EndoCompass- Chapter Growth

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Introduction

Growth during infancy, childhood and adolescence is the result of a complex interplay of many factors. The control is mainly related to internal factors, such as genes, hormones (growth hormone (GH), insulin-like growth factors (IGFs)), and external factors, such as nutrition and environment. (Brook's Textbook Clinical Pediatric Endocrinology, Wiley-Blackwell, 7th edition, 2019, ISBN 978-1119152712).

Growth hormone, secreted by the pituitary gland, and IGF1, mainly produced by the liver, have a leading role in the longitudinal growth while other hormones, like sex hormones, contribute. GH and IGF1 promote endochondral ossification, which occurs in the growth plates. Growth plates are thin layers of cartilage located at the ends of long bones and vertebrae. Within the growth plates, chondrocytes are neatly organised into zones where they undergo rapid division, enlargement, and secretion of the cartilage's extracellular matrix. The extracellular matrix at the outer zone of the growth plate eventually calcifies, and then transforms into bone. This sequence of events produces fresh cartilage, which is later transformed into bone tissue. Consequently, the continuous formation of new cartilage and bone at the growth plates causes lengthening of bones, making children grow taller (PMID: 26437621, 12748651).

Some children have growth retardation, leading to short stature. Short stature is defined as a height ≤ -2 standard deviation score (SDS), equivalent to the 2.3rd centile, and thus has an incidence of 1:43. Severe short stature of ≤ -3SDS has an incidence of 1:1000 (0.1st centile). In 2019, UNICEF estimated there were 144 million children with short stature below the age of 5 years worldwide (https://www.who.int/publications/i/item/9789240003576).

Studies suggest that GH deficiency, small for gestational age (SGA) birth, Silver-Russell syndrome and other methylation disorders, Prader-Willi syndrome, Noonan syndrome and skeletal dysplasias have associated metabolic, cardio-vascular and mental health risks, and lower health-related quality of life, therefore having a large societal impact (eg annual costs for PWS can be as high as €65,000 per patient) (PMID: 31242363, 36635911, 38330234, 20173020, 33382187, 23609338, 33975197, 36823445, 35304302, 27038627), but much more research is warranted. More research is also required for the understanding of the underlying pathophysiology of many short stature conditions.

Tall stature syndromes consist of a group of overgrowth-intellectual disability (OGID) syndromes and a group of conditions characterised by tall stature syndromes without an intellectual disability. The OGID syndromes are a heterogenous group of conditions characterised by increased height and/or head circumference, in association with an intellectual disability (PMID: 23606607). Tall stature syndromes without learning difficulties consist of a variety of conditions, of which Marfan syndrome is the most common (PMID: 3447541). However, most syndromes are rare and the natural history and consequences on health and wellbeing are not well known. The molecular mechanisms of tall stature have not been fully elucidated and many patients with tall stature syndromes do not have an underlying cause identified.

This chapter describes the epidemiology, associated pathology, social impact, societal impact, and current knowledge in 5 fields of growth disorders to then outline the future research priorities for these fields.

Subtopic 1. Short stature and growth hormone, IGF-I and growth plate disorders

1. Epidemiology, societal impact, research state of art

As discussed above, short stature is defined as a height ≤ -2 standard deviation score (SDS), equivalent to the 2.3rd centile, and thus has an incidence of 1:43 whereas severe short stature (SDS ≤-3SD) has an incidence of 1:1000 (0.1st centile). Ten percent of those born SGA (height or weight ≤2SDS for gestational age) do not show catch-up growth (PMID 7478827) and SGA with persistent short stature at age 4 occurs in 1:500 (PMID: 36635911).

Eighty to ninety percent of the variation of adult height within a specific population is attributable to genetic factors. An individual's height is substantially determined by the additive effects of both common and rare genetic variants. Recent genome-wide association studies have identified over 7,000 different loci associated with stature covering ~21% of the genome (PMID: 36224396). In individuals with severe short stature, rare monogenic aetiologies can now be found, and many of the genes involved relate to growth plate function.

For the past 4 decades, the primary treatment for short stature has been recombinant human growth hormone regardless of the underlying aetiology. Additional efforts to increase height have included modulating the duration of the growth period either through pubertal suppression using GnRH agonists or delaying epiphyseal closure using aromatase inhibitors. Rare patients with growth hormone resistance are eligible for treatment with recombinant IGF-1. As understanding increases regarding the diverse molecular aetiologies of short stature, there is increased need for molecular stratification and novel precision therapeutics targeting these disorders. Currently, novel precision medicine approaches are being developed for specific skeletal dysplasia's such as C-type natriuretic peptide agonists for achondroplasia (PMID: 37704353). Further understanding of genetic pathways involved in growth plate function, and improved diagnostics of short stature are required to improve care and develop more novel precision medicine approaches.

The long-term safety of GH treatment has been thoroughly studied in the last decade, but studies on long-term safety and efficacy of other treatments are lacking (PMID: 32707116).

2. Future Research Priorities

The key future research areas in short stature/GH-IGF1/growth plate are in genetics, growth plate and personalized medicine and include strategies to 1. Further identify aetiology of short stature and predict height outcomes, 2. Assess current and develop new drugs to stimulate growth, 3. Study response to growth promoting therapies, 4. Assess effects of short stature/IUGR and treatment on health in adulthood.

2.1 Aetiology and prediction of height outcomes

- Improved methods, pathways and gene panels to diagnose congenital growth failure/short stature of monogenic and polygenic as well as epigenetic causes.
- Characterisation of interaction between multiple genetic variants, including abnormalities of GH and IGF1 secretory and signalling pathways.
- Creation of large data sets of populations with short stature to assess genetic aetiology, to create a genomic predictor of height / a polygenic risk score, including the effects of rare variants.
- Refine polygenic risk scores to accurately predict adult height in patients from all racial and ethnic backgrounds.
- Develop real world evidence of the utility of genomic prediction models in clinical practice and develop digital tools that allow for integration of prediction models into clinical care.
- Develop personalized *in vitro* and *in vivo* models to understand the underlying pathophysiology of individual growth disorders. This could include development of easier access to individual patient's chondrocytes or other cell-based models such as organoids using patient derived tissues.
- Increase insight in the cause and mechanism of absent catch-up growth after being born SGA.

2.2 Current drugs and drug development

- Development of new drugs for the treatment of short stature, including drugs targeting the growth plate directly.
- Assessment of efficacy and safety of drugs developed for skeletal dysplasia including achondroplasia, for the stimulation of growth in other forms of short stature.
- Exploration of the use of *in vitro* models e.g. growth plate organoids (growth plate in a dish) or induced pluripotent stem cell (iPSC) derived chondrocytes and introduction of specific mutations therein as a model to develop and test new drugs.
- Development of appropriately controlled clinical trials for definitive assessment of long-term safety and efficacy of aromatase inhibitors, and of delaying puberty, to increase adult height.
- Assessment of long-term safety and efficacy of long-acting GH drugs.

2.3 Response to Growth Promoting Therapies

- Explore the role of genetic variation including genetic heterogeneity and rare genetic variants in patients' responses to growth promoting therapies and understand how to use this data to guide therapy for patients.
- Develop new and more accurate biomarkers of longitudinal growth, which can be used to assess and predict response to growth promoting therapy.
- Use of personalized *in vitro* models for the prediction of response to growth promoting treatment.
- Develop and implement AI and machine learning based approaches to predict response to growth promoting agents and direct choice of treatment.

2.4 Long-term health throughout the life span

- Characterise health problems in adult life in patients with syndromic and non-syndromic short stature, and IUGR, including quality of life assessments.

- Facilitate international collaboration to aggregate registry data for such current and long-term health outcomes and future growth promoting therapies.
- Assessment of long-term effect and safety of paediatric IGF1 treatment in adulthood.
- Assessment of quality of life and psychological wellbeing in treated and untreated people with short stature during the life span, including research into prediction of who will gain most in quality of life with growth promoting treatment. This will help to find a balance between gain in quality of life, cost of treatment and health care budget.

3. Anticipated impact of the research

Improved diagnosis of growth disorders will have long reaching benefits for the individual suffering from a growth disorder as well as for the society as a whole as it would allow for personalized medical monitoring and treatment of a larger fraction of the patients and also contribute to the development of novel, safe and efficacious treatments.
Advances in our knowledge of the growth plate and ability to model growth *in vitro* will also allow for development and trials of drugs, which will ultimately improve outcomes, thereby improving quality of life. Advances in our ability to predict response to growth promoting therapies, whether via genetic profiles, individualized disease model, or use of artificial intelligence, will allow practitioners to truly practice personalised precision medicine. Prediction of who will gain most in quality of life from growth promoting therapy, will help to determine who should receive treatment in our changing society with more acceptance of inter-individual differences and scarce health care resources.
Gaining more knowledge on the prevalence and type of health problems in adults with short stature, will lead to health risk awareness in professionals and patients, which will help in preventing long-term negative health outcomes.

Subtopic 2. Silver-Russell Syndrome and other Imprinting Disorders associated with short stature

1. Epidemiology, societal impact, research state of art

Imprinting disorders (ImpDis) such as Silver–Russell syndrome (SRS, OMIM #180860) and Temple syndrome (TS14, OMIM #616222) are increasingly recognized as an important cause of short stature but are frequently overlooked and misdiagnosed, as the clinical and molecular diagnosis is challenging. However, making a diagnosis is key for bespoke management, treatment, peer-support and tailored health surveillance. These conditions are multisystem disorders requiring multidisciplinary care and demand significant health resources, particularly in childhood. The prevalence of ImpDis is more frequent than previously appreciated (PMID: 31186545). Evidence is accumulating that these conditions are associated with adverse cardiometabolic health.

SRS is associated with severe prenatal and postnatal growth retardation, characteristic features (relative macrocephaly, prominent forehead, body asymmetry) and severe feeding difficulties (PMID: 27585961). The diagnosis is suspected in presence of four or more of these six items. The reported incidence of SRS ranges from 1:30,000-100,000, but it is probably more common.

An underlying molecular cause is currently identified in around 60% of patients fulfilling the criteria of SRS: 30-60% with a molecular alteration in 11p15 (11p15 loss of methylation (LOM) and 5–10% in maternal uniparental disomy of chromosome 7 (UPD(7)mat). Rare mutations affecting *CDKN1C*, *HMGA2*, *PLAG1* and *IGF2* are also reported together with imprinting defects responsible for Temple Syndrome (PMID: 29250858).
However, 40% of individuals with a clinical diagnosis of SRS do not have a molecular diagnosis and are labelled "clinical SRS". A greater understanding of the genetic causes of clinical SRS is needed to optimize health care.

Children with SRS have phenotypic features in common with other ImpDis, e.g. lack of appetite during infancy, growth failure, pubertal abnormalities, high serum IGF-I levels, while other features are distinct. The underlying causes explaining these similarities and differences are important for clinical care but are yet unknown. One hypothesis is that imprinted genes are co-regulated or that some genes have an impact on the expression of others, within a network of imprinted genes (IGN) (PMID: 26842569; PMID: 30801013). However, the regulation mechanisms and interactions of most of the imprinted loci are far from being understood. C Both clinical features of SRS and effects of growth hormone (GH) therapy during childhood have been reported (PMID: 27585961), but the consequences and optimal management of SRS and many of the rarer ImpDis across the life span are unknown.

2. Future Research Priorities

The key future research in SRS and ImpDis targets on the identification of the full spectrum of molecular alterations, their causes and functional consequences. By combining this knowledge with deep phenotyping, the clinical relevance of imprinting disturbances will be evaluated, and personalised clinical regimens can be developed. Another key research area regards the clinical consequences of SRS/ImpDis across the life span.

Specific aims to achieve these goals include:

2.1 Building the base for research

- Creation of a pan-EU database of ImpDis that includes phenotypical and molecular data
- Establishment of a biobank with samples from individuals with different imprinting disturbances
- Generation of suitable *in vitro* and *in vivo* models for ImpDis
- Comprehensive studies to determine the prevalence of ImpDis

2.2 Implementation and use of high throughput omics technologies (genomics, epigenomics, transcriptomics, proteomics, liquid biopsy) and artificial intelligence:

- Identify genome-wide episignatures, in different tissues
- Identify new imprinting disorders
- Study(epi)genotype-phenotype correlations to explain the clinical features and predict prognosis
- Improve the genetic testing algorithms and include prognostic markers
- Develop single cell transcriptome analysis for imprinting disorders

- Characterise effects of imprinting defects in germ cells
- Development of artificial intelligence and machine learning to improve epidemiological insight, diagnosis and prediction of future complications of imprinting disorders, eg epigenetic methylation signatures, facial recognition

2.3 Identification of the causes of aberrant imprinting

- Decipher the molecular causes of imprinting defects, eg enable genetic and reproductive counselling
- Understand the regulation within imprinted regions, and the role of epigenetic regulation in human development

2.4 Delineation of the functional impact of disturbed genomic imprinting on cellular processes and the clinical outcome

- Study the functional interactions between imprinted genes and their products
- Develop novel treatments for imprinting disorders using experimental *in vitro*/*ex vivo*/*in vivo* models

2.5 Answering key clinical questions:

Phenotype of SRS and related ImpDis associated with short stature:

- Can deep phenotyping find genetic causes for specific features such as feeding difficulties, changing appetite, poor pubertal growth spurt with rapid bone age progression, abnormal body composition, insulin resistance, gonadal dysfunction)
- What is the contribution of genomic imprinting to growth retardation, appetite, metabolism, puberty, reproductive function and cognitive development?
- Does imprinting affect the hypothalamic regulation of appetite/satiety?
- Why does early adrenarche and rapid evolving puberty occur?
- Why is serum IGF-1 often high?
- What causes testicular dysfunction in males with 11p15 LOM?
- What are the phenotypic consequences of multi-locus imprinting disturbances?
- Why do children with UPD(7)mat have more psychiatric problems than those with 11p15 LOM?
- What are the key clinical and developmental features and/or biomarkers pointing to a growth-related imprinting disorder?

Effect of age:

- Why does appetite change with increasing age/ across the life course?
- Why are some clinical features age-specific?

Pregnancy and fertility:

- Why is the rate of children born after ART higher in ImpDis and Silver-Russell Syndrome (SRS) than in the general population?
- Does LOM affect gametes?
- Why do fetuses with SRS and related ImpDis associated with short stature have small placentas?
- What is the role of IGF2 in the growth restriction in ImpDis related to short stature?

Treatment:

- What is the impact of growth hormone (GH) therapy on body composition, glucose/insulin regulation and lipid metabolism, cognition and Health Related QoL during and after treatment?
- Why do many children with SRS and associated ImpDis have high serum IGF-I levels before start of GH therapy and very high levels during therapy?'
- Which treatment can preserve growth potential when there is early adrenarche and rapidly progressing puberty?
- What is the optimal treatment for other ImpDis than SRS e.g. GH in Temple-syndrome?
- Development of personalised therapeutic regimens

2.6 Long-term consequences throughout the lifespan

What are the long-term consequences of SRS and related ImpDis on:

- Cognition, vitality, HRQol, education, work, socio-economic status, relationships, offspring
- Cardiovascular health, glucose/insulin regulation and lipid metabolism
- Body composition (fat mass, lean body mass, visceral fat)
- Bone density and joints
- Reproductive function
- Treatment, including positive and negative effects

3. Anticipated impact of future research

Establishing databases, animal models and a biobank, as well as application of high-throughput omic-based methods will not only improve the diagnostic algorithm and yield but also our understanding of disturbed genomic imprinting and epigenetic regulation in general. Altogether, these strategies will lead to the identification of diagnostic prognostic biomarkers, improvement of current treatment, development of novel and personalised therapies and improvement and development of guidelines. Inclusion of AI-based diagnostic workflows and predictive methods will facilitate cost-effective decisions regarding the most appropriate treatment. The evaluation of these improvements on the care, health and quality of life for patients and their families will help to introduce procedures preventing deterioration of mental health, thus preventing high societal costs. A greater appreciation of the natural history of these conditions will help the design of life-long health surveillance strategies. Additionally, studying SRS might also give insights into metabolic consequences related to SGA in general, of relevance for a much larger population than SRS only. Such new insights have the potential to influence wider healthcare decisions for this population born SGA and reduce health care costs.

Subtopic 3. Prader-Willi Syndrome

1. Epidemiology, societal impact, research state of art

Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder (NDD) due to loss of expression of paternally expressed genes in the chromosome 15q11-q13 region (OMIM

176270), either due to paternal deletion of the chromosomal region (55-60%), maternal disomy (40-45%), imprinting mutations or epimutations (2-5%) (PMID: 34389046), or chromosomal rearrangements including PWS chromosomal region. Diagnosis is in the first few months of life. Incidence is approx. 1:15,000-25.000 (PMID: 28659150).

PWS is characterized by a specific trajectory including neurodevelopment, nutritional, endocrine/metabolic and behavior dimensions due to impaired hypothalamic development. At birth, neonates display severe muscular hypotonia with feeding difficulties. This is then followed by reduced calory requirement, excessive weight gain and early severe obesity with hyperphagia and poor satiety (PMID: 21465655). Hypothalamic impairment may lead to hormone deficiencies (PMID: 33647242, 27288456), such as growth hormone (GH) deficiency, hypogonadism, hypothyroidism, and impaired insulin secretion. PWS is the only genetic obesity with elevated ghrelin levels at all ages (PMID: 18460565, 25989955, 37839403) and poor muscle mass, high fat mass with low visceral fat. Short stature is common. Dysautonomic features are also frequently observed together with multiple comorbidities (orthopedic, ocular problems).

People with PWS display mild or moderate learning disabilities, speech and communication disorders, social disabilities, difficulties with emotional control leading to temper tantrums, compulsive and ritualistic behaviors, skin picking, and some features of autism spectrum disorder (PMID: 35268524, 28592997, 28100688).

PWS is a complex and severe condition with high morbidity and mortality that has large impact on the person, the family, the carers and society (PMID: 27854358, 31684997). Recombinant human GH was licensed in 2002 and improves body composition and growth but treatment for other PWS features does not exist. Treatment should target obesity, hyperphagia, impaired satiety, anxiety and behavior. This requires further efforts to disentangle the mechanisms and pathophysiology of the condition, as well as understand specific needs of persons living with PWS at all ages.

2. Future Research Priorities

2.1 Genetics and genomics

- Identification of the full genetic variation in the PWS locus to establish role of genes and non-protein coding RNAs and their individual and combined contribution to the PWS phenotypes
- Expansion of genetic profiling beyond PWS locus to uncover complex gene-network effects: genome-wide methods such as Genome-Wide association Studies (GWAS) and Whole-Genome Sequencing (WGS) could help define phenotypic variability and its dependence on genetic factors outside chromosome 15.
- Using larger cohorts to probe extensively the genotype-phenotype relationships of PWS genetic subtypes.
- Define the epigenetic landscape of PWS locus at different stages of the disease and across tissues, particularly in brain and placenta. Expansion of the epigenetic profiling of PWS beyond methylation to also include histone modification and chromatin topology.

- Understand the interplay between environment and PWS epigenetic marks and how it might contribute to the development of features of PWS.
- Prenatal and newborn screening: evaluating the feasibility and efficacy of incorporating PWS screening into existing prenatal screening protocols across different countries, e.g. non-invasive prenatal testing (NIPT), as well as developing novel minimally invasive and cost-effective newborn screening assays for PWS.

2.2 Animal models, IPS cells and pathophysiological research

- Maximize the utility of iPSC and CRISPR/Cas9 engineered cellular models of PWS to decipher precise effects of genomic variance in PWS. It will be informative to expand the type of neuronal and non-neuronal differentiation models and employ organ-on-chip and 3D organoid technologies.
- Animal models: none of the mice models recapitulate all the symptoms observed in PWS patients. There is an important need to keep developing animal models (e.g., by deleting multiple PWS genes or by studying other species that are closer to humans) that would display symptoms that are of primary importance for PWS, particularly the hyperphagia.
- Modification of natural trajectory: To determine whether the postnatal and peripubertal periods can be used as critical windows for interventions with lasting behavioral effects
- research to understand what drives the abnormal development of hypothalamic and extra-hypothalamic circuits involved in appetite regulation in PWS.

2.3 Biomarkers

- Use of additional -omics technologies, such as metabolomics and lipidomics to identify known and potentially further PWS subtypes, and biomarkers for their detection.
- Identify biomarkers and use AI to predict lasting effects of early treatment /intervention
- Use functional brain MRI to find targets to treat hyperphagia.
- Expand biobanking of post-mortem tissues, including placenta and fetal brains

2.4 Clinical issues and endocrine abnormalities

- Unravel the mechanism of excessive fat mass with decreased lean mass, and assess the role of oxytocin, GH, IGF-1 and insulin
- Understand the mechanism of dysautonomia and the role of oxytocin
- Unravel the mechanism of the increased GH sensitivity and the role of IGFBP-7 and IGFBP-3.
- Find the optimal treatment in poorly controlled type 2 diabetes.
- Unravel the mechanism of rapidly evolving early pubarche and develop adequate treatment.
- Understand the mechanism of combined (central and gonadal) hypogonadism both in men and women and identify a marker for fertility in women.

- Identify the optimal treatment regimen to induce and progress puberty and maintain optimal testosterone concentrations during adulthood.

2.5 Transition of adolescents to young adults

- Research to optimize transition care from Pediatric to Endocrinology and Nutrition Departments.
- Assessment of long-term effects GH treatment on body composition, and of safety and economic value of GH treatment in adolescents and adults
- Better characterize the needs for adolescents and adults with PWS to optimize socialization, self-determination and daily living.
- Investigate how to optimize the quality of life of people with PWS e.g. by improving their environment

2.6 Behaviour and psychiatric issues

- Determine genetic risk factors for psychosis.
- Understand the pathophysiology of compulsivity/impulsivity including skin picking, thinking rigidity and social disabilities.
- Understand the biological substrates underlying the switch in feeding behavior and the specifics of PWS hyperphagia.

2.8 Clinical trials

- Use pharmacogenomics to understand lack of reduction of hyperphagia in previous trials in PWS vs other conditions with hyperphagia
- Develop early treatment with disease modifier effects (e.gt., drug/interventions with epigenetic effects).
- Develop and support trials with innovative treatments for children and adults with PWS.

2.9 Ageing

- Investigate brain anatomy and function in longitudinal studies from adolescence to late adulthood.
- Understand the mechanisms of accelerated biological ageing (role of telomere length, GH treatment, genotype) and develop potential methods for intervention.
- Develop and test tools to evaluate cognitive impairment in adults with PWS

3. Anticipated impact of the research

Developing animal models that replicate the natural history of the syndrome, establishing extensive clinical databases with lifetime information, and creating biobanks to identify new biomarkers, along with using high through-put omic techniques, will not only improve early diagnostic algorithms and outcomes but also enhance our understanding of the syndrome's natural progression (trajectory) and particularly the links between endocrine, metabolic and behavioural difficulties, and lead to new approaches and therapies including critical periods and disease modifying drugs. Incorporating AI-based diagnostic workflows and predictive methods will enable cost-effective treatment decisions. Evaluating the impact of these advancements on patient care, health, and quality of life for patients and their families will

help implement effective procedures to prevent cognitive decline and reduce significant societal and public costs. A deeper understanding of these conditions' natural course will guide lifelong health monitoring strategies.

Subtopic 4. Noonan syndrome

1. Epidemiology, societal impact, research state of art

Noonan syndrome (NS; MIM # 163950) is a relatively common developmental disorder with an estimated incidence of 1/2000 to 1/2500 live births (PMID: 23312968, 246453). The phenotype varies in severity and can affect multiple organ systems. Major features include a distinctive facial gestalt, cardiac defects (*i.e.* pulmonary valve stenosis and hypertrophic cardiomyopathy), short stature, skeletal abnormalities (*i.e.* pectus deformities, scoliosis), variable cognitive deficits, and predisposition to certain cancers. In addition to the classic clinical features of NS, new important endocrine aspects have been reported in recent years, including metabolic abnormalities (glucose intolerance/insulin resistance, low HDL) and reduced bone mass (PMID: 33910978, 33382187, 37588986, 3796495, 34492361). Gonadal dysfunction with deficient spermatogenesis has been reported in NS men (PMID: 30325180, 21551165), while fertility in women appears less affected. Very little data are available about quality of life of both children and adults (PMID: 22494877). Recombinant human GH was approved by the US Food and Drug Administration in 2007 and the European Medicines Agency (EMA) in 2020 as treatment for short children with NS. Although studies have shown an increase in height without serious side effects on the medium term (PMID: 37084633), there are still unanswered questions.

NS belongs to a group of phenotypically overlapping genetic disorders, including NS with multiple lentigines (NSML), Mazzanti syndrome (also known as NS-like syndrome with loose anagen hair), cardio-facio-cutaneous (CFC) syndrome, Costello syndrome, neurofibromatosis type 1 (NF1), Legius syndrome and other emerging disorders (PMID: 21396583). All of these syndromes are caused by germline pathogenic variants in genes encoding components of the RAS/mitogen-activated protein kinase (MAPK) signalling pathway (PMID: 29924299 , 36428239). This family of disorders is known as RASopathies and is one of the largest groups of multiple congenital anomaly disorders.
A better understanding of the molecular mechanisms underlying the different manifestations of NS and RASopathies has led to the identification of molecular targets for specific pharmacological interventions (PMID: 37863846). Many specific agents (*e.g.* SHP2 and MEK inhibitors) have already been developed for the treatment of RAS/MAPK-driven malignancies. In addition, other molecules with the property of modulating RAS/MAPK activation are indicated in non-malignant diseases (*e.g.* C-type natriuretic peptide analogues in

achondroplasia or statins in hypercholesterolemia), and may offer opportunities to develop target treatment for RASopathies.

2. Future research priorities on the endocrine aspects

2.1. Molecular bases and genotype – phenotype correlations

- Identification of new genes. Identification of the missing genes responsible for NS and other RASopathies or alternative diagnoses for individuals presenting with RASopathy-like phenotypes.
- Search for genotype-phenotype correlations. Expand knowledge of clinically relevant genotype-phenotype correlations at both the gene and variant levels.
- Develop NS-specific growth charts according to the genotype. Assess whether the origin of short stature may vary among different genotypes (*e.g.* GH secretion pattern, partial GH insensitivity, as well as defective chondrocyte differentiation) (PMID: 36060964, 22371576).
- Develop in vitro and in vivo model systems to understand pathogenetic mechanisms, and develop functional assays to characterise the impact of genetic variants

2.2. Natural history and long-term health consequences throughout the lifespan

Although the course of the disease is well known in childhood, there is still very limited information available on the natural history of NS in adulthood. An important challenge is to better describe the outcome in adulthood, particularly in terms of fertility, bone health and possible metabolic dysfunction.

- Quality of life. Little is known on health-related quality of life of people with Noonan syndrome (PMID: 22494877), and further research is needed.
- Fertility. Gonadal dysfunction with deficient spermatogenesis has been reported in NS men (PMID: 30325180, 21551165). Prospective studies are needed to investigate the prevalence and mechanisms of infertility in both men and women.
- Bone health. Decreased bone mass has been reported in NS and in other RASopathies (PMID: 3796495, 34492361). Investigation of bone mass accrual and assessment of bone fragility in adults and the elderly are needed.
- Metabolic dysfunction. Prospective long-term follow-up studies to further investigate a possible risk of type 2 diabetes or other metabolic disturbances.

2.3. Current and future therapeutic perspectives

- Growth hormone treatment. To address the following unresolved issues:
    - Differential response to therapy by genotype.
    - Potential beneficial effects of GH treatment on muscle hypotonia and motor development.
    - Safety of GH treatment in patients with pre-existing hypertrophic cardiomyopathy.

- Safety of GH treatment on tumour risk.
- Final adult height and the actual gain in height, using controlled trials that take into consideration the late growth due to late puberty.

- Future therapeutic perspectives.
  - Study drug repurposing of compounds modulating RAS/MAPK activation as a new approach to treat or prevent medical complications associated with RASopathies.
  - Identify other potential targets for selective therapies, e.g. correction of functional defects at the subcellular, cellular or tissue levels (*i.e.* dysfunction of the myelomonocytic lineage or mitochondrial bioenergetics).

3. Anticipated impact of future research

The development of national and international registries would be valuable to collect data on the natural history of these patients, including the medical complications that may arise during their lifetime, and to assess the efficacy and safety of specific medical interventions. A better understanding of the disease will help to establish evidence-based recommendations for the management of patients with NS and may lead to the identification of drug targets and development of therapy.

Subtopic 5. Tall stature

1. Epidemiology, societal impact, research state of art

Tall stature syndromes encompass the family of OGID syndromes, characterised by increased height and / or head circumference, in association with an intellectual disability (PMID: 23606607) and tall stature without an intellectual disability.

The OGID syndromes, are rare and prevalence is not accurately known. Several monogenic causes of the OGID syndromes have been identified, including *NSD1* (Sotos syndrome, OMIM 117550), *NFIX* (Malan syndrome, OMIM 614753), *EZH2* (Weaver syndrome, OMIM 277590), *DNMT3A* (Tatton-Brown-Rahman syndrome, OMIM 615879), *PTEN* (PTEN hamartoma tumour syndrome, OMIM 601728), *CHD8* (OMIM 615032), *GPC3* (Simpson Golabi Behmel, OMIM 312870) and *MTOR* (Smith-Kingsmore syndrome, OMIM 616638). Whilst each condition is characterised by a unique phenotype and often recognisable facial gestalt, differentiation can be challenging and requires genetic investigation (PMID: 28475857, 31793186). There is societal impact of these conditions as they are complex multi organ syndromes that affect physical health and require lifelong multi-disciplinary medical input for assessment and treatment of complications. People with OGID syndromes often are not able to work and require lifelong support from others.

Tall stature syndromes without learning difficulties encompass a variety of conditions. Marfan syndrome (MFS, OMIM 154700), caused by a pathogenic variant in the *FBN1* gene, is the most common (approx. 1:5000) (PMID: 3447541). Phenotypically related conditions are those due to variants of genes encoding components of the TGFβ signalling pathway, notably *TGFβR1* and *TGFβR2* genes, such as Loeys-Dietz syndromes (LDS, OMIM 609192 and 610168) (PMID: 34807423), and other tall stature syndromes without learning disability exist. Familial tall stature may have monogenic or polygenic genetic causes and is often not further investigated.

MFS affects multiple organs and tissues including cardiovascular (*i.e.* mitral valve prolapse, aortic root aneurysm and dissection), ocular (*i.e.* severe myopia and ectopia lentis), and skeletal (*i.e.* disproportionately tall stature, arachnodactyly, pectus deformity, and scoliosis) systems (PMID: 3447541). With the advances in the diagnosis and management of life-threatening cardiovascular events over the past 50 years, individuals with MFS currently have a life expectancy that approaches that of the general population (PMID: 30573797). However, patients with MFS continue to face many morbidities, including the sequelae of multiple surgeries as well as musculoskeletal impairments. Health-related quality of life in MSF is highly correlated with musculoskeletal defects, aerobic capacity, and physical deconditioning (PMID: 38685042) but little is known about psychosocial functioning. Due to their rarity, natural history and consequences of most other syndromic and non-syndromic tall stature conditions on health and wellbeing in today's society are not known well.

Tall stature syndromes are often diagnosed late after a long diagnostic odyssey. Earlier diagnosis will allow for earlier appropriate management (PMID: 31793186), for example screening for aorta pathology in Marfan syndrome.

There are limited pharmacological options to inhibit growth and no drugs are licensed. As knowledge of signalling pathways for growth is expanding, and pharmacological targets have been identified, drugs with high efficacy and long-term safety have yet to be developed.

2. Future research priorities

The main aim for future research is to develop personalised medicine, determined by the underlying gene variant, leading to gene directed therapy and surveillance for tall stature syndromes (with or without intellectual disability).
To achieve this aim, the following topics and research questions need addressing:

2.1 Molecular bases and genotype-phenotype correlations

- Identification of new genes or new genetic / epigenetic mechanisms of tall stature syndromes.
- Use of methylation signatures to discover new genes involved in tall stature syndromes.
- Investigation of genotype – phenotype correlations to determine whether syndrome information (including prognosis) and management guidance should be variant rather than gene based.
- Understanding of the biological mechanisms that result in aberrant growth and tall stature, both at cellular level and organ level, including the growth plate.

2.2 Natural history and long-term consequences throughout lifespan

- Clarification and expansion (where appropriate) of the phenotype of tall stature syndromes, including longitudinal studies to determine adult phenotype.
- Assessment of natural history and long-term health consequences of OGID and non-syndromic tall stature in adulthood, including quality of life and psychosocial functioning.

2.3 Therapeutic perspectives

- Development of new therapies for the treatment of monogenic tall stature syndromes including:
    - Using molecular targets for specific pharmacological interventions, including development of drug trials (*i.e.* TGFβ pathway inhibitors or modulators)
    - Identification of new molecular targets and drugs for inhibition of growth.
- Translation of knowledge of mechanisms of tall stature into drugs for treatment of short stature.
- Further investigate the use of epiphysiodesis for tall stature (outcomes, complications, optimal age etc)

2.4 Clinical care

- Enabling earlier recognition and diagnosis of OGID.
- Development of specific management guidelines (including surveillance) based on the evolving phenotypic understanding and genotype-phenotype correlations.

3. Anticipated impact of future research

Earlier diagnosis will allow for earlier appropriate management, for example early screening for aorta pathology in Marfan syndrome or screening for the intellectual disability and/or associated medical complications (including, for some, an increased tumour risk) in OGID syndromes.

The better understanding of the molecular mechanisms underlying the different manifestations of tall stature syndromes will help to identify molecular targets for specific pharmacological interventions. Pharmacological intervention may improve the quality of life in these patients. Knowing about the long term psychological and physical well-being of these groups of patients will allow for improvement in supporting them from a medical and psychological point of view.