Current Pediatric Reviews, 2019, *15*, 10-21

REVIEW ARTICLE

Tall Stature: A Challenge for Clinicians

Beatriz Corredor[1], Mehul Dattani[1,2], Chiara Gertosio[3] and Mauro Bozzola[3,4,*]

[1]*Department of Endocrinology, Great Ormond Street Hospital for Children, WC1N 1EH, London, UK;* [2]*Section of Genetics and Epigenetics in Health and Disease, Genetics and Genomic Medicine Programme, UCL GOS Institute of Child Health, London, UK;* [3]*Department of Internal Medicine and Therapeutics, Pediatrics and Adolescent Care Unit, University of Pavia, Strada Nuova 65, 27100 Pavia, Italy;* [4]*Onlus Il bambino e il suo pediatra, via XX Settembre 28, 28066 Galliate (Novara), Italy*

ARTICLE HISTORY

Received: January 16, 2018
Revised: October 12, 2018
Accepted: October 29, 2018

DOI:
10.2174/1573396314666181105092917

Abstract: Clinicians generally use the term "tall stature" to define a height more than two standard deviations above the mean for age and sex. In most cases, these subjects present with familial tall stature or a constitutional advance of growth which is diagnosed by excluding the other conditions associated with overgrowth. Nevertheless, it is necessary to be able to identify situations in which tall stature or an accelerated growth rate indicate an underlying disorder. A careful physical evaluation allows the classification of tall patients into two groups: those with a normal appearance and those with an abnormal appearance including disproportion or dysmorphism. In the first case, the growth rate has to be evaluated and, if it is normal for age and sex, the subjects may be considered as having familial tall stature or constitutional advance of growth or they may be obese, while if the growth rate is increased, pubertal status and thyroid function should be evaluated. In turn, tall subjects having an abnormal appearance can be divided into proportionate and disproportionate syndromic patients. Before initiating further investigations, the clinician needs to perform both a careful physical examination and growth evaluation. To exclude pathological conditions, the cause of tall stature needs to be considered, although most children are healthy and generally do not require treatment to inhibit growth progression.

In particular cases, familial tall stature subject can be treated by inducing puberty early and leading to a complete fusion of the epiphyses, so final height is reached. This review aims to provide proposals about the management of tall children.

Keywords: Tall stature, proportionate syndromes, disproportionate syndromes, challenge, clinicians, puberty.

1. INTRODUCTION

Normal growth is one of the fundamental characteristics of childhood and adolescence, of which all clinicians should be aware. Drop from a normal pattern of growth can be the first sign of a wide variety of disease processes, including endocrine and non-endocrine disorders [1]. Postnatal growth occurs in four separate phases. In each of them, the pre-eminent influence on linear growth is different. The first is the intrauterine phase, depending on maternal factors, nutrition and placental function. The second is the phase occurring mainly during the first 2-3 years of post-natal life and is influenced mainly by nutritional factors, although Growth Hormone (GH) plays an increasingly important role from the age of 6 months onwards. The third phase of growth is the childhood phase, regulated mainly by growth hormone and thyroid hormones, however other hormones such as thyroxine, adrenal androgens, sex steroids, glucocorticoids, ghrelin, leptin and insulin contribute to growth through their interaction with the GH- Insulin-Like Growth Factor I (IGF-1) axis.

Lastly, the pubertal growth spurt is predominantly under control of the synergistic action of the GH-IGF-I axis and pubertal steroids [2]. In general terms, human growth is influenced by environmental, genetic and hormonal factors.

2. TALL STATURE DEFINITION

Conventionally, tall stature is defined as a height more than two standard deviations (SD) above the mean for age, *i.e.* greater than the 97th percentile for sex and age [3, 4]. It is important to take into consideration the ethnic background of the patient in order to utilize the appropriate growth charts [3, 4]. Secondly, parental height is required to calculate the target height percentile and evaluate height prediction. A child can also be defined tall in relation to his/her Midparental Height (MPH), if his/her height is more than two SD above the MPH (height SD-MPH SD >2.0) [4].

*Address correspondence to this author at the Department of Internal Medicine and Therapeutics, Pediatrics and Adolescent Care Unit, University of Pavia, Strada Nuova 65, 27100 Pavia, Italy; Tel: +39 339 5469483; E-mail: mauro.bozzola@unipv.it

1875-6336/19 $58.00+.00

Referrals to a pediatric endocrinologist for an assessment of a child with tall stature are much less frequent than for short stature. This is because tall stature has a wider social acceptance.

3. DIAGNOSTIC APPROACH: OVERVIEW

Although most tall children are healthy, clinicians should exclude any pathological cause in these subjects and rule out chromosomal, genetic and endocrine disorders [3]. In the first evaluation, height, growth velocity, weight, head circumference and body mass index measurement should be performed. Additional information that would be of diagnostic value includes the birth data (weight, length, and head circumference), family history including the heights of both parents and pubertal timing of the parents (age of the mother at first menstruation and age of the father at growth pubertal spurt) and developmental history. An important aspect in the evaluation of the growth of a child is the analysis of the evolution of height over time; that is, construction or reconstruction from the data provided by the parents of a graph of height and weight for age. It can enable further understanding of the time of commencement of the alteration in the trajectory of growth, and its possible etiology. Additionally, the assessment of body proportions is also critical and should include the following measurements:

- Lower body segment: Sub-Ischial Leg Length (SILL), distance from the top of pubic symphysis to the floor, also calculated by detracting sitting height from standing height.
- Upper body segment: sitting height.
- Arm span: Measurement of the length from one end of a patient's arms (measured at the fingertip) to the other with the arms raised parallel to the ground at shoulder height.
- Body proportion measurements must be evaluated in relation with the patient's age [1].
- Head circumference, a measure > + 2 SD associated with tall stature could help clinician to identified overgrowth syndrome such as the most common syndrome Beckwith-Wiedemann Syndrome, Sotos, and Weaver syndrome [5].

Clinical examination should include examination for cardiovascular abnormalities such as a pathological heart murmur, evidence of thyrotoxicosis, skin anomalies, skeletal malformations such as pectum excavatum, facial dysmorphism and abnormalities of the genitalia, which could be of diagnostic help. A careful medical history may indicate a syndromic cause: lenticular dislocation may address to homocystinuria or Marfan syndrome, developmental abnormalities may be associated with other syndromes including Beckwith-Wiedemann, Klinefelter, Triple X, fragile X, homocystinuria, Simpson-Golabi-Behmel, Soto and Weaver syndromes (Table **1**).

Table 1. Characteristics of the main overgrowth syndromes.

Type	Syndrome	Prenatal Onset Overgrowth	Main Features
Proportionate	Sotos syndrome	Yes	Dolichocephaly, macrocephaly, prominent forehead, down-slanting palpebral fissures, mild hypertelorism, broad range of learning disabilities.
	Weaver syndrome	Yes	Macrocephaly, broad forehead, large ears, hypertelorism, hypotonia, loose skin, deep-set nails, prominent wide philtrum and micrognathia. camptodactyly
	Fragile X syndrome	No	Long and narrow face, protruding ears, flexible fingers, hypotonia and macroorchidism. Intellectual disability
	Simpson-Golabi-Behmel syndrome	Yes	Coarse facial features, macrostomia, macroglossia, short and broad hands with feet dysplastic nails, neonatal hypoglycaemia, cutaneous syndactyly, talipes equinovarus, pectus excavatum, postaxial polydactyly and supernumerary nipples. Increased risk of neoplasms. Mental development often normal.
Disproportionate	Marfan syndrome	No	Hyperextensible joints, long limbs with narrow hands and long slender fingers, arm span > height, lower segment > upper segment. Cardiac and ophthalmological abnormalities. Normal intelligence.
	Homocystinuria	No	Marfan phenotype. Learning difficulties. Predisposition to thromboembolism.
	Klinefelter syndrome	No	Disproportionately long limbs, poorly developed secondary sexual characteristics, mild learning difficulties
	Beckwith-Wiedemann syndrome	Yes	Macrosomia, hemihypertrophy, macroglossia, abdominal wall defects, neonatal hypoglycaemia. Increased risk of neoplasms.
	Triple X (XXX) syndrome	No	Clinodactyly and epicanthal folds. Intelligence within the normal range
	Proteus syndrome	Yes	Macrocephaly, epidermal nevi, vascular malformations, large hands and feet with macrodactyly. Normal psychomotor development

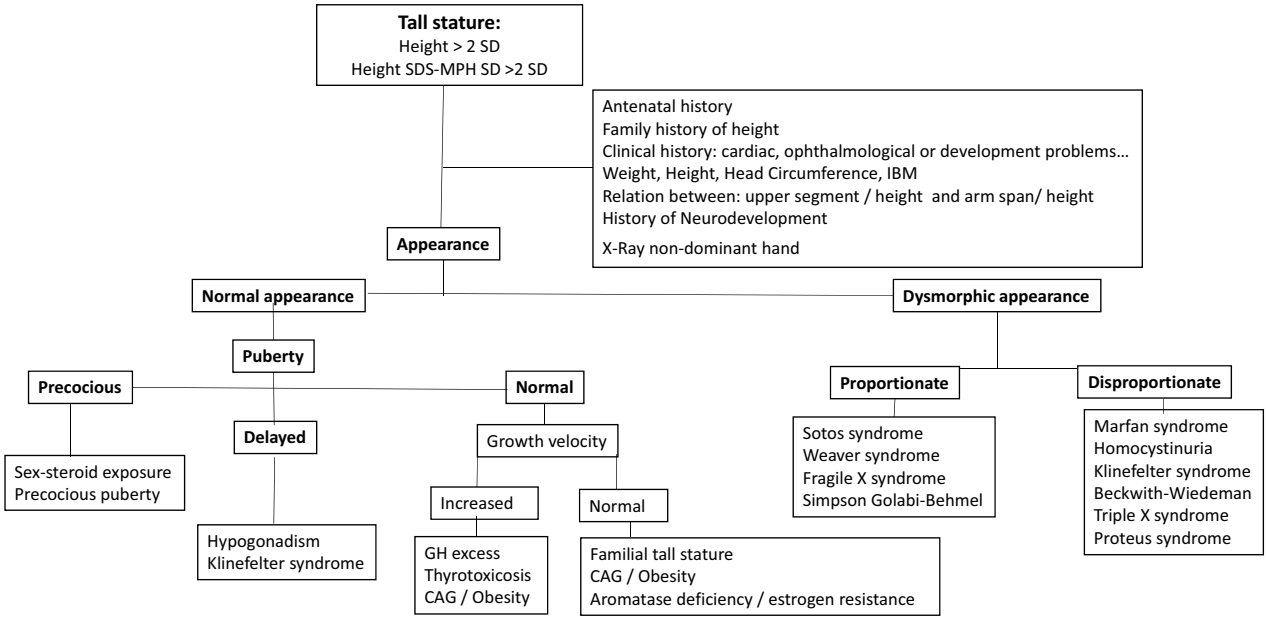

Fig. (1). Diagnostic approach to tall children. SD: Standard Deviations, MPH: Midparental Height, IBM: Body Mass Index, CAH: Congenital Adrenal Hyperplasia, GH: Growth Hormone, CAG: Constitutional Advance of Growth.

The knowledge of the degree to which a child's skeleton has matured over time gives the physician a window into the true physical developmental age of that child. An X-ray of the left hand should be used to evaluate the skeletal maturity of tall children and it is useful to predict adult height. Basically, the clinical history, physical examination and the evaluation of the growth on specific charts may be sufficient to conclude whether the cause of tall stature is benign [1, 4, 6, 7].

4. DIAGNOSTIC APPROACH: Search for the Etiology

No evidence-based guideline has been reported about referral criteria, diagnostic process and surveillance for tall stature subjects. A height beyond +2 SD from the genetic target height or an acceleration of growth needs careful investigation. A careful physical evaluation allows the categorization of tall subjects into two groups: those with a normal appearance and those with an abnormal appearance with dysmorphism. In the case of children with a normal appearance, clinicians must evaluate the growth rate and the stage of puberty (Fig. **1** and Table **2**).

4.1. Normal Variant Tall Stature

Non-pathological tall stature may be considered as a normal variant, probably due to multiple gene variants with a positive effect on growth [7].

4.1.1. Familial Tall Stature

The subject shows a normal growth rate with normal Body Mass Index (BMI), and grows in accordance with the MPH or with the tallest parent in cases of a big discrepancy between parental heights. Therefore, an exhaustive familial history of tallness in one or both parents is essential in order not to omit a diagnosis. Bone age approximates to chronological age; however, an advanced bone age may be ob-

Table 2. Etiology of tall stature.

Normal Variant	**Familial Tall Stature** **Constitutional Advance of Growth**
Endocrine or secondary growth disorders	Obesity Aromatase deficiency Estrogen receptor α deficiency Precocious puberty GH/IGF-1 excess Thyrotoxicosis McCune-Albright Syndrome
Syndrome	
Proportionate	Sotos syndrome / Sotos-like syndrome
	Tatton-Brown-Rahman Syndrome
	Weaver syndrome / Weaver-like syndrome
	Fragile X syndrome
	Susceptibility to Autism 18
	Simpson-Golabi-Behmel syndrome
Disproportionate	Marfan syndrome
	Homocystinuria
	Klinefelter syndrome
	Beckwith-Wiedemann syndrome
	Triple X (XXX) syndrome
	Proteus syndrome

served, and there is a normal age of onset of puberty related to tall stature. This is the most frequent reason for referral for tall stature and is usually evident by 4 years of age. Parental anxiety is common mainly in girls. If the history is suggestive for familial tall stature and the physical examination is normal, laboratory tests may be not required. Bone Age (BA) is indicated to predict adult height, which serves to discuss with the family and decide the management of the subject.

4.1.2. Constitutional Advance of Growth (CAG)

Tall children without pubertal signs and an increase in growth rate may have a diagnosis of constitutional advance of growth. It is the mirror image of constitutional delay of growth and puberty. They show an accelerated growth after birth and reach their peak centile by 2-4 years of age, and then they grow along the 97th centile until 9 years of age, when their growth rate drops to the 50th percentile [4, 8, 9]. These children are different from those with familial tall stature since they are born with an above average birth length and they are tall in comparison with their parental height with coincident BA advance, but who therefore would be expected to end up with a normal adult height for the parents [3, 6, 9]. Sometimes CAG can be associated with obesity. It has been postulated that it could predict the late onset of childhood obesity in non-obese children [9, 10]. Puberty often occurs earlier in these children. In CAG children, increased Insulin-like Growth Factor (IGF)-II secretion and IGFs/IGF Binding Proteins (BPs) molar ratio prior to puberty may be considered as a possible mechanism of tall stature [4, 11].

4.2. Endocrine or Secondary Growth Disorders

4.2.1. Obesity

Body Mass Index (BMI) should be calculated from the height and weight and then plotted on BMI charts. Obese children are often taller than controls average for their age. If bone maturity is also advanced, puberty may occasionally occur earlier [4, 12]. However, their final height will usually be normal. Obesity probably influences growth through hormonal pathways, such as GH/IGF1/ghrelin/ insulin and leptin/GnRH, but the exact mechanisms are still unclear [7].

4.2.2. Prolonged Growth Due to Delayed Fusion of Growth Plate

This comprises a heterogenous group of diseases, including hypogonadism, aromatase deficiency and estrogen resistance. In contrast to precocious puberty, these patients do not show a growth spurt due to the absence of, or resistance to sex steroids. Growth velocity is slow but, as the epiphyseal plate fusion retarded, these patients keep growing into adulthood, developing tall stature with eunuchoid proportions (increased arm span and upper-to-lower segment ratio) only later in life [7].

4.2.3. Aromatase Deficiency

Aromatase deficiency is a rare condition with autosomal recessive inheritance. In males the diagnosis is made later in adulthood in presence of tall stature, incomplete epiphyseal closure, eunuchoid proportions of the skeleton, osteoporosis and obesity [4]. Estrogen concentrations are low, while Follicle Stimulating Hormone (FSH), luteinizing hormone (LH) and testosterone are slightly increased. The most interesting features are the presence of steatohepatitis, insulin resistance with acanthosis nigricans and high concentrations of triglycerides. Low-dose estrogen administration allows completion of bone maturation after the complete closure of the epiphyses and thereafter leads to an increase in bone density. More than 30 mutations (point mutations, deletions and insertions) have been found in the gene *CYP19A1* encoding for the human P450 aromatase enzyme located in the membrane of the endoplasmic reticulum of several tissues, such as gonad, brain, placental syncytiotrophoblast, breast, and adipose tissue, and which catalyzes biosynthesis of estrogens from androgens [4, 13].

4.2.4. Estrogen Receptor α (ERα) Deficiency

Rare cases of estrogen receptor α (ERα) deficiency have been reported with considerable phenotypic similarity to that of aromatase deficiency with tall stature and eunuchoid body proportions. The patients present a constant linear growth into adulthood due to incomplete epiphyseal closure and osteoporosis in males [4, 14], and absent breast development with markedly elevated serum estrogen concentrations and multicystic ovaries in females [4, 15]. To date, the rare estrogen-resistant patients have had homozygous point missense mutations in the ERα gene [14, 15].

4.2.5. Precocious Puberty

Central Precocious Puberty (CPP) is defined by the presence of breast tissue (Tanner stage 2) before eight years in females and enlargement of testicular volume (>4 ml) before the age of 9 years in males, associated with signs of secondary sexual characteristics, rapid growth, tall stature, and an advanced bone age. A gonadotropin-releasing hormone (GnRH) stimulation test is required to confirm the diagnosis of central precocious puberty, and a therapy with GnRH analogues should be promptly started in order to inhibit pituitary gonadotropin secretion. The presence of pubertal signs may also suggest other forms of puberty that are gonadotropin-independent, with high steroid, androgen or estrogen secretion. [4] Causes include congenital adrenal hyperplasia which may be salt-losing or simple-virilising due to *CYP21A2* mutations as well as 11-beta hydroxylase deficiency due to *CYP11B1* mutations, secondary to an ovarian cyst in females or, more rarely to virilising adrenal, testicular or ovarian tumors. Congenital adrenal hyperplasia is mainly (90% of cases) due to a 21-hydroxylase deficit encoded by the gene *CYP21A2* and tall stature, premature pubarche, irregular menstruation, acne, hirsutism and bone age advancement characterize the late-onset form of this condition (Table **3**) [4, 16, 17].

4.2.6. GH/IGF-1 Excess

A condition of GH excess or hyperthyroidism may be suggested in the subjects with absence of pubertal signs and an increased growth velocity. The former is observed before epiphyseal fusion and is characterized by increased growth without advance of bone age, metabolic changes similar to those found in acromegalic patients, and high serum IGF-I concentrations. GH concentrations may be elevated on an overnight GH [4] profile, with no detectable troughs. Additionally, serum GH concentrations are not suppressed by oral

Table 3. Etiology of precocious puberty. CNS: central nervous system, CAH: congenital adrenal hyperplasia.

Type	
Gonadotrophin Dependent	Idiopathic Brain abnormality: hypothalamic hamartoma, hydrocephalus, arachnoid cysts, septo-optic dysplasia CNS damage: trauma, infiltration, infection, irradiation Tumors CNS Genetic mutation: Activation of the *KISS1/KISS1R* pathway, inactivating mutations of *MKRN3* and *DLK1*.
Gonadotrophin Independent	CAH McCune-Albright Syndrome Tumor (ovary, testis, adrenal) Testotoxicosis (LH receptor mutation) Human chorionic gonadotropin (hCG) secreting germ cell tumors Primary hypothyroidism Exogenous sex steroids

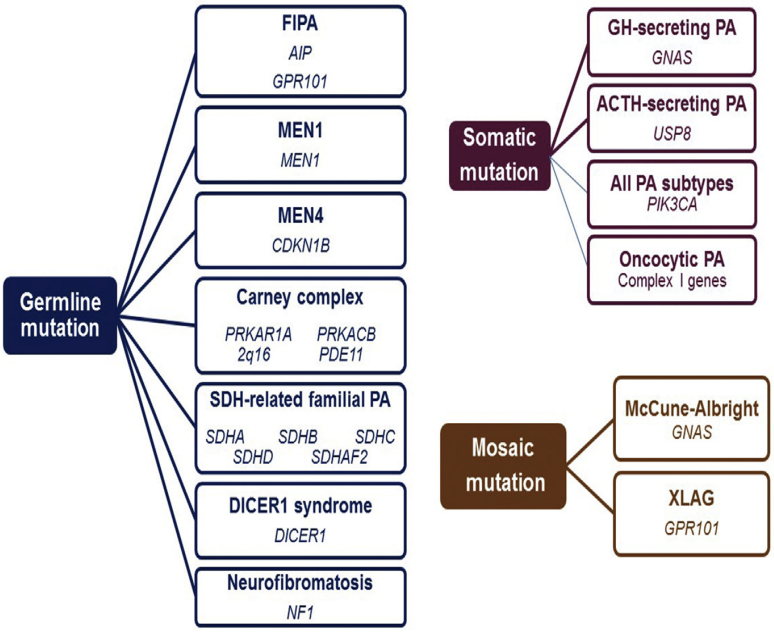

Fig. (2). Genetic of pituitary adenomas (from *Marques P. et al*, 2017) [18].

glucose administration during an oral glucose tolerance test. MRI may reveal a pituitary tumor in the form of a micro- or macro-adenoma. Recent advances have revealed a genetic cause in a significant proportion of these patients. Somatic *GNAS1, PIK3CA* and *USP8* mutations may be identified, or the tumor may occur as a component of syndromes such as the Carney complex, the McCune-Albright syndrome, Multiple Endocrine Neoplasia Type 1 and Type 4, and DICER1 and Succinate Dehydrogenase (SDH)-related syndromes. Mutations in Arylhydrocarbon-interacting protein (AIP) have been associated with Familial Pituitary Adenomas (FIPA), and more recently, duplications of X incorporating duplication of *GPR101* have been associated with pituitary gigantism due to pituitary tumors as part of the X-LAG syndrome (Fig. **2**).

4.2.6.1. Familial Pituitary Adenomas (FIPA)

This condition is characterized by 2 or more cases of pituitary adenomas (PAs) in a family in the absence of other associated tumors. Acromegaly/Gigantism is associated with 54% of tumors, prolactinoma with 27%, and non-functioning pituitary adenomas (NFPA) in 17%; prolactinoma and gigantism/acromegaly may occur in the same pedigree. *AIP* (a tumor suppressor gene) mutations were present in 15-30% of FIPA families, and in 20% of sporadic pediatric PAs. The penetrance of PAs among AIP mutation-positive carriers is around 12% to 30%, suggesting the role of other disease modifiers. The mean age at diagnosis is 18-24 years; almost all *AIP* mutation positive cases were diagnosed by 40 years of age. *AIP* mutation-positive PAs are more likely to be macroadenomas (90%) and aggressive, needing multimodal therapy [18].

4.2.6.2. X-LAG Syndrome

This is associated with microduplications of Xq26.3 including the orphan G-protein coupled receptor *GPR101*,

which is significantly over-expressed in the pituitary of these patients. Mutations may be sporadic de novo as well as familial germline Xq26.3 microduplications, and mutations may be mosaic. *GPR101* is also highly expressed in the hypothalamus and nucleus accumbens. Affected patients usually have gigantism of early onset, usually before the age of 5 years, and may have an increased appetite, acanthosis, coarse facial features, and excess sweating. There is a female preponderance, and the condition is associated with macroadenomas, hyperplasia and/or PAs. Hyperprolactinaemia has been described in 85% of cases. *AIP* mutations account for 30% of pituitary gigantism, while X-LAG accounts for 10% cases [18].

The treatment of pituitary gigantism can be highly complex, and includes medical therapy using somatostatin analogs, which results in biochemical cure in 70% with tumor shrinkage in 75%. Cabergoline can also be used, and is particularly effective in patients with tumors secreting both GH and prolactin. The GH antagonist, Pegvisomant, can also be used although there is no tumor shrinkage. Trans-sphenoidal resection of the tumor is associated with biochemical cure in 75-95%. Radiotherapy is used in resistant cases, but may be associated with complications including hypopituitarism, visual impairment, and possibly secondary tumors [18].

4.2.7. Thyrotoxicosis

In hyperthyroidism, an increased growth rate may be associated with an advanced bone age. The diagnosis is based on the measurements of free thyroxine and thyroid stimulating hormone (TSH) values. The commonest cause is autoimmune thyroiditis (Graves' disease), although other causes include a TSH-secreting pituitary adenoma, and constitutively activating TSH receptor mutations. It may also be associated with McCune-Albright syndrome. Treatment may be medical with the use of Carbimazole or Methimazole in combination with beta-blockade, or surgical with a total thyroidectomy, or radioiodine.

4.2.8. McCune-Albright Syndrome

McCune-Albright Syndrome (MAS) is a rare cause of gonadotropin-independent precocious puberty, GH excess and hyperthyroidism. It is a genetic disease due to an activating mutation in the *GNAS* gene encoding the alpha subunit of the stimulatory G protein involved in G-protein signalling. This mutation arises early in embryogenesis and is distributed in a mosaic pattern [19, 20]. It is characterized as the triad of polyostotic fibrous dysplasia of bone, precocious puberty and café-au-lait skin pigmentation. Moreover, other associated endocrinopathies have been found including hyperthyroidism, GH excess, FGF23-mediated phosphate wasting and hypercortisolism [19, 20]. Skin manifestations are common and usually observed at or shortly after birth. The café-au-lait spots typically show irregular margins giving them a "coast of Maine" appearance, and usually are associated to the midline of the body. In MAS, fibrous dysplasia of bone typically occurs at several sites (polyostotic), and commonly presents with fracture, deformity and/or bone pain. Radiographs show characteristic expansive lesions with a "ground glass" appearance [4, 19, 20].

4.3. Syndromic Causes

4.3.1. Proportionate Syndromes

4.3.1.1. Sotos Syndrome

Sotos syndrome (1/14,000) is an autosomal dominant condition due to mutations in *NSD1*. Deletions and point mutations in the *NSD1* gene, with consequent loss of function, account for the majority of cases and there may be autosomal dominant transmission. It is also known as cerebral gigantism, and presents at birth with increased length, weight and head circumference. They are large-for-gestational age infants and have an increased growth in early childhood (about the first 4 years of life) with an advanced bone age, but do not reach an excessively tall adult height. Pre- and post-natal overgrowth and disproportionately long limbs have been usually reported. Characteristic features include dolichocephaly with macrocephaly, prominent forehead, down-slanting palpebral fissures, mild hypertelorism, high-arched palate, prominent ears and jaw with a small pointed chin, large hands and feet, and acromegalic appearance [3, 21]. Most have intellectual disability that is usually mild to moderate, but can be severe and motor incoordination. Although they continue to grow rapidly during the early years of life, puberty occurs early and causes premature epiphyseal fusion leading to a normal height in adulthood. They have normal GH and IGF-I secretion, thyroid, adrenal and gonadal function [3, 4, 21, 22]. These patients have a slight risk to present tumors, about 3%. Although awareness of cancer risk is important, routine surveillance is not recommended [22, 23].

4.3.1.2. Malan Syndrome

Malan syndrome, also known as Sotos-like syndrome or Sotos Syndrome 2, has similar physical characteristics to Sotos syndrome but has a different underlying molecular basis. It is caused by heterozygous variants or deletions of the gene nuclear factor I X(*NFIX*), located at chromosome 19p13.2. There is no genotype-phenotype correlation except for an increased risk for epilepsy with 19p13.2 microdeletions. The growth pattern in Malan syndrome resembles the growth pattern in Sotos syndrome in which initial overgrowth is very common but adult height is above 2 SD in only one-third of individuals [24, 25].

4.3.1.3. Weaver Syndrome

Patients with Weaver syndrome, also known as EZH2-related overgrowth, show pre- and post-natal overgrowth, and typical features include large ears, depressed nasal bridge, downslanting palpebral fissures, dimpled chin, prominent wide philtrum, deep-set nails, hypotonia, loose skin, and micrognathia [4, 20]. Augmented skeletal maturation and camptodactyly are reported. Developmental delay and learning difficulties may be observed in many patients. Mutation in *EZH2* gene, encoding for histone methyltransferase, are reported [4, 21, 26]. Embryonal and hematologic tumors may occur in up to 5% of the patients. There is no recommendation for tumor surveillance but clinicians should have a low threshold for investigating any findings that may be tumor, especially neuroblastoma [23].

It has recently described mutations in *EED* and *SUZ12* genes. Patients with these mutations have overgrowth from birth, developmental delay/mild to moderate intellectual disability, and facial features resembling Weaver syndrome. It is also known as Weaver-like syndrome. Mutations in *EED* and *SUZ12* could lead to overgrowth via similar molecular mechanisms to *EZH2* mutation reducing H3K27 methylation [5, 27, 28].

4.3.1.4. Tatton-Brown-Rahman Syndrome

Clinical features of TattonBrown-Rahman syndrome, also known as DNMT3A-overgrowth syndrome, include tall stature, macrocephaly, intellectual disability (most frequently in the moderate range), characteristic facial features including a round face, heavy horizontal eyebrows, and narrow, small or downslanting palpebral fissures. A "marked philtrum with triangular interpillar space" has been described. In 20–80% of individuals with constitutive *DNMT3A* variants, included joint hypermobility, obesity, heart defects, hypotonia, behavioural/psychiatric issues (autistic spectrum disorder), kyphoscoliosis and afebrile seizures [5, 29].

4.3.1.5. Fragile X Syndrome

Fragile X syndrome is a genetic disease including intellectual disability and features such as a long and narrow face, protruding ears, flexible fingers, hypotonia and large testes (macroorchidism). These patients show increased growth velocity until puberty [4]. The patients often present with autism, delayed speech and hyperactivity. The frequency is about 1 in 4,000 males and 1 in 8,000 females [4, 30]. Partial or complete loss-of-function mutations in the *FMR1* gene, mapped on chromosome Xq27.3, cause fragile X syndrome. Most affected patients show hypermethylated CGG-repeat stretches in the 5'-untranslated region of the *FMR1* exon 1 [4, 30]. This hypermethylation results in constriction of the X chromosome which appears 'fragile' under the microscope at that point, a phenomenon that gave the syndrome its name. Fragile X syndrome has traditionally been considered an X-linked dominant condition with variable expressivity. Prenatal testing with chorionic villous sampling or amniocentesis allows diagnosis of *FMR1* mutations while the foetus is in utero and appears to be reliable [31].

4.3.1.6. Susceptibility to Autism 18

Recently has been described a group of patients with autism and tall stature. Susceptibility to autism 18 is due to a mutation in *HD8* at chromosome 14q11.2 It is characterized by early autism, 86% have tall stature, 80% macrocephaly, features such as prominent supraorbital ridges, down slanting palpebral fissures, a broad nose with full nasal tip, pointed chin, tall slender build, and flat feet [5, 32].

4.3.1.7. Simpson-Golabi-Behmel Syndrome

Simpson-Golabi-Behmel syndrome is a rare inherited congenital disease including craniofacial, skeletal, cardiac and renal abnormalities. The first signs of Simpson-Golabi-Behmel syndrome may be observed as early as 16 weeks of gestation. Possible clinical features include macrosomia, macroglossia, advanced bone age, organomegaly, neonatal hypoglycaemia, congenital diaphragmatic hernia, "bulldog" or "coarse" face, short broad hands and feet with dysplastic nails, polydactyly, pectus excavatum, talipes equinovarus, vertebral segmentation defects, supernumerary nipples, structural and conductive cardiac defects, multicystic dysplastic kidneys, hypotonia, brain malformations, developmental disabilities and, rarely, mental retardation [33, 34]. The syndrome is inherited in an X-linked recessive fashion, where males express the phenotype and females usually do not, or may express varying degrees of the phenotype. Despite the multiple congenital anomalies present in Simpson–Golabi–Behmel syndrome, mental development has often been reported as normal. These patients show an increased risk of neoplasms, in particular Wilms tumor and hepatoblastoma. [21, 33, 34] Simpson-Golabi-Behmel syndrome type I patients, a mutation of the *GPC3* gene (especially expressed in kidney, liver and lung) on the X chromosome locus q26.1 has been described, while Simpson-Golabi-Behmel syndrome type II may be caused by duplication of the *GPC4* gene, which helps to regulate cell division and growth [3].

4.3.2. Disproportionate Syndromes

4.3.2.1. Marfan Syndrome

Marfan syndrome is an autosomal-dominant condition resulting from a mutation in the Fibrillin (*FBN-1)* gene on chromosome 15q, encoding a 350-kDa extracellular matrix glycoprotein that takes part in the formation of microfibrils, which are important for elasticity and structural support of numerous tissues [35]. The frequency is approximately 1 in 5,000 people. The characteristic features include long limbs with narrow hands and long slender fingers, arm span greater than height and the lower segment much greater than the upper segment. These patients can show also mild hyperextensible joints, skin striae, kyphoscoliosis, deformities of the rib cage, high arched palate and upward lens dislocation. Aortic root dilatation, aortic aneurysms, and mitral valve prolapse are important cardiac features and associated with increased mortality in young adults. Death from a dissecting aneurysm may occur in young adults. Echocardiographic and ophthalmic assessment should be required in a child with marfanoid features. Two important clinical findings in making the diagnosis are the wrist sign and thumb sign. In particular, the "wrist sign" is positive when the thumb overlaps the fifth finger when grasping the contralateral wrist, while the "thumb sign" is positive when the thumb extends well beyond the ulnar border of the hand when overlapped by the fingers [4, 36].

4.3.2.2. Homocystinuria

Homocystinuria is a rare (1:250,000) autosomal-recessive disease caused by an absence of the enzyme cystathionine β-synthase (CBS). The phenotype resembles that of Marfan subjects, but they usually have subnormal intelligence, learning difficulties, an increased predisposition to psychiatric disorders, osteopenia, and a tendency to fatal thromboembolism. Lenticular dislocation also occurs, usually in a downward direction [36]. A multitude of genes are related to homocystinuria, but mutations in the gene that encodes CBS are the most prevalent. Alterations in CBS result in the disruption of enzyme activity, which consequently leads to elevated homocysteine, a potentially toxic aminoacid responsible for the clinical manifestations ob-

served in homocystinuric patients. To date, 150 CBS mutations have been identified and 67% are missense mutations [4, 37].

4.3.2.3. Klinefelter Syndrome

Klinefelter syndrome occurs in around 1 in 500-1,000 live born males, with an incidence increasing with maternal age. Most have the 47, XXY karyotype, and about 10% show mosaicism (*i.e.* 47,XXY/46,XY). Children usually present with tall stature and poor sexual development, while adults present with infertility. Patients are tall with disproportionately long limbs, feminine distribution of body fat, gynaecomastia and mild learning difficulties. Onset of puberty is not retarded, but testicular volume does not increase more than 8-10 ml. Histological examination of testes shows seminiferous dysgenesis, increase in Leydig cells and interstitial fibrosis. The patients may develop breast cancer or metabolic syndrome [4].

4.3.2.4. Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome is associated with excessive overgrowth apparently due to an excess availability of IGF-II. It is characterized by macrosomia, asymmetric overgrowth (hemihypertrophy), macroglossia, abdominal wall defects (umbilical hernia, omphalocele, diastasis recti), neonatal hypoglycaemia, transverse ear creases, visceromegaly, renal malformations, facial nevus flammeus, and an increased occurrence of embryonal tumors. Approximately 85% of Beckwith-Wiedemann cases are sporadic; the other 15% are familial showing autosomal dominant inheritance. The molecular etiology is complex and involves epigenomic and genomic alterations in the imprinting clusters on chromosome 11p15 [18, 38]. The defined abnormalities include:

- Paternal uniparental disomy of chromosome 11p15.5.
- Hypermethylation at the H19 differentially methylated region.
- Mutations in the maternally inherited copy of *CDKN1C*.
- Hypomethylation at *KvDMR1*.
- Duplications of 11p15 and translocations or inversions involving 11p15.

4.3.2.5. Triple X (XXX) Syndrome

The incidence of this syndrome is 1 in 1,000 female births, but the majority are undiagnosed because of the considerable variation in the phenotype. About 10% of subjects may be mosaic (*i.e*. 46 XX/47 XXX, 47 XXX/48 XXXX, 45 X/47 XXX, 45 X/46 XX/47 XXX). Features include increased linear growth in mid-childhood, tall stature, epicanthal folds, hypertelorism, upslanting palpebral fissures, clinodactyly, hypotonia, joint hyperextensibility, genitourinary abnormalities, congenital hip dysplasia, premature ovarian failure, congenital heart defects, seizure disorders, and electroencephalogram abnormalities. Normal fertility is usually observed. Females with Triple X often have intelligence within the normal range, although they may show an increased risk for attention deficit and early developmental delay, mainly in the form of speech-language disorders [39, 40].

4.3.2.6. Proteus Syndrome

Proteus syndrome is caused by activating mutations of the *AKT1* and *PTEN* genes. Proteus syndrome presents with asymmetric overgrowth with skeletal defects, epidermal nevi, vascular malformations, dysregulated adipose tissue, and pulmonary abnormalities [4]. Characteristic signs include macrocephaly with frontotemporal exostosis, large hands and feet with macrodactyly, normal psychomotor development, predisposition to cancer and thromboembolic diseases [4, 21].

5. MANAGEMENT OF A CHILD WITH TALL STATURE

Investigating the causes of tall stature in a child is rather important for a possible therapy, especially if there are endocrine disturbances for which treatment can be started. Obviously, not all causes of tall stature can or should be treated. However, a genetically proven diagnosis is also relevant because it provides a definite explanation and may provide reassurance regarding the natural course to be expected. For instance, in Sotos syndrome, treatment is usually unnecessary because it is known that while prepubertal growth is increased, final height is mostly within normal limits [4, 41].

Basically, to investigate a syndromic subject with tall stature, the following assessments should be initially required on the basis of diagnostic suspicion:

- Karyotype if Klinefelter syndrome or triple X syndrome are probable.
- In patients showing autism, intellectual disability, and congenital malformations, chromosomal microarray may be useful for a correct diagnosis.
- The *FMR1* gene should be analyzed in patients with tall stature and mental retardation, and in these patients the *NSD1* gene can be considered whenever some features of Sotos syndrome are present.
- Evaluation by ophthalmologist, cardiologist and clinical geneticist, followed by *FBN1* gene sequencing if Marfan syndrome is suspected.
- Plasma homocysteine concentration if there are criteria for homocystinuria.
- Genetic tests, such as whole exome or gene panel sequence, have to be considered in syndromic cases with high suspicion for genetic causes. (Please see above).

However, a large number of syndromes course with tall stature and the phenotypes often overlap with patients exhibiting similar clinical findings. Because of that an exome sequencing or gene panel design will therefore be the most useful investigation as we explain bellow [5].

6. GENETICS OF TALL STATURE

Human growth and adult height are highly heritable [42, 43]. Initially, the first studies of genetic determinants of height mainly focused on short stature, with many possible candidate genes identified. Some recent studies focused on genetics in extremely tall individuals and found some common genetic variations. Additionally, exome sequencing has been demonstrated to be useful for identifying novel genes

involved in the etiology of tall stature [5]. For example, a common polymorphism in the high-mobility group A2 (*HMGA2*) gene was significantly associated with tall stature [4, 44]. Furthermore, overproduction of C-type natriuretic peptide by chromosomal translocation [45, 46] and gain-of-function mutations in natriuretic peptide receptor-2 (*NPR2*) gene have been associated with overgrowth syndromes [47, 48] or extreme tall stature without skeletal deformities [49]. Heterozygous loss-of-function mutations of the gene encoding fibroblast growth factor receptor-3 (*FGFR3*) result in a phenotype characterized by camptodactyly, tall stature and hearing loss (CATSHL syndrome) [4, 50, 51]. Finally, a recent article identified an association between a novel homozygous mutation in Sec23 homolog A (*SEC23A*) and a previously reported homozygous mutation in mannosidase alpha class 1B member 1 (*MAN1B1*) in two patients born to a consanguineous family of Lebanese origin, presenting with somatic overgrowth, macrocephaly, mild dysmorphic features, hypertelorism, malocclusion teeth, intellectual disability and flat feet [4, 52].

We recently found significantly higher GH receptor gene expression levels in tall children compared with short and normal stature children, suggesting that GH sensitivity could be yet another factor implicated in the etiology of tall stature [53]. An activating *IGF1R* variant (p.Arg1353His) has been recently described in boys with tall stature due to a possible deregulation of collagen turnover and increased androgen sensitivity causing tall stature in male carriers. Also, gain of *IGF1R* copy number due to a microduplication of 15q26.3 is believed to cause an overgrowth phenotype [54].

Finally, some epidemiological studies have shown that taller people present an elevated risk of common cancers such as breast, ovary, prostate and large bowel [55, 56]. In particular, tall women have a greater risk of developing breast, endometrium, colon and ovarian cancer [57] and total cancer risk and risks of breast cancer and melanoma were higher with increasing height [58].

7. TREATMENT OF TALL STATURE

Generally, tall stature does not require any treatment except when it is pathological in origin.

No evidence-based guideline has been created with respect to the selection of potential candidates for adult height reduction. Children and their parents look for treatment to reduce growth if they find their predicted adult height unacceptable. An X-ray of the left hand is useful to evaluate the skeletal maturity of tall children and predict adult height. The available methods to predict adult height are, however, controversial as the Bayley-Pinneau method overestimates adult height and Tanner-Whitehouse Mark 1 and 2 overestimate or underestimate it depending on the bone age [4, 59, 60]. However, treatment is generally only considered for adolescents with predicted adult height more than 2.5 SD above the population mean.

Tall patients may cause anxiety to parents, who may then request treatment to block up growth progression. Specific therapy depends on the prediction of the final height. Various types of treatment, either hormonal or surgical, have been used to reduce growth.

The most accepted and effective treatment for an excessive height prediction is to induce puberty early leading to complete fusion of the epiphyses with achievement of final height, using testosterone in males and estrogens in females (Table **4**) [4, 61-63]. High doses estradiol or testosterone have been used to limit final height prognosis by inducing epiphyseal closure. However, high doses of sex steroids are no recommended to block up growth due to their short-and long-term consequences. In the short term, boys treated with androgens may present with myalgia, acne, gynecomastia and weight gain, whereas girls treated with high doses of estrogen may have weight gain, night cramps, galactorrhea, ovarian cysts and predisposition to thrombosis [3, 4, 64-67]. Some have encouraged promoting puberty by the use of more physiological doses of sex steroid before the tall child progresses into puberty as a means of decreasing final adult height. One method of trying to achieve a limitation to the final height is to discuss an acceptable final height with the family, and to then induce puberty with the knowledge that puberty will add 25-30 cm to the height at onset in boys, and 20 cm or so in girls. Nevertheless, there remains a significant amount of uncertainty regarding the efficacy of exogenous sex steroids in limiting final height whether used as part of a high or lower dose strategy [68]. (Fig. **3** & Table **4**).

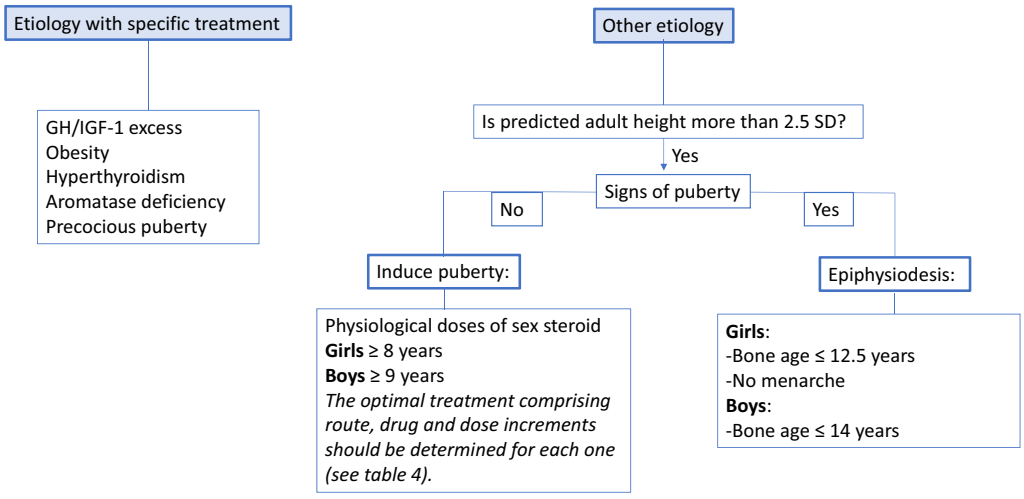

Fig. (3). Tall stature treatment schedule.

Table 4. Hormone supplementation for pubertal induction.

25 µg 17β- estradiol Matrix Patch	1 mg 17β-estradiol Tablets	2 µg / 10 µg Ethinylestradiol Tablets	Intramuscular Injection of an Ester of Testosterone (Enanthate, Cypionate) or Mixture of Esters ^	2% Testosterone Transdermal Gel (10 mg) ^ *Apply in Shoulders, Arms or Abdomen at Bedtime*	Duration
¼ patch M, to Th No patch* Th to Su	0.5mg alternate days	2 µg daily	50 mg monthly	1-2 metered applications daily	6 month
¼ patch M to Th ¼ patch Th to Su	0.5mg daily	4 µg daily	100 mg monthly	2-3 metered applications daily	6 month
½ patch M to Th ¼ patch Th to Su	1 mg alternate days	6 µg daily	100 mg three weekly	3-4 metered applications daily	6 month
½ patch M to Th ½ patch Th to Su	0.5mg and 1mg alternate days	10 µg daily	100 mg two weekly	4-5 metered applications daily	6 month
1 patch M to Th 1 patch Th to Su	1 mg daily	15 µg daily	150 mg two weekly	5-6 metered applications daily	6 month
[+] Combined oral contraceptive pill / Combined patch or 50/100 µg patch twice weekly[1] or 1/2 mg 17β-estradiol[1] or 20 µg ethinylestradiol daily[1] + Utrogestan® 200 mg / medroxyprogesterone acetate 5 mg once daily in 12–14 day blocks every 1-3 months.				6-7 metered applications daily	6 month
				7-8 metered applications daily	6 month

M: Monday, Th: Thursday, Su: Sunday. *Unused patch fractions may be stored in their packaging in the fridge for up to 1week. [+] Progestogens are usually introduced after a suitable duration of unopposed estrogen (2–3 years) or if more than one episode of significant breakthrough bleeding occurs. ^ Boys taking testosterone for pubertal induction may have serum testosterone levels measured to monitor therapy. Adjust the dose according to testosterone levels. [1] Consider adult regimens when they reach adulthood.

Others therapies such as a nocturnal infusion of octreotide, a somatostatin analogue (201-995), seems to reduce GH secretion and height prediction in tall children [69, 70]. However, a recent study showed that long-term treatment with a somatostatin analogue (201-995) does not reduce final height in a manner sufficient to justify treatment in tall stature [4, 71].

In the last years, it has been considered a surgical closure of the epiphyses, a great option especially in patients whose bone age is 12 years or above, when any medical intervention is unlikely to produce significant reductions in adult height [72]. Upners *et al.* showed a 1.6 cm reduction in 18 of 26 girls treated with physiological doses of 17β-estradiol at the bone age above 12 years [65]. The most common surgical procedure for reducing growth is bilateral percutaneous epiphysiodesis of the distal femur and proximal tibia and fibula. The procedure itself is short (about 60-70 minutes) and patients are allowed to stand on their legs directly afterwards but are advised not to engage in athletic activities for 4 weeks. Few complications are observed when patients are treated by expert clinicians. It is difficult to recommend when to perform the operation. This is more effective when is done at an early bone age. The operation should be performed preferably at a bone age not exceeding 12.5 years in girls and 14 years in boys to achieve a significant height reduction. According to Goedegebuure *et al*, epiphysiodesis produces reductions of between 5 and 7 cm as seen in smaller studies [72-76]. (Figure **3** & Table **4**).

CONCLUSION

The majority of tall subjects have a diagnosis of familial tall stature or constitutional advanced growth, which is a diagnosis obtained by exclusion. A pathological cause of tall stature must be sought, although the majority of children are healthy. However, some tall subjects may develop severe complications including a dissecting aneurysm in young adults with Marfan syndrome. A careful physical examination, evaluation of the growth pattern and careful surveillance until adult life in some cases are required. The therapeutic approach depends on the growth prognosis.

DISCLOSURE

Part of this article has previously been published in "Tall stature: A difficult diagnosis?" Italian Journal of Pediatrics. 2017; 43:66-74.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

MTD receives funding from the Great Ormond Street Hospital Children's Charity

REFERENCES

[1] Backeljauw P, Dattani M, Cohen P, Rosenfeld R. Disorders of Growth Hormone/Insulin-Like Growth Factor. In: Sperling MA, Eds. Pediatric endocrinology 4th Ed. Eselvier Philadelphia 2014; pp. 299-405.

[2] Wei C, Gregory JW. Physiology of normal growth. Paediatr Child Health 2009; 19: 236-40.

[3] Davies JH, Cheetham T. Investigation and management of tall stature. Arch Dis Child 2014; 99: 772-7.

[4] Meazza C, Gertosio C, Giacchero R, Pagani S, Bozzola M. Tall stature: A difficult diagnosis? Ital J Pediatr 2017; 43: 66-74.

[5] Kamien B, Ronan A, Poke G, et al. A clinical review of generalized overgrowth syndromes in the era of massively parallel sequencing. Mol Syndromol 2018; 9(2): 70-82.

[6] Coutant R, Donzeau A, Decrequy A, Louvigné M, Bouhours-Nouet N. How to investigate a child with excessive growth? Ann Endocrinol 2017; 78(2): 98-103.

[7] Albuquerque E, Scalco R, Jorge A. Management of endocrine disease: Diagnostic and therapeutic approach of tall stature. Eur J Endocrinol 2017; 176(6): 339-53.

[8] Dickerman Z, Loewinger J, Laron Z. The pattern of growth in children with constitutional tall stature from birth to age 9 years. A longitudinal study. Acta Paediatr Scand 1984; 73: 530-6.

[9] Barstow C, Rerucha C. Evaluation of short and tall stature in children. Am Fam Phy 2015; 92: 43-50.

[10] Papadimitriou A, Nicolaidou P, Fretzayas A, Chrousos GP. Clinical review: Constitutional advancement of growth, a.k.a. early growth acceleration, predicts early puberty and childhood obesity. J Clin Endocrinol Metab 2010; 95: 4535-41.

[11] Garrone S, Radetti G, Sidoti M, *et al*. Increased Insulin-like Growth factor (IGF)-II and IGF/IGF-binding protein ratio in prepubertal constitutionally tall children. J Clin Endocrinol Metab 2002; 87: 5455-60.

[12] Júlíusson PB, Brannsether B, Kristiansen H, *et al*. Should children with overweight or obesity be excluded from height references? Arch Dis Child 2015; 100: 1044-8.

[13] Marino R, Perez Garrido N, Costanzo M, *et al*. Five new cases of 46, XX aromatase deficiency: Clinical follow-up from birth to puberty, a novel mutation, and a founder effect. J Clin Endocrinol Metab 2015; 100: E301-7.

[14] Smith EP, Boyd J, Frank GR, *et al*. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994; 331: 1056-61.

[15] Quaynor SD, Stradtman EW Jr, Kim HG, *et al*. Delayed puberty and estrogen resistance in a woman with estrogen receptor alpha variant. N Engl J Med 2013; 369: 164-71.

[16] Neely E, Crossen S. Precocious puberty. Curr Opin Obstet Gynecol 2014; 26(5): 332-8.

[17] El-Maouche D, Arlt W, Merke D. Congenital adrenal hyperplasia. The Lancet 2017; 390(10108): 2194-210.

[18] Marques P, Korbonits M. Genetic aspects of pituitary adenomas. Endocrinol Metab Clin N Am 2017; 46: 335-74.

[19] Pratt V, McLeod H, Dean L, Malheiro A, Rubinstein W, Eds. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012.

[20] Boyce AM, Collins MT, Pagon RA, *et al*., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.

[21] Edmondson A, Kalish J. Overgrowth syndromes. J Pediatr Genet 2015; 4(3): 136-43.

[22] Tatton-Brown K, Douglas J, Coleman K, *et al*. Genotype-phenotype associations in sotos syndrome: An Analysis of 266 Individuals with NSD1 Aberrations. AJHG 2005; 77(2): 193-204.

[23] Villani A, Greer M, Kalish J, Nakagawara A, *et al*. Recommendations for cancer surveillance in individuals with rasopathies and other rare genetic conditions with increased cancer risk. Clin Cancer Res 2017; 23(12): e83-e90

[24] (a) Klaassens M, Morrogh D, Rosser E, J *et al*. Malan syndrome: Sotos-like overgrowth with de novo NFIX sequence variants and deletions in six new patients and a review of the literature. Eur J Human Genet 2014; 23(5). (b) Kant S, Wit J, Breuning M. Genetic Analysis of Tall Stature. Horm Res Paediatr 2005; 64(3): 149-156.

[25] Priolo M, Schanze D, Tatton-Brown K, *et al*. Further delineation of Malan syndrome. Hum Mutat 2018; 39(9): 1226-37.

[26] Tatton-Brown K, Murray A, Hanks S, Douglas J, *et al*. Childhood Overgrowth Consortium, Rahman N. Weaver syndrome and EZH2 mutations: Clarifying the clinical phenotype. Am J Med Genet A 2013; 161A: 2972-80.

[27] Cohen A, Gibson W. EED-associated overgrowth in a second male patient. J Hum Genet 2016; 61(9): 831-4.

[28] Imagawa E, Albuquerque E, Isidor B, et al. Novel SUZ12 mutations in Weaver-like syndrome. Clin Genet 2018; 94(5): 461-6.

[29] Brown K, Zachariou A, Loveday C, *et al*. The Tatton-Brown-Rahman Syndrome: A clinical study of 55 individuals with *de novo* constitutive DNMT3A variants. Wellcome Open Res 2018; 3: 46.

[30] Rajan-Babu IS, Chong SS. Molecular correlates and recent advancements in the diagnosis and screening of FMR1-related disorders. Genes (Basel) 2016; 7: pii:E87.

[31] Terracciano A, Chiurazzi P, Neri G. Fragile X syndrome. Am J Med Genet C Semin Med Genet 2005; 137C: 32-7.

[32] Bernier R, Golzio C, Xiong B, *et al*. Disruptive chd8 mutations define a subtype of autism early in development. Cell 2014; 158(2): 263-76.

[33] Garganta CL, Bodurtha JN. Report of another family with Simpson-Golabi-Behmel syndrome and a review of the literature. Am J Med Genet 1992; 44:129-35.

[34] DeBaun MR, Ess J, Saunders S. Simpson Golabi Behmel syndrome: Progress toward understanding the molecular basis for overgrowth, malformation, and cancer predisposition. Mol Gen Metab 2001; 72: 279-86.

[35] Verstraeten A, Alaerts M, Van Laer L, Loeys B. Marfan syndrome and related disorders: 25 years of gene discovery. Hum Mutat 2016; 37: 524-31.

[36] De Maio F, Fichera A, De Luna V, Mancini F, Caterini R. Orthopaedic aspects of Marfan syndrome: The experience of a referral center for diagnosis of rare diseases. Adv Orthop 2016; 2016: 8275391.

[37] Silao CL, Fabella TD, Rama KI, Estrada SC. Novel cystathionine β-synthase gene mutations in a Filipino patient with classic homocystinuria. Pediatr Int 2015; 57: 884-7.

[38] Soejima H, Higashimoto K. Epigenetic and genetic alterations of the imprinting disorder Beckwith-Wiedemann syndrome and related disorders. J Hum Genet 2013; 58(7): 402-9

[39] Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47,XXX). Orphanet J Rare Dis 2010; 5: 8.

[40] Wigby K, D'Epagnier C, Howell S, *et al*. Expanding the phenotype of Triple X syndrome: A comparison of prenatal versus postnatal diagnosis. Am J Med Genet Part A. 2016; 170(11): 2870-81

[41] Kant S, Wit J, Breuning M. Genetic analysis of tall stature. Horm Res Paediatr 2005; 64(3): 149-56.

[42] Perola M, Sammalisto S, Hiekkalinna T, *et al*. Combined genome scans for body stature in 6,602 European twins: Evidence for common Caucasian loci. PLoS Genet 2007; 3: e97.

[43] Silventoinen Iventoinen K, Sammalisto S, Perola M, *et al.* Heritability of adult body height: A comparative study of twin cohorts in eight countries. Twin Res 2003; 6: 399-408.

[44] Hendriks AE, Brown MR, Boot AM, Oostra BA, Drop SL, Parks JS. Genetic variation in candidate genes like the HMGA2 gene in the extremely tall. Horm Res Paediatr 2011; 76: 307-13.

[45] Bocciardi R, Giorda R, Buttgereit J, *et al.* Overexpression of the C-type Natriuretic Peptide (CNP) is associated with overgrowth and bone anomalies in an individual with balanced t(2;7) translocation. Hum Mutat 2007; 28: 724-31.

[46] Moncla A, Missirian C, Cacciagli P, *et al*. A cluster of translocation breakpoints in 2q37 is associated with overexpression of NPPC in patients with a similar overgrowth phenotype. Hum Mutat 2007; 28:1183-8.

[47] Miura K, Namba N, Fujiwara M, *et al*. An overgrowth disorder associated with excessive production of cGMP due to a gain-of-

function mutation of the natriuretic peptide receptor 2 gene. PLoS One 2012; 7: e42180.

[48] Miura K, Kim OH, Lee HR, *et al*. Overgrowth syndrome associated with a gain-of-function mutation of the natriuretic peptide receptor 2 (NPR2) gene. Am J Med Genet A 2014; 164A: 156-63.

[49] Hannema SE, van Duyvenvoorde HA, Premsler T, *et al*. An activating mutation in the kinase homology domain of the natriuretic peptide receptor-2 causes extremely tall stature without skeletal deformities. J Clin Endocrinol Metab 2013; 98: E1988-98.

[50] Toydemir RM, Brassington AE, Bayrak-Toydemir P, *et al*. A novel mutation in FGFR3 causes camptodactyly, tall stature, and hearing loss (CATSHL) syndrome. Am J Hum Genet 2006; 79: 935-41.

[51] Makrythanasis P, Temtamy S, Aglan MS, Otaify GA, Hamamy H, Antonarakis SE. A novel homozygous mutation in FGFR3 causes tall stature, severe lateral tibial deviation, scoliosis, hearing impairment, camptodactyly, and arachnodactyly. Hum Mutat 2014; 35: 959-63.

[52] Gupta S, Fahiminiya S, Wang T, *et al*. Somatic overgrowth associated with homozygous mutations in both MAN1B1 and SEC23A. Cold Spring Harb Mol Case Stud 2016; 2: a000737.

[53] Pagani S, Radetti G, Meazza C, Bozzola M. Analysis of growth hormone receptor gene expression in tall and short stature children. J Pediatr Endocrinol Metab 2017; 30: 427-30.

[54] Lin Y, van Duyvenvoorde H, Liu H, *et al*. Characterization of an activating R1353H insulin-like growth factor 1 receptor variant in a male with extreme tall height. Eur J Endocrinol 2018; 179(2): 85-95.

[55] Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: A systematic review. Epidemiol Rev 2001; 23: 313-42.

[56] Schouten LJ, Rivera C, Hunter DJ, *et al.* Height, body mass index, and ovarian cancer: A pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev 2008; 17: 902-12.

[57] Green J, Cairns BJ, Casabonne D, Wright FL, Reeves G, Beral V. Height and cancer incidence in the Million Women Study: Prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. Lancet Oncol 2011; 12: 785-94.

[58] Benyl E, Linder M, Adami J, Palme M, Savendahl L. Positive association between height and cancer in the Swedish population. ESPE Abstracts (2015) 84 FC4.6

[59] Joss EE, Temperli R, Mullis PE. Adult height in constitutionally tall stature: Accuracy of five different height prediction methods. Arch Dis Child 1992; 67: 1357-62.

[60] de Waal WJ, Greyn-Fokker MH, Stijnen T, *et al*. Accuracy of final height prediction and effect of growth-reductive therapy in 362 constitutionally tall children. J Clin Endocrinol Metab 1996; 81: 1206-16.

[61] Matthews D, Bath L, Högler W, Mason A, Smyth A, Skae M. Hormone supplementation for pubertal induction in girls. Arch Dis Child 2017;102(10): 975-80.

[62] Boehm U, Bouloux P, Dattani M, *et al*. European consensus statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Natr Rev Endocrinol 2015; 11(9): 547-64.

[63] Howard, S. and Dunkel, L. Sex Steroid and Gonadotropin Treatment in Male Delayed Puberty. Puberty from Bench to Clinic Lessons for Clinical Management of Pubertal Disorders. Endocr Dev Basel Karger 2016; 29: 185-97.

[64] Reinehr T, Gueldensupp M, Wunsch R, Bramswig JH. Treatment of tall stature in boys: Comparison of two different treatment regimens. Horm Res Paediatr 2011; 76: 343-7.

[65] Upners EN, Juul A. Evaluation and phenotypic characteristics of 293 Danish girls with tall stature: Effects of oral administration of natural 17β-estradiol. Pediatr Res 2016; 80: 693-701.

[66] de Waal W, Torn M, de Muinck Keizer-Schrama S, Aarsen R, Drop S. Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. Arch Dis in Childhood 1995; 73(4): 311-5.

[67] Hendriks AE, Boellaard WP, van Casteren NJ, *et al*. Fatherhood in tall men treated with high-dose sex steroids during adolescence. J Clin Endocrinol Metab 2010; 95: 5233-40.

[68] Brook CG, Stanhope R, Preece MA, *et al*. Oestrogen treatment of tall stature. Arch Dis Child 1998; 79: 199.

[69] Hindmarsh PC, Pringle PJ, Di Silvio L, Brook CG. A preliminary report on the role of somatostatin analogue (SMS 201-995) in the management of children with tall stature. Clin Endocrinol (Oxf) 1990; 32: 83-91.

[70] Hindmarsh PC, Pringle PJ, Stanhope R, Brook CGD. The effect of a continuous infusion of a somatostatin analogue (octreotide) for two years on growth hormone secretion and height prediction in tall children. Clin Endocrinol 1995; 42: 509-15.

[71] Noordam C, van Daalen S, Otten BJ. Treatment of tall stature in boys with somatostatin analogue 201-995: Effect on final height. Eur J Endocrinol 2006; 154: 253-7.

[72] Hindmarsh PC. Long-term follow-up after bilateral percutaneous epiphysiodesis around the knee to reduce excessive predicted final height. Arch dis in childhood 2018; 103(3): 219-23.

[73] Stalman SE, Pons A, Wit JM, Kamp GA, Plotz FB. Diagnostic work-up and follow-up in children with tall stature: A simplified algorithm for clinical practice. J Clin Res Pediatr Endocrinol 2015; 7: 260-7.

[74] Hannema ES, Savendahl L. The evaluation and management of tall stature. Horm Res Paediatr 2016; 85: 347-52.

[75] Benyi E, Berner M, Bjernekull I, *et al*. Efficacy and safety of percutaneous epiphysiodesis operation around the knee to reduce adult height in extremely tall adolescent girls and boys. Int J Pediatr Endocrinol 2010; 2010:1-7.

[76] Goedegebuure WJ, Jonkers F, Boot AM, *et al*. Long-term follow-up after bilateral percutaneous epiphysiodesis around the knee to reduce excessive predicted final height. Arch Dis Child 2018; 103: 219-23.