# Clinica Pediatrica
# Ospedale dei Bambini
# Azienda Ospedaliero-Universitaria
# Parma

## Terapia con GH: nuove indicazioni e riflessioni

**S. Bernasconi**

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Tabarka 2006

# Terapia con GH: nuove indicazioni

BEST PRACTICE

# NEW INDICATIONS FOR GROWTH HORMONE

Nicola Bridges

*Arch Dis Child Educ Pract Ed* 2005;90:ep7–ep9. doi: 10.1136/adc.2004.061382

**Table 1** The use of growth hormone (GH) therapy in short stature

- Treatment recommended by NICE guidelines 2002 in the UK[1]
  - GH deficiency, isolated or as part of multiple pituitary hormone deficiency
  - Turner syndrome
  - Prader Willi syndrome
  - Short stature associated with chronic renal failure
- Licensed indications in Europe
  - GH deficiency, isolated or as part of multiple pituitary hormone deficiency
  - Turner syndrome
  - Prader Willi syndrome
  - Short stature associated with chronic renal failure
  - Short stature associated with low birth weight
- Licensed in the USA, but not in Europe
  - Idiopathic short stature
- Short stature conditions where there have been trials of treatment with GH but outcome is not clear (not licensed indications)
  - Noonan syndrome
  - Skeletal dysplasia
  - Rheumatoid arthritis
  - Down syndrome
  - Short stature associated with prolonged steroid use
  - Aarskog's syndrome

NICE, National Institute for Clinical Excellence.

**Table 1.** Ranges for adult height irrespective of gender [2–4]

| | Adult height, cm |
|---|---|
| *Short-limbed conditions* | |
| Achondroplasia | 106–142 |
| Hypochondroplasia | 132–147 |
| Diastrophic dysplasia | 86–122 |
| Diastrophic dysplasia (Finnish) | 98–158 |
| Pseudoachondroplasia | 80–130 |
| Metaphyseal dysplasia | |
| McKusick type | 105–145 |
| McKusick type (Finnish) | 104–149 |
| Schmid type | 130–160 |
| Chondrodysplasia punctata | |
| Conradi-Hünermann type | 130–160 |
| Chondroectodermal dysplasia | 106–153 |
| Grebe chondrodysplasia | 99–104 |
| Acromesomelic dysplasia | 97–123 |
| Multiple epiphyseal dysplasia | |
| Fairbank type | 137–155 |
| Pyknodysostosis | 130–150 |
| *Short trunk conditions* | |
| Spondyloepiphyseal dysplasia tarda | 132–156 |
| Spondyloepiphyseal dysplasia congenital | 84–132 |
| Dyggve-Melchior-Clausen dysplasia | 130–135 |
| Kniest dysplasia | 104–145 |

**Skeletal Dysplasia, Growth Hormone Treatment and Body Proportion: Comparison with Other Syndromic and Non-Syndromic Short Children**

L.Hagenäs, T.Hertel

*Hormone Research* 2003;60 (Suppl. 3):65-70

In summary, it seems that short-term GH treatment in achondroplasia is effective to a similar extent as in some other cases of syndromic and non-syndromic short stature. Reports of final height in achondroplasia are expected to be available within a couple of years.

**Leri and Weill**

***Une affection congénital et symétrique du developpement osseux: la dyschondrostéose***

**Bull. Mém. Soc. Med. Hosp. 1929**

# Leri and Weill

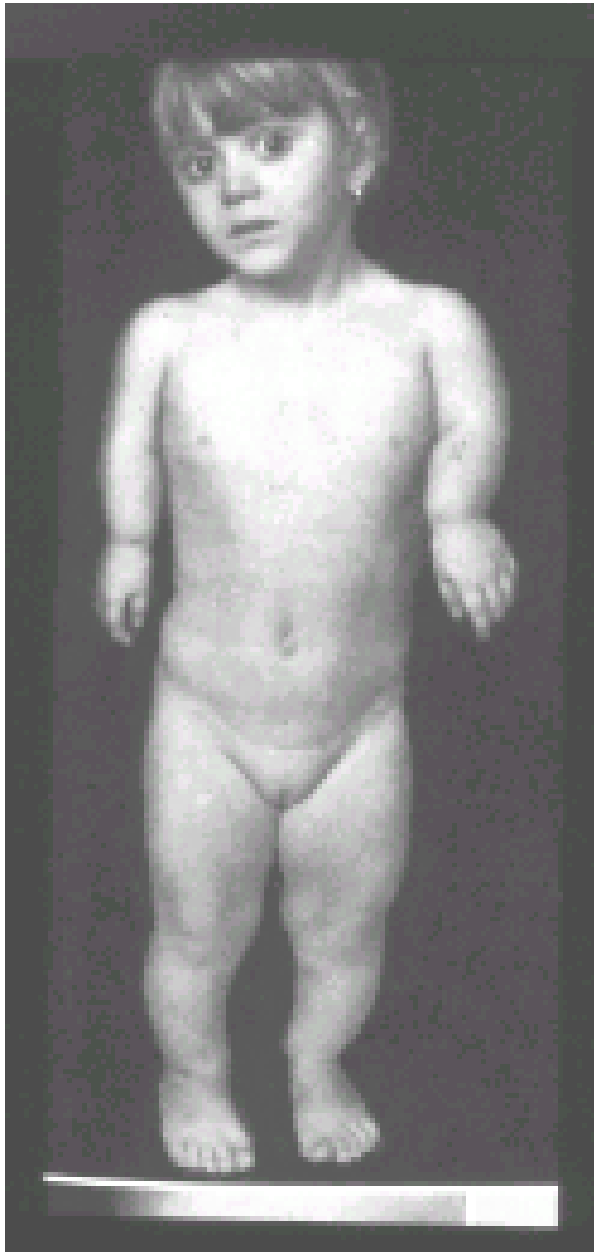


**Figure 2: Lateral and Dorsal Bowing of a Shortened Radius in Madelung Deformity**

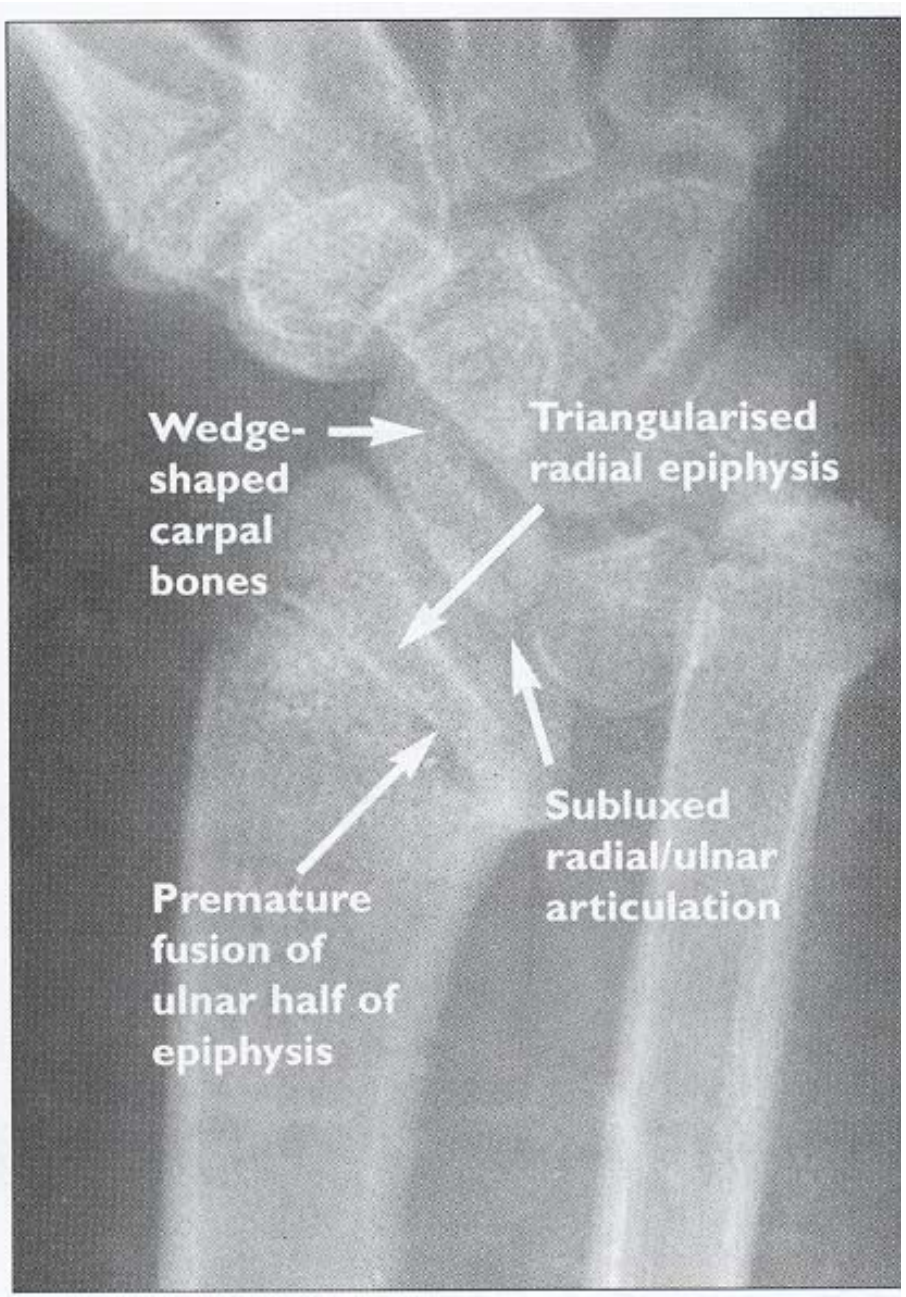
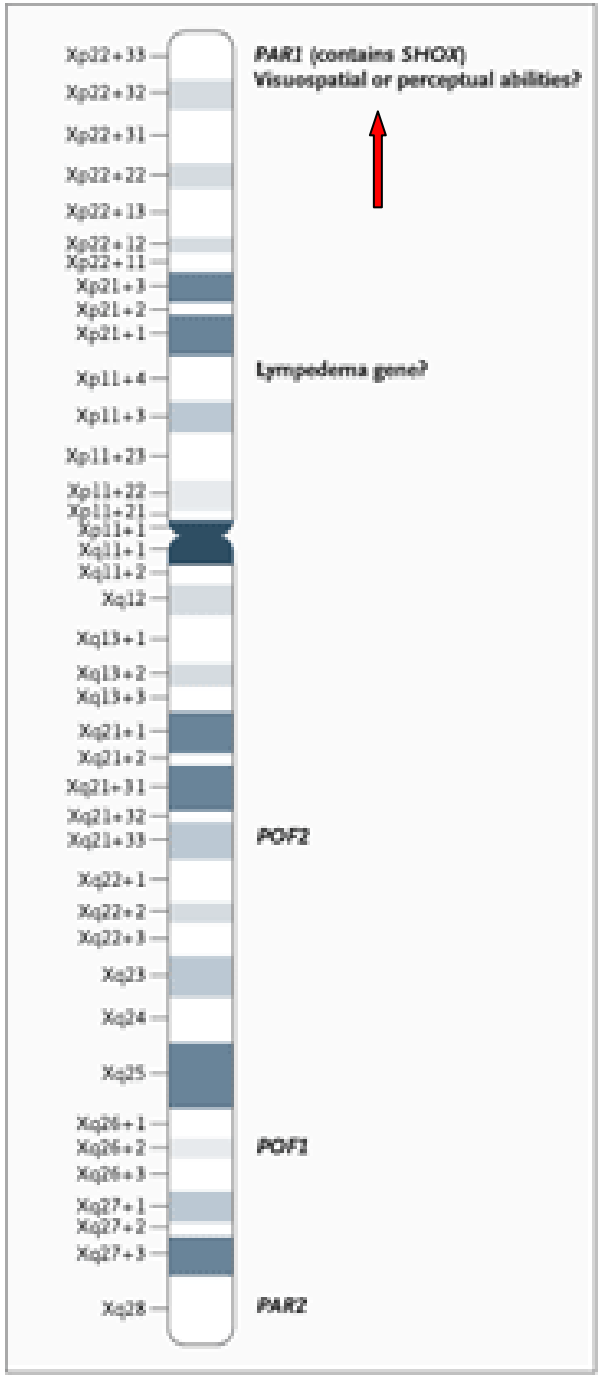


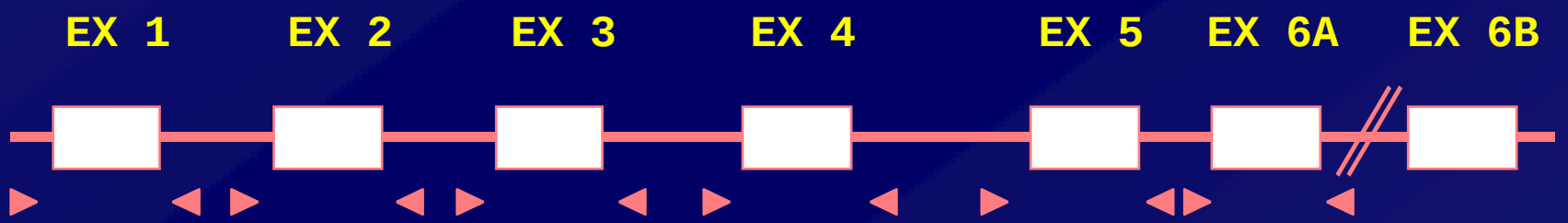

**Figure 3: Features of Madelung Wrist Deformity**



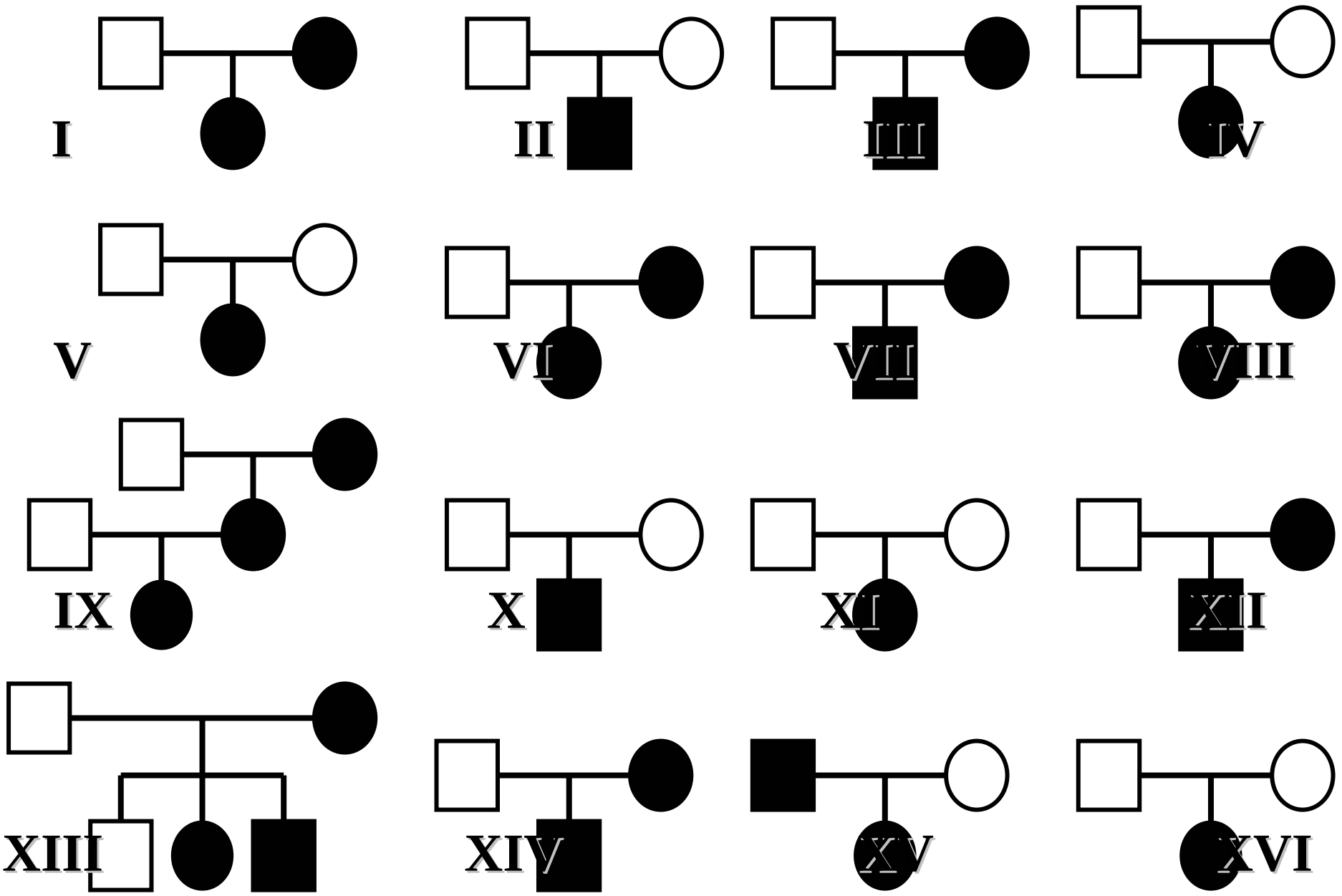

# X CHROMOSOME

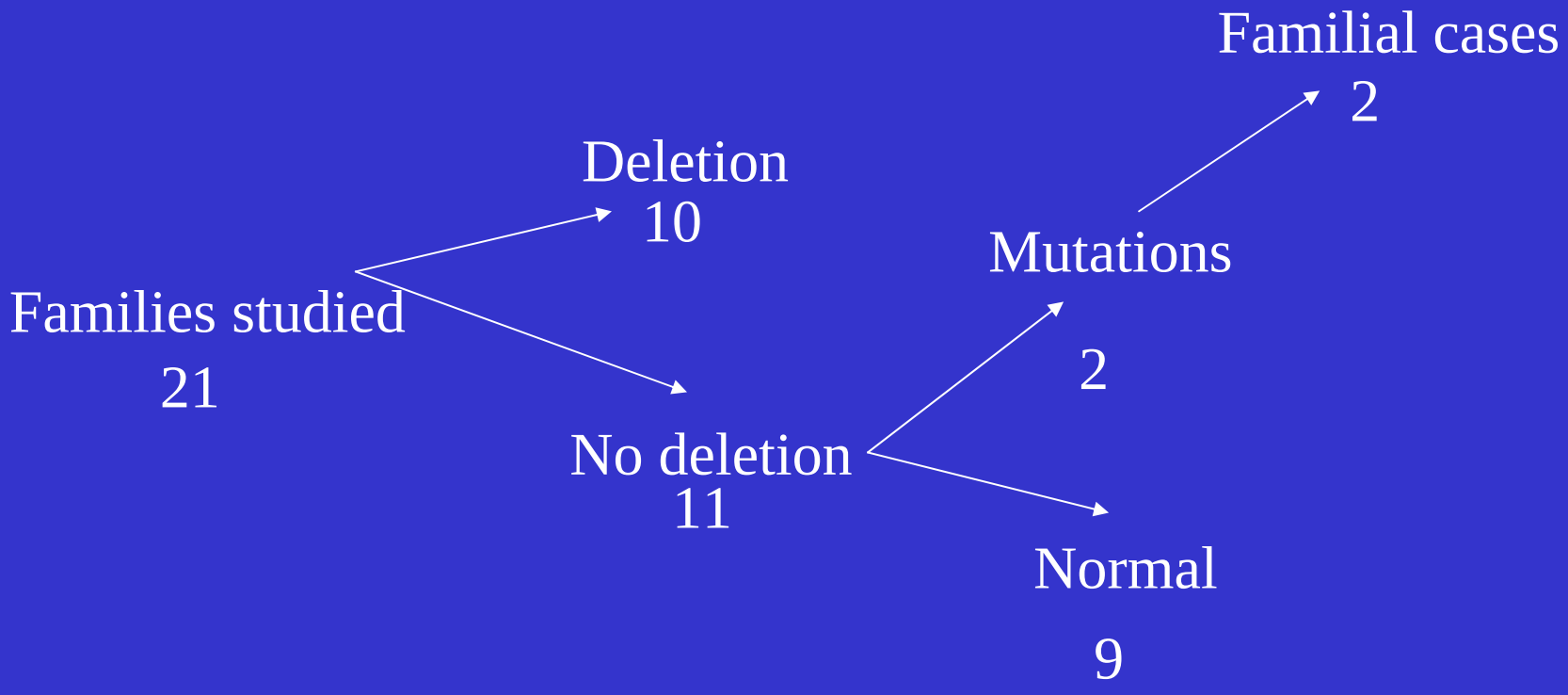
*SHOX* is located within *PAR1*.

# SCHEMATIC DIAGRAM OF THE GENOMIC STRUCTURE OF SHOX GENE



# LWD FAMILIES

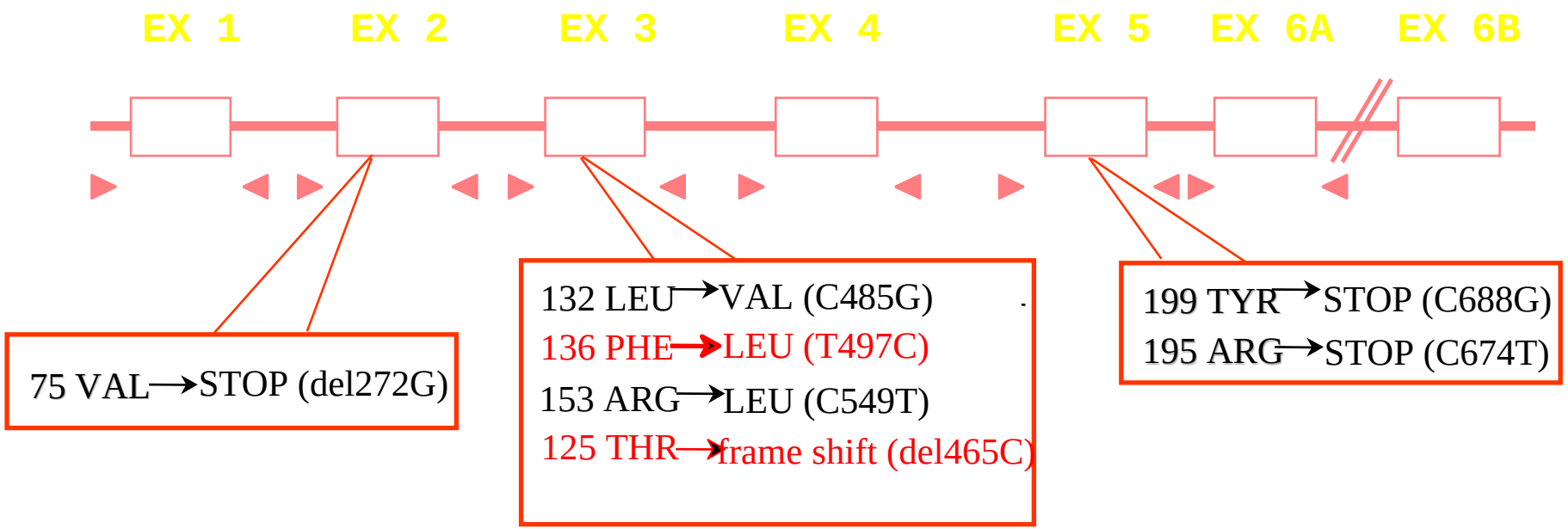





S.Bernasconi et al J Med Genet 2002

# Schematic diagram of the genomic structure of SHOX gene and position of point mutations identified

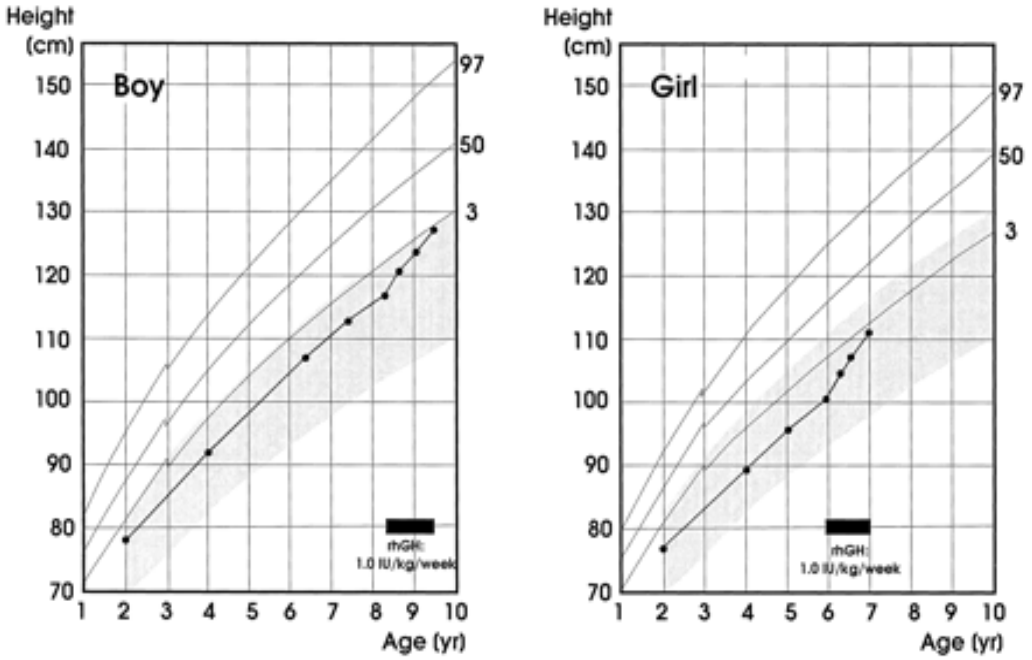
S.Bernasconi et al J Med Genet 2002



# Identification of Short Stature Caused by SHOX Defects and Therapeutic Effect of Recombinant Human Growth Hormone

**G. Binder, C. P. Schwarze and M. B. Ranke**

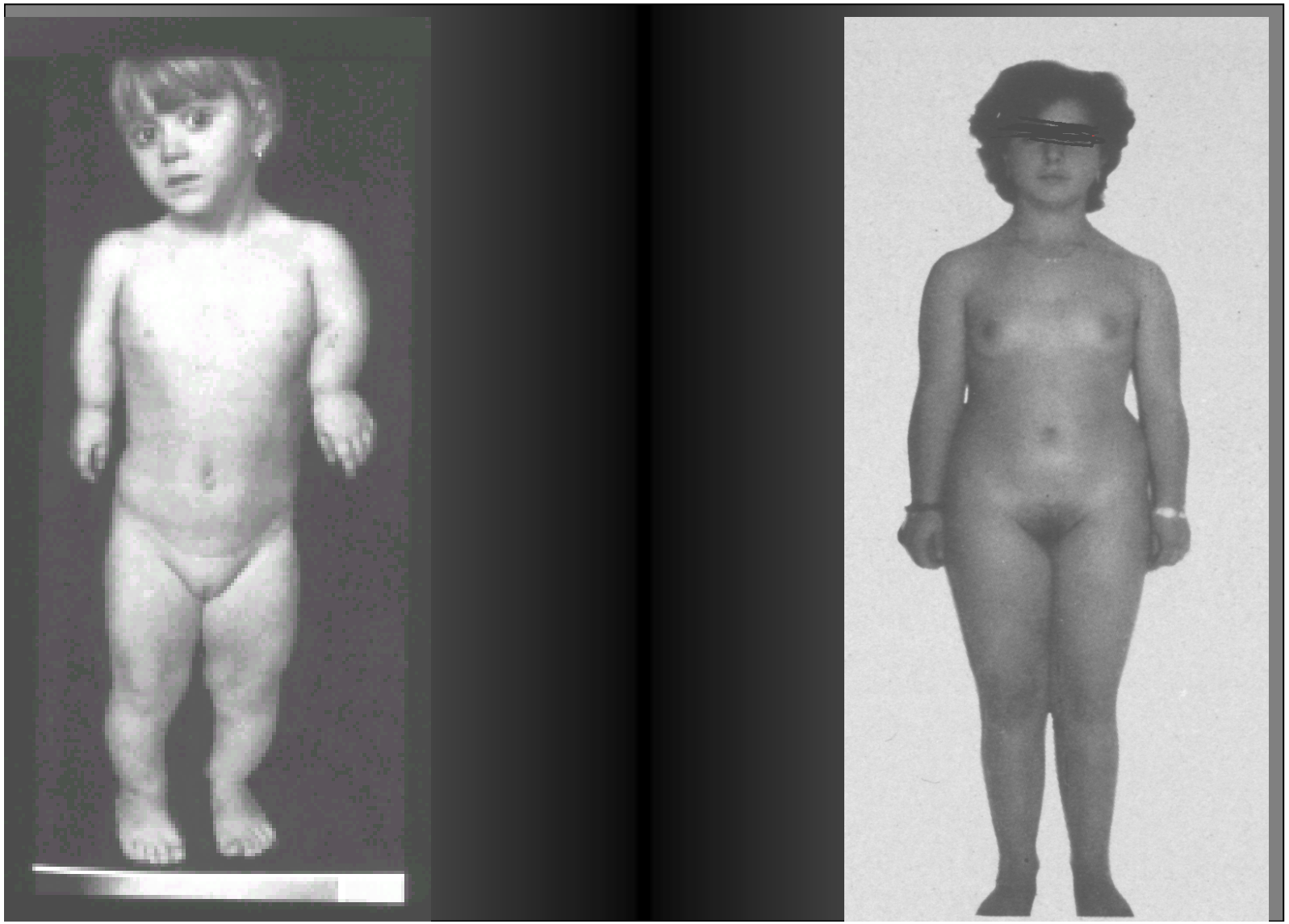
**J Clin Endocrinol Metab 85, 245-249,2000**



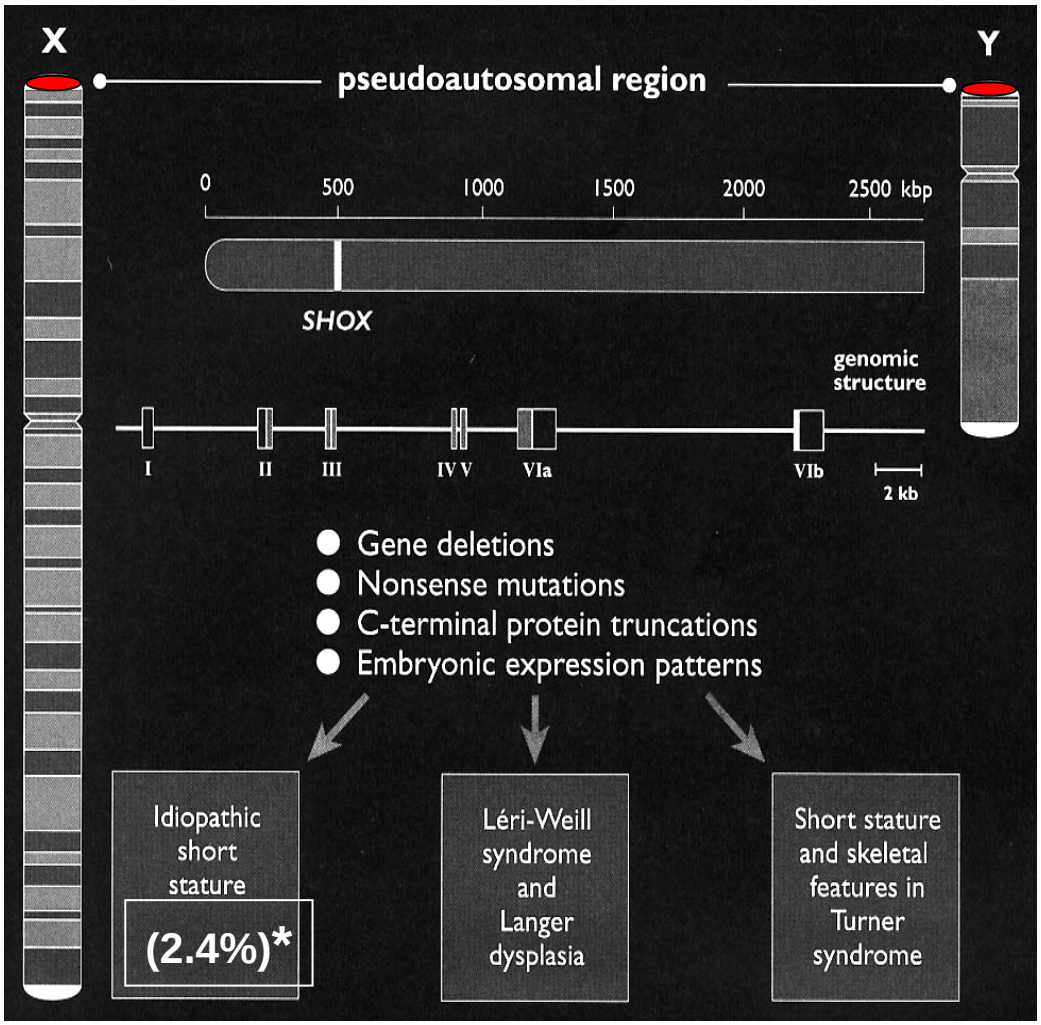

Growth charts of the two siblings with the SHOX point mutation (C674T) treated with rhGH. Normal standards are according to Prader *et al.* (9 ). The *shadowed area* comprises the normal growth spectrum of females with Turner syndrome (±2 SD) .

•

# Leri and Weill



# SHOX Gene Organization, Mutations and Related Disorders




***Rappold G et al**, *JCEM 87:1402, 2002*

# Le scelte terapeutiche problematiche : la terapia con l'ormone della crescita negli "short normal"

## Definizione :

1) Taglia normale alla nascita in rapporto all'età gestazionale
2) Normali proporzioni corporee
3) Assenza di deficit ormonali
4) Assenza di malattie croniche organiche o psichiatriche
5) Normale stato nutrizionale
6) Velocità di crescita basso-normale

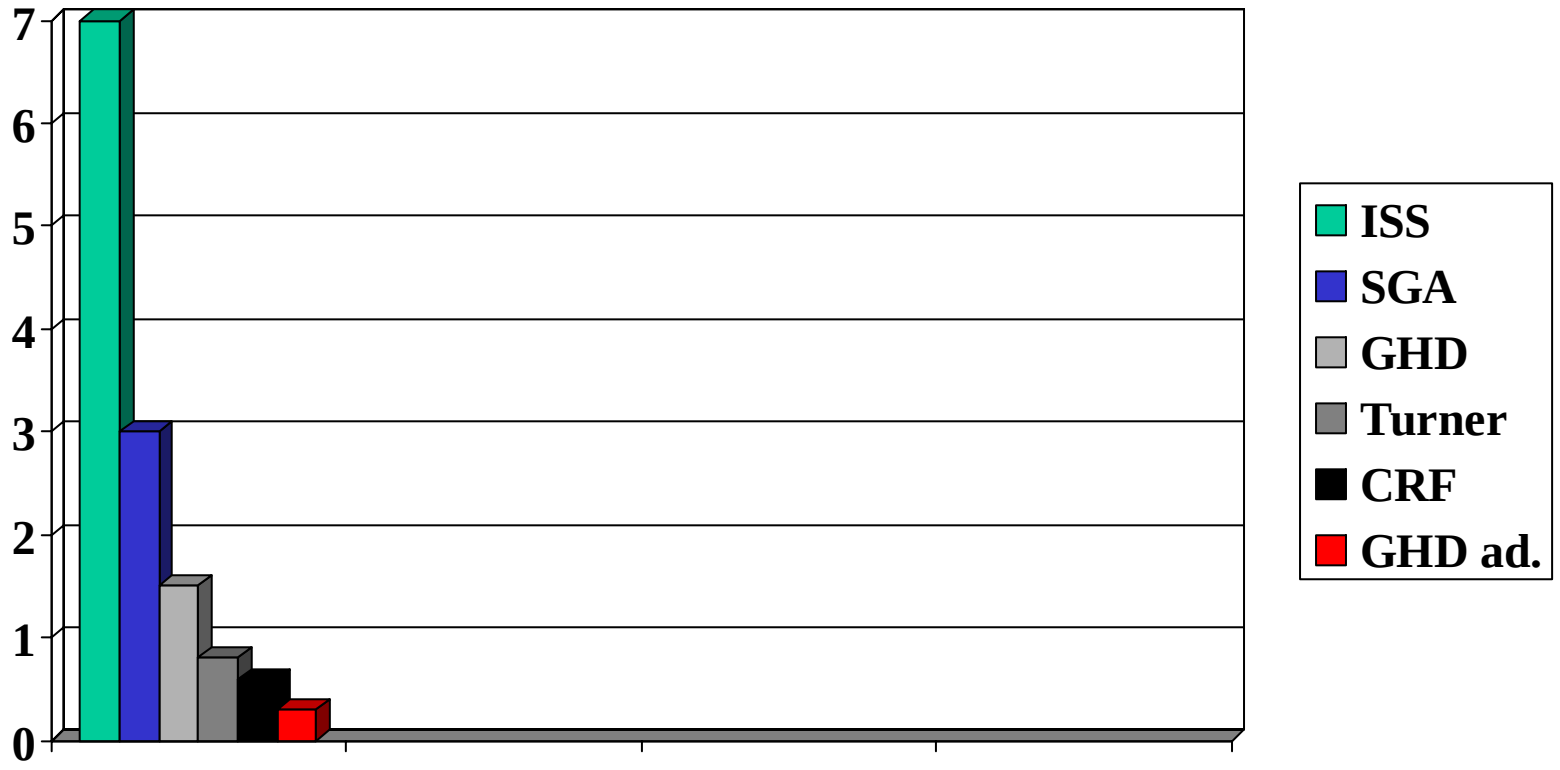
Ranke MB  Horm Res 1996

# Le scelte terapeutiche problematiche : la terapia con l'ormone della crescita negli "short normal"

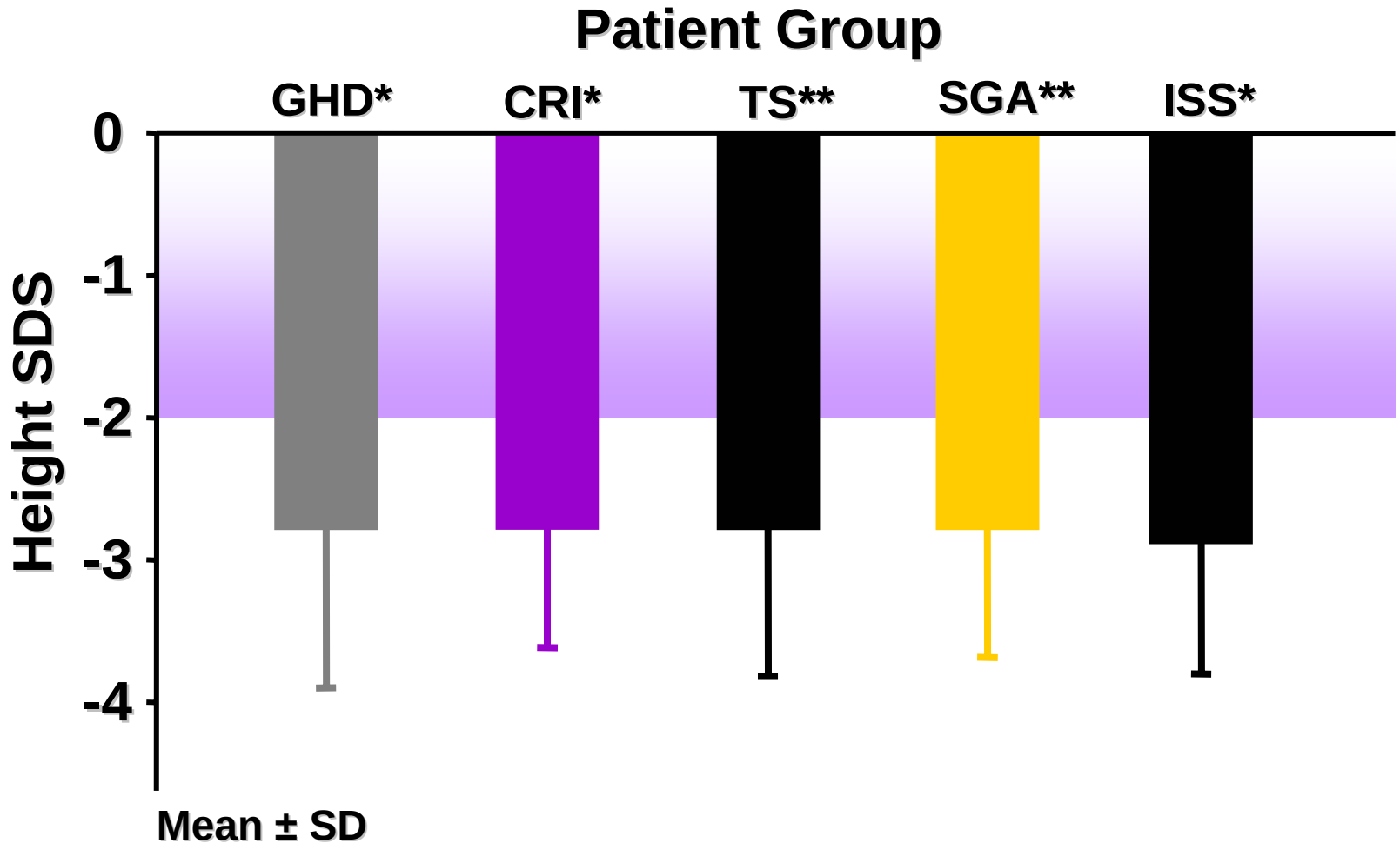
…idiopathic short stature defined by height SDs < 2.25 and associated with growth rates unlikely to permit attainement of adult height in the normal range…

FDA 2003

# Le scelte terapeutiche problematiche : la terapia con l’ormone della crescita negli “short normal”

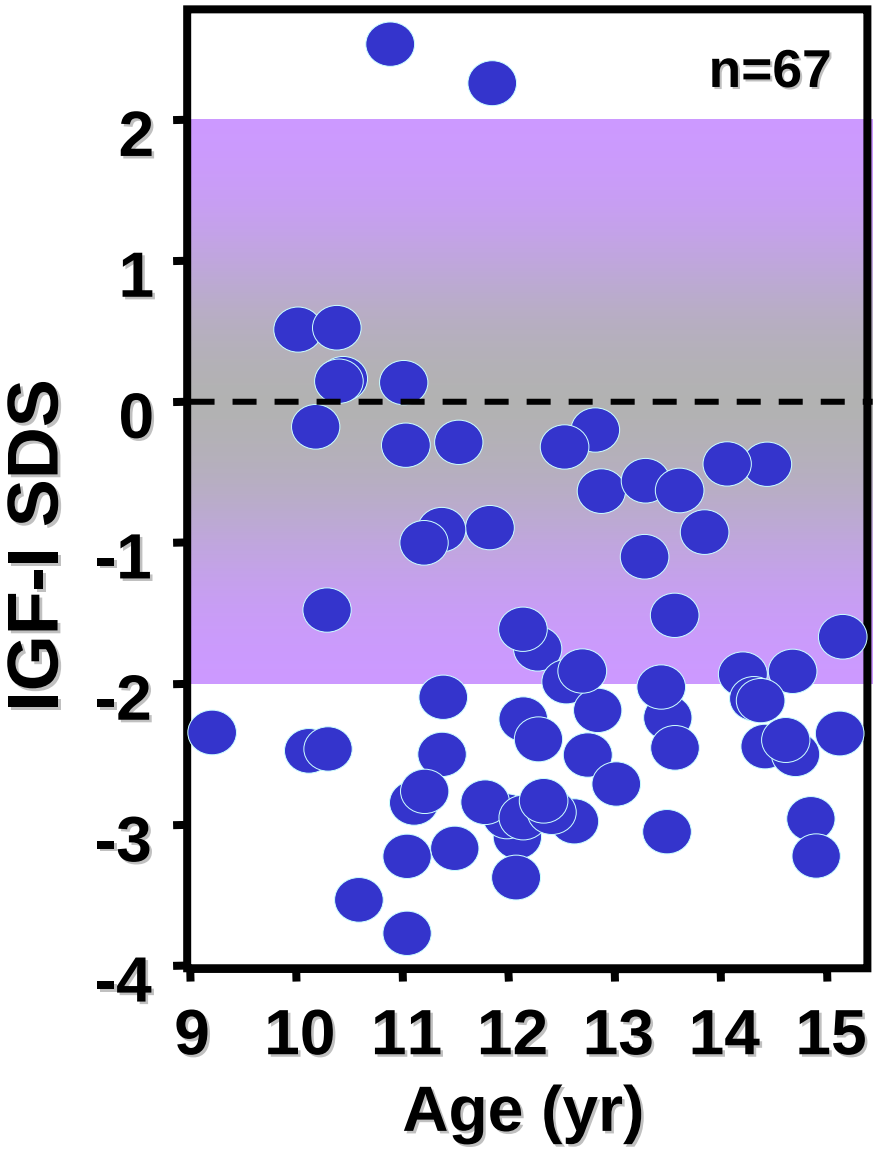


# Patients with ISS Have Similar Severity of Short Stature to Other Disorders



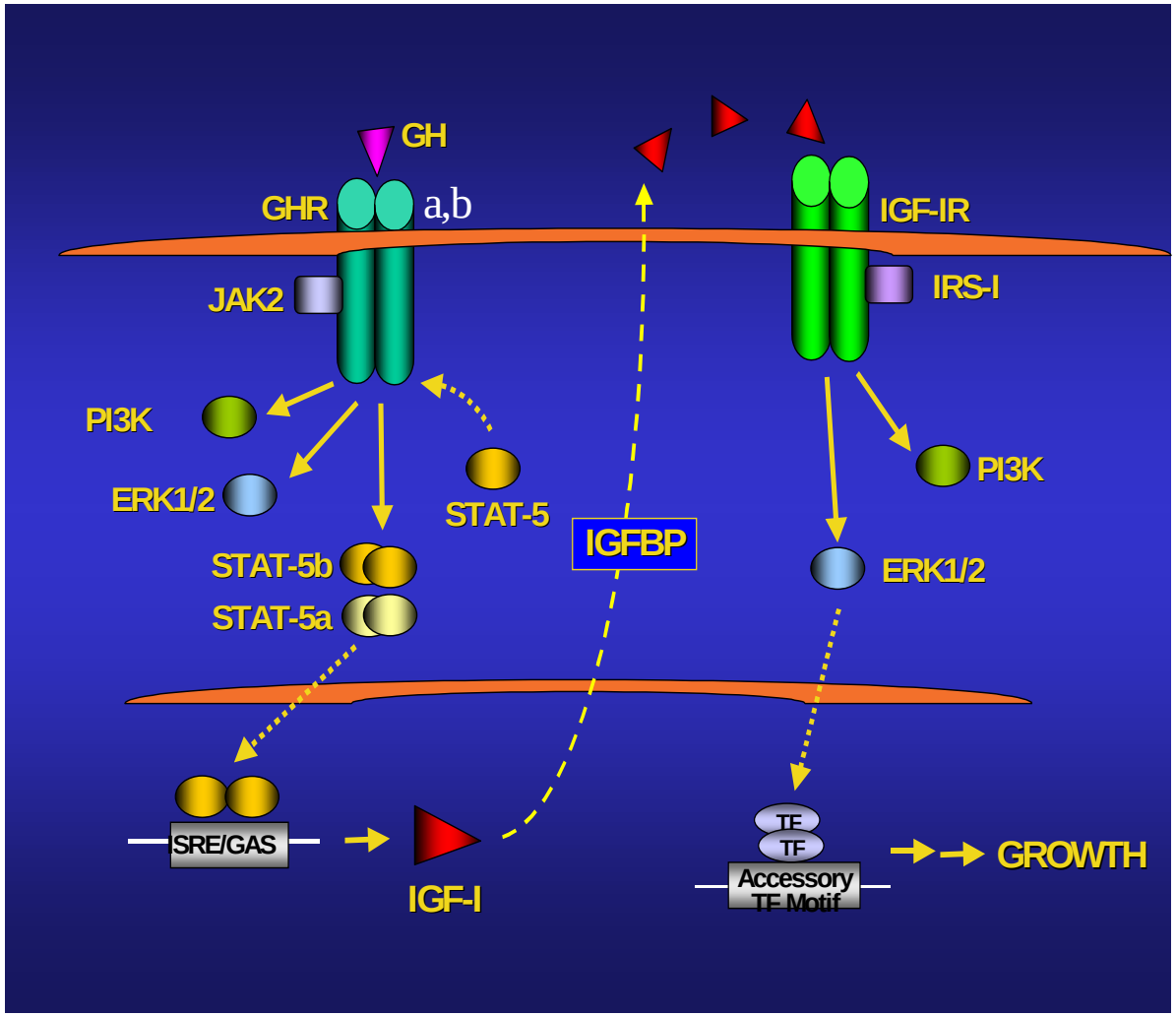

*National Cooperative Growth Study
**Kabi International Growth Study

# IGF-I in Patients with Idiopathic Short Stature




Baseline IGF-I SDS for all patients enrolled in placebo-controlled study

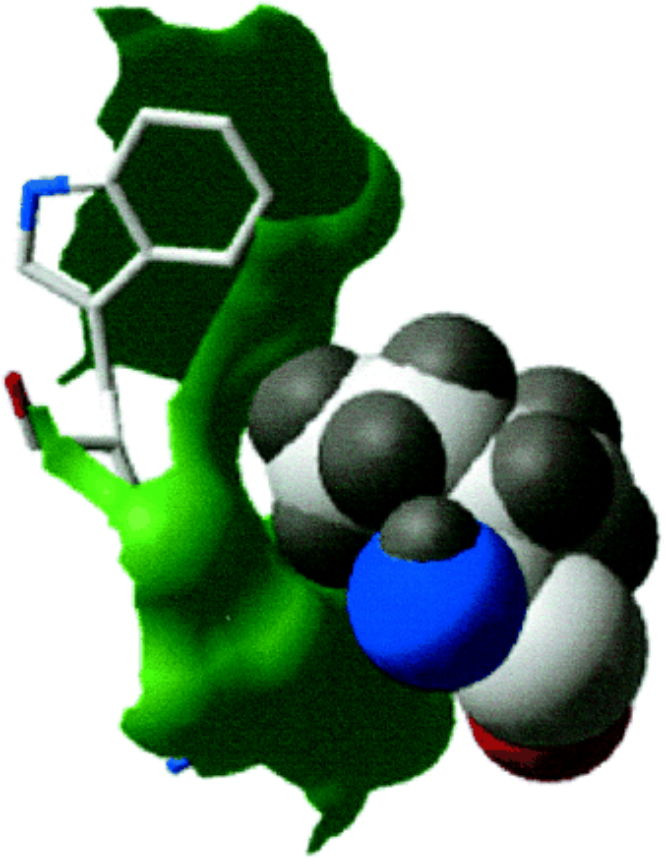
# NEW MOLECULAR MECHANISMS OF GH RESISTANCE




a) Defects of the extracellular domain of the GHR;

b) defects in GHR dimeritation

**A Novel Dysfunctional Growth Hormone Variant (Ile179Met) Exhibits a Decreased Ability to Activate the Extracellular Signal-Regulated Kinase Pathway**
**M.D.Lewis et al J Clin Endocrinol Metab 2004**



The tight interaction between the side chain of GH residue Ile179 and GHR residue Trp169. The Ile179 residue is depicted by a space-filling model. Trp169 is represented as a stick model, whilst the molecular surface of GHR residues 167–169 is shown in *green*.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

# Deficiency of the Circulating Insulin-like Growth Factor System Associated with Inactivation of the Acid-Labile Subunit Gene

Horacio M. Domené, M.S., Sonia V. Bengolea, M.D., Alicia S. Martínez, M.D., M. Gabriela Ropelato, M.S., Patricia Pennisi, Ph.D., Paula Scaglia, M.S., Juan J. Heinrich, M.D., Ph.D., and Héctor G. Jasper, M.D.

350:570-577,2004

# HEIGHTISM

# Cina, corsa a diventare più alti dal chirurgo per avere successo

almeno il 30 per cento dei pazienti, ma davanti a qualcuno che minaccia di togliersi la vita cosa posso fare?».

Allungarla, appunto. Xia Hetao ha cliniche in tutto il paese. La sua fortuna è nata quando ha operato una nipote del presidente Deng Xiao Ping.

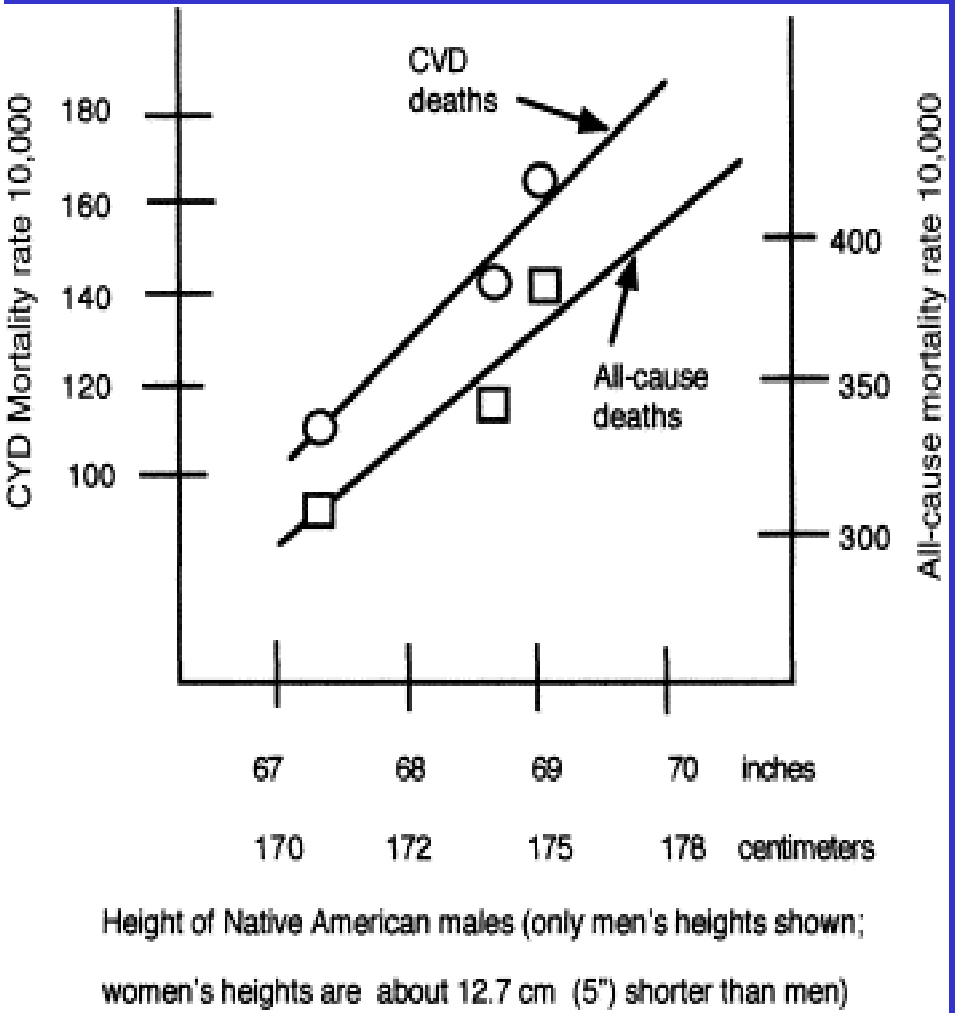
Non è il solo a vendere centimetri. Ce ne sono molti altri. In Cina la sanità è privata. Da Canton una ragazza di 24 anni ulula le sue sofferenze al telefono: «Non riesco ad alzarmi dal letto. Volevo ammazzarmi dal dolore. mi hanno legato al tavolo a quattro di bastoni, mi hanno messo 17 chiodi nelle gambe, per cinque mesi dallo strazio ho dormito solo

La Repubblica

20 Luglio 2004

# Terapia con GH: riflessioni

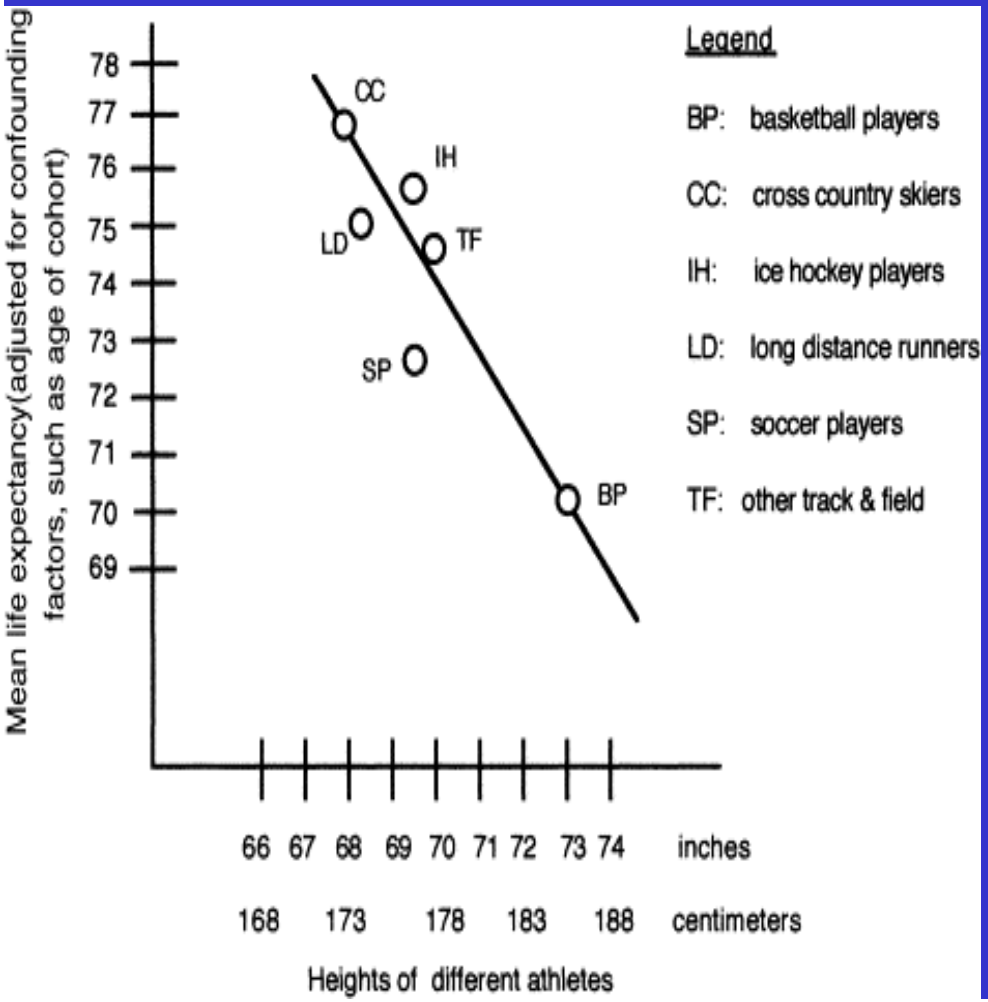
# Is height related to longevity?
# Samaras TT, Elrick H, Storms LH.




Height of Native American males (only men's heights shown; women's heights are about 12.7 cm (5") shorter than men)

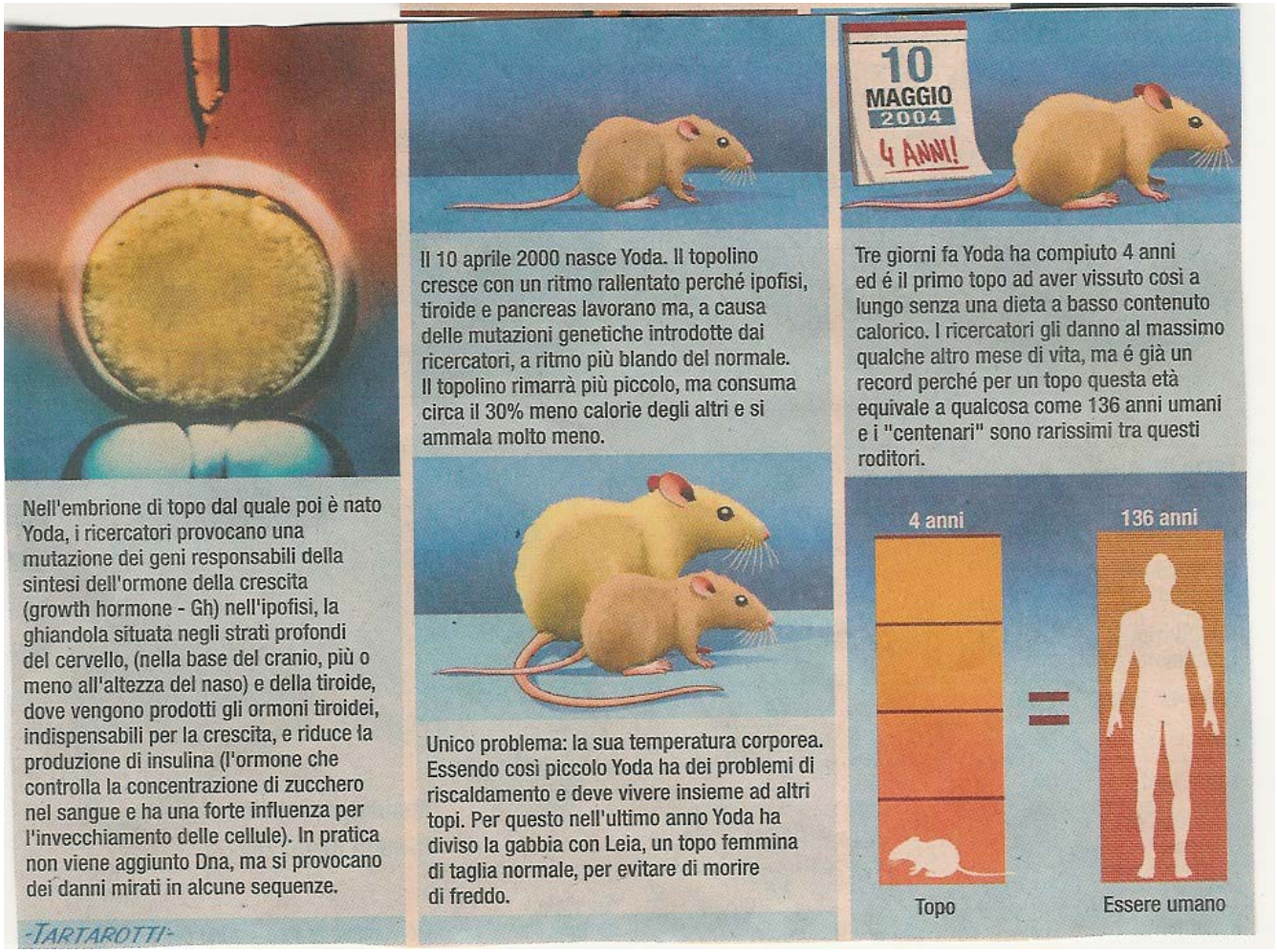
**Life Sci. 2003 Mar 7;72(16):1781-802**

# Is height related to longevity?
# Samaras TT, Elrick H, Storms LH.




**Life Sci. 2003 Mar 7;72(16):1781-802**

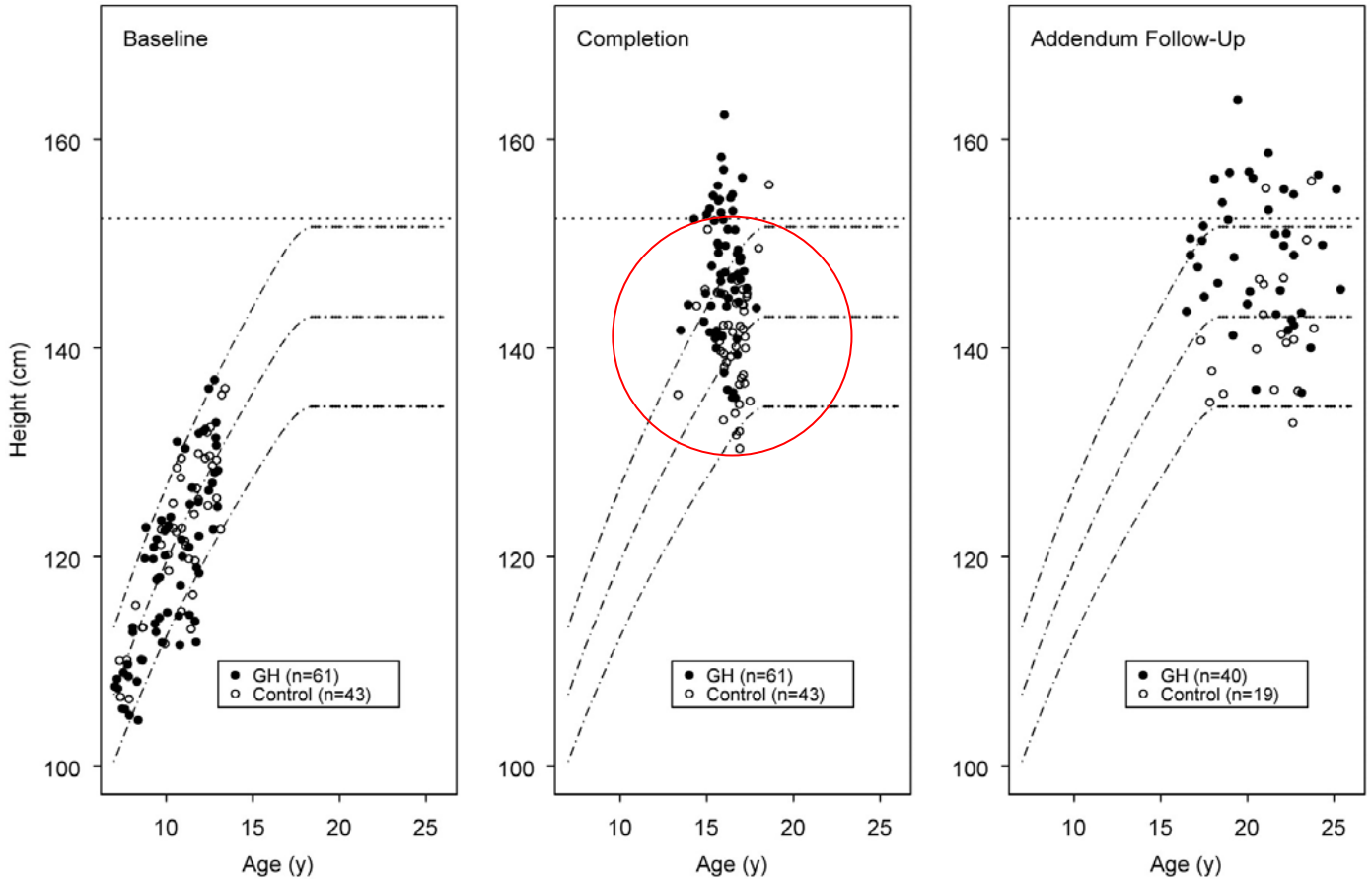
# Un matusalemme da laboratorio




Il Sole 24 ore

14/4/2004

**FIG. 2. Height at baseline, protocol completion, and addendum follow-up (at least 1 yr after completion) vs. age, plotted with 10th, 50th, and 90th percentile growth curves for Turner syndrome (1 ) for patients who completed the core protocol**




**The Canadian Growth Hormone Advisory Committee, J Clin Endocrinol Metab 2005;90:3360-3366**

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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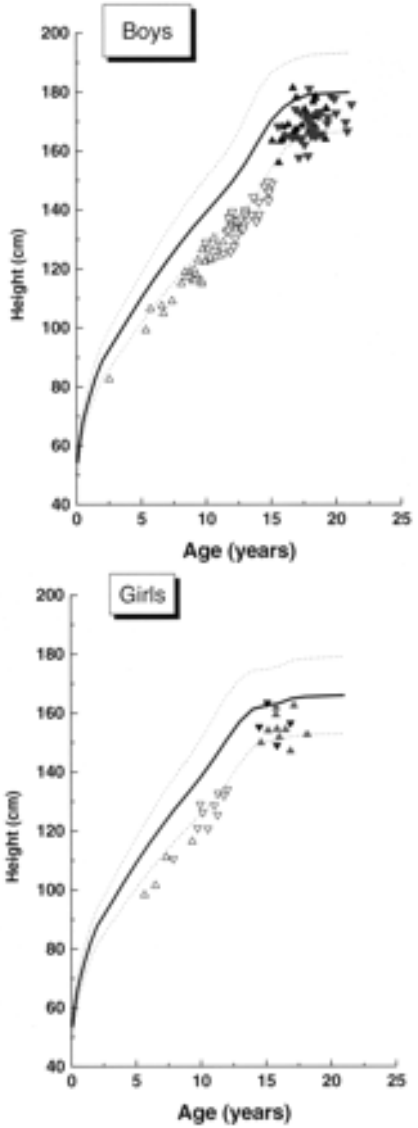
# Final Height in Short Children Born Small for Gestational Age Treated with Growth Hormone

J DAHLGREN, K ALBERTSSON WIKLAND ON BEHALF OF THE SWEDISH STUDY GROUP




Height SDS at start and FH. Height SDS in boys and girls at the start of GH treatment (*open triangles*) and at final height (*filled triangles*). The *regular triangles* denote the patients treated >2 yr before puberty, and *inverted triangles* are those treated <2 yr before puberty. The growth curves are from the reference population.

*Pediatric Research*
57:216-222 (2005)

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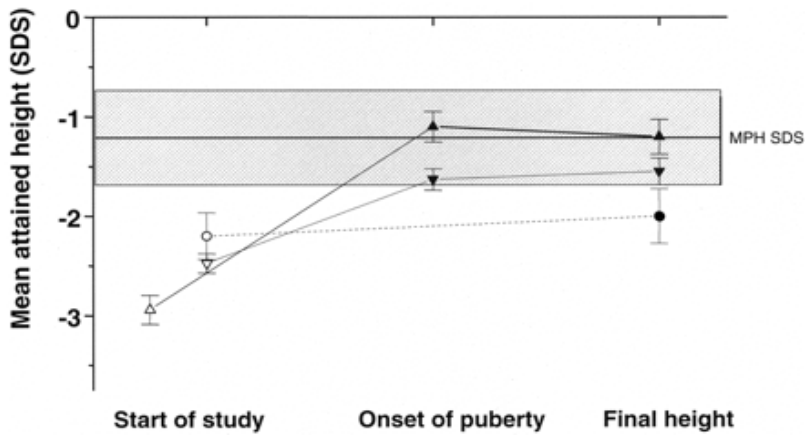


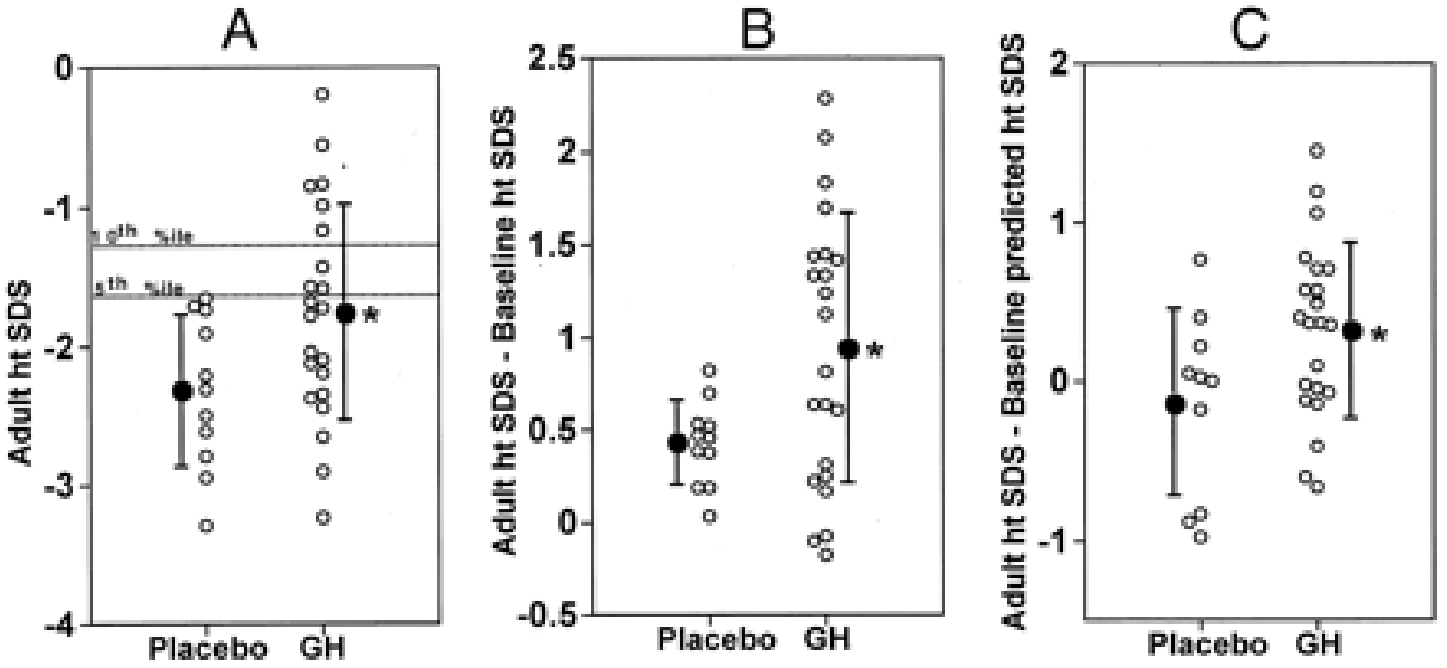

The mean attained height. The prepubertal and pubertal height gain (SDS) in the two GH-treated groups, expressed as man and SE: *regular triangles* = treated >2 y before puberty, and *inverted triangles* = treated <2 y before puberty. Attained height in the untreated group is shown as *circles* and *broken line*, expressed as mean and SE. Mean MPH ± 0.5 SD, is shown as *shadowed area*.

*Pediatric Research*
57:216-222 (2005)

# Effect of Growth Hormone Treatment on Adult Height in Peripubertal Children with Idiopathic Short Stature: A Randomized, Double-Blind, Placebo-Controlled Trial

E.W.Leschek et al

The Journal of Clinical Endocrinology & Metabolism Vol. 89, No. 7 3140-3148
2004



BEST PRACTICE

# NEW INDICATIONS FOR GROWTH HORMONE

Nicola Bridges

*Arch Dis Child Educ Pract Ed* 2005;90:ep7–ep9. doi: 10.1136/adc.2004.061382

**Table 2** Adverse events reported during GH treatment

| |
|---|
| Benign intracranial hypertension |
| Slipped upper femoral epiphyses |
| Worsening of scoliosis |
| Gynaecomastia |
| Oedema (almost exclusively in adults) |
| *Possibly related to GH treatment* |
| Malignancy |
| Reduced insulin sensitivity |
| Unexpected deaths in obese patients with Prader Willi syndrome |

# Safety of GH therapy in short children born SGA

- GH therapy is safe and well-tolerated in short children born SGA

- GH treatment in children may have an adverse impact on glucose metabolism

# Other characteristics of short children born SGA

Compared with healthy controls, SGA children may be at increased risk of:

- Low body mass index (BMI)[1]
- Low food intake and poor appetite[2]
- Reduced self-confidence[3]
- Developing the “metabolic syndrome“ in later life[4] (thrifty hypothesis)
- Low bone density and subsequent osteoporosis[5,6]

**1.** Sas T et al. J Clin Endocrinol Metab 2000;85:3786–92. **2.** Arends NJ et al. Horm Res 1998;50(Suppl. 3):47.
**3.** van der Reijdeman-Lakeman I et al. Horm Res 1996;46:88–94. **4.** Barker D. Horm Res 1994;42:223–30.
**5.** Gale CR et al. J Clin Endocrinol Metab 2001;86:267–72. **6.** Cooper C et al. Osteoporos Int 2001;12:623-9.

# Safety of GH therapy in short children born SGA

- Thus, glucose metabolism should be carefully monitored during therapy

# Le scelte terapeutiche problematiche : la terapia con l'ormone della crescita negli "short normal"

Il costo stimato è di 35.000 dollari ogni 2,5 cm guadagnati

Finkelstein 2002

# Grazie per l’attenzione