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IGF-1 DEFICIENCY

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DISCLOSURES

Grants/Honoraria from Ascendis, Genexine, Ipsen, Merck KGaA, NovoNordisk, Pfizer, Sandoz

IGF-1 DEFICIENCY

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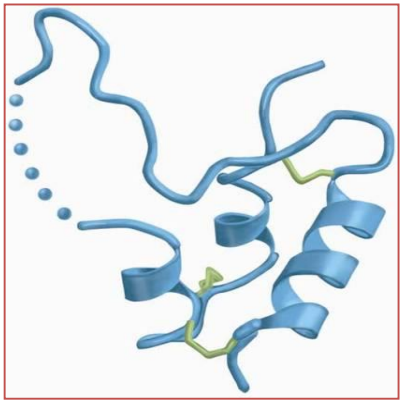
PLAN OF PRESENTATION

- What is IGF-1?
- Factors that influence IGF-1 production
- Causes of IGF-1 deficiency
- Primary IGF-1 deficiency
- Treatment of IGF-1 deficiency

IGF-1, insulin-like growth factor-1

REGULATION OF IGF-1 SECRETION AND ACTION

Crystal structure of human insulin-like growth factor-1 (IGF-1)



- IGF-1 is a small (7.5 kDa) **intracellular protein** produced in response to growth hormone (GH)
- Nutrition, through insulin, regulates **IGF-1 synthesis in the liver**
- The **primary effect** of IGF-1 is to provide a signal to cells that adequate nutrient is available to:
  - avoid apoptosis
  - enhance cellular protein synthesis
  - enable cells to undergo hypertrophy in response to stimulus
- Each process is **regulated together with insulin** in the appropriate target tissue

GH, growth hormone; IGF-1, insulin-like growth factor-1

METABOLIC ACTIONS OF IGF-1

'IGF-1 has structural homology with insulin related to the evolution of proinsulin, IGF-1 and IGF-2 from a single precursor molecule.

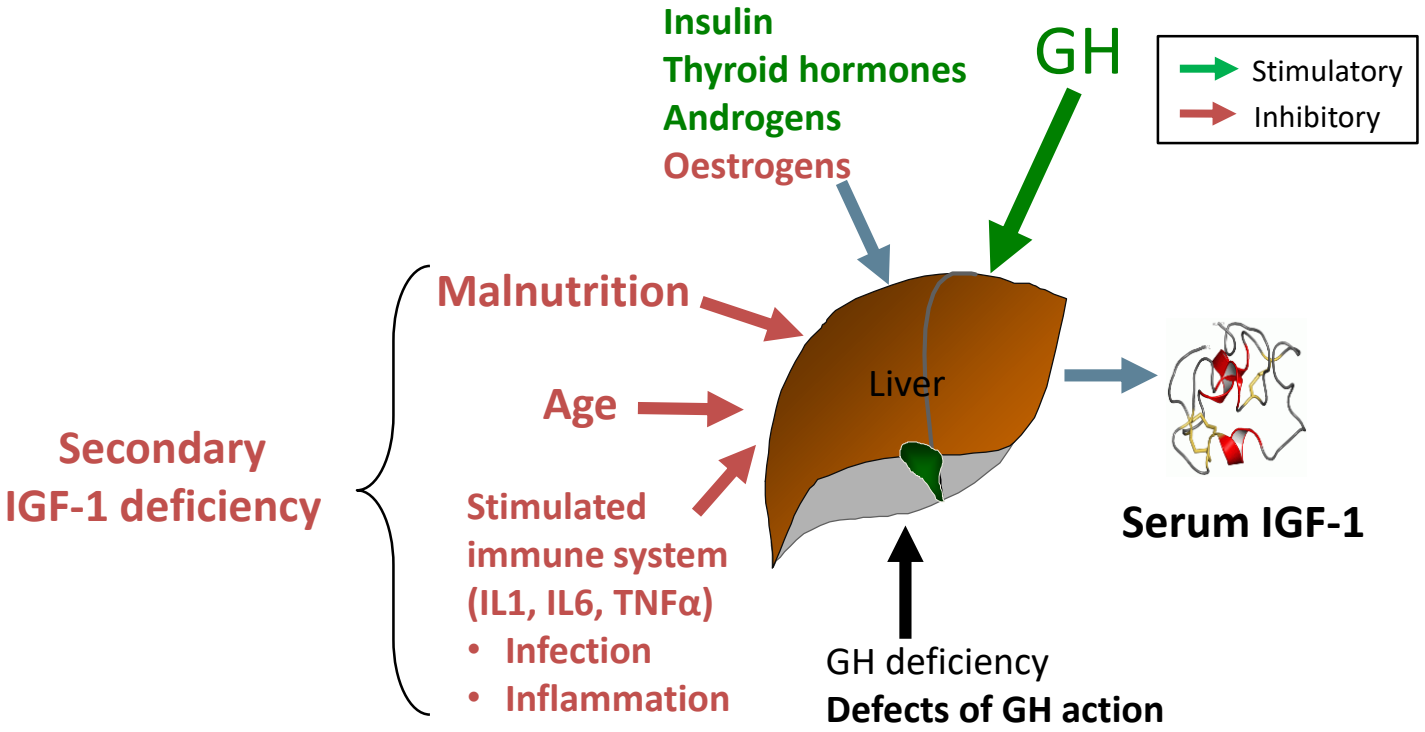
The function of the precursor molecule was to provide a chemical signal to cells within primitive organisms that adequate nutrient was present for protein synthesis and cell proliferation.

The primary variable regulating plasma IGF-1 concentrations is nutrient intake'.

GH, growth hormone; IGF-1, insulin-like growth factor-1

Clemmons DR. Endocrinol Metab Clin North Am. 2012;41:425-43

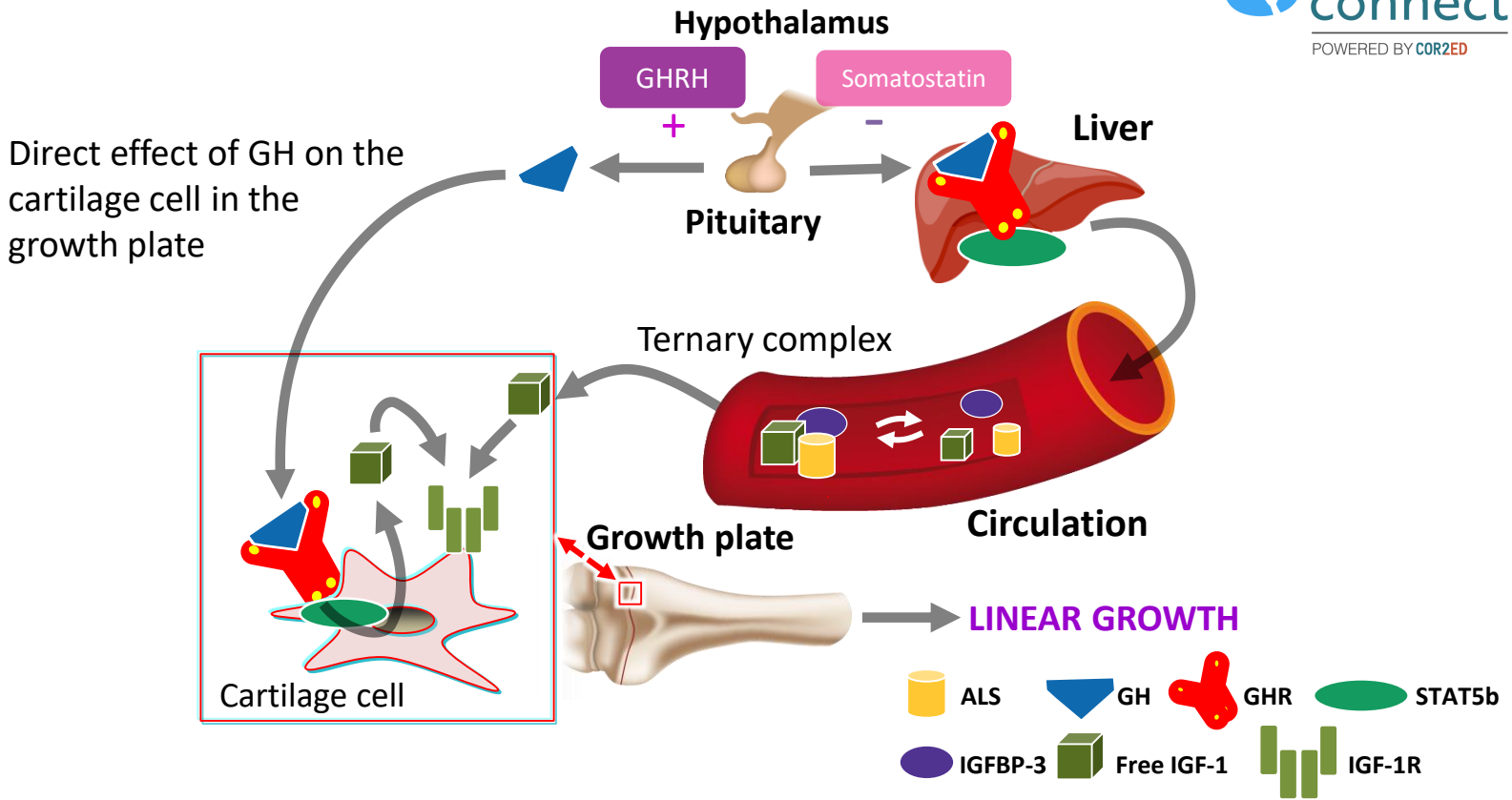
FACTORS THAT INFLUENCE SERUM IGF-1



GH, growth hormone; IGF-1, insulin-like growth factor-1; IL, interleukin; TNFα, tumour necrosis factor alpha

Adapted from Bogin B, et al. Int J Environ Res Public Health. 2015;12:4816-32

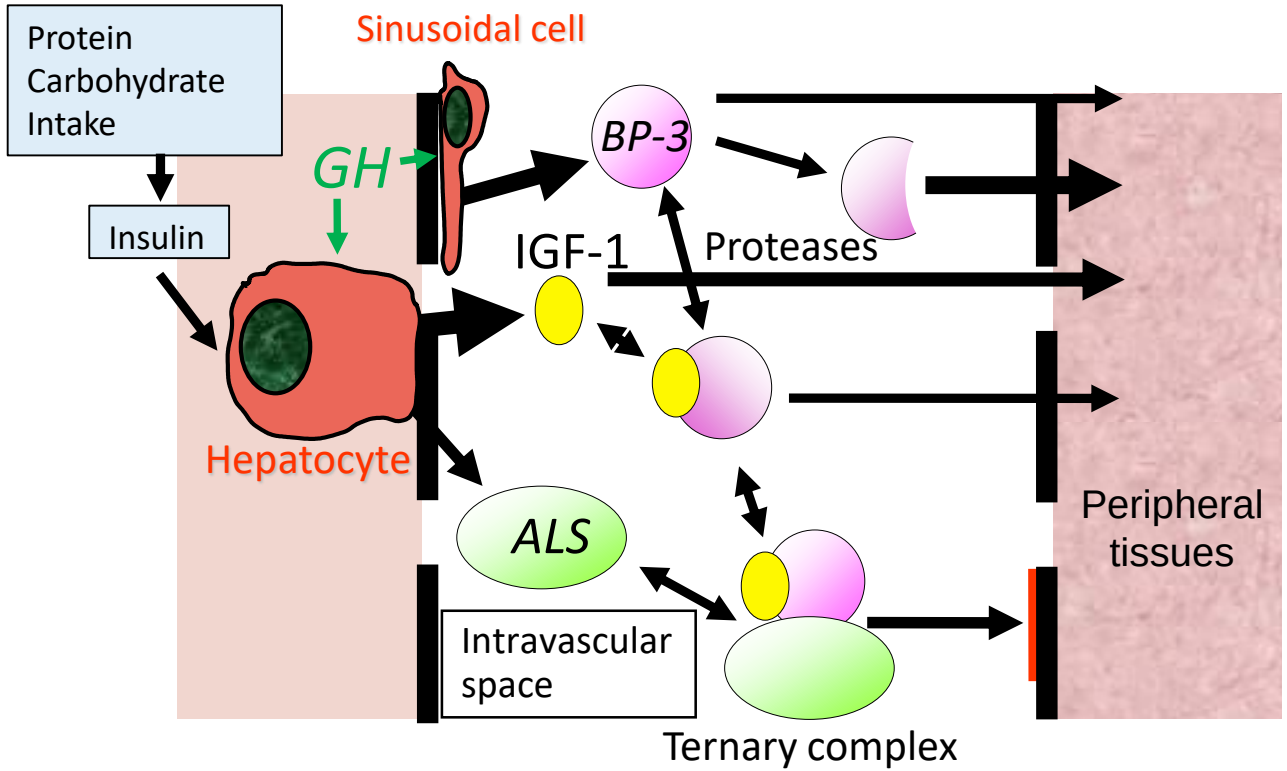
DIAGRAM OF THE GH–IGF-1 AXIS



ALS, acid-labile subunit; GH, growth hormone; GHR, growth hormone receptor; GHRH, growth-hormone releasing hormone; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor receptor; IGFBP-3, insulin-like growth factor-binding protein 3; STAT5b, signal transducer and activator of transcription 5B

Adapted from **Bang P, et al. Horm Res. 2001;55 Suppl 2:84-93**

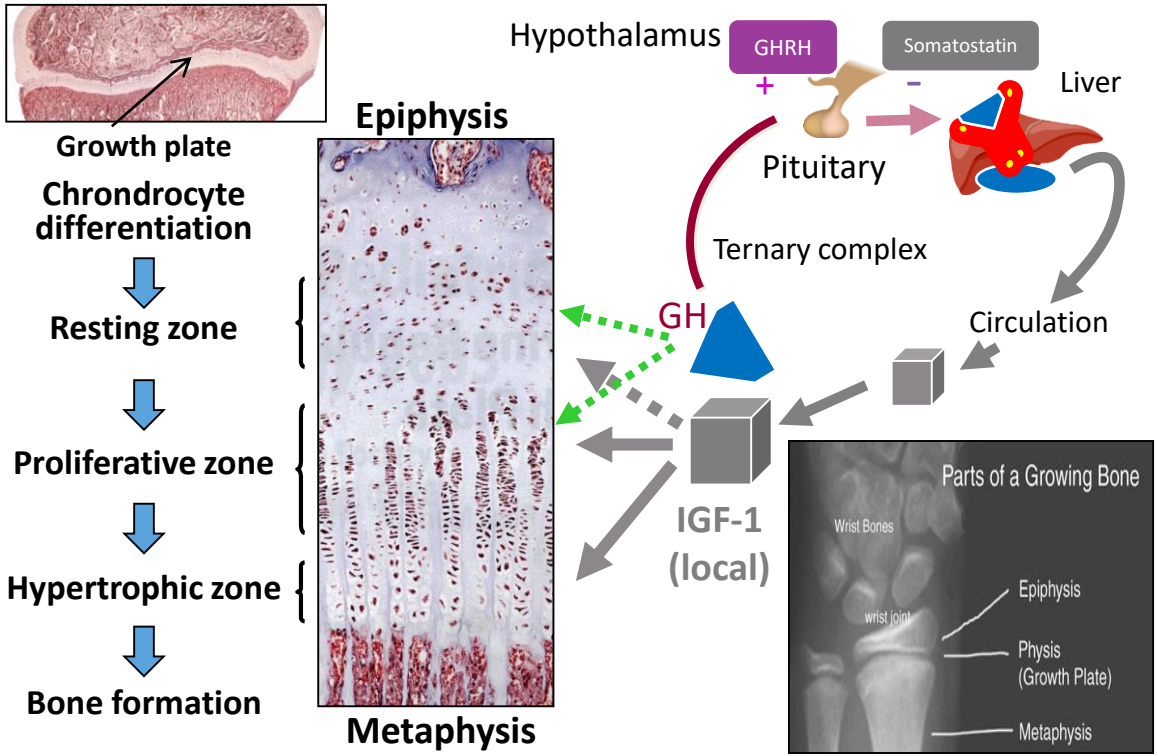
GH-STIMULATED GENERATION OF IGF-1 AND IGFBP-3



ALS, acid-labile subunit; BP-3, binding protein 3; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein 3

Adapted from **Blum WF, et al. Endocr Connect. 2018;7:R212-22**

ACTIONS OF GH AND IGF-1 ON CHONDROCYTE DEVELOPMENT



GH, growth hormone; GHRH, growth-hormone releasing hormone; IGF-1, insulin-like growth factor-1

Adapted from Nilsson O, et al. Horm Res. 2005;64:157-65

GENETIC MUTATIONS INVOLVING KEY PROTEINS FOR NORMAL GH ACTION

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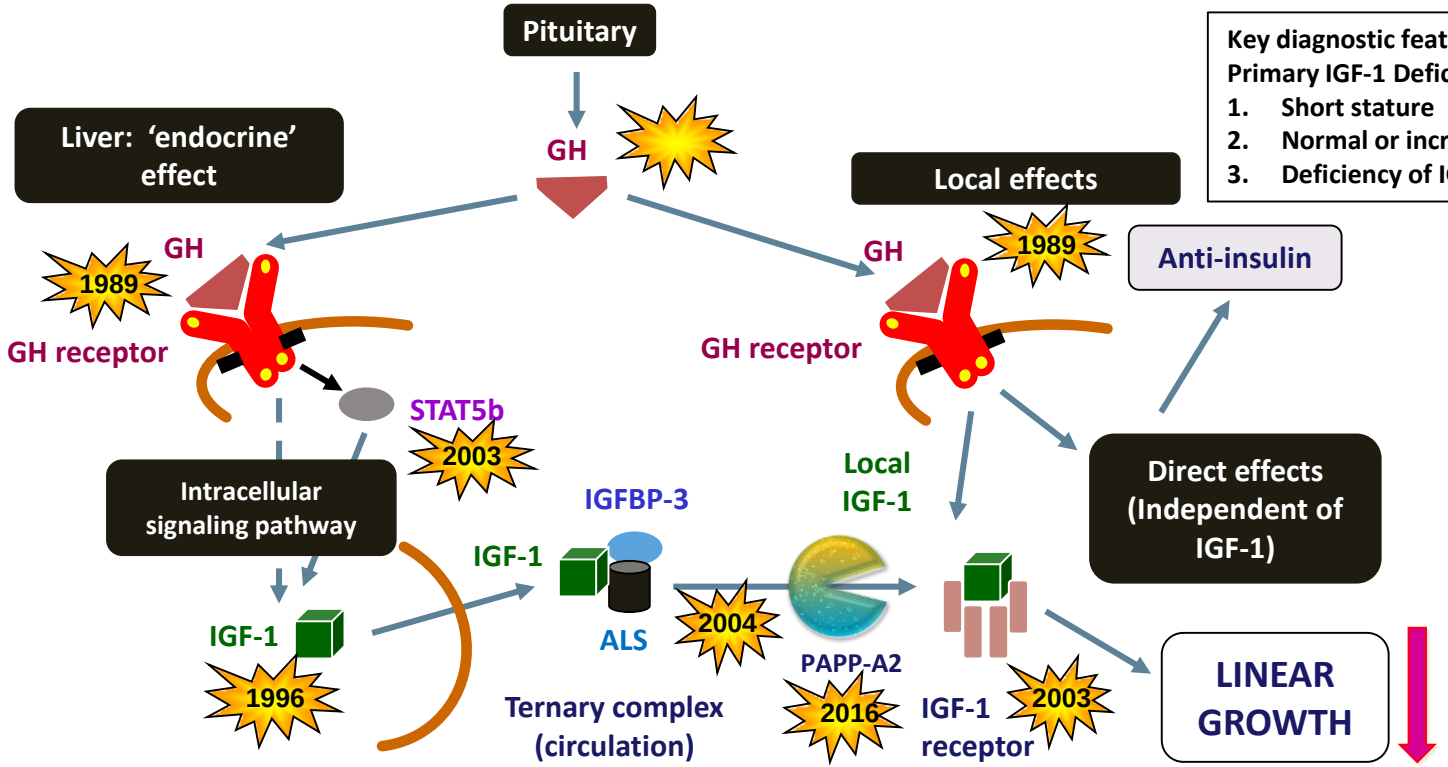
Key diagnostic features of Primary IGF-1 Deficiency
1. Short stature
2. Normal or increased GH
3. Deficiency of IGF-1



ALS, acid-labile subunit; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein 3; PAPP-A2, pregnancy-associated plasma protein-A2; STAT5b, signal transducer and activator of transcription 5B

Adapted from Rosenfeld RG, et al. Horm Res. 2009; 71 Suppl 2:36-40

PRIMARY AND SECONDARY GH RESISTANCE (IGF-1 DEFICIENCY)

Primary IGF-1 Deficiency

1. GH receptor (*GHR*) mutations
   Extracellular, transmembrane, intracellular mutations
2. GH signal transduction defects (STAT5b)
3. Mutations of SHP-2 (encoded by *PTPN-11*), K-RAS, H-RAS
4. *IGF-I* gene mutations or deletions
   a. Defects causing IGF-I deficiency
   b. Bio-inactive IGF-I
5. Acid-labile subunit mutations (*IGFALS*)
6. *PAPP-A2* mutations
7. GH neutralising antibodies in patients with *GH* gene deletion

Abnormal GHR or GH signal transduction

Abnormal IGF1gene

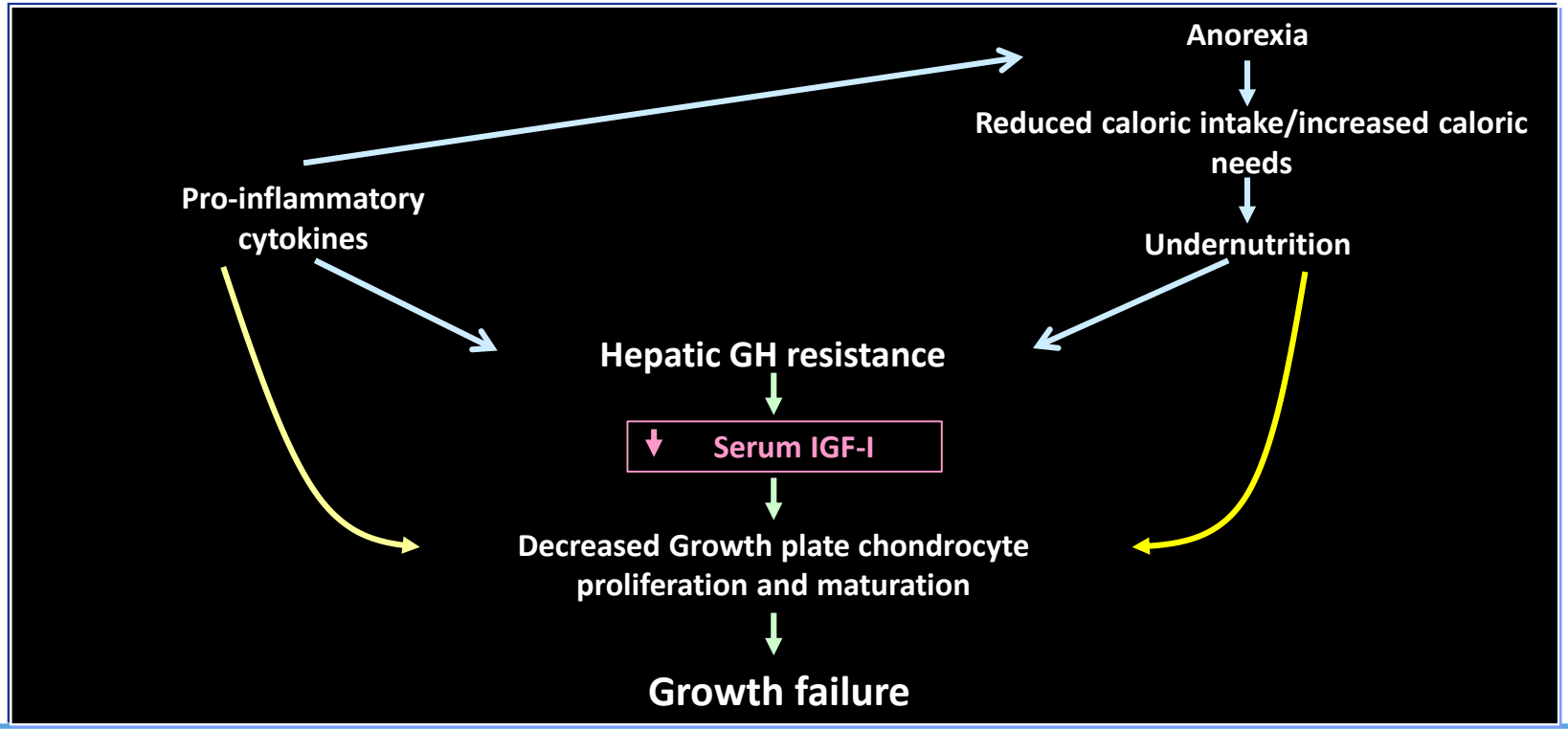
Abnormal IGF-1 transport in the circulation

Secondary IGF-1 Deficiency

1. GH deficiency, Acute illness, critical states
2. Chronic illness, inflammation, nutritional deficiency etc

Storr HL, Chatterjee S, Foley C, Metherell LA, Backeljauw PF, Rosenfeld RG, Dauber A, Savage MO, Hwa V. Non-classical Growth Hormone Insensitivity (GHI): Characterization of Mild Abnormalities of GH Action. Endocrine Reviews 2019, 40: 475-505

SECONDARY IGF-1 DEFICIENCY; EFFECTS OF NUTRITIONAL DEFICIENCY AND INFLAMMATION



Savage MO, et al. In: Paediatric Adrenal Disease, Endocrine Development Vol 18. Ghizzoni L, et al. 2011; pp 194-201.

PRIMARY
IGF-1 DEFICIENCY

PRIMARY IGF-1 DEFICIENCY: A SPECTRUM OF PHENOTYPES FROM SEVERE TO MILD SHORT STATURE

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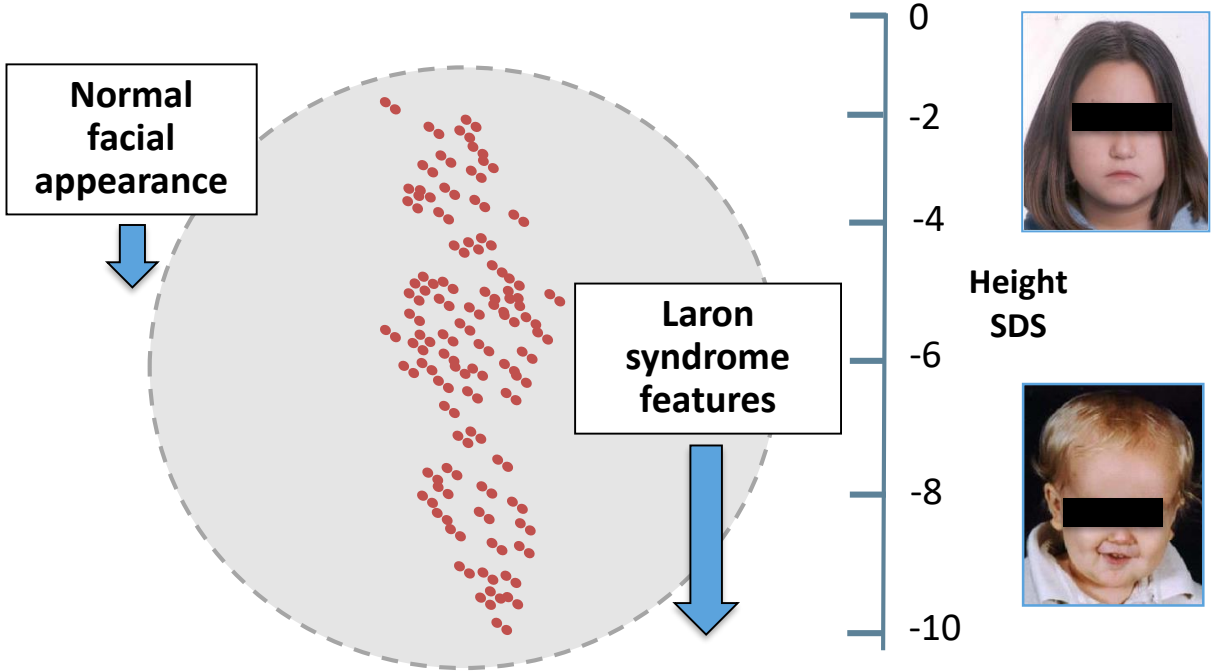
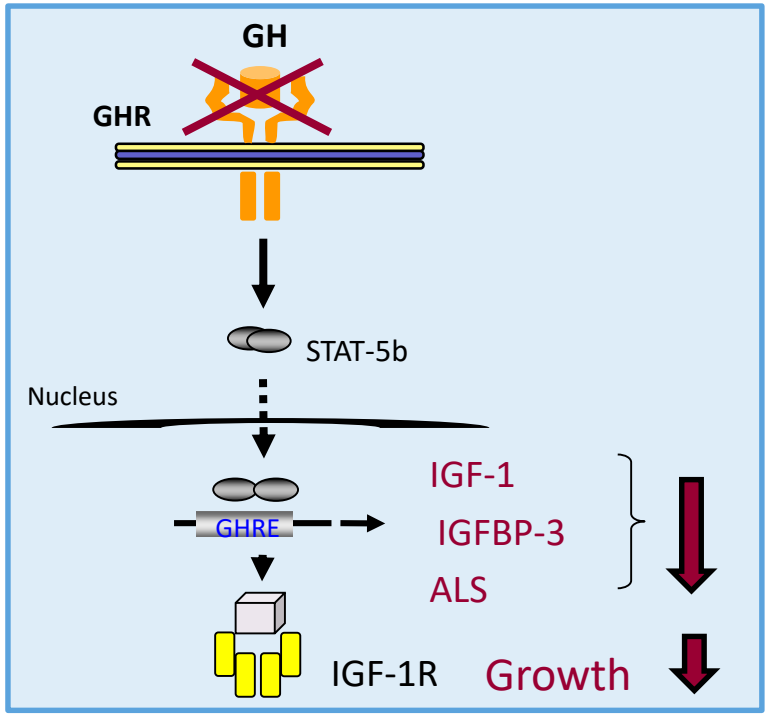
Heights of children with short stature and Primary IGF-1 Deficiency (n=70)



IGF-1, insulin-like growth factor-1; SDS, standard deviation score

1. David A, et al. Endocr Rev. 2011;32:472-97. 2. Storr HL et al. Endocr Rev. 2019;40:476-505

GH RECEPTOR DEFECT LEADS TO IGF-1, IGFBP-3 AND ALS DEFICIENCY AND IMPAIRED GROWTH

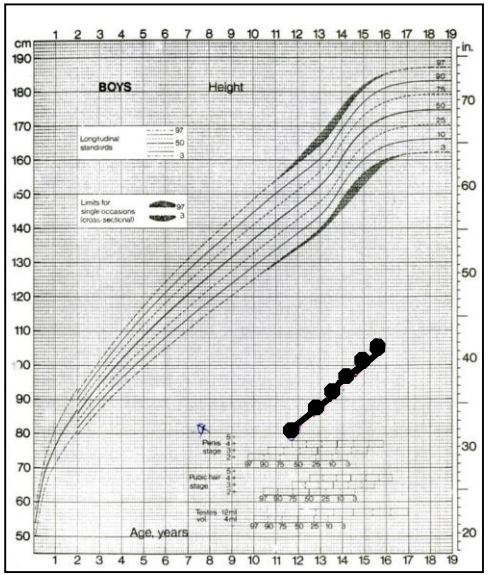


Severely disturbed physiology of the GH-IGF-1 axis

ALS, acid-labile subunit; GH, growth hormone; GHR, growth-hormone receptor; GHRE, external part of the growth-hormone receptor; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor receptor 1; IGFBP-3, insulin-like growth factor-binding protein 3; STAT5b, signal transducer and activator of transcription 5B

David A, et al. Endocr Rev. 2011;32:472-97

EVOLUTION OF THE SPECTRUM OF GH RESISTANCE



- Description of **GH insensitivity syndrome** (1966)[1]
- GH receptor **mutation identified** (1989)[2]
- Identification of **severe and mild phenotypes** (2011; 2019)[3,4]

GH, growth hormone; SD, standard deviation

1. Laron Z, et al. Isr J Med Sci. 1966;2:770-3. 2. Godowski PJ, et al. Proc Natl Acad Sci U S A. 1989;86:8083-7. 3. David A, et al. Endocr Rev. 2011;32:472-97. 4 Storr HL et al. Endocr Rev. 2019;40:476-505

CLASSICAL GH INSENSITIVITY SYNDROME

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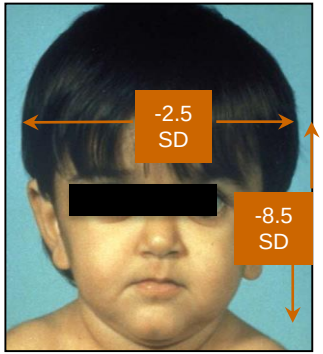
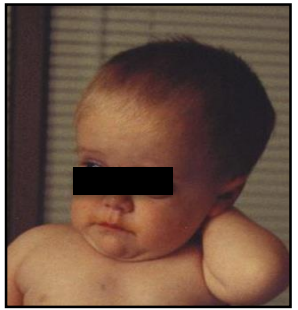


Homozygous *GHR* mutations with features of Laron syndrome, heights <-6 SDS

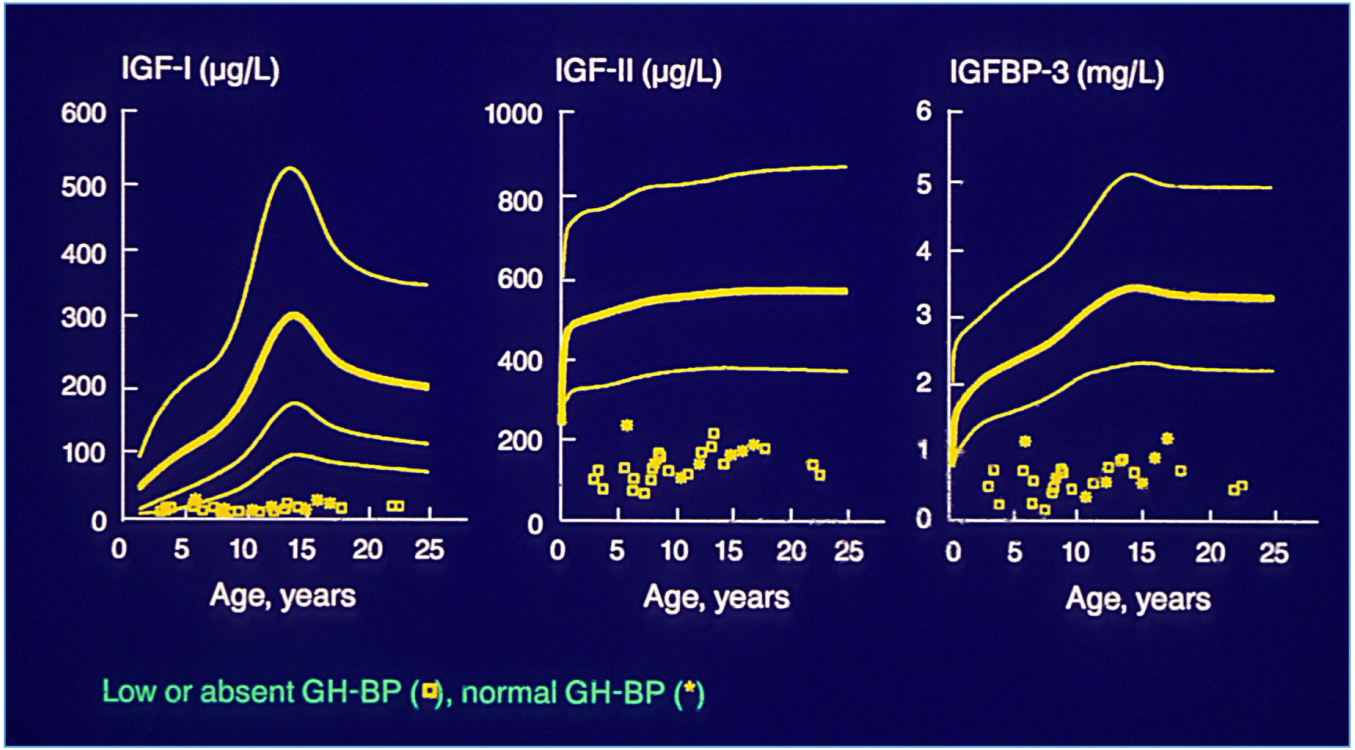
Severe Primary IGF-1 Deficiency

Mid-facial hypoplasia secondary to the effect of IGF-1 deficiency on the growth of the sphenoid bone



GH, growth hormone; GHR, growth-hormone receptor; IGF-1, insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score

DEFICIENCIES OF IGF-1, IGF-2 AND IGFBP-3 IN CHILDREN WITH CLASSICAL GH RESISTANCE



GH, growth hormone; GH-BP, growth hormone-binding protein; IGF-1, insulin-like growth factor-1; IGF-2, insulin-like growth factor-2; IGFBP-3, insulin-like growth factor-binding protein

Savage MO, et al. JCEM 1993;77:1465-71

SHORT STATURE RELATED TO GH RECEPTOR PSEUDOEXON MUTATION

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'GH Insensitivity without Laron syndrome'

gDNA

Height SDS -5.6 -4.4 -3.3 -3.9

2 3 4 5 6 7 8 9 10

RNA

Pseudoexon inclusion

2 3 4 5 6 6ϕ 7 8 9 10

Translation extra 36 aa

Abnormal GHR Protein

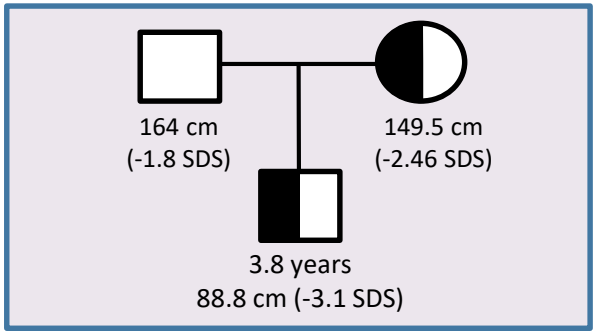
Signal Extracellular TM Intracellular

Abnormal GHR Function

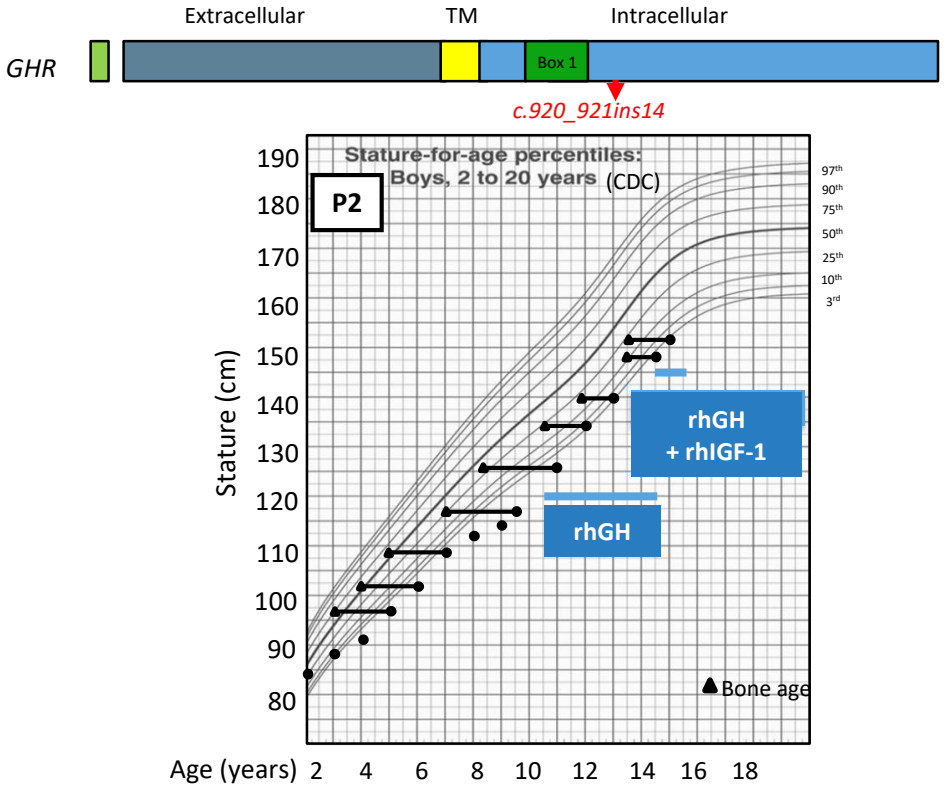
aa, amino acid; gDNA, genomic deoxyribonucleic acid; GH, growth hormone; GHR, growth-hormone receptor; RNA, ribonucleic acid; SDS, standard deviation score; TM, transmembrane domain

1. Metherell LA, et al. Am J Hum Genet. 2001;69:641-6. 2. Bjarnasson R, et al. Clin Endocrinol (Oxf). 2002;57:357-61

DOMINANT-NEGATIVE GHR MUTATION



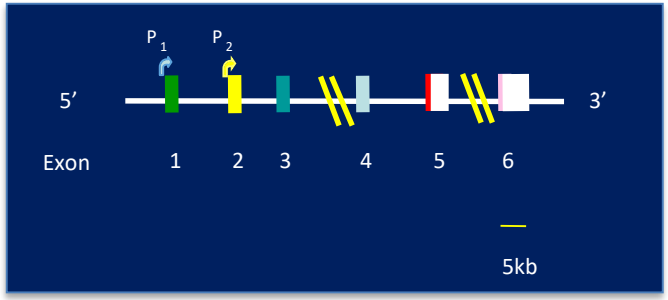
Sex	Male
Age, years	3.8
Height SDS	-3.1
GH max, ng/ml	8.8
IGF-1, ng/ml	69 (55–297)
IGFBP-3, mg/L	NA
ALS, mg/L	NA



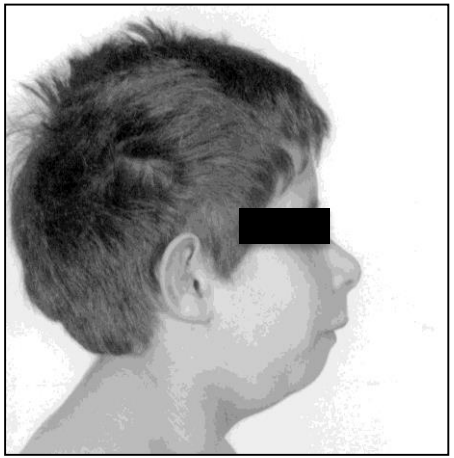
ALS, acid-labile subunit; CDC, Centers for Disease Control and Prevention; GH, growth hormone; GHR, growth-hormone receptor; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein 3; NA, not available; rh, recombinant human; SDS, standard deviation score; TM, transmembrane domain

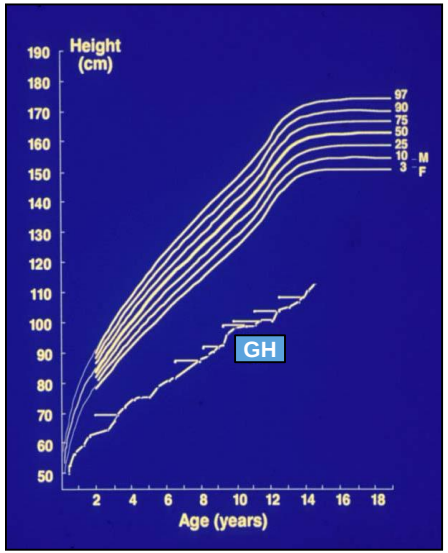
Vairamani K, et al. J Endocr Soc. 2017;1:345-58

IGF-1 GENE DELETION



Deletion of exons 4 and 5 leading to a functionless IGF-1 protein

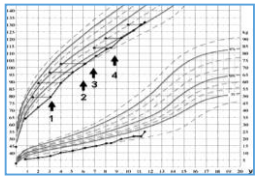




GH, growth hormone; IGF-1, insulin-like growth factor-1

Woods KA, et al. New Eng J Med. 1996;335:1363-7

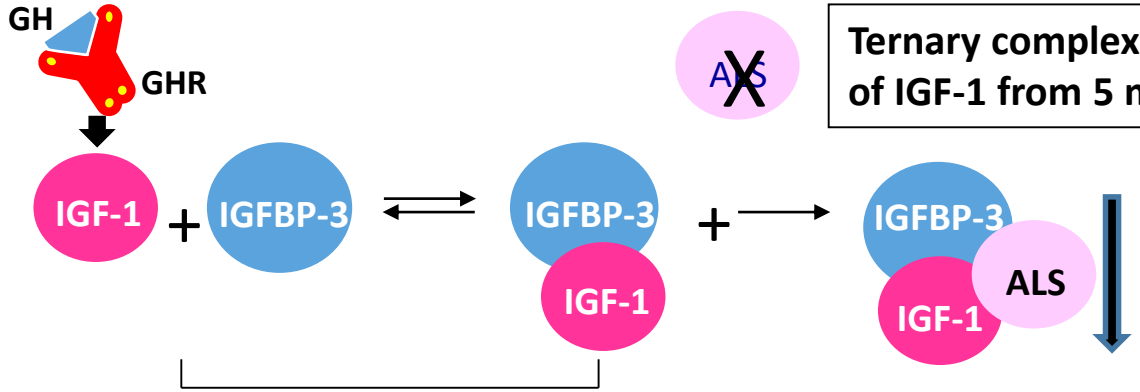
IGF-1 GENE DEFECTS – CLINICAL FEATURES

Intrauterine growth retardation		birth weight	birth length
IGF-1 deletion[1]		-3.9 SDS	-5.4 SDS
IGF-1 mutation[2]		-3.9 SDS	-4.3 SDS
IGF-1 mutation[3]	 	-3.7 SDS	-2.4 SDS
IGF-1 mutation[4]	Homozygous missense variant IUGR, deafness, growth failure IGF-1-1.15 to 2.95 SDS		

IGF-1, insulin-like growth factor-1; IUGR, intrauterine growth restriction; SDS, standard deviation score

1. Woods KA, et al. New Eng J Med. 1996;335:1363-7. 2. Walenkamp MJ, et al. J Clin Endocrinol Metab. 2005;90:2855-64.
3. Netchine I, et al. J Clin Endocrinol Metab. 2009;94:3913-21. 4. Keselman AC et al. Eur J Endocrinol. 2019;181:K43-K53

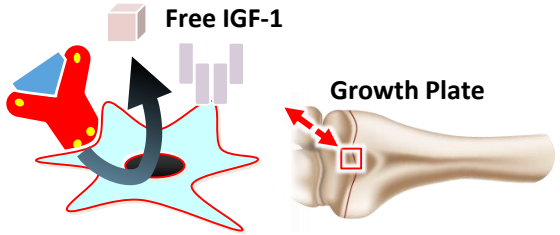
FUNCTION OF ALS AND EFFECT OF *IGFALS* MUTATION



Ternary complex prolongs half life of IGF-1 from 5 min to 16 hours

Extension of IGF-1 half-life

Regulation of IGF-1 bioactivity and reservoir



Local production and paracrine action of IGF-1 is not affected

ALS, acid-labile subunit; GH, growth hormone; GHR, growth-hormone receptor; IGF-1, insulin-like growth factor-1; IGFALS, insulin-like growth factor binding protein, acid labile subunit; IGFBP-3, insulin-like growth factor-binding protein 3

David A, et al. Endocr Rev. 2011;32:472-97

SERUM IGF-1 AND IGFBP-3 CONCENTRATIONS IN THE THREE SUBJECTS WITH *IGFALS* MUTATIONS

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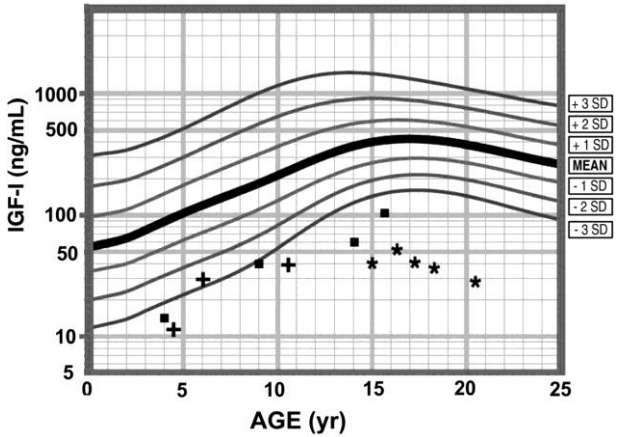
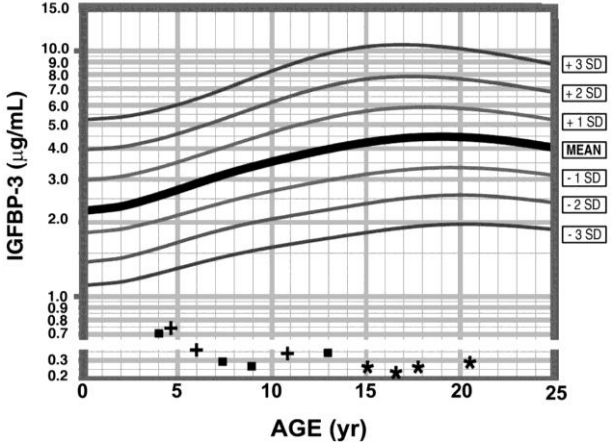
Mismatch between serum IGF-1 and IGFBP-3 and height

Heights
-3.9 to -2.4 SDS





IGF-1, insulin-like growth factor-1; IGFALS, insulin-like growth factor binding protein, acid labile subunit; IGFBP-3, insulin-like growth factor-binding protein 3; SD, standard deviation; SDS, standard deviation score

Heath KE, et al. J Clin Endocrinol Metab. 2008;93:1616-24

IGFALS MUTATION: MILD SHORT STATURE PHENOTYPE WITH SEVERE IGF-1 AND IGFBP-3 DEFICIENCY

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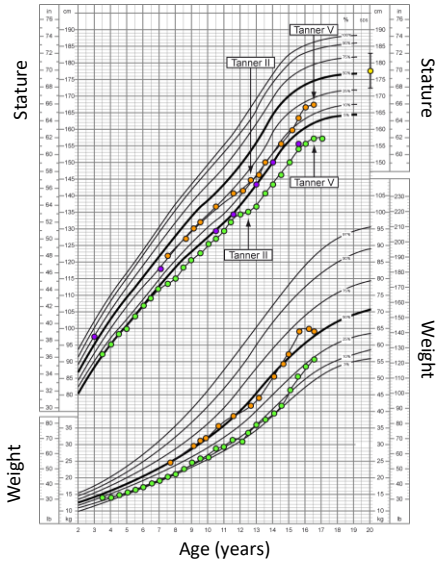
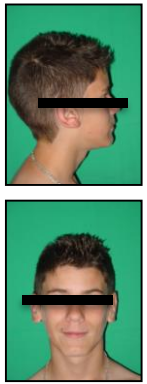
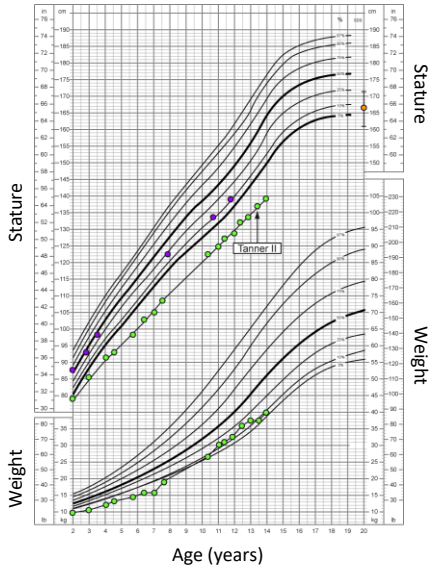
Proband 1, heterozygous (pink circles) and homozygous (green circles)



Proband 2, homozygous

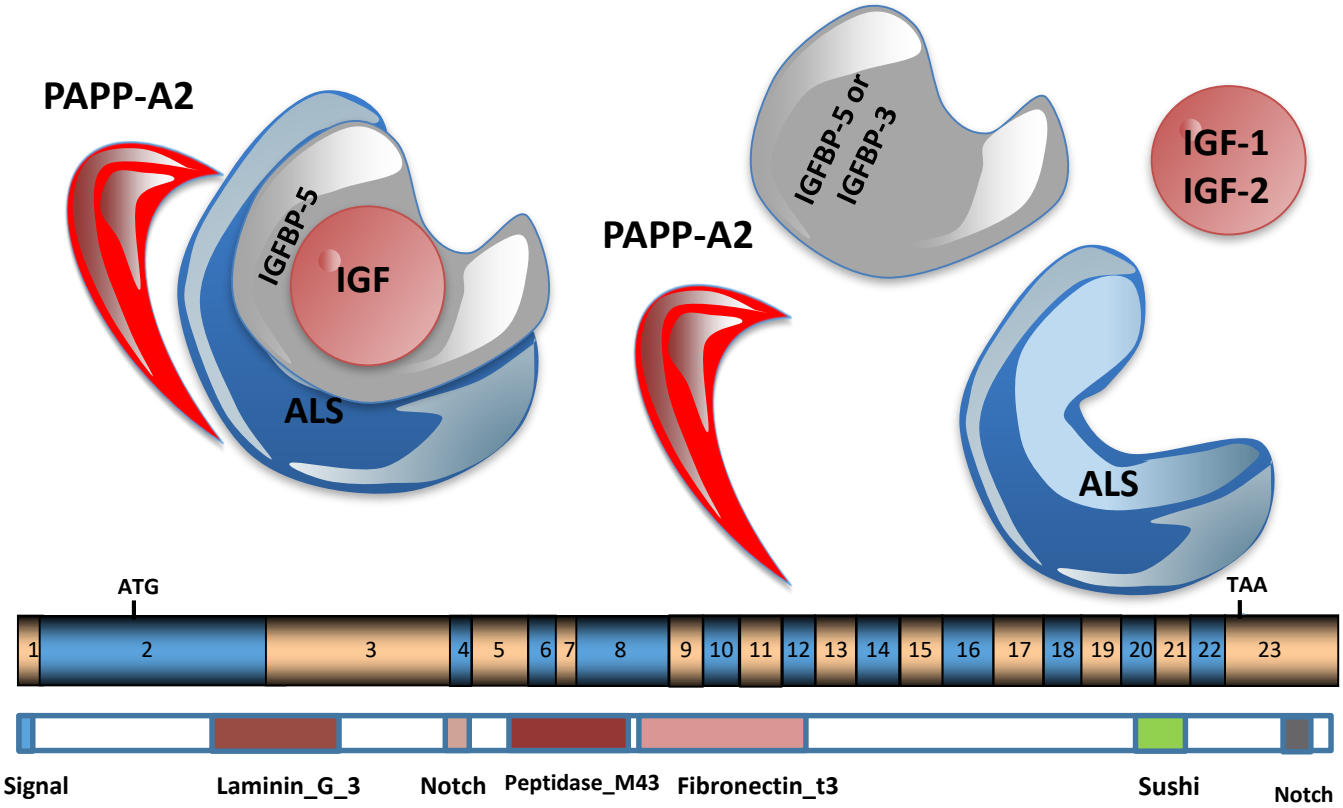




IGF-1, insulin-like growth factor-1; IGFALS, insulin-like growth factor binding protein, acid labile subunit; IGFBP-3, insulin-like growth factor-binding protein 3; SDS, standard deviation score. Photographs courtesy of Prof. J Argente, Madrid, Spain

Heath KE, et al. J Clin Endocrinol Metab. 2008;93:1616-24

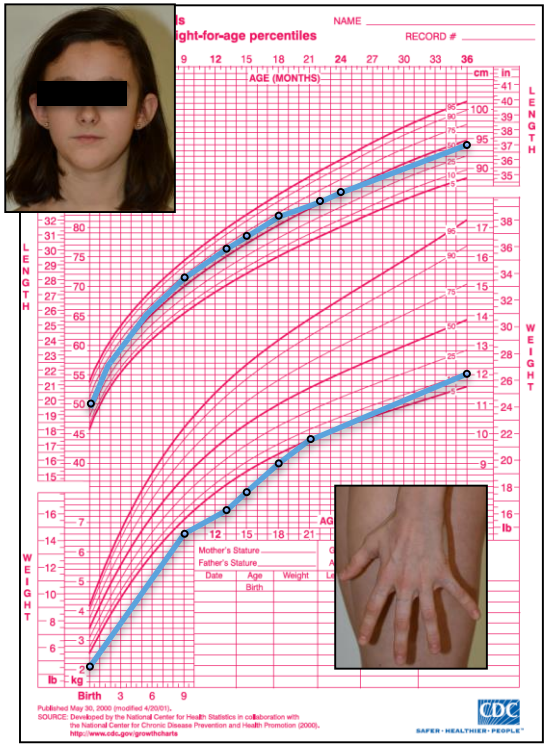
PAPP-A2 – A PROTEOLYTIC FACTOR

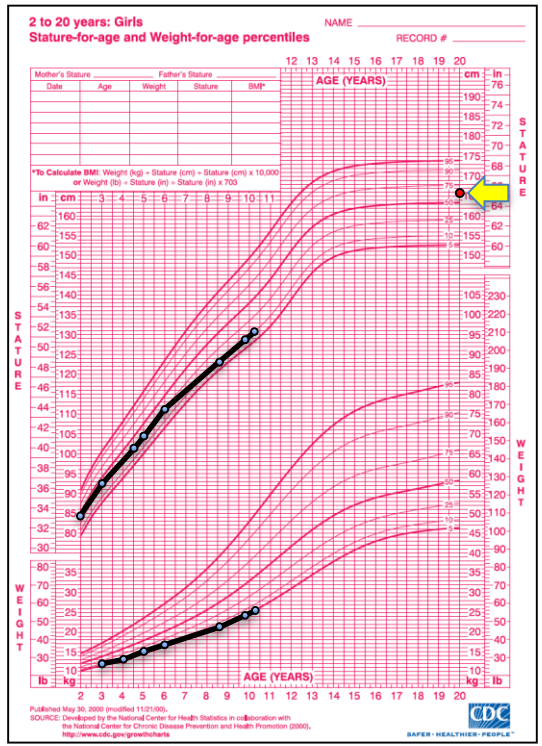


ALS, acid-labile subunit; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; PAPP-A2, pregnancy-associated plasma protein-A 2

Dauber A, et al. EMBO Mol Med. 2016;8:363-74

HOMOZYGOUS *PAPP-A2* DEFICIENCY



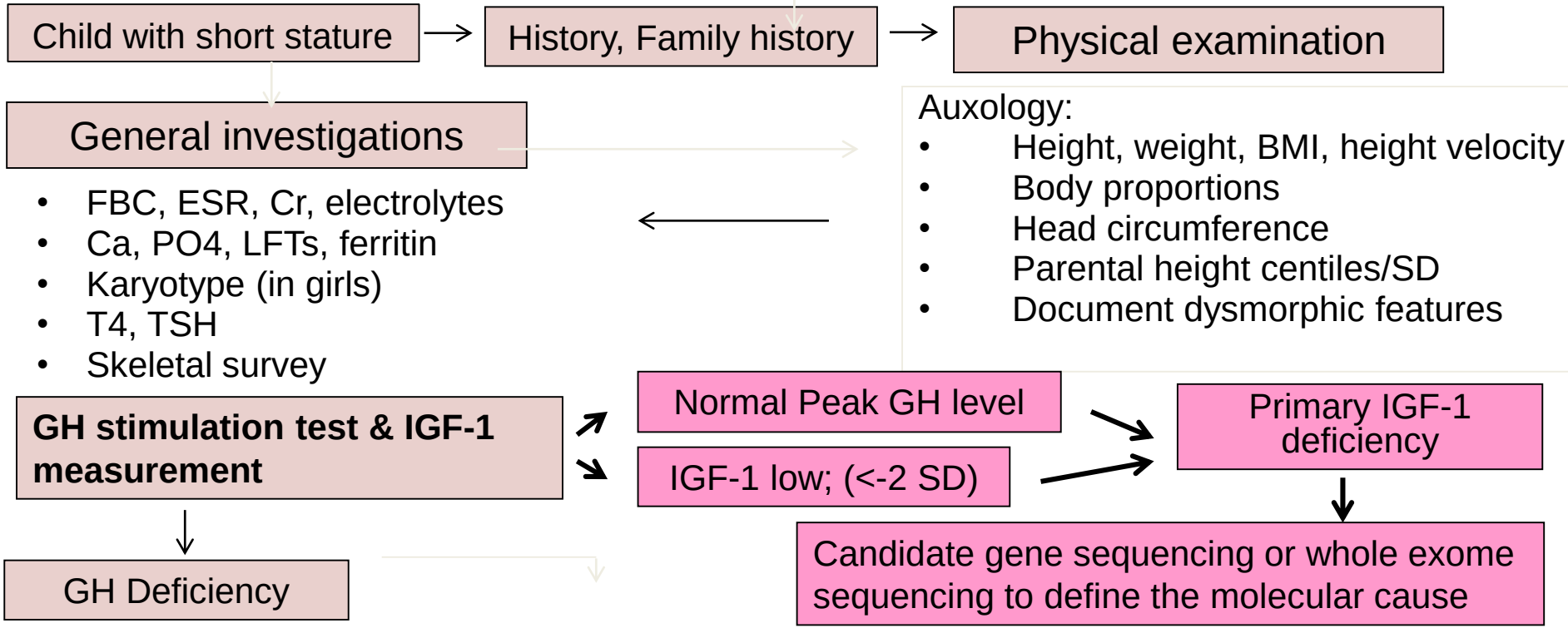


- **IGF-1:** 980-1200 ng/mL (> + 3 SD) ↑↑↑
- **IGFBP-3**: 5,912-6,834 ng/mL (≈ + 3 SD) ↑↑↑
- **ALS**: 3,745-3,945 mIU/mL (≈ + 3 SD) ↑↑↑

ALS, acid-labile subunit; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein-3; PAPP-A2, pregnancy-associated plasma protein-A 2; SD, standard deviation

Photographs courtesy of Prof. J Argente, Madrid, Spain. Dauber A, et al. EMBO Mol Med. 2016;8:363-74.

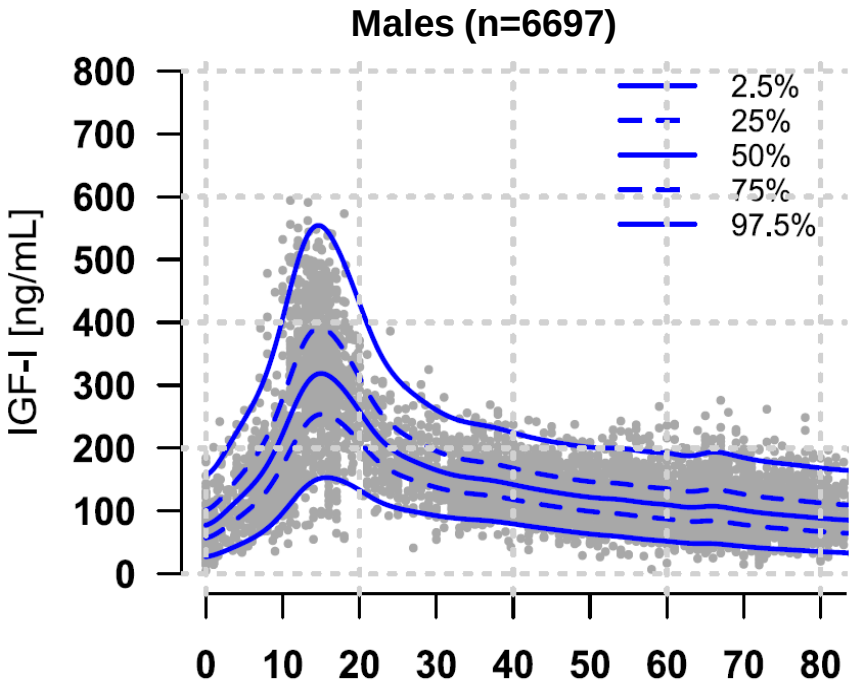
DIAGNOSTIC ALGORITHM FOR PRIMARY IGF-1 DEFICIENCY

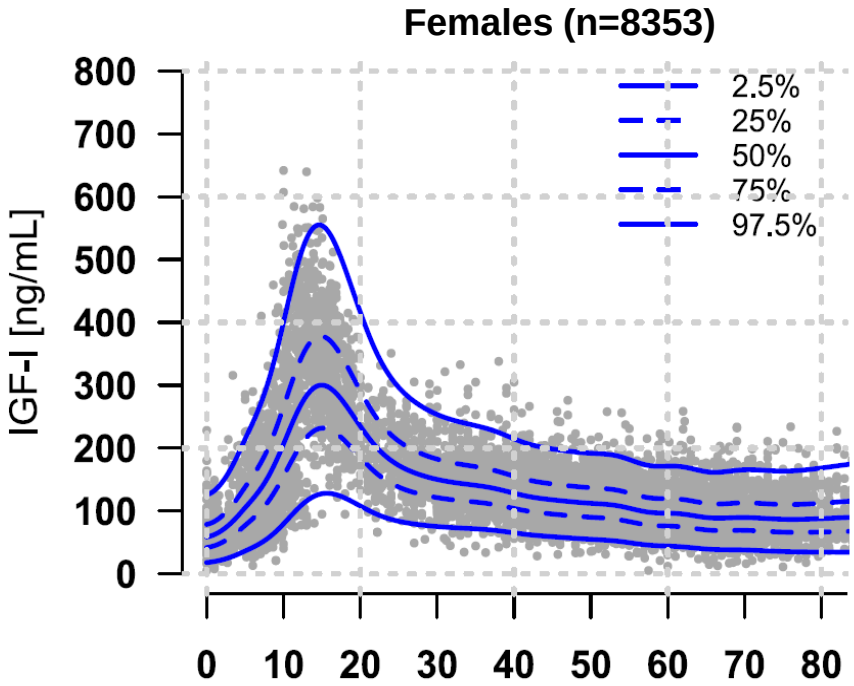


BMI, body mass index; Ca, calcium; Cr, creatinine; GH, growth hormone; IGF-1, insulin-like growth factor-1; LFTs, liver function tests; PO4, phosphate; SD, standard deviation; TSH, thyroid stimulating hormone

David A, et al. Endocr Rev. 2011;32:472-97

IGF-1 REFERENCE INTERVALS FOR THE IDS ISYS IGF-1 (*international multicentre study*)





Centiles: LMS method

IGF-1, insulin-like growth factor-1

Bidlingmaier M, et al. J Clin Endocrinol Metab 2014;99:1712-21

MEAN IGF-1 AND IGFBP-3 SDS VALUES IN VARIOUS GROUPS OF PATIENTS WITH SHORT STATURE

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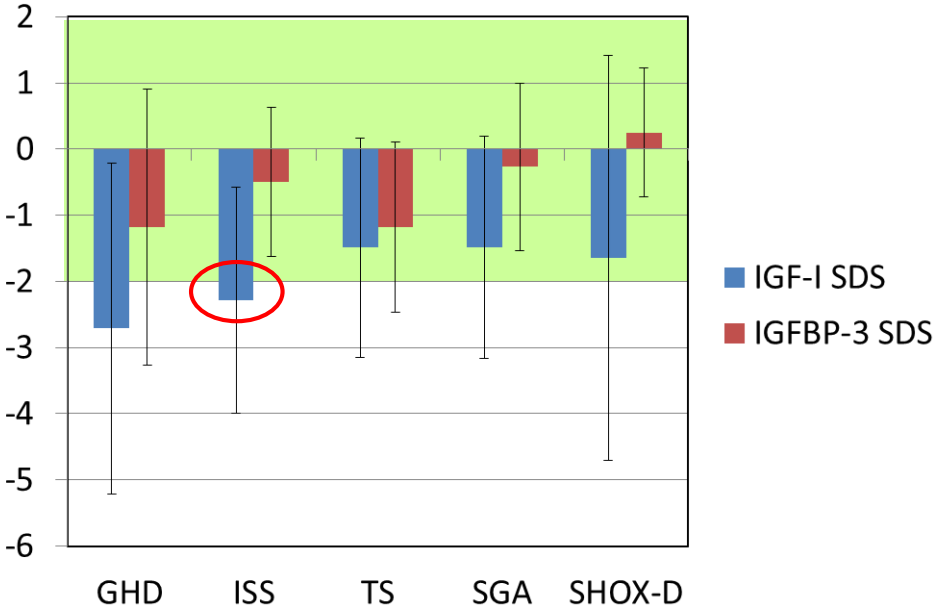
Point to note:

In mild GH deficiency,
IGF-1 may be normal and
IGFBP-3 is likely to be normal

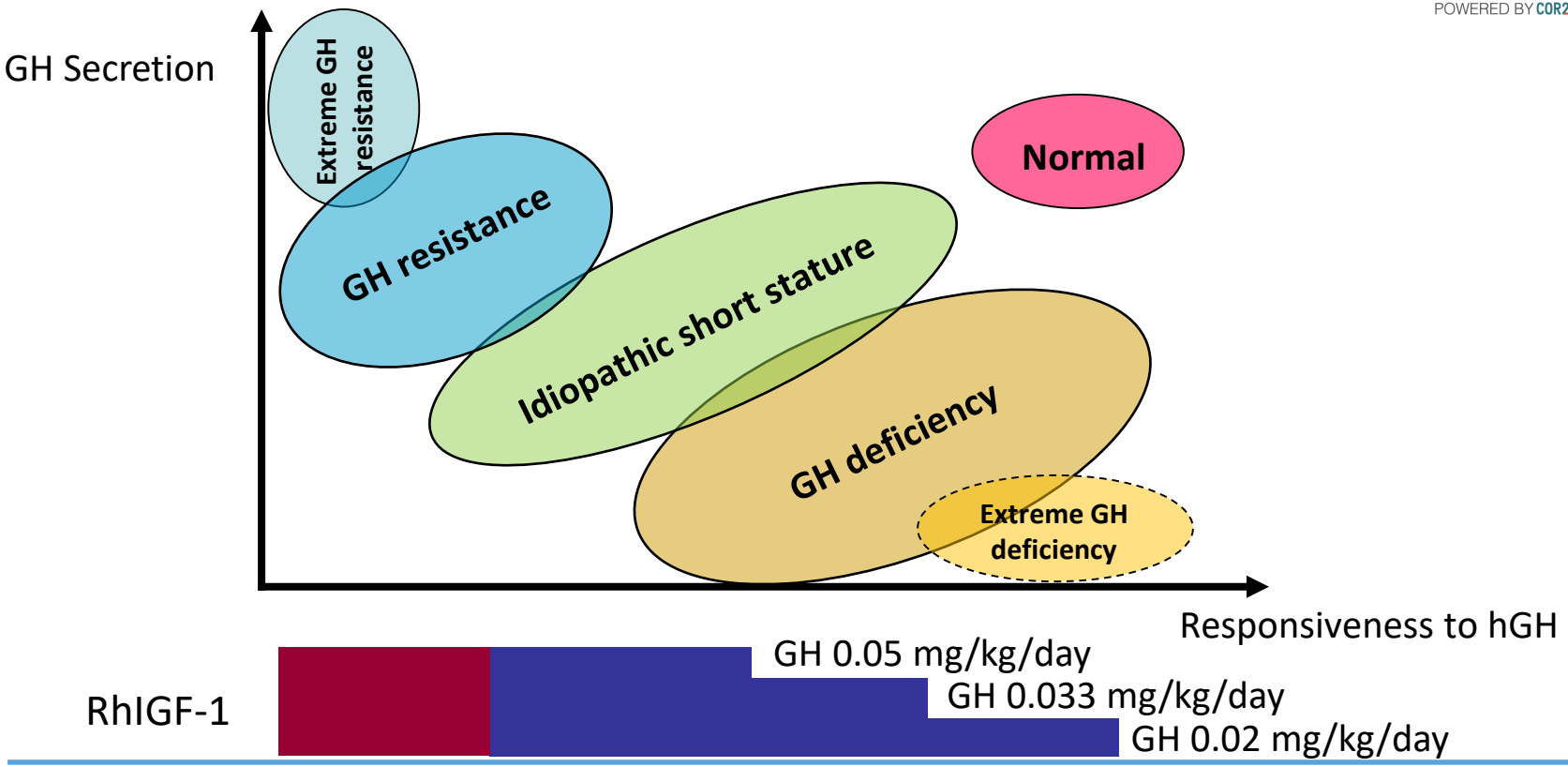


Idiopthic GHD mean peak GH 6.6 µg/L

GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein-3; ISS, idiopathic short stature; SDS, standard deviation score; SGA, small for gestational age; SHOX-D, short stature homeobox containing gene deficiency; TS, Turner syndrome

Deal C, et al. Horm Res Paediatr. 2013;79:283-92. Eli Lilly data, shown with permission from Werner Blum

CONTINUUM MODEL OF GH-IGF-1 DEFECTS: HGH AND RHIGF-1 THERAPY



GH, growth hormone; hGH, human growth hormone; IGF-1, insulin-like growth factor-1; RhIGF-1, recombinant human insulin-like growth factor-1

Savage MO, et al. Clinical Endocrinology 2010;72:721-8

APPROVAL OF rhIGF-1 FOR TREATMENT OF SEVERE PRIMARY IGF-1 DEFICIENCY

2002 Tercica Inc

rhIGF-1 (Increlex, mecasermin) received approval by the FDA in 2005 and by the EMEA in 2007
Tercica acquired by Ipsen Pharma in 2008

- Growth failure due to Severe Primary IGF-1 deficiency (SPIGFD)
- Height ≤ -3 SDS
- IGF-1 ≤ -3 SDS / < 2.5th centile
- GH normal

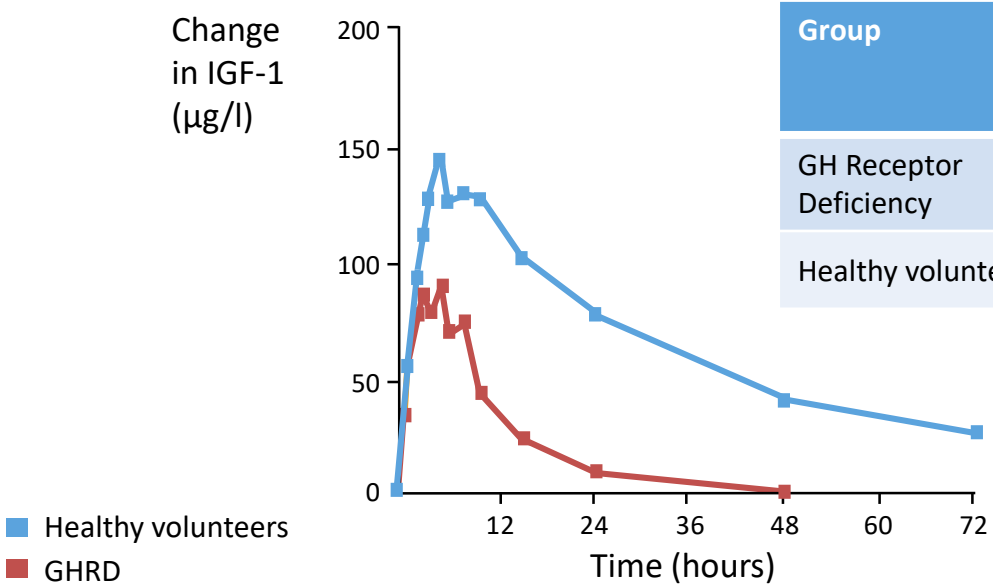
https://www.ema.europa.eu/en/medicines/human/EPAR/increlex;

https://ww.bsped.org.uk **GUIDELINES for SPIGFD**

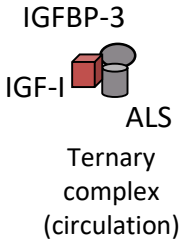
EMEA, European Medicines Agency; FDA, Food and Drug Administration; GH, growth hormone; IGF-1, insulin-like growth factor-1; rhIGF-1, recombinant insulin-like growth factor-1; SDS, standard deviation score

PHARMACOKINETICS OF rhIGF-1

IGF-1 levels after a single sc injection of rhIGF-1 40 μg/kg in healthy volunteers and patients with Laron syndrome



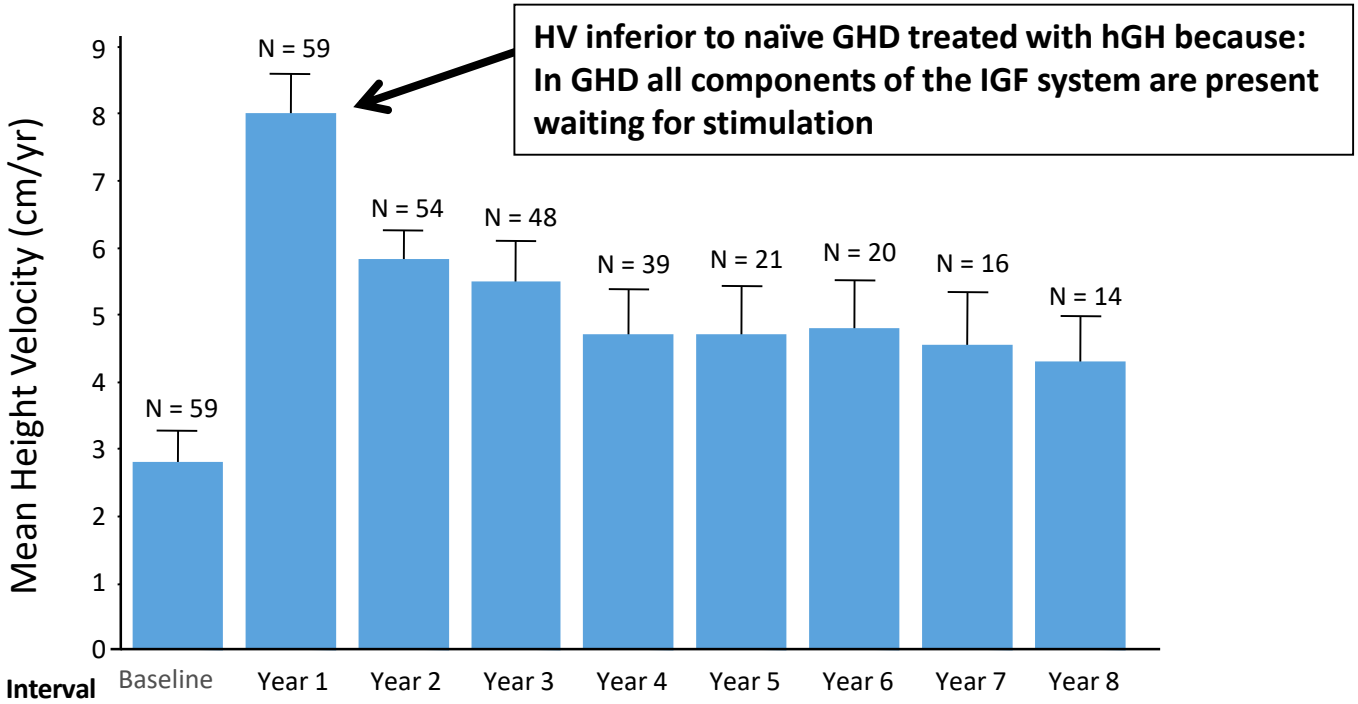
Group	IGF-1 clearance (ml/min/kg)	IGF-1 half-life (hours)
GH Receptor Deficiency	0.6	5.7
Healthy volunteers	0.2	17.0



ALS, acid-labile subunit; GHRD, growth hormone receptor deficiency; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein-3; rhIGF-1, recombinant insulin-like growth factor-1; sc, subcutaneous

Grahnen A, et al. Acta Paed Suppl. 82 Suppl 1993;391:9-13

rhIGF-1 60-120 Mg/Kg IN SEVERE GH RESISTANCE PATIENTS (N=76)

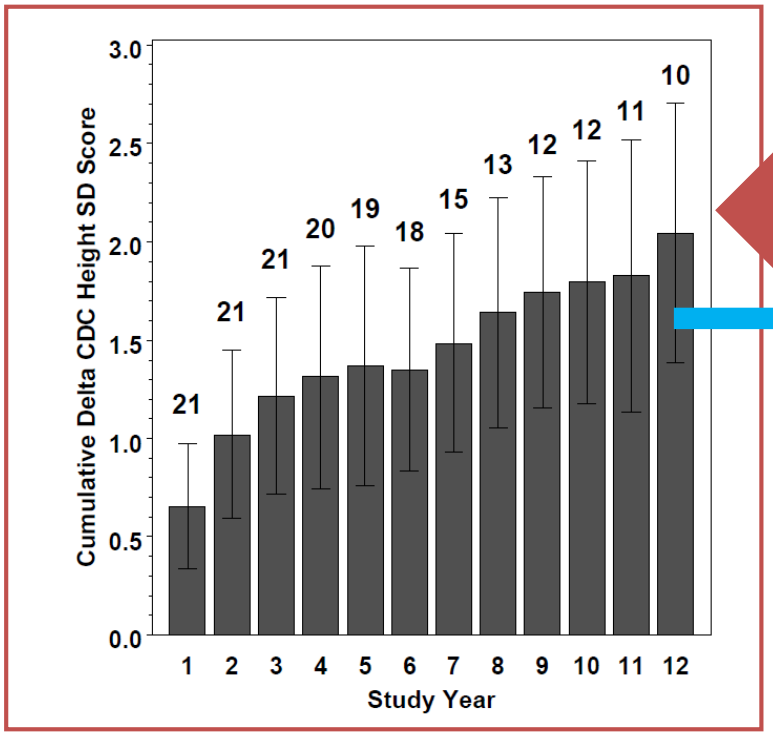


± 95% Confidence Interval

bid, twice daily; GH, growth hormone; GHD, growth-hormone deficiency; hGH, human growth hormone; HV, height velocity; IGF, insulin-like growth factor; rhIGF-1, recombinant insulin-like growth factor-1

Chernausek S. et al. J Clin Endocrinol Metab. 2007; 92: 902-910

LINEAR GROWTH RESPONSE – HEIGHT SDS – TO ADULT HEIGHT



ΔHeight SDS for the 9 patients also treated with GnRH analogue therapy was +2 SDS

Better than non-GnRH analogue-treated patients (+1.6 SDS)

± 95% Confidence Interval

CDC, Centers for Disease Control and Prevention; GnRH, gonadotropin-releasing hormone; SDS, standard deviation score

Backeljauw PF, et al. Horm Res Paediatr. 2013;80:47-56

IGF-1 DEFICIENCY

CONCLUSIONS

- IGF-1 is a metabolic hormone that informs the cell about the suitability for anabolism
- The serum concentration depends on nutritional status and absence of cytokine suppression which will over-ride the influence of GH stimulation
- Primary IGF-1 deficiency appears to be rare, being caused by single gene defects in the pathway of GH action
- Long-term difficulties with supply of rhIGF-1 have resulted in minimal data on optimisation of replacement therapy for IGF-1 deficiency
- RhIGF-1 therapy has not been studied in cases of secondary IGF-1 deficiency

Thank you !

GH, growth hormone; IGF-1, insulin-like growth factor-1; rhIGF-1, recombinant insulin-like growth factor-1