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touchCONGRESS webinar

Continuing the conversation in paediatric endocrinology – how do the latest advances in understanding biology translate to improved patient care?

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Webinar overview

Continuing the conversation in paediatric endocrinology – how do the latest advances in understanding biology translate to improved patient care?

- Part 1: ESPE 2019 – Improving patient care for severe primary IGF-1 deficiency
- Part 2: ESPE 2019 – Improving patient care for growth hormone deficiency
- Part 3: ESPE 2019 – Improving patient care for all paediatric growth disorders

ESPE, European Society for Paediatric Endocrinology; IGF-1, insulin-like growth factor-1

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Part 1.
European Society for Paediatric Endocrinology 2019 – Improving patient care for severe primary IGF-1 deficiency

Focus on the latest biological, diagnostic, and treatment data

IGF-1, insulin-like growth factor-1.

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Severe primary IGF-1 deficiency (SPIGFD)

SPIGFD describes a category of defects characterized by deficiency of IGF-1 production due to impaired action of GH in peripheral tissues resulting in slower growth compared to healthy children of the same age.[1]

Causes[1]

- **Mutations** in genes coding for functional proteins in the pathway of GH action, e.g. the GH receptor. signalling molecules, IGF-1 and IGF-1 transporters
- **Alterations** to GH signalling pathways

Diagnosis[1,2]

- **Demonstration of**
  - IGF-1 deficiency
  - Normal or increased GH secretion
  - Short stature
- An IGF-1 generation test can confirm SPIGFD

Treatment[1,3]

- **RhIGF-1**
- **EMA label:**
  - height SD score ≤ –3.0
  - basal IGF-1 levels < 2.5th percentile for age and gender
  - GH sufficiency
  - Exclusion of secondary IGF-1 deficiency, e.g. malnutrition, hypothyroidism
- **Regular follow-up**

EMA, European Medicines Agency; GH, growth hormone; IGF-1, insulin-like growth factor 1; rhIGF-1, recombinant human insulin-like growth factor 1; SD, standard deviation; SPIGFD, severe primary insulin-like growth factor deficiency.

1. Savage M et al. *Front Endocrinol*. 2011;**2**:95; 2. Cohen J et al. *Drugs R D*. 2014;**14**(1):25–29; 3. Ipsen Pharma. Mecasermin – summary of product characteristics.

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How do I diagnose growth hormone insensitivity?

Walenkamp M-J

New genetic techniques are identifying non-classical clinical and biochemical features of GH Insensitivity (GHI) (another term for SPIGFD)

Classical vs. non-classical

- **Classical GHI:** severe postnatal growth failure and midfacial hypoplasia
- **Non-classical GHI:** moderate short stature, low or normal birth weight and variable phenotype

New genetic techniques

- Monogenetic defects responsible for milder forms of GHI that are likely more prevalent than classical severe forms
- Defects in genes involved in GH action – e.g. *STAT5B, IGF-1, IGF1R, IGFALS, PAPPA2*

Proposed diagnostics

- If a patient scores ≥3 on the following criteria, *IGF1R* analysis recommended: birth weight and/or length < -1 SDS; height at presentation < -2.5 SDS, head circumference < -2 SDS; IGF-1 > 0 SDS
- The proposed diagnostic score offers 76% sensitivity and 87% specificity

Genetic defects present with variable phenotypes and biochemical profiles, providing new diagnostic strategies for GHI. This variability also highlights the need for diagnostic teamwork across medical disciplines.

GH, growth hormone; GHI, growth hormone insensitivity; GHR, growth hormone receptor; *IGFALS*, insulin-like growth factor binding protein and labile subunit; *IGF-1*, insulin-like growth factor-1; *IGF1R*, insulin-like growth factor-1 receptor; *PAPPA2*, pappalysin 2; SDS, standard deviation scores; SPIGFD, severe primary insulin-like growth factor deficiency; *STAT5B*, signal transducer and activator of transcription 5B

Walenkamp M-J. Abstract S5.1. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

Clinical characteristics, puberty pattern and adult or near-adult-height data in a group of patients with growth failure due to SPIGFD (GROWPATI study)

Stoupa A, et al.

Assessment of pubertal onset and growth spurt in patients with growth retardation due to SPIGFD

49 patients with SPIGFD:

- Historical cohort from the Paediatric Endocrinology Department of Necker Children's University Hospital, Paris (n=30; mean age = 17 years) and new cohort (n=19; mean age = 9.5 years)
- All pubertal stage 1 at baseline
- Treated with GH or, for Laron syndrome, mecasermin

Patient characteristics:

- Born SGA (n=29)
- Constitutional bone disease (n=5)
- Laron syndrome (n=1)
- Heterozygous GHR mutations (n=2)
- Noonan syndrome (n=1)
- Silver-Russell syndrome (n=2)

Endpoints*	Boys	Girls
Mean age for Tanner stage 2 (pubertal onset)	12.5 years (n=11)	12 years (n=8)
Adult height/near-adult height (mean, SD)	-2.2 SDS(0.3) (n=5)	-2 SDS(1) (n=3); AH=128.5cm for Laron syndrome (n=1)
Predicted adult heights with available final heights	-1.5 SDS(0.4)	1.8 SDS(0.6)
Other	2 advanced evolutive central puberty (treated by GnRH agonist)	Mean age of menarche = 13.6 years with regular menstrual cycles

***Outcomes for subgroup of 19 from both cohorts**

Final heights were below predicted heights, with height velocity during puberty varying. Long-term follow-up and genetic investigations are necessary for personalized care

AH, adult height; GHR, growth hormone receptor; GnRH, gonadotropin-releasing hormone agonist; GROWPATI, growth retardation due to SPIGFD; SPIGFD, severe primary insulin-like growth factor deficiency; SD, standard deviation; SDS, standard deviation scores; SGA, small for gestational age.

Stoupa A, et al. Abstract P1-80. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

The European Increlex® growth forum database (EU-IGFD) registry: Do treatment practices differ between European countries?

Bang P, et al.

Analysis of baseline data from the EU-IGFD registry to examine if mecasermin treatment for SPIGFD practices differs between EU countries

- **The EU-IGFD registry is an ongoing, multi-centre, open-label, observational study to monitor the safety and efficacy of mecasermin**
- **Data from 280 patients from 10 EU countries (as of 9 October 2018)**

Mean age of first mecasermin intake	•Similar between countries, ranging from 8.6 years (Spain) to 9.9 years (Germany)
Mean height (SDS) ±SD at first mecasermin intake	•Wide variation: Lowest in the UK (-4.75 ±1.02) and highest in 'other' countries – Sweden, Austria, Belgium, Netherlands (-3.15 ±1.00)
Treatment naivety	•Patients from Poland (100%) and Germany (79.5%) less likely to have received previous growth therapy •France (60.6%), Spain (58.8%), UK (64.5%), Italy (56.0%) and Other (55.6%)
Treatment discontinuation	•Therapy discontinued because adult height achieved in France (5.9%), Spain (23.1%), Germany (31.7%), UK (36.4%), Italy (38.9%), Poland (40%) and Other (44.4%)
Dose and titration	•Median dose at baseline in all countries = 40 µg/kg BID •Median dose titrated up to 120 µg/kg BID after 12 months in Germany and France, but more slowly titrated in other countries, particularly Spain

Treatment with mecasermin varies within the EU on several levels, highlighting the need for international collaboration to determine best practice for mecasermin therapy

CI, confidence interval; EU-IGFD, European Increlex growth forum database; SD, standard deviation; SDS, standard deviation scores; SPIGFD, severe primary insulin-like growth factor deficiency.

Bang P, et al. Abstract P1-214. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

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Hypoglycaemia adverse events in SPIGFD: Association with patient diagnosis, age, time-course and dosage of mecasermin: 10-year data from the EU-IGFD

Woelfle J, et al.

Analysis of 10-year data from the EU-IGFD registry to examine frequency, predictive factors, and the potential impact of suspected or documented hypoglycaemia on mecasermin efficacy outcomes

Key findings (n=280; 64 experienced hypoglycemia):

- **Mean age = 8.6 years (hypoglycaemia) vs. 9.7 years (no hypoglycaemia)**
- **Predictors of hypoglycaemia:**
  - Laron syndrome: OR 0.33 [95% CI. 0.16; 0.68], p=0.003
  - History of hypoglycaemia: OR 0.26 [95% CI. 0.10; 0.65], p=0.004
- **Mean first year mecasermin dose (≤100 µg/kg BID vs. >100 µg/kg BID) not associated with time to hypoglycaemia (P=0.554).**
- **Mean change in height SDS from baseline over the first 6 years of mecasermin similar between patients who did (0.95) or did not experience hypoglycaemia (0.96)**

Mecasermin may have hypoglycaemic effects and must be monitored closely in young children, those with Laron syndrome and children with a history of hypoglycaemia

CI, confidence interval; EU-IGFD, European Increlex growth forum database; OR, odds ratio; SDS, standard deviation scores; SPIGFD, severe primary insulin-like growth factor deficiency.

Woelfle J, et al. Abstract P1-212. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

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Summary

- ✓ New genetic techniques are identifying non-classical cases of SPIGFD
- ✓ The combination of clinical, biochemical and genetic assessment comprise these new diagnostic strategy features
- ✓ Heterogeneity of SPIGFD means that genetic investigations can contribute to diagnosis by confirming the primary pathogenesis
- ✓ Long-term follow-up is particularly important with paediatric SPIGFD patients with predictions of compromised adult height
- ✓ Close monitoring is also necessary for young children, particularly those with Laron syndrome and a history of hypoglycaemia who are taking mecasermin as they may have increased risk of hypoglycaemia
- ✓ There are differences in clinical practice and prescription of mecasermin between 10 EU countries, suggesting much work is still needed to increase awareness of SPIGFD and establish the most effective diagnostic and treatment pathways for its effective management

EU, European Union; GHI, growth hormone insensitivity; SPIGFD, severe primary insulin-like growth factor deficiency.

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Part 2.
European Congress of Endocrinology 2019 – Improving patient care for growth hormone deficiency

Focus on the latest biological, diagnostic, and treatment data

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Growth hormone deficiency (GHD)

GHD is caused by inadequate GH production from the anterior pituitary gland, resulting in a slowing down or cessation in growth.[1,2]

Three kinds of GHD[1]

- **Congenital –** when a child is born with the condition
- **Acquired –** e.g. due to trauma, central nervous system infection, radiation therapy or brain tumour
- **Idiopathic –** no identifiable cause

Diagnosis[2,3]

- **Clinical evaluation** – including growth criteria and medical history
- **Imaging studies** – bone age, MRI
- **Blood tests** – IGF-1 and IGFBP-3 levels
- **Provocative tests of GH secretion** – arginine infusion, clonidine, levodopa, glucagon
- **Evaluation of causes of short stature other than GHD** – other pituitary hormones and other causes of poor growth

Treatment[2,4]

- Recombinant human GH
- Regular follow-up

GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1 ; IGFBP-3, insulin-like growth factor binding protein 3; MRI, magnetic imaging resonance.

1. National Organization for Rare Diseases. Growth Hormone Deficiency. Available at: https://rarediseases.org/rare-diseases/growth-hormone-deficiency (Accessed September 2019); 2. Great Ormond Street Hospital for Children. Growth hormone deficiency. Available at: https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/growth-hormone-deficiency (Accessed September 2019); 3. MSD Manual. Growth Hormone Deficiency in Children. Available at: https://www.msdmanuals.com/en-gb/professional/pediatrics/endocrine-disorders-in-children/growth-hormone-deficiency-in-children (Accessed September 2019); 4. UpToDate. Treatment of growth hormone deficiency in children. Available at: https://www.uptodate.com/contents/treatment-of-growth-hormone-deficiency-in-children (Accessed September 2019).

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GHD: Assessing burden of disease in children and adolescents: The GHD – child impact measures (GHD-CIM)

Brod M, et al.

A multi-clinic (US and UK) psychometric validation study of an 11-item observer-report disease impact measure for children who are 4 to <13 years old (n=98 parents/guardians)

The questionnaire comprises three domains, as identified via factor analysis:

- 4-item Physical functioning (PF)
- 3-item Social well-being (SWB)
- 4-item Emotional well-being (EWB)

Psychometric	Result
Internal reliability	Acceptable for all domains and the overall score (Cronbach's alpha >0.70)
Test-retest reliability	Acceptable for EWB and overall questionnaire (>0.70), but lower for PF (0.59) and SWB (0.65)
Convergent validity	At least one hypotheses proven for each domain and overall questionnaire (r>0.30)
Known groups validity	EWB and SWB could significantly discriminate between levels of coping (p <0.05). Trends demonstrated: • Younger children = greater disease impact • Children reporting large increase in growth at 12-weeks = better PF
Responsiveness	Associated effect size = -0.40 to -0.58

Accurate assessment of disease impact within trials and clinical practice can help personalize the management and treatment of GHD, improve adherence, and enhance doctor-patient communication

EWB, emotional well-being; GH, growth hormone; GHD, growth hormone deficiency; GHD-CIM, growth hormone deficiency – child impact measure; PF, physical functioning; SWB, social well-being.

Brod M, et al. Abstract RFC14.6. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

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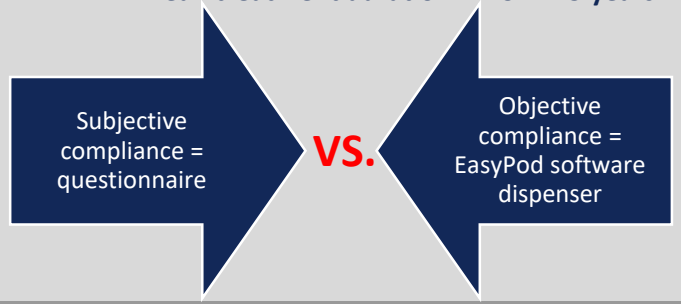
Assessment of subjective and objective compliance to GH therapy of children with GHD

Vlachopapadopoulou E, et al.

A comparison of subjective compliance to rhGH therapy with objective compliance

- GH deficient children and adolescents (n=94; 70 male)
- Mean age = 12.6 ± 1.9 years
- Administration by child alone (n=31), child and parent (n=33), or parent/caregiver (n=30)
- Mean treatment duration = 1.9 ± 1.5 years



- **Level of compliance high (a loss of <2 injections per month) in 87.5% of patients**
- **Moderate agreement between subjective and objective measures: ICC = 0.531 (95% CI 0.313-0.692) (F (64.64) = 3.588, *P* = 0.0005)**
- **Objective compliance positively correlated with child's age: rs (64) = 0.272, *P* = 0.030)**

The success of rhGH therapy is dependent on adherence, necessitating objective assessment to guide effective dose adjustments and increase efficacy

CI, confidence interval; F, test of variance; GH, growth hormone; GHD, growth hormone deficiency; ICC, intraclass correlation coefficient; rhGH, recombinant human growth hormone.

Vlachopapadopoulou E, et al. Abstract P1-96. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

Once-weekly TransCon hGH vs. daily hGH in pediatric GHD: The Phase 3 heiGHt trial

Vlachopapadopoulou E, et al.

A 52-week global Phase 3 trial investigating the safety, tolerability and efficacy of weekly TransCon hGH vs. daily hGH in 161 treatment-naïve prepubertal children with GHD

Endpoints at 52 weeks	TransCon hGH 0.24 mg/kg/wk (n=105)	Genotropin (34 µg/kg/daily)** (n=56)
AHV cm/yr (CI, cm/yr)	11.2* (10.71-11.62)	10.3 (9.73-10.89)
IGF-1 (SDS)	Normal range	Normal range
BA/CA ratio	Increased by 0.06 to 0.75	Increased by 0.05 to 0.76

***p*=0.0088; **Equivalent to TransCon dose

- **AHV consistently favoured TransCon hGH across subgroups:**
  - Age (<6 years; ≥6 years)
  - Sex
  - Baseline GH-stimulation (≤5 ng/mL; >5 ng/mL)
  - Aetiology and extent of GHD
- **Incidence of poor response (AHV <8 cm/yr) approx. 3x lower in TransCon group**
- **TEAEs similar for TransCon (77%) and Genotropin (70%)**

Once-weekly TransCon hGH demonstrated AHV superiority over once-daily genotropin, while maintaining a similar safety profile. Once-weekly treatment could be more convenient for patients.

AHV, annualized height velocity; BA/CA, bone age/chronological age; CI, confidence interval; GHD, growth hormone deficiency; hGH, human growth hormone; IGF-1, insulin-like growth factor 1; SDS, standard deviation score; TEAEs, treatment-emergent adverse events.

Vlachopapadopoulou E, et al. Abstract FC14.4. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

Once-weekly somapacitan vs. daily GH (norditropin®) in childhood GHD: One-year results from a randomized phase 2 trial

Sävendahl L, et al.

REAL 3: A 52-week multicentre, open-label, double-blind phase 2 RCT evaluating the efficacy and safety of once-weekly somapacitan vs. daily norditropin in treatment-naïve prepubertal children with GHD (n=59)

Groups)	Height velocity (cm/yr)	Derived mean IGF-1 (SDS)
Somapacitan 0.04 mg/kg/wk (n=16)	7.8 (1.8)	-1.62 (0.86)
Somapacitan 0.08 mg/kg/wk (n=15)	9.7 (1.8)	-1.08 (0.81)
Somapacitan 0.16 mg/kg/wk (n=14)	11.5 (2.6)*	0.41 (1.05)
Norditropin 0.034 mg/kg/day (n=14)	10.0 (2.2)	-0.40 (1.50)

***Statistically higher compared to norditropin**

AEs:

- Mild to moderate
- Rate in somapacitan 0.16 group same as norditropin group
- Five patients had one single low-titre measurement of non-neutralizing anti-somapacitan antibodies

The efficacy, safety and tolerability of once-weekly somapacitan was similar to daily GH, with the highest dose of 0.16 mg/kg/wk providing the closest efficacy match

AEs, adverse events; AHV, annualized height velocity; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor-1; SDS, standard deviation score.

Sävendahl L, et al. Abstract FC14.5. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

Summary

- ✓ For GH therapy to be effective, patients with GHD must adhere to often inconvenient GH injections
- ✓ Advances are being made in the treatment of GHD that may make adherence easier
- ✓ In particular, once-weekly GH could offer a more convenient alternative to once-daily GH, while also offering superior efficacy outcomes with similar adverse events
- ✓ In addition to more patient-centred treatment for enhancing adherence, it is important to assess compliance both subjectively and objectively to guide effective dose adjustment and increase treatment efficacy
- ✓ Questionnaires are available to assess adherence while at the same time improving doctor-patient communication and aiding personalized treatment

GH, growth hormone; GHD, growth hormone deficiency.

Part 3.
European Society for Paediatric Endocrinology 2019 – Improving patient care for all paediatric growth disorders

Focus on the latest biological, diagnostic, and treatment data

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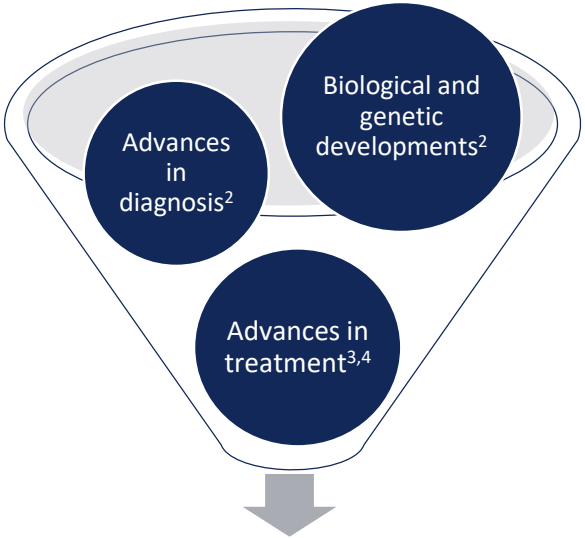
Paediatric growth disorders

Growth disorders in children are heterogeneous, with key risk factors being family history, systemic disease and genetic disorders[1]



1. University of Rochester Medical Center. Growth Problems in Children. Available at: https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=90&contentid=P01956 (Accessed September 2019); 2. Joseph K. How has genetic testing changed the diagnosis of short stature in children? *Endocrinology Advisor*. 2019; 3. Wit JM, et al. *Horm Res in Paed*. 2013;**79**:257–270; 4. Mullis P-E. *Curr Indic Growth Horm Ther* 2010;**18**:67–82; 5. Grimberg A, et al. *Horm Res Paediatr* 2016;**86**:361–397.

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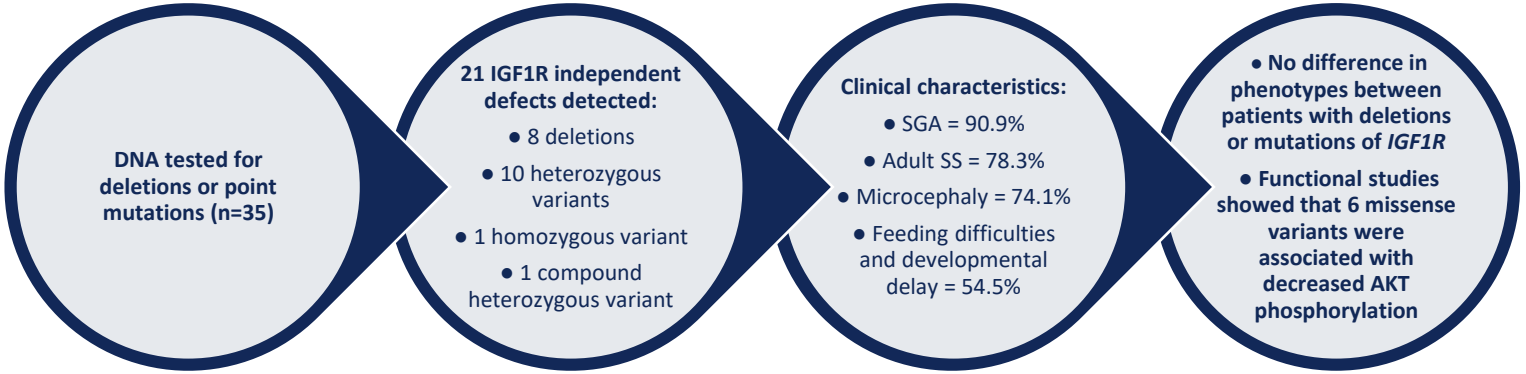
Increasing knowledge in IGF1R defects: Lessons from 20 new patients

Giabicani E, et al.

To validate a clinical score for diagnosing IGF1R defects and establish a functional test for the classification of unknown significance variants *in vitro*



New pathogenic variants of IGF1R have been identified, adding to heterogeneity. A recently proposed clinical score can accurately diagnose *IGF1R* defects and a functional test has been developed to assess pathogenicity of variants.

AKT, protein kinase B; DNA, deoxyribonucleic acid; IGF1R, insulin-like growth factor-1 receptor; SGA, small for gestational age; SS, short stature.

Giabicani E, et al. Abstract FC12.1. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

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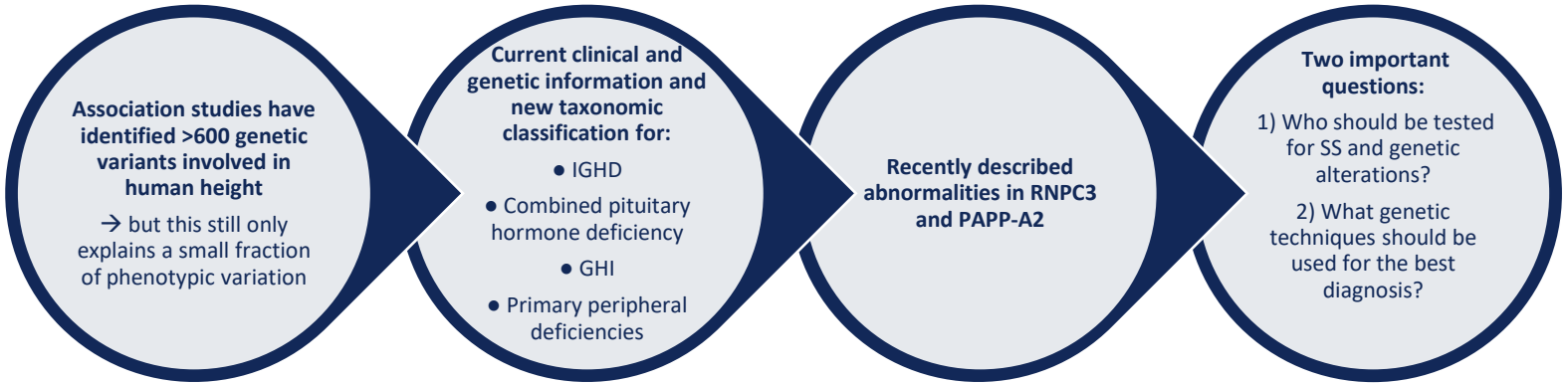
Novel insights into genetic disorders of growth

Argente J.

A review of current clinical and genetic information and a proposed new classification of growth disorders based on clinical, endocrinological and genetic characteristics



Paediatric endocrinologists must be aware of the multifactorial and polygenic contributors to height for early diagnosis and clinical management

GH, growth hormone; GHI, growth hormone insensitivity; IGHD, isolated growth hormone deficiency; PAPP-A2, pregnancy-associated plasma protein-A2; RNPC3, RNA-binding region-containing protein 3; SS, short stature.

Argente J. Abstract S5.1. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

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Bioactive IGF-1 concentration compared to total IGF-1 concentration before and after 1 year of high-dose GH in short children born SGA – North European SGA study (NESGAS)

Jensen R, et al.

A multicentre study exploring: 1) variations in total IGF-1 and bioactive IGF after 1-year of high-dose GH, and 2) associations with growth and glucose metabolism

Baseline

- 110 prepubertal short SGA children
  → 69 males

1-year GH therapy (67µg/kg/day)

- 68% of cohort had increased total IGF-1 >2SD
  → only 15% had bioactive IGF > 2SD
- Bioactive IGF significantly correlated with baseline height (SDS): r=0.29, p=0.01
  → association was stronger than between baseline IGF-1 and height: r=0.17, p=0.10
- Bioactive IGF (SDS) correlated positively with total IGF-I (SDS): r=0.35, p=0.001
  → and IGFBP-3: r=0.62, p=0.001
- Bioactive IGF (SDS) correlated negatively with insulin sensitivity (HOMA-S): r=-0.29, p=0.01
  → and IGFBP-1: r=-0.18, p=0.08

Bioactive IGF showed a strong association to height at baseline, but was not a good predictor of response to 1-year high-dose GH treatment. Fortunately, supra-physiological levels of bioactive IGF were lower post-treatment compared to elevated total IGF-1

GH, growth hormone; HOMA-S, homeostasis model assessment; IGF-1, insulin-like growth factor-1; IGFBP-1/3, insulin-like growth factor binding protein 1/3; NESGAS, North European SGA study; SDS, standard deviation scores; SGA, small for gestational age.

Jensen R, et al. Abstract RFC14.5. *Horm Res Paediatr* 2019;**91**(suppl 1):1–682.

Summary

- ✓ New genetic defects and variants are coming to light, encouraging a new classification of different growth disorders
- ✓ A deeper understanding of the biological processes underlying disorders of growth can be applied in clinical practice to establish which patients need to be tested and which tests might be best for diagnosis
- ✓ This deeper biological understanding is also contributing to the development of clinical scores to aid early diagnosis and treatment
- ✓ Precise diagnosis, based on clinical, biochemical and genetic assessment will help the establishment of personalized pathways for effective management