5th Joint Meeting on Adolescence Medicine

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PAST, PRESENT AND FUTURE USE OF GH

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Past, present and future use of GH: Summary

- ⇨ **Past indications for GH therapy**
- ⇨ **Current indications for GH therapy**
  - **Small for Gestational Age (SGA)**
- ⇨ **New perspectives for use of GH**
  - **Noonan Syndrome (NS)**
  - **Cystic Fibrosis (CF)**
  - **Thalassemia Major (TM)**
  - **Short-Stature Homeobox Containig Gene (SHOX) Deficiency**
  - **Idiopathic Short Stature (ISS)**
- ⇨ **Future of GH therapy**
  - **Background**
  - **Pharmacogenomics**
  - **Expressional studies**
  - **Pharmacoproteomics**
- ⇨ **Conclusions**

Past indications for GH therapy

Note AIFA 2006-2007 per l'uso appropriato dei farmaci
pubblicate sul Supplemento Ordinario alla Gazzetta Ufficiale n°7 del 10 Gennaio 2007

NOTA 39 AIFA *Ormone della crescita (somatotropina)*

La prescrizione a carico del SSN, su diagnosi e piano terapeutico di centri specializzati, Universitari o delle ASO, individuati dalle Regioni e dalle Province autonome di Trento e Bolzano, è limitata alle seguenti indicazioni:

Età evolutiva

- bassa statura da deficit di GH
- sindrome di Turner
- deficit staturale nell'IRC
- sindrome di Prader-Willi in soggetti prepuberi

Current indications for GH therapy

9-12-2009 Supplemento ordinario n. 229 alla GAZZETTA UFFICIALE *Serie generale n. 286*

DETERMINAZIONE 26 novembre 2009

Modifica alla nota AIFA 39 cui alla determinazione del 22 settembre 2009

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- bassa statura da deficit di GH
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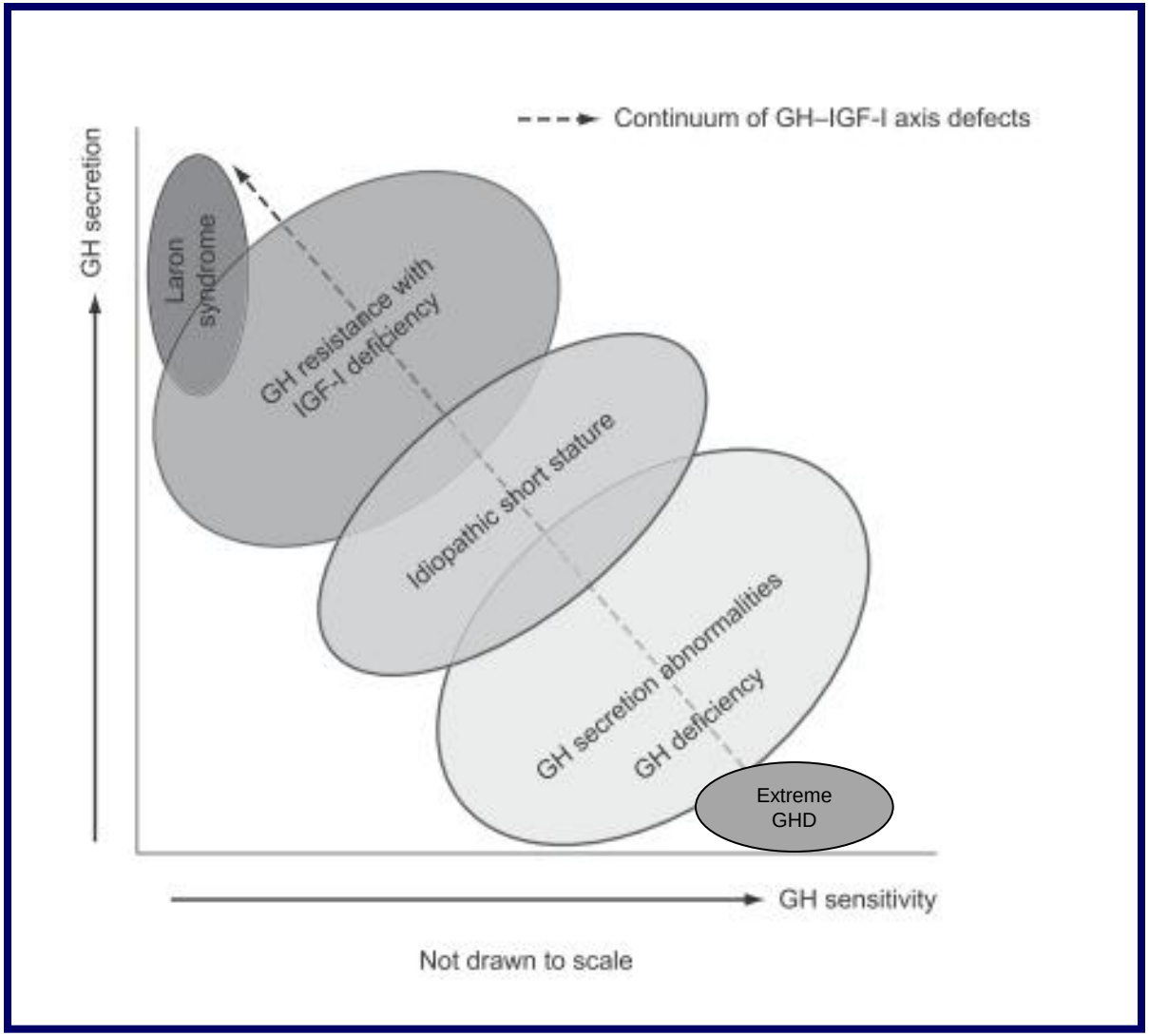
- sindrome di Prader-Willi in soggetti prepuberi
- bambini nati piccoli per l'età gestazionale (SGA - Small for Gestational Age) con età uguale o superiore a 4 anni

The continuum of GH-IGF-I axis defects



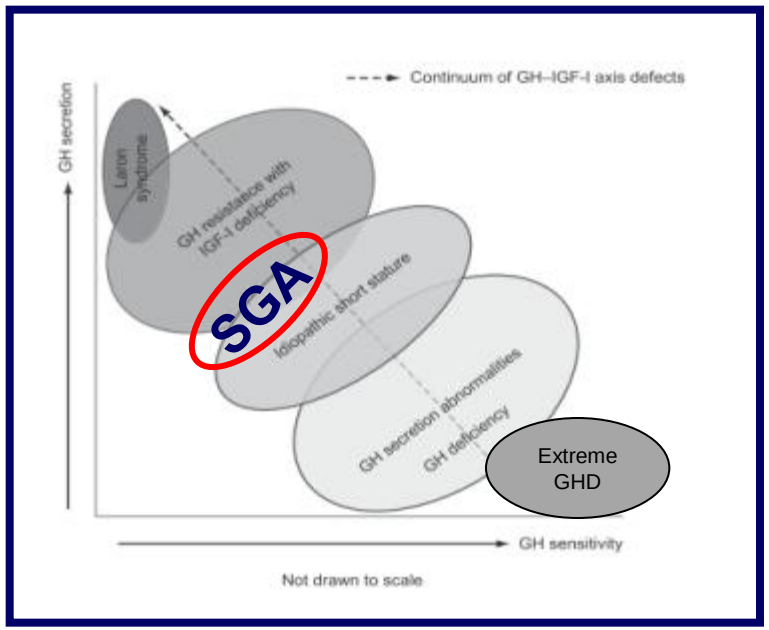
Adapted from M.O. Savage et al. Clin Endocrinol (Oxf). 2010

Current indications for GH therapy: Small for Gestational Age (SGA)

Approximately 10% of children born SGA will remain ≤ -2 SD for height throughout childhood and adolescence and into adulthood

In these children hormonal levels at birth and in early life are comparable to those found in patients with chronic diseases

⇨ Normal or elevated **GH** levels with low **IGF-I** and **IGFBP-3**



They show a partial peripheral resistance to GH

These children are potential candidates for GH therapy

SGA: Growth Hormone treatment

TABLE 1. GH use in short SGA children

	FDA-approved indication (2001)	EMEA-approved indication (2003)
Age at start (yr)	2	4
Height SDS at start	Not stated	−2.5 SD
Growth velocity before treatment	No catch-up	<0 SD for age
Reference to midparental height	Not stated	Height SDS > 1 SD below midparental height SDS
Dose (μg/kg·d)	70	35

EMEA, European Agency for the Evaluation of Medicinal Products; FDA, Food and Drug Administration.

Final height increases of **7-12 cm**, compared to untreated children

The dose (**0.48mg/kg/sett**) are double compared with those used in GHD patients, highlighting a **partial peripheral resistance**

To get a good catch-up growth, therapy should be initiated **as soon as possible** (difference between FDA and EMA)

P.E. Clayton. J Clin Endocrinol Metab. 2007

New perspectives for use of GH

1) Noonan Syndrome (NS)

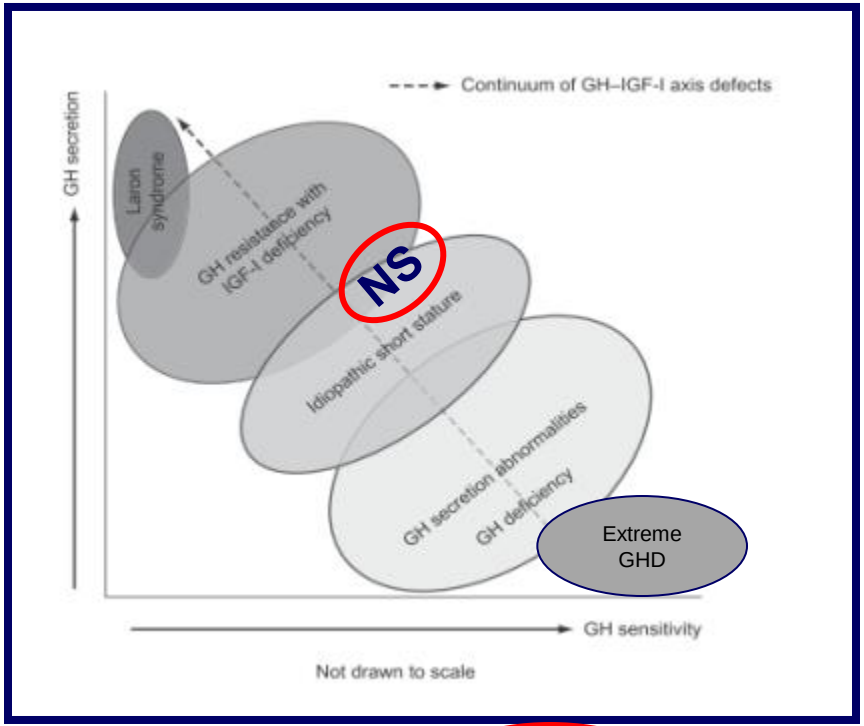
2) Cystic Fibrosis (CF)

3) Thalassemia Major (TM)

4) Short-Stature Homeobox- Containing (SHOX) Gene deficiency

5) Idiopathic Short Stature (ISS)

Noonan Syndrome (NS)



Short stature is reported in more than 80% of patients

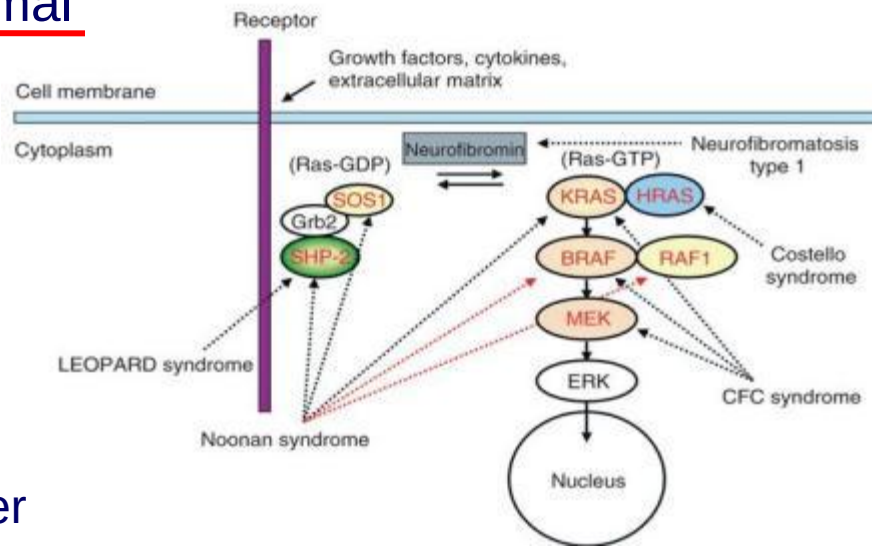
Mean adult height is 167.4 cm in males and 152.7 cm in females. Overall, mean adult height is approximately –2 SD

The secretion of growth hormone is normal

50% of NS presents PTPN11 mutations

Mutations lead to gain in function of SHP-2

New mutations have been identified in other genes involved in RAS-MAPK cascade (KRAS,SOS1,RAF1)



M.A. Razzaque et al. Nat Genet. 2007

R. Padidela. Horm Res. 2008

NS: Growth Hormone treatment

Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-receptor-type 11

Table 3 Evolution of height SDS (H-SDS) during growth hormone treatment in 29 children.

	At start	After 1 year	At final height
National standards	−2.8 (0.7, −4.1 to −1.8)	−2.3 (0.7, −3.8 to −1.2)*	−1.5 (0.8, −3.0 to −0.3)*
Noonan standards	0.0 (0.8, −1.4 to +1.2)	+0.6 (0.7, −1.0 to +2.1)*	+1.2 (0.8, −1.1 to +2.9)*

Data are presented as mean (s.d., range). *Significantly different from H-SDS at start ($P<0.0001$).

The subjects included were treated with GH until final height was reached, demonstrating the effectiveness of this therapy

Results:

- Final hight SDS increased of -1.5 and +1.2 in national standards and Noonan standards, respectively
- Response is comparable both in subjects with the PTPN11 mutation (tyrosine phosphatase-dependent) and in patients without this mutation

C. Noordam. Eur J Endocrinol. 2008

Cystic Fibrosis (CF)

Growth Hormone Treatment Improves Growth and Clinical Status in Prepubertal Children with Cystic Fibrosis: Results of a Multicenter Randomized Controlled Trial

Background:

- ⇨ Difficulty to gain weight and to attein a normal linear growth
- ⇨ Growth deficit not corrected during puberty
- ⇨ Poor weight gain associated with worsened clinical status

TABLE 1. Baseline characteristics of randomized subjects

	GH (16 females, 16 males)	NT (13 females, 16 males)
Age (yr)	10.3 ± 2.2	9.7 ± 1.7
Height SDS	−1.8 ± 0.7	−1.9 ± 0.6
Weight SDS	−1.7 ± 0.9	−1.6 ± 0.8
Body mass index	15.2 ± 1.4	15.4 ± 1.2
LM (kg)	20.2 ± 4.1	18.7 ± 3.6
BMC (g)	933 ± 265	893 ± 256
FVC (liter)	1.7 ± 0.5	1.6 ± 0.4
FEV1 (liter/min)	1.4 ± 0.4	1.3 ± 0.4

Two groups:

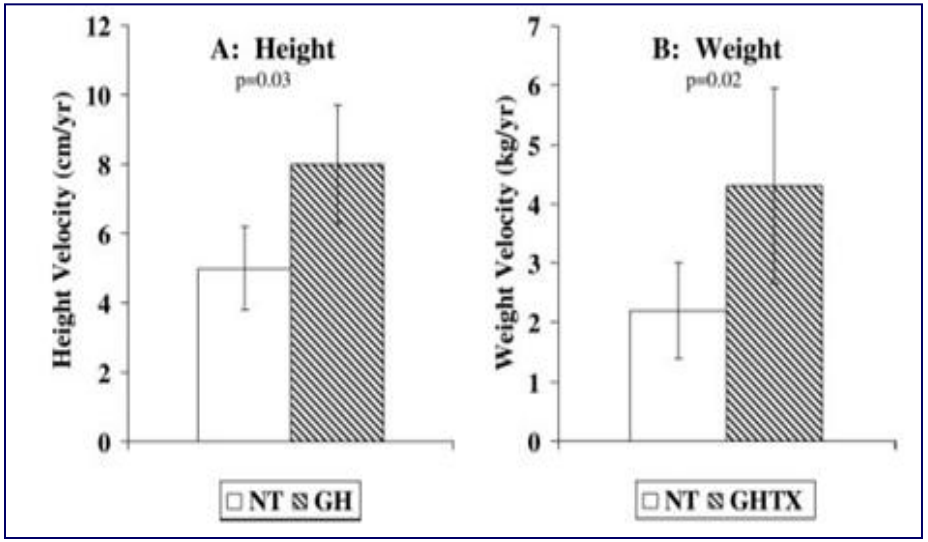
- controls (NT);
- GH treated

Dose:

0,3 mg/kg/wk

D.S. Hardin et al. J Clin Endocrinol Metab. 2006

CF: Growth Hormone treatment



Growth velocity & weight increase:

GV:

- NT: 3,8 +/- 1,4 cm/yr
- GH: 8,1 +/- 2.4 cm/yr

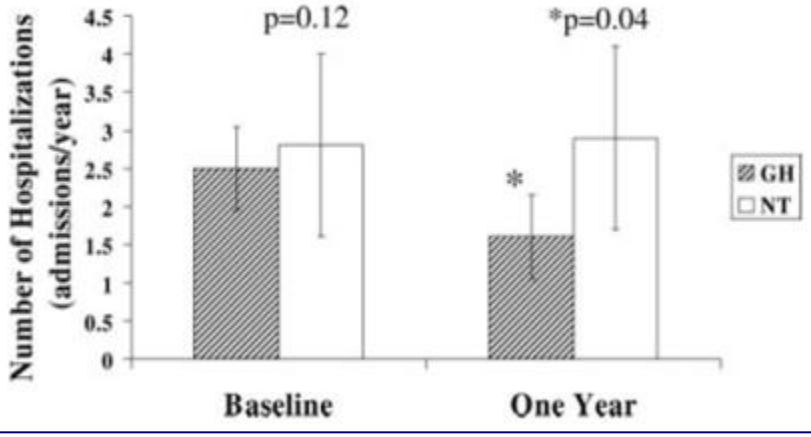
Weight increase:

- non GH: 2,1 +/- 0,9 kg/yr
- GH: 4,5 +/- 1.1 kg/yr

Lean body mass increase:

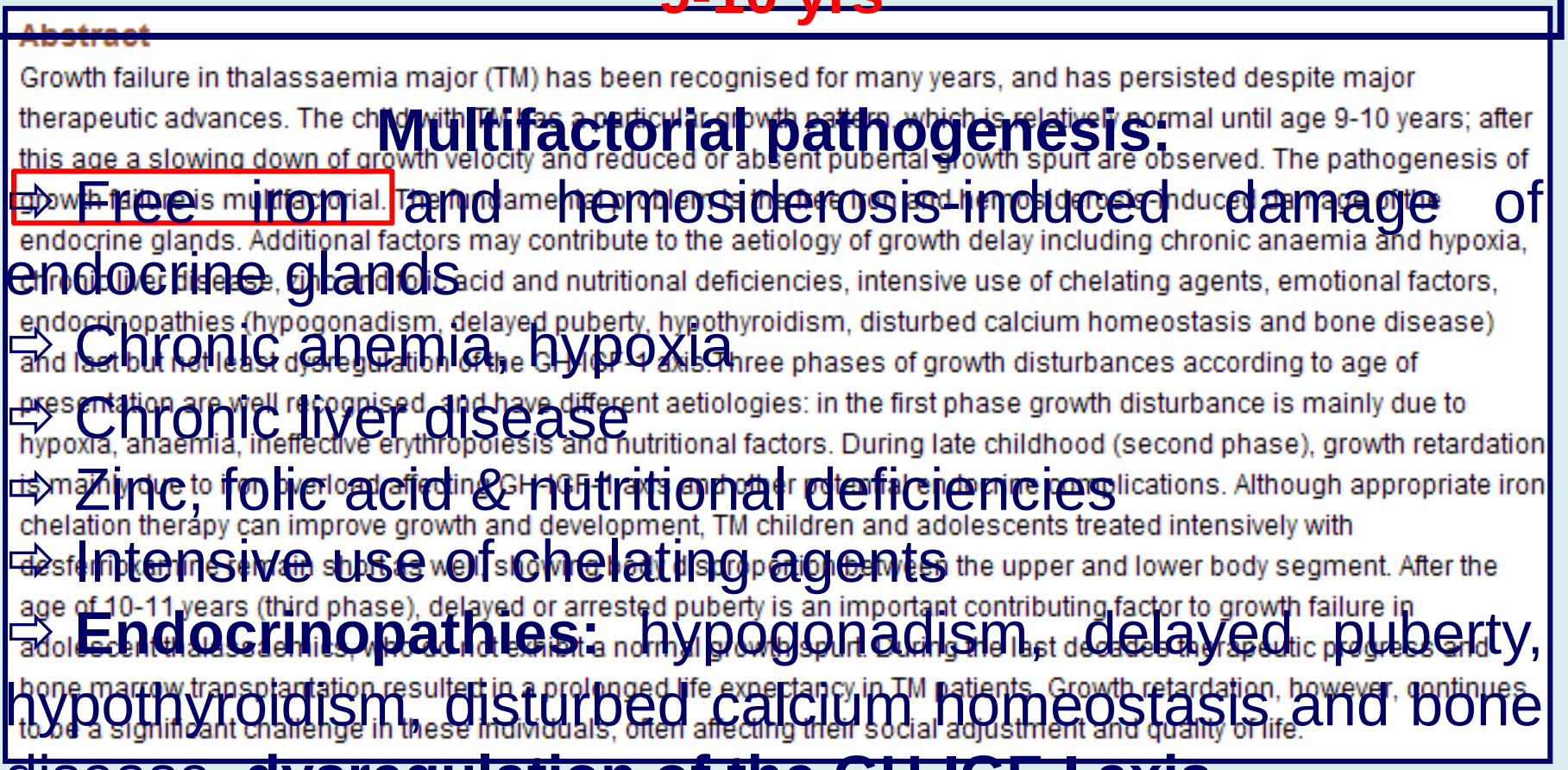
- NT: 2,1 +/- 1,6 kg;
- GH: 4,7 +/- 1,7 kg

Significant **reduction of hospitalizations for lung diseases** in subjects treated with GH



Thalassemia Major: Growth Failure

Growth, in well treated patients, is normal until 9-10 yrs



Abstract

Growth failure in thalassaemia major (TM) has been recognised for many years, and has persisted despite major therapeutic advances. The child with TM has a particular growth pattern, which is relatively normal until age 9-10 years; after this age a slowing down of growth velocity and reduced or absent pubertal growth spurt are observed. The pathogenesis of growth failure is multifactorial. The fundamental components are tissue hypoxia induced damage of the endocrine glands. Additional factors may contribute to the aetiology of growth delay including chronic anaemia and hypoxia, chronic liver disease, zinc and folic acid and nutritional deficiencies, intensive use of chelating agents, emotional factors, endocrinopathies (hypogonadism, delayed puberty, hypothyroidism, disturbed calcium homeostasis and bone disease) and last but not least dysregulation of the GH-IGF-I axis. Three phases of growth disturbances according to age of presentation are well recognised, and have different aetiologies: in the first phase growth disturbance is mainly due to hypoxia, anaemia, ineffective erythropoiesis and nutritional factors. During late childhood (second phase), growth retardation is mainly due to iron overload affecting GH-IGF-I axis and other potential endocrine complications. Although appropriate iron chelation therapy can improve growth and development, TM children and adolescents treated intensively with desferrioxamine several studies have shown that disproportion between the upper and lower body segment. After the age of 10-11 years (third phase), delayed or arrested puberty is an important contributing factor to growth failure in adolescent thalassaemics, who do not exhibit a normal growth spurt. During the last decades therapeutic progress and bone marrow transplantation resulted in a prolonged life expectancy in TM patients. Growth retardation, however, continues to be a significant challenge in these individuals, often affecting their social adjustment and quality of life.

Multifactorial pathogenesis:

⇨ Free iron and hemosiderosis-induced damage of endocrine glands

⇨ Chronic anemia, hypoxia

⇨ Chronic liver disease

⇨ Zinc, folic acid & nutritional deficiencies

⇨ Intensive use of chelating agents

⇨ **Endocrinopathies:** hypogonadism, delayed puberty, hypothyroidism, disturbed calcium homeostasis and bone disease, **dysregulation of the GH-IGF-I axis**

N. Skordis & A. Kyriakou. Pediatr Endocrinol Rev. 2011

Thalassemia Major: Growth Hormone treatment

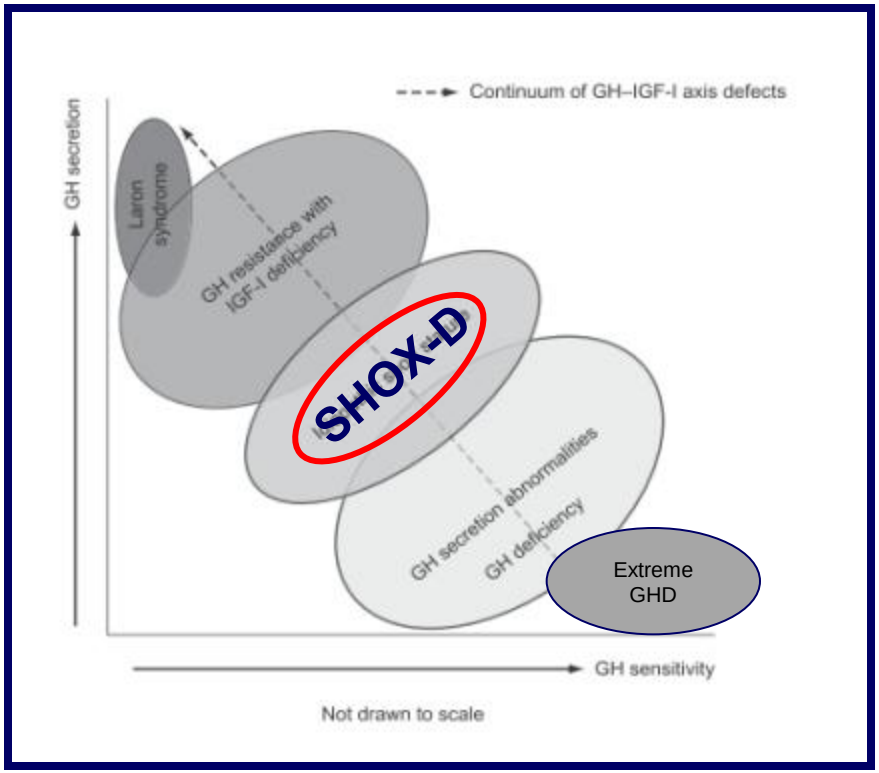
Table 1 - *Overview of efficacy of recombinant human GH in thalassemia major.*

Reference	No. pts	Treatment duration (yr)	FH	GH reserve	mg/kg/week *mg/m²/week	Efficacy	IGF-I	Bone age
Scacchi M. (51)	8	1		Decreased	0.2	GV 4.1 *vs* 2.1	NR	Not assessed
Low L.C.K. (52)	13	1		Normal	0.33	GV 8.3 *vs* 3.8	Increased	ΔBA/CA 0.95
De Sanctis V. (53)	15	1		Decreased	0.2	6 responders GV 6.36 *vs* 2.8 9 poor responders GV 4.76 *vs* 3.5	Increased	
Low C.P.K. (54)	6	4		Normal	0.33	GV persistently increased		
Cavallo L. (55)	28	1		Decreased	0.2	ΔH: +0.19 SDS-CA –0.10 SDS-BA	Increased	ΔBA/CA 0.80
Soliman A.T. (33)	6	1		Decreased	6*	GV 7.2 *vs* 3.8 ΔH +0.19 SDS-CA	Increased	
Theodoridis C. (7)	13	1.7-9.0	Yes	Decreased	0.17	ΔH *vs* start +1.95 (M) and +1.22 (F) SDS-CA		
Arcasoy A. (56)	10	1		Decreased	0.23	GV 6.27 *vs* 2.47	NR	
Katzos G. (57)	10	1		Normal	9.3*	GV 7.61 *vs* 4.22 ΔH +0.47 SDS-CA	Increased	ΔBA/CA 1.35
Sartorio A. (58)	5	1		Decreased	0.2	GV 6.1 *vs* 2.3	Increased	
Kwan E.Y.W. (59)	8	3		Normal	0.33	ΔH +0.99 SDS-CA +0.76 SDS-BA	NR	
Cavallo L. (60)	15	2		Decreased	0.2	ΔH +0.40 SDS-CA –0.22 SDS-BA	Increased	ΔBA/CA 1.10
Cavallo L. (60)	8	3		Decreased	0.2	ΔH +0.79 SDS-CA –0.15 SDS-BA	Increased	ΔBA/CA 1.00
Masala A. (61)	35	4.9 (2.2-10.3)		Decreased	0.2	persistently increased	Increased	
Wu K.H. (62)	8	2		Decreased	0.2	GV 7.1 (1st yr) and 6.8 (2nd yr) *vs* 3.1		
Cavallo L. (63)	25	3.3 (1.3-5.2)	Yes	Decreased	0.2	ΔH +0.86 SDS-CA –1.16 SDS-BA		
Low L.C.K. (9)	10	2.5-7	Yes	Normal	0.33	ΔH *vs* start + 0.61 SDS-CA		

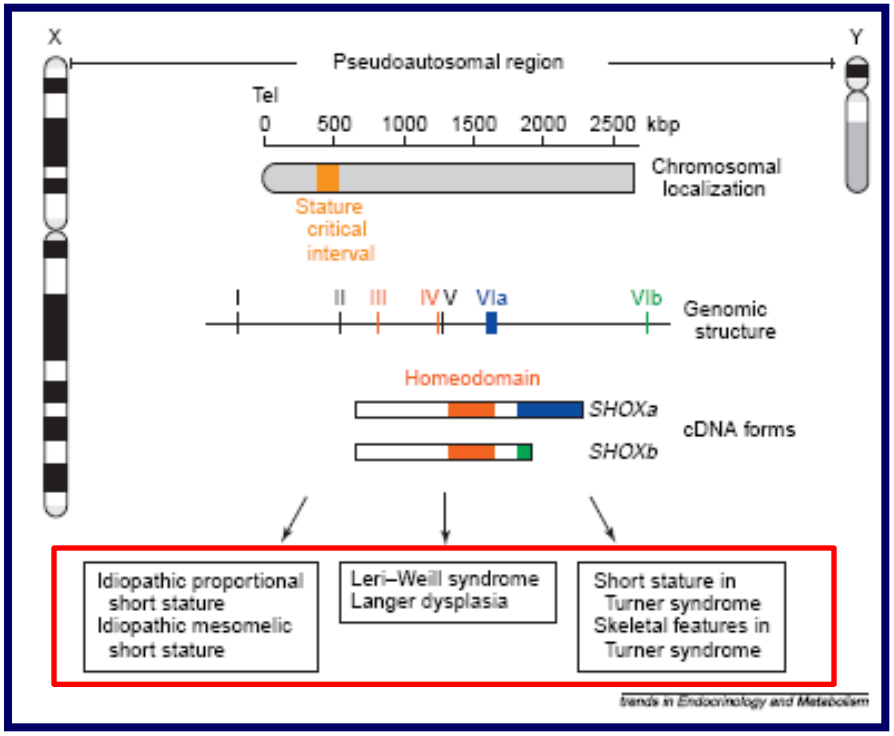
Pts: patients; GV: growth velocity (cm/yr); CA: chronological age; BA: bone age; FH: final height; NR: not reported; H: height; -BA: calculated for BA; -CA: calculated for CA; SDS: SD score.

M. Delvecchio & L. Cavallo. J Endocrinol Invest. 2010

Short-Stature Homeobox- Containing (SHOX) Gene deficiency



SHOX deficiency causes short stature with a **highly variable phenotype** which is frequently nonspecific in preschool children



2-3% of children with **ISS** shows SHOX mutations (pseudoautosomal region of X and Y chromosomes)

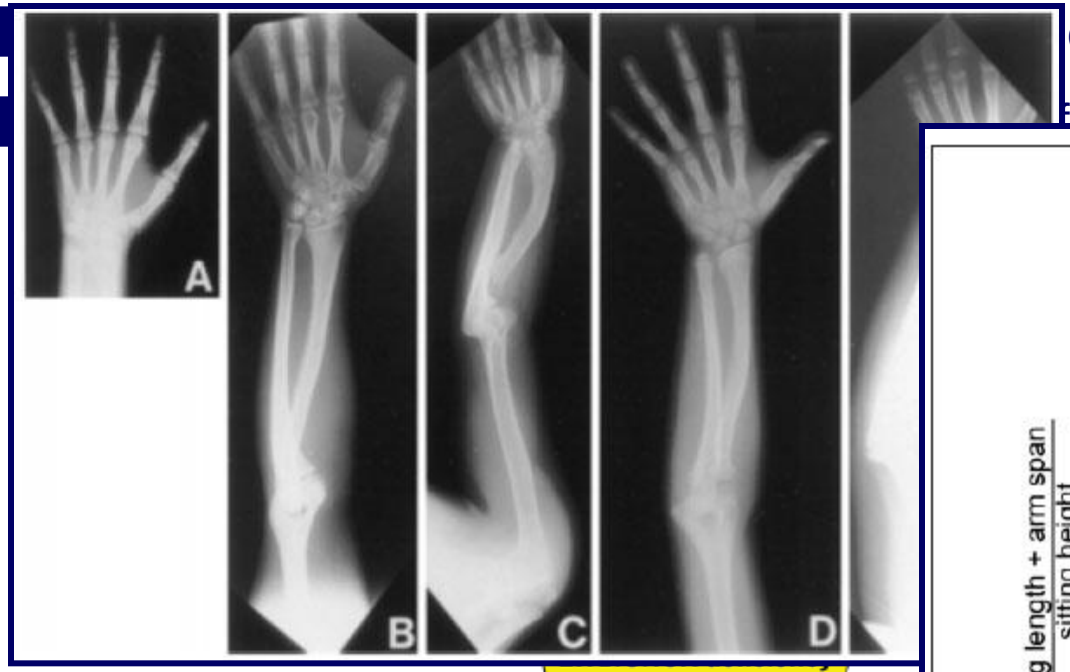
P. Cohen. J Clin Endocrinol Metab. 2008

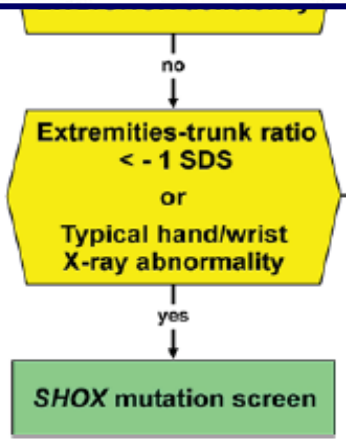
G.A. Rappold. Trends Endocrinol Metab. 2002

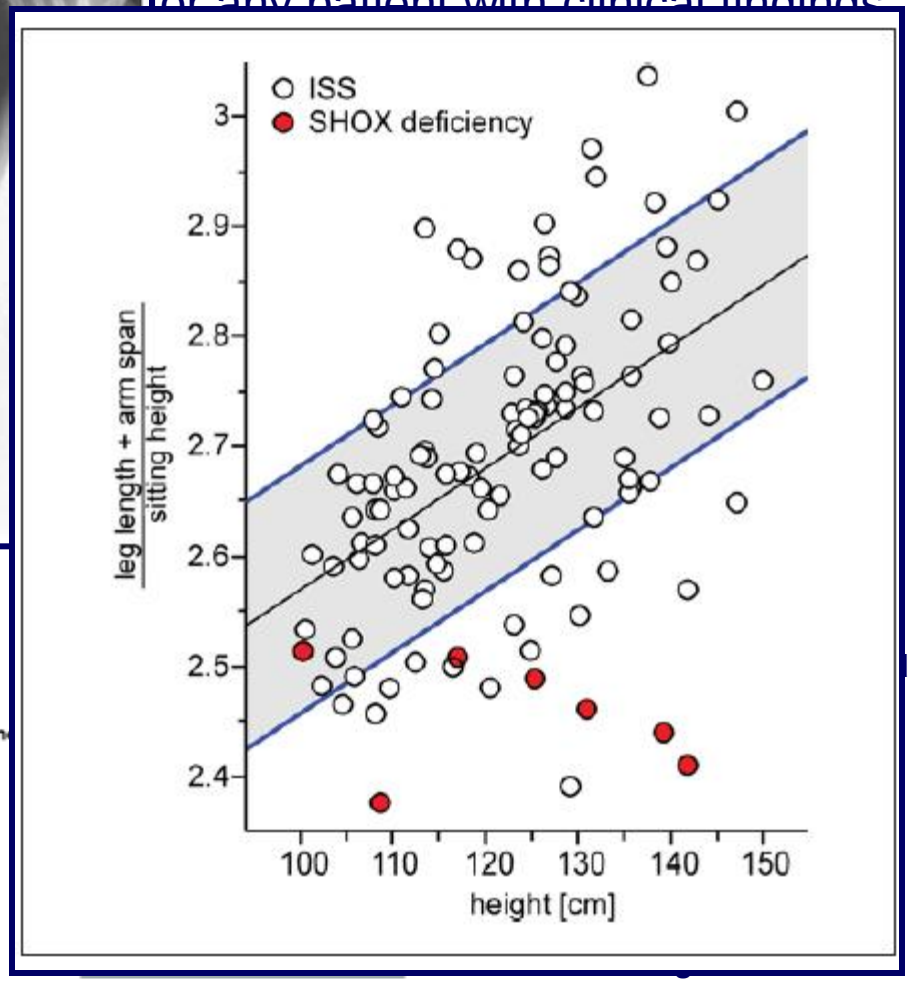
SHOX Deficiency: Diagnostic algorithm

ertaken in all chidren with ISS

or any patient with clinical findings



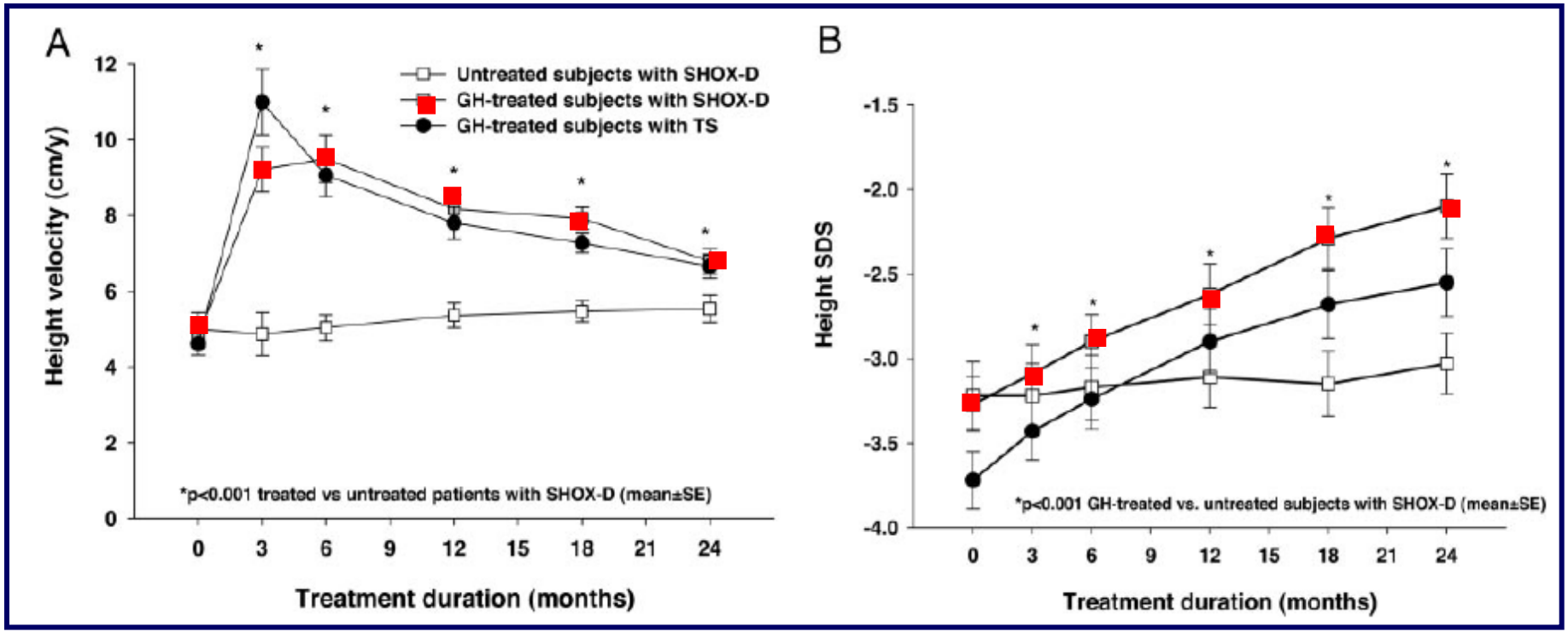




G. Binder et al. Horm Res Paediatr. 2011

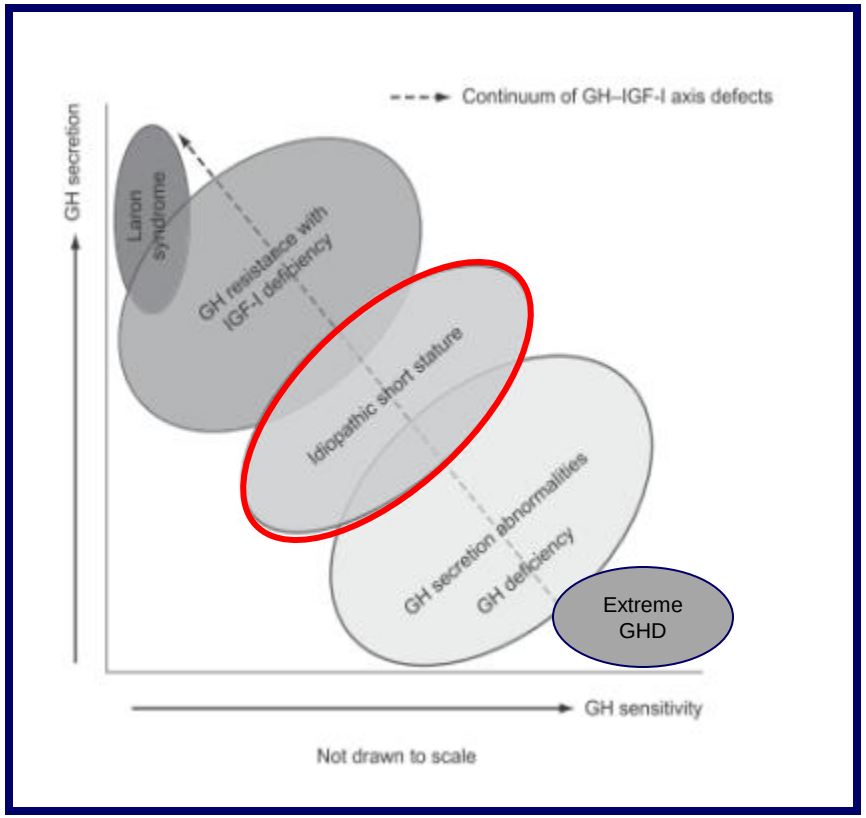
SHOX Deficiency: Growth Hormone treatment

Growth Hormone Is Effective in Treatment of Short Stature Associated with Short Stature Homeobox-Containing Gene Deficiency: Two-Year Results of a Randomized, Controlled, Multicenter Trial



W.F. Blum et al. J Clin Endocrinol Metab. 2007

Idiopathic Short Stature (ISS)



- ISS is a condition in which the height of an individual is more than 2 SD score below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional or chromosomal abnormalities
- Children with ISS have a normal birth weight and are GH sufficient
- It is estimated that approximately 60-80% of all short chidren, at or below -2 SDS, fit the definition of ISS

ISS: Growth Hormone treatment

Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature: A Summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop

In the United States and seven other countries, the regulatory authorities approved GH treatment (at doses up to **53 µg/kg/d**) for children shorter than 2.25 SDS

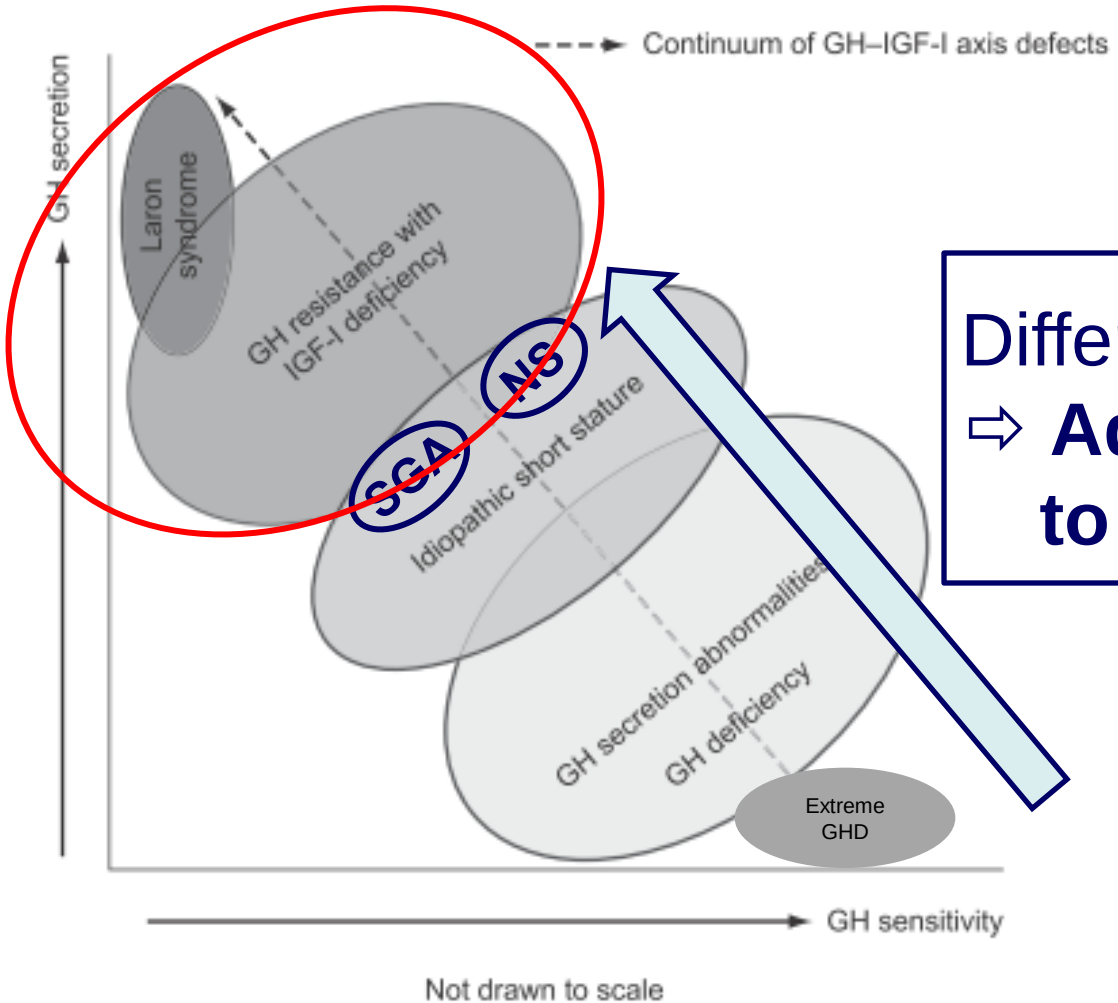
Successful first-year response to GH treatment includes an increase in height SDS of more than **0.3– 0.5**
The mean increase in adult height in children with ISS attributable to GH therapy (average duration of 4–7 yr) is **3.5–7.5 cm**

GH therapy for children with ISS has a **similar safety profile to other GH indications**

P. Cohen. J Clin Endocrinol Metab. 2008

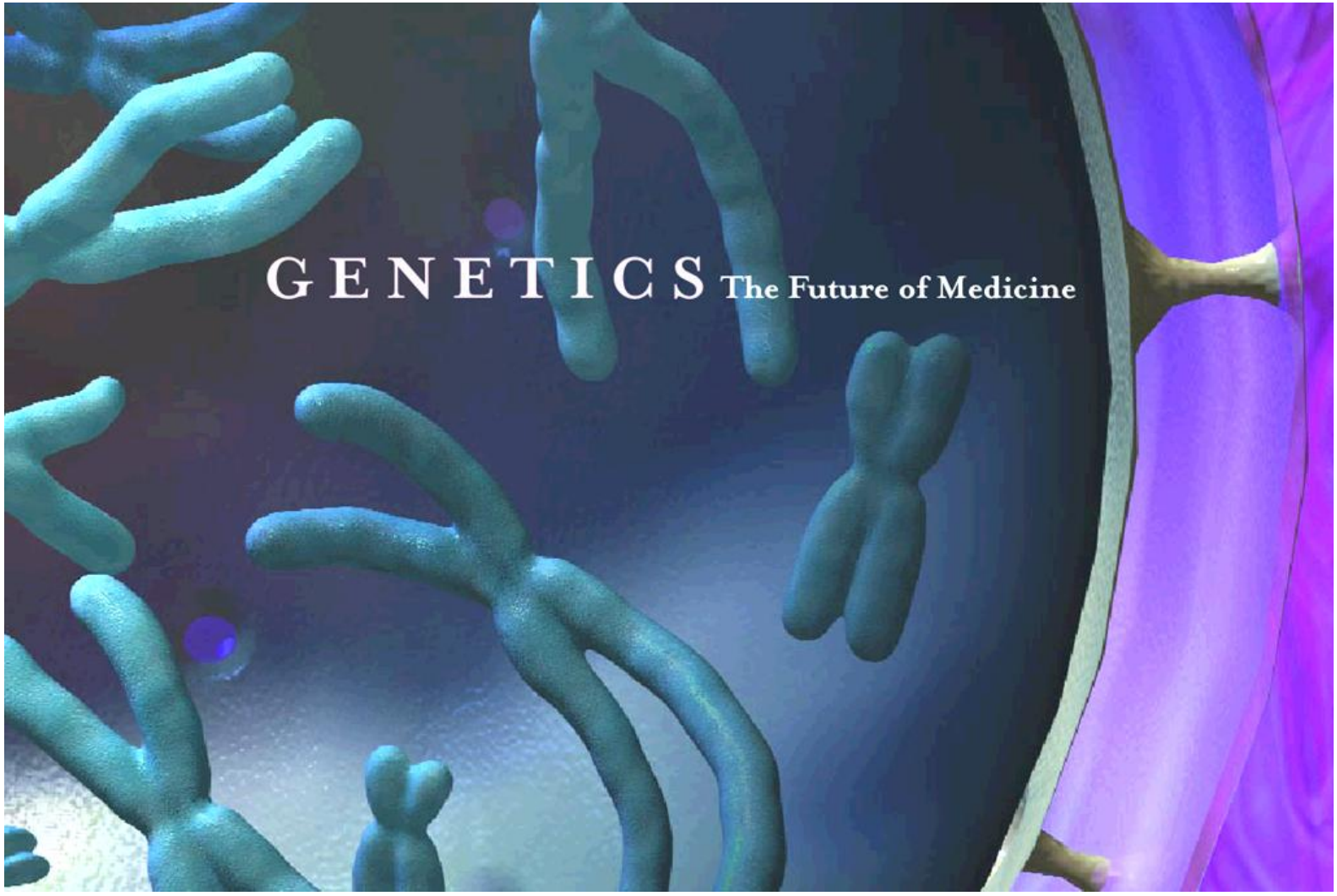
rhGH Doses & New Options

New treatment options: **rhIGF-I**



Different dose of rhGH
⇨ **Adjust the therapy to GH sensitivity**

Future of GH therapy



Mutational spectrum of GHD

Microdeletions

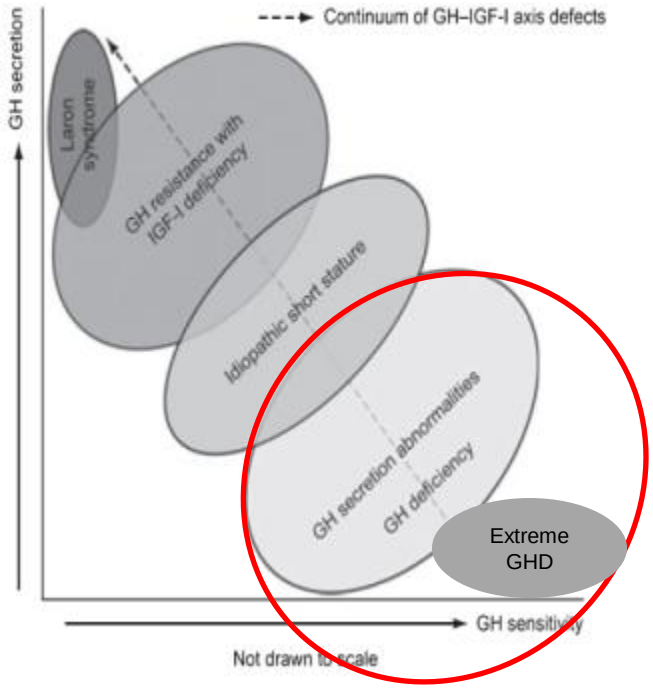
Deficiency type	Deletion	Codon	GH-antibodies on treatment	References
IA	TGcCTG	−10	yes	16
IA	GGCcTGC	−12	yes	Mullis unpublished.
II	CGGggatggggagacctgtaGT	5'IVS-3del+28 to +45	no	58
IA	GagTCTAT	55	no	17

Single base-pair substitutions in the *GH-1* gene coding region

Deficiency type	Mutation	Codon nucleotide	AB on treatment	References
IA	TGG –> TAG Trp –> stop	−7	yes	18
IA	GAG –> TAG Glu –> stop	−4	no	19
II	R183H	G6664A	no	67
II	V110F	G6191T	no	55
II	P89L	C6129T	no	68
II/bio-inactivity	CGC –TGC Arg –> Cys	77	no	91–95

Single base-pair substitutions affecting mRNA splicing

Deficiency type	5'IVS-3	Δ exon 3	Origin	References
II	GTGAGT –> GTGAAT	yes	Chile	51
II	GTGAGT –> GTGACT	yes	Turkey	Mullis unpublished
II	GTGAGT –> GTGAGC	yes	Turkey, Asia	52
II	GT –> AT	yes	Europe, America, Africa	53
II	GT –> CT	yes	Turkey	54
II	GT –> TT	yes	India	Mullis unpublished
II	GT–> GC	yes	Germany, Holland	55
	Exon splice enhancer	yes		
II	ESE1m1: +1 G–> T	yes	Japan	59
II	ESE1m2: +2A–>C	yes	Switzerland	Mullis unpublished
II	ESE1m3: +5A–> G	yes		60
	Intron splice enhancer	yes		
II	ISEm1:IVS-3 + 28 G –> A	yes		58
II	ISEm3:IVS-3 del28-45	yes		58
	Length of the intron	yes		
II	IVS3 del56–77	yes	Italy	66
	5'IVS-4			
IB	GT –> CT	no	Saudi Arabia	18
IB	GT –> TT	no	Saudi Arabia	20



P.E. Mullis et al. Best Pract Res Clin Endocrinol Metab. 2011

Mutational spectrum of GHI or IGF-I Deficiency

GH receptor d

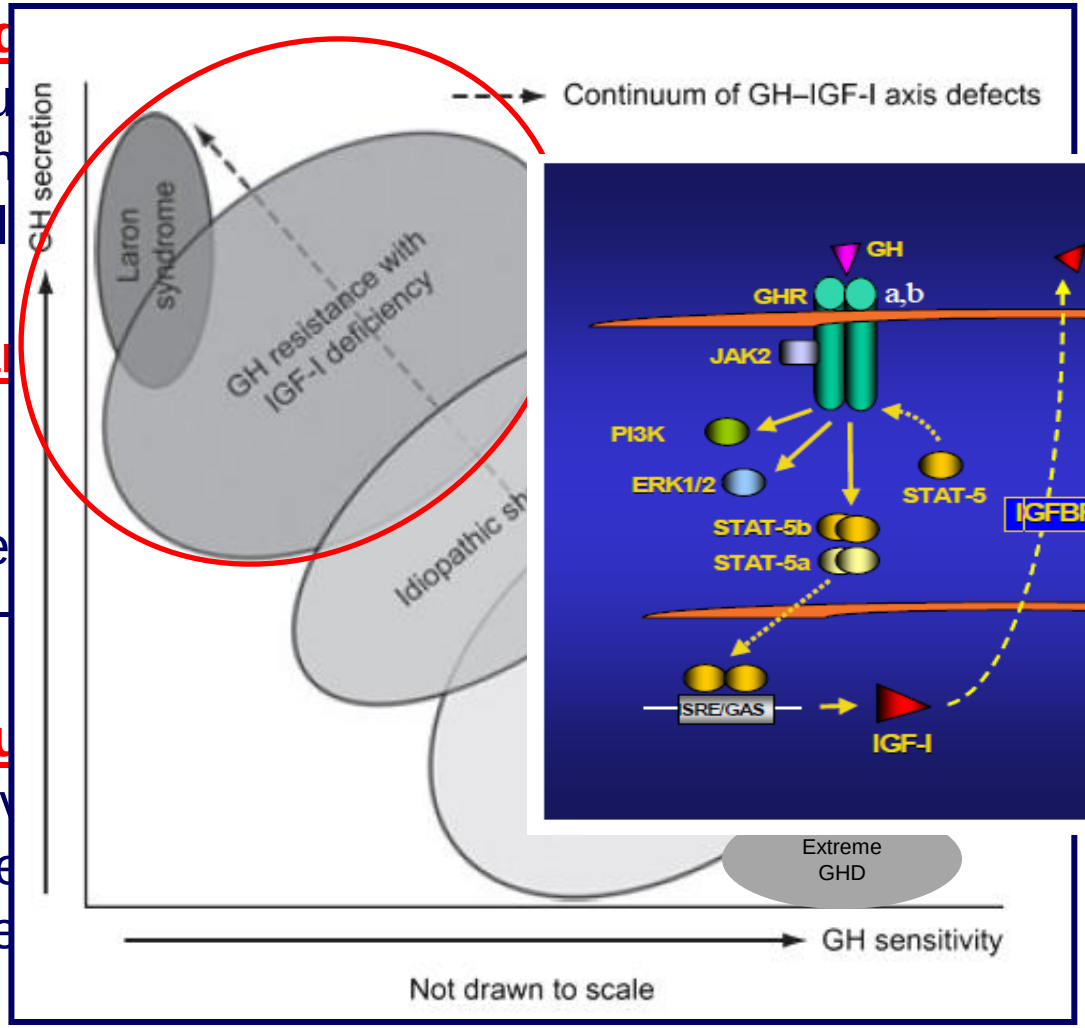
- Extracellu
- Transmem
- Intracellul

GH signal tra

- STAT 3
- STAT 5b
- SHP-2 (e
  K-RAS, H-

IGF-I gene mu

- Bio-inactiv
- Acid-labile
- IGF-I rece



M.O. Savage et al. Clin Endocrinol. 2010

Causes of short stature according to ESPE classification

A Primary growth disorders

A1 Clinically defined syndromes
- Turner syndrome
- Cornelia de Lange syndrome
- DiDeorge syndrome (velocardiofacial syndrome)
- Down syndrome
- Noonan syndrome
- Prader-Willi-Labhart syndrome
- Von Recklinghausen's disease (neurofibromatosis type 1)
- Silver-Russell syndrome

A2 Small for gestational age with failure of catch-up growth
- IGF-I deficiency, IGF resistance
- Due to known cause, e.g. prenatal infections, drugs, smoking, alcohol
- Idiopathic

A3 Skeletal dysplasias
- Achondroplasia
- Hypochondroplasia
- Dyschondrosteosis (Leri-Weill and other defects in the SHOX gene)
- Osteogenesis imperfecta I–VI
- Mucopolysaccharidosis (type IH, IS, II–VII)
- Mucolipidosis (type II and III)

A4 Dysplasias with defective mineralization

B Secondary growth disorders

B1 Insufficient nutrient intake (malnutrition)

B2 Disorders in organ systems
- Cardiac disorders
- Pulmonary disorders, e.g. cystic fibrosis
- Liver disorders
- Intestinal disorders, e.g. Crohn's disease, malabsorption syndromes
- Short bowel syndrome
- Renal disorders, e.g. Fanconi syndrome, renal acidosis
- Chronic anemia

B3 Growth hormone deficiency (secondary IGF-I deficiency)
- Idiopathic
- Genetic (HESX1, PROP1, POU1F1, LHX3, LHX4, GHRHR, GH)
- Head trauma
- Central nervous system infections
- Granulomatous diseases, e.g. histiocytosis

B4 Other disorders of the growth hormone-IGF axis (primary IGF-I deficiency and resistance)
- Bioinactive growth hormone
- Abnormalities of the growth hormone receptor (growth hormone insensitivity syndrome, Laron syndrome)
- Abnormalities of GH signal transduction, e.g. STAT5B defect
- ALS (acid-labile subunit) deficiency
- IGF-I deficiency
- IGF resistance (IGF1R defects, postreceptor defects)

B5 Other endocrine disorders
- Cushing syndrome
- Hypothyroidism
- Leprechaunism
- Diabetes mellitus (poorly controlled)
- Short adult stature caused by accelerated bone maturation, e.g. precocious puberty, hyperthyroidism, congenital adrenal hyperplasia, exogenous estrogens or androgens

B6 Metabolic disorders
- Disorders of calcium and phosphorus metabolism
- Disorders of carbohydrate metabolism
- Disorders of lipid metabolism
- Disorders of protein metabolism

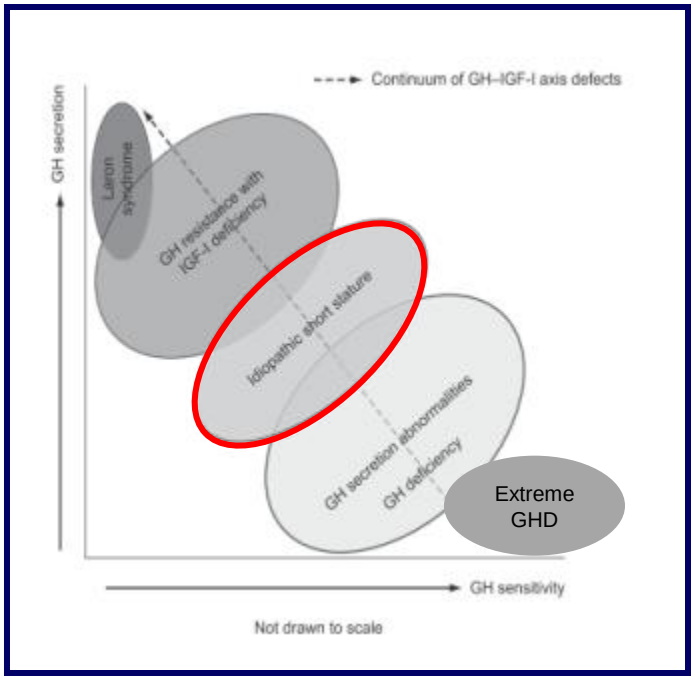
B7 Psychosocial
- Emotional deprivation
- Anorexia nervosa
- Depression

B8 Iatrogenic
- Systemic glucocorticoid therapy
- Local glucocorticoid therapy (inhalation, intestinal, other)
- Other medication
- Treatment of childhood malignancy
- Total body irradiation
- Chemotherapy
- Other specified iatrogenic causes

C Idiopathic short stature

C1 Familial (idiopathic) short stature

C2 Non-familial (idiopathic) short stature



>80% of causes of short stature are idiopathic

J.M. Wit. Horm Res. 2007

The “grey zone”: Background

⇨ GH is not the only mediator of skeletal growth

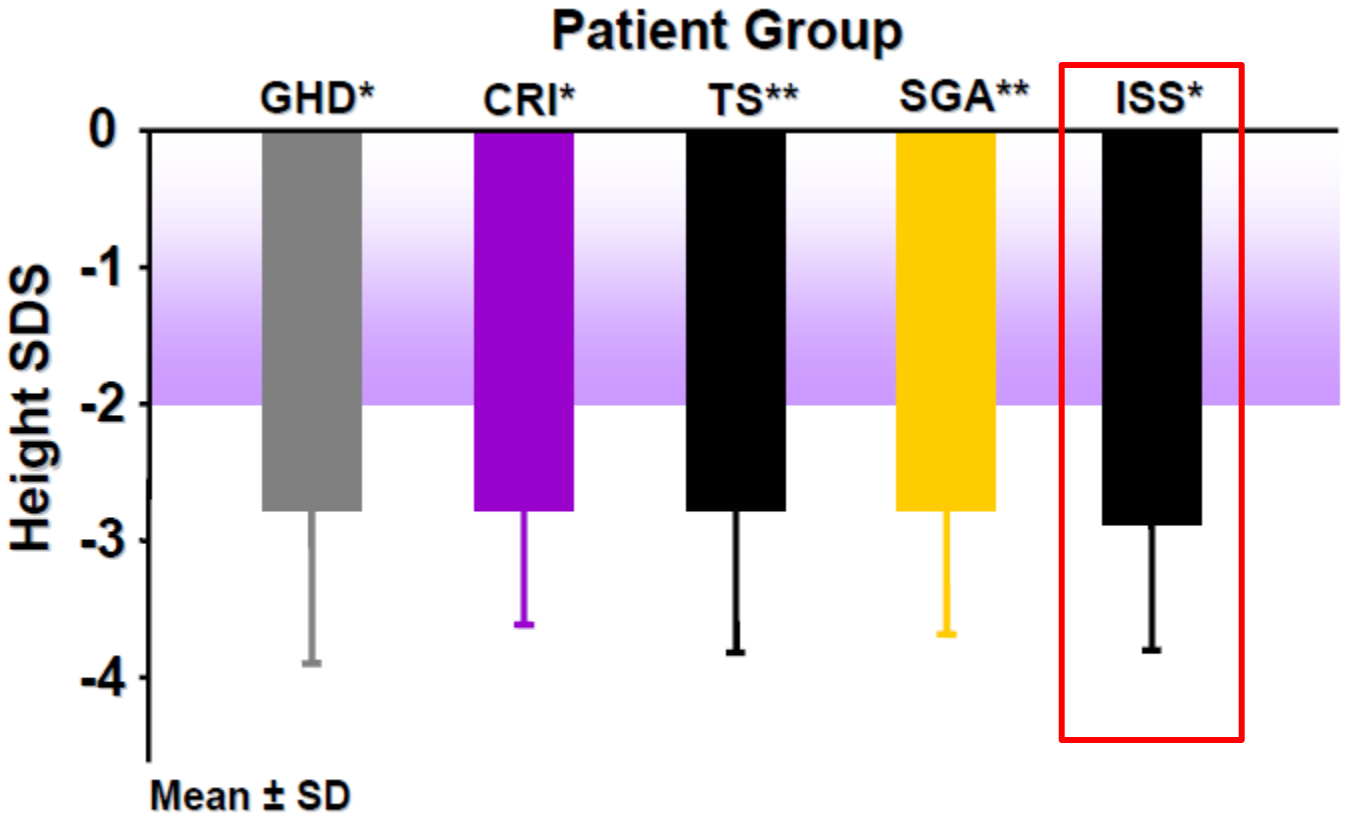
⇨ Tests use to diagnose GH deficiency presents arbitrary cut-off levels and low accurancy

⇨ Many genetic defects have been described and have presented important insights into the molecular basis of GHD and non-GHD growth failure

⇨ The problem of ISS: our diagnostic tools are not able to find an etiological diagnosis

The “grey” zone: Background (2)

⇨ Patients with ISS show a similar severity of short stature compared to other disorders



*National Cooperative Growth Study
**Kabi International Growth Study

The future: Pharmacogenomics & Personalized Medicine

Biological Determinants of Responsiveness to Growth Hormone: Pharmacogenomics and Personalized Medicine

Primus-E. Mullis

Paediatric Endocrinology, Diabetology and Metabolism, University Children's Hospital, Inselspital, Bern, Switzerland

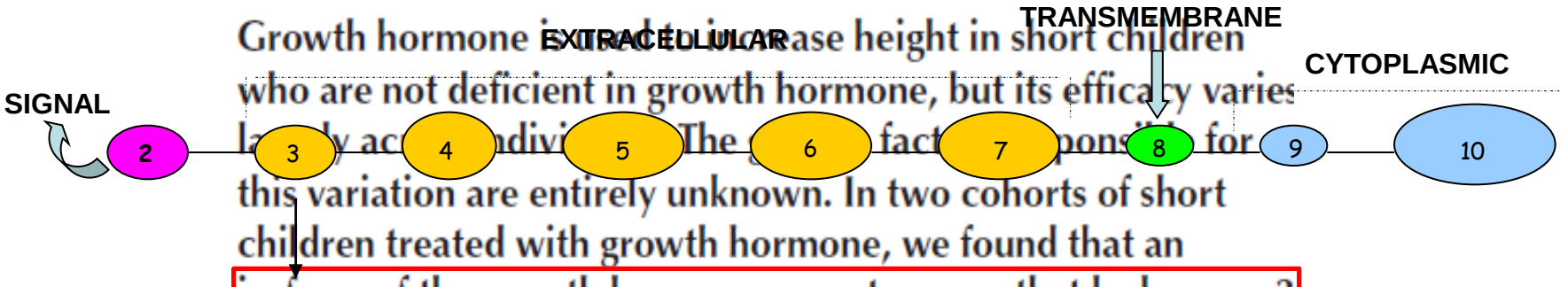
Pharmacogenetics (impact of one gene) and **pharmacogenomics** (impact of several genes, genome) is the study how a person's gene/genome can influence his response to GH treatment

In future the use of specifically designed and personalized prediction models may well facilitate the decision about whether the growth response to a given therapy (rhGH; rhIGF-1) in an individual child is appropriate or not

With regard to GH treatment, pharmacogenomics may play a major role in the individual response to therapy

Endocr Dev. 2010

The future: Pharmacogenomics



Growth hormone increases height in short children who are not deficient in growth hormone, but its efficacy varies largely according to individual. The genetic factors responsible for this variation are entirely unknown. In two cohorts of short children treated with growth hormone, we found that an isoform of the growth hormone receptor gene that lacks exon 3 (d3-GHR) was associated with 1.7 to 2 times more growth acceleration induced by growth hormone than the full-length isoform ($P < 0.0001$). In transfection experiments, the transduction of growth hormone signaling through d3-GHR homo- or heterodimers was ~30% higher than through full-length GHR homodimers ($P < 0.0001$). One-half of Europeans are hetero- or homozygous with respect to the allele encoding the d3-GHR isoform, which is dominant over the full-length isoform. These observations suggest that the polymorphism in exon 3 of *GHR* is important in growth hormone pharmacogenetics.

Table 2 Response

GHR genotype[a]	ort 2 d3/d3	*P*
Age at onset of treatment with growth hormone (y)	7.9 ± 0.7	NS
Growth hormone dose, year 1 (U per k per wk)	0.72 ± 0.2	NS
Growth hormone dose, year 2 (U per k per wk)	0.71 ± 0.2	NS
Δgr[b], year 1 (cm y^{-1})	4.88 ± 0.25	$<10^{-5}$
Δgr[b], year 2 (cm y^{-1})	3.69 ± 0.59	$<10^{-4}$

[a]fl, allele encoding the full- ... inistration.

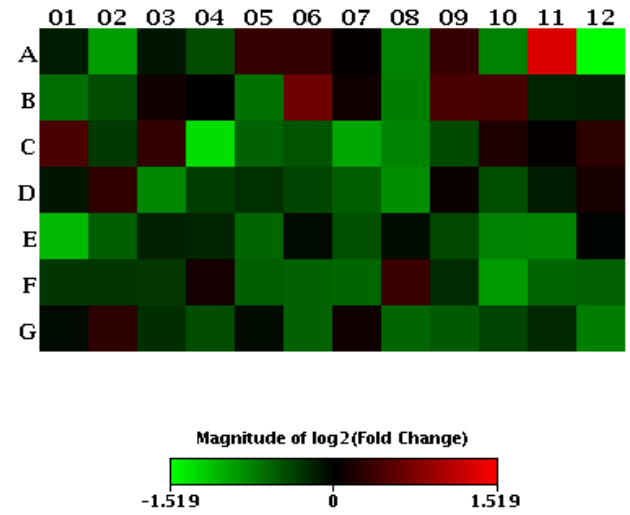
Values shown are mean ± s.e.m.

C. Dos Santos. Nat Genet. 2004

The future: Expressional studies, JAK/STAT pathway; ISS & SGA

ISS

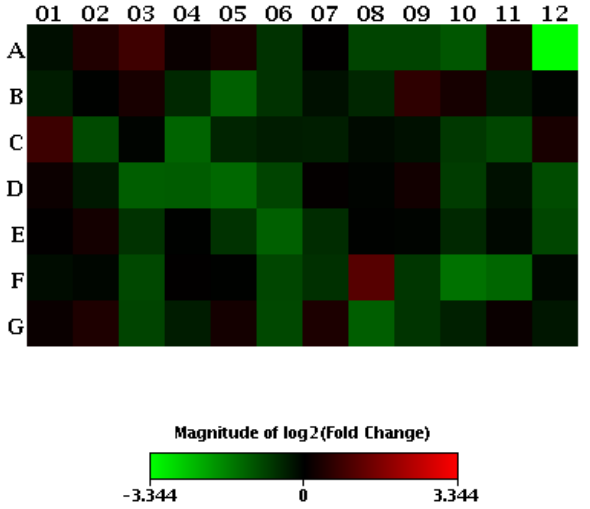
75% of genes (63/84) is down-regulated;
25% (21/84) is up-regulated



Gene name	Well	Fold change	P-value
JAK2	D2	1.22	0.220
STAT1	G2	1.20	0.237
STAT3	G4	-1.37	0.204
STAT5a	G6	-1.50	0.083
STAT5b	G7	1.06	0.815
IFNγ	C1	1.34	0.349
GHR	B10	1.33	0.637
CXCL9	A11	2.48	0.014

SGA

73% of genes (61/84) is down-regulated;
27% (23/84) is up-regulated



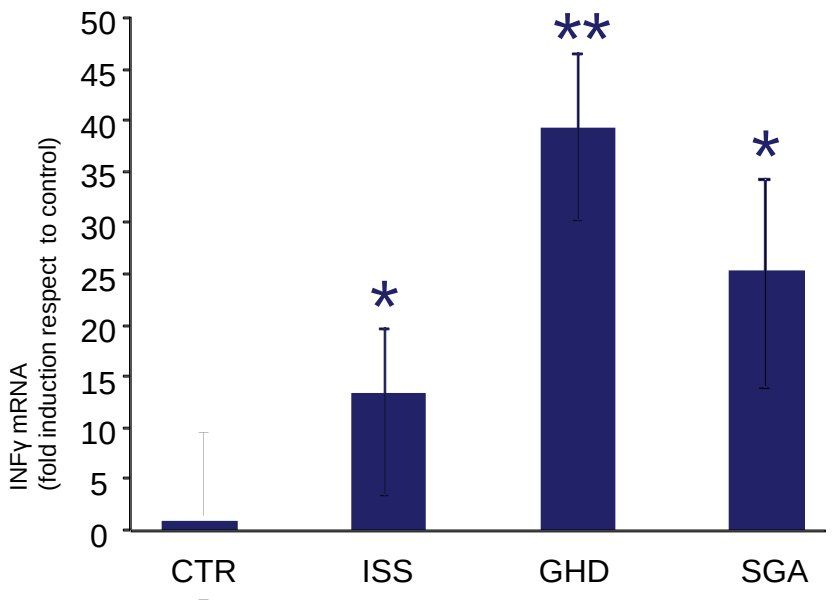
Gene name	Well	Fold change	P-value
JAK2	D2	-1.25	0,348
STAT1	G2	1.32	0,170
STAT3	G4	-1.29	0,053
STAT5a	G6	-1.92	0,114
STAT5b	G7	1.28	0.253
GHR	B10	1.21	0,540
CXCL9	A11	1.24	0,524
IFNγ	C1	1.74	0,011
GBP1	B9	1.51	0.019

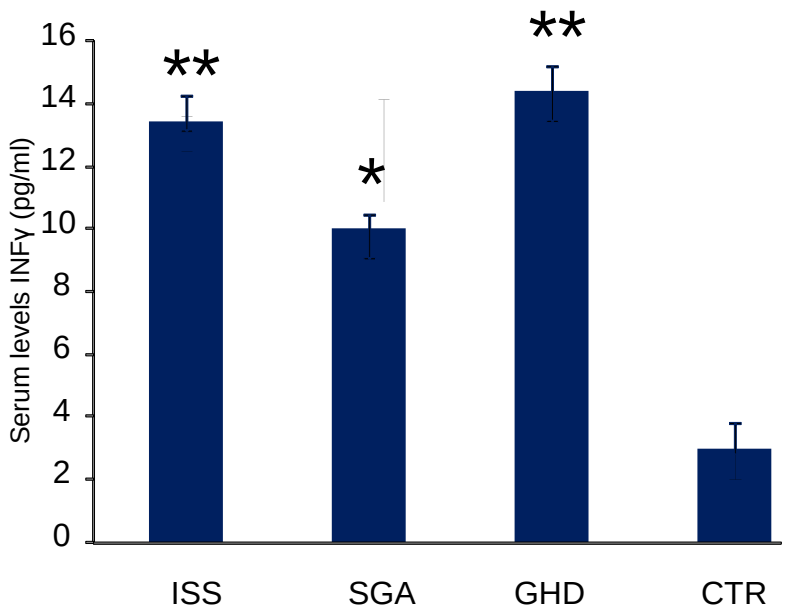
L. Trovato et al. Pituitary. 2011. In press

The future: Expressional studies, role of INFγ

IFNγ: mRNA expression & serum levels in the different study groups

*p<0,05; **p<0,01





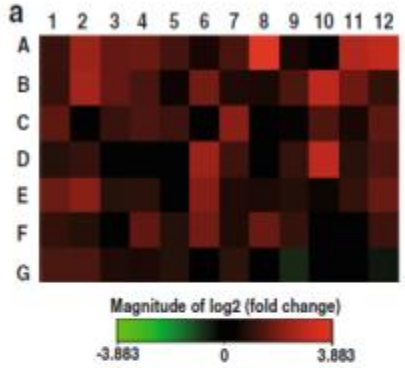
We showed an increase of IFNγ both as mRNA quantitative expression and serum levels in ISS, GHD and SGA patients without catch-up growth

L. Trovato et al. Pituitary. 2011. In press

The future: Expressional studies, JAK/STAT pathway; GHD

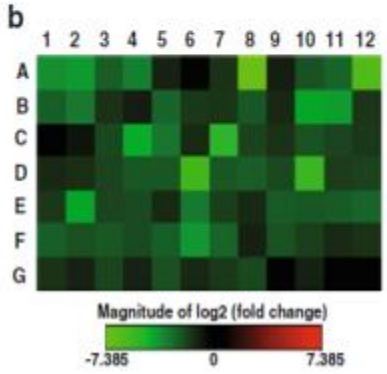
Isolated GHD: investigation and implication of JAK/STAT related genes before and after rhGH treatment

Letizia Trovato · Stefania Riccomagno · Flavia Prodam · Giulia Genoni · Gillian E. Walker · Stefania Moia · Simonetta Bellone · Gianni Bona



Over-Expressed genes in GHD children vs.Control Group

Position	Gene Symbol	Fold Regulation	p-value
A08	CRP	14.67	0.0500
B2	F2	5.95	0.0294
B10	GHR	7.93	0.0003
D06	MMP3	5.38	0.0183
D10	NOS2A	8.02	0.0356



Under-Expressed genes in GHD children after six month of GH

Position	Gene Symbol	Fold Regulation	p-value
A08	CRP	-167.15	0.047
B10	GHR	-19.49	0.037
C07	IL4	-33.24	0.040
D06	MMP3	-48.50	0.012

Abstract Isolated GH deficiency (IGHD) is a rare disorder that occurs as an idiopathic form in most cases. The pathway JAK/STAT promotes cellular growth and it could be implicated in this condition. In order to characterize IGHD in the pediatric population and identify genes differently expressed before and after GH therapy, we performed a quantitative evaluation of 84 genes related to the JAK/STAT pathway which, by promoting cellular growth. RT^2 Profiler PCR Array and the other/subsequent evaluations were performed in three children with severe IGHD before and after 6 months of GH therapy and in three matched normal children. Gene profiling was modified by the IGHD status and the GH therapy, with a modulation of GHR and some inflammatory genes such as CRP. We found a heterozygous nonsense mutation R43X in the GHR gene in two out of three IGHD subjects, despite a good response to therapy. After therapy cardiovascular markers linked to genes as IL6, IL8 and TNF-α displayed a trend toward reduction. Pre- and post therapy status differently affects gene expression. Mutational screening of GHR may be useful in investigating IGHD's etiology. Genes linked to inflammation suggest to evaluate cardiovascular risks also in pediatric IGHD subjects.

Pituitary. 2011

The future: Pharmacoproteomics

Pharmacogenomics and pharmacoproteomics in the evaluation and management of short stature

Ron G Rosenfeld

Nagalla and Rosenfeld have evaluated protein expression patterns in patients with GHD and GHI resulting from mutations of the GHR gene using a variety of **proteomic techniques**, and have identified discriminatory serum protein patterns

Patients with GHI or GHD could be distinguished from controls with greater than 99% confidence; GHI and GHD serum patterns could be discriminated from each other with greater than 96% confidence

These observations require large-scale confirmation, but strongly support the diagnostic value of high throughput proteomic technologies

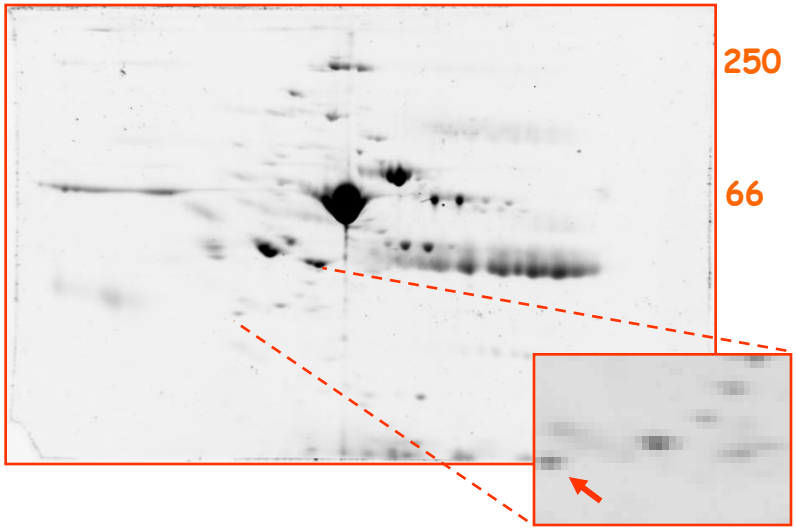
Eur J Endocrinol. 2010

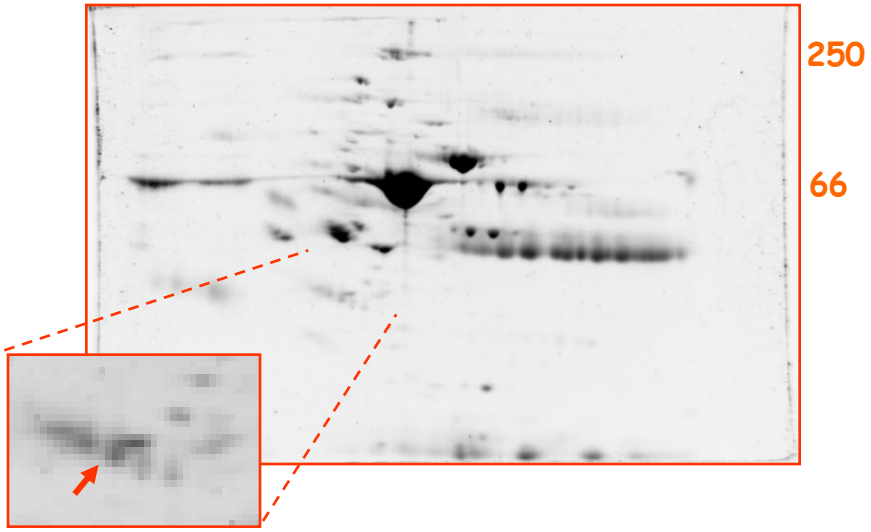
Proteomics: GHD vs BS

GHD 1,9 yrs

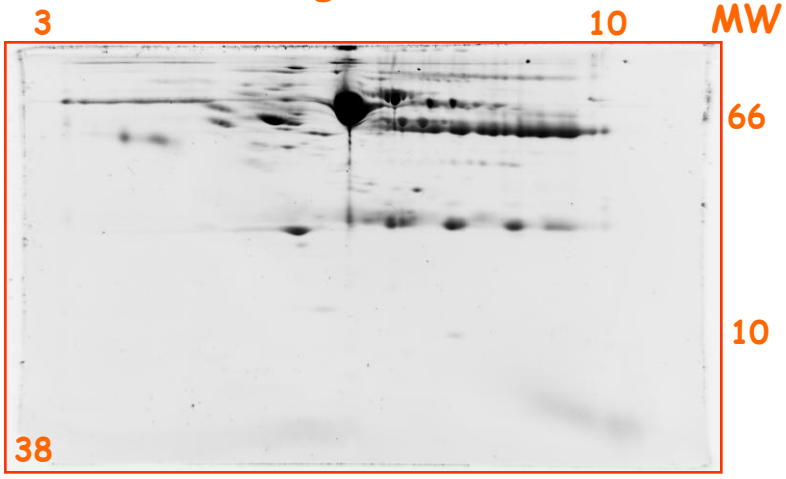
BS 12,2 yrs

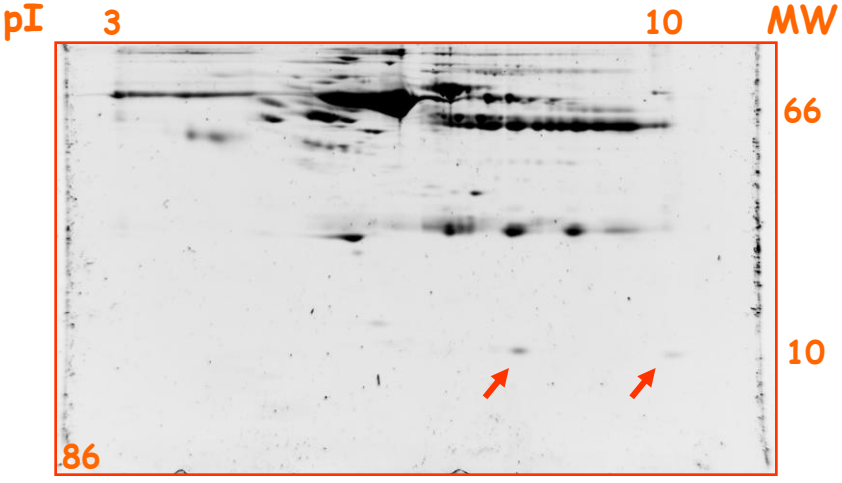
High Molecular Weight





Low Molecular Weight

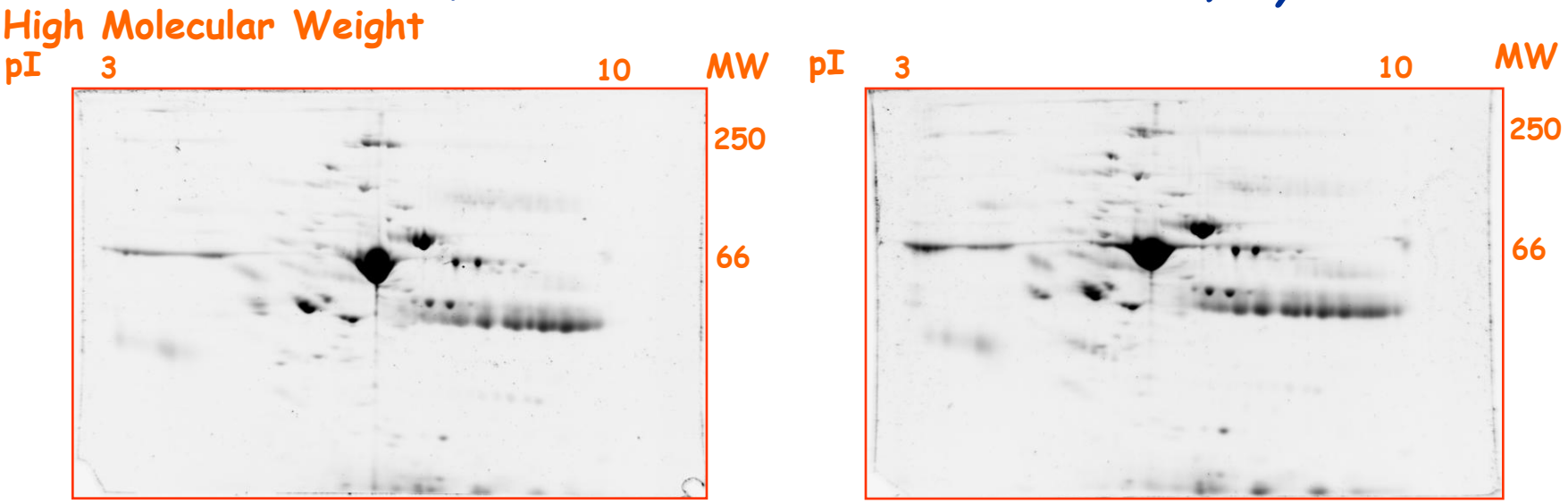




Proteomics: GHD vs ISS

GHD 11,9 yrs

BS 12,2 yrs



n=3	*GHD Female 11,9 yrs*	*ISS Female 12,2 yrs*
# Spot	198	266
# NO Spot	68	0
↑↓ Expression (2-fold)	8	42

Conclusions

- There are a lot of new indications and future perspectives for GH therapy
- Many genetic defects have been described and have presented important insights into the molecular basis of GHD and non-GHD growth failure
- Many causes of short stature still remain idiopathic and ISS represents a “grey zone” where our diagnostic tools are not able to find an etiological diagnosis and consequently an adeguate treatment
- Future approaches in the management of short stature will be pharmacogenomics, expressional studies and pharmacoproteomics