S.BERNASCONI
DIPARTIMENTO DELL'ETA' EVOLUTIVA
UNIVERSITA' DI PARMA

Novità nella terapia della bassa statura

PERCORSI DECISIONALI PER LA GESTIONE DEL BAMBINO E DELL'ADOLESCENTE

sbernasconi@ao.pr.it

FAMAGOSTA12-17 GIUGNO 2010

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

0031-3998/95/3805-0733$03.00/0
PEDIATRIC RESEARCH
Copyright © 1995 International Pediatric Research Foundation, Inc.

Vol. 38, No. 5, 1995
Printed in U.S.A.

Growth in Full-Term Small-for-Gestational-Age Infants: From Birth to Final Height

J. KARLBERG AND K. ALBERTSSON-WIKLAND

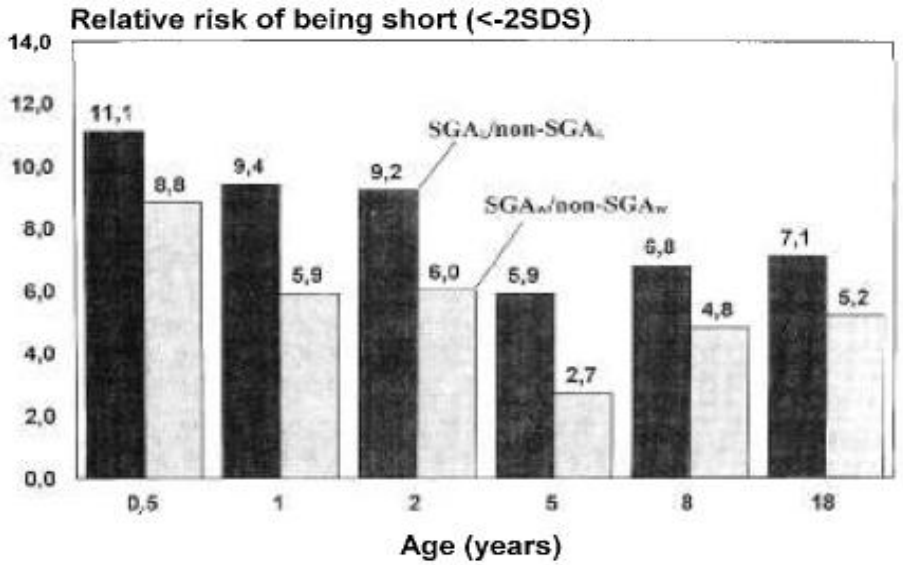


Figure 3. The relative risk of being short at different ages for SGA infants in relation to non-SGA infants. The ratio is given for the two SGA definitions used, *i.e.* a birth length below −2 SDS (SGA_L) or a birth weight below −2 SDS (SGA_W).

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Cianfarani 2008

TABELLA III. Criteri per l'impiego del GH nei bambini SGA secondo la FDA (Food and Drug Administration) e l'EMEA (European Agency for the Evaluation of Medicinal Products).

	FDA	EMEA
Età di inizio (anni)	2	4
Statura	Non definita	≤ -2,5 DS
Velocità di crescita	Non definita	< 0 DS
Confronto con la statura genetica	Non definito	Statura oltre 1 DS al di sotto della statura genetica

2001 2003

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

- Selezione dei pazienti
- Terapia con GH : efficacia sulla statura finale
- Efficacia su altri parametri
- Eterogeneità dei risultati
- Safety

Selezione dei pazienti

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

ALLEGATO 1

NOTA 39

Per poter accedere al trattamento con GH in individui nati SGA è necessario rispondere ai seguenti criteri:

Bambini nati piccoli per l'età gestazionale (SGA - Small for Gestational Age) con età uguale o superiore a 4 anni.

Peso alla nascita nei nati singoli uguale o inferiore a –2 DS (< 3° centile) per l'età gestazionale, basato sulle tabelle di Gagliardi e comunque inferiore a 2500 gr.

Età al momento della proposta di somministrazione del GH uguale o superiore ai 4 anni;

Statura inferiore o uguale a –2.5 DS e velocità di crescita inferiore al 50° centile.

Selezione dei pazienti

Terapia con GH : efficacia sulla statura finale

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Impact of Growth Hormone Therapy on Adult Height of Children Born Small for Gestational Age

Arianna Maiorana and Stefano Cianfarani

Pediatrics 2009

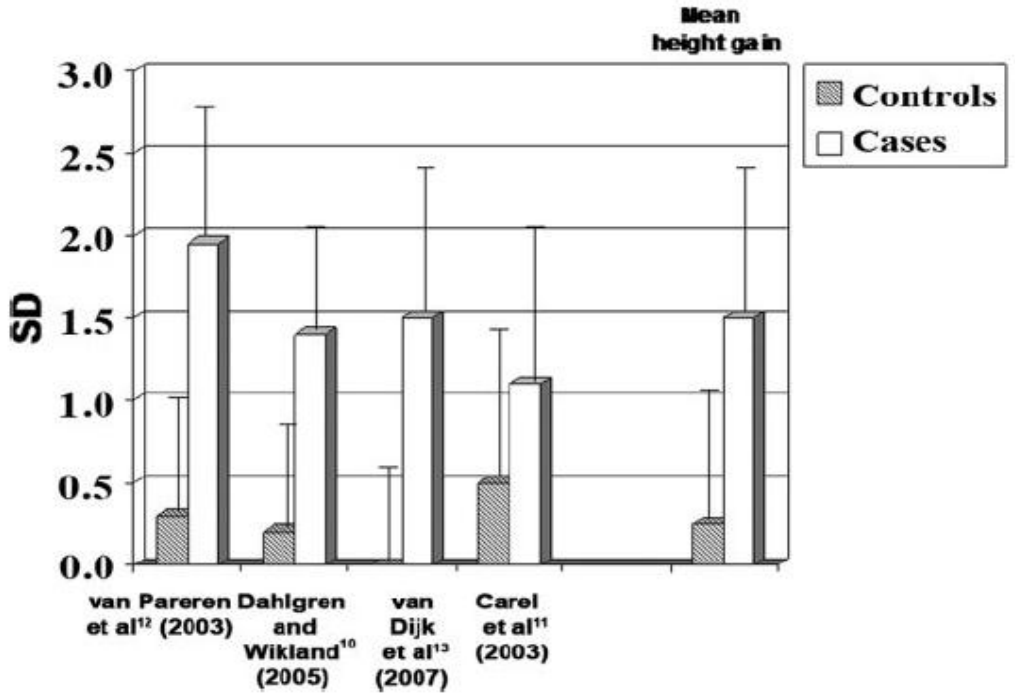


FIGURE 4
Effect of long-term GH therapy on height gain in RCTs.

Selezione dei pazienti

Terapia con GH: efficacia sulla statura finale

Efficacia su altri parametri

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

TERAPIA CON GH

SVILUPPO NEUROCOGNITIVO:
- QI
- Comportamento

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Quality of Life in Adolescents Born Small for Gestational Age: Does Growth Hormone Make a Difference?

Ellen M.N. Bannink[a] Yvonne K. van Pareren[a] Nicolet C.M. Theunissen[b]
Hein Raat[c] Paul G.M. Mulder[d] Anita C.S. Hokken-Koelega[a]

Horm Res 2005

….adolescents born SGA, with a GH-induced improved height, had in many aspects a better QoL than untreated adolescents born SGA, according to the disorder-specific questionnaire.

Table 2. Results of the TACQOL-S

	GH-treated SGA group (n = 24)	Untreated SGA group (n = 15)	Effect size *(d)*	p value
Physical abilities				
HS	90.8 (9.8)[b]	74.3 (19.8)	0.83	0.004
HRQoL	93.6 (7.4)[b]	78.6 (16.6)	0.90	0.002
Vitality[2]				
HS	75.0 (18.4)	65.8 (21.9)	0.42	0.234
HRQoL	79.2 (16.5)	69.6 (23.8)	0.40	0.283
Contact with peers				
HS	81.0 (18.5)	73.8 (21.9)	0.33	0.296
HRQoL	85.7 (16.4)	76.3 (19.9)	0.47	0.110
Contact with adults				
HS	85.2 (10.6)[a]	70.9 (18.8)	0.76	0.017
HRQoL	92.9 (4.4)[b]	80.0 (15.1)	0.85	0.002
Body image				
HS	88.4 (8.0)[a]	74.1 (24.1)	0.59	0.038
HRQoL	91.2 (6.9)	81.8 (20.1)	0.47	0.191

Data are expressed as the mean (±SD). There were no differences between the 2 dosage groups. [a] $p < 0.05$; [b] $p < 0.01$, compared to the untreated group (0 mg/m^2/day). Higher scores = Better health-related QoL (HRQoL)/health status (HS).

[1] Effect size = Positive effect size indicate better QoL in the GH-treated SGA group: $0.2 \leq d < 0.5$ = small effect; $0.5 \leq d < 0.8$ = moderate effect; $d \geq 0.8$ = large effect. Negative effect size (not present) indicates better QoL in the untreated SGA group.

[2] Cronbach's alpha was 0.57.

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

European Journal of Endocrinology (2007) 156 195–201 ISSN 0804-4643

CLINICAL STUDY

Effect of 2 years of high-dose growth hormone therapy on cognitive and psychosocial development in short children born small for gestational age

K Lagrou, J Vanderfaeillie[3], C Froidecoeur, M Thomas, G Massa[8], S Tenoutasse[2], M Craen[4], M C Lebrethon[7], D Beckers[6], I Francois[5], R Rooman[1], G Thiry-Counson[9], C de Beaufort[10] and J De Schepper[3]

In conclusion, the findings of our study **do not support an improvement of cognitive function and behavioral profile** after 2 years of GH therapy in young prepubertal short SGA children.

Table 2 WPPSI-R or WISC-R scores[a] in the treated group (TRG; $n=17$) and in the untreated group (UTRG; $n=17$) at start (T0) and after 2 years (T2).

	At start (T0)	After 2 years (T2)	*P* T0–T2
Total IQ scores			
Total group ($n=34$)	91.7 (16.9)	95.76 (16.9)	
TRG ($n=17$)	93.1 (15.7)	93.5 (16.0)	NS
UTRG ($n=17$)	90.4 (18.4)	98.0 (17.9)	<0.05
P TRG–UTRG	NS	NS	
Verbal IQ scores			
Total group ($n=34$)	91.6 (17.9)	95.9 (17.3)	
TRG ($n=17$)	92.3 (15.6)	93.6 (16.5)	NS
UTRG ($n=17$)	90.9 (20.4)	98.1 (18.3)	<0.01
P TRG–UTRG	NS	NS	
Performance IQ scores			
Total group ($n=34$)	93.5 (15.87)	96.7 (15.5)	
TRG ($n=17$)	94.9 (16.6)	94.8 (15.9)	NS
UTRG ($n=17$)	92.1 (15.3)	98.5 (15.3)	<0.05
P TRG–UTRG	NS	NS	

[a]Data are expressed as mean ± s.d.

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

TERAPIA CON GH

COMPOSIZIONE CORPOREA:
- BMI
- Massa grassa/massa magra
- BMD

SVILUPPO NEUROCOGNITIVO:
- QI
- Comportamento

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Body Composition, Blood Pressure, and Lipid Metabolism before and during Long-Term Growth Hormone (GH) Treatment in Children with Short Stature Born Small for Gestational Age Either with or without GH Deficiency*

THEO SAS, PAUL MULDER, AND ANITA HOKKEN-KOELEGA

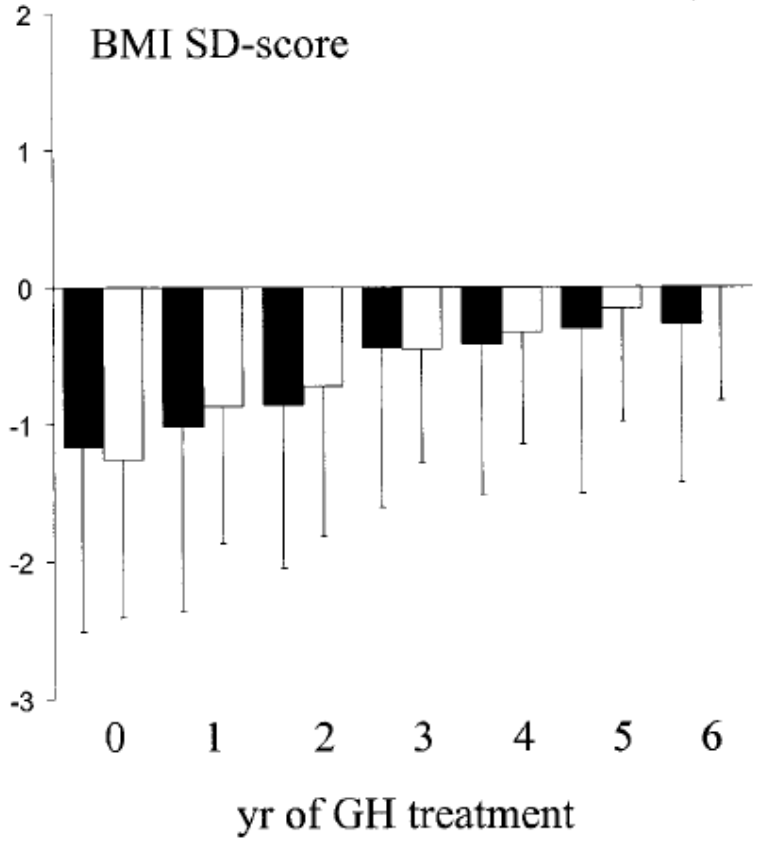


FIG. 1. Mean (SD) BMI SD-score before and during 6 yr of GH treatment for group A (■) and for group B (□).

J Clin Endocrinol Metab 2000

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Longitudinal Changes in Insulin Sensitivity and Body Composition of Small-For-Gestational-Age Adolescents after Cessation of Growth Hormone Treatment

Ruben H. Willemsen, Sten P. Willemsen, and Anita C. S. Hokken-Koelega

J Clin Endocrinol Metab 2008

TABLE 2. Longitudinal changes in body composition after stop of GH treatment

	SGA on GH, mean (95% CI)	SGA after stop GH, mean (95% CI)	*P* value, on *vs.* off GH	AGA, mean (95% CI)
Percent fat SDS[a]	−0.20 (−0.53–0.12)	0.14 (−0.16–0.44)	<0.0005	0.26 (−0.06–0.58)
FM SDS_{height}[b]	−0.04 (−0.32–0.23)	0.25 (−0.01–0.49)	<0.0005	0.30 (0.01–0.60)
LBM SDS_{height}[b]	0.06 (−0.27–0.39)	−0.21 (−0.53–0.12)	<0.0005	−0.41 (−0.80 to −0.03)
Trunk fat/total fat ratio	0.50[c] (0.48–0.51)	0.49 (0.48–0.50)	0.158	0.47 (0.45–0.49)
BMI SDS	0.05 (−0.20–0.29)	0.03 (−0.22–0.27)	0.648	−0.01 (−0.40–0.38)

CI, Confidence interval.

[a] SDS adjusted for age and sex.

[b] SDS_{height} adjusted for height and sex.

[c] $P < 0.05$ *vs.* AGA.

Discontinuation of GH treatment is, however,also associated with an increase in percent body fat and with a decrease in lean body mass,without changes in fat distribution.

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Long-term effects of growth hormone (GH) treatment on body composition and bone mineral density in short children born small-for-gestational-age: six-year follow-up of a randomized controlled GH trial

Ruben H. Willemsen*, Nicolette J. T. Arends*, Willie M. Bakker-van Waarde†, Maarten Jansen‡, Edgar G. A. H. van Mil§, Jaap Mulder¶, Roelof J. Odink**, Maarten Reeser††, Ciska Rongen-Westerlaken‡‡, Wilhelmina H. Stokvis-Brantsma§§, Johan J. J. Waelkens** and Anita C. S. Hokken-Koelega*

Clinical Endocrinology 2007

Table 4. Six-year changes in lumbar spine bone mineral density (BMD_{LS}) and bone mineral apparent density ($BMAD_{LS}$) SDS of the GH- and control groups

	SGA GH group
BMD_{LS} SDS	
Baseline	−1·5 (1·0)‡
1-year	−0·8 (0·8)†,**
2-year	−0·4 (0·8)**,††
3-year	−0·1 (0·6)**,‡‡
4-year	−0·2 (0·7)**,††
5-year	−0·3 (0·6)**
6-year	−0·3 (0·7)**,††
$BMAD_{LS}$ SDS	
Baseline	−0·7 (1·3)*
1-year	−0·4 (1·0)
2-year	−0·3 (1·0)¶
3-year	0·1 (0·9)**
4-year	0·0 (1·1)**
5-year	−0·2 (0·9)
6-year	−0·2 (1·0)§

Selezione dei pazienti
Terapia con GH: efficacia sulla statura finale
Efficacia su altri parametri

Eterogeneità dei risultati

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Impact of Growth Hormone Therapy on Adult Height of Children Born Small for Gestational Age

Arianna Maiorana and Stefano Cianfarani

Pediatrics 2009

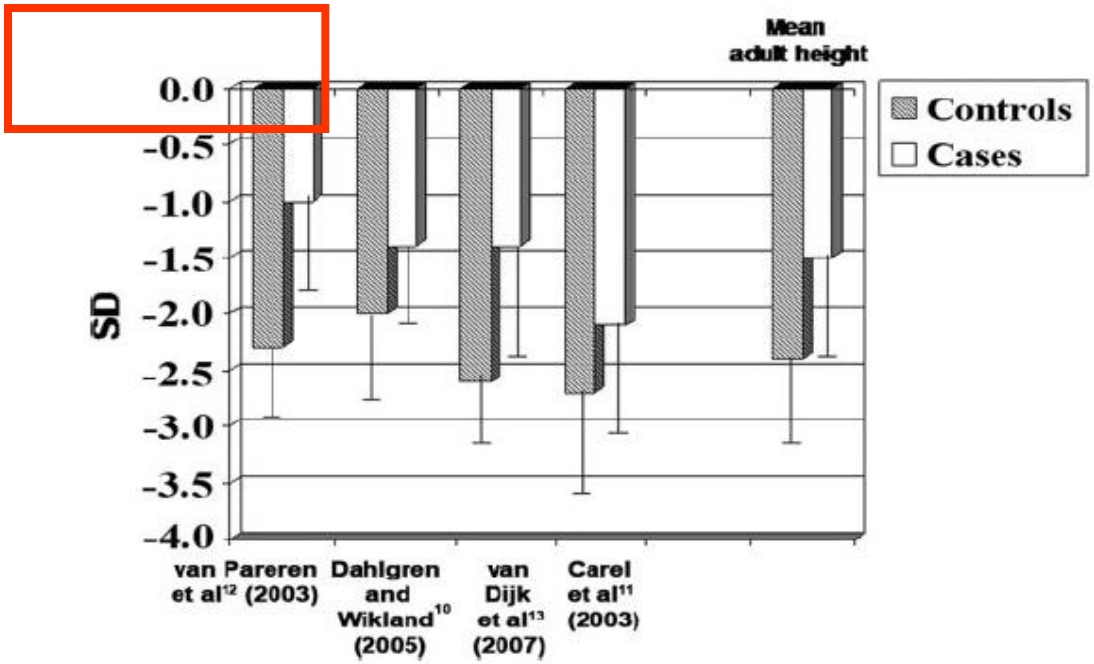


FIGURE 3
Effect of long-term GH therapy on adult height in RCTs.

Improvement in Adult Height after Growth Hormone Treatment in Adolescents with Short Stature Born Small for Gestational Age: Results of a Randomized Controlled Study

JEAN-CLAUDE CAREL, PIERRE CHATELAIN, PIERRE ROCHICCIOLI, AND JEAN-LOUIS CHAUSSAIN

GH induced a mean gain in adult height of 0.6 SDS units, allowing 47% of treated children to attain adult heights in the normal range.
Gain was directly correlated to treatment duration.

J Clin Endocrinol Metab 2003

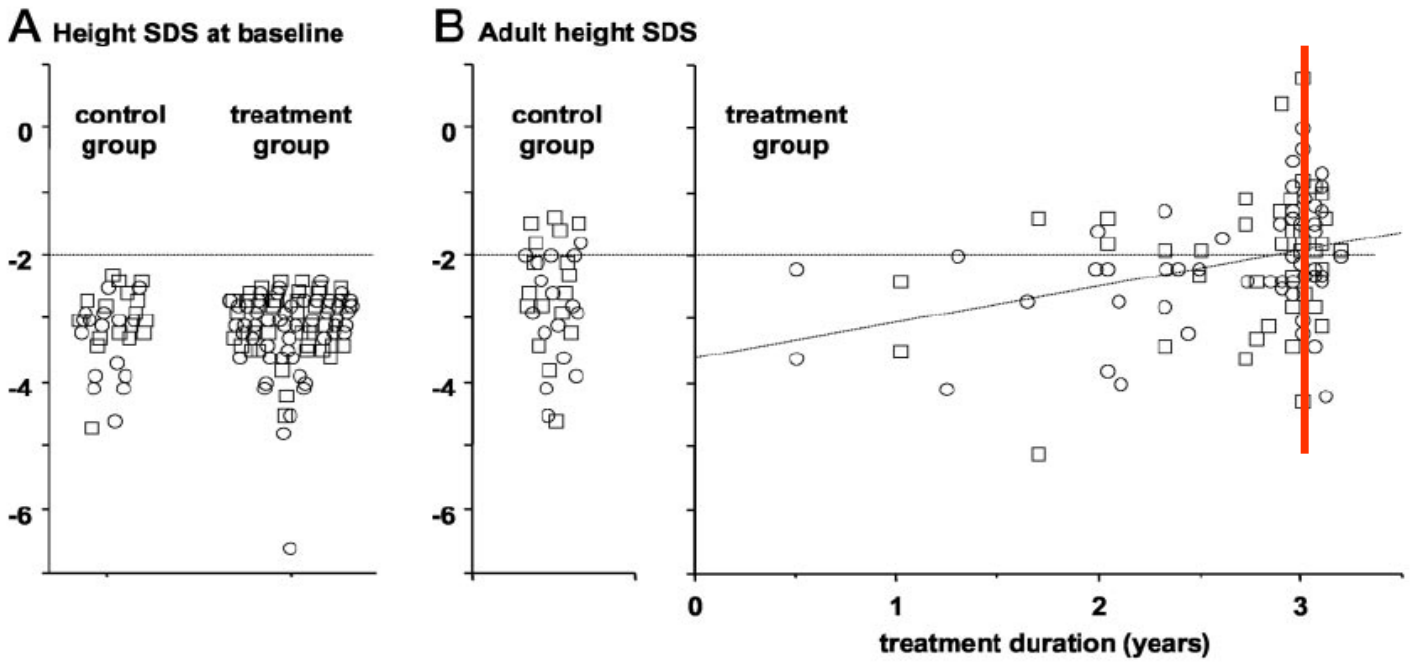


FIG. 2. Baseline (A) and adult (B) heights expressed in SDS in control and treated boys (□) and girls (○); the *horizontal dashed line* represents −2 SDS; the univariate correlation between treatment duration and adult height is also presented (*sloping dashed line*).

Eterogeneità dei risultati

- eterogeneità delle cause degli SGA

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Small for Gestational Age: Short Stature and Beyond

Paul Saenger, Paul Czernichow, Ieuan Hughes, and Edward O. Reiter

Endocrine Reviews 2007

TABLE 1. Factors associated with IUGR

Medical complications
Preeclampsia
Acute or chronic hypertension
Antepartum hemorrhage
Severe chronic disease
Severe chronic infections
Systemic lupus erythematosus
Antiphospholipid syndrome
Anemia
Malignancy
Abnormalities of the uterus
Uterine fibroids
Maternal social conditions
Malnutrition
Low pregnancy BMI
Low maternal weight gain
Delivery at age <16 or >35 yr
Low socioeconomic status
Drug use
Smoking
Alcohol
Illicit drugs
Fetal problems
Multiple births
Malformation
Chromosomal abnormalities
Inborn errors of metabolism
Intrauterine infections
Environmental problems
High altitude
Toxic substances
Abnormalities of the placenta
Reduced blood flow
Reduced area for exchange
Infarcts
Hematomas
Partial abruption

Adapted from Bryan and Hindmarsh (48).

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Is the Response to Growth Hormone in Short Children Born Small for Gestational Age Dependent on Genetic or Maternal Factors?

Horm Res 2009

O. Mehls[a] A. Lindberg[c] M. Bettendorf[b] H.-G. Doerr[d] B.P. Hauffa[e] S. Kaspers[f]
T. Rohrer[g] N. Stahnke[h] M.B. Ranke[i] on behalf of the German KIGS Board

Table 2. Growth response to GH treatment during first and second treatment year

	All patients	Silver Russell syndrome	Congenital heart defect	Smoking of mother	Serious infection of mother	Others	p*
Height velocity, cm/1st year	10.0 ± 1.85	10.3 ± 1.94	10.1 ± 1.66	9.7 ± 1.57	9.7 ± 1.72	9.9 ± 1.98	n.s.
Δ Height velocity (height velocity 1st year – height velocity pretreatment year), cm	4.54 ± 1.99	4.16 ± 2.02	4.02 ± 1.62	4.72 ± 1.97	5.99 ± 1.58	4.55 ± 1.81	n.s.
Δ Height velocity (height velocity 2nd year – height velocity pretreatment year), cm	2.43 ± 1.75	2.18 ± 2.06	1.57 ± 1.62	2.37 ± 1.68	3.54 ± 1.80	2.48 ± 1.83	n.s.
Height response (Δ height – SDS 1st year)	1.03 ± 0.56	1.12 ± 0.7	1.28 ± 0.19	0.98 ± 0.59	0.98 ± 0.73	1.07 ± 0.54	n.s.
Height response (Δ height – SDS per 2 years)	1.55 ± 0.67	1.78 ± 0.8	1.50 ± 0.58	1.50 ± 0.54	1.56 ± 0.59	1.59 ± 0.62	n.s.

* Kruskal-Wallis test. n.s. = Not significant.

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Subclassification of Small for Gestational Age Children with Persistent Short Stature: Growth Patterns and Response to GH Treatment

Wietske Ester[a] Ellen Bannink[a] Marije van Dijk[a] Ruben Willemsen[a]
Danielle van der Kaay[a] Maria de Ridder[b] Anita Hokken-Koelega[a]

Horm Res 2008

Table 3. Effect of GH treatment on growth parameters in the total population and in the short SGA groups

		Total	SGA_L	SGA_{L+W}	SGA_{L+W+HC}	p value*
Sex	boys/girls	75/68	24/29	23/22	28/17	0.24
Age at start	years	6.81 ± 2.29	7.12 ± 2.42	6.49 ± 2.28	6.79 ± 2.14	0.40
GH dose	mg/m²/day	1.11 ± 0.29	1.10 ± 0.28	1.13 ± 0.31	1.09 ± 0.29	0.76
Height						
Start[1]	SDS	−3.04 ± 0.62	−3.05 ± 0.62	−3.10 ± 0.62	−2.96 ± 0.62	0.54
After 1 year[2]	SDS	−2.18 ± 0.65	−2.25 ± 0.64	−2.21 ± 0.64	−2.07 ± 0.63	0.35
Changes during 1 year[2]	SDS	0.86 ± 0.36	0.81 ± 0.24	0.89 ± 0.24	0.89 ± 0.24	0.13
Weight						
Start[1]	SDS	−3.00 ± 0.92	−2.59 ± 0.85	−3.32 ± 0.85	−3.18 ± 0.85	0.00007[a]
After 1 year[2]	SDS	−2.22 ± 0.87	−1.92 ± 0.84	−2.50 ± 0.84	−2.29 ± 0.84	0.003[a]
Changes during 1 year[2]	SDS	0.78 ± 0.43	0.67 ± 0.37	0.82 ± 0.37	0.88 ± 0.37	0.02[b]
HC						
Start[1]	SDS	−1.11 ± 0.88	−0.77 ± 0.85	−1.19 ± 0.85	−1.43 ± 0.85	0.002[a]
After 1 year[2]	SDS	−0.80 ± 0.92	−0.46 ± 0.87	−0.88 ± 0.87	−1.12 ± 0.87	0.001[a]
Changes during 1 year[2]	SDS	0.31 ± 0.39	0.30 ± 0.36	0.33 ± 0.37	0.31 ± 0.36	0.91

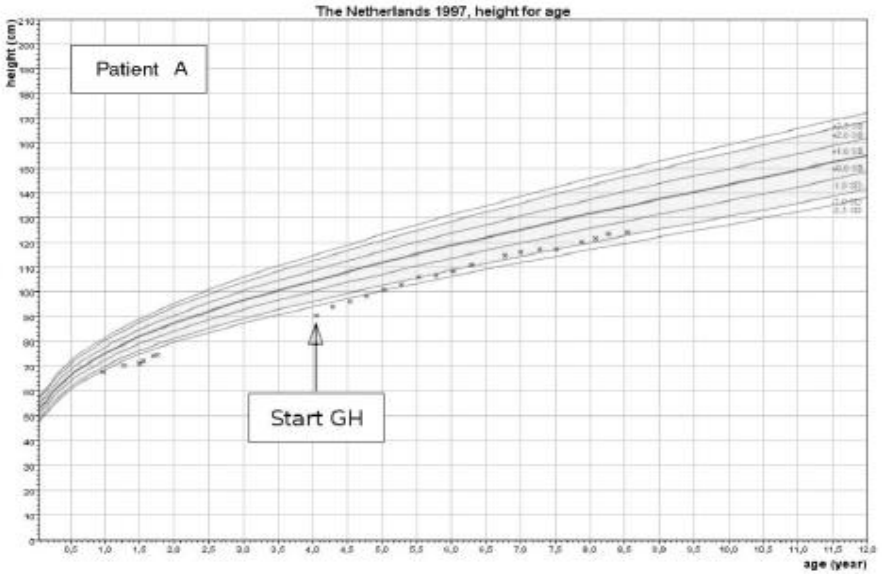
Values are means (SD).
HC = Head circumference; SDS = standard deviation score.
* Overall p value is presented of the SGA groups.
Post-hoc testing showed: [a] SGA_L differed in comparison to the SGA_{L+W} and SGA_{L+W+HC} groups; [b] the SGA_L group differed from the SGA_{L+W+HC} group.
[1] Means are adjusted for age at start of GH treatment.
[2] Means are adjusted for age at start of GH treatment and GH dose.

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Two Short Children Born Small for Gestational Age with Insulin-Like Growth Factor 1 Receptor Haploinsufficiency Illustrate the Heterogeneity of Its Phenotype

Wietske A. Ester, Hermine A. van Duyvenvoorde, Caroline C. de Wit, Alexander J. Broekman, Claudia A. L. Ruivenkamp, Lutgarde C. P. Govaerts, Jan M. Wit, Anita C. S. Hokken-Koelega, and Monique Losekoot

J Clin Endocrinol Metab 2009



Efficacia del trattamento con GH nello SGA e suoi effetti secondari

European Journal of Endocrinology (2009) **160** 557–560 ISSN 0804-4643

CLINICAL STUDY

Smallness for gestational age interacts with high mobility group A2 gene genetic variation to modulate height

Nabila Bouatia-Naji[1,2,3,4], Marion Marchand[3,4], Christine Cavalcanti-Proença[3,4], Samia Daghmoun[1,2], Emmanuelle Durand[1,2], Jean Tichet[5], Michel Marre[6,7], Beverley Balkau[8], Philippe Froguel[3,4,9] and Claire Lévy-Marchal[1,2]

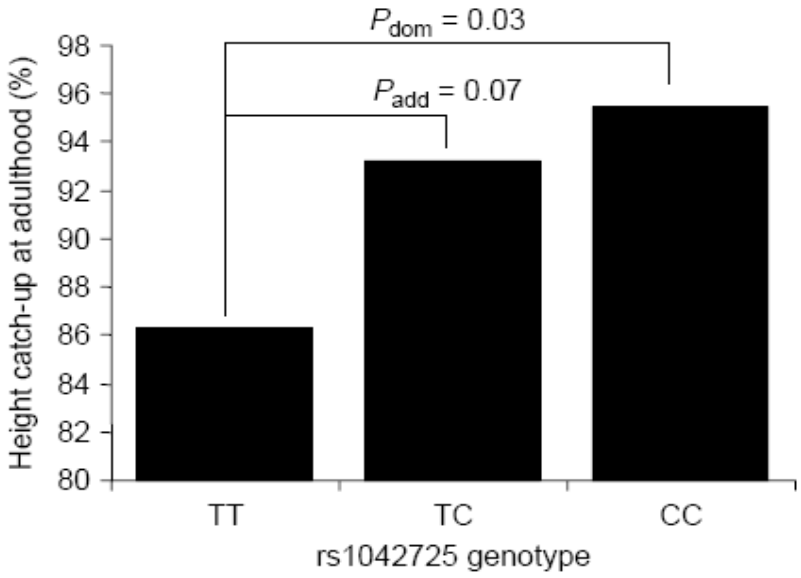


Figure 1 Height catch-up at adulthood in SGA men. Height catch-up was defined as height at examination above −2 S.D. of mean height in AGA participants. *P* value is for χ^2 test comparing height catch-up frequency in TT genotype carriers (n=95) versus CT or CC genotype carriers (n=147 and n=66 respectively). *P* values are indicated for the additive (P_{add}) and dominant (P_{dom}) models.

SGA men carrying at least one C allele copy of rs1042725 show an increased height catch-up frequency at adulthood (PdomZ0.03; PaddZ0.07)

Eterogeneità dei risultati

- eterogeneità delle cause degli SGA

- target genetico

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Prediction of Response to Growth Hormone Treatment in Short Children Born Small for Gestational Age: Analysis of Data from KIGS (Pharmacia International Growth Database)

MICHAEL B. RANKE, ANDERS LINDBERG, CHRISTOPHER T. COWELL, KERSTIN ALBERTSSON WIKLAND, EDWARD O. REITER, PATRICK WILTON, AND DAVID A. PRICE, ON BEHALF OF THE KIGS INTERNATIONAL BOARD

J Clin Endocrinol Metab 2003

TABLE 3. Regression equation variables for predicting the first-year growth response (cm/yr) to GH therapy in 613 children born SGA

	Parameter estimate	Rank	Partial R^2
Intercept (constant)	9.4		
Age at start (yr)	−0.31	2	0.11
Weight SD score at start	0.30	3	0.05
GH dose (mg/kg · d)	56.51	1	0.35
MPH SD score	0.11	4	0.01
R^2	0.52		
Error SD (cm)	1.3		

Eterogeneità dei risultati

- eterogeneità delle cause degli SGA
- target genetico
- **età di inizio della terapia**

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Prediction of Response to Growth Hormone Treatment in Short Children Born Small for Gestational Age: Analysis of Data from KIGS (Pharmacia International Growth Database)

MICHAEL B. RANKE, ANDERS LINDBERG, CHRISTOPHER T. COWELL, KERSTIN ALBERTSSON WIKLAND, EDWARD O. REITER, PATRICK WILTON, AND DAVID A. PRICE, ON BEHALF OF THE KIGS INTERNATIONAL BOARD

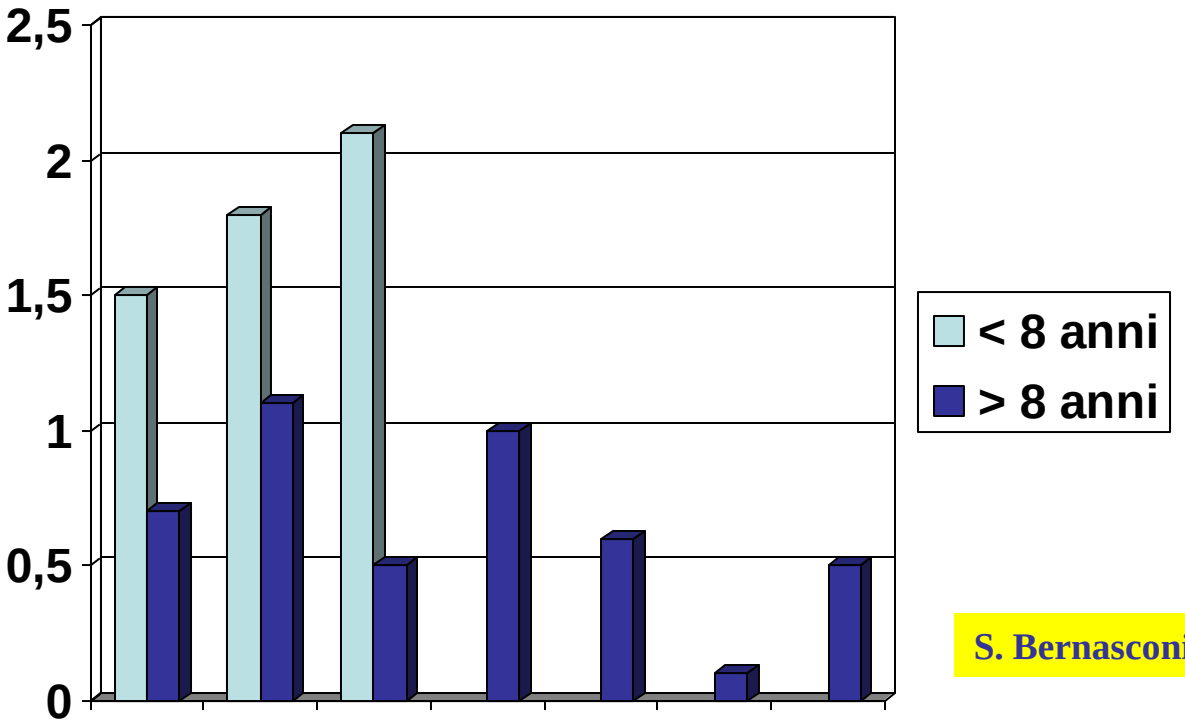
J Clin Endocrinol Metab 2003

TABLE 3. Regression equation variables for predicting the first-year growth response (cm/yr) to GH therapy in 613 children born SGA

	Parameter estimate	Rank	Partial R^2
Intercept (constant)	9.4		
Age at start (yr)	−0.31	2	0.11
Weight SD score at start	0.30	3	0.05
GH dose (mg/kg · d)	56.51	1	0.35
MPH SD score	0.11	4	0.01
R^2	0.52		
Error SD (cm)	1.3		

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Guadagno di statura finale (SDS) in funzione dell'età di inizio della terapia con GH (da 10 studi pubblicati)



Eterogeneità dei risultati

- eterogeneità delle cause degli SGA
- target genetico
- età di inizio della terapia
- **dose di GH**

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Cianfarani 2008

TABELLA III. Criteri per l'impiego del GH nei bambini SGA secondo la FDA (Food and Drug Administration) e l'EMEA (European Agency for the Evaluation of Medicinal Products).

	FDA	EMEA
Età di inizio (anni)	2	4
Statura	Non definita	≤ -2,5 DS
Velocità di crescita	Non definita	< 0 DS
Confronto con la statura genetica	Non definito	Statura oltre 1 DS al di sotto della statura genetica
Dose (μg/kg/die)	70	35

2001 2003

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Growth response to an individualized versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study

Heike Jung, Christof Land[1], Claudia Nicolay, Jean De Schepper[2,3], Werner F Blum and Eckhard Schönau[1]

European Journal of Endocrinology 2009

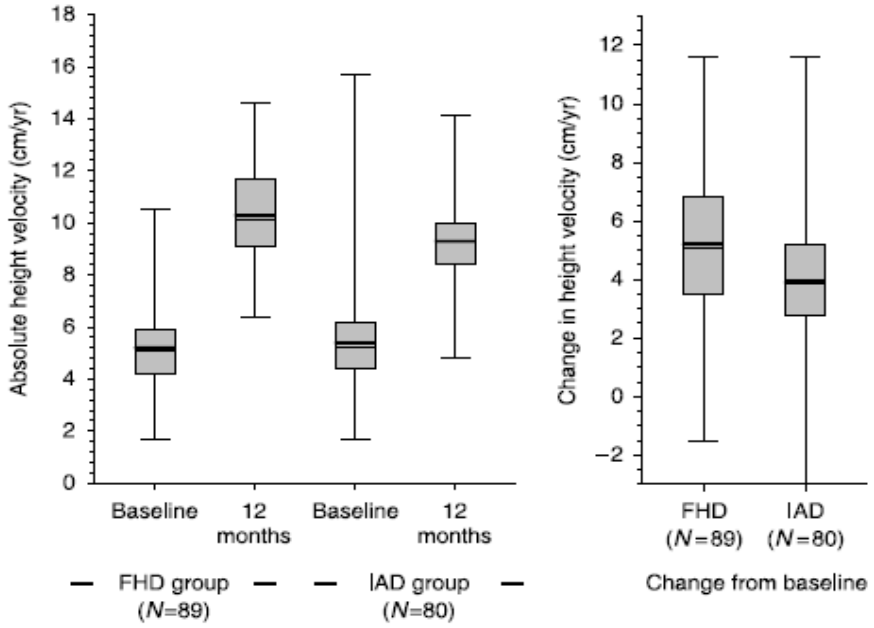


Figure 3 Height velocity at baseline and after 12 months of GH treatment at either a fixed high dose (FHD) or individually adjusted dose (IAD); box plots present mean (fat line), median (slim line), 25th and 75th percentiles (box), minimum and maximum values (whiskers).

Eterogeneità dei risultati

- eterogeneità delle cause degli SGA
- target genetico
- età di inizio della terapia
- dose di GH
- **polimorfismo del recettore del GH**

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

GH responsiveness in a large multinational cohort of SGA children with short stature (NESTEGG) is related to the exon 3 GHR polymorphism

M. Tauber*†, W. Ester‡, F. Auriol*, C. Molinas*, J. Fauvelt§, J. Caliebe¶, T. Nugenttt, L. Fryklund**, M. B. Ranke¶, M. O. Savagett, A. J. L. Clarktt, L. B. Johnstontt and A. C. S. Hokken-Koelega‡ on behalf of the NESTEGG group

J Clin Endocrinol Metab 2007

The *exon 3-deleted/full-length* Growth Hormone Receptor Polymorphism Does Not Influence the Effect of Puberty or Growth Hormone Therapy on Glucose Homeostasis in Short Non-Growth Hormone-Deficient Small-for-Gestational-Age Children: Results from a Two-Year Controlled Prospective Study

L. Audí,* A. Carrascosa,* C. Esteban, M. Fernández-Cancio, P. Andaluz, D. Yeste, R. Espadero, M. L. Granada, H. Wollmann, L. Fryklund and the Spanish SGA Study Group

J Clin Endocrinol Metab 2008

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Growth Hormone Receptor Exon 3 Isoforms and Their Implication in Growth Disorders and Treatment

Horm Res 2009

Alexander A.L. Jorge Ivo J.P. Arnhold

Table 2. Common confounding factors observed in association studies that evaluated the *GHR* exon 3 genotype

Confounding factors	Suggestions for future studies
Type 1 error (false-positive results caused by multiple tests or small sample size) and type 2 error (false-negative results due to scarcity of sufficient power to generate reliable and reproducible results)	– Large prospective studies to achieve a large enough sample size for sufficient power – Meta-analysis studies – In the case of multiple tests, adopt appropriate statistical significance levels for interpreting results – Choose adequate endpoints and the best statistical strategy to optimize results and avoid false-positive results caused by statistical error – Avoid subgroup analysis
Genotype error	– For *GHR* exon 3 genotype, always confirm *GHR*d3 homozygous status – Routinely confirm 10% of genotyped samples, to assess the presence of genotype error
Phenotype error	– Analysis of homogeneous populations
Population stratification	– Use genomic control to assess population stratification

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Selezione dei pazienti
Terapia con GH: efficacia sulla statura finale
Efficacia su altri parametri
Eterogeneità dei risultati

Safety

INSULINO-RESISTENZA

Rischio stimato maggiore in soggetti SGA che vanno incontro a <u>catch-up growth spontaneo</u>

→ non candidati alla terapia con GH

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Insulin Sensitivity Decreases in Short Children Born Small for Gestational Age Treated with Growth Hormone

SARA BACHMANN, MD, SUSANNE BECHTOLD, MD, WALTER BONFIG, MD, STEPHANIE PUTZKER, MD, MATTHIAS BUCKL, MD, AND HANS PETER SCHWARZ, MD, PHD

J Pediatr 2009

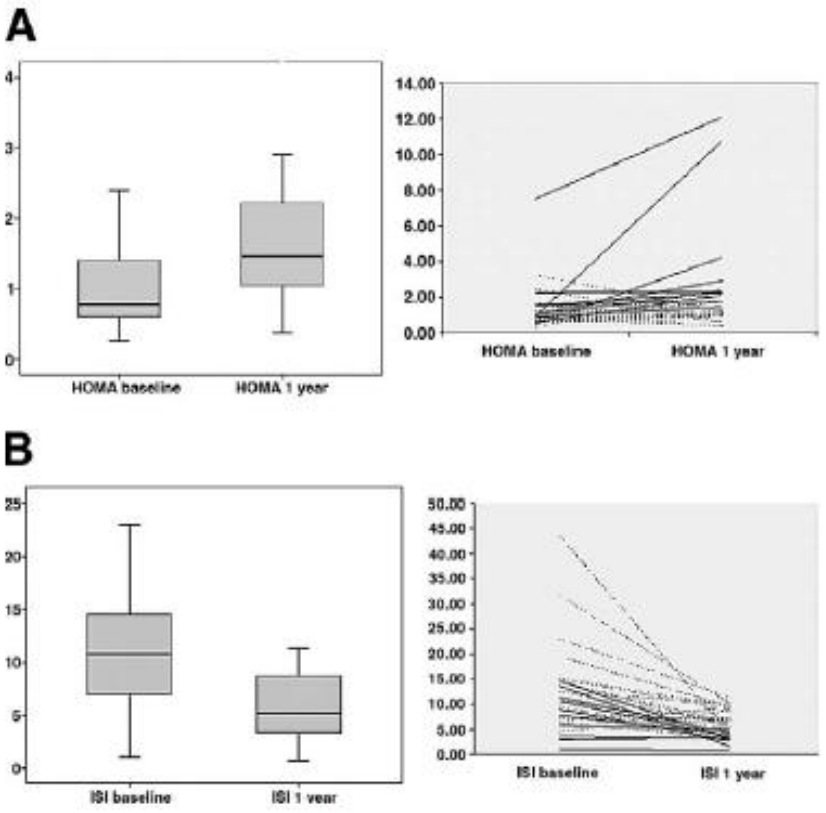


Figure 1. A, Changes in HOMA after 1 year of GH treatment ($P = .02$), and **B,** Changes in ISI after 1 year of GH treatment ($P < .001$). Left panels: Boxplots showing medians, first and third quartiles and ranges, extreme values excluded. Right panels: Individual patient values. Continuous lines represent pubertal children; dashed lines represent prepubertal children.

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Small for Gestational Age: Short Stature and Beyond

Paul Saenger, Paul Czernichow, Ieuan Hughes, and Edward O. Reiter

Endocrine Reviews 2007

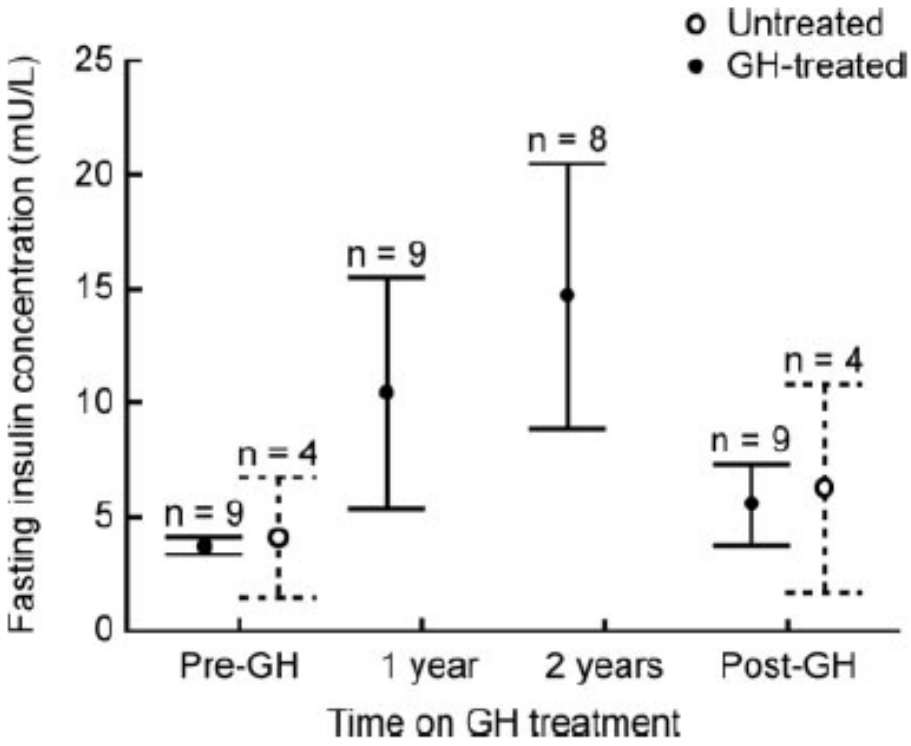


FIG. 14. Fasting insulin concentrations (mean and 95% confidence intervals) in untreated short children born SGA and in those receiving GH therapy at a dose of 100 μg/kg·d for up to 2 yr. [Adapted with permission from de Zegher *et al.* (357).]

Efficacia del trattamento con GH nello SGA e suoi effetti secondari

Risk Factors for Diabetes Mellitus Type 2 and Metabolic Syndrome Are Comparable for Previously Growth Hormone-Treated Young Adults Born Small for Gestational Age (SGA) and Untreated Short SGA Controls

J Clin Endocrinol Metab 2007

Marije van Dijk, Ellen M. N. Bannink, Yvonne K. van Pareren, Paul G. H. Mulder, and Anita C. S. Hokken-Koelega

TABLE 3. BP, BMI, serum lipids, and IGF-I and IGFBP-3 levels in previously GH-treated SGA subjects and untreated SGA controls

	GH-treated SGA group				Untreated short SGA controls
	Baseline	6 yr of GH	6 months after GH	6.5 yr after GH	
Glucose (mmol/liter)	4.2 (1.0)	5.0 (0.6)[a]	4.7 (0.5)	4.9 (0.5)[a,b]	5.0 (0.4)
Insulin (mU/liter)	6.2 (3.5)	16.0 (8.0)[c]	8.8 (7.4)	9.3 (3.9)[c]	10.7 (5.4)
Fasting G/I	1.1 (1.4)	0.4 (0.2)	0.7 (0.4)	0.6 (0.2)	0.6 (0.3)
HbA1c (%)	5.0 (0.3)	4.8 (0.4)[c]	4.7 (0.4)[c]	5.2 (0.3)[d,e]	5.4 (0.3)
Systolic BP (mm Hg)	106.7 (11.1)	111.4 (12.7)[f]	115.3 (12.6)[c]	111.9 (8.9)	121.5 (11.6)
Diastolic BP (mm Hg)	57.9 (9.5)	55.7 (7.2)	59.4 (9.2)	63.8 (6.3)[a,b,g]	75.7 (6.3)
Systolic BP SDS	1.1 (0.9)[h]	0.3 (1.2)[c]	0.3 (1.2)[c]	0.0 (1.7)[c,g]	1.3 (0.9)
Diastolic BP SDS	0.0 (1.1)	−0.5 (0.6)[a,f]	0.3 (0.8)	0.1 (0.6)[b,f,g]	1.0 (0.5)[h]
BMI (kg/m²)	14.7 (1.8)	19.1 (2.8)[c]	20.6 (2.8)[c]	22.4 (2.2)[c,d]	22.6 (3.3)
BMI SDS	−0.9 (1.3)[c]	0.1 (1.0)[c]	0.2 (1.0)[c]	−0.1 (0.7)[c]	0.2 (1.2)
Waist circumference (cm)				74.9 (6.7)	74.9 (9.2)
Cholesterol (mmol/liter)	4.6 (0.8)	3.6 (0.6)[c]	4.1 (0.6)[c]	4.3 (0.8)[f,b,e]	4.8 (1.1)
LDL-c (mmol/liter)	2.8 (0.8)	2.2 (0.6)[c]	2.5 (0.6)[c]	2.6 (0.7)[c]	
HDL-c (mmol/liter)	1.4 (0.3)	1.1 (0.2)[c]	1.1 (0.2)[c]	1.3 (0.3)[d]	1.2 (0.3)
TGs (mmol/liter)	1.0 (0.6)	1.4 (0.8)	1.2 (0.6)	1.4 (1.3)	1.0 (0.6)
IGF-I SDS	−0.9 (1.1)[h]	1.9 (0.7)[c,h]		−0.4 (0.7)[f,j]	−0.6 (1.0)[j]
IGFBP-3 SDS	−0.9 (0.9)[h]	1.2 (1.0)[c,h]		−1.6 (0.6)[c,e,h]	−1.2 (0.7)[h]

S.BERNASCONI
DIPARTIMENTO DELL'ETA' EVOLUTIVA
UNIVERSITA' DI PARMA

PERCORSI DECISIONALI PER LA GESTIONE DEL BAMBINO E DELL'ADOLESCENTE

SHOX-D: una nuova indicazione per la terapia con rhGH

sbernasconi@ao.pr.it

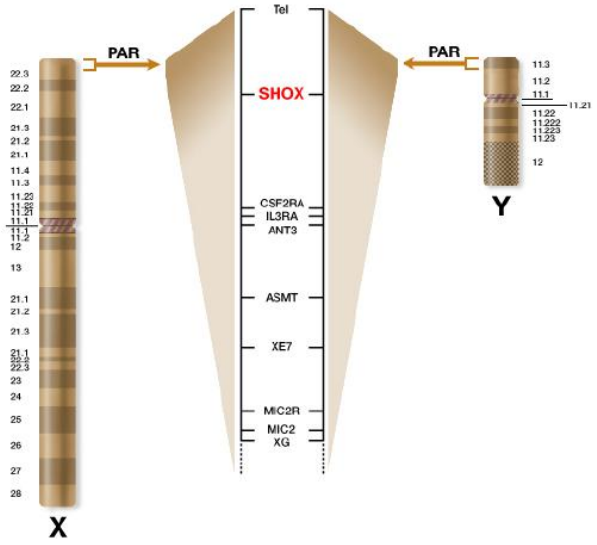
FAMAGOSTA12-17 GIUGNO 2010

SHOX-D: una nuova indicazione per la terapia con rhGH

Il gene viene definito come Short Stature Homeobox-containing gene (gene della bassa statura contenente homeobox – SHOX)

SHOX-D: una nuova indicazione per la terapia con rhGH

***SHORT STATURE HOMEBOX containing gene (SHOX)* è un gene collocato sui cromosomi sessuali umani (X ed Y)**



- **Due coppie attive del gene SHOX sono necessarie per un normale sviluppo**

SHOX-D: una nuova indicazione per la terapia con rhGH

- Mutazioni/Delezioni SHOX e fenotipo

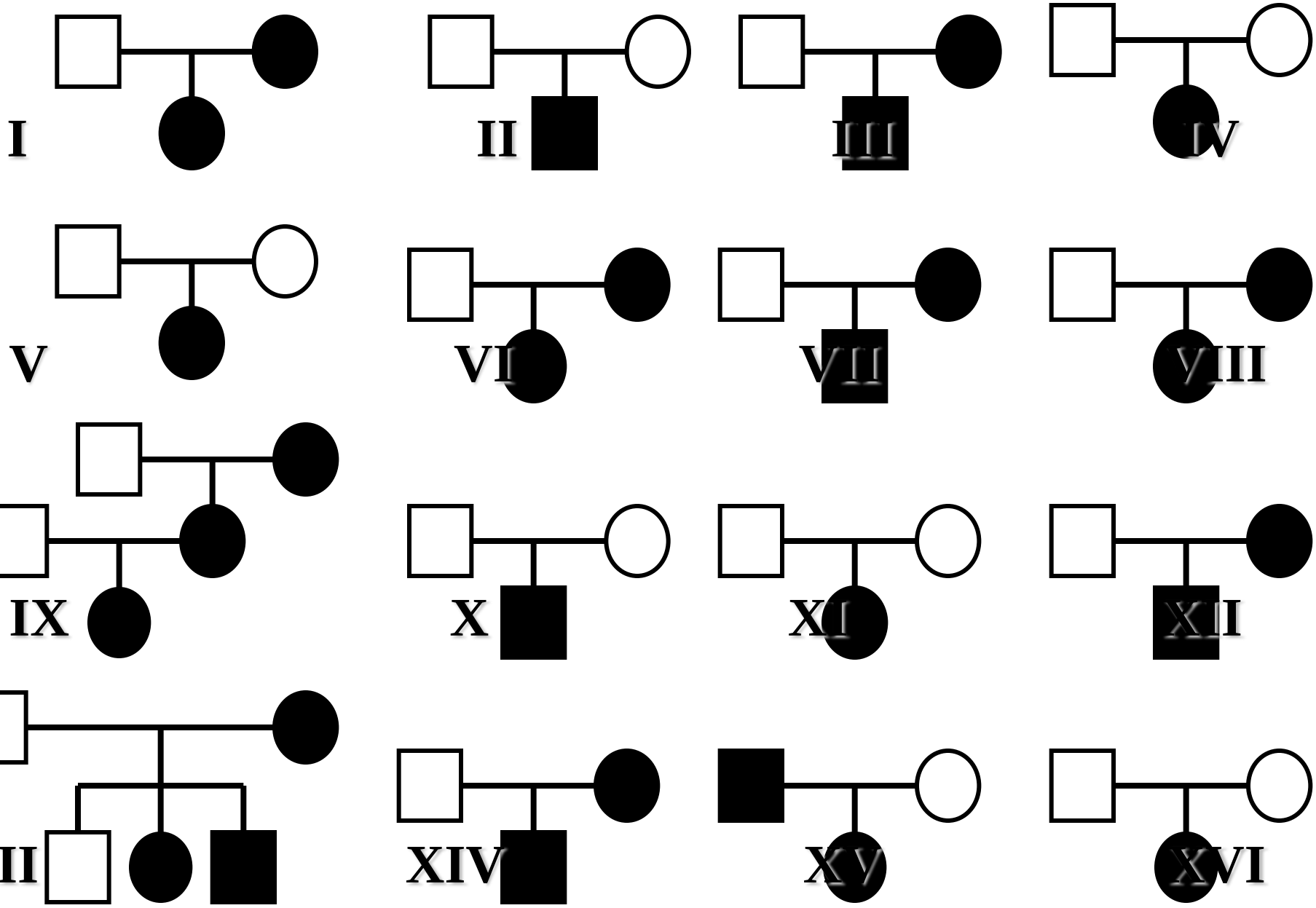
ALTERAZIONI GENETICHE E OSTEOCONDRODISPLASIE

Sindrome	Cromosoma	Gene/Proteina	Ereditarietà
Displasia tanatofora	4p	FGFR3	AD
Acondroplasia	4p	FGFR3	AD
Ipocondroplasia	4p	FGFR3	AD
Displasia diastrofica	5q	DTDST	AR
Acondrogenesi 1B	5q	DTDST	AR
Pseudoacondroplasia	19p	COMP	AD
SEDC	2q	Coll Tipo II	AD
SEMD	12q	Coll Tipo II	AD
Displasia di Kniest	12q	Coll Tipo II	AD
Displasia di Stickler	12q/6p	Coll Tipo II/XI	AD
Displasia metafisaria di Schmid	6q	Coll Tipo X	AD
Condrodisplasia punctata	Xp	Arilsulfatasi E	XLR
Displasia metafisaria tipo Jansen	3p	PTH recettore	AD
Leri-Weill	Xp	SHOX	AD
Langer	Xp	SHOX	AD

SINDROME di LERI-WEILL: STUDIO MULTICENTRICO ITALIANO

TO - De Sanctis
BS - Buzi
BZ - Radetti
MI - Chiumello,Weber
PV- Cisternino,Danesino
PD - Tenconi
PR - Ghizzoni
Roma - Pasquino,Borrelli
CH - Chiarelli
ME - De Luca

LWD FAMILIES



SHOX point mutations and deletions in Leri-Weill dyschondrosteosis

- *SHOX* (Short HOmeoboX containing) gene mutations have been investigated in 21 unrelated families affected by Leri-Weill dyschondrosteosis (LWD), included in the study because of the presence of Madelung deformity of the forearms and disproportionate stature.

- Ten out of the 21 families studied showed *SHOX* gene deletions. In the remaining 11 families, sequence analysis showed three novel point mutations (one frameshift and two missense).

- Thirteen out of 21 (62%) families with typical LWD harbour a *SHOX* gene mutation; point mutations, predominantly involving the homeobox region, occur less frequently than large deletions.

***Journal of Medical Genetics* 2002;39:e33-e33**

Leri and Weill

Une affection congénital et symétrique du developpement osseux: la dyschondrostéose

Bull. Mém. Soc. Med. Hosp. 1929

Sindrome di Leri Weill (OMIM 127300). Quadro clinico

- Apparato scheletrico
- osteocondrodisplasia
- Crescita
- basssa statura/nanismo mesomelico
- Facies
- normale
- Arti
- deformità di Madelung
- avambraccio corto
- radio e/o ulna ipoplasici
- dislocazione dorsale dell'ulna distale
- tibia corta

- Articolazioni
- limitazione dei movimenti di polsi e gomiti
- Sviluppo mentale
- normale
- Incidenza
- rapporto maschi/femmine 1:4
- Ereditarietà
- autosomica dominante

SHOX-D: una nuova indicazione per la terapia con rhGH ed un nuovo sub-study in GeNeSIS

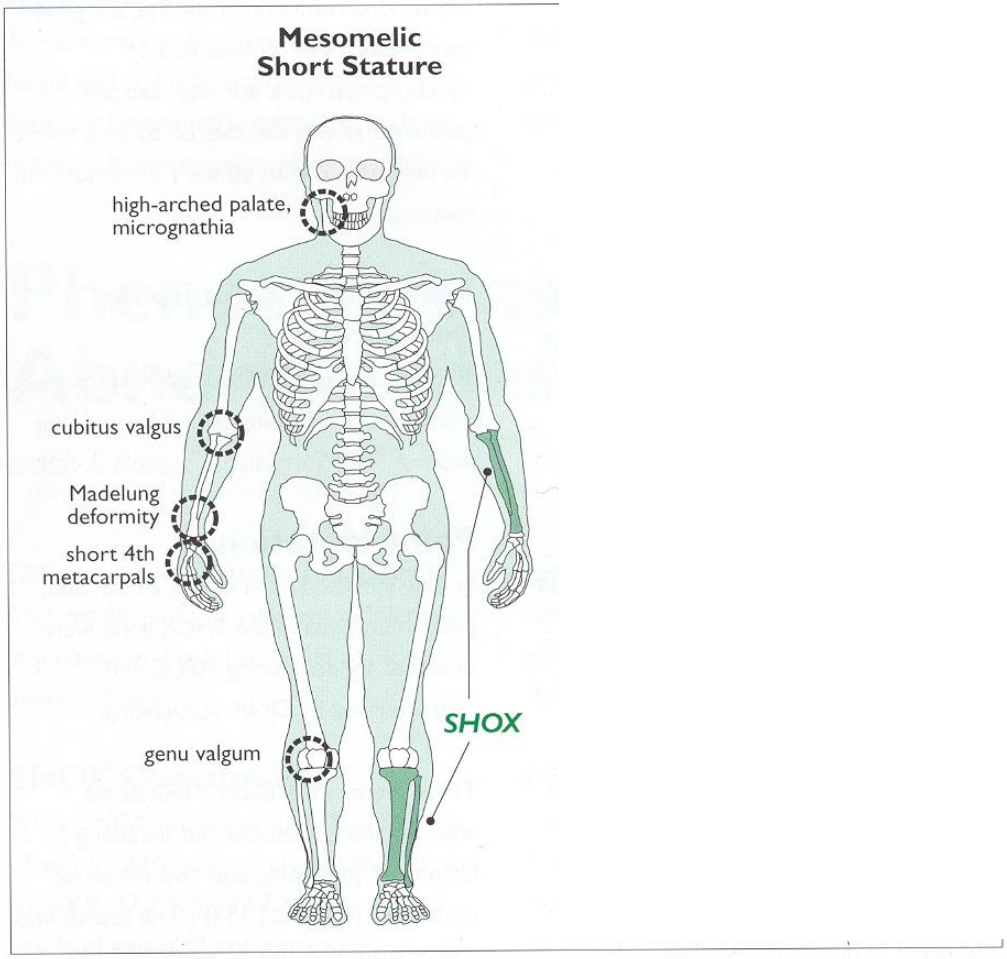


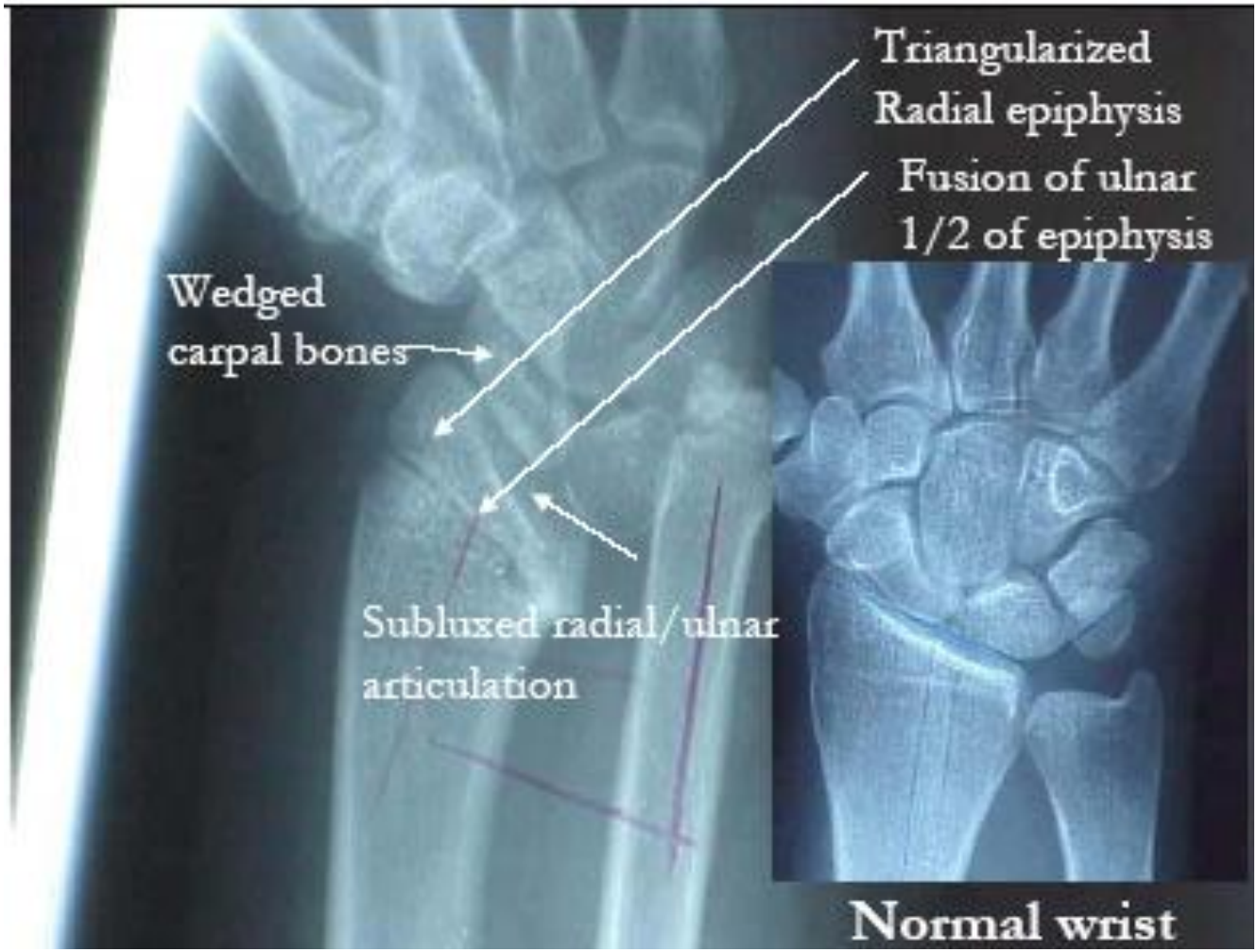
Figure 2: *SHOX* and *SHOX2* in Short Stature Phenotypes

Clinical Features: Madelung Wrist Deformity

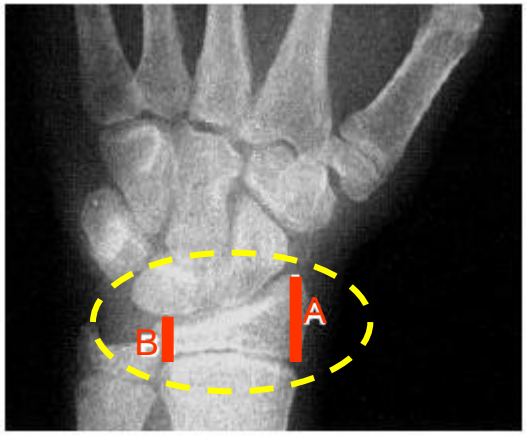
6 Typical examples of Madelung deformity of the forearm in two patients with Léri-Weill dyschondrosteosis. Note the 'dinner fork' appearance of the forearm

Clinical Features:
Lower Limb Bowing, Muscular Hypertrophy

Clinical Features: Radiographic Signs



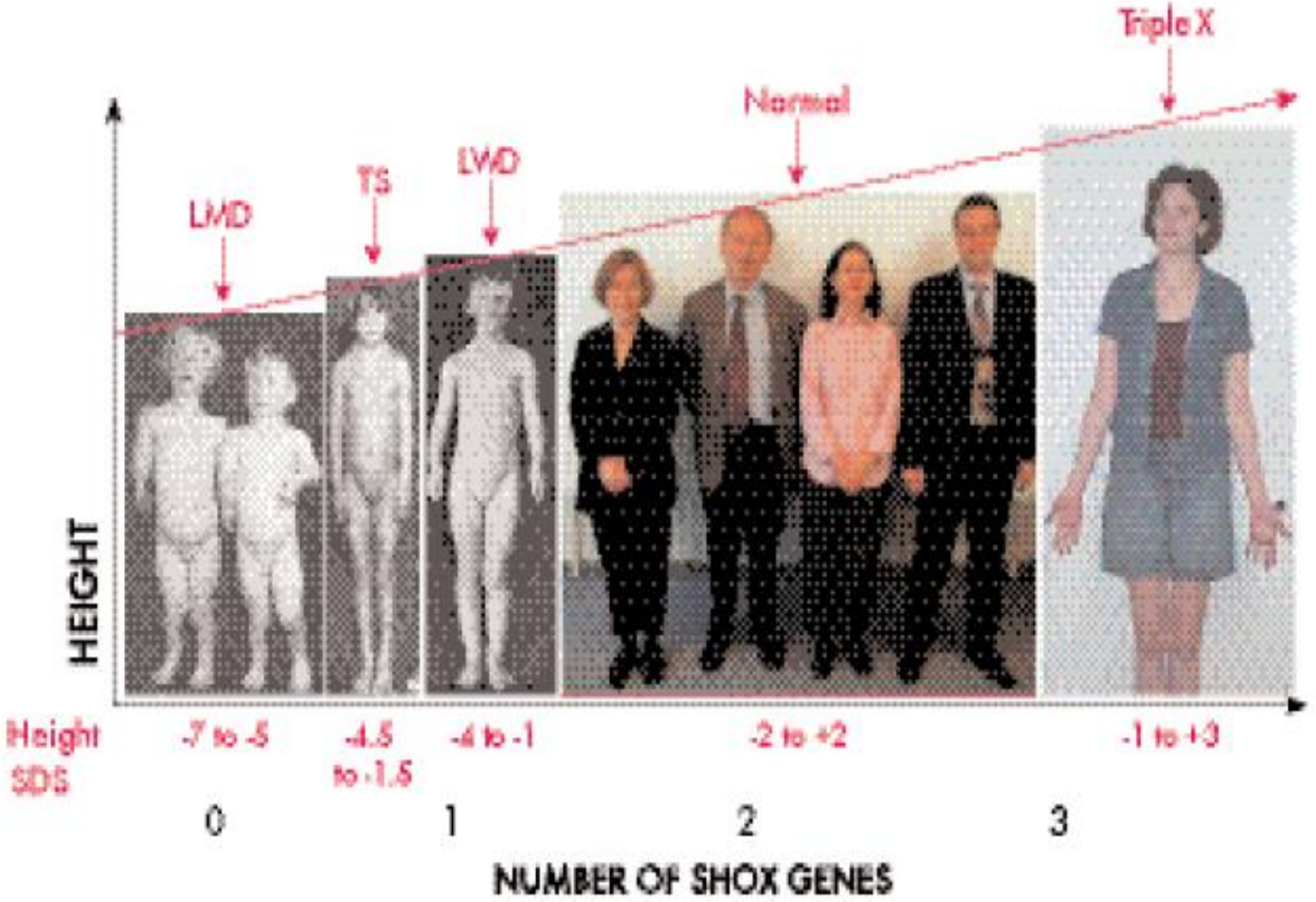
From: Ross JL *et al.* 2001 *J Clin Endocrinol Metab 86*:5674-80

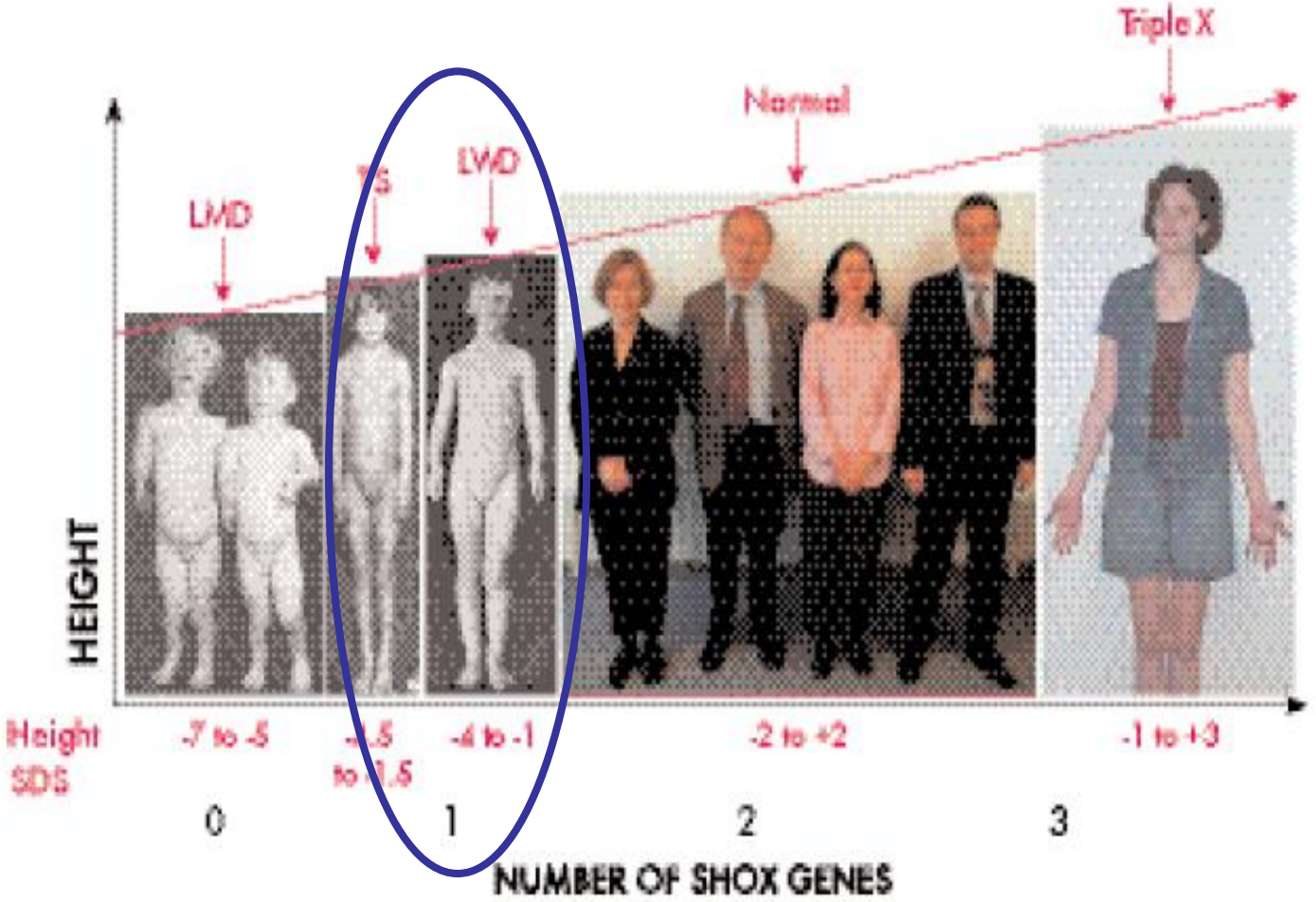


Courtesy W. Blum, Bad Hamburg

<u>Triangularization Index (A/B):</u>

Score of >4 indicates potential skeletal malformation


Triple X
Normal
LMD
TS
LMD
HEIGHT
Height SDS
-3 to -2
-4.5 to -1.5
-4 to -1
-2 to +2
-1 to +3
0
1
2
3
NUMBER OF SHOX GENES


Triple X
Normal
LMD
LMD
HEIGHT
Height SDS
-2 to +2
-1 to +3
0
1
2
3
NUMBER OF SHOX GENES

Frequenza delle anomalie del gene SHOX nei bambini con ISS (Jorge)

Table 3. Summary of studies that evaluated the frequency of *SHOX* gene mutation in ISS children

		SHOX defect		
Study reference	Screening methodology	Point mutation	Deletion	Overall frequency
Rao *et al.* 1997[1]	SSCP + MS*	1/91	0/91	1·1%
Binder *et al.* 2000[12]	SSCP + MS	0/68	1/68	1·5%
Rappold *et al.* 2002[6]	SSCP + FISH	3/750	3/150	2·4%
Binder *et al.* 2003[18]	MS	N.A.	3/140	2·1%
Stuppia *et al.* 2003[13]	DS + FISH	4/56	3/56	12·5%
Huber *et al.* 2006[14]	DS + MS*	3/78	8/78	14%
Present study	DS + MS + FISH or SB	2/63	0/63	3·2%

SSCP, single-strand conformation polymorphism; DS, direct sequencing; MS, study of microsatellite markers; MS*, study of > 2 microsatellite markers; SB, Southern blot; NA, not available.

SHOX mutations in idiopathic short stature and Leri-Weill dyschondrosteosis: frequency and phenotypic variability. Alexander A. L. Jorge. Clinical Endocrinology (2007) 66 , 130–135

Variabilità fenotipica dello SHOX
Deficit: un continuum

Langer syndrome

No *SHOX* gene

- Displasia scheletrica severa
- Grave sbassa statura
- Colpisce sia I maschi che le femmine

Léri-Weill syndrome

- Bassa statura con disproporzioni
- Deformità di Madelung
- Colpisce sia I maschi che le femmine

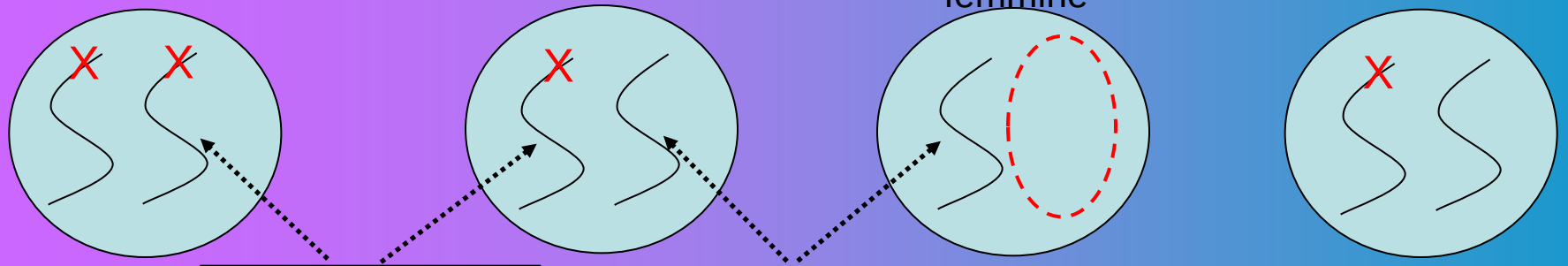
Turner syndrome

- Bassa statura
- Disgenesia ovarica, anomalie scheletriche, disturbi cardiaci e renali, etc.
- colpisce solo le femmine

"Idiopathic" short stature*

- Bassa statura
- Nessun segno clinico
- Colpisce sia I maschi che le femmine

Solo 1 allele SHOX attivo



X chromosome w/ *SHOX* mutation/deletion

Normal X chromosome: no *SHOX* mutation/deletion

*~2-10% degli ISS potrebbero essere SHOX deficit

SHOX-D: una nuova indicazione per la terapia con rhGH ed un nuovo sub-study in GeNeSIS

Quando ricercare le mutazioni del gene SHOX?

Indicazioni certe :

LWS

Bassa statura in parenti di 1° grado di LWS

Indicazioni in discussione

tutte le basse stature idiopatiche?

sulla base di uno screening auxologico ?

Frequenza delle anomalie del gene SHOX e variabilità fenotipica

- Pazienti con anomalie del gene SHOX presentano una ampia variabilità fenotipica rispetto alla bassa statura ed alla deformità di Madelung

- Anomalie del gene SHOX sono molto frequenti nella sindrome di Leri Weil (89%), a differenza degli ISS (3·2%) nel gruppo che abbiamo studiato

- L'uso del rapporto "altezza seduta/altezza" (SH/H) come criterio di selezione aumenta la frequenza dello SHOX deficit fino al 22% e dovrebbe essere usato per selezionare i bambini ISS in cui ricercare le anomalie del gene SHOX

Jorge et al Clin Endocrinol (2007) 66 , 130–135

SHOX-D: una nuova indicazione per la terapia con rhGH ed un nuovo sub-study in GeNeSIS

28 BSI con SH/H
>2 SDS

5 con delezione SHOX = 18%
Vs 3,2 % in non selezionati

Jorge non pubblicato

Correlazione tra genotipo e fenotipo in una grande popolazione di bambini con ISS da 14 paesi (Rappold)

- 1608 bambini ISS
- Determinate deformità scheletriche e segni dismorfici differiscono in modo significativo tra i soggetti con presenza o assenza di difetti del gene SHOX
- Viene proposto uno Score System basato sul fenotipo per aiutare ad identificare i soggetti più appropriati per testare il gene SHOX

Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. G Rappold. J. Med. Genet. 2007;44;306-313

Clinical indicators of SHOX: phenotype scoring system

Table 7 Scoring system for identifying patients that qualify for short-stature homeobox containing gene (SHOX) testing based on clinical criteria

Score item	Criterion	Score points
Arm span/height ratio	<96.5%	2
Sitting height/height ratio	>55.5%	2
Body–mass index	>50th percentile	4
Cubitus valgus	Yes	2
Short forearm	Yes	3
Bowing of forearm	Yes	3
Appearance of muscular hypertrophy	Yes	3
Dislocation of ulna (at elbow)	Yes	5
Total		24

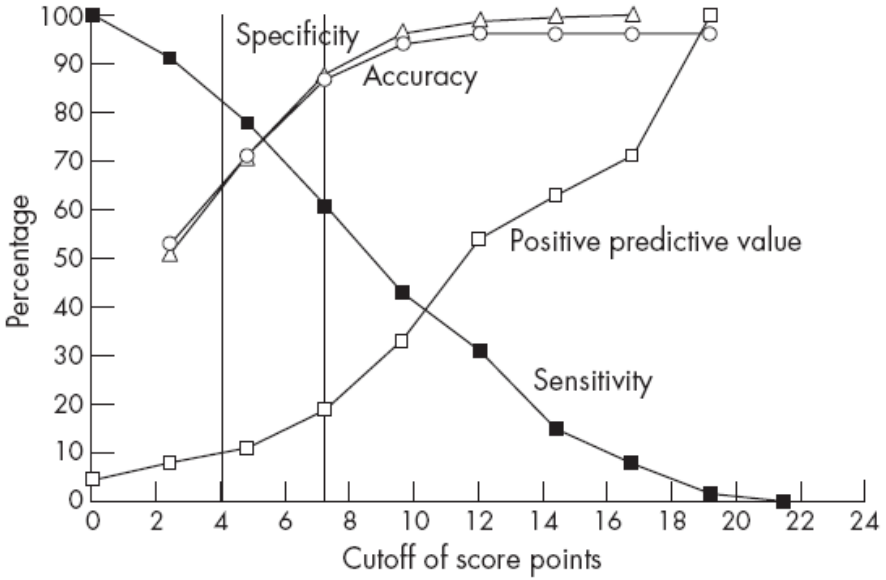


Figure 1 Dependence of sensitivity, specificity, accuracy and positive predictive value on cut-off score point; the vertical lines represent cut-offs of >4 and >7 score points, respectively.

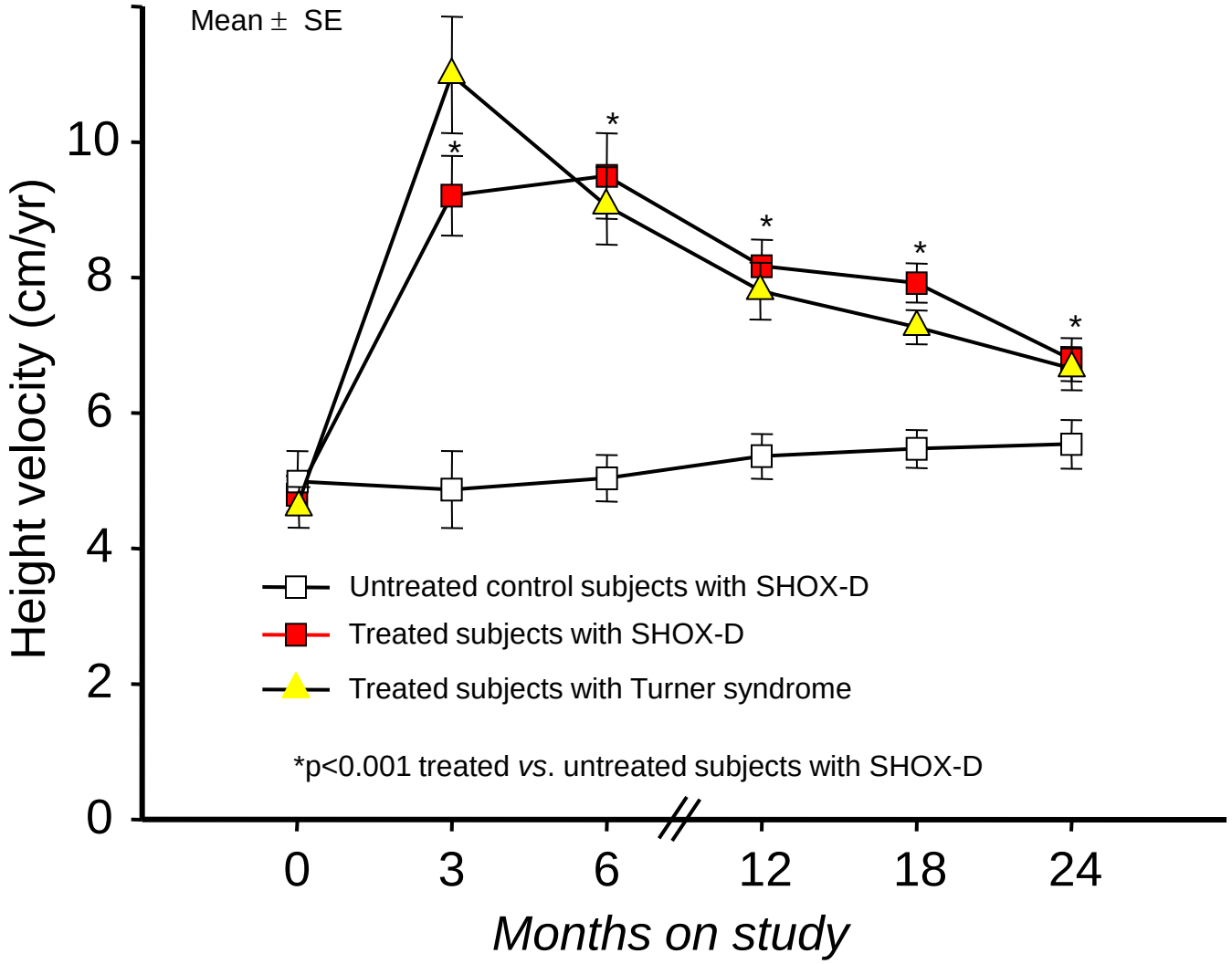
- **The suggested scoring system includes three anthropometric variables (arm span/ height, sitting height/height and body mass index (BMI)) and five dysmorphic signs**
- **At a cut-off of 4 points, sensitivity was 71% and the positive predictive value was 11%; at 7 points the sensitivity dropped to 61% while the positive predictive value increased to 19%**

Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. G Rappold. J. Med. Genet. 2007;44;306-313

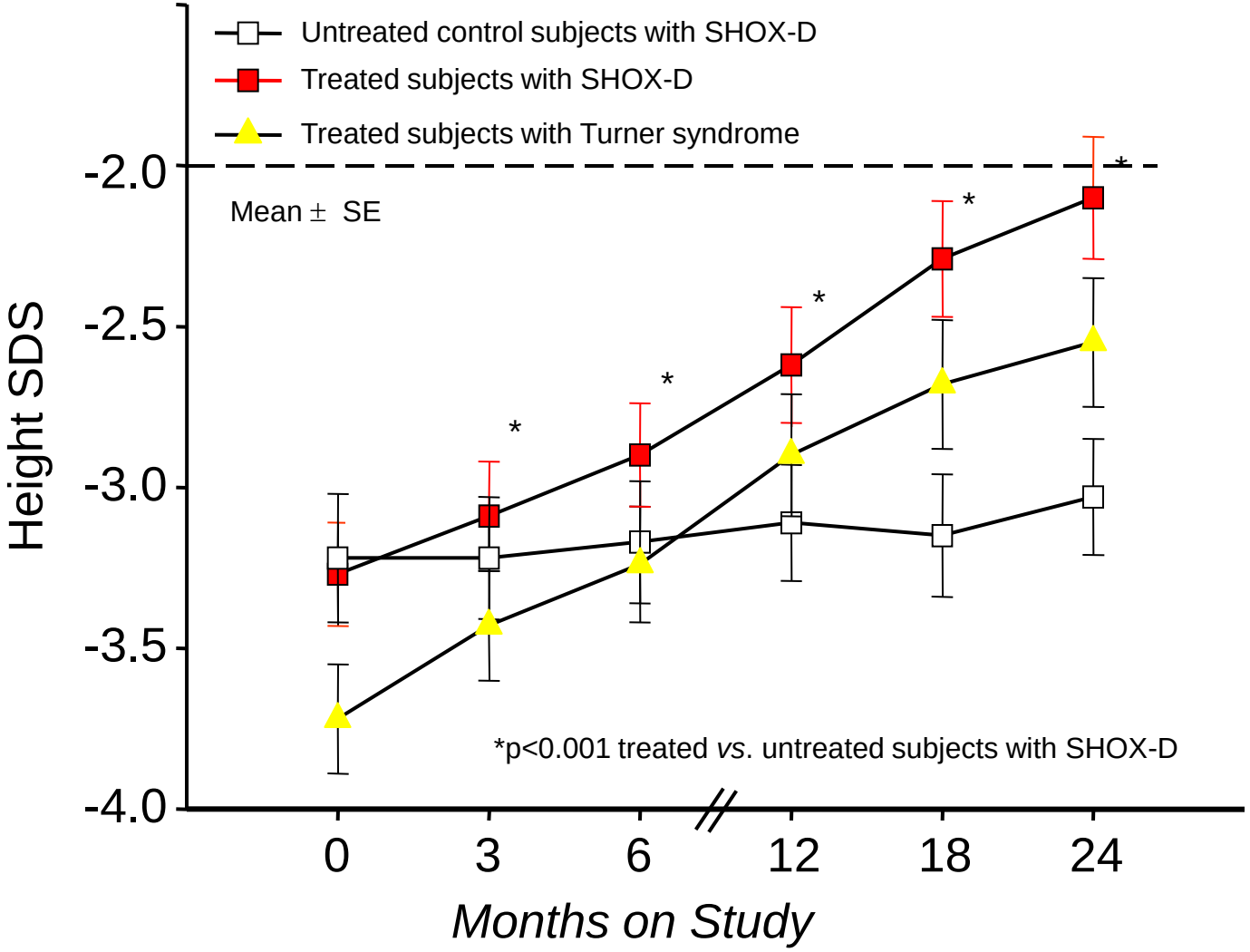
SHOX-D: una nuova indicazione per la terapia con rhGH

- Clinical Trial con Humatrope

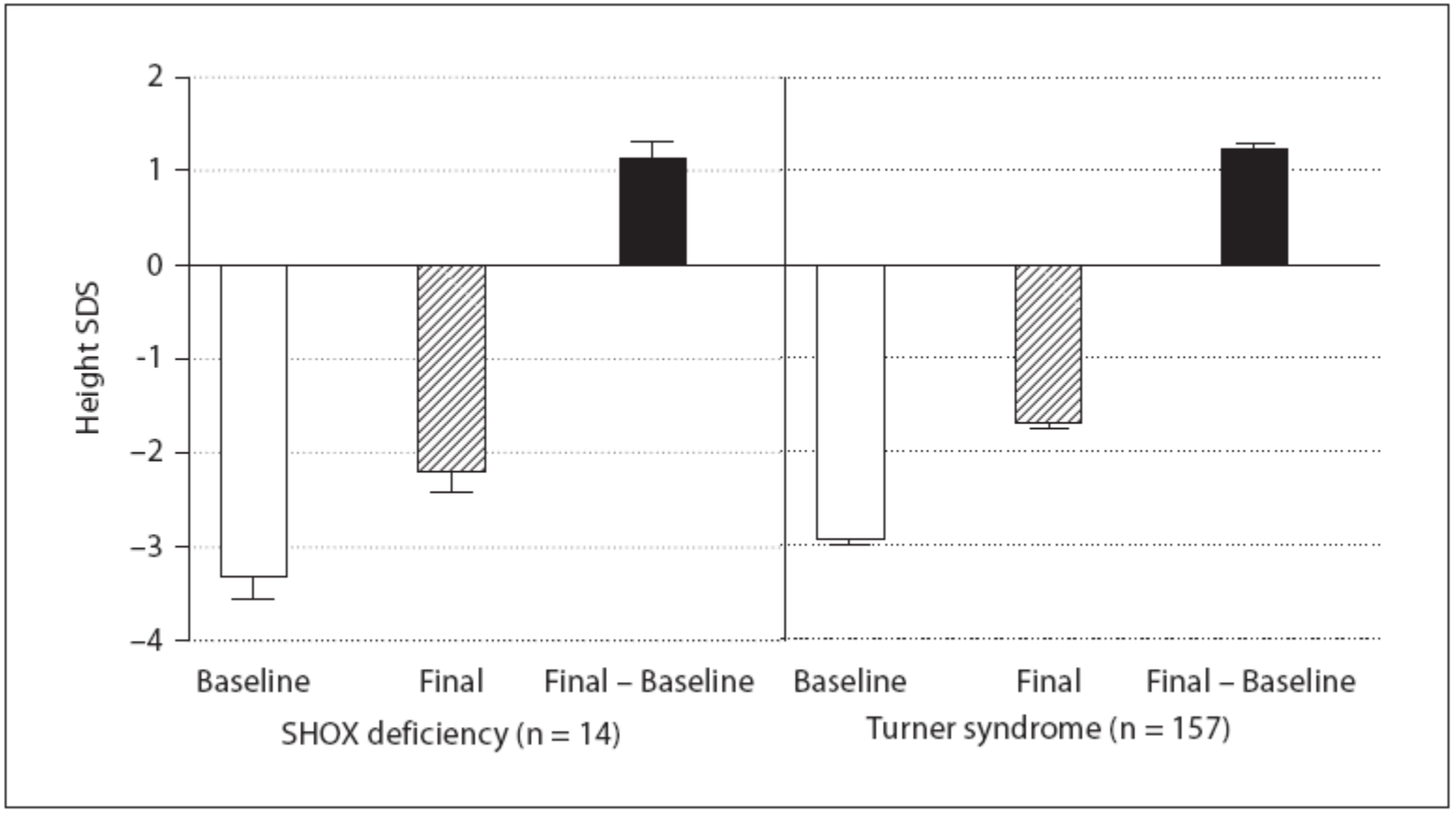
Height Velocity (cm/yr)



Height SDS Mean Values

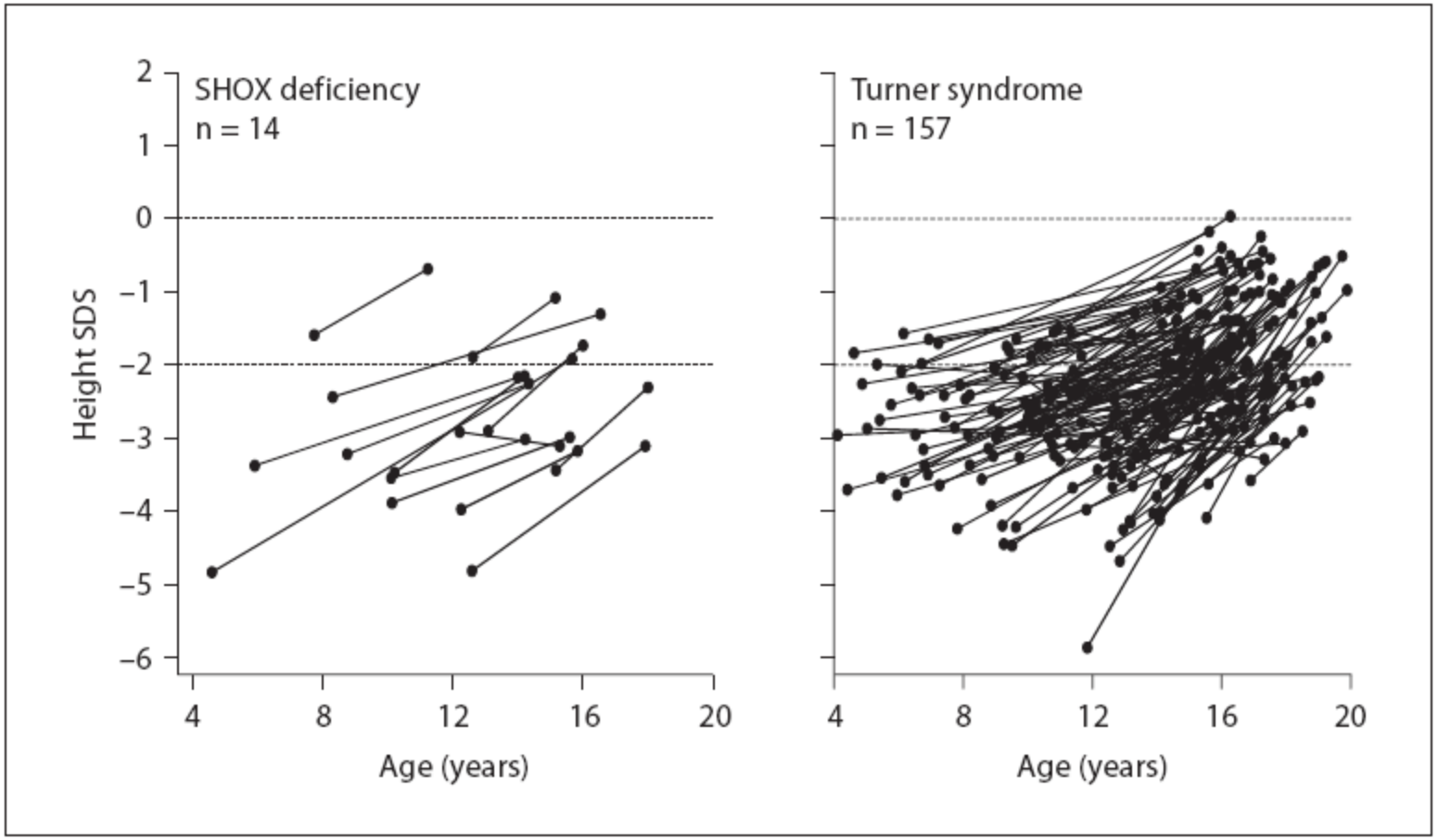


Height SDS



Height Gains in Response to Growth Hormone Treatment to Final Height Are Similar in Patients with SHOX Deficiency and Turner Syndrome. Werner F. Blum. Horm Res 2009;71:167–172

Height SDS



Height Gains in Response to Growth Hormone Treatment to Final Height Are Similar in Patients with SHOX Deficiency and Turner Syndrome. Werner F. Blum. Horm Res 2009;71:167–172

S.BERNASCONI
DIPARTIMENTO DELL'ETA' EVOLUTIVA
UNIVERSITA' DI PARMA

PERCORSI DECISIONALI PER LA GESTIONE DEL BAMBINO E DELL'ADOLESCENTE

Inibitori dell'aromatasi

sbernasconi@ao.pr.it

FAMAGOSTA12-17 GIUGNO 2010

L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

The Aromatase Cytochrome P-450 and Its Clinical Impact

Udo Meinhardt Primus E. Mullis

Horm Res 2002;57:145–152

Aromatase (P450arom): the key enzyme for estrogen biosynthesis

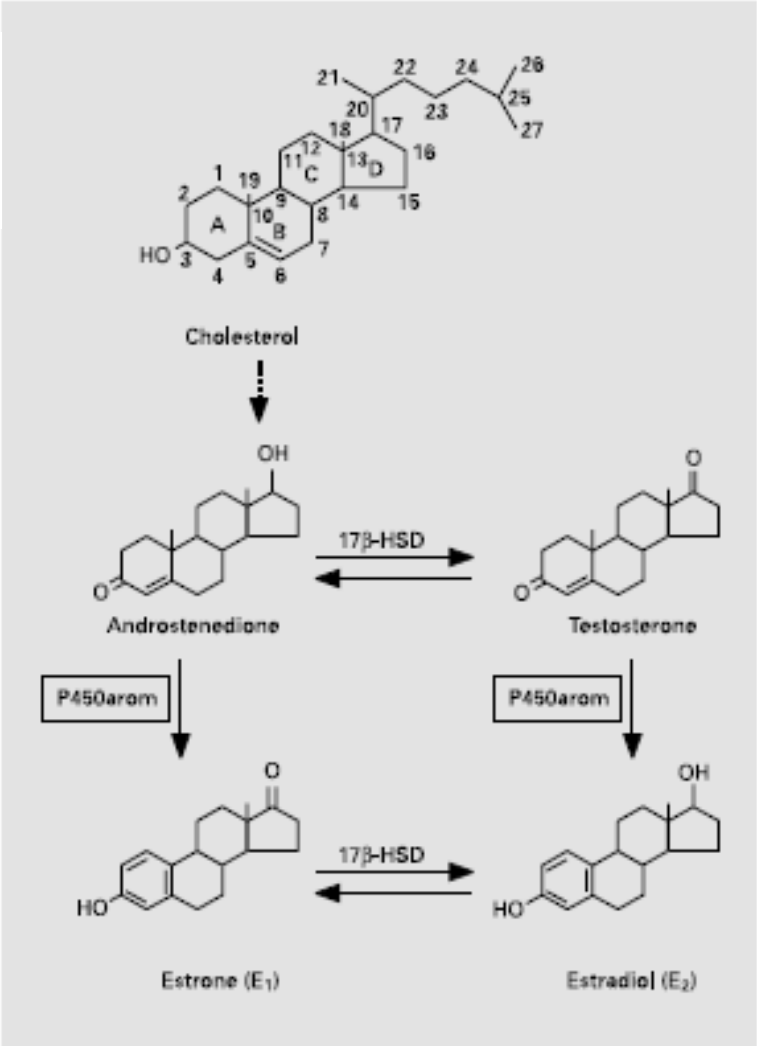


Fig. 2. Steroidogenesis within the ovary. Conversion of pregnenolone to dehydroepiandrosterone (Δ^5 pathway not shown), then further from androstenedione to androgens and to estrogens. The Δ^5 pathway is predominant in the ovarian follicles.17β-HSD = 17β-Hydroxysteroid dehydrogenase.

L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Genetic and Clinical Spectrum of Aromatase Deficiency in Infancy, Childhood and Adolescence

A. Belgorosky G. Guercio C. Pepe N. Saraco M.A. Rivarola

Horm Res 2009;72:321–330

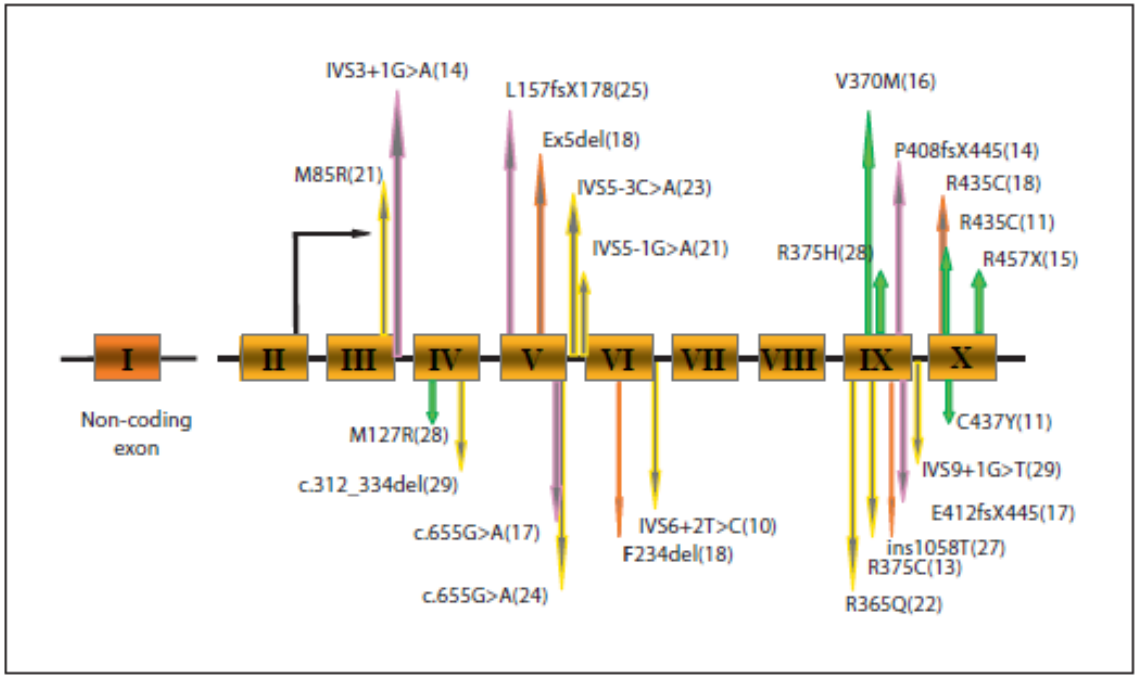
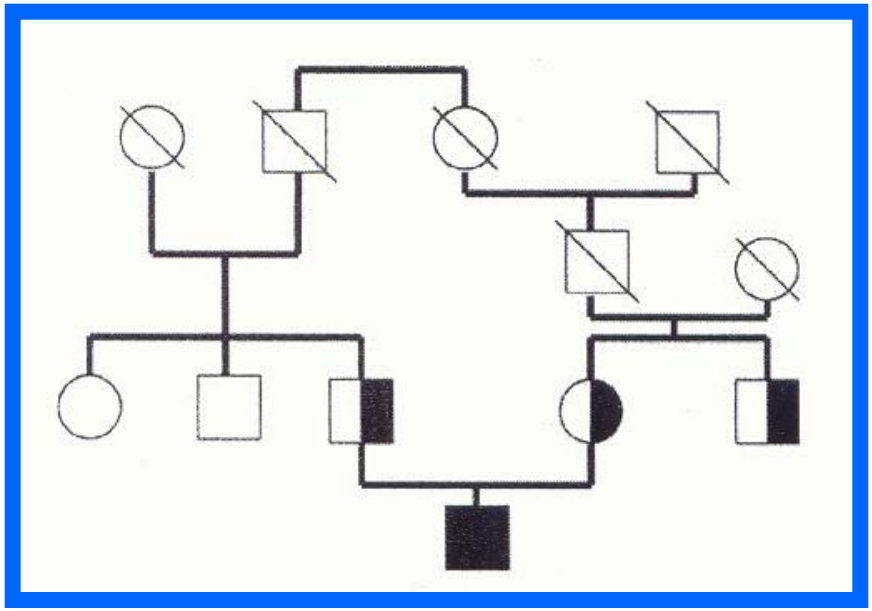
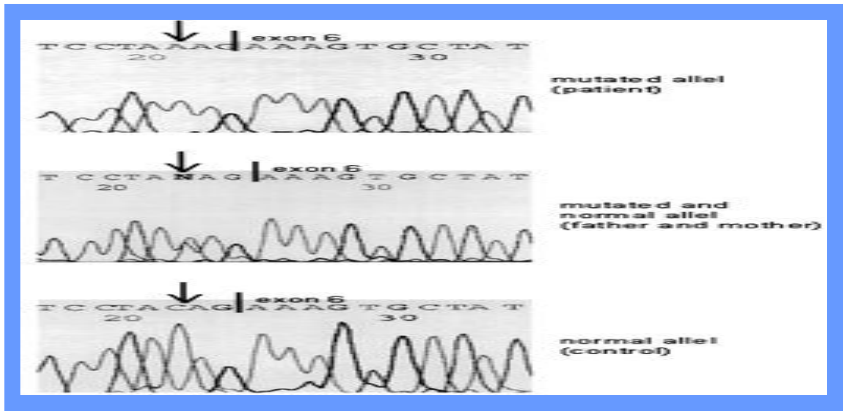


Fig. 1. The human *CYP19* (cP450arom) gene, located in the 21.2 region on the long arm of chromosome 15 (15q21.2). Its regulatory region contains at least 10 distinct promoters regulated in a tissue- or signaling pathway-specific manner. The coding exons, namely exons II–X, are shown, along with the location of the reported mutations.

Caratteristiche cliniche dei pazienti (XY) con deficit di aromatasi

Pedigree del paziente affetto





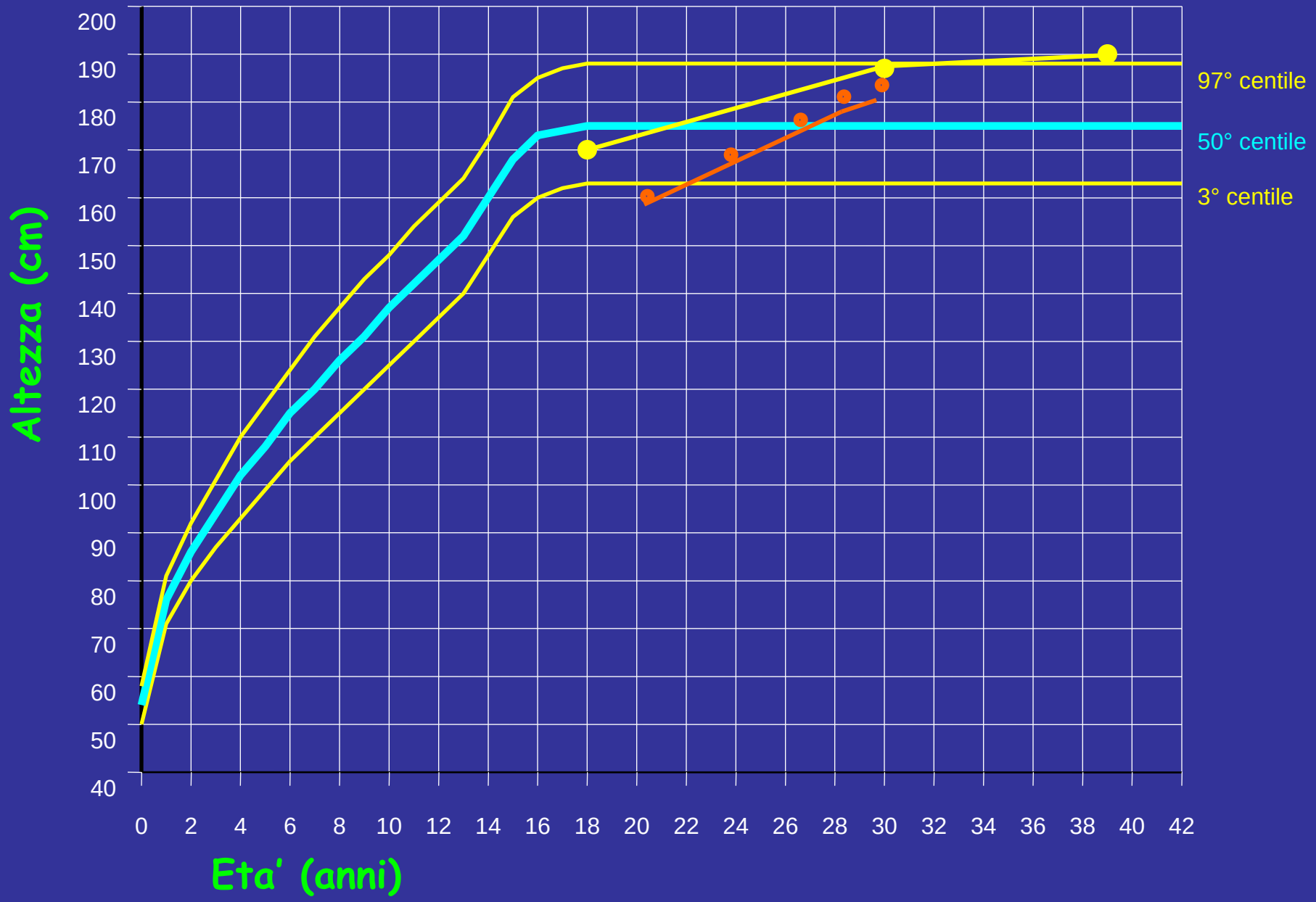
27 anni

Herrmann et al, J Clin Endocrinol Metab 87:5456-84, 2002

Features of estrogens deficiency in adult males

- osteoporosis
- abnormal blood lipid profile
- low or normal or high testosterone levels
- normal to high levels of gonadotropins
- hyperinsulinemia, *acanthosis nigricans*
- hepatosteatosis
- defect in germ cell development
- **continuous linear growth**

Deficit di aromatasi



L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Tall Stature without Growth Hormone: Four Male Patients with Aromatase Deficiency

Vincenzo Rochira, Lucia Zirilli, Laura Maffei, Valeria Premrou, Claudio Aranda, Matteo Baldi, Ezio Ghigo, Gianluca Aimaretti, Cesare Carani, and Fabio Lanfranco

J ClinEndocrinol Metab 95: 1626–1633, 2010

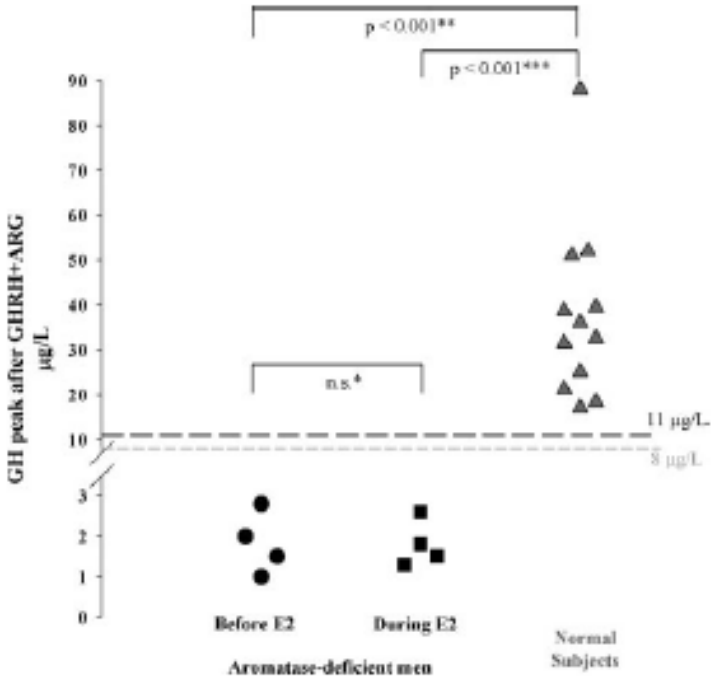


FIG. 1. GH peak after GHRH-ARG test in patients with aromatase deficiency before and during estradiol (E2) therapy and in normal subjects. n.s., Not significant. *, *t* test for paired data; **, *t* test for unpaired data for the comparison of patients before estrogen treatment (E2) and normal subjects; ***, *t* test for unpaired data for the comparison of patients during estrogen treatment (E2) and normal subjects. The *long black dash line* refers to the threshold for men with a normal BMI (25–29), whereas the *short gray dash line* refers to the threshold for overweight men with a BMI between 25 and 30 kg/m^2 (26).

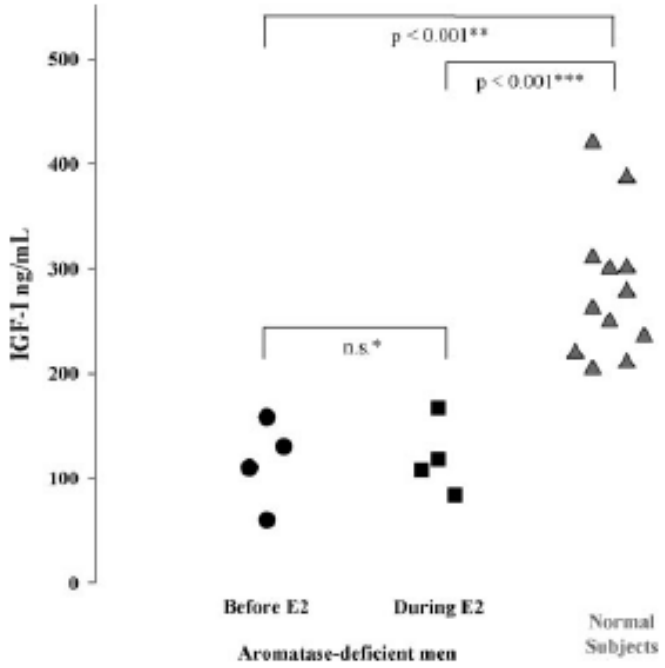


FIG. 2. IGF-I levels in patients with aromatase deficiency before and during estradiol (E2) therapy, and in normal subjects. n.s., Not significant. *, *t* test for paired data; **, *t* test for unpaired data for the comparison of aromatase-deficient patients before estrogen treatment (E2) and normal subjects; ***, *t* test for unpaired data for the comparison of aromatase-deficient patients during estrogen treatment (E2) and normal subjects.

Features of estrogens deficiency in adult males

- osteoporosis
- abnormal blood lipid profile
- low or normal or high testosterone levels
- normal to high levels of gonadotropins
- hyperinsulinemia, *acanthosis nigricans*
- hepatosteatosis
- defect in germ cell development
- **continuous linear growth**
- **delayed epiphyseal closure and skeletal maturation**

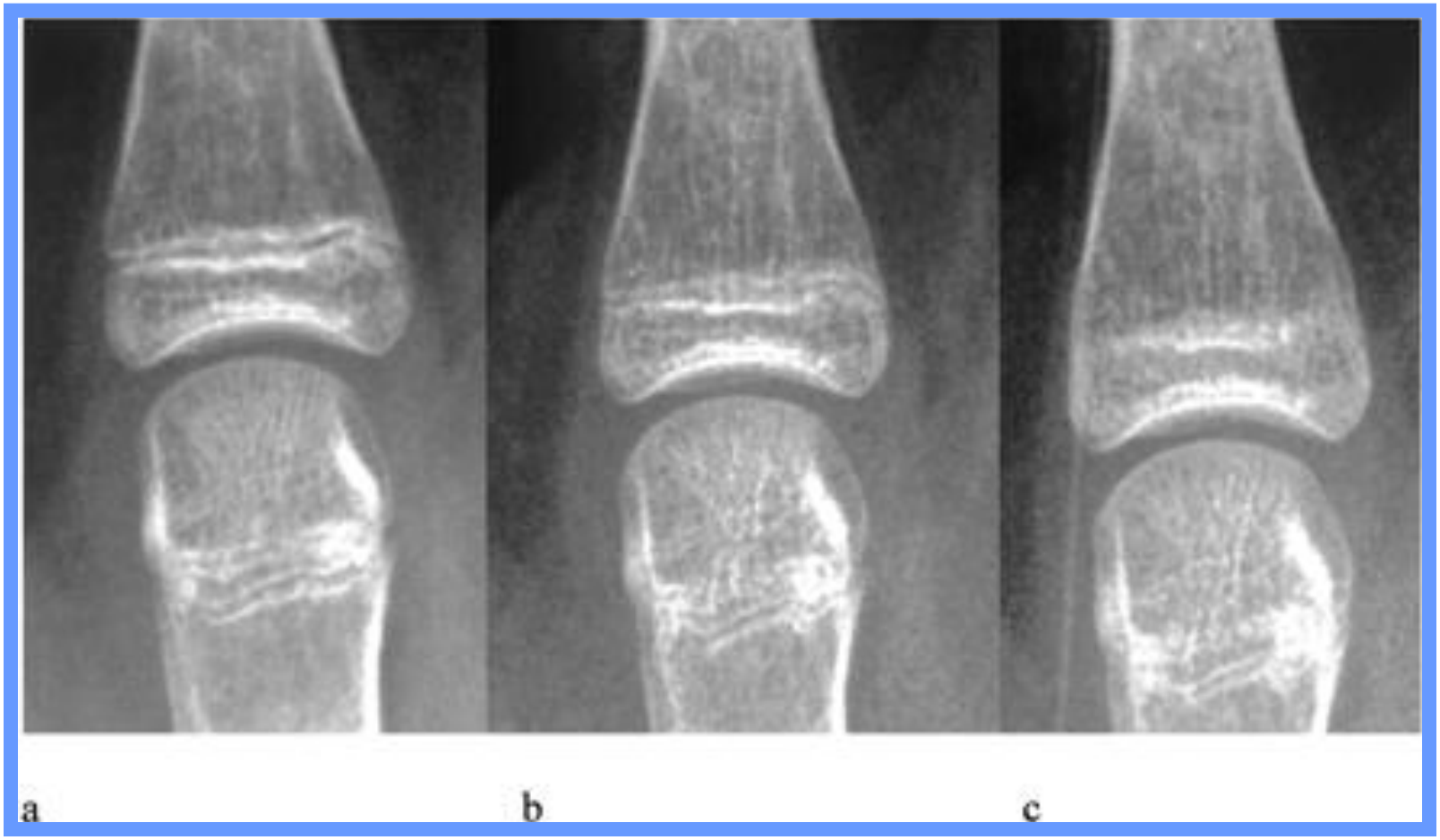
Deficit di aromatasi

Deficit di aromatasi

Prima della terapia

Dopo 2 anni di terapia con testosterone

Deficit di aromatasi



Prima della terapia

Dopo 3 e 6 mesi di terapia con estradiolo

Herrmann et al.

AROMATASE INHIBITORS AS THERAPY FOR SHORT STATURE ?

L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development

Dorothy I. Shulman, Gary L. Francis, Mark R. Palmert, Erica A. Eugster and for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

Pediatrics 2008;121;e975-e983

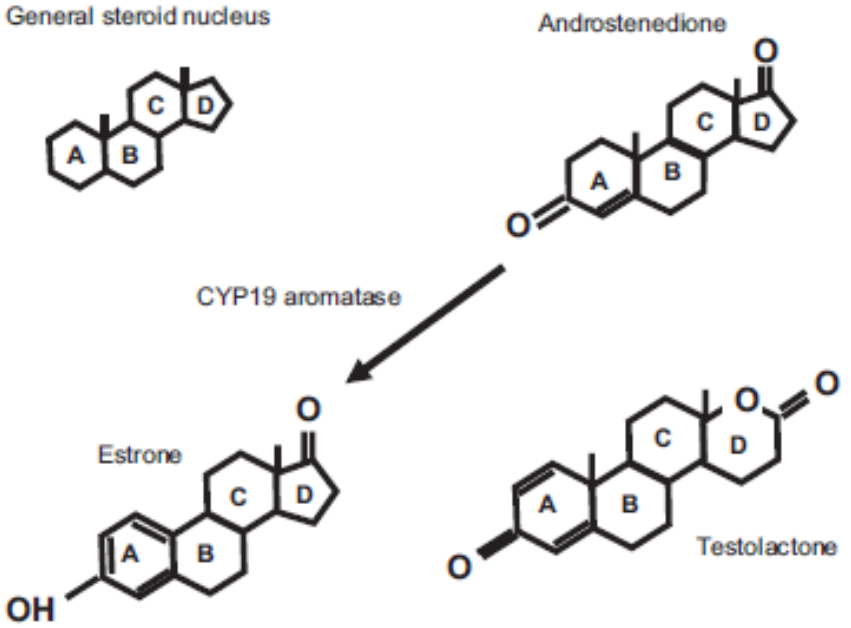


FIGURE 1

Structural comparisons of aromatase substrates. The general steroid ring structure and nomenclature are shown along with the structure of androstenedione, a known substrate for CYP19 (aromatase). Reaction of androstendione with CYP19 (aromatase) generates the aromatic ring structure in the steroid A ring leading to estrone. For comparison, the structure of testolactone, a widely known inhibitor of CYP19 (aromatase), is shown. Note the similarity in structure to that of androstenedione.

L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development

Dorothy I. Shulman, Gary L. Francis, Mark R. Palmert, Erica A. Eugster and for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

Pediatrics 2008;121;e975-e983

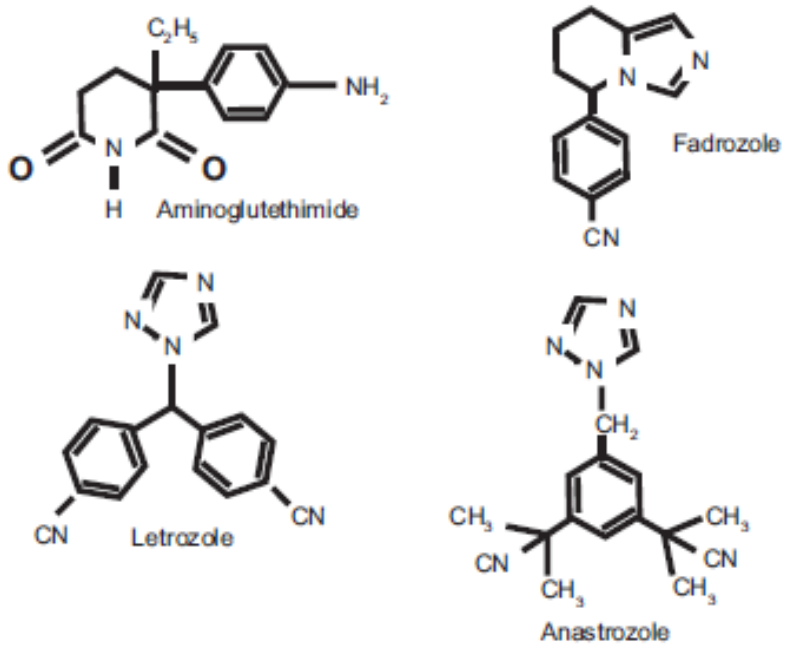
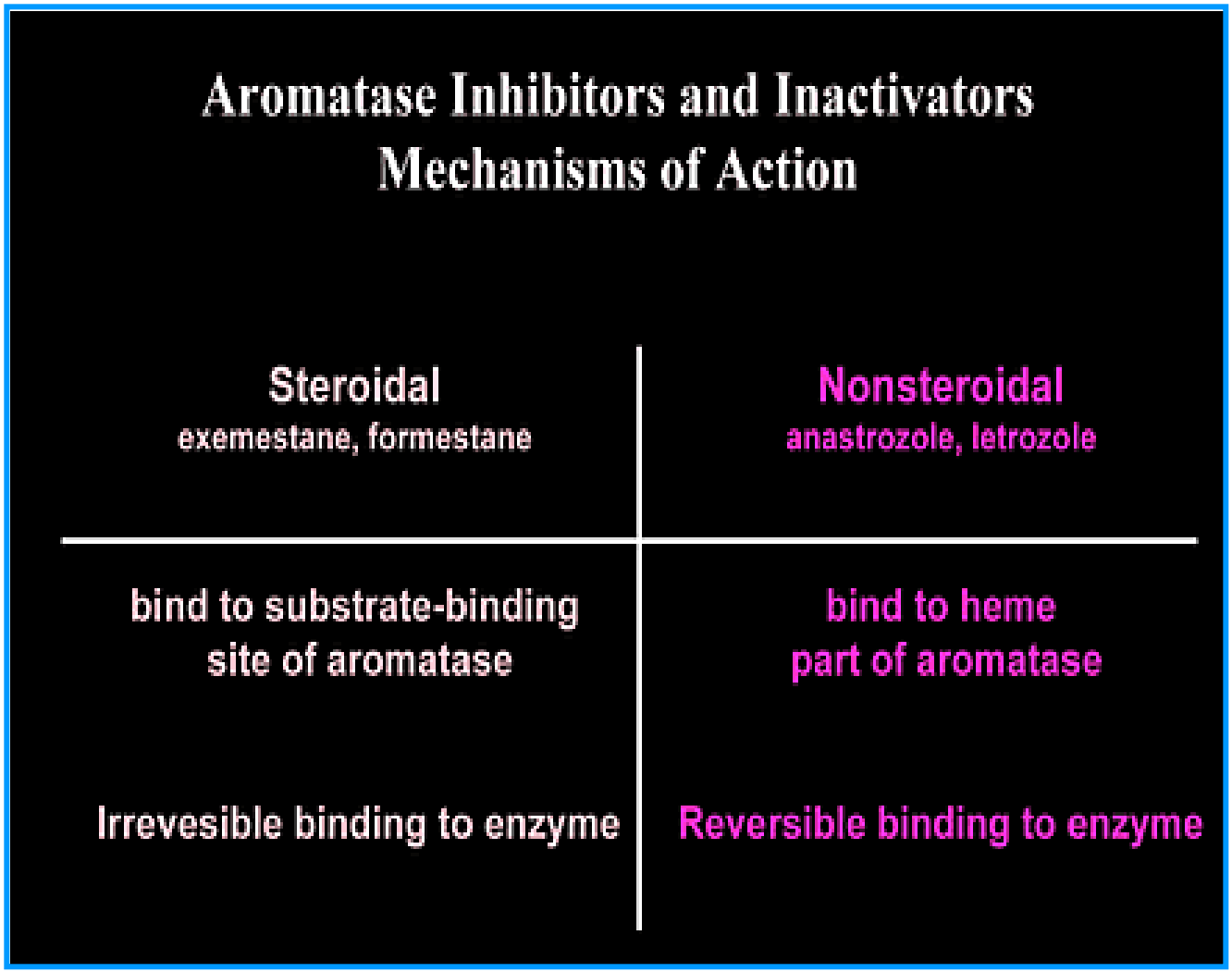


FIGURE 2

Type II, nonsteroidal AIs. The imidazole/triazole compounds or derivatives of phenobarbitone have activity against CYP19 (aromatase), including aminoglutethimide fadrozole, and more potent third-generation AIs such as letrozole and anastrozole.

L’aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.



L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Generazione	Non steroidei	Steroidei
Prima	Aminoglutethimide	Testolactone
Seconda	Fadrozole	Formestane
Terza	**Anastrozole** **Letrozole**	Exemestane

L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development

Dorothy I. Shulman, Gary L. Francis, Mark R. Palmert, Erica A. Eugster and for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

Pediatrics 2008;121;e975-e983

TABLE 1 Relative Potency of Select AIs

Compound	Dosage	% Aromatase Inhibition
Aminoglutethimide	250 mg 4 times daily	90.6
Testolactone	10 mg/kg 4 times daily	<90.0
Formestane	125 mg twice daily	91.9
Fadrozole	2 mg twice daily	92.6
Anastrozole	1 mg once daily	97.3
Letrozole	2.5 mg once daily	>99.1

Update on the Role of Aromatase Inhibitors in Growth Disorders

Horm Res 2009;71(suppl 1):57–63

Leo Dunkel

Table 1. Studies with aromatase inhibitors in children with disorders affecting growth

Condition	Study design	Compound	Adjuvant treatment	Efficacy	Reference
Familial male-limited precocious puberty	Uncontrolled clinical trial	Testolactone	Spironolactone, GnRHa	No change in PAH after 2-4.2 years of treatment; 12.9 cm increase in PAH after 6 years of treatment	13–15
	Two case reports	Anastrozole	None	Decrease in BA progression, increase in PAH	16
McCune-Albright syndrome	Uncontrolled clinical trial	Testolactone	GnRHa	Decrease in BA progression, no change in PAH	17, 18
	Uncontrolled clinical trial	Fadrozole	GnRHa	No change in BA progression or PAH	19
	Uncontrolled clinical trial	Letrozole	None	Some decrease in BA progression	20
Congenital adrenal hyperplasia	Randomised clinical trial	Testolactone	Flutamide, hydrocortisone, fludrocortisone, GnRHa	Decrease in BA progression, no change in PAH	21, 22
Constitutional delay of growth and puberty	Double-blind, placebo-controlled randomised trial	Letrozole	Testosterone	Decrease in BA progression, 5.1 cm increase in PAH	23
Idiopathic short stature	Double-blind, placebo-controlled randomised trial	Letrozole	None	Decrease in BA progression, 5.9 cm increase in PAH	24
Mixed population of short adolescent boys	Retrospective uncontrolled study	Letrozole	None	Decrease in BA progression, 5.5 cm increase in PAH	25
GH deficiency	Open-label controlled trial	Anastrozole	GH	No change in BA progression or PAH at 1 year	26
	Double-blind, placebo-controlled randomised trial	Anastrozole	GH	Decrease in BA progression, 5.7 cm increase in PAH at 3 years	27

PAH = Predicted adult height; BA = bone age.

Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty

Matti Hero*, Sanna Wickman* and Leo Dunkelt

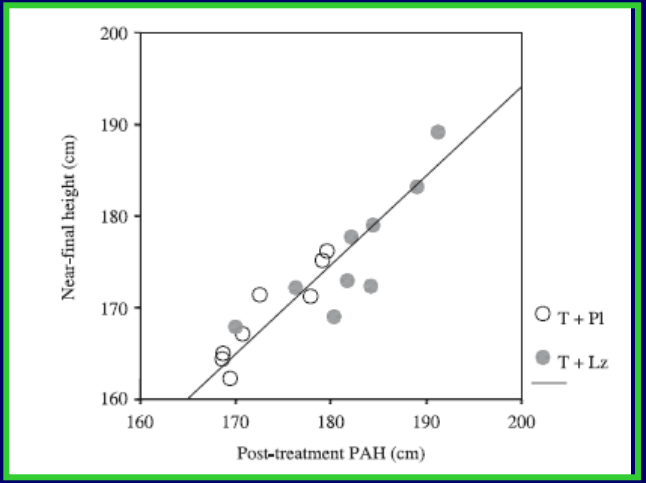
Clinical endocrinology 2006

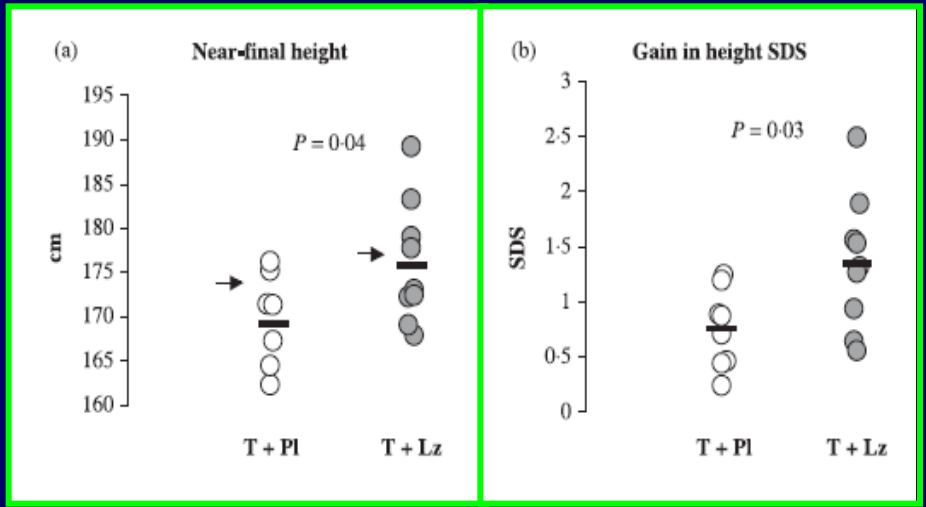
23 boys with constitutional delay of puberty randomly assigned to receive either letrozole (Lz) (2.5mg/day orally) or placebo (Pl) in combination with low-dose testosterone (T) (1mg/Kg i.m. every 4 weeks) (12 months)

1. Boys treated with T+Lz were taller and reached a higher mean near-final height comparable to their mid-parental target height (PAH increased by 5.1 cm)

2. Boys treated with T+Lz had significantly greater increase in height SDS over the pretreatment level

In adolescent boys an increase in adult heigh can be attained by use of aromatase inhibitors





0021-972X/05/$15.00/0
Printed in U.S.A.

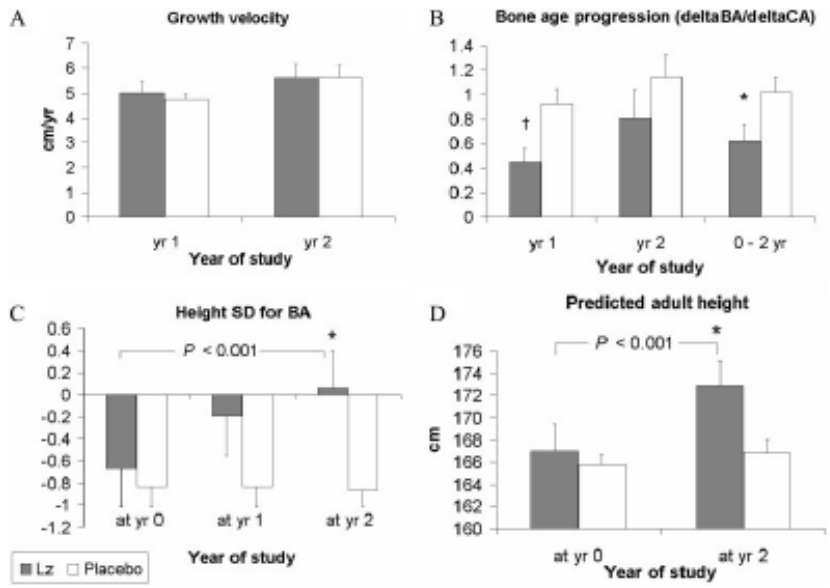
The Journal of Clinical Endocrinology & Metabolism 90(12):6396–6402
Copyright © 2005 by The Endocrine Society
doi: 10.1210/jc.2005-1292

Inhibition of Estrogen Biosynthesis with a Potent Aromatase Inhibitor Increases Predicted Adult Height in Boys with Idiopathic Short Stature: A Randomized Controlled Trial

Matti Hero, Ensio Norjavaara, and Leo Dunkel

Hospital for Children and Adolescents, University of Helsinki and Helsinki University Central Hospital (M.H.), Helsinki 00029 HUS, Finland; Goteborg Pediatric Growth Research Center, Institute for the Health of Women and Children, Goteborg University (E.N.), Goteborg S-41685, Sweden; and Department of Pediatrics, Kuopio University Hospital (L.D.), Kuopio 70211, Finland

- Thirty-one boys, aged 9-14.5 yr, with ISS were treated with Letrozole (2.5 mg/day) for 2 yr



A. Similar growth velocity during the study

B. Slower bone age advancement during the 2-yr treatment in the letrozole-treated group (1.2 *vs* 2.05 yr)

C. Height SD score for BA increased by 0.7 SD score in the letrozole-treated group

D. Predicted adult height increased by 5.9 cm in the letrozole-treated group

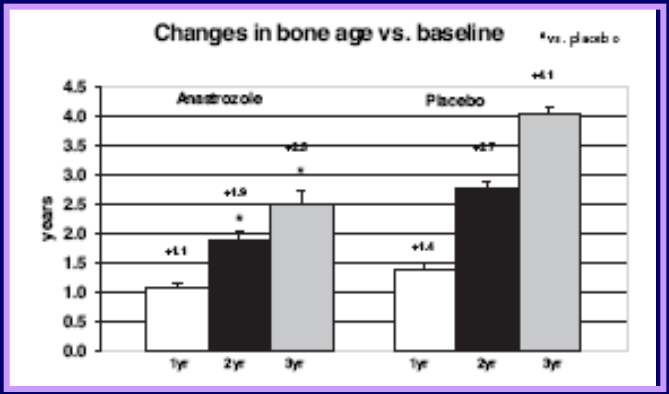
Endocrine Care

Anastrozole Increases Predicted Adult Height of Short Adolescent Males Treated with Growth Hormone: A Randomized, Placebo-Controlled, Multicenter Trial for One to Three Years

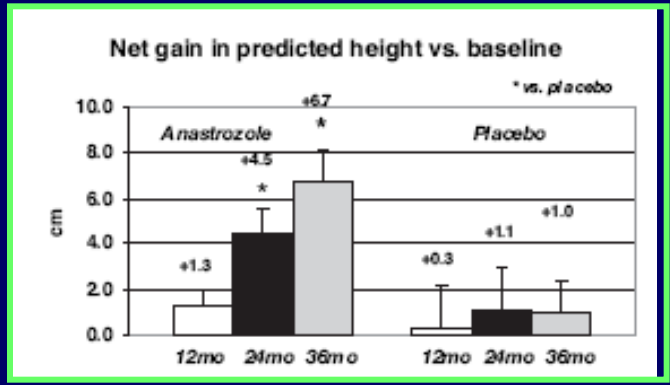
JCEM 2008

Nelly Mauras, Lilliam Gonzalez de Pijem, Helen Y. Hsiang, Paul Desrosiers, Robert Rapaport, I. David Schwartz, Karen Oerter Klein, Ravinder J. Singh, Anna Miyamoto, and Kim Bishop

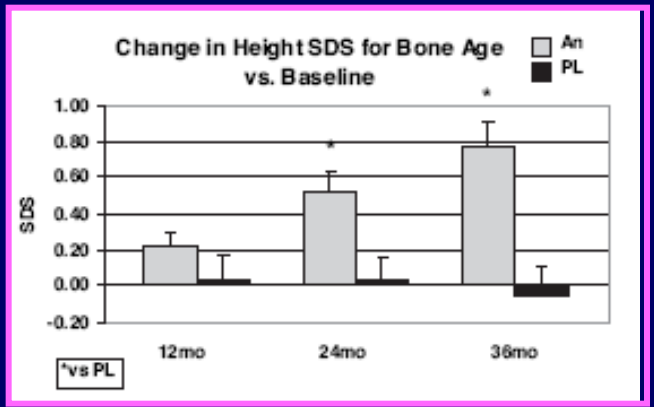
- **Fifty-two adolescent males with GH deficiency treated with GH were randomized to cotreatment with anastrozole (1 mg daily) or placebo daily for up to 36 months**



There was a corresponding improvement in the gain in height SD score adjusted for BA at 2 and 3 yr



Significantly slower increase in BA advancement from baseline after 2 and 3 yr



This resulted in a net increase in PAH of +4.5±1.2 cm at 2 yr and +6.7±1.4 cm at 3 yr

L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Use of AIs in boys with idiopathic short stature and short stature associated with growth hormone deficiency or constitutional delay may increase adult height; however, data on adult height are few, and there is no information identifying which children are likely to benefit most. Additional controlled studies are required before this therapy can be routinely recommended to augment adult height.

L’aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

SAFETY ISSUES

Potential effect on bone mineral density (BMD) (?)

Potential effect on spematogenesis and sperm motility (?)

Potential effect on lipid and carbohydrate metabolism (?)

Cognitive effect ?

L'aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Cognitive effects of aromatase inhibitor therapy in peripubertal boys

Hero M[1], Maury S[2], Luotoniemi E[3], Service E[4], Dunkel L[5]

EJE 2010

Table 3. Cognitive performance during 2-year treatment with letrozole or placebo. Values are mean (SD). [a] ANOVA comparing Lz and placebo groups.

	Letrozole			Placebo			P[a]
	Baseline	Yr 1	Yr 2	Baseline	Yr 1	Yr 2	
Verbal Performance:							
Similarities	13.7 (4.7)	14.7 (4.3)	16.3 (4.1)	17.5 (4.9)	17.6 (4.3)	20.0 (5.5)	0.70
(WISC-III)	n=15	n=15	n=15	n=13	n=12	n=13	n=27
Comprehension	15.7 (5.3)	15.9 (6.4)	18.3 (4.8)	19.3 (7.1)	21.3 (6.7)	21.2 (6.3)	0.22
(WISC-III)	n=15	n=15	n=15	n=13	n=12	n=13	n=27
Visuospatial Performance:							
Rotation task hits	66.1 (14.5)	67.3 (14.0)	70.0 (11.6)	72.2 (13.7)	73.9 (13.0)	71.5 (11.1)	0.61
	n=15	n=15	n=14	n=13	n=11	n=12	n=25
Rotation task RT	1706 (579)	1433 (731)	1212 (405)	1684 (579)	1417 (434)	1032 (214)	.82
(ms)	n=14	n=14	n=14	n=10	n=10	n=10	n=24
Block Design	44.0 (9.0)	46.9 (9.0)	54.3 (7.9)	38.8 (13.6)	46.4 (15.1)	53.3 (13.8)	0.16
(WISC-III)	n=15	n=15	n=15	n=13	n=12	n=13	n=27
Rey-Osterrieth	29.1 (5.2)	30.5 (4.1)	30.4 (4.2)	25.4 (9.9)	28.5 (7.9)	29.3 (7.5)	0.35
(copying)	n=15	n=15	n=15	n=13	n=12	n=13	n=27

L’aromatasi e i suoi inibitori : dalla genetica alla terapia in età pediatrica.

Vertebral morphology in aromatase inhibitor treated males with idiopathic short stature or constitutional delay of puberty

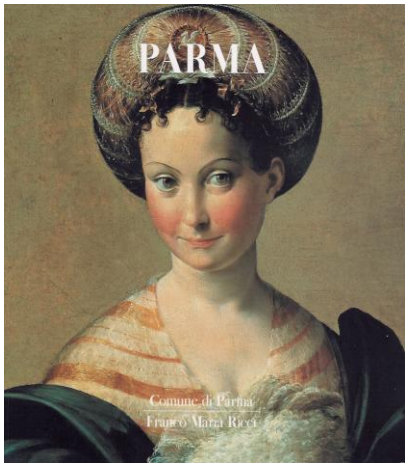
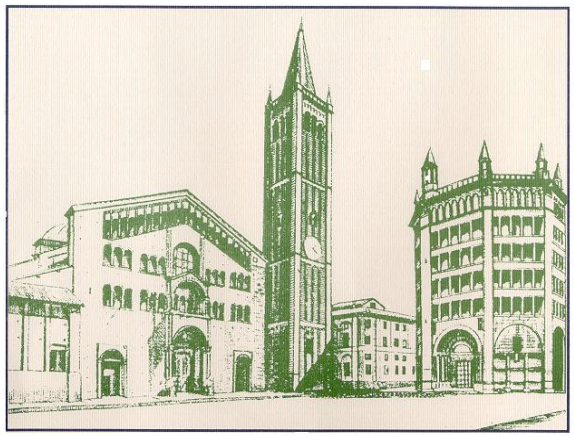
Matti Hero [1], Sanna Toiviainen-Salo [2], Sanna Wickman [1], Outi Mäkitie [1], Leo Dunkel [3]

Journal of Bone and Mineral Research 2010

A: Normal vertebrae and intervertebral discs on MRI in a placebo-treated participant with ISS (T2-weighted midsagittal slice, TR 4500 msec, TE120 msec).

B: Grade 3a vertebral body deformities in Th7-8 (arrows) in a letrozole-treated participant with ISS.

C: Grade 2a and 3a vertebral body deformities (Th7-9, arrows) with endplate irregularities and intervertebral disc changes in a letrozole-treated participant with ISS.

D: Normal vertebrae with disc and endplate abnormalities (arrow heads) including Schmorl’s node (arrow) in a letrozole-treated participant with ISS.

Grazie per l’attenzione