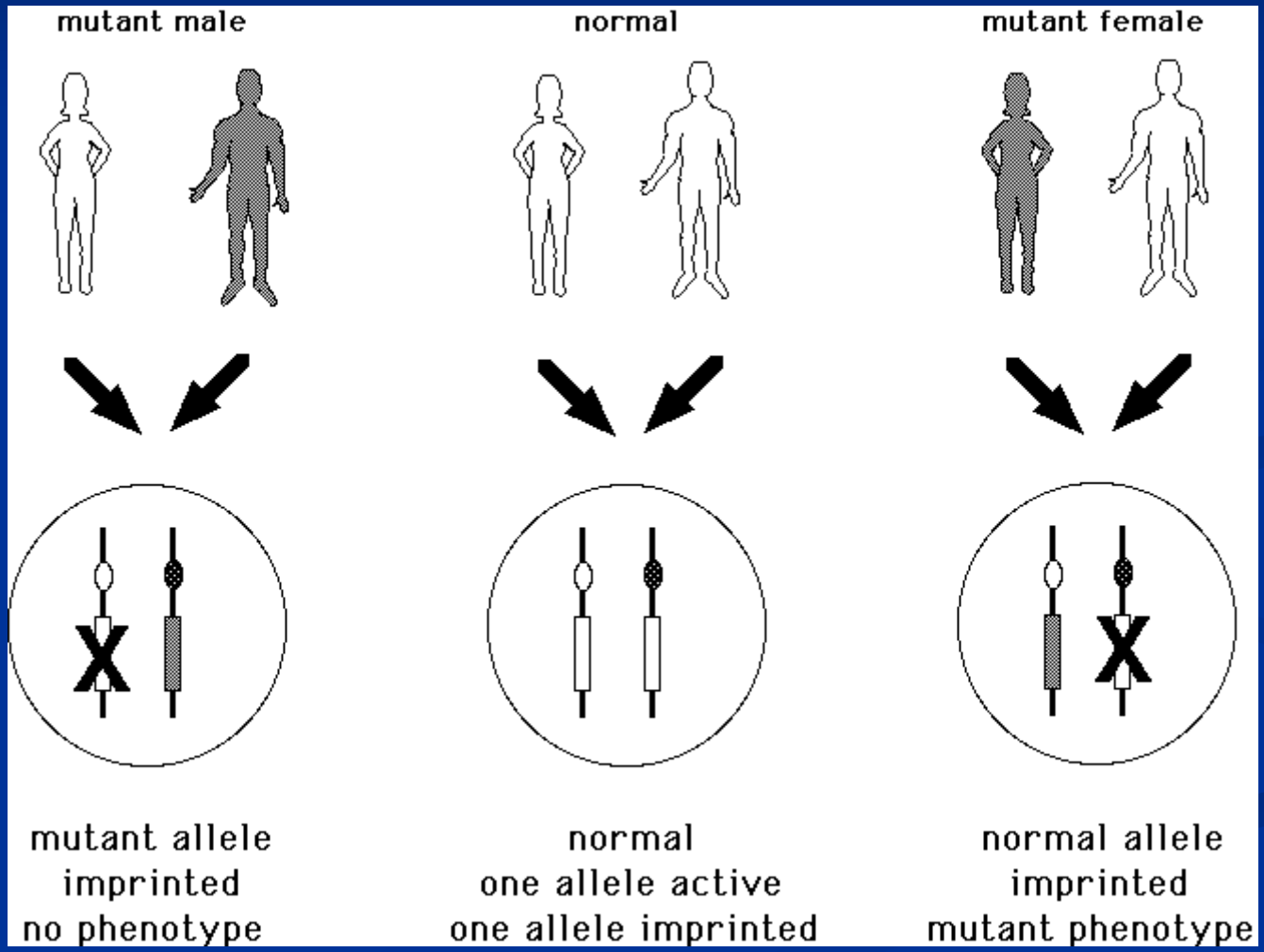
GNAS locus and PHP

The human Gs-α gene is located at 20q13.2-13.3

GNAS **is a complex imprinted gene that generates multiple gene products through the use of multiple promoters and first exons that splice onto a common set of downstream exons (exons 2–13)**

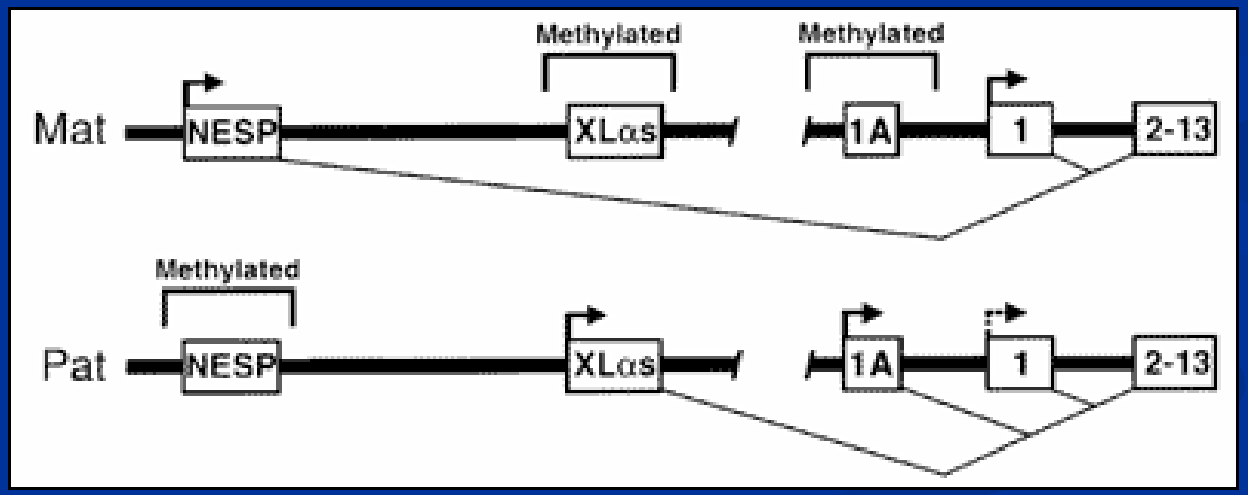


Imprinting is epigenetic phenomenon affecting a number of genes, which leads to transcriptional silencing of one parental allele and is often associated with methylation of the inactive promoter



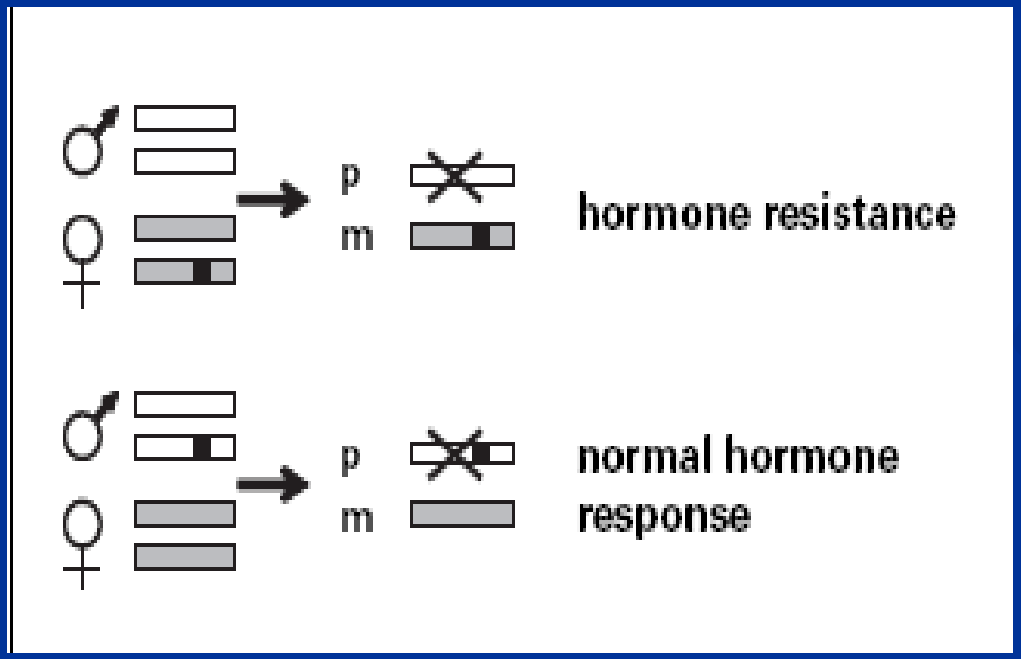
GNAS structure and function

- **NESP55** (chromogranin-like protein) ⟹ **maternal** allele
- **XLαs** ⟹ **paternal** allele
- The promoter and **exon 1A** generates ubiquitously expressed transcripts that are presumed to be untranslated ⟹ **paternal** allele
- **Gs-α** protein is biallelic ⟹ imprinting tissue-specific of **paternal** allele



Epigenetic mechanisms in PHP

Tissue-specific imprinting



PHP Ia

AHO

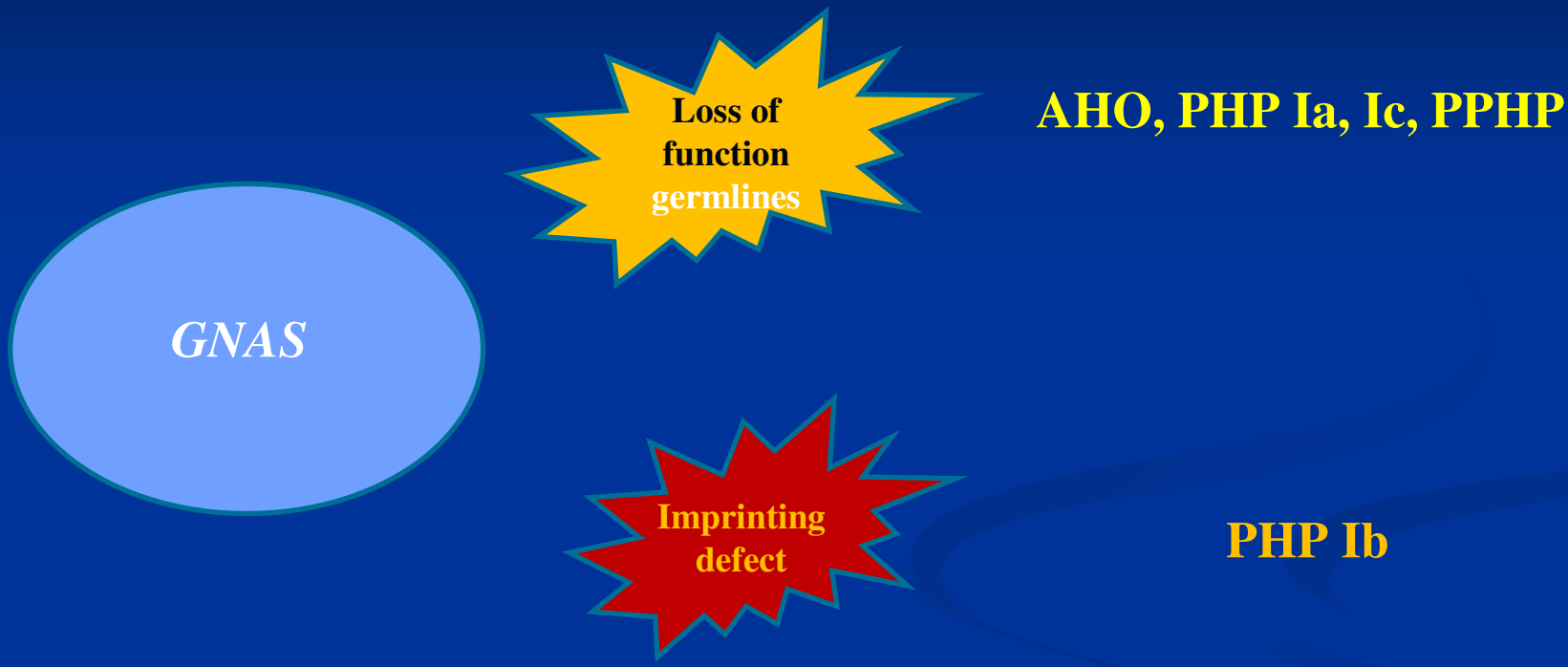
PPHP

renal proximal tubules
thyroid
pituitary
ovary

Clinical and molecular features of different PHP forms

	PTH resistance	Additional hormone resistance	Typical AHO features	Gs-α actrivity	*GNAS* defect
PHP Ia	yes	yes	yes	reduced	**Gsα mutation (maternal)**
PPHP	no	no	yes	__	**Gsα mutation (paternal)**
PHP Ib	yes	some cases	no	normal	***STX16* deletion affecting *GNAS* imprinting**
PHP Ic	yes	yes	yes	normal	**Gsα mutation in PTH1 receptor coupling**
PHP II	yes	no	no	__	__

GNAS mutations and PHP

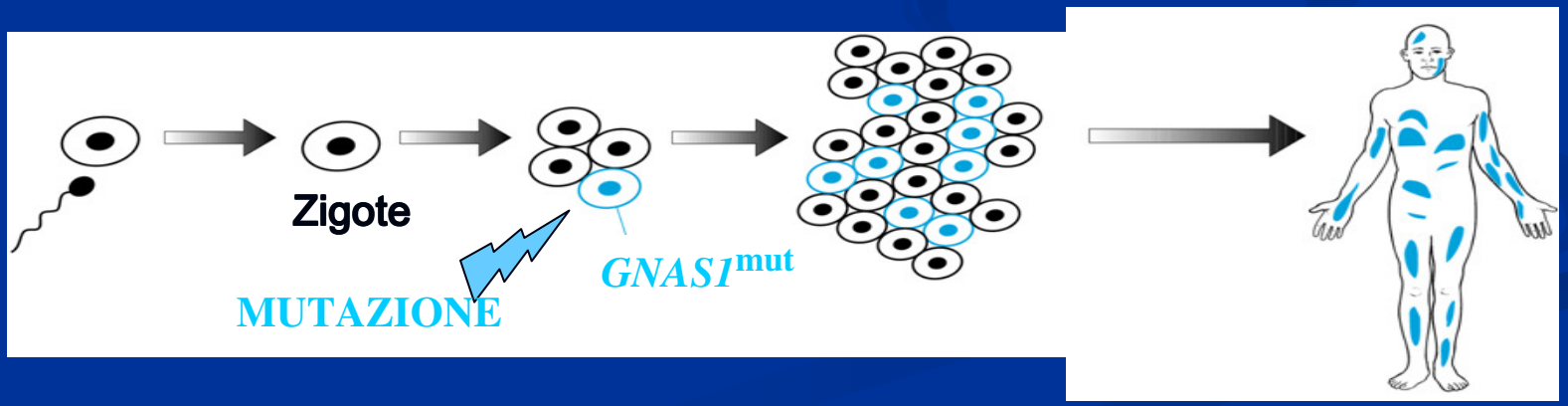


GNAS mutations

Gain of function somatic

Endocrine tumours
Fibrous dysplasia
McCune Albright Syndrome

Gsα activating mutations → **AMPc hyperproduction**



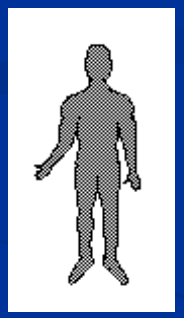
GNAS inactivating mutations

GNAS loss of function

AHO
PHP Ia

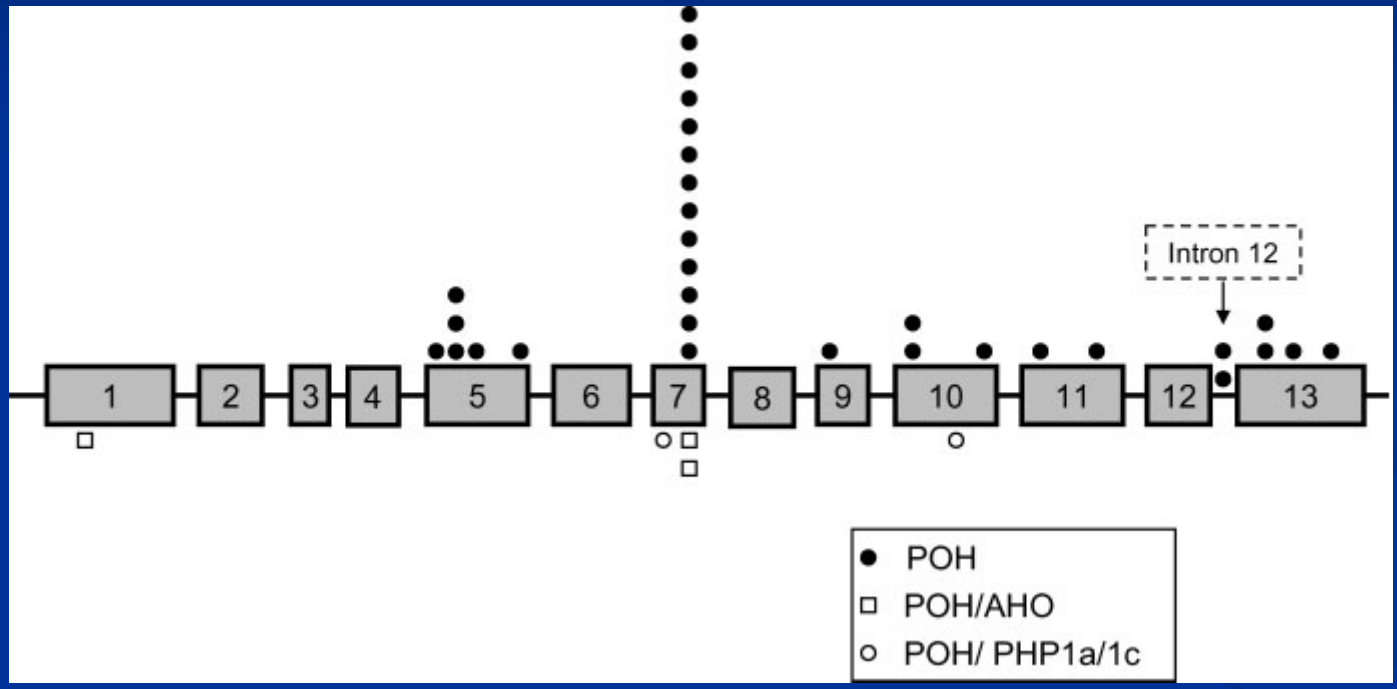
MATERNAL INHERITANCE

PPHP
POH



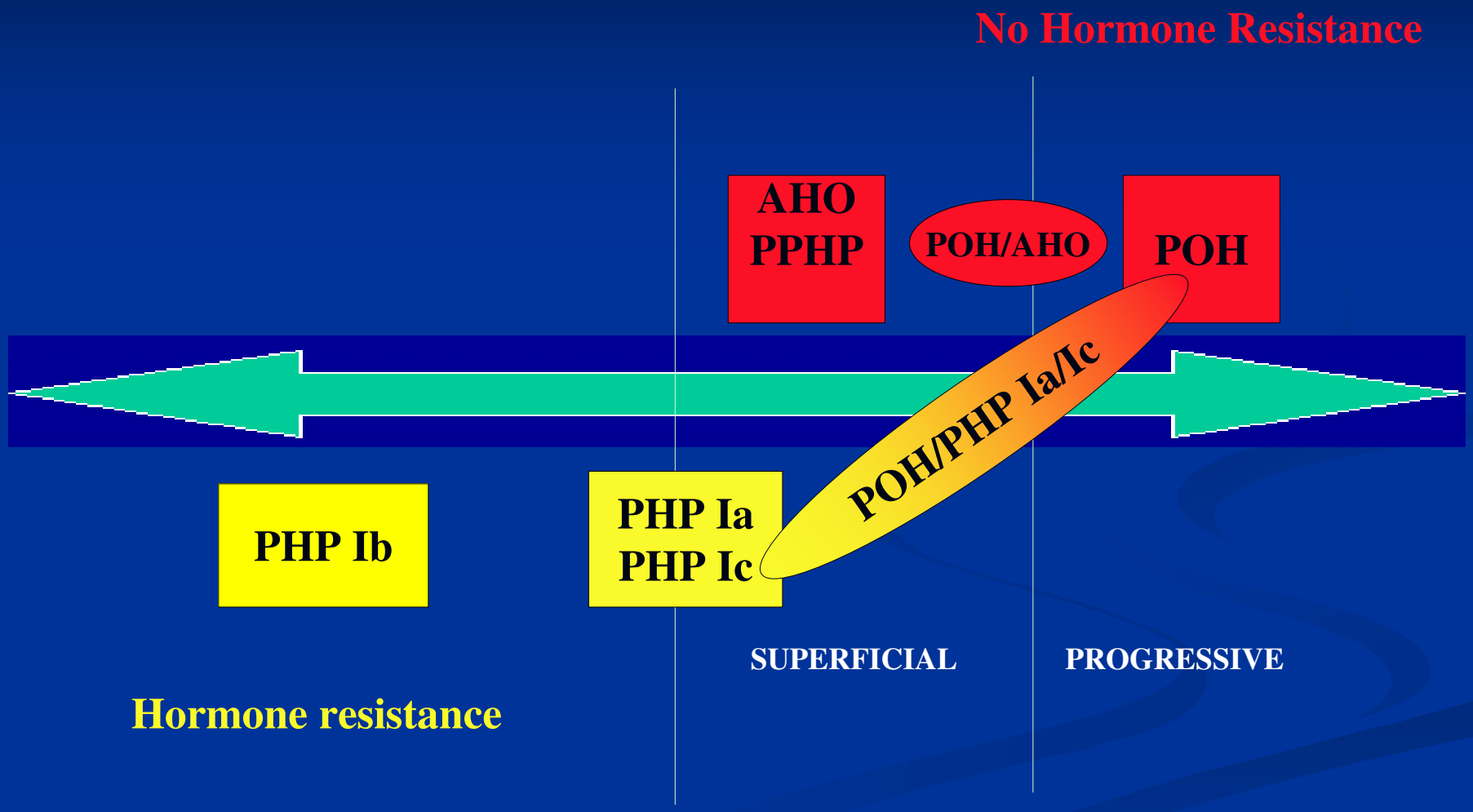
PATERNAL INHERITANCE

Distribution of *GNAS* mutations in conditions with progressive heterotopic ossification



Adegbite NS, Xu M, Kaplan FS et al. Am J Med Genet Part A 2008;146A:1788-1796

Phenotypic spectrum of *GNAS* loss of function mutations



Thank you for your attention