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ADDRESSING DIAGNOSTIC CHALLENGES OF SEVERE PRIMARY IGF-I DEFICIENCY

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IGF-I, insulin-like growth factor I

THIS MODULE HAS BEEN DEVELOPED BY TWO INTERNATIONAL EXPERTS

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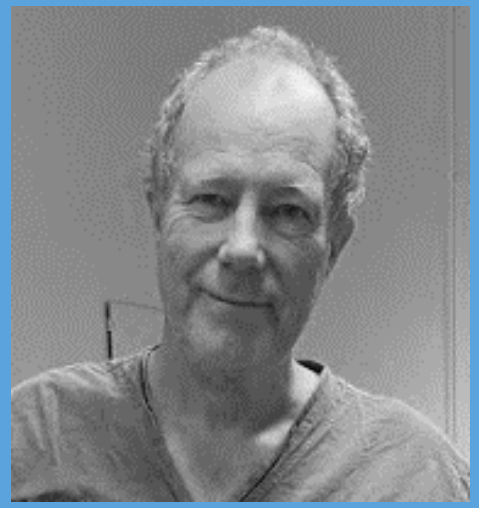

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Prof. Peter Bang is a consultant for Ipsen and Lilly.

EDUCATIONAL OBJECTIVES

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Upon completion of this microlearning, you will:

- Be able to differentiate **Severe Primary IGF-I deficiency** (SPIGFD) from other conditions of short stature
- Understand **how to diagnose patients with SPIGFD** based on clinical presentation and biochemical assessment of the GH-IGF axis
- Have an awareness of the **challenges related to diagnosis of SPIGFD** patients

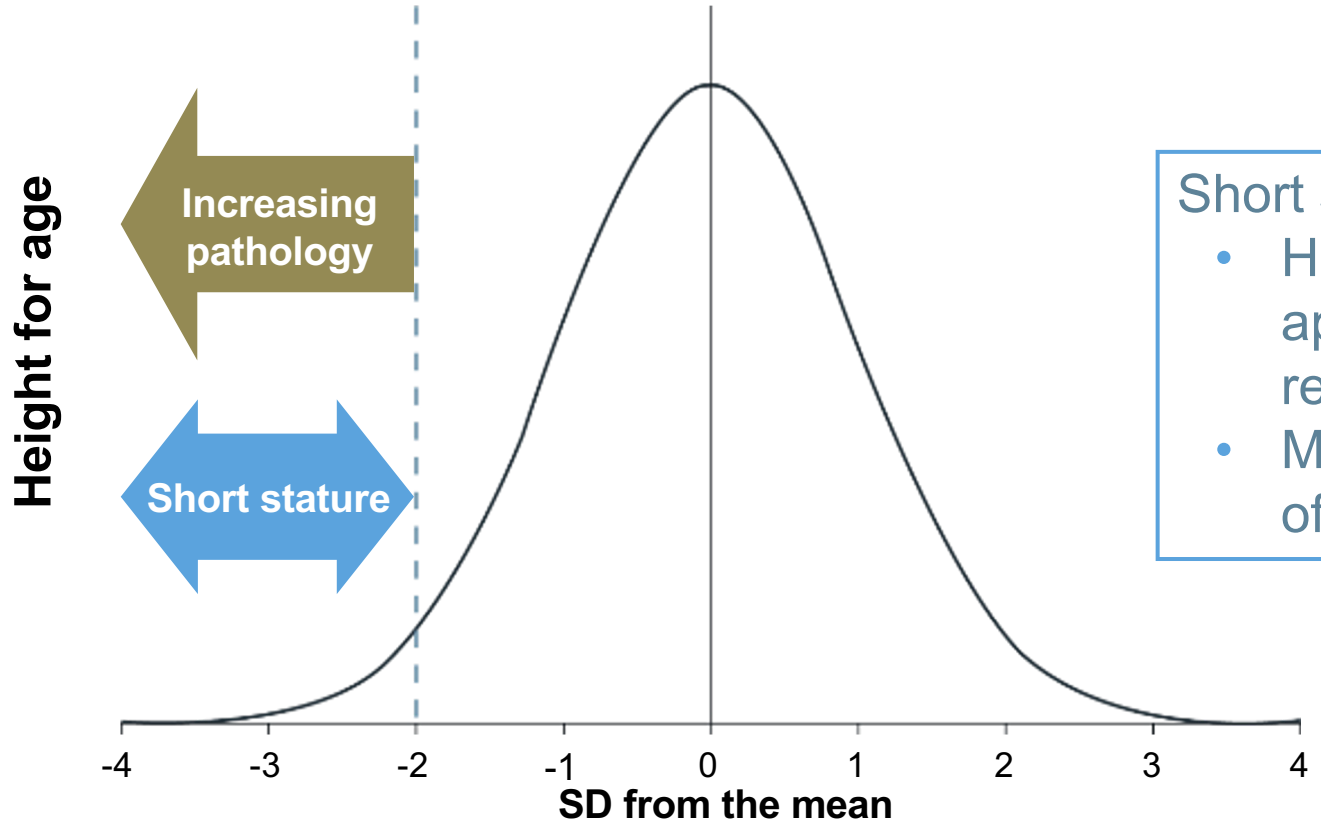
CLINICAL TAKEAWAYS

- **Severe primary IGF-I deficiency** (SPIGFD) generally presents as **classical Laron syndrome** but **non-classical cases with mild or moderate phenotypes** should also be considered
- **An endocrine investigation** should be conducted **to assess the GH-IGF-I axis** to ensure appropriate diagnosis
- **Diagnosis of severe primary IGF-I deficiency** requires severe short stature, low serum IGF-I and normal or increased growth hormone secretion as well as lack of other pathology
- **An early and correct diagnosis** is essential to allow children to achieve their full growth potential with appropriate treatment

INTRODUCTION TO GROWTH FAILURE AND THE GROWTH HORMONE/IGF-I AXIS

INTRODUCTION TO GROWTH FAILURE (SHORT STATURE)

- **Short stature is caused by a variety of aetiologies – an early and correct diagnosis is essential[1]**
- **Children have a limited time to reach their growth potential with treatment before fusion of the physes[2]**



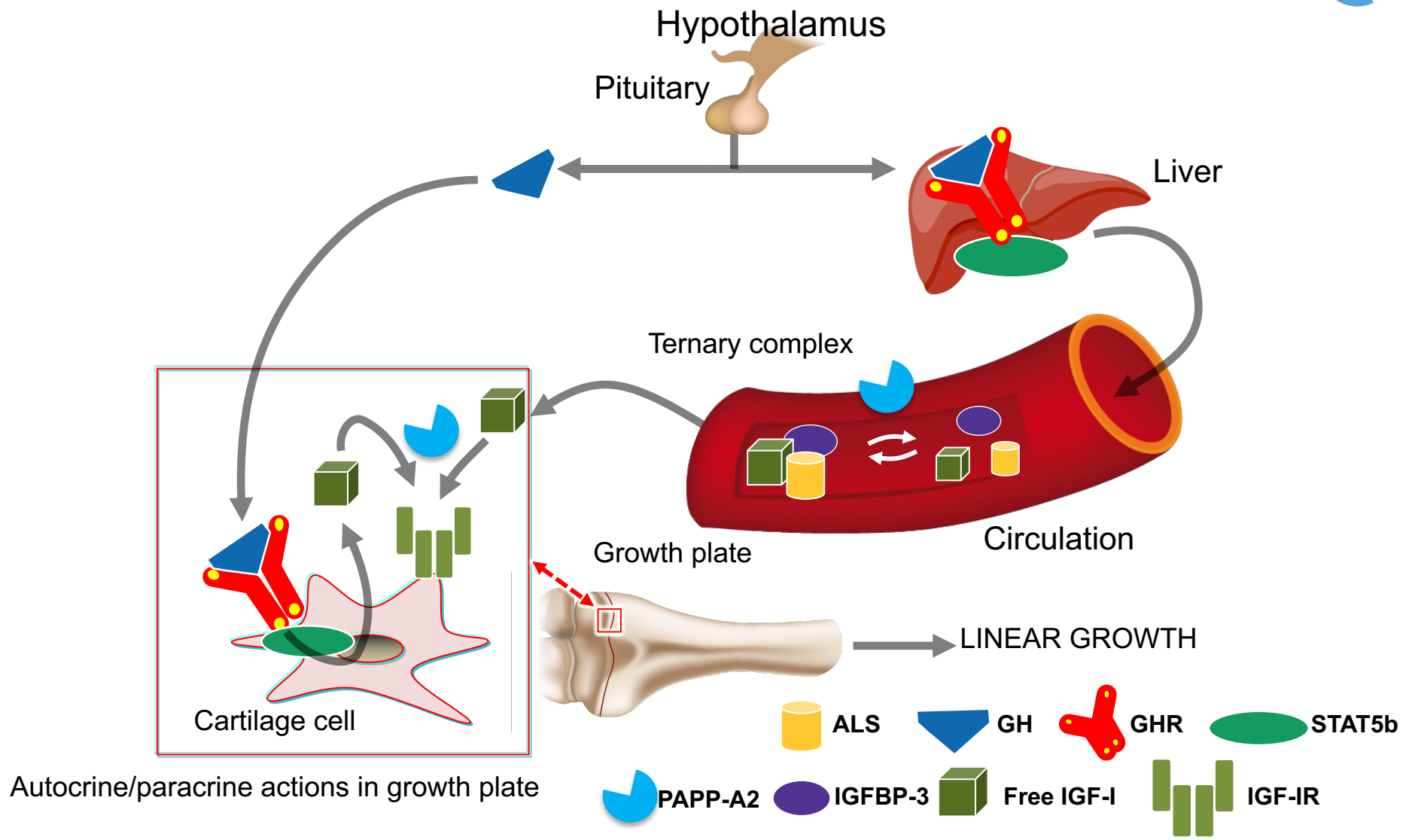
Short stature definition:

- Height <-2 SDS based on appropriate age/gender reference population [3]
- May be due to dysregulation of the GH/IGF-I axis[4]

SD, Standard deviation; SDS, standard deviation score; GH, growth hormone; IGF-I, insulin-like growth factor-I

1. Rani D, et al. Short Stature. [Updated 2022 May 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2. Shim, KS. Ann Pediatr Endocrinol Metab. 2015 Mar; 20(1): 8–12; 3. Cohen P, et al. J Clin Endocrino Metab. 2008;93:4210-7; 4. Savage M, et al. Clinical Endocrinology 2010; 72: 721-728

DIAGRAM OF THE NORMAL GH-IGF-I AXIS



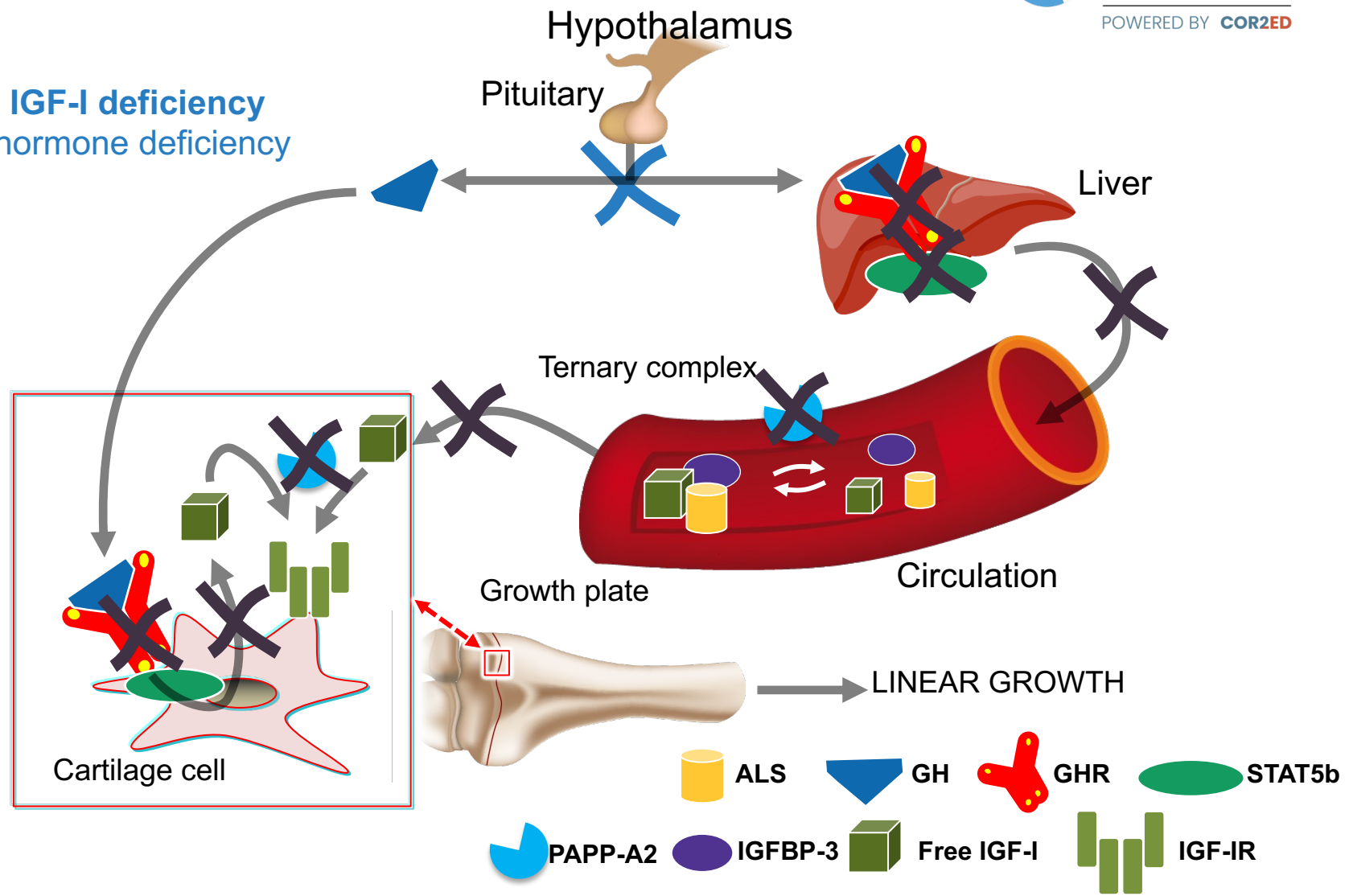
ALS, acid-labile subunit; GH, growth hormone; GHR, growth hormone receptor; GHRH, growth-hormone releasing hormone; IGF-I, insulin-like growth factor-I; IGF-IR, insulin-like growth factor receptor; IGFBP-3, insulin-like growth factor-binding protein 3; STAT5b, signal transducer and activator of transcription 5B
Adapted from Bang P, et al. Horm Res. 2001;55 Suppl 2:84-93

DIFFERENTIATING IGF-I DEFICIENCY FROM OTHER CONDITIONS OF SHORT STATURE

PRIMARY AND SECONDARY IGF-I DEFICIENCY

Secondary IGF-I deficiency
- Growth hormone deficiency

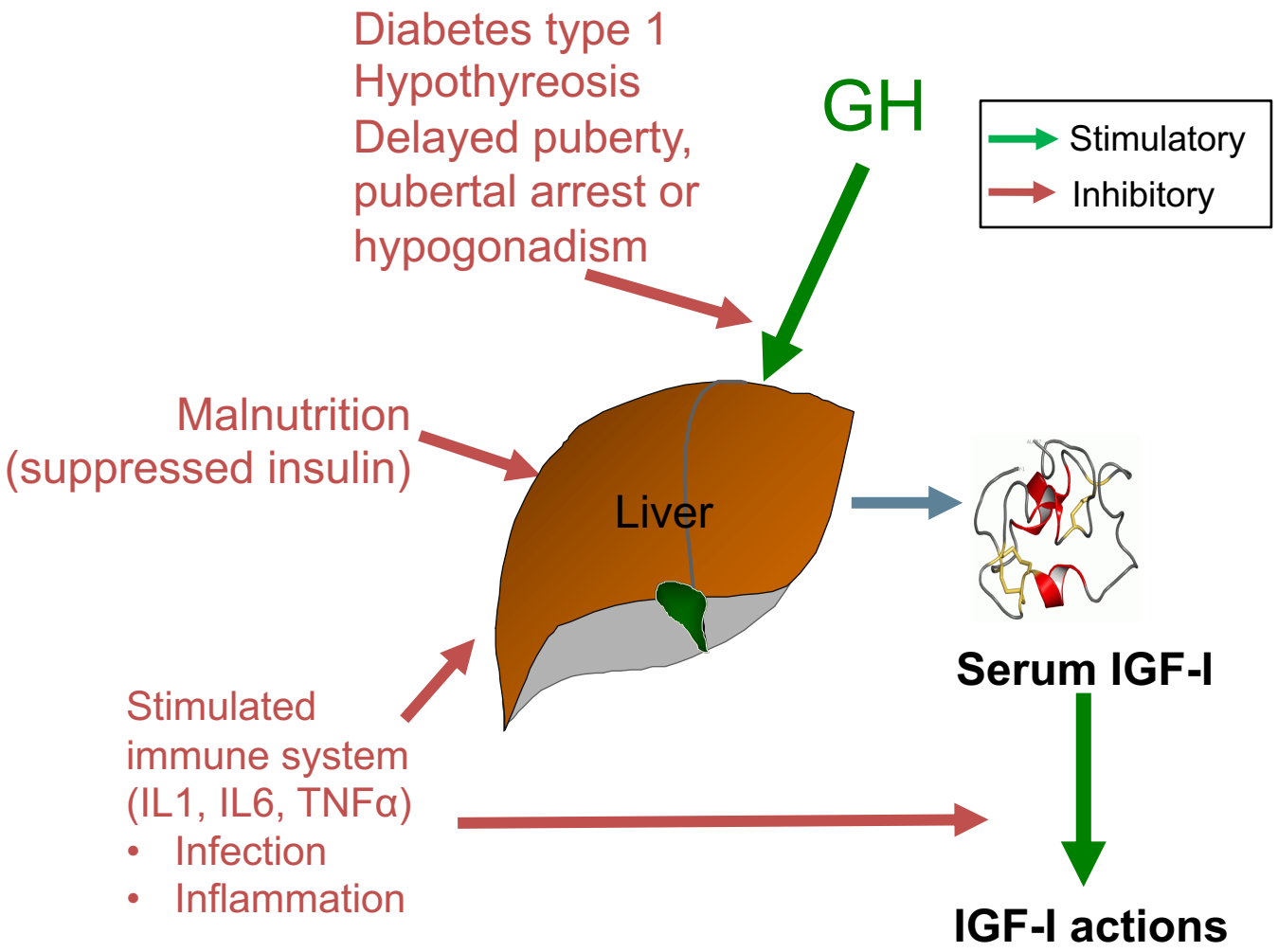
Primary IGF-I deficiency
- GHR gene defects (Laron syndrome)
- Post-GHR signaling defects (Stat5b deficiency)
- IGF and ALS gene defects
- PAPP-A2 gene defects (decreased free IGF-I)



ALS, acid-labile subunit; GH, growth hormone; GHR, growth hormone receptor; GHRH, growth-hormone releasing hormone; IGF-I, insulin-like growth factor-I; IGF-IR, 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; Cohen J, et al. Drugs R D. 2014 Mar; 14(1): 25–29; Rosenfeld RG, et al. Horm Res. 2009; 71 Suppl 2:36-40; David A, et al. Endocrine Reviews 2011; 32: 472-497; Dauber A, et al. EMBO Mol Med. 2016; 8(4): 363-374

ACQUIRED IGF-I DEFICIENCY (POTENTIALLY REVERSIBLE)



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

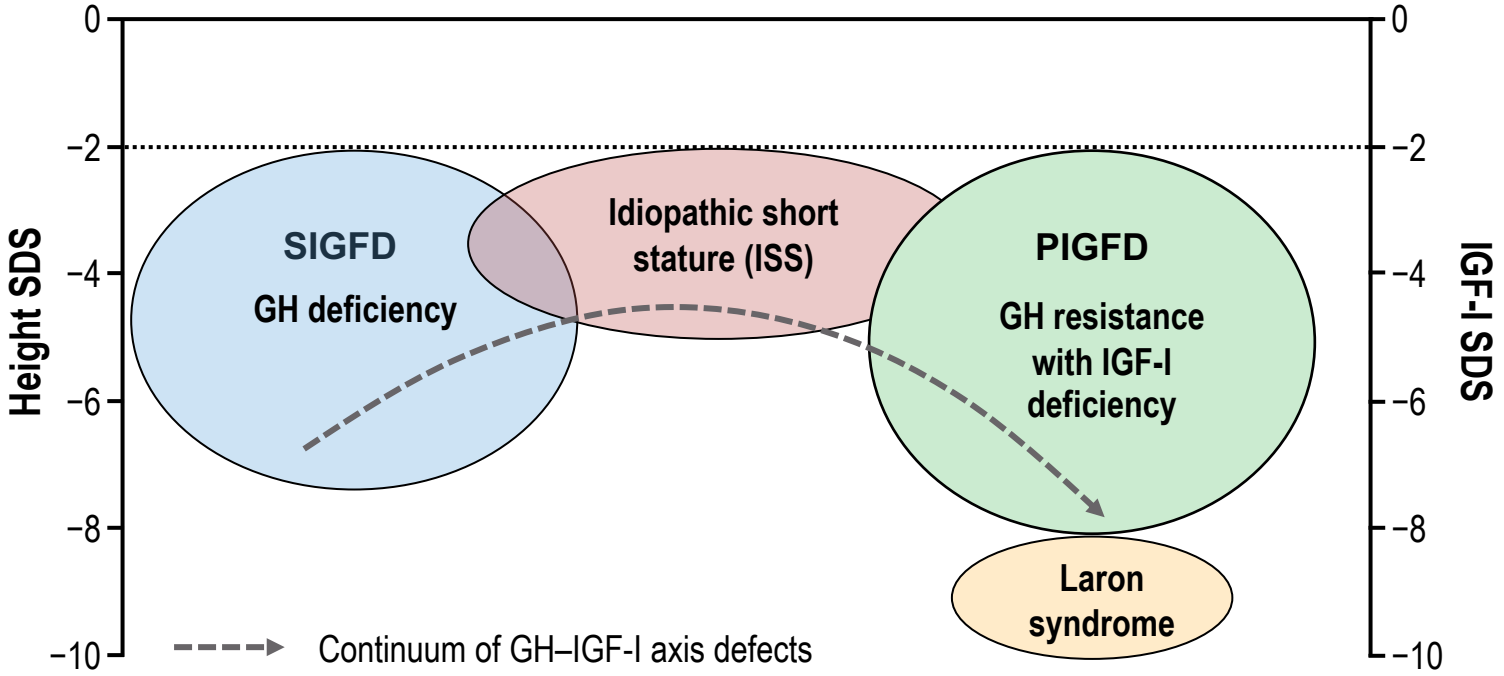
Adapted from Bogin B, et al. Int J Environ Res Public Health. 2015;12:4816-32; Blum W, et al. Endocrine Connections 2018; 7(6): R212-R222

CONTINUUM OF GH-IGF-I AXIS DEFECTS

RANGING FROM SEVERE GHD TO SEVERE PIGFD

- **Extreme cases are easier to diagnose** due to well-studied physical and biochemical features
- **Milder cases** of GHD and SPIGFD are separated from Idiopathic Short Stature (ISS) by **arbitrary definitions of height deficit, IGF-I and GH concentrations**

The continuum model of GH-IGF-I axis defects in the context of height SDS and IGF-I SDS ranges



GH, growth hormone; GHD, growth hormone deficiency; GHI, growth hormone insensitivity; IGF-I, insulin-like growth factor-I; ISS, idiopathic short stature; PIGFD, primary IGF-I deficiency; SIGFD, secondary IGF-I deficiency; SDS, standard deviation score

Savage M, et al. Rev Endocr Metab Disord 2021; 22(1): 91-99; Savage M, et al. Clinical Endocrinology 2010; 72: 721-728

DESCRIPTION OF GH-IGF-I AXIS GROWTH DISORDERS

FROM INTERNATIONAL CONSENSUS GUIDELINES

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Secondary IGF-I Deficiency/ Growth Hormone deficiency (GHD)[1[a],2[b],3]

- Postnatal growth failure due to inadequate secretion/activity of endogenous GH
- Congenital (mutations or structural brain defects), acquired, or idiopathic
- Isolated or in combination with multiple pituitary hormone deficiency
- Low GH secretion may be a result of downregulation of the GH secretion prior to puberty or in obese hyperinsulinaemic children with increased GHR signaling/GH sensitivity

Idiopathic short stature (ISS)[4[c]]

- In the absence of primary, secondary or acquired IGFD and other conditions that could explain short stature such as skeletal dysplasia (e.g. SHOX deficiency), systemic disease, or chromosomal abnormalities (e.g. Down syndrome) the default diagnosis is ISS
- Children with ISS usually have normal birthweight and are IGF-I and GH sufficient

Primary IGF-I Deficiency (PIGFD)[2,5]

- Postnatal (may be combined with prenatal) growth failure due to IGF-I deficiency:
  - Serum IGF-I concentrations for age and gender below an arbitrary defined threshold
  - Normal/elevated GH
  - Absence of acquired IGFD
- Acquired IGFD due to impaired GHR signaling/ GH sensitivity with impaired IGF-I production in conditions such as malnutrition, hypothyroidism, inflammation, etc.
- Growth failure can vary in severity from mild (height SDS ≤-2) to severe (Height SDS ≤-3)
- In severe PIGFD dysmorphic signs and genetic defects are more likely observed

Diagnostic challenges often blur the distinction between GHD, PIGFD, and ISS

[a] Consensus of the Growth Hormone Research Society, endorsed by the following international societies: the Councils and Drug and Therapeutics Committees of the European Society for Pediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, the Councils of the Australasian Pediatric Endocrinology Group, the Japanese Society for Pediatric Endocrinology, and the Sociedad Latinoamericana de Endocrinologia Pediatrica

[b] Consensus guidelines were generated by a taskforce of seven pediatric endocrinologists from USA and Canada, and a pediatric bioethicist, and was supported by the pediatric endocrine society

[c] Consensus statement from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology

GH, growth hormone; GHD, growth hormone deficiency; GHR, growth hormone receptor; IGF-I, insulin-like growth factor-I; ISS, idiopathic short stature; (P)IGFD, (primary) insulin-like growth factor I deficiency; SDS, standard deviation score

1. Growth Hormone Research Society. J Clin Endocrino Metab. 2000;85:3990-3; 2. Grimberg A, et al. Horm Res Paediatr. 2016;86:361-97; 3. Berryman D, et al. Nature Reviews Endocrinology 2013; 9: 346-356; 4. Cohen P, et al. J Clin Endocrino Metab. 2008;93:4210-7; 5. David A, et al. Endocrine Reviews 2011; 32 (4): 472-497

HOW IS SEVERE PRIMARY IGF-I DEFICIENCY DEFINED?

- **IGF-I deficiency which is due to pathology** downstream of growth hormone
- SPIGFD is defined by:

SEVERE PRIMARY IGF-I DEFICIENCY DEFINITION:

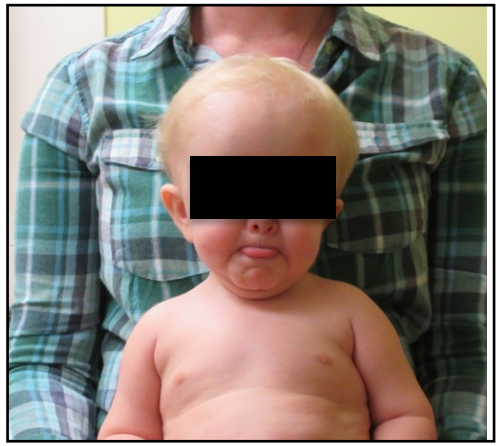
- Height ≤-3 SDS
- Basal IGF-I ≤-3 SDS [FDA] or IGF-I <2.5th percentile (~-2 SDS) [EMA]
- Normal or elevated growth hormone concentration
- Exclude secondary and acquired IGFD

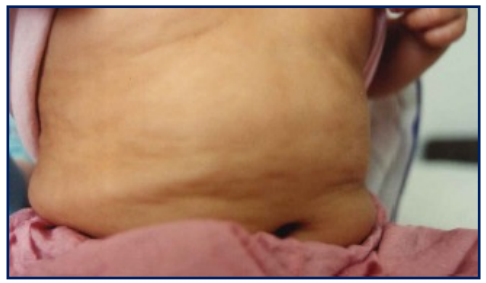
EMA, European Medicines Agency; FDA, Food and Drug Administration; IGF-I, insulin-like growth factor I; IGFD, insulin-like growth factor I deficiency; SDS, standard deviation score; SPIGFD, severe primary IGF-I deficiency

Mecasermin Prescribing Information and SmPC, December 2019

SEVERE PRIMARY IGF-I DEFICIENCY CLINICAL PRESENTATION

CASE PRESENTATION: CLASSIC GROWTH HORMONE INSENSITIVITY (LARON SYNDROME)





- 5-year-old boy with proportionate short stature
- Frontal bossing
- Sparse, thin hair growth
- Micrognathia
- Acromicria
- High-pitched voice
- Increased weight/height ratio

- Normal pregnancy
- BW: 3 kg
- BL: 47.8 cm
- Postnatal growth failure
- Height: -5.6 SDS
- Weight: -3.5 SDS
- Delayed BA

BA, bone age; BL, body length; BW, body weight; SDS, standard deviation score

Backeljauw P. Growth Hormone & IGF Research. 2020;51:22-6

PRIMARY IGF-I DEFICIENCY: EVIDENCE FOR AN EVOLVING PHENOTYPE

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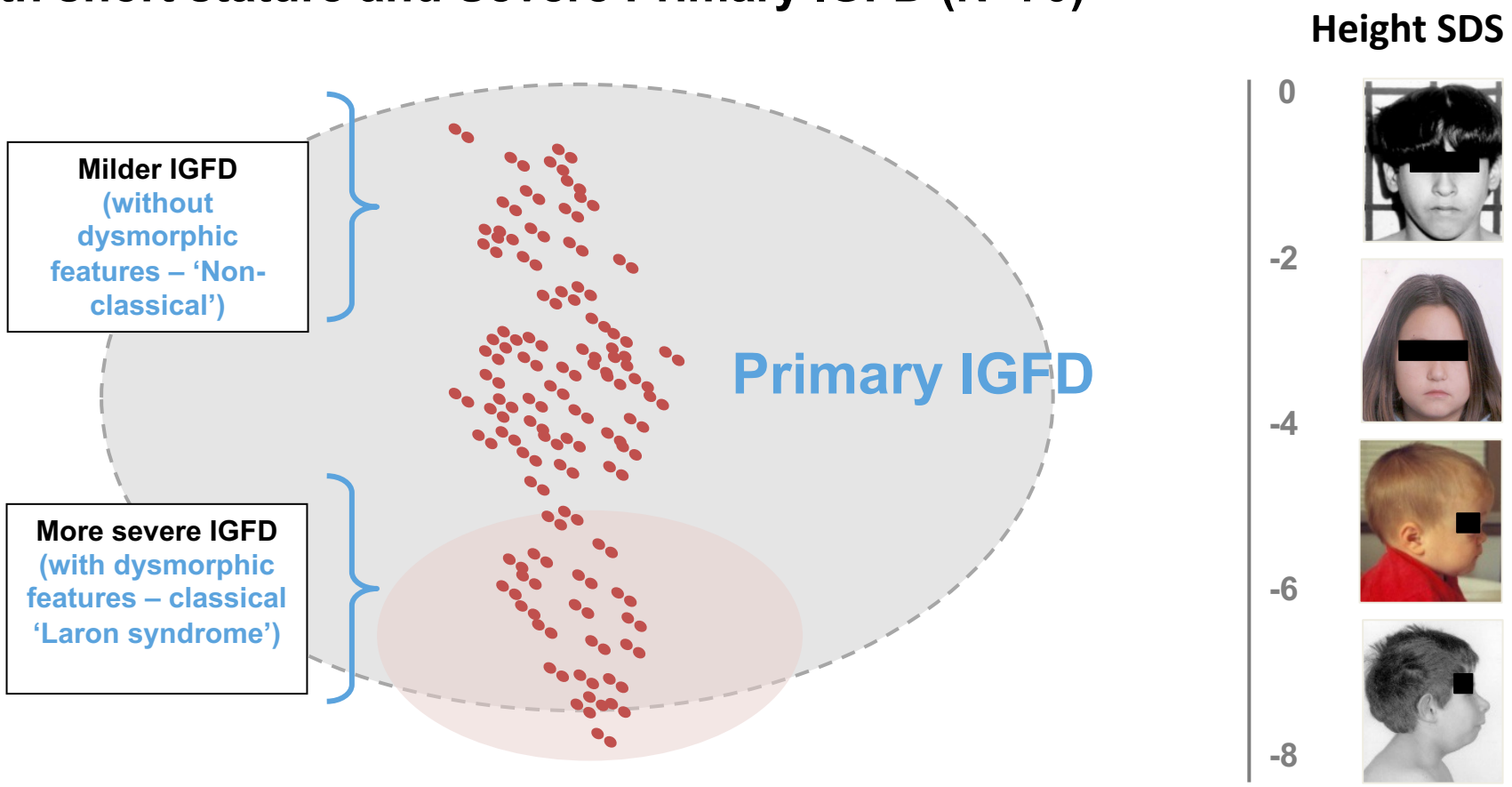
SPECTRUM OF PRIMARY IGF-I DEFICIENCY

Children with short stature and Severe Primary IGFD (N=70)[1]

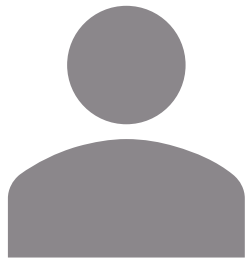


IGF-I, insulin-like growth factor I; IGFD, IGF-I deficiency

David A, et al. Endocrine Reviews. 2011; 32 (4): 472-497

Modified slide courtesy Martin Savage. Permission given for publication of photograph and results of all investigations

CASE PRESENTATION: NON-CLASSICAL GROWTH HORMONE INSENSITIVITY



No dysmorphic features identified

- 6.9-year-old boy with proportionate short stature
- Naïve to growth promoting therapy
- Pre-pubertal
- Parental heights: +0.6 SDS/ -2.4 SDS

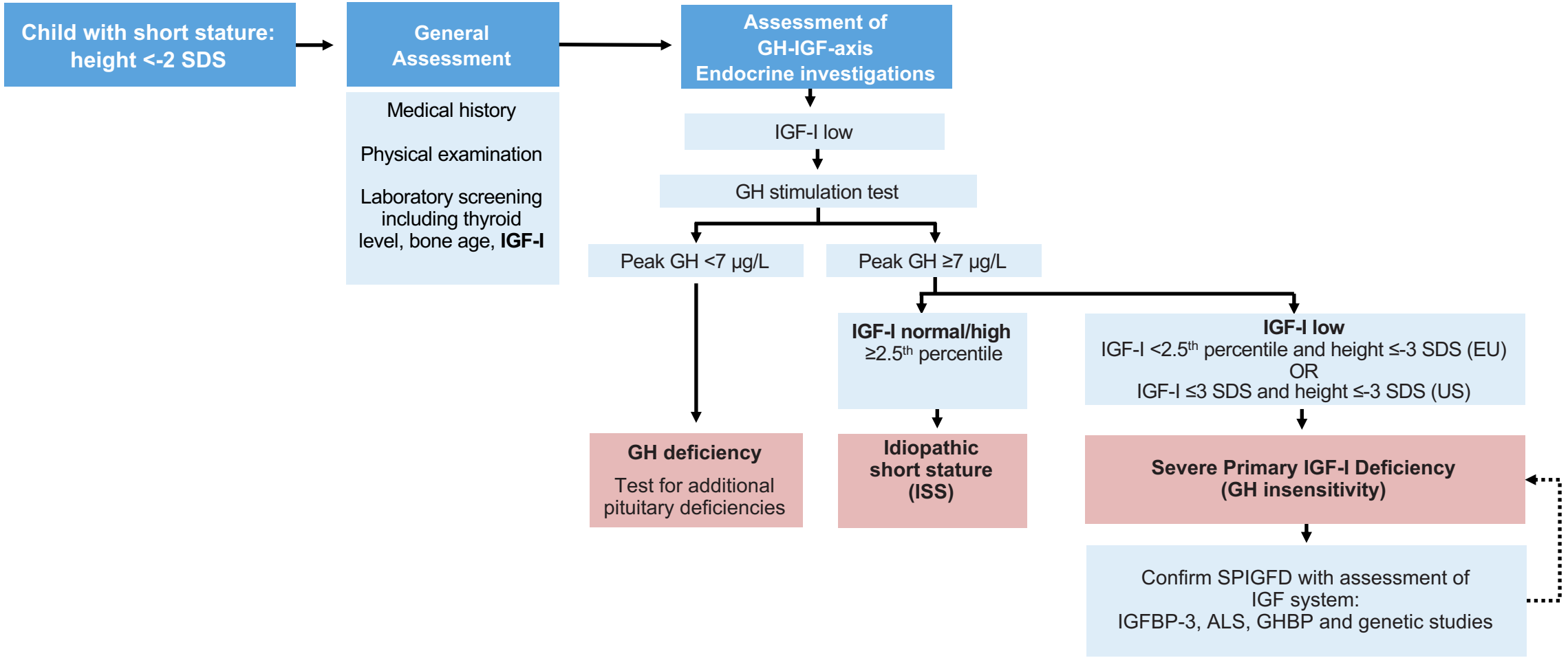
- Normal pregnancy
- GA 38 weeks
- BW: 2.7 kg
- BL: 47 cm
- Postnatal growth failure
- Height: -4.8 SDS
- Weight: -4.2 SDS
- BMI: +1.0 SDS

BL, body length; BMI, body mass index; BW, body weight; GA, gestational age; SDS, standard deviation score
Data from EU-IGF registry

INSIGHTS TO THE ASSESSMENT OF THE GH-IGF AXIS

Diagnosis, confirmatory tests and challenges

ALGORITHM FOR THE INVESTIGATION OF SHORT STATURE



ALS, acid labile subunit; GH, growth hormone; GHBP, growth hormone binding protein; IGFBP-3, IGF-I binding protein-3; IGF-I, insulin-like growth factor I; SDS, standard deviation score

Adapted from: Savage M, et al. Rev Endocr Metab Disord. 2021;22(1):91-9

SUMMARY OF PHENOTYPIC FEATURES OF MAJOR FORMS OF IGF-I DEFICIENCY

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Phenotype	Gene defect					
	GHR	STAT5b	IGF-I	IGFALS[a]	Bioinactive GH	GH1 with anti-GH antibodies
Severe growth failure	+/-	+	+	-	-	+
Mild growth failure	-/+	-	-	+	+	-
Mid-face hypoplasia	+/-	+/-	-	-	-	+
Other facial dysmorphism	-	-	+	-	-	-
Deafness	-	-	+/-	-	-	-
Microcephaly	-	-	+	-	-	-
Intellectual delay	-	-	+	-	-	-
Puberty delay	+/-	+/-	-	+	-	-
Immune deficiency	-	+	-	-	-	-

+ = positive - = negative +/- = predominantly positive -/+ = predominantly negative

[a]IGFALS is the name of the gene that encodes the ALS protein

ALS , Acid Labile Subunit; GH, Growth Hormone; GHR, Growth Hormone Receptor; IGF-I, Insulin-like growth factor I; IGFALS, Insulin-like growth factor binding protein, STAT5b, Signal Transducer and Activator of Transcription 5b

David A, et al. Endocr Rev. 2011;32:472-97; El Kholy M, et al. Horm Res Paediatr. 2011;76:300-6

SHORT STATURE INVESTIGATIONS EVALUATING THE GH-IGF-I AXIS

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REQUIRED

- IGF-I concentrations - repeated on 2 or more occasions
- GH stimulation test
- General work up has excluded acquired IGFD

RECOMMENDED TO SUPPORT SPIGFD DIAGNOSIS

- IGFBP-3
- GH-binding protein (GHBP)
- Acid-labile subunit (ALS)
- IGF-I generation testing
- Genetic analysis

Key diagnostic features of PIGFD

1. **Short stature**
2. **Normal or increased GH**
3. **Deficiency of IGF-I**

ALS , Acid Labile Subunit; GH, Growth Hormone; IGF-I, Insulin-like growth factor I; IGFBP-3, Insulin-like growth factor I binding protein-3; PIGFD, primary insulin-like growth factor I deficiency

Grimberg A, et al. Horm Res Paediatr. 2016;86:361-97; Savage M, et al. Rev Endocr Metab Disord. 2021;22(1):91-9; Blum WF, et al. Endocrine Connections. 2018;7:R212-R222; Collett-Solberg PF, et al. Horm Res Paediatr. 2019;92(1):1-14; Wit J, et al. Horm Res Paediatr 2021; 94: 81-104

REQUIRED ENDOCRINE INVESTIGATIONS

Test	Purpose	Considerations
IGF-I	**Distinguishes short stature due to defects in the GH-IGF-axis** **Confirms IGFD**	• Use IGF-I assay you have experience with • Reliable reference data, with normative ranges based on age, gender, and pubertal status • Consider methodological issues – How interference of IGFBPs is avoided eg. by using excess IGF-II – Normative data should be established with that particular assay and preferably published – Consider assay in reference laboratory or consult expertise – Repeated measures should be obtained (at least two) • Consider patient conditions that affect IGF-I concentration; malnutrition/malabsorption, systemic illness • Low IGF-I in young children is difficult to interpret. • An IGF-I >0 SDS at any age makes IGFD unlikely • Correlates with the severity of the IGFD phenotype
GH stimulation test	**Differentiates GH deficiency from PIGFD**	• Evaluation of GH secretion has low reproducibility and low sensitivity/specificity for SPIGFD diagnosis • Normative references limited, cut-off for SPIGFD not defined • Elevated baseline GH secretion is a characteristic of SPIGFD but difficult to evaluate in stimulation tests • **Should be performed, when:** – IGF-I is repeatedly low – In children with features of growth failure without classical features of SPIGFD – History and physical examination compatible with SPIGFD, low height velocity, or low IGF-I • **Not essential for diagnosis of SPIGFD in:** – Patients with a clearly classical presentation i.e. positive family history, consanguineous pedigree, severe short stature, clinical features of Laron syndrome, high baseline GH and low or undetectable serum IGF-I

GH, Growth Hormone; IGF-I/II, Insulin-like growth factor I/II; (SP)IGFD, (severe primary) IGF-I deficiency

Coutant R, et al. European Journal of Endocrinology. 2012;166:351-7; Blum WF, et al. Endocrine Connections. 2018;7:R212-R222; Collett-Solberg PF, et al. Horm Res Paediatr. 2019;92(1):1-14; Grimberg A, et al. Horm Res Paediatr. 2016;86:361-97; Guevara-Aguirre J. et al. JCEM 1993;76:417-423; Storr H. https://www.bsped.org.uk/media/1866/uk-igf1-users-group-guidelines-2021.pdf, Accessed 09-Nov-22; Cohen J, et al. Drugs R D 2014; 14: 25-29

RECOMMENDED ENDOCRINE INVESTIGATIONS

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Test	Purpose	Considerations
IGFBP-3	**Distinguishes short stature due to GH deficiency from other conditions**	• IGFBP-3 can provide confirmatory information • Assays not widely available in all countries • More reliable biomarker than IGF-I in children <3 yrs of age but less sensitive than IGF-I after 3 yrs • Correlates with the severity of the SPIGFD phenotype • Extremely low IGFBP-3 is also found in ALSD
IGF-I generation test	**Valuable in diagnosis of severe IGFD (*GHR*, *STAT5B* defects)** **Value is unclear in less severe forms of IGFD**	• Clinical utility of this test in the diagnosis of SPIGFD has not been definitively demonstrated • Evaluation of GH responsiveness by measuring IGF-I after a short course of GH (~3-10 days) • Sensitivity and specificity of the IGF-GT are not high enough to appropriately identify SPIGFD in children with milder degrees of short stature • No consensus on best protocol, normative data not established and lower cutoff not well established • Dependent on IGF-I assay • Association with growth response to rhIGF-1 therapy not established • **Should be performed, when:** IGF-I is low • **Not essential for diagnosis of SPIGFD in:** – Patients with a clearly classical presentation i.e., positive family history, consanguineous pedigree, severe short stature, clinical features of Laron syndrome, high baseline GH and low or undetectable serum IGF-I

ALSD, acid-labile subunit deficiency; GH, Growth Hormone; IGF-I, Insulin-like growth factor I; (SP)IGFD, (severe primary) IGF-I deficiency

Coutant R, et al. European Journal of Endocrinology. 2012;166:351-7; Blum WF, et al. Endocrine Connections. 2018;7:R212-R222; Collett-Solberg PF, et al. Horm Res Paediatr. 2019;92(1):1-14; Grimberg A, et al. Horm Res Paediatr. 2016;86:361-97; Rosenfeld R, et al. Journal of Clinical Endocrinology. 1995;80:1532-40; Storr H. https://www.bsped.org.uk/media/1866/uk-igf1-users-group-guidelines-2021.pdf, Accessed 09-Nov-22; Burren CP, et al. Hormone Research, 55(3), 125-130; Domené H, et al. Best Pract Res Clin Endocrinol Metab. 2011; 25 (1): 101-13

RECOMMENDED ENDOCRINE INVESTIGATIONS

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Test	Purpose	Considerations
GHBP	**Most clinically relevant use is to confirm GH insensitivity due to GH receptor defect**	• Assays for GHBP are not widely available • GHBP is low in children with defects in the extracellular part of the GH receptor • SPIGFD is not limited to Laron syndrome with an extracellular defect in GHR gene and low GHBP • Other forms of GH receptor insensitivity, may have normal or high GHBP • If GHBP is very low or undetectable, mutation analysis of GHR gene is recommended • Genetic analysis is easier, more specific, generally available and provides more information
Acid-labile subunit	**Value in the characterization of individual patients with PIGFD** **Consider if ↓ IGF-I and ↓ IGFBP-3 with only moderate growth failure**	• Commercial ALS assays not generally available • IGFBP-3 more pronounced low than IGF-I indicates ALSD • Collaborate with specialised labs to determine ALS, if not genetics can provide evidence • Correlates with the severity of the IGFD phenotype

GH, Growth Hormone; IGF-I, Insulin-like growth factor I; IGFBP-3, IGF-I binding protein-3; (SP)IGFD, (severe primary) IGF-I deficiency

Coutant R, et al. European Journal of Endocrinology. 2012;166:351-7; Blum WF, et al. Endocrine Connections. 2018;7:R212-R222; Collett-Solberg PF, et al. Horm Res Paediatr. 2019;92(1):1-14; Grimberg A, et al. Horm Res Paediatr. 2016;86:361-97; Domené H, et al. Best Pract Res Clin Endocrinol Metab. 2011; 25 (1): 101-13

SUMMARY OF BIOCHEMICAL FEATURES OF MAJOR FORMS OF IGF-I DEFICIENCY

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Biochemical feature	Gene defect					
	GHR	STAT5b	IGF-I	IGFALS	Bioinactive GH	GH1 with anti-GH antibodies
Hypoglycaemia	+	-/+	-	-	-	-
Hyperinsulinaemia	-	-	+/-	+	-	-
IGF-I deficiency	+	+	+/-	+	+	+
IGFBP-3 deficiency	+	+	-	+	+	+
ALS deficiency	+	+	-	+	+	+
GH excess	+	+	+/-	+	-	-
GHBP deficiency	+/-	-	-	-	-	-

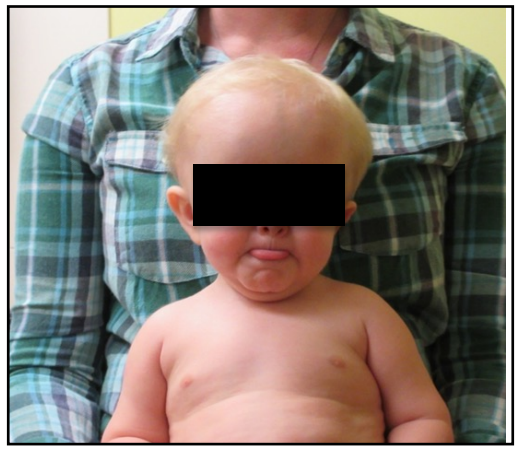
+ = positive - = negative +/- = predominantly positive -/+ = predominantly negative

ALS , Acid Labile Subunit; GH, Growth Hormone; GHBP, growth hormone binding protein; GHR, Growth Hormone Receptor; IGF-I, Insulin-like growth factor I; IGFALS, Insulin-like growth factor binding protein, IGFBP-3, Insulin-like growth factor I binding protein 3; STAT5b, Signal Transducer and Activator of Transcription 5b

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

DIAGNOSTIC OUTCOMES
PATIENT CASES

CASE PRESENTATION: CLASSIC GROWTH HORMONE INSENSITIVITY (LARON SYNDROME)



ENDOCRINE INVESTIGATIONS

- Bone age = 2 years (chronological age of 5.2 years)
- IGF-I = 3.0 ng/ml (<0.1 percentile; <-3 SDS)
- IGFBP-3 = 0.2 mg/l (normal 1.2-5.2 mg/l)
- GHBP = 40 pmol/l (normal 320-3820)
- Basal GH = 29 to 51 ng/ml
- Peak stimulated GH = >100 ng/ml
- IGF-I generation test (0.1 mg GH SC daily x 4): IGF-I = 3.0 → 5.6 ng/ml

GENETIC TESTING

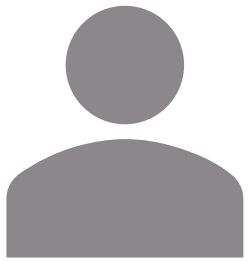
- Homozygous for a GH receptor mutation c.723 C>T (exon 7)

Diagnosis of SPIGFD

GH, Growth Hormone; GHBP, growth hormone binding protein; IGF-I, Insulin-like growth factor I; IGFBP-3, IGF-I binding protein-3; SC, subcutaneous; SDS, standard deviation scores; SPIGFD, severe primary IGF-I deficiency

Backeljauw P. Growth Hormone & IGF Research. 2020;51:22-6

CASE PRESENTATION: NON-CLASSICAL GROWTH HORMONE INSENSITIVITY



No dysmorphic features identified

ENDOCRINE INVESTIGATIONS

- Bone age not reported
- IGF-I = 23 ng/ml (<-2 SD)
- Basal GH = 34.6 ng/ml
- Peak stimulated GH = 40 ng/ml

GENETIC TESTING

- No mutations/defects reported in registry

Diagnosis of non-classical SPIGFD

GH, Growth Hormone; GHBP, growth hormone binding protein; IGF-I, Insulin-like growth factor I; IGFBP-3, IGF-I binding protein-3; SPIGFD: severe primary IGF-I deficiency

Data from EU-IGF registry

REAL-WORLD DATA FROM THE EU-IGFD REGISTRY

SIGNIFICANT NUMBER OF PATIENTS HAVE MILDER FORMS OF PRIMARY IGF-I DEFICIENCY

Baseline characteristics	NPP-LS (N=21)		NPP-non LS (N=117)		P value[b]
	Mean (SD)	95% CI	Mean (SD)	95% CI	
Females		24.5; 63.5		30.9; 48.4	0.76[c]
Age at first injection, years	6.07 (3.49)	4.49; 7.66	8.44 (3.45)	7.81; 9.07	0.006[d]
Height, SDS	**-5.62 (1.95)**	-6.66; -4.58	**-3.46 (1.05)**	-3.66; -3.26	<0.001[d]
Height velocity, cm/year	5.67 (1.10)	4.66; 6.69	4.74 (1.77)	4.29; 5.19	0.174[d]
Weight, SDS	-4.63 (1.35)	-5.32; -3.93	-3.04 (1.12)	-3.26; -2.83	<0.001[d]
BMI, SDS	-0.24 (1.30)	-0.94; 0.45	-0.80 (1.34)	-1.07; -0.53	0.126[e]
Mother's height, cm	156.0 (7.4)	152.3; 159.7	157.8 (7.2)	156.4; 159.2	–
Father's height, cm	168.5 (7.6)	164.7; 172.3	172.6 (8.1)	171.0; 174.1	–
IGF-I, ng/mL	**39.37 (16.25)**	26.89; 51.86	**88.30 (67.89)**	75.04; 101.57	0.007[d]
Peak stimulated GH level, ng/mL	35.50 (20.53)	23.10; 47.91	24.61 (24.87)	19.22; 30.01	0.014[d]
Primary diagnosis: SPIGFD[a]		84.5; 100.0		83.9; 94.7	–
History of hypoglycaemia		7.7; 40.0		0.9; 7.3	0.011[f]

>50% of non-LS are responders and have a mean first year Ht SDS response to rhIGF-1 therapy not different from LS

[a]Including LS, as reported by the investigator; [b] NPP-non-LS vs NPP-LS; [c] Chi-square test; [d] Wilcoxon test; [e] ANOVA; [f] Fisher's test

BMI, body mass index; Ht, height; IGF-I, insulin-like growth factor I; IGFD, insulin-like growth factor I deficiency; LS, Laron Syndrome; non-LS, non-Laron Syndrome; NPP, naïve to treatment and prepubertal; SDS, standard deviation score; SPIGFD, severe primary IGF-I deficiency

Bang et al. Eur J Endocrinol. 2021;184:267-76

SUMMARY

SUMMARY – DIAGNOSTIC CHALLENGES OF SPIGFD

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- **Short stature** can be **caused by a variety of aetiologies** and an early correct diagnosis is essential
- **Diagnostic challenges** often blur the distinction **between GHD, PIGFD, and ISS**
- GH-IGF-I defects form a **continuum ranging from severe GHD (SIGFD) to severe GHI (PIGFD)**
- **Severe primary IGF-I deficiency** (SPIGFD) generally presents as **classical Laron syndrome** but **non-classical cases with mild or moderate phenotypes** should also be considered
- **Diagnosis of SPIGFD** requires severe short stature, **measurement of serum IGF-I and the demonstration of normal or increased GH secretion** as well as lack of other pathology in the general work-up of short stature
- **Once a diagnosis of SPIGFD is made, genetic analysis is recommended** to confirm the clinical diagnosis prior to commencing treatment

GH, Growth Hormone; GHD growth hormone deficiency; IGF-I, Insulin-like growth factor I; IGFBP-3, IGF-I binding protein-3; SIGFD, severe IGF-I deficiency; (S)PIGFD: (severe) primary IGF-I deficiency

Rani D, et al. Short Stature. [Updated 2022 May 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.; Storr H, et al. Endocrine Reviews. 2019; 40: 476-505; Bang et al. Eur J Endocrinol. 2021; 184:267-27; Savage M, et al. Rev Endocr Metab Disord 2021; 22(1): 91-99; Grimberg A, et al. Horm Res Paediatr. 2016;86:361-97; Savage M, et al. Frontiers in Endcorinology 2021; 12: 781044

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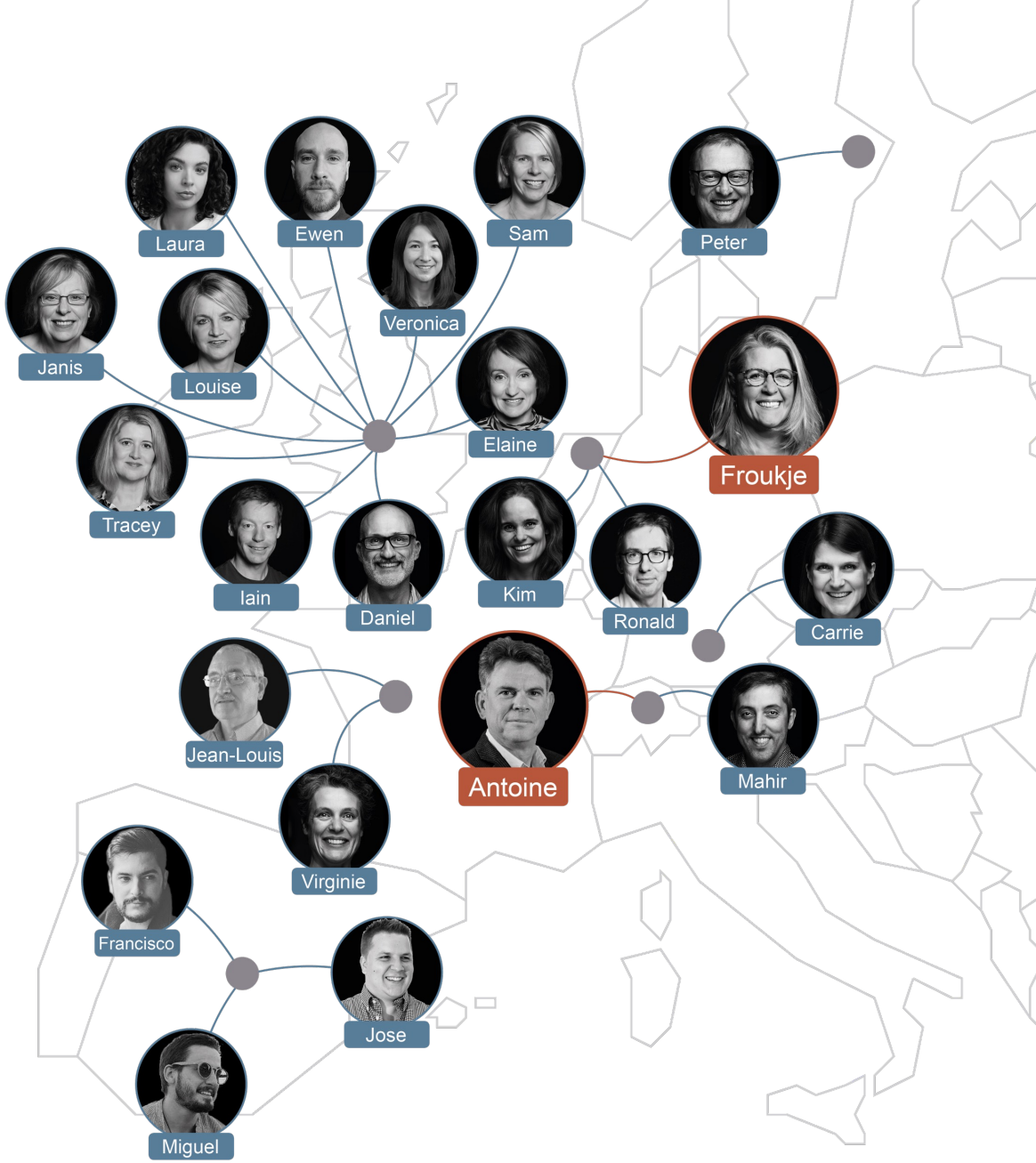

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