International guideline on genetic testing of children with short stature

Supplementary Information

Authors: Andrew Dauber[1^], Alexander A L Jorge[2^], Ola Nilsson[3], Olaf M Dekkers[4], Jesús Argente[5], Irene Netchine[6], Philippe Backeljauw[7], Jeffrey Baron[8], Debora Bertola[9], Peter Clayton[10], Justin H Davies[11], Thomas Edouard[12], Thomas Eggermann[13], Evelien Gevers[14], Giedre Grigelioniene[15]; Karen E. Heath[16], Youn Hee Jee[17], Pablo Lapunzina[18], Geert Mortier[19], Stepanka Pruhova[20], Helen L Storr[21], Emma Wakeling[22], Carlos R. Fereira[23], Mehul Dattan[24], Stefano Cianfarani[25]#, Jan M Wit[26] on behalf of the International Growth Genetics Guideline Consortium*

^ These authors contributed equally

Corresponding author

* Other members of the consortium include Tomonobu Hasegawa[27], Anita Hokken-Koelega[28], Agnes Linglart[29], Xiaoping Luo[30], Xiumin Wang[31] , Vivian Hwa[32], Louise Gregory[33] and Federica Buenocore[34]

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Supplementary information 1: Update of Diagnostic Classification of Growth Failure

Part 1: Initial clinical categorization of short stature

Short stature (SS) can be categorized along several dimensions based on the initial clinical evaluation. Taken together, these categorizations are important for the diagnostic process and often point toward a likely set of diagnoses. However, the diagnostic process is complicated because many disorders can have a variable clinical presentation. We suggest that children evaluated for SS are classified according to the following five clinical parameters.

1. Prenatal onset vs postnatal onset

SS of prenatal onset is identified when a short child is born small for gestational age (SGA), defined by a birth weight SDS and/or length SDS < -2. If birth length is unavailable, the first length SDS for age before 3 months of age, or birth weight, can be used as a proxy indicator of prenatal linear growth. Prenatal onset can result from maternal disease or substance exposure (e.g., alcohol), placental insufficiency, or a wide variety of fetal disorders. In most children, the growth abnormality will resolve after birth, allowing catch-up growth. In others, little or no catch-up growth occurs. For some disorders, prenatal growth failure will be followed by postnatal growth failure, causing further deviation from the normal range[1,2]. A short birth length in contrast to a normal birth weight in an infant without postnatal catch-up growth should be considered a warning sign of a monogenic cause compromising the growth plate[3,4].

With knowledge of intrauterine growth performance, it is possible to identify intrauterine growth retardation (IUGR; slow fetal growth based on two ultrasound measurements), which may result in a SGA baby. IUGR irrespective of birth size may lead to permanent SS.

SS of early postnatal onset (first 1-2 years of life) is typical of many congenital disorders, both primary disorders (e.g., Turner syndrome and *SHOX* haploinsufficiency) and secondary disorders (e.g., congenital GH deficiency or congenital hypothyroidism) although children with many genetic forms of SS can also present with a later postnatal onset, e.g., SHOX deficiency, Noonan syndrome or mild skeletal dysplasia without a clear growth spurt.

2. Skeletal malformation/disproportion vs no skeletal malformation/disproportion

Skeletal malformation is identified when the shape of individual bones is abnormal, either by physical or radiological examination. Skeletal disproportion is typically identified by anthropometric measurements or ratios of these measurements, such as the sitting height index or relative arm span. Skeletal malformation and/or disproportion suggest a primary growth disorder, typically an abnormality in a gene that plays a role in growth plate chondrogenesis. These conditions are usually termed skeletal dysplasias or chondrodysplasias[5].

3. Presence or absence of syndromic characteristics (non-skeletal abnormalities)

The presence of abnormal facies, significant dysmorphisms, microcephaly, (relative) macrocephaly, minor or major congenital anomalies, or neurodevelopmental disorders[6,7,8] characterize syndromic SS. It often results from variants in a gene that plays an important role in growth plate chondrogenesis and in the development of non-skeletal tissues.

4. Isolated SS vs non-isolated SS

When a short child, born either with a normal or low birth size, does not show any signs of skeletal malformation, body disproportion, syndromic conditions, nor any laboratory indications of a secondary cause of SS (e.g., defects in the GH/IGF1 axis), it can be labelled as isolated SS. All other short children can be labelled non-isolated SS.

5. Familial vs non-familial SS

SS is traditionally classified as familial and non-familial. The term "familial SS" has been defined as a subgroup of idiopathic SS (if the child's height SDS is within the parental target height range)[9] or as an initial clinical characterization (if the child's height SDS is close to that of one of the parents[10]. However, with advancement in genetic diagnostics, particularly in identifying monogenic conditions, it is now more clinically useful to differentiate whether the condition is more likely to have a mono- or polygenic basis. The inheritance pattern is assessed by drawing a pedigree of the extended family. The pedigree may suggest a monogenic condition (for example, autosomal dominant, autosomal recessive, X-linked recessive, and imprinted inheritance patterns) or a polygenic condition. A polygenic inheritance[11] suggests a benign condition, generally considered a normal variant. A nonfamilial (sporadic) occurrence suggests a causative dominant variant that occurred *de novo* or causative recessive variants but can also be seen in children with delayed skeletal maturation, some of whom can later be diagnosed as constitutional delay of growth and puberty (CDGP).

Part 2: Etiological classification of SS

A. Primary growth disorders

Primary growth disorders are defined by SS that results from an abnormality intrinsic to growth plate cartilage[12]. When the genetic disorder affects bone elongation or bone shape, the condition is termed a skeletal dysplasia, chondrodysplasia or genetic skeletal disorder. When the genetic disorder affects growth of some bones substantially more than that of other bones, the condition is often termed disproportionate SS. When the genetic disorder affects not only the growth plate but also non-skeletal tissues, the condition is often termed syndromic SS[12].

Primary growth disorders have been categorized here based on the type of genetic defect and the cellular localization of the causative molecular pathway. For each category, examples of specific disorders are provided, but this list is not exhaustive. For those disorders that present as a skeletal dysplasia, a more complete listing is provided elsewhere[13].

A.1. Single gene defects

Many genetic defects in this category present with dysmorphic features and/or body disproportion, but for many defects such clinical features can be so mild that these patients may be initially considered “isolated SS”.

A.1.a. Intracellular pathway defects

Growth plate chondrocyte proliferation and differentiation are affected by numerous intracellular molecular pathways, involving, for example, transcription factors, signal transduction, and DNA repair mechanisms[12,14].

Examples:

- Isolated SS, SHOX-related
- Noonan syndrome and RASopathies
- Bloom syndrome
- Seckel syndrome spectrum disorders
- Albright hereditary osteodystrophy

A.1.b. Paracrine signaling defects

Normal growth plate chondrogenesis requires signaling between growth plate chondrocytes involving multiple paracrine growth factors, including PTHrP, CNP, IHH, IGF-1, IGF-2, FGFs, and BMPs. Consequently, abnormalities in these signaling systems can impair linear growth[12]. Molecular defects in the ligands and receptors have been placed in this category, while defects more distal in the signal transduction pathways have been placed in the “intracellular” category.

Examples:

- *NPR2* loss-of-function variants
- *FGFR3* gain-of-function variants (e.g., achondroplasia, hypochondroplasia)
- *IHH* loss-of-function variants
- *PTH1R* loss-of-function and gain-of-function variants

A.1.c. Extracellular matrix defects

Examples:

SS with advanced bone age, *ACAN*-related

Type 2 collagenopathies

Osteogenesis imperfecta

FBN1-associated acromelic dysplasia

A.1.d. Monogenic disorders of unclear mechanism

A.2. Chromosomal anomalies / multigene CNVs

Examples:

Turner syndrome

45,X/46,XY mosaicism

Trisomy 21

22q11.2 microdeletion syndrome

Various pathogenic CNVs

B. Secondary growth disorders

Secondary growth disorders are defined by SS that results from an abnormality extrinsic to the growth plate. Secondary growth disorders occur when an abnormality in another organ system or in the child's environment (such as inadequate food supply) produces an abnormal concentration of hormones, cytokines, nutrients, electrolytes, minerals, or other components of the extracellular fluid surrounding the growth plate chondrocytes, secondarily impairing growth plate chondrogenesis[12]. In general, secondary growth failure tends to cause proportionate SS as all growth plates in the body are similarly affected[12,6].

The classification of secondary growth disorders outlined here is primarily organized according to the organ system most affected by the underlying disorder or condition.

B.1 Insufficient nutrient intake (Malnutrition)

Malnutrition is still globally the most important cause of growth failure.

B.1a Undernutrition, including wasting (low weight-for-height), stunting (low height-for-age) and underweight (low weight-for-age). Undernutrition can be caused by external factors (inadequate food supply) or psychosocial or psychiatric conditions (psychosocial deprivation, anorexia nervosa, depression).

B.1b Micronutrient deficiency (e.g., phosphate)

B.1c Maternal disease/placental insufficiency

Most infants born small for gestational age due to maternal disease, substance exposure or placental insufficiency show catch-up in linear growth in the first 2 years of life, but some may remain short for their age.

B.2 Disorders in organ systems other than skeletal and endocrine

B.2a Cardiac disorders

B.2b Pulmonary disorders, e.g. cystic fibrosis

B.2c Liver disorders

B.2d Gastrointestinal disorders e.g. celiac disease, Crohn's disease, malabsorption syndromes, short bowel syndrome

B.2e Chronic kidney disease, such as infantile cystinosis, juvenile nephronophthisis, renal tubular acidosis and Fanconi syndrome

B.2f Chronic anemia

B.2g Muscular and neurological disorders

B.2h Connective tissue disorders

B.2i Autoimmune disorders, e.g. juvenile arthritis

B.2j Multiorgan disorders

B.3 Endocrine disorders

Normal levels of several hormones are required for normal growth plate chondrogenesis[12]. Defects in hormone secretion, transport and receptors have been placed in this category, while defects more distal in the signal transduction pathways have been placed in the A.1a or A.1b categories, with a few exceptions.

B.3a Growth hormone deficiency (synonym: secondary IGF-1 deficiency)

Growth hormone deficiency (GHD) can be congenital or acquired. If combined with other deficiencies the condition is referred to as hypopituitarism, multiple pituitary hormone deficiency or combined pituitary hormone deficiency.

B.3b Growth hormone insensitivity

B.3b.1 *GHR* variant (including Laron syndrome and partial GH insensitivity forms)

B.3b.2 *STAT5B* defect

B.3c.3 *QSOX2* deficiency

B.3c Defects of the IGFs-IGF1R system

B.3c.1 IGF-1 deficiency (*IGF1* defect)

B.3c.2 IGF-2 deficiency (*IGF2* defect)

B.3c.3 IGF1R deficiency (*IGF1R* defect)

B.3d Defects disrupting transport and release of circulating IGF-1

B3d.1 ALS deficiency (*IGFALS* defect)

B.3d.2 PAPPA2 deficiency (*PAPPA2* defect)

B.3e Delayed or advanced secretion of sex steroids

B.3e.1 Delayed production/secretion of sex steroids in adolescence causes SS in adolescence (constitutional delay of growth and puberty, CDGP)

B.3e.2 Precocious puberty causes accelerated linear growth and growth plate closure in childhood, resulting in SS in adulthood

B.3f Decreased thyroid hormone effect

B.3f.1 Hypothyroidism, primary or secondary (central)

B.3f.2 Non-goitrous congenital hypothyroidism-6 (CHNG6), caused by heterozygous variants in *THRA*

B.3g Glucocorticoid excess

B.3g.1 Endogenous: Cushing syndrome, e.g., Cushing disease, glucocorticoid-producing tumor in the adrenal

B.3g.2 Exogenous: Glucocorticoid treatment (systemic or local)

B.4 Metabolic disorders

Normal metabolism of nutrients, minerals and electrolytes are required for normal growth plate chondrogenesis. Consequently, disorders in metabolic systems often affect growth. Many of these processes occur primarily in the liver and kidney.

B.4a Disorders of calcium and phosphorus metabolism

B.4a.1 Disorders of vitamin D and its metabolism or other forms of calcipenic rickets

B.4a.2 Disorders of phosphate metabolism (hypophosphatemic rickets)

B.4a.3 Hypophosphatasia

B.4b. Disorders of carbohydrate metabolism

B.4c Disorders of lipid metabolism

B.4d Disorders of protein metabolism

B.5 Psychosocial/psychiatric disorders

B.5a Psychosocial deprivation

B.5b Anorexia Nervosa

B.6 Iatrogenic

B.6a Treatment of childhood malignancy (irradiation, chemotherapy, stem cell transplant)

B.6b Other medications (e.g., pharmacological treatment of ADHD)

C. Short stature of unknown origin with normal birth size (traditionally called "idiopathic short stature") or low birth size (we suggest calling this "idiopathic short SGA")

C.1 SS in a child born with a normal birth size in whom the diagnostic evaluation does not reveal a primary or secondary cause of growth impairment: Idiopathic SS (ISS) according to the 2008 ISS consensus definition[9]

C.1a Isolated idiopathic SS

C.1b Non-isolated idiopathic SS (SS plus one or more clinical or laboratory features associated with increased likelihood of a genetic cause)

C.2 SS of a child born with a low birth size (birth length and/or weight <-2 SDS) (the idiopathic subgroup of the SGA definition according to the SGA consensus[2]

C.2a Isolated idiopathic SS of a child born with a low birth size

C.2b Non-isolated SS of a child born with a low birth size (SS plus one or more clinical or laboratory features associated with increased likelihood of a genetic cause)

Supplementary Information 2. Level of evidence of the association of a gene with a given phenotype

Over the last two decades, each year, several novel associations between genes and phenotypes have been described. It is critical for clinicians to understand the strength of the evidence linking variants in a gene to a specific phenotype. Clinical genetic testing should focus on genes that are well established as causing the patient's phenotype and directly related to the clinical motivation for the test. This is straightforward for candidate gene approaches, but not so for exome or genome sequencing. The NIH-funded Clinical Genome Resource (ClinGen) framework offers a structured approach, categorizing gene-disease associations as "Definitive," "Strong," "Moderate," "Limited," "No Reported Evidence," or "Conflicting Evidence", helping clinicians interpret genetic results[15].

Monogenic causes

Positive results, incomplete genotype, negative results, VUS

A genetic test result should be interpreted in the context of the disease associated with the gene, the identified variant, the inheritance mode, and the concordance between the altered gene function and the patient's phenotype. The primary finding in genetic tests typically corresponds to the reason the test was requested and may completely or partially explain the phenotype.

The laboratory must classify genetic variants according to the American College of Medical Genetics and Genetics and the Association for Molecular Pathology (ACMG/AMP) recommendations[16] (see **R3**). Since this landmark publication, several updates and amendments have been proposed, and a new, updated version of these recommendations is anticipated soon. Clinicians should remain vigilant regarding the need to reassess variant classifications as new knowledge and tools become available. Clinicians should also be aware that adding a new patient with a VUS to

clinical databases (e.g., ClinVar) may result in assigning a new classification for the variant if the new patient has a similar phenotype to reported patients with the identical variant.

A genetic test result may be considered positive, and clinically actionable, when a likely pathogenic or pathogenic variant identified in a specific gene is consistent with the phenotype and inheritance model observed in the patient being evaluated. This includes, for example, biallelic (homozygous or compound heterozygous) variants for a recessive disease. In cases of recessive diseases where only a single heterozygous variant is identified, the result should be interpreted as an incomplete genotype, as a second variant may not have been detected due to limitations of the testing method.

A genetic test is considered negative when no variants capable of explaining the patient's phenotype are identified. However, a negative result does not rule out the possibility that a patient carries one or more causal variants. Various technical limitations may prevent the identification or recognition of a causal variant as deleterious. Some clinical diagnostic laboratories report variants only in known genes associated with the presenting phenotype, while other laboratories may also report variants in genes which have been predicted to cause or be associated with the phenotype based on various evidence (e.g., animal model). The identified benign/likely benign variants should not be listed in the routine report from the laboratory.

A genetic result may also include the identification of variants of uncertain significance (VUS). A VUS is a genetic alteration detected during testing that cannot be definitively classified as either pathogenic/likely pathogenic (disease-causing) or benign/likely benign (non-disease-causing) based on current evidence[17]. We recommend that the laboratory should report a VUS if the respective gene may be implicated in the phenotype that motivated the genetic study, emphasizing that there is inconclusive evidence.

These findings pose significant challenges for clinical interpretation. It is essential for physicians, patients, and their families to understand that a VUS is not definitive evidence and should

not guide clinical decision making. Unnecessary follow-up testing (e.g., imaging) solely based on a VUS should be avoided. However, in collaboration with the clinical geneticist, specific testing to refine a phenotype may allow for more accurate assessment of the pathogenicity of the VUS. A VUS test result should not be used for pre-implantation/prenatal testing or for predictive testing in other relatives. Family studies (if relevant) should be encouraged to clarify segregation, and re-evaluation should be performed in 2–5 years or if new clinical features emerge (see **R 6**). Comprehensive pre- and post-test genetic counseling is necessary to explain the ambiguous nature of a VUS to patients and their caregivers, helping to minimize the risk of misinterpretation. Clinicians, in collaboration with a clinical geneticist, should consider adding a new patient with a VUS to ClinVar, which may have future consequences for the pathogenicity classification.

The reclassification of a VUS into a more definitive category (pathogenic/likely pathogenic or benign/likely benign) requires further evidence, such as new phenotypic information, segregation analyses in family members, population studies, identification of additional affected families, and functional studies. Despite these efforts, most variants initially classified as VUS remain in this category over time. Development of advanced bioinformatics tools will assist with the burden of reinterpretation. Among those reclassified, the majority are downgraded to likely benign or benign[18]. However, significant efforts are underway to achieve definitive classification of genetic variants, particularly those in coding regions, which is expected to substantially reduce the number of variants classified as VUS in the coming years[19].

Digenicity, oligogenicity and polygenicity

The interaction between two rare variants can occur within a phenotype modulation context, where one gene plays a predominant role in determining the phenotype, while a variant in a second gene either exacerbates or mitigates the effect of the primary alteration. In other scenarios, the co-

occurrence of deleterious variants in two distinct genes may be required for the phenotype to manifest, representing a digenic inheritance model[20,21,22].

Another scenario to consider involves patients who carry two or more non-overlapping genetic disorders, where the combination of phenotypes contributes to greater clinical complexity and severity of SS[8]. One should also consider the possibility of a multilocus imprinting disturbance resulting in mixed phenotypes [e.g., SRS or Beckwith-Wiedemann syndrome with a Temple syndrome (TS14) imprinting signature][23]. While it is plausible that a proportion of patients with SS exhibit digenicity, oligogenicity, or interactions between rare and common variants across multiple genes, only a limited number of convincing examples with well-characterized molecular mechanisms have been reported to date[24].

Further studies, including analyses of large families, well-defined patient cohorts, and population-level genetic datasets combined with rigorous functional investigations are needed to enhance our understanding of the genetic basis of growth disorders. This understanding must also encompass the polygenic component, which is currently assessed using the polygenic risk score (PRS), also called polygenic score (PGS). PRS is a quantitative measure that estimates an individual's genetic predisposition to a specific trait or disease. It is calculated by aggregating the effects of multiple single nucleotide polymorphisms (SNPs) across the genome, with each variant weighted according to its effect size, as determined by genome-wide association studies (GWAS). While still primarily a research tool, PRS holds potential for improving the prediction of adult height and identifying children at risk of developing SS[25,26,27].

Secondary findings

In tests that employ a genetic approach, where multiple regions and genes are evaluated simultaneously, secondary findings may occur. These refer to variants with clinical significance that

are not directly related to the reason for ordering the genetic test. Extensive medical literature is available on this topic[28], see also **Supplementary Information 3**.

Supplementary information 3. Benefits and risks of genetic testing

Potential benefits

Prior to embarking on genetic testing, one should carefully consider the potential benefits and risks from pursuing genetic investigations. First, obtaining a definitive diagnosis can be gratifying to patients and their families as this facilitates understanding of the cause of the patient's SS[29]. Additionally, establishment of a genetic diagnosis may obviate the need for further extensive diagnostic tests to determine the etiology of the child's SS[9]. Additionally, genetic testing may identify a condition associated with SS before the full phenotypic expression, which is particularly important in younger children, as it enables an earlier diagnosis and the possibility of timely clinical intervention. Perhaps most importantly, a genetic diagnosis may eliminate the need for GH stimulation tests, which have a high rate of false-positive findings leading to overdiagnosis and treatment of GH deficiency (GHD)[30]. A genetic diagnosis can also help guide therapeutic decisions, either by identifying conditions for which there is an effective treatment to stimulate growth or by preventing the unnecessary use of recombinant human growth hormone (rhGH) in conditions for which rhGH has shown to be ineffective such as in patients with *GHR* mutations (Laron syndrome)[31] or patients with specific growth plate disorders such as achondroplasia[32]. Additionally, it may have consequences for dosing rhGH (e.g., accepting elevated serum IGF-1 in children with heterozygous *IGF1R* defects on rhGH treatment[33] and a higher rhGH dosage for children with heterozygous *SHOX* defects than usual for short SGA children[34]. Finally, there are conditions for which rhGH treatment is contraindicated due to the potential for harm, as in individuals with a cancer predisposition syndrome (e.g., Bloom syndrome)[35].

In addition to helping guide therapy, a genetic diagnosis may highlight the need to screen for significant comorbidities associated with the underlying condition. Prompt identification of some comorbidities is critical for early intervention and improved patient outcomes. For example, Turner syndrome is commonly associated with SS and often results in cardiovascular anomalies such as

coarctation of the aorta, making early diagnosis essential for preventing life-threatening complications[36]. Similarly, Noonan syndrome can predispose individuals to lymphoproliferative disorders, where timely identification helps in monitoring and managing the risk of cancer development[37]. Finally, a genetic diagnosis aids accurate genetic counseling, including on family planning. Examples of benefits of establishing the diagnosis in ten prevalent genetic causes of isolated SS are presented in **Suppl Information 4**, **Suppl Table 1**.

Some types of genetic testing, such as exome sequencing (ES) and genome sequencing (GS), have the potential to identify not only primary findings (i.e. variants related to the child's SS) but also clinically relevant secondary findings (i.e. actionable variants that are unrelated to the child's SS). The American College of Medical Genetics and Genetics (ACMG) guidelines recommend that laboratories should limit these additional findings by only analyzing a set of genes deemed to be highly medically actionable to detect pathogenic variants that may predispose to a severe but preventable outcome[38,39]. Practices on analysis of secondary and incidental findings vary by country and medical center.

Potential risks

While many benefits of genetic testing clearly exist, one must also carefully consider the potential risks. Genetic variants can be difficult to interpret. A false positive genetic diagnosis occurs when a variant is mistakenly interpreted as pathogenic, leading to incorrect assumptions about the cause of disease. Such misinterpretation of genetic variants can lead to unnecessary anxiety, mismanagement, and inappropriate testing and treatment. In addition, secondary findings, even if accurate, can lead to anxiety in the affected family and, if erroneously classified, expose individuals to unnecessary surveillance or diagnostic testing.

Secondary findings can also affect insurance coverage. In terms of life and health insurance, the discovery of a genetic predisposition to certain diseases may lead to increased premiums or denial of coverage altogether. Although many countries, like the United States and members of the

European Union, have regulations preventing discrimination based on genetic information in health insurance, this protection does not always extend to life, disability, or long-term care insurance[40].

Supplementary information 4: Benefits of establishing the genetic diagnosis in ten prevalent genetic causes detected in children with isolated SS

In order to present an example of the clinical consequences of establishing a genetic diagnosis in a child with isolated SS, we performed a literature search on the clinical features in childhood and beyond of patients carrying a pathogenic genetic variant in 10 prevalent genetic causes of isolated childhood SS [heterozygous variants of *ACAN, COL2A1, FBN1, FGFR3, GHSR, IHH, NF1, NPR2, PTPN11* or *SHOX* (hemizygous in males)][41,42,3,43,44]. The clinical consequence of making a genetic diagnosis for each of these genes is mainly derived from studies in children with non-isolated SS. Consequences for management are summarized in **Suppl Table 1**.

Regarding management, for all syndromes discussed below a molecular genetic diagnosis can help the family and medical care providers by facilitating an understanding of the cause and natural history of the condition and by obviating the need for additional diagnostic testing.

ACAN

Protein: ACAN encodes aggrecan, which is the most abundant proteoglycan in hyaline cartilage and is essential for the structural integrity and function of growth plate, articular cartilage, and intervertebral discs[12].

Syndromes: Biallelic pathogenic *ACAN* variants cause a rare and severe skeletal dysplasia termed spondyloepimetaphyseal dysplasia, aggrecan type[45], while monoallelic pathogenic variants result in milder phenotypes, such as spondyloepiphyseal dysplasia, Kimberley type[46]. Monoallelic *ACAN* pathogenic variants can also present as isolated SS, with or without advanced bone age or early-onset osteoarthritis and/or osteochondritis dissecans[47,48].

Phenotype: Autosomal dominant ACAN-related SS is associated with a range of variable, but potentially informative clinical features that, while not specific, may aid in diagnosis. These include advanced bone age, early growth cessation, osteochondritis dissecans, early onset osteoarthritis,

early onset intervertebral disc disease, midface hypoplasia and brachydactyly. An additional distinguishing feature is relatively preserved arm span compared to height, in contrast to relatively short legs[49]. However, all of these features are variable and may not be observed in all patients and affected family members.

Several studies in idiopathic SS (ISS) cohorts suggest that heterozygous pathogenic *ACAN* variants are a relatively frequent cause, accounting for 1-2 percent of cases[50], although their prevalence varies across populations[3]. Pathogenic variants in *ACAN* have also been identified in short SGA children who had advanced bone age and two or more additional characteristics including midface hypoplasia, joint problems, or broad great toes[51].

Management: In children and families with ACAN-related SS, a genetic diagnosis helps facilitate ongoing monitoring and counseling regarding the risk of early-onset osteoarthritis and intervertebral disc disease. Preventive strategies should emphasize a joint-friendly lifestyle, including low-impact physical activity and prevention of obesity, in the hope that these interventions will reduce the risk of long-term disability and chronic pain[48].

Treatment: Data on the response to rhGH treatment in individuals with pathogenic *ACAN* variants are limited and primarily based on retrospective case series, most of which lack adult height outcomes and often involve combined therapies with GnRH analogues or aromatase inhibitors[48,52,51,53].

In a prospective study involving 10 prepubertal children with *ACAN* variants treated with rhGH (50 µg/kg/day), a significant increase in growth velocity and an average height SDS gain of 0.7 during the first year of treatment was observed and a median height gain of 1.2 SD at 3 years[54,55]. Treatment did not accelerate bone age maturation during the study period. However, this study as well as retrospective data suggest a reduced response to rhGH beyond the first year of therapy[51,53]. Currently available data do not allow for any conclusions on long-term efficacy up to adult height of rhGH alone or in combination with puberty modulation in this condition[48,51].

COL2A1

Protein: COL2A1 encodes the alpha-1 chain of type-II procollagen. Type II collagen is a major constituent of cartilage extracellular matrix, including both growth plate and articular cartilage, and plays a role in other structures, including the vitreous humor of the eye and the inner ear[56].

Syndromes: Monoallelic pathogenic *COL2A1* variants are associated with a diverse group of conditions known as type-II collagen disorders, including spondyloepiphyseal dysplasia congenita, Kniest dysplasia, Stickler syndrome type I, hypochondrogenesis, achondrogenesis type II, and multiple other recognized disorders[57]. There is phenotypic overlap among these conditions and genotype-phenotype correlation is generally not clear-cut[58].

Phenotype: The phenotype can include skeletal dysplasia with SS, ophthalmologic abnormalities (e.g., lens subluxation, vitreous disorders, retinal detachment, cataracts, myopia), impaired hearing, cleft palate, and characteristic facial features[58]. The severity of these disorders ranges from perinatal-lethal disorders to milder disorders that present in the neonatal period, childhood, adolescence, or adulthood[58,13]. The diagnosis of a type II collagen disorder is usually prompted by clinical and radiographic findings, including disproportionate SS, palate abnormalities, ophthalmological manifestations, hearing loss, and radiographic spondyloepiphyseal dysplasia[57].

COL2A1 variants thought to be pathogenic have been reported in individuals who present clinically with isolated proportionate or disproportionate SS[42,59,60]. In this situation, the mild presenting phenotype may imply that the molecular diagnosis will have fewer clinical consequences.

Management: Identifying a pathogenic variant in *COL2A1A*, along with clinical and radiological findings, contributes to a diagnosis of a specific type 2 collagenopathy. Recognizing the diagnostic category can help avoid unnecessary additional diagnostic testing, understand the prognosis, plan anticipatory health supervision, and inform genetic counselling. Practice guidelines regarding the diagnosis and management of patients with type II collagen disorders have been published by the Skeletal Dysplasia Management Consortium[57]. Anticipatory health supervision

includes monitoring by an ophthalmologist, radiological monitoring for cervical instability, and monitoring for hearing loss[57].

Treatment: In two retrospective case series, rhGH therapy has been associated with increased growth velocity and height SDS gain in patients with heterozygous *COL2A1* variants[61,62], but many of these variants were classified as a rare variant of uncertain significance (VUS). Controlled studies are needed to determine the efficacy of rhGH treatment in short children carrying pathogenic *COL2A1* variants.

FBN1

Protein: *FBN1* encodes fibrillin-1, the major constitutive element of extracellular microfibrils which has widespread distribution in both elastic and nonelastic connective tissue throughout the body. Fibrillin-1 is essential for the mechanical integrity of tissues but also regulates TGF-β signaling in extracellular matrix, which plays a role in growth and development.

Syndromes: Monoallelic pathogenic *FBN1* variants are best known for their association with tall stature syndromes, particularly Marfan syndrome, where pathogenic *FBN1* variants impair tissue elasticity and regulation of TGF-β signaling, leading to long limbs and tall stature. In contrast, specific missense *FBN1* variants involving the exon 41 and 42 are associated with three SS syndromes: Weill-Marchesani syndrome (WMS2), acromicric dysplasia (AD) and geleophysic dysplasia 2 (GD).

WMS2 is caused by specific in-frame or missense *FBN1* variants, leading to a reduced availability of functional fibrillin-1, resulting in decreased growth and short limbs. Recessive forms of WMS2 are caused by other genes participating in extracellular microfibrils or TGF- β signaling, such as biallelic variants in *ADAMTS10*, *ADAMTS17* and *LTBP2*[63,64], whereas AD and GD are also associated with *LPBP3* and *ADAMTSL2* variants.

Phenotype: AD, GD and WMS2 belong to the group of acromelic dysplasias, defined by SS, brachydactyly and joint limitations. Other clinical features include muscular hypertrophy, congenital heart defects (especially, valvular issues) and eye abnormalities.

Native American ancestry is associated with reduced height in an ethnically diverse group of Peruvian individuals, and a population-specific missense variant in *FBN1* (E1297G) significantly associated with lower height[65]. Additionally, cases of pathogenic variants in *FBN1* have been described in children with SS without typical syndromic features[66,43].

Management: Cardiac and ophthalmological assessment is indicated with follow-up dependent on findings.

Treatment: Response to long-term rhGH treatment has been reported in one patient with a pathogenic *FBN1* variant without clear effect on adult height[66].

FGFR3

Protein: FGFR3 encodes one of the receptors for fibroblast growth factors, a family of polypeptide growth factors involved in a variety of activities, including mitogenesis, angiogenesis, and wound healing. FGF receptors, such as FGFR3, contain an extracellular domain with either 2 or 3 immunoglobulin (Ig)-like domains, a transmembrane domain, and a cytoplasmic tyrosine kinase domain.

Syndromes: Gain-of-function variants in *FGFR3* impair growth plate chondrogenesis, causing SS. The severity of the phenotype can vary widely, depending on the variant, ranging from (most to least severe) thanatophoric dysplasia, achondroplasia, hypochondroplasia, and isolated SS.

Achondroplasia

Phenotype: Achondroplasia is the most common FGFR3-related disorder, characterized by disproportionate SS with rhizomelic shortening of the limbs, macrocephaly, and characteristic facial features[67]. Other major clinical manifestations include thoracolumbar kyphosis, spinal stenosis, obstructive sleep apnea, restrictive pulmonary disease and conductive hearing loss.

In children with achondroplasia, suspicion of skeletal dysplasia often arises during fetal life due to an abnormal ultrasound study or soon after birth because of clinical manifestations. Genetic

testing serves to confirm the specific etiology. In infancy, craniocervical junction compression can cause central apnea which can be lethal.

Management: The diagnosis of achondroplasia, confirmed by genetic testing, has many clinical repercussions, increasing vigilance for the varied clinical problems and facilitating anticipatory health supervision[68]. Because craniocervical junction compression may be life-threatening, early recognition and, if needed, decompression is particularly important[68].

Genetic diagnosis also informs genetic counselling. Approximately 80% of individuals with achondroplasia arise from *de novo* pathogenic *FGFR3* variants in which case the recurrence risk has been estimated at 0.2%, presumably due to parental germline mosaicism[69]. If the condition was inherited from an affected parent, the recurrence risk is 50%.

Some of the manifestations of achondroplasia can be treated medically or surgically. Surgical interventions include ventriculoperitoneal shunt, suboccipital decompression for craniocervical junction compression, adenotonsillectomy, pressure-equalizing tubes for middle ear dysfunction, and procedures for bowing of the legs, kyphosis, and spinal stenosis. Recently, medical treatment to augment bone growth has been introduced.

Treatment: Clinical trials with rhGH have shown a modest long-term effect (3 cm) on adult height[70]. rhGH treatment for achondroplasia is only registered in Japan. Vosoritide, a C-type natriuretic peptide (CNP) analog, increases linear growth rate[71]. Infigratinib, a non-selective FGFR1–3 tyrosine kinase inhibitor, has shown favorable results in clinical trials[72]. For both drugs, no long-term data on efficacy or safety are yet available. In addition, adjustments to the environment and psychosocial support are often introduced.

Hypochondroplasia

Phenotype: This condition, which is less severe than achondroplasia, presents primarily with disproportionate SS characterized by limb length that is decreased relative to trunk length[73]. Many of the clinical problems occurring in achondroplasia are either not associated with hypochondroplasia

or tend to be less severe and less frequent than in achondroplasia (e.g., joint pain and spinal stenosis). Because the clinical and radiological manifestations are more subtle than in achondroplasia, genetic testing is especially useful to distinguish this condition from other causes of SS. Some genotype-phenotype correlations have been reported[73].

Similar to achondroplasia, hypochondroplasia can be inherited in an autosomal dominant manner, which is associated with a 50% recurrence risk for siblings of the proband. However, most individuals with hypochondroplasia have a *de novo* pathogenic variant, in which case the recurrence risk to sibs is estimated to be 1%, as a result of parental germline mosaicism.

FGFR3 variants thought to be pathogenic have been identified in individuals who were considered to have mild disproportionate SS or even proportionate SS at clinical presentation[60,42,74]. In this situation, the mild presenting phenotype may imply that the molecular diagnosis will have fewer clinical consequences. The extent of these clinical consequences will likely become more apparent as additional patients in this situation are reported.

Treatment: Only few retrospective case series have been reported on the effect of rhGH in children with hypochondroplasia, showing a positive short-term growth response but disappointing long-term results[75,76]. However, several novel therapies targeting either the CNP or FGFR3 pathways are currently in clinical trials. So far, one study on the efficacy of Vosoritide in children with hypochondroplasia has been published, showing that height velocity rose by ~1.8 cm/year over 6 months and height SDS increased by ~0.4 SD compared to baseline[77].

GHSR

Protein: *GHSR* encodes a G protein-coupled receptor (GHSR) expressed mainly in the pituitary and hypothalamus. It mediates the biologic effects of ghrelin (GHRL), a pleiotropic hormone secreted by the stomach that promotes food-seeking behavior and positive energy balance. GHSR can also signal in the absence of ligand due to high constitutive activity and selectively modulate

dopamine signaling through heterodimerization with dopamine receptors. Experimental data have shown that GHSR signaling stimulates GH secretion[78].

Syndrome: Loss-of-function of *GHSR* is associated with "isolated partial growth hormone deficiency", first described in 2006[79].

Phenotype: Missense variants in *GHSR* have been associated with proportionate SS, low-normal serum IGF-1 and isolated partial GHD or SS with normal serum GH responses to GH stimulation testing. Other reported clinical features include failure to thrive with low appetite and late puberty. Segregation studies have shown incomplete penetrance. The largest cohort studied to date included 26 patients with proportionate SS with a mean (SD) height SDS of −2.8 (0.5), mean (SD) serum IGF-I SDS of −1.6 (0.7) and a normal stimulated GH response, in line with previous smaller studies[80]. Pathogenicity of the *GHSR* variants was studied *in vitro* using total protein levels, cell surface expression, and receptor activity in basal, stimulated, and inhibited states[80].

Management: The genetic diagnosis of *GHSR* haploinsufficiency is important because these patients often show a phenotype resembling ISS. Although partial GHD has been reported, most patients have a normal stimulated GH peak as the traditionally used pharmacological agents test the intact GHRH/somatostatin system[80].

Treatment: The short-term growth response to rhGH treatment in nine patients showed a mean height gain of 0.9 and 1.5 SDS after 1 and 2 years, respectively[80], in line with results reported on smaller cohorts.

IHH

Protein: IHH encodes a member of the hedgehog family of proteins and forms a feedback loop with PTHrP to regulate chondrocyte proliferation and differentiation in the growth plate cartilage[81]. Consequently, IHH is essential in endochondral bone formation, growth plate chondrogenesis[82,83] and trabecular bone formation[84,85], dependent or independent of PTHrP.

Syndromes: Monoallelic pathogenic variants cause brachydactyly type A1 (BDA1)[86,87], a constellation of shortening or malformation of middle phalanges/toes and SS (height ranging between –4 and 0 SDS)[88]. Biallelic pathogenic variants cause a rare dwarfism (height ranging between -9 and -2.3 SDS) called acrocapitofemoral dysplasia, also affecting hands and hips[89,90,91].

Most of the identified pathogenic variants associated with BDA1 have been located in the functionally important N-terminal segment of IHH [Byrnes_AM;2009;Brachydactyly;19277064]. In contrast, several series of patients with isolated SS with or without mild skeletal findings associated with BDA1 were found to have missense and loss-of-function variants distributed more diffusely in *IHH*[88,9293].

Phenotype: BDA1 is characterized by mild SS and shortening of the middle phalanges of the digits of the hand, with or without symphalangism (a condition where the interphalangeal joints of the fingers and/or toes fuse, leading to stiffness and limited mobility). Considerable inter- and intrafamilial variability has been observed, with all or only some digits affected, and complete absence of the middle phalanx in some cases. Metacarpals may also be shortened, and clinodactyly, camptodactyly and ulnar deviation have been reported. Some patients exhibit abnormalities of the feet. Mild body disproportion was observed in the Brazilian cohort (mean sitting height to height ratio +2.4 SDS, range +0.3 to +4.4)[92]. Most affected children had mildly delayed bone age, but advanced bone age has also been observed. Abnormal hand radiographs were observed in 50% of patients with varying degrees of shortening of the middle phalanx of the second and fifth fingers with cone-shaped epiphyses.

Management: No special needs for surveillance.

Treatment: Five patients with SS due to *IHH* variants treated with rhGH showed a modest mean effect (0.6 SDS gain) for one year of treatment[92]. A case report on two siblings showed a significant height SDS increase of +2.4 and +1.9 after 4 years of rhGH treatment[94]. Further studies will be needed in a large cohort of patients to establish the full phenotypic spectrum, comorbidities, genotype-phenotype, and to determine the treatment efficacy of rhGH in terms of adult height.

NF1

Protein: NF1 encodes neurofibromin, a known tumor suppressor[95,96], which also plays a role in other regulatory systems of the body. Regarding linear growth regulation, neurofibromin is a negative regulator of the intracellular protein Ras, which regulates MAPK-ERK phosphorylation[97,98] and PI3K activation downstream signaling[99]. Loss of neurofibromin function leads to an increase in ERK phosphorylation causing reduced growth plate chondrogenesis by altering chondrocyte proliferation and differentiation [97,98], similar to the molecular pathophysiology of Noonan syndrome[100].

An alternative pathophysiological explanation of growth retardation was suggested by observations in brain-specific *Nf1* knockout mice showing small anterior pituitary glands and reduced GHRH, pituitary GH and liver IGF-1 production[101]. However, in the human, evidence for a role of GH deficiency was unconvincing in two cohort studies[102, 103] except for a single case with empty sella and hypopituitarism[104].

Syndrome: NF1 is a common genetic disorder affecting approximately 1 in 2,500 births[105] and is caused by heterozygous loss-of-function variants in neurofibromin. Children with NF1 are at high risk for various tumors (i.e., neurofibroma, plexiform neurofibroma, glioma, hamartoma), although pathogenic *NF1* variants have shown highly variable clinical expressivity and poor genotype-phenotype correlation[95,96].

NF1 is inherited in an autosomal dominant fashion, but approximately 50% of patients have sporadic NF1 due to a *de novo* pathogenic *NF1* variant. NF1 shows 100% penetrance by adolescence; therefore, close monitoring and follow-up of physical examination to detect any of the seven clinical manifestations can establish the diagnosis during childhood unless patients meet the clinical diagnosis criteria at presentation [95,96].

Phenotype: According to the NIH Consensus Development Conference Criteria, the diagnosis of NF1 requires at least two of seven clinical manifestations[106,107]: *i)* six or more café-au-lait macules

(coast of California), *ii)* two more neurofibromas of any type or one plexiform neurofibroma, *iii)* freckling in the axillary or inguinal region, *iv)* optic glioma, *v)* two or more iris hamartomas (Lisch nodules), *vi)* osseous lesion (sphenoid wing dysplasia or long-bone dysplasia with or without pseudoarthrosis), and *vii)* a first-degree relative with clinical NF1.

Although genetic confirmation may not be absolutely needed for NF1 diagnosis, genetic testing for *NF1* in blood or affected tissues may be helpful for diagnosis in children who present with atypical features, or may assist in genetic counseling and family planning [106,107].

Consistent with the role of neurofibromin in growth regulation, approximately 50% of children with NF1 develop postnatal growth delay with reduced pubertal growth spurt, leading to SS or a height below target height[108]. Growth patterns of children with NF1 in several longitudinal studies were reported to aid in growth assessment. On average, children with NF1 are 0.5 SDS shorter than reference children[109,110,111].

Endocrine dysfunctions are also frequent in NF1. For example, in two large cohorts 23-30% of children with NF1 developed endocrine dysfunctions, including central precocious puberty, GH hypersecretion or a low GH peak at a GH stimulation test[112,103]. Children with NF1 with accelerated growth velocity or tall stature in childhood with or without precocious puberty should be evaluated for associated gliomas involving the chiasm and/or hypothalamic-pituitary axis[113,114] . In addition, two recent systematic reviews and meta-analyses showed that NF1 is associated with decreased BMD at the lumbar spine and femur[115,116]. Children with NF1 may also develop focal skeletal abnormalities that can cause morbidity[107].

Management: Because children with NF1 develop multiple complex clinical presentations, multidisciplinary approaches are required to monitor disease and provide adequate treatment. The detailed workup and management are well-summarized elsewhere[117].

Treatment: rhGH therapy should be used only when patients are short, have poor height velocity and show definitively confirmed GHD[107]. The reason for caution is that GH receptors are

expressed in plexiform neurofibroma[118] and IGF receptors in Schwann cells[119], suggesting that rhGH treatment may affect the progression or recurrence of tumors[120].

NPR2

Protein: *NPR2* encodes the homodimeric transmembrane natriuretic peptide receptor B (NPRB). When activated by its endogenous ligand, C-type natriuretic peptide (CNP), it produces cyclic GMP from GTP. In the growth plate, NPRB signaling promotes chondrogenesis and therefore longitudinal bone growth. This effect is mediated, at least in part, by activation of p38, which inhibits the activation of MEK by RAF in the MAPK signaling pathway. This, in turn, leads to inhibition of FGFR3 signaling and its inhibitory effect on proliferation and differentiation of chondrocytes[121,122,123]. This pathway underlies the rationale for the use of CNP analogues to inhibit the excessive signaling through FGFR3 in achondroplasia.

Syndromes: Bi-allelic pathogenic variants in *NPR2* cause acromesomelic dysplasia (Maroteaux type, autosomal recessive) with only the skeletal system consistently affected[124] while obligate carriers of *NPR2* variants are shorter than matched controls[121,125]. *NPR2* mono-allelic loss-of-function variants are found in cohorts with isolated SS[126], while gain-of-function variants have been identified in those with tall stature[127].

NPR2 variants have also been found in children with disproportionate SS, who had screened negative for *SHOX* pathogenic variants[128], in short SGA children (the majority being small for length)[3] and children with dominant SS[129].

Phenotype: The clinical phenotype of patients with heterozygous *NPR2* variants includes SS (mean height SDS -2.7), facial anomalies and skeletal features, such as brachydactyly, shortened metacarpals or metatarsals (particularly fourth to fifth), and clinodactyly[130]. The SS can be disproportionate, but this finding has been insufficient to guide a candidate gene approach[60]. Height SD scores progressively decrease as heterozygous children mature in contrast to remaining

unchanged in their normal siblings[131]. An increase in BMI with age during childhood and adolescence (mean SDS gain +1.4) has been reported[132].

GH-IGF-1 status in carriers of monoallelic *NPR2* variants has been reported as normal in most patients[133]. In some children serum IGF-1 has been low[134], as often observed in children with isolated SS[135].

Management: No special needs for surveillance.

Treatment: Short-term, uncontrolled trials of treatment with rhGH have been undertaken, with variable growth responses. The average response has been a gain in height SDS of +1 over an average treatment period of 3 years [133,129,61,130,136]. Height SDS change correlated negatively with initial age of treatment and was associated with location of the monoallelic variants; height SDS gain was greater for those with mutations in the carboxyl-terminal guanylyl cyclase catalytic domain compared to the extracellular ligand-binding domain[130]. Adjuvant treatments to delay puberty with gonadotrophin releasing hormone analogues have also been trialed.

For children with isolated SS and minor skeletal anomalies without a clinical diagnosis, a screen for a heterozygous *NPR2* variant is worthwhile. No other major long-term health issues have been reported in these subjects.

PTPN11

Protein: *PTPN11* encodes a signaling molecule (PTPN11) within the protein tyrosine phosphatase (PTP) family. PTPs regulate cell growth, differentiation, the mitotic cycle, and oncogenic transformation. *PTPN11* contains two tandem Src homology-2 domains, hence its alternative name of SHP2, and is involved in signaling in a range of cellular functions - mitogenic activation, metabolic control, transcription regulation, and cell migration. *PTPN11* acts downstream of various receptors and positively regulates MAPK signaling.

Syndromes: Germline monoallelic pathogenic variants in *PTPN11* are the commonest cause of Noonan syndrome (NS; Noonan syndrome type 1)[137,138], whereas somatic variants are found in juvenile myelomonocytic leukemia and acute myeloid leukemia.

Phenotype: Features of NS may include feeding difficulties, SS, a distinctive facial appearance, a broad or webbed neck, congenital heart defects (i.e., pulmonary valve stenosis, hypertrophic cardiomyopathy), bleeding problems, bone malformations (i.e., pectus, scoliosis), cryptorchidism in males and developmental delay (https://rarediseases.info.nih.gov/diseases/10955/noonan-syndrome). Other mutations within the RAS/MAPK pathway cause NS and related conditions (e.g. Leopard, Cardio-facio-cutaneous and Costello syndromes, and Neurofibromatosis type 1), which are collectively known as RASopathies.

The finding of *PTPN11* variants in screens of children with isolated / idiopathic SS indicates that there are children who have NS but do not have sufficient clinical features to flag up the possibility of this diagnosis[139].

Both sexes at 5 years of age with *PTPN11* variants were shorter and lighter than those with other gene variants[140]. A range of abnormalities in the GH/IGF-1 axis have been described with low or normal GH with low IGF-I and neurosecretory dysfunction[141,142].

Learning difficulties as well as psychological problems may occur in NS. A behavioral phenotype in which social and emotional recognition and expression are abnormal has been described[143]. ADHD and anxiety disorders have also been reported[144].

Management: Finding a pathogenic *PTPN11* variant has important implications for health surveillance and management. Cardiac abnormalities, including pulmonary stenosis, hypertrophic cardiomyopathy and progressive aortic annular dilation and aneurysm, are reported in NS[145], and therefore echocardiography at diagnosis and appropriate follow-up should be undertaken. Bleeding problems most commonly related to Factor XI deficiency are associated with NS and may require attention[138,146]. Therefore, assessment and support may be required. In boys, delayed puberty may occur, which may require investigation and treatment. Early feeding problems are common in NS,

but they can also develop later in childhood. This too may require intervention[147]. In summary, the finding of a *PTPN11* variant in a child with isolated SS should prompt a targeted health and well-being assessment.

Treatment: rhGH can be considered and there are numerous reports indicating a positive response to treatment and in general no major safety issues, including cardiac issues and malignancy occurrence[141]. rhGH is registered for NS in most parts of the world. Regarding mutation status, the mean gain in height SDS after 4 years on rhGH was +1.3 (SD 0.8) in those with *PTPN11* variants which was not different to those with other variants at +1.5 (SD 0.7)[148]. Reports on adult height after rhGH treatment have been reported in small cohorts [141].

SHOX

Protein: The short stature homeobox gene (*SHOX*) encodes a transcription factor and is located on the pseudoautosomal regions of the X- and Y-chromosomes. It is expressed in the growth plate and promotes growth plate chondrogenesis and therefore linear growth[149].

Syndromes: Biallelic inactivating variants in *SHOX* cause Langer mesomelic dysplasia, which includes severe, disproportionate SS with short and often bowed radius and tibia[150]. Heterozygous (in females) and hemizygous (in males) inactivating variants or deletions of *SHOX* or its enhancer regions cause a milder skeletal dysplasia, Leri-Weill dyschondrosteosis[150] or can present clinically as idiopathic SS (ISS), with body proportions that are mildly affected or sometimes within the normal range[151,152]. Heterozygous or hemizygous variants of *SHOX* are a fairly frequent finding in ISS and account for ~2% of growth failure in cohort studies of ISS[153].

Phenotype: Birth length is only mildly affected, but growth failure occurs during early postnatal life and is usually established during the 2nd or 3rd year of life[153,154], with additional loss of height percentiles sometimes occurring during puberty[155,156].

In addition to wrist deformities, there are several variable signs indicating possible SHOX deficiency, including shortening of the fourth and fifth metacarpals, high arched palate, increased

771 carrying angle of the elbow, scoliosis, and micrognathia. In addition, muscular hypertrophy of the
772 calves is found in one third of affected individuals[157]. Importantly, the absence of any of these signs,
773 including Madelung deformity, does not exclude SHOX haploinsufficiency. Consequently, auxology is
774 a large part of the proposed scoring systems for the diagnosis of SHOX deficiency[157,153,151,152].
775 *Management*: Monitoring for linear growth, tempo of pubertal development, scoliosis and
776 Madelung deformity are warranted.
777 *Treatment*: A randomized controlled trial demonstrated the benefit of rhGH in prepubertal
778 patients with SHOX haploinsufficiency treated for 2 years[158]. Subsequently, similar adult height gains
779 to those observed in girls with Turner syndrome were demonstrated[159]. SHOX haploinsufficiency is a
780 registered indication for rhGH treatment in most parts of the world.
781

782 **Concluding remarks**

783 For the conditions reviewed, molecular genetic diagnosis has the potential to provide
784 benefits, to help the child and family understand the cause and prognosis of the condition, to avoid
785 unnecessary additional diagnostic testing, to identify comorbidities, to inform treatment decisions,
786 genetic counselling and to guide targeted health surveillance.

787 Regarding treatment, rhGH is registered for two of these genetic conditions (*SHOX* and
788 *PTPN11* haploinsufficiency). In patients with mono- or biallelic pathogenic *GHSR* variants, it seems
789 plausible that spontaneous GH secretion may be decreased, and a case series[80] and various case
790 reports have suggested that rhGH treatment increases linear growth. Preliminary uncontrolled data
791 on rhGH treatment of short children carrying a heterozygous variant of *IHH*[9], *NPR2*[130], and *ACAN*[54]
792 have suggested a modest growth response to rhGH in the first years of treatment; the effect on adult
793 height is still uncertain. Variants in some of these genes may predispose to neoplasia (*PTPN11*, *NF1*)
794 and, prior to initiating therapy, caregivers should be counselled on the potential benefits and risks of
795 rhGH therapy in each situation. For several genetic defects adjunctive treatment has been

796 investigated with GnRHa (SHOX and others). Alternative interventions for growth are available for
797 some genetic diagnoses, such as vosoritide treatment for mono-allelic *FGFR3* variants.

798 Regarding early detection of comorbidities, long-term monitoring is warranted in eight of the
799 10 genetic disorders (**Supplementary Table 1**); so far, no comorbidities are known for individuals
800 with *GHSR* or *NPR2* haploinsufficiency.

801

Supplementary Table 1. Clinical consequences of establishing a genetic diagnosis in children with SS based on the 10 prevalent genetic causes of isolated SS#

Gene	Associated clinical features in addition to SS	Available Interventions	Recommended surveillance for presentations with non-isolated SS[&]	Effect of making a genetic diagnosis on relatives' health
ACAN	*Mid-facial hypoplasia *Advanced bone age *Osteochondritis dissecans *Early-onset osteoarthritis *Early-onset intervertebral disc disease	*Orthopedic interventions including joint replacement	*Advise to seek early medical assessment for joint pain *Joint-friendly activities, low impact physical activity *Prevention of excess weight gain	*Advise to seek early medical assessment for joint pain *Joint-friendly activities, low impact physical activity
COL2A1	*Eye abnormalities (lens subluxation, retinal detachment, cataracts) *Hearing impairment *Cleft palate *Cervical spine abnormalities *Atlantooccipital instability *Early-onset osteoarthritis	*Spinal surgery *Cleft palate repair *Advice on signs and symptoms of retinal detachment	*Life-long ophthalmological assessment – follow-up dependent on findings *Ongoing audiological assessment *Clinical and radiological surveillance for cervical instability and spinal cord compression *Monitor for scoliosis	*Advise early ophthalmological, audiological, radiological and spinal assessment
FBN1	*Brachydactyly *Congenital heart disease *Joint stiffness * Eye abnormalities (microspherophakia, lens ectopia, glaucoma) potentially leading to visual impairment	*Orthopedic, cardiac and ophthalmological intervention as required	*Initial cardiac assessment, follow-up dependent on findings *Initial ophthalmological assessment – follow-up dependent on findings	*Requirement for cardiac and ophthalmological assessment
FGFR3	*Spinal stenosis (Increases with age and is very common in adults with achondroplasia) *Tibial bowing *Obstructive sleep apnea *Foramen magnum stenosis *Hydrocephalus	*Vosoritide *Surgical interventions for certain comorbidities	*Orthopedic surveillance *Monitor for sleep-disordered breathing *Audiological follow-up *Brain MRI in infancy to assess foramen magnum	

	*Short extremities			
GHSR	*Failure to thrive *Poor appetite *Delayed puberty	*rhGH therapy for GHD in childhood and possibly in adulthood	Unknown	rhGH therapy for SS
IHH	Brachydactyly (usually mild)	N/A	Unknown	
NF1	*Neurocutaneous stigmata *Neoplasia (neurofibroma, optic pathway glioma, phaeochromocytoma) *Osseous lesions (sphenoid wing dysplasia) *Scoliosis *Osteopenia, osteoporosis *GHD, GH excess *Precocious puberty	*rhGH therapy for GHD in childhood and adulthood *GnRHa for precocious puberty *Somatostatin analogue for GH excess *Neoplasia: surgery, chemotherapy, radiotherapy	**Children** *Growth monitoring (6-monthly) * Assessment of puberty stage and tempo * Ophthalmological assessment *Annual examination for neoplasia *Neurodevelopmental assessment *Monitor for scoliosis *Annual blood pressure **Adults** *Annual examination for neoplasia *Breast cancer assessment from 30y (women) *Annual neurological assessment *Monitor for osteoporosis *Annual blood pressure and cardiac assessment	*Life-long institution of detailed screening for complications of NF-1
NPR2	*Facial features (prominent forehead, short nose, potential midface hypoplasia) *Brachydactyly *Short metacarpals and metatarsals *Clinodactyly	N/A	N/A	N/A
PTPN11	*Distinctive facies *Broad/webbed neck	*rhGH therapy	*Linear growth monitoring 6-monthly	*Cardiac assessment

	*Pectus carinatum/excavatum *Scoliosis *Congenital heart disease (pulmonary valve stenosis and hypertrophic cardiomyopathy) *Feeding difficulties, failure to thrive *Bleeding diathesis *Delayed puberty *Cryptorchidism *Intellectual disability *Juvenile myelomonocytic leukemia *Eye abnormalities (strabismus, amblyopia, nystagmus) *Hearing defect	*Sex hormone substitution for delayed puberty *Educational psychologist support *Treatment of factor XI deficiency	*Assessment of puberty stage and tempo *Cardiac assessment and follow-up *Ophthalmological assessment *Hematological assessment for easy bruising, bleeding or monocytosis * renal ultrasound scan at diagnosis	*Ophthalmological assessment *Hematological assessment *Children: timely access to rhGH therapy
SHOX	*Calf hypertrophy *Short 4th metacarpal *Scoliosis *High arched palate *Madelung deformity	*rhGH therapy (children) *GnRHa as adjuvant therapy?	*Growth monitoring 6-monthly *Assessment of puberty stage and tempo *Madelung deformity may cause pain - advice to support wrist *Monitor for scoliosis	Children: timely access to GH therapy to optimize growth outcomes

For all gene defects, establishing the diagnosis provides explanation of familial SS to end diagnostic odyssey.

& Recommended surveillance for presentations with isolated SS (ISS) is unknown for all gene defects, except for *NF1, PTPN11* and *SHOX* variants.

^ Hypochondroplasia can present as isolated SS

N/A information not available

Supplementary Information 5. Diagnostic clues for a primary growth disorder

Medical history

Important diagnostic clues include intrauterine growth monitored with at least two ultrasound scans, a small birth size (small-for-gestational age, SGA), microcephaly or relative macrocephaly (indicative for Silver-Russell syndrome, SRS) at birth, feeding problems in infancy, neurodevelopmental disorders (including developmental delay (DD), intellectual deficit (ID) and behavior problems), progressive poor bone growth, bone fragility or recurrent fractures and/or signs of skeletal dysplasia (e.g., disproportionate SS, bowing). While many genetic causes of SS are characterized by postnatal growth failure, others show a combination of prenatal and postnatal growth failure. Birth length SDS is usually lower than birth weight SDS[1,160,7].

A history of feeding problems is often present in patients with SRS[161], Temple syndrome (TS14), *IGF1R* haploinsufficiency[33], Noonan syndrome[147] and Prader-Willi syndrome (PWS)[162].

A history of developmental delay, learning disability or behavior problems (e.g., autism spectrum disorder, ASD) increases the likelihood of a genetic syndrome[163]. A history of frequent or low impact fractures suggests a form of osteogenesis imperfecta or another underlying bone disorder.

While most primary growth disorders have a genetic cause, others are caused by prenatal damage to the growing fetus, e.g., due to alcohol abuse or maternal medication in pregnancy.

Family history

A three-generation pedigree, with information about parental consanguinity and heights in siblings, parents and grandparents, can help identify patients with monogenic forms of SS with recessive, dominant, X-linked or mitochondrial inheritance. Detailed information regarding other relatives with SS may provide diagnostic clues. This includes age of onset, presence of disproportion,

childhood treatment with rhGH, dysmorphic features, psychomotor delay, learning disability, skeletal abnormalities and other medical issues. It is also useful to ask whether there are adult family members with specific clinical features typical for relatively frequent dominant genetic disorders, such as early-onset arthritis or a growth pattern with early arrest (pointing towards ACAN haploinsufficiency)[48], a Madelung deformity (pointing at SHOX haploinsufficiency), a family history of SGA (suggestive for *IGF1R* and *IGF2* variants), etc. However, in certain genetic disorders (e.g., Noonan syndrome and SRS), clinical manifestations (facial dysmorphisms) become less evident with age.

A pedigree analysis may also provide important clues to the likely mode of inheritance. Where one parent is similarly affected, autosomal dominant inheritance is most likely. Where siblings alone are affected, autosomal recessive inheritance should be considered, particularly in the presence of parental consanguinity. Affected males linked via unaffected or mildly affected females are suggestive of X-linked inheritance. Incomplete penetrance or imprinting effects may result in apparent skipping of generations. Parental history of infertility and recurrent miscarriage is compatible with severe recessive conditions or the presence of a balanced translocation in one of the parents. The use of assisted reproductive technology may point to an underlying imprinting defect[164], but it has not been established whether the assisted reproductive technology increases the rate of *de novo* variants[165]. Where there is a known genetic cause for SS in the family, testing can be targeted at the familial gene variant. For those patients with a *de novo* autosomal dominant variant, SS is sporadic, and family history will be uninformative.

Anthropometry and Pubertal Status

Height, weight, head circumference, sitting height and arm span are essential measures and should be expressed as SDS for age and sex. Body mass index (BMI) and SH/H and relative arm span should also be calculated and expressed as SDS. Pubertal status is usually rated according to Tanner and either visually compared with reference data or expressed as SDS[166,167,168].

860 The clinician should make every effort to collect as many growth measurements as possible
861 from previous years in order to construct a comprehensive growth curve. Several primary growth
862 disorders are characterized by a specific growth pattern. This was first shown for Turner
863 syndrome[169,170] and later also for other genetic syndromes[171,157,128,48,92,172]. The usual pattern is a low
864 or low-normal birth length, decreasing length SDS for 2–3 years, a stable height SDS (HSDS) in
865 childhood, and further HSDS decrease during adolescence with no or attenuated growth spurt. A
866 HSDS similar to the height SDS of one of the parents obviously increases the likelihood of a dominant
867 condition. It is plausible that stable but extreme SS (HSDS <–3) increases the likelihood of a primary
868 growth disorder[173,163]], while growth faltering is more compatible with severe GHD or GH
869 insensitivity[174] or other secondary growth disorders.

870 It is plausible that microcephalic SS increases the likelihood of a genetic cause[175,1], but the
871 available evidence for this is weak due to heterogeneous patient cohorts[163]. In infants and toddlers,
872 fontanelles and dentition including timing of the eruption should be evaluated[176].

873 Relative macrocephaly at birth has been defined as a head circumference at least 1.5 SDS
874 above birth weight and/or length SDS[177,161] and is a key diagnostic clue to SRS. In a study on the
875 phenotype in 69 patients referred with a possible diagnosis of SRS[177], the Netchine-Harbison clinical
876 scoring system (NH-CSS), validated by this study, was found to have 98% sensitivity for detection of
877 patients with molecularly-proven SRS. Relative macrocephaly at birth, one of the six criteria of the
878 NH-CSS, was present significantly more frequently in individuals with SRS 11p15 (96.9%) and SRS
879 mUPD7 (81.8%) compared to those with no molecular diagnosis who scored ≤ 3/6 (25%). Relative
880 macrocephaly at birth and protruding forehead were the two criteria in the NH-CSS which best
881 distinguished SRS from non-SRS SGA[161].

882 In childhood and beyond relative macrocephaly is usually defined as a relatively mild degree
883 of macrocephaly in which the head circumference is not above two standard deviations from the
884 mean but appears disproportionately large when other factors such as body stature are taken into

885 account, thus for example 2 SD above the regression line of head circumference vs height[178]. It can
886 point to achondroplasia, hypochondroplasia, RASopathies[179], 3M syndrome[180], neurofibromatosis
887 1[181], Turner syndrome[182], Temple syndrome[183], and Mulibrey Nanism.

888 A relatively high sitting height/height ratio (SH/H) SDS is seen in several skeletal dysplasias
889 (e.g., in Turner syndrome and SHOX or ACAN deficiency) [151,152,48]. A decreased SH/H SDS is observed in
890 children with axial segment abnormalities[176], such as biallelic variants of *PAPSS2*[184]. Reference data
891 for SH/H are available from various countries[185,186,187,188,189,190,191]. Measuring sitting height is
892 preferred above measuring lower segment because the latter has a relatively low accuracy and
893 recent reference data for upper/lower segment ratio are scarce[192].

894 The relationship between arm span and height can be expressed as a relative arm span (arm
895 span minus height, arm span/height ratio or arm span for height)[49]. In most primary growth
896 disorders, arm span is shorter than body height, except for heterozygous *ACAN* mutations, where it is
897 generally normal for age and sex, but increased in adolescents[49].

898 The ratio between length of the upper arm and lower arm (and upper leg versus lower leg) is
899 important for the differentiation between hypochondroplasia (short upper arms and legs, rhizomelia)
900 versus *SHOX* or *NPR2* haploinsufficiency (short forearms and lower legs, mesomelia)[128,157], although
901 in hypochondroplasia short forearms have also been reported[193].

902

903 Dysmorphic Features

904 Special attention should be given to dysmorphic features, since these can offer clues for specific
905 genetic conditions. Selected dysmorphic features were recently summarized[194] (for more details:
906 London Medical Database via www.Face2Gene.com [Face2Gene. London Medical Databases. Boston,
907 MA, USA; 2019.51] and seven reviews on elements of morphology and standard terminology (quoted
908 in Wit JM et al[194].

Supplementary Information 6. Diagnostic clues for a secondary growth disorder

Medical history

A decreasing BMI, anorexia, fatigue, or abdominal complaints can suggest malnutrition, inflammatory bowel disease or celiac disease. An increasing BMI, particularly if combined with growth faltering, should be considered a red flag because it can be an early symptom of Cushing syndrome, hypothyroidism or acquired GHD. Fatigue can suggest juvenile hypothyroidism. A history of brain trauma raises the pre-test likelihood of acquired hypopituitarism. Symptoms of increased intracranial pressure (headache, vomiting, disturbed visual acuity) warrant a full neurological assessment. A full inventory of medication should be made, with specific attention to the use of corticosteroids (oral, inhaled, or topical) and medication for attention-deficit hyperactivity disorder (not limited to methylphenidate). Psychosocial/psychiatric issues should be assessed for emotional deprivation, or anorexia nervosa.

Family history

This should contain questions about familial occurrence of autoimmune diseases and puberty timing and past growth-promoting treatment in parents. A more exhaustive list of symptoms and signs of primary and secondary growth disorders was published previously[194].

Physical examination

A decreasing height SDS (low height velocity for age and height SDS) is an important sign of a secondary growth disorder, so besides the height at presentation, the clinician should collect all available length and height measurements. A key diagnostic clue is a high or recently increased BMI SDS in combination with growth faltering, which may raise suspicion for conditions such as Cushing syndrome, hypothyroidism, GHD, or a brain tumor (e.g., craniopharyngioma). However, an increasing BMI SDS is also observed in several primary growth disorders of genetic origin, e.g. Temple

syndrome, Prader-Willi syndrome and GNAS-inactive associated phenotypes. Clinicians should also remain vigilant for additional clinical features of Cushing syndrome, such as Cushingoid appearance (yearly school photographs may provide useful longitudinal evidence), hypertension, virilization, and striae. Palpation of the thyroid gland is crucial for detecting the presence of a goiter which may be associated with hypothyroidism (mostly secondary to autoimmune thyroiditis). Other clinical features of this condition include a slow heart rate, pasty skin and a slow Achilles tendon reflex.

A low or decreasing BMI SDS in combination with growth faltering is a possible symptom of celiac disease or inflammatory bowel disorders (particularly Crohn's disease)[195,196,197,198]. Height and BMI deceleration in inflammatory bowel disorders may start during early childhood, but progress very gradually, delaying the suspicion/diagnosis unless patient is monitored for growth routinely. Growth faltering and decreasing BMI are also observed in other chronic systemic illnesses such as renal tubular acidosis[199] or anorexia nervosa[200].

A general neurological assessment should be performed in order to detect neurological abnormalities (suspicious for a brain tumor). A thorough visual inspection of the skin can help identify vitiligo, which may indicate an underlying multi-organ autoimmune disease, as well as dermatological manifestations associated with celiac disease (dermatitis herpetiformis, chronic urticaria, atopic dermatitis, psoriasis, rosacea and alopecia areata)[201] or Neurofibromatosis 1 (neurocutaneous stigmata).

Radiology

A markedly delayed bone maturation detected on a radiograph of the hand and wrist is consistent with either a secondary growth disorder or slow maturation of the epiphyseal growth plates that may later develop into constitutional delay of growth and puberty (CDGP). However, delayed bone age is also observed in some genetic causes of SS.

Laboratory screening

957 Guidelines on laboratory screening in short children are mainly aimed at detecting secondary

958 growth disorders (see **Suppl Information 12).**

Supplementary Information 7. Diagnostic yield of genetic testing in a short child born small for gestational age

The diagnostic yield of CMA in short SGA children[202,203,204] is quite variable (16-46%), probably associated with varying percentages of syndromic SS. The frequency of imprinting disorders in SGA children was tested by quantitative DNA methylation analysis at differentially methylated regions (DMRs) of germline DMRs of several genes in 98 short SGA patients and 50 controls, showing DNA methylation changes in six SGA children (6%)[205]. Exome (n = 16) or targeted gene panel (n = 39) sequencing in isolated short SGA resulted in (likely) pathogenic genetic variants in 8 out of 55 patients (15%)[3]. In syndromic short SGA, ES analysis identified a genetic cause in 34%[7]. In twenty-four SGA children with persistent SS associated with dysmorphic features and/or developmental delay, CNVs were present in 11/24 (46%) SGA children carrying (likely) pathogenic gene variants[204]. Since 2020, a combination of gene panels, ES and methylation analysis is the usual diagnostic approach. The diagnostic yield has varied between 11% and 55% [Scalco;SystRev;pending].

Silver-Russell syndrome (SRS) is an imprinting disorder in short SGA with heterogeneous (epi)genetic causes[161]. The Netchine-Harbison clinical scoring system can be used to assess whether molecular testing should be requested. We recommend starting with methylation analysis of the genomically imprinted loci on chromosomes 11p15, 7, and 14q32. If negative, genetic testing for differential diagnoses (SNVs, CNVs and UPDs) should be considered[161,206,207].

Besides the relatively high diagnostic yield and the importance of genetic counselling for future pregnancies and the wider family, there are several other reasons for recommending genetic testing in short children born SGA (see **Supplementary information 3**)**.**

Supplementary Information 8. Current list of genetic causes associated with SS and increased cancer risk (thus considered contra-indications for rhGH therapy)

rhGH treatment is not recommended in several disorders with a high predisposition to develop cancer, such as chromosomal breakage syndromes and DNA repair disorders[2]. Although rhGH therapy is indicated for short SGA children, it is essential to recognize that some of these children may have underlying cancer-predisposing conditions. Identifying such conditions is crucial to avoid potentially harmful treatments. Examples include (in alphabetical order, not exclusive): Ataxia telangiectasia, Bloom syndrome, Cartilage-hair hypoplasia, Cockayne syndrome, Costello syndrome, Dubowitz syndrome, Fanconi anemia, Mulibrey dwarfism, LIG4 deficiency, Louis-Bar syndrome, Neurofibromatosis type 1, Nijmegen breakage syndrome, PLK4 deficiency, Rothmund-Thomson syndrome, Seckel syndrome spectrum disorders, SLF2 deficiency, SMC5 deficiency, xeroderma pigmentosa, and XRCC4 deficiency[35].

Supplementary Information 9. Examples of clinical features derived from the medical history that may increase the likelihood of a genetic origin.

Developmental delay (DD) and/or intellectual disability (ID), neurological, psychiatric symptoms and behavior problems

In two overlapping cohorts[163,208], the diagnostic yield of exome sequencing appeared higher in short children with ID or DD, compared with those without ID/DD (81.8% *vs* 17.2%) and compared with the total cohort (70% vs 44%). However, the number of such patients was still limited (n=11[208]). Some genetic syndromes are associated with a specific developmental profile, such as severe expressive speech delay in Floating Harbor syndrome[209] and verbal dyspraxia in SRS caused by upd(7)mat[161]. Neurologic (e.g., seizures) or neurocognitive symptoms (e.g., autism spectrum disorder) are seen in association with a wide number of syndromic conditions including SS.

Genetic testing of neurodevelopmental disorders is considered good clinical practice irrespective of body stature[210].

Early feeding problems

Early feeding difficulties are reported in many genetic disorders [200]). Usually, feeding problems occur in early infancy and typically resolve by the age of 4-6 years and may be later associated with obesity in imprinting disorders (particularly PWS and Temple syndrome). Early feeding problems can be associated with poor suck due to hypotonia (e.g. in PWS and Temple Syndrome), oromotor dysfunction, gastroesophageal reflux, gastrointestinal dysmotility[211] or delayed gastric emptying[212,213]. The diagnostic yield of genetic disorders in short infants with feeding difficulties is unknown.

Hearing loss

Many skeletal dysplasias are associated with conductive deafness. Severe SS and

sensorineural deafness have been reported in patients with complete loss of function variants of *IGF1*[214,215].

Immune dysfunction

A history of recurrent infections may be associated with various SS syndromes, e.g., Artemis syndrome, Bloom syndrome, Cartilage-hair hypoplasia, DiGeorge syndrome, Kabuki syndrome, Rubinstein-Taybi syndrome, Schimke immuno-osseous dysplasia, X-linked agammaglobulinemia with GHD, various forms of GH insensitivity (*STAT5B*, *NFKB1*, *STAT3*, *QSOX2*), and *RGS10* variants[216,217,218,219,220,211].

Immune dysregulation (e.g. autoimmune thyroiditis, celiac disease, Crohn's disease, immune thrombocytopenic purpura, and autoimmune hemolytic anemia) is observed in RASopathies, Kabuki syndrome, Turner syndrome, and *STAT3* deficiency[221] or *STAT5B* variants[179,216,222,223].

Bleeding tendency

Noonan syndrome is the most common syndromic cause of SS to be associated with a bleeding diathesis[137], but SS associated with a bleeding disorder is observed in several other rare genetic defects.

Chronic kidney disease

Faltering growth can be the first sign of a chronic kidney disease, such as infantile cystinosis caused by a bi-allelic *CTNS* variant and juvenile nephronophthisis associated with multiple gene defects. High throughput sequencing identified the cause of kidney disease in approximately 1 in 4 individuals without a previously known cause of kidney disease. A family history of kidney disease was reported in 32% in children with P/LP variants[224].

Cardiac abnormalities

Cardiac abnormalities in short children are linked to various genetic disorders, including Turner syndrome[225], RASopathies[226,227], Kabuki syndrome[228] and Down syndrome[229]. The type of congenital heart defect can orient the diagnosis: for instance, pulmonary valve stenosis and hypertrophic cardiomyopathy in Noonan syndrome, bicuspid aortic valve in Turner syndrome, and conotruncal defects in 22q11 microdeletion syndrome.

Maternal history of recurrent miscarriages

A maternal history of recurrent miscarriages increases the likelihood of genetic defects in the offspring, including those encompassing SS[163]. Familial translocations might be the most common explanation in this situation – i.e. a child with an unbalanced translocation inherited from a parent with a balanced translocation. Variants in 'maternal effect' genes (eg: *NLRP2*, *NLRP5*) have been reported in mothers who have a history of recurrent miscarriage and/or children with multilocus imprinting disturbance (MLID), including loss of methylation at 11p15 (SRS) and /or 14q32 (Temple syndrome) (for review, see Mackay et al[23]).

Supplementary Information 10. Genetic testing of the short child presenting with information from family history associated with increased pre-test probability of a genetic cause

The most common mode of inheritance for monogenic SS is autosomal dominant. In 200 patients with suspected genetic SS investigated via exome sequencing, the overall diagnostic rate was 38%[42]. In those genes with causative variants, the primary mode of inheritance was autosomal dominant (65%). Of the remainder, 19% were autosomal recessive and 15% X-linked.

In a cohort of 102 children with ISS[60], 58 had familial SS (FSS). Of 17 pathogenic/likely pathogenic variants identified, 13 (76%) were in the FSS group, although the effect of FSS alone on diagnostic yield did not reach statistical significance (p=0.175).

Plachy et al.[10] reported the outcome of genetic testing (both retrospective and prospective) in 95 children with FSS who had been treated with rhGH. A monogenic cause, also present in the affected parent, was identified in 36 (38%). Of the 36 children with a monogenic cause of FSS, 29 (81%) had a causative gene variant expected to affect the growth plate.

Several autosomal dominant genes are now recognized to be associated with isolated SS with relatively high prevalence. These include *PTPN11*[230], *SHOX*[153], *NPR2*[126], *ACAN*[50], *IHH*[92] and *NPPC*[172]. Variants in these and other dominantly inherited genes may arise *de novo* and often have variable expression and penetrance.

Several genes, including *SHOX, ACAN* and *NPR2*, known to be associated with common dominant SS, have also been linked to autosomal recessive skeletal dysplasias. In one study, causative heterozygous variants in genes also known to cause recessive skeletal dysplasia were seen in 3.5%[42]. Furthermore, variants in genes affecting somatotrophs (*HESX1* or *POU1F1*) or the GH-IGF1 axis (*GH1, IGF1R, STAT5B*) can be associated with both dominant and recessive inheritance[231], complicating the attempts to assign causality and determine diagnostic yield for genes in this pathway.

Dominant inherited variants expressing a phenotype of SS only through paternal transmission or only through maternal transmission are in favor of an imprinting status of the gene involved. Several

genes, including *IGF2* and *CDKN1C,* known to be imprinted, have been linked to SRS: paternally transmitted for *IGF2*[232] and maternally transmitted for *CDKN1C*[233].

Consanguinity, as well as the presence of more than one affected sibling, increases the likelihood of an autosomal recessive disorder. One recent paper[234] described extensive genetic analysis in 42 children with SS from 34 consanguineous families. The diagnostic yield in this cohort was high (76% of families), particularly in those with additional clinical features: severe GH deficiency or insensitivity, microcephaly and syndromic SS. Most causative variants were homozygous (21/26). In another recent paper[235] a genetic cause of SS was elucidated in 31 of 51 (61%) children of consanguineous parents.

The range of autosomal recessive conditions which have been reported in association with isolated and syndromic SS is very wide. However, there are clues which can increase diagnostic yield. In the consanguineous cohort [234], a candidate gene approach (based on endocrine investigations) led to the diagnosis in all patients with a suspected GH-IGF1 axis defect. In addition, some conditions are more prevalent in specific ethnic populations due to founder effects. One example is a recurrent *GHR* splice variant [c.594A>G, p.V199_M208 del, (rs121909360) previously known as E180splice] causing GH insensitivity syndrome (Laron syndrome), which is common in both Ecuador and the Sephardic Jewish community, likely due to emigration from the Iberian Peninsula to Central America[236].

Furthermore, in children where SRS is suspected but the child presents with a history of consanguinity or evocative clinical signs, rarer recessive diagnoses such as 3M syndrome, Mulibrey Nanism and Bloom syndrome need to be considered[161]. Such diagnoses have also to be considered when parents are not consanguineous, for example if parents carry a different variant in the same gene, leading to compound heterozygous pathogenic variants.

Supplementary information 11. Examples of anatomical abnormalities that can be observed on a radiograph of the hand and wrist in certain cases of genetic short stature

Key findings associated with genetic causes of SS include the following examples:

- Madelung deformity, particularly triangularization of the distal radial epiphysis and radiolucency of the medial radius, malpositioned lunate between ulna and radial epiphysis, associated with *SHOX* haploinsufficiency[237].
- Shortening of the middle phalanx (second and fifth finger) with cone-shaped epiphyses, associated with IHH haploinsufficiency[92]
- Short metacarpals and cone-shaped epiphyses, linked with *NPR2* haploinsufficiency[238]
- Short metacarpals (especially the 4th and 5th) seen in *GNAS* defects, including pseudohypoparathyroidism[239] or Turner syndrome
- Clinodactyly and a short fifth finger, observed in SRS and SGA[161]
- Various types of brachydactyly syndromes observed in heterozygous defects of several genes (e.g., *IHH*, *NPR2*, *FGFR3*)[87]
- SS with an age appropriate or advanced bone age (e.g., *ACAN* defect, Pseudohypoparathyroidism 1A)[48,240]
- SS with multiple exostoses (e.g., *EXT1* and *EXT2* pathogenic variants)[241]

Supplementary information 12. Laboratory screening as part of the initial assessment of the short child

In this document we propose an annotated list of laboratory measurements built upon a previous report[194].

Hematological screening is included since anemia and macrocytosis can suggest a genetic hemoglobinopathy, e.g. Fanconi anemia[242]. Autoimmune cytopenia in short children could be related to genetic syndromes such as Kabuki syndrome[216]. Examples of secondary growth disorders associated with anemia include celiac disease and inflammatory bowel disease (IBD).

Endocrine screening usually includes serum FT4, TSH and insulin-like growth factor 1 (IGF-1). In some centers this is combined with IGFBP-3 at screening, while in other centers assessment of serum IGFBP-3 is added to a repeat serum IGF-1 determination. A decreased serum IGF-1 in a short child suggests GHD or GH insensitivity[243] and usually leads to further testing of the GH-IGF-1 axis (e.g., GH stimulation testing, GHST). In case of a combination of a low serum IGF-1, low GH peak at GHST and central hypothyroidism, congenital hypopituitarism is suspected[244] and should lead to further testing of pituitary function (pituitary-adrenal axis, pituitary-gonadal axis and prolactin). In a child with a low IGF-1 and normal or increased GH peak at GHST, further genetic testing is needed to detect a *GH1* or *GHSR* variant (associated with a normal GH sensitivity) or one of the syndromes characterized by GH insensitivity, e.g., a GH-receptor gene (*GHR*) variant (Laron syndrome) or a mutation in the GH post-receptor signaling pathway[245], e.g., a genetic variant in *STAT5B*, *IGFALS* or *IGF1*. A serum IGF-1 in the upper half of the reference range or above in a short child can be caused by an IGF1-receptor (*IGF1R*) deletion or variant[246], a *PAPPA2* variant[6], SRS, Temple syndrome or Floating-Harbor syndrome[247]. If an *IGFALS* defect is likely, serum ALS can be tested in a specialized laboratory.

Biochemical screening may be limited to serum sodium, potassium, creatinine, calcium, phosphorus, alkaline phosphatase, and a blood gas or bicarbonate in children <3 years of age[194]. Metabolic acidosis and hyper/hypokalemia can be observed in patients with renal tubular acidosis[248]. Alterations in serum calcium, phosphate and/or parathyroid hormone levels may indicate a genetic mineral metabolism disorder such as hypoparathyroidism, pseudohypoparathyroidism, or hypophosphatemic rickets[249]. Phosphate concentrations are higher in children than adults, and an age based normal range should be used. A concentration of < 1.0 mmol/L in growing children is always abnormal. Patients with 22q11.2 deletion syndrome may present with hypocalcemia, cytopenia or GH deficiency[250]. In several countries, liver function tests are part of laboratory screening; increased liver enzymes, coupled with an elevated lipid profile, metabolic acidosis and hypoglycemia could indicate a glycogen storage disease[251] . However, the extreme rarity of these disorders in children with isolated SS can be a reason to omit these determinations from the screening panel for financial reasons[194].

Urinalysis has been advised in many textbooks as part of the screening. Though the level of evidence is low [194], in many centers a urine dipstick analysis is carried out for proteinuria and glycosuria. Theoretically, abnormalities in acid-base homeostasis and electrolytes, as well as abnormal urinalysis, can be found in chronic renal disease of which some have a known genetic cause[252].

Supplementary Table 2 presents a list of potential components of laboratory screening that can be considered.

Supplementary Table 2. Potential components of laboratory screening

Category	Test	Clue for primary growth disorder	Clue for secondary growth disorder	Comment (e.g. efficacy/cost)
Hematology	Hb, Ht, erythrocytes, cell indices	Fanconi anemia, Kabuki syndrome	Haemoglobinopathy, celiac disease, IBD	
	Inflammation markers (leukocytes, CRP, ESR)		IBD	Possibly limit to >10 yrs if BMI SDS decreases
Biochemistry	Na, K, creatinine		Renal disorder	
	Ca, P, Alkaline phosphatase, PTH		Metabolic bone disorders	
	Blood gas (acid-balance)		Renal tubular acidosis	Possibly limit to age<3 yrs
	Liver function tests (AST and ALT or full liver panel		Glycogen storage disease	
	Glucose			
Immunology	Anti-TTG IgA, total IgA		Celiac disease	
Endocrine	IGF-1		Low: GHD, GHI, malnutrition High: IGF1R haploinsufficiency	Less sensitive than IGFBP-3 if <3 yrs
	IGFBP-3		GHD, GHI	Less sensitive than IGF-1 if >3 yrs.
	FT4, TSH		Hypothyroidism	
Urinalysis	Proteinuria, glucosuria (dipstick)		Renal disorders and urinary tract infections	
Feces	Calprotectin		IBD	[a]Possibly limit to >10 yrs if BMI SDS decreases or in the presence of GI symptoms
Genetic	Karyotype, microarray, ES, GS DNA methylation	Turner syndrome, CNVs, uniparental disomy and monogenic causes epigenetic disorders		Traditionally tested by karyotyping all short girls. With newer techniques higher diagnostic yield

Abbreviations: BMI, body mass index; GHD, growth hormone deficiency; GHI, growth hormone insensitivity; IBD, inflammatory bowel disease; ES, exome sequencing; GS, whole genome sequencing

Since IBD is rare before the age of 10 years, a previous guideline[194] advised to measure feces calprotectin from that age in children with decreasing BMI SDS. Reference data are available from 4-16 years[253].

Supplementary Information 13. Genetic causes of congenital hypopituitarism

Supplementary Table 3 summarizes phenotypes of congenital hypopituitarism (CH) and their population frequency and lists the most commonly identified genes associated with each of these phenotypes. **Supplementary Table 4** summarizes the genes currently associated with CH and their mode of inheritance.

Variants within the same gene, usually involved in early hypothalamo-pituitary development, may give rise to variable clinical manifestations of CH. For example, variants in *GLI2*, which is one of the most frequently identified genes associated with CH, may be associated with isolated growth hormone deficiency (IGHD), combined pituitary hormone deficiency (CPHD), and holoprosencephaly (HPE), respectively[254]. The severity and manifestation of CH in some patients may be due to oligogenicity, whereby variants in more than one gene are required for phenotypic expression. We therefore recommend caution in interpretation of genetic findings that are not recessively inherited, particularly those variants that are variably penetrant, and in the communication of these findings to families for genetic counselling.

Other genes may be associated with more specific clinical features, such as *POUIF1* recessive and dominant variants which are associated with GH, TSH and prolactin deficiencies, with a small but structurally normal pituitary gland on imaging[255,256].

ES and GS have led to the identification of variants in a broad range of genes involved in transcription, translation, signaling, splicing, cilia formation and function, and more recently, fatty acid metabolism[244,257]. While current literature suggests a low overall frequency of functionally significant genetic variants (10%)[258], with some studies showing higher frequencies of variants in some genes depending on the cohort of patients screened, it is likely that this approach will lead to the identification of further novel genes implicated in this clinical presentation.

Supplementary Table 3: Congenital hypopituitarism phenotypes and their population frequency

Congenital hypopituitarism phenotype	Frequency	Description	Genes associated
Combined pituitary hormone deficiency (CPHD) without midline defects	1/4000	Deficiencies in 1 or more of the 7 pituitary hormones: GH, TSH, LH, FSH, PRL, ACTH, AVP	*LHX3, LHX4, PROP1, POU1F1, HESX1, RNPC3, FGF8, SOX3, OTX2, GLI2, ANOS1, AVP*
Isolated growth hormone deficiency (IGHD)	1/4000 - 1/10,000	The most common isolated deficiency - short stature, delayed growth velocity and skeletal maturation	*GH1, GHRHR, RNPC3, HESX1, OTX2, SOX3, POU1F1*
Septo-optic dysplasia (SOD)	1/10,000	Optic nerve hypoplasia (ONH), midline neuroradiological abnormalities. Structural HP abnormalities with endocrine deficits	*SOX2, OTX2, HESX1, FGF8, FGFR1, ANOS1, TCF7L1*
Holoprosencephaly (HPE)	1/10,000 - 1/20,000	Incomplete cleavage of the prosencephalon, affecting both the forebrain and the face: Alobar (no forebrain division) Semilobar (some separation) Lobar (complete separation) Microcephaly, hypotelorism, a single central maxillary incisor, cleft lip and/or palate	*SHH, GLI2, ZIC2, SIX3, TGIF1, PCTH1, FGF8* Sub-microscopic deletions at a number of loci

Abbreviations: ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; FSH, follicle-stimulating hormone; GH, growth hormone; HP, hypothalamo-pituitary; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone;

Supplementary Table 4. Genes associated with congenital hypopituitarism*

Gene with pathogenic variants	Phenotype	Inheritance
ANOS1	HH/KS; SOD	X-linked
ARNT2	CPHD, congenital abnormalities of the kidneys and urinary tract	Recessive
CDON	PSIS	Dominant
EIF2S3	GHD, TSHD, Glucose dysregulation, MEHMO syndrome	X-linked
FASN	Hypopituitarism, Hypoparathyroidism, Sensorineural hearing loss, retinal dystrophy	De Novo
FGF8	HH/KS; HPE	Dominant/Recessive (HPE)
FGFR1	HH/KS, SOD	Dominant
FOXA2	CPHD, HI, childhood-onset diabetes, choroidal coloboma, biliary atresia (cardiac/endoderm-derived organ abnormalities)	Dominant
GH1	IGHD Type IA	Recessive
	IGHD Type IB	Recessive
	IGHD Type II	Dominant
GHRHR	IGHD Type IB	Recessive or Dominant (rare)
GHSR	Isolated partial GHD	Dominant
GLI2	HPE, IGHD/CPHD, polydactyly, single central incisor	Dominant: haploinsufficiency
GPR161	PSIS	Recessive
HESX1	IGHD, CPHD, SOD	Dominant or Recessive
IFT172	GHD, retinopathy, metaphyseal dysplasia, renal failure (ciliopathies)	Compound heterozygous
IGSF1	TSHD, hypoprolactinemia, transient GHD; usually with macroorchidism	X-linked, (female carriers may have TSHD)
KCNQ1	GHD, maternally inherited gingival fibromatosis	Dominant
LHX3	CPHD, short neck with limited rotation	Recessive
LHX4	CPHD, Chiari malformation, cerebellar abnormalities, respiratory distress	Dominant or Recessive
L1CAM	GHD, arthrogryposis, hydrocephalus	X-linked
MAGEL2	GHD, ACTHD, arthrogryposis (joint contractures), AVPD, Schaaf-Yang syndrome (SHFYNG)	Maternally imprinted or de novo
OTX2	IGHD, CPHD, SOD, anophthalmia/microphthalmia, retinal dystrophy	Dominant: haploinsufficiency or dominant negative
PCSK1	AVPD, IAD, GHD, TSHD, malabsorption	Dominant, Compound heterozygous
PNPLA6	Oliver–McFarlane and Laurence–Moon syndrome; GH and gonadotrophin deficiencies	Recessive
POMC	IAD; early-onset obesity and red hair pigmentation	Recessive
POU1F1	GHD, TSHD and ACTHD	Dominant or Recessive
PROKR2	HH/KS	Recessive

PROP1	CPHD, pituitary tumors	Recessive
RAX	Anophthalmia/microphthalmia, AVPD, CPHD, and Cleft Palate	Recessive
RNPC3	IGHD/CPHD	Recessive
ROBO1	PSIS	Dominant
SOX2	HH, anophthalmia/microphthalmia, learning difficulties, hypothalamo-pituitary tumors	Dominant
SOX3	GHD, CPHD, absent infundibulum, persistent craniopharyngeal canal	X-linked GOF or LOF
TBC1D32	CPHD, GHD, oral-facial-digital syndrome (OFDS)	Recessive
TCF7L1	SOD	Dominant

*This list contains genes that are associated with GH deficiency. It does not include isolated deficiencies of other pituitary hormones, i.e. TSH, LH, FSH, PRL, ACTH, AVP and prolactin.

Abbreviations: ASD, autism spectrum disorder; AVPD, arginine vasopressin deficiency; CPHD, combined pituitary hormone deficiency; GHD, growth hormone deficiency; HH, hypogonadotropic hypogonadism; HI, congenital hyperinsulinism; HPE, holoprosencephaly; IAD, isolated adrenocortical deficiency; IGHD, isolated growth hormone deficiency; KS, Kallmann syndrome; MEHMO, mental retardation, epileptic seizures, hypogonadism with hypogenitalism, microcephaly and obesity; PSIS, pituitary stalk interruption syndrome; SOD, septo-optic dysplasia; TSHD, thyroid-stimulating hormone deficiency.

Supplementary Information 14. Genetic causes of other disorders in the GH-IGF-1 axis

Supplementary Table 5 shows a summary of the clinical features of syndromes leading to complete or partial insensitivity to GH or IGFs**.** Genes along the GH-IGF axis documented to be associated with growth failure (height SDS below -2.0) and GH insensitivity are listed. Birth size appropriate for gestational age (AGA) indicates post-natal growth failure; birth size not AGA ("-") indicates growth failure that starts in utero. Post-natal growth failure ranges from severe ("+") to mild/moderate ("-") within each gene, depending on the impact of the genetic defect on structure and function of the protein encoded by the gene. Key genes in which defects perturb response to GH and/or production of IGF-1, include the growth hormone receptor (*GHR*), defects in GH signal transduction (*STAT5B*), IGF-1 production (*IGF1*; *QSOX2*), IGF-1 transport (*IGFALS*), IGF-1 bioavailability (*PAPPA2*), and IGF-1 action (*IGF1R*). *STAT3* and *IGF2* defects lead to growth failure which is independent of GH actions and IGF-1 production. Genetic defects along the GH-IGF axis can be associated with multiple co-morbidities which are indicated as "+" or "-", but not listed as co-morbidities vary widely, depending on the defective gene.

Supplementary Table 5. Summary of phenotypic and biochemical features in the range of genetic defects along the GH-IGF axis causing GH insensitivity.

	GHR		*STAT5B*		*STAT3* (GOF)	*IGF1*		*IGF2*	*IGFALS*	*PAPPA2*	*IGF1R*		*QSOX2*
	AR	**AD**	**AR**	**AD**	**AD**	**AR**	**AD**	**ADp**	**AR**	**AR**	**AR**	**AD**	**AR**
Birth - AGA	+	+	+	+	-/+	-	-/+	-	+/-	+/-	-	-	+
Severe growth failure	+	+/-	+	+/-	+/-	+	+/-	+	-	-	+	-/+	+/-
Midface hypoplasia	+	+/-	+/-	+/-	-	-	-	-	-	-	+	-/+	-
Other facial dysmorphism	-	-	-	-	-	+	-	+	-	-	+	-/+	-/+
Deafness	-	-	-	-	-	+/-	+/-	-	-	-	+/-	-/+	-
Microcephaly	-	-	-	-	-	+	-	-	-	+/-	+	-/+	-
Bone age delay	+	+	+	+	+/-	+	-	+	+	+	+	+	-
Intellectual delay	-	-	-	-	-	+	-	-	-	-	+	-/+	-/+
Developmental delay	-/+	-/+	-/+	-/+	-	+	+	-/+	-	+	+	-/+	-/+
Puberty delay	+	-	+	+/-	na	-	-	-	+	+	-/+	-/+	na
Immune deficiency	-	-	+	+	+	-	-	-	-	-	-	-	+
Eczema	-	-	+	+	+/-	-	-	-	-	-	-	-	+
Hypoglycemia	-/+	-	-	-/+	-	-	na	na	-	-	-	-	-
Hyperinsulinemia	-	-	-	-	-	+/-	na	na	+	+	-/+	-/+	-
IGF-1	↓	↓/n	↓	↓/n	↓/n	↓/n	↓/n	n/↓	↓	↑	↑	n/↑	n/↓

IGFBP-3	↓	↓/n	↓	↓/n	↓/n	n	n	n	↓	↑	n/↑	n	n
IGFALS	↓	↓/n	↓	↓/n	↓/n	n	n	n	↓	↑	↑	n	na
GH	↑	↑/n	↑	↑/n	↓/n	n/↑	n/↑	n	↑	↑	↑	n/↑	n/↑
GHBP deficiency	+/-	-	-	-	-	-	-	-	-	-	-	-	na
Other comorbidities	+	-	+/-	-	+	+	-	+	-	-	+	-/+	+

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Supplementary information 15. Examples of epigenetic processes that stably alter gene expression patterns and/or transmit the alterations at cell division

Cytosine methylation

The human genome harbors more than 100 genes that are expressed from either the paternal or the maternal allele only. DNA methylation is the mainstay of establishing imprinting marks on either paternal or maternal alleles[259]. One feature of the complexity of genetic imprinting is that it works in a tissue-specific manner. For example, Gs-alpha from the guanine nucleotide-binding protein, alpha stimulating (GNAS) locus on chromosome 20q13 is only maternally expressed in the renal proximal tubule, thyroid, pituitary, and ovary and certain endocrine tissues, while it is expressed biallelically in most other tissues[260].

Certain genes are either biallelically expressed or imprinted in a time dependent manner. For example, *IGF2* is biallelically expressed in the fetal brain during the first trimester while it is expressed predominantly from the paternal allele in other tissues[261]. In adulthood, some brain regions (i.e. hypothalamus and globus pallidus) show paternal monoallelic expression of *IGF2*, whereas others (i.e. pons) show biallelic expression of *IGF2*[262].

Finally, individual genes often produce several transcripts[263], which can show either imprinted or non-imprinted expression patterns. Silver-Russell syndrome, Temple syndrome, Prader-Willi syndrome, and pseudohypoparathyroidism (PHPIa and PPHP) are imprinting disorders characterized by severe SS.

Post-translational modification of histone proteins and remodeling of chromatin

Histones undergo extensive posttranslational modifications, including methylation, acetylation, and phosphorylation which affects chromatin structure and gene expression. For example, Sirtuin 6 (SIRT6) is a NAD+-dependent histone deacetylase that targets acetylated H3K9 and

acetylated H3K56 and is expressed in proliferating and hypertrophic chondrocytes in the growth plate. Sirt6 knockout mice show an increased resting zone thickness and reduced proliferative and hypertrophic zones[264].

RNA-based mechanisms

MicroRNAs are short, non-coding RNAs of approximately 22 bases that regulate gene expression and are involved in many processes including chondrocyte differentiation in the growth plate. A skeletal dysplasia has been associated with a gain-of-function mutation in the skeletal specific miRNA-140 in two unrelated families[265]. The clinical implications of fine epigenetic tuning of growth plate physiology are still largely unknown and the introduction of epigenetics and transcriptomics in the evaluation of children with SS of unknown origin will expectedly elucidate the underlying cartilage molecular abnormalities leading to a conclusive diagnosis and a better categorization of SS conditions. Besides microRNAs, long non-coding RNAs (lncRNAs) may also play a role in the regulation of linear growth[266].

We predict that in the coming decade the rapidly developing knowledge of the genetic and epigenetic causes of SS will lead to more accurate molecular diagnosis and personalized therapies.

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