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# Tall stature and/or accelerated growth: diagnostic and therapeutic approach

## Talla alta y/o crecimiento acelerado: diagnóstico y enfoque terapéutico

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**Abstract**

The clinical assessment of children with tall stature and/or accelerated growth (TS/AG) is complicated because of several reasons. First, there are different criteria with arbitrary cut-off limits (tall for the population, tall for target height, accelerated growth). Second, there are many possible causes, and most are rare to extremely rare, and usually, no cause can be found (idiopathic tall stature, familial or non-familial). Third, the conditions with the most important therapeutic implications (Klinefelter syndrome and Marfan syndrome) may be difficult to diagnose in childhood by mere physical exam and growth trajectories alone. Fourth, these three issues have made it difficult to establish effective guidelines for referring patients from preventive health care to paediatric clinics, and for an appropriate diagnostic approach, including genetic analysis. In addition to obtaining a proper diagnosis, an additional goal is to predict adult height and offer rational advice to patients and parents on possible interventions to reduce adult height. Since the administration of high doses of sex steroids has shown to be associated with later fertility problems in females, and the balance between the limitation of adult height and adverse events is suboptimal in males, bilateral percutaneous epiphysiodesis of distal femur and proximal tibia is currently the only available treatment to reduce adult height.

**Introduction**

The diagnostic approach of children and adolescents who are referred to the clinic of the paediatrician and paediatric endocrinologist because of tall stature (TS) and/or accelerated growth (AG) is challenging for several reasons.

The first issue concerns the definition of this patient group. A child can be tall in relation to population reference charts or in relation to parental heights or both, and the shape of the growth curve can show an upward trend compared with the standard deviation score (SDS) lines of the population reference charts, or not. This implies that the clinician has to assess these three criteria. For each of these criteria cut-off limits are needed, but obviously these are statistical and to some extent arbitrary. In this review paper we use the abbreviation TS/AG for a clinical presentation in which at least one of the criteria is met.

The second challenge is that there are many possible causes of TS/AG, which are different in terms of frequency (but usually the incidence is low to extremely low), growth pattern, additional clinical features (and therefore associated with variable degrees of difficulty to diagnose in childhood), and clinical relevance. In this context it is important to mention that the two clinical syndromes that are relatively frequent causes of tall stature in childhood with also significant clinical relevance, Klinefelter syndrome (KS) and Marfan syndrome (MFS) (with an estimated incidence of 1-1.5/1000 and 2.3/10,000, respectively [1]), may present with a height SDS of <2 for population reference charts. However, this does not only apply to these two syndromes: in almost all syndromes associated with tall stature mean height SDS is increased, but the spread of the distribution of height SDS overlaps with the spread of height SDS in the reference population.

The third issue is that for these two disorders an early diagnosis has shown to be very difficult. For KS, the main reason appears to be that the most common presentation includes behavioural problems, learning disabilities, and delayed motor and speech development, which is rarely reason to visit a doctor, and even more rarely reason to be referred to a paediatrician. The only physical sign in infancy or childhood that may be a reason to be referred to a doctor is micropenis and/or cryptorchidism, but this is usually insufficient reason to carry out a genetic assessment. Only in late adolescence a delayed puberty, small testicular size, scoliosis, kyphosis or gynaecomastia can be an indication to visit the paediatrician or paediatric endocrinologist. For MFS the physical signs can be mild and height can be within the reference range and close to the mid-parental height (Target height, TH), especially if there is an undiagnosed, affected parent with MFS. This leads to a substantial delay in referral to paediatricians and paediatric endocrinologists.

Fourth, these three challenges have made it complicated to design effective guidelines for referral criteria that can be used by preventive child health organisations and family practitioners. Equally difficult has it been to develop an optimal diagnostic approach for children presenting with TS/AG at the office of the paediatrician or paediatric endocrinologist. In the Netherlands, two multidisciplinary working groups have recently published practical guidelines on referral criteria for physicians working in preventive child health [2] and on the diagnostic approach for general paediatricians [1], but their efficacy has still to be assessed under field conditions.

In the present contribution we wish to focus on several complicating issues in the diagnostic approach of children referred for TS/AG to the paediatric (endocrine) clinic, including the role of genetic analysis. We shall also shortly discuss the management of such children and adolescents.

**The role of the three growth criteria in the definition of tall stature and/or growth acceleration**

As explained previously [1], we chose to define TS/AG in childhood or adolescence if linear growth complies with one or more of the following criteria:

1) tall for the ethnic population;

2) tall in comparison to parental heights; or

3) growth acceleration, defined as a positive change of height SDS (HSDS).

For practical purposes, tall for the ethnic population is defined as a HSDS >+2.0, based on suitable reference charts for height for age, sex and ethnicity.

The criterion for being tall for the genetic background (represented by parental heights) is based on the difference between HSDS and the sex-corrected mid-parental height SDS (Target height, TH). Unfortunately, there is no consensus among paediatric endocrinologists about which mathematical equation for TH should be used, which difference between HSDS and THSDS is statistically abnormal, and whether secular trends should be incorporated. As explained in more detail elsewhere [1], we favour the use of the conditional THSDS (adjusted for assortative mating and regression bias) and a cut-off of 1.6 SDS around HSDS-THSDS [3].

For the third criterion (AG) it appears logical to use a positive change in HSDS over time, away from the THSDS. We favour to use the delta HSDS rather than height velocity (cm/year), because we assume that the former is less age dependent. We took a pragmatic approach and consider a positive change of HSDS > 1 SDS over an undetermined time interval, before the onset of puberty, as “accelerated”.

During puberty none of the three indicators is believed to have a good sensitivity or specificity for detecting pathological causes, and the clinician should try to compare the growth pattern with what he or she expects at the pertinent pubertal phase.

**Causes of TS/AG, and their estimated frequency, presentation and clinical relevance**

In accordance with the ICPED classification [4], the causes of TS/AG are divided into three main groups: primary growth disorders (assumed to be associated with a disorder within the epiphyseal growth plate), secondary growth disorders (influencing the growth plate via the blood circulation) and idiopathic tall stature (ITS) (subdivided into familial, non-familial and constitutional advanced growth (CAG)) [1].

Table 1 shows the list of major causes, with their estimated incidence, presenting growth patterns (regarding the three indicators mentioned above), additional clinical features, and clinical relevance. Regarding estimated frequency, the great majority of causes is rare (<1/1000) to extremely rare (<1/100.000). Most relatively frequent causes (estimated incidence of >1/1000) have a low clinical relevance (e.g. idiopathic tall stature) or are easily diagnosed at physical examination (e.g. obesity and precocious puberty).

The only relatively frequent condition associated with a high clinical relevance is KS (for detailed arguments in favour of early diagnosis, see [1,5,6]). Unfortunately, this diagnosis is rarely established in childhood and adolescence [7], because the growth curve is usually within the population reference, the growth acceleration is mild and confined to a special age interval (3-8 years), and the clinical presentation is nonspecific and

Table 1. Major causes of tall stature and/or growth acceleration and their estimated frequency, presentation and clinical relevance.

| Cause[a] | Freq[b] | Tall[c] | Tall for parents[d] | Acc[e] | Additional clinical features[f] | Clinical relevance[g] |
|---|---|---|---|---|---|---|
| **Primary disorders** | | | | | | |
| Klinefelter S, other sex chromosome abnormalities | **F** | ± | ± | 3-8y | Behavioural problems, autism, delayed motor and speech development, late puberty, cryptorchidism, scoliosis, kyphosis, gynaecomastia, hypotonia | + |
| Triple SHOX | VR | + | ± | | Long extremities, gonadal failure | - |
| Fragile X S | VR | ± | + | ± | Behavioural problems, autism, developmental delay, facial dysmorphisms | + |
| Marfan(-like) S | R | ± | ± | ± | Scoliosis, lens dislocation, retinal detachment, wrist and thumb sign, arach-nodactyly, pectus excavatum, cardiac anomalies, thin, joint hypermobility | + |
| MEN 2B[h] | ER | ± | ± | ± | Mucosal neuromas, risk of malignancies | + |
| Simpson-Golabi-Behmel S | ER | + | + | | Behavioural problems, dysmorphisms, risk of malignancies | + |
| Sotos S | VR | + | + | 0-3y | Behavioural problems, macrocephaly, autism, intellectual disability, hypoto-nia, macrocephaly, advanced bone age, kidney and heart anomalies | + |
| Weaver S | ER | + | + | | Developmental delay, macrocephaly, facial dysmorphisms, advanced bone age, risk of malignancy | + |
| Beckwith-Wiedemann S | ER | ± | + | | Neonatal hypoglycaemia, macrosomia, macroglossy, hemihyperplasia, omphalocele, renal abnormalities, risk of malignancy (Wilms) | + |
| PTEN-related syndromes[i] | ER | ± | ± | | Developmental delay, macrocephaly, risk of malignancy | + |
| **Secondary disorders** | | | | | | |
| Pituitary gigantism | ER | + | + | + | Neurologic symptoms, hypertension, thick palmar skin | + |
| Hyperthyroidism | VR | ± | + | + | Heat intolerance, sweating, goitre, weight loss, palpitations, advanced bone age | + |
| Precocious puberty | **F** | ± | + | + | Early puberty, advanced bone age | + |
| Familial glucocorticoid def[j] | ER | + | + | + | Hyperpigmentation, hypoglycaemia, recurrent infections, failure to thrive | + |
| Gonadotrophin deficiency | ER | ± | + | - | Amenorrhea, stagnation of puberty, micropenis, cryptorchidism, anosmia | + |
| Oestrogen deficiency | ER | + | + | - | Osteoporosis, eunuchoid body proportions | + |
| Obesity | **F** | ± | ± | ± | Advanced bone age | - |
| **Idiopathic** | | | | | | |
| Familial | **F** | + | - | - | | ± |
| Non-familial | **F** | + | + | - | | ± |
| Constitutional advanced growth | | ± | ± | + | | - |

Adapted from Lauffer et al, 2019. [a]Based on International Classification of Pediatric Endocrine Diagnoses. [b]Estimated incidence (F=relatively frequent, >1/1000; R=rare, <1/1000; VR=very rare, <1/10,000; ER=extremely rare, <1/100,000. [c]The symbol + indicates that virtually all children with this condition have a height>2 SDS; ± indicates that mean height SDS is in the upper half of the reference range.[d]the symbol + indicates that almost all children have a height SDS above the TH range; ± indicates that children have a height within the TH range or slightly above; - indicates that height SDS is usually within the TH range. [e]the symbol + indicates that height usually increased >1 SD in the previous time interval; ± indicates that growth acceleration is usually less than 1 SD; - indicates no change in height SDS over time. [f]Summary of reported clinical features. [g]Estimated clinical relevance regarding secondary prevention: + signifies relevant; – little relevant. [h]Children with MEN2B syndrome are usually short; tall stature only seen in 2/24 patients [(10)]. [i]In children with PTEN-related syndromes height is usually normal. Tall stature was observed in 20% of males and 0% of girls [(11)]. [j]Mean (SD) height SDS 1.8 (1.5) in familial glucocorticoid def [(13)]. Abbreviations: Acc, accelerated growth; def, deficiency; Freq, frequency (estimated incidence); S, syndrome; TH, target height.

mainly associated with behavioural problems (Table 1). We assume that most KS cases are not seen by a medical specialist before young adulthood, and even less by a paediatrician or paediatric endocrinologist.

Another condition with a high clinical relevance is MFS (or one of the Marfanoid syndromes), with an estimated incidence of 0.2/1000 [8]. This disorder also frequently escapes medical attention [9], because the physical signs can be mild and nonspecific, and height can be within the population reference range and often within the TH range (particularly if one of the parents is also affected). In a Danish cohort, the diagnosis only became apparent because of a major cardiac event in 12.9% of patients [9].

Other examples of primary growth disorders associated with TS are very or extremely rare, and usually present with typical clinical features (Table 1), which usually enable the clinical geneticist or paediatrician to suspect the diagnosis and confirm this by genetic analysis. For some syndromes tall stature is a less frequently occurring clinical feature than previously assumed. For example, in a retrospective study on MEN2B syndrome, only 2 out of 24 children were tall and most patients were short [10]. In children with PTEN-related syndromes, height is usually normal, and tall stature was observed in 20% of males and none of the affected girls, while macrocephaly was observed in almost all patients [11].

There are only few secondary growth disorders associated with TS/AG, and most are extremely rare, except for hyperthyroidism (estimated incidence 1-6.5/100.000) [12], precocious puberty (boys <5/10,000, girls: 20/10,000) and obesity (prevalence dependent on the country). Also in these conditions height SDS can be within the reference range. For example, the mean (SD) height of children with familial glucocorticoid deficiency in a large cohort was 1.8 (1.5) SDS [13].

If no cause can be found in a tall child, the term "constitutional tall stature" has often been used. We prefer the term "idiopathic tall stature" (ITS), mirroring the term "idiopathic short stature (ISS). ITS is further subdivided into familial and non-familial, based on the distance between HSDS and THSDS. "Constitutional advancement of growth" (CAG) is the assumed mirror image of constitutional delay of growth and puberty (CDGP) [14].

In the few available reports the diagnostic yield of a pathologic cause of TS/AG was low (1.5-12%) [15-17].

## Initial diagnostic approach of the child with TS/AG

In our recent guideline [1], we proposed a stepwise diagnostic approach, with an emphasis on trying to increase the percentage of children with KS or MFS diagnosed in childhood, and other pathological causes. A secondary goal is to adequately predict adult height based on the growth pattern and bone age, which allows for appropriate information and advice to the patients and parents [1].

A simplified version of the flow chart [1] is shown in Figure 1. The flow chart aims at offering the most ra-

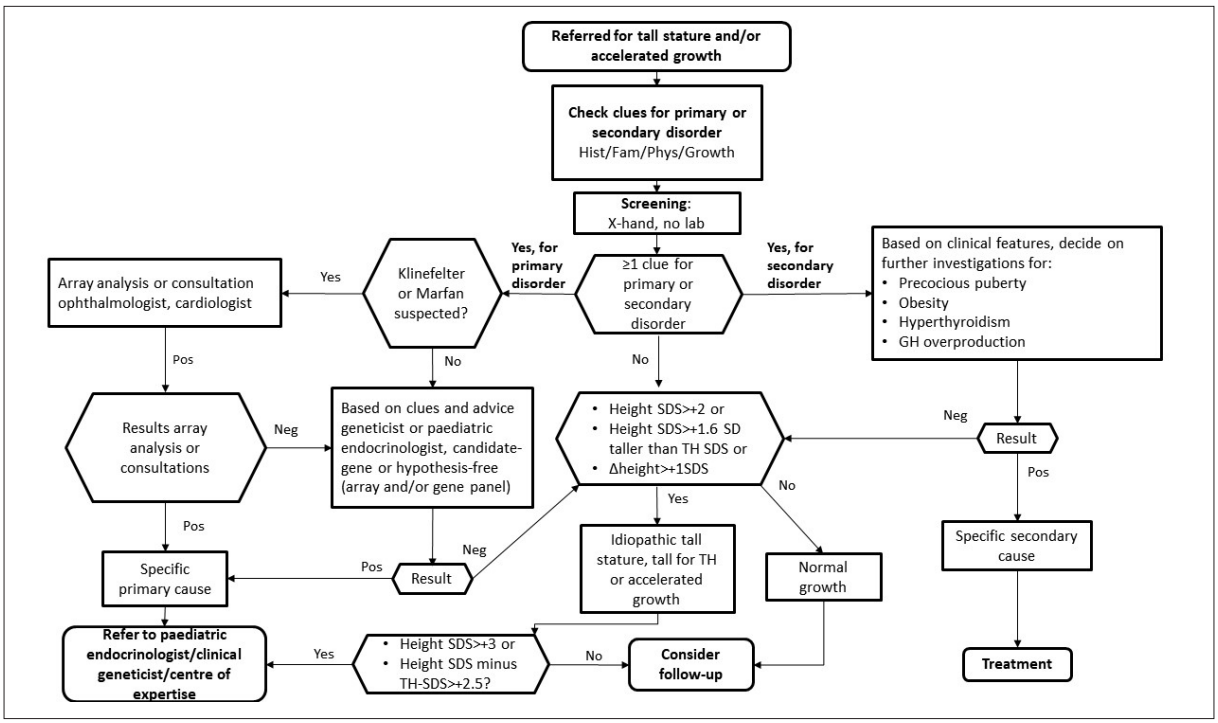


Figure 1. Simplified flow chart for diagnosis of children referred for tall stature and/or accelerated growth.

tional and efficient diagnostic approach for children referred for TS/AG, focusing on important diagnostic clues in medical history and physical examination, the shape of the growth curve as a diagnostic clue, and the role of additional laboratory and genetic testing.

When taking a full medical history, performing a full physical examination and examining the growth curve, the clinician should have a basic knowledge of the symptoms, physical signs and growth patterns associated with pathological causes of TS/AG. We believe that such clinical assessment should be done irrespective of whether the growth pattern is "abnormal" in the statistical sense, since several syndromes associated with TS/AG often present with a height within the population range. Tables with diagnostic clues for a primary of secondary growth disorder can be found in our previous publication [1]. Based on the presence or absence of diagnostic clues for primary or secondary growth disorders, the clinician may decide to perform laboratory investigations or third-line consultations.

Without going into much detail, we wish to mention a few important issues regarding the medical history (for an exhaustive list, please see Table 1 in Lauffer et al [1]). For example, information on foetal growth (particularly birth length, or first measured postnatal length) is vital, since excessive foetal growth is suggestive of a primary growth disorder. Another diagnostic clue for primary growth disorders is any form of developmental delay (including delay in development of speech and language), or behavioural problems. Information about the onset and presentation of pubertal signs (as a clue for a central or pseudo-precocious puberty) should of course be collected. In the family history, information should be collected about a possible dominant pattern of tall stature, cardiac or eye conditions at a relatively young age in family members (as a clue for MFS) and a positive history in one or both of the parents for advancement of growth in the first decade of life with a normal adult height (for constitutional acceleration of growth).

Regarding relevant issues in the physical examination (for more details, see Table 2 in Lauffer et al [1]), we emphasize that besides height, weight and head circumference, it is generally advised to assess body proportions. The main reason is that increased length of the extremities is considered a diagnostic clue for MFS, KS and *SHOX* duplications [16].

There are two body measurements needed to assess body proportions: sitting height and arm span. Sitting height is used to calculate the sitting height/height ratio, and convert this to an SDS based on suitable reference data (for example [18] in Spain). Arm span is used to assess the relationship between arm span and height, either by calculating arm span minus height [19] or arm span/height ratio [20]. However, there is some

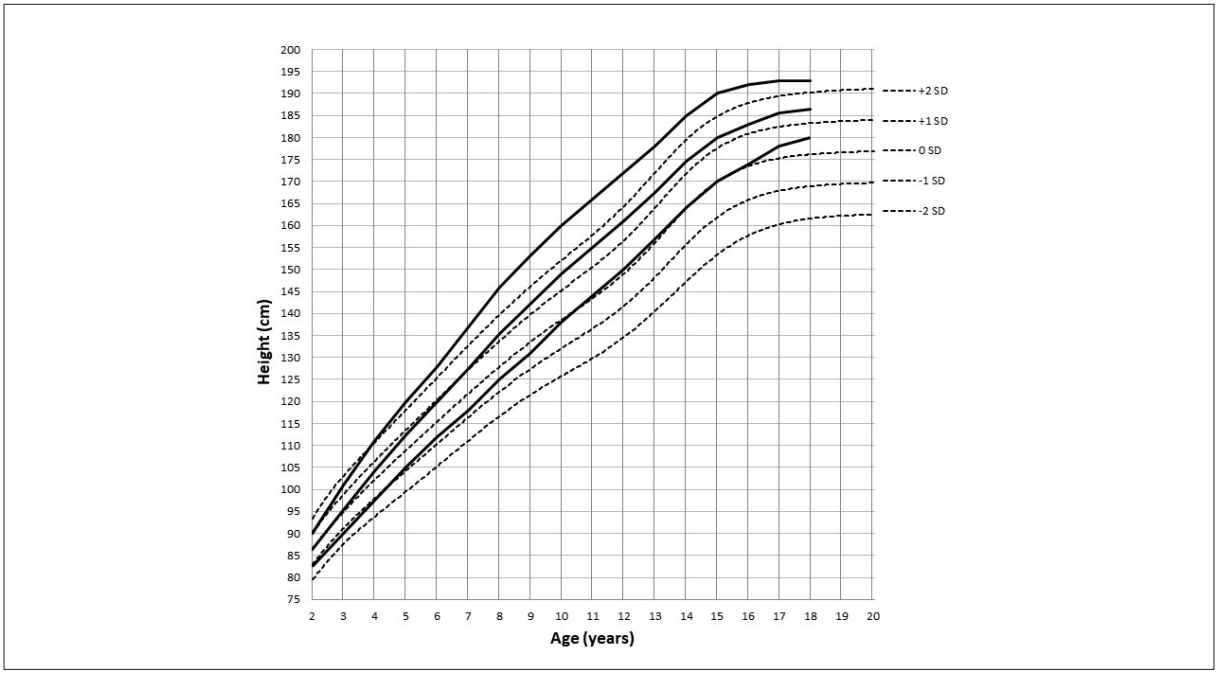


Figure 2. Range of growth curves of boys with Klinefelter syndrome against populations references.
The middle continuous line is the mean of the cohort, and the upper and lower continuous lines show the upper and lower ranges of the cohort, respectively. While in most boys HSDS stays within the population range, mean height of the cohort accelerates from 3 years onward, which is particularly clear between 5 to 8 years. The population references (dotted lines) are based on the 2000 CDC (Centers for Disease Control and Prevention) stature-for-age charts for males aged 2 to 20 [51]. Redrawn from Ratcliffe et al [5]. Previously published by Lauffer et al [1]. Reproduced with permission from the Publisher S. Karger AG, Basel, and authors.

doubt about the diagnostic value of body proportions as part of the criteria to perform genetic testing for these two conditions. If sitting height/height ratios of adolescents with MFS were plotted on a graph of sitting height/height ratio SDS versus height SDS in healthy children [21], only 3 out of 10 adolescents showed a value of -2 SDS adjusted for height SDS.

There is also doubt about the diagnostic value of arm span/height ratio as part of the criteria for MFS. In the revised Ghent nosology [20] an increased arm span/height ratio (>1.05) is still part of the guideline for adults [20], but its diagnostic value may be limited in children [22] and in people of Asian origin [23,24]. This limitation may be related to the fact that arm span/height is age dependent and also varies across ethnicities [25,26].

Similarly, the diagnostic value of an increased arm span/height ratio for children and adolescents with KS may be less than initially estimated. Adult KS patients typically show a positive arm span/height ratio, with span length exceeding height with at least 2 centimeters [27], but this cut-off applies to more than half of the healthy male population in Western countries [25], and there is little information about its value in children and adolescents. Still, arm span appears to vary depending on the origin of the supernumerary X-chromosome [28]. More data are needed of body proportions in genetically confirmed individuals with MFS and KS.

Special attention have to be paid to dysmorphic features that are associated with growth disorders, as well as Tanner stage (details are shown in Table 3 in Lauffer et al [1]). Observations obtained at physical examination can be compared with the lists of clinical features of KS [7] and MFS [20]. Regarding MFS, it has been argued that in children a lower threshold (≥ 3-4 points compared to ≥ 7 points in adults) should be sufficient to consider cardiac ultrasonography and/or genetic testing for MFS [29]. Expert consensus and/or review articles are also available for many other syndromes associated with TS (listed in [1]).

As discussed in the first paragraph, the analysis of the linear growth curve essentially includes three elements: HSDS, HSDS minus THSDS and change of HSDS. Several syndromes are associated with characteristic growth patterns. While most boys with KS have a height within the population range, growth accelerates from 3 years onward, which is particularly clear between 5 to 8 years, predominantly due to an increased leg growth, while the pubertal growth spurt varies [5,7,28,30,31] (Figure 2). Most boys have an HSDS in the upper half of the reference range [32] and average adult height is 4-10 cm above the mean for the population [5,32].

Figure 3 shows growth curves of Korean male and female MFS patients [24], compared with the Korean reference chart. The mean HSDS is consistently above +2 SDS from age 2 onwards, but not all patients have a height >2 SDS. For a typical growth curve of a child with a growth hormone producing pituitary adenoma we refer to our previous publication [1].

The last element of the clinical assessment is the radiograph of the left hand and wrist. The first purpose

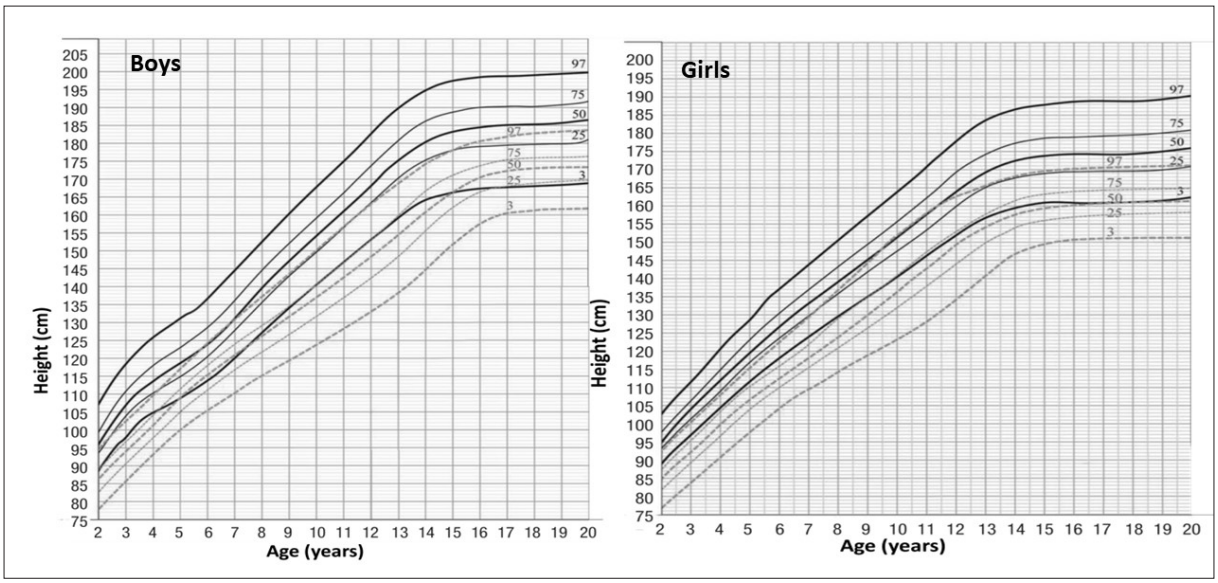


Figure 3. Range of growth curves of Korean boys and girls with Marfan syndrome against population references.
The mean HSDS in this cohort is consistently above +2 SDS from age 2 onwards. The population references (dotted lines) are for Korean boys and girls, respectively. The ranges are given in percentiles. It is noteworthy that not all patients are tall compared with the reference charts. Redrawn from Kwun et al. [24]. Reproduced by permission of the Korean Academy of Medical Sciences. Previously published by Lauffer et al [1]. Reproduced with permission from the Publisher S. Karger AG, Basel, and authors.

is to assist in the diagnostic process, because several pathological causes are associated with severely advanced bone age (e.g. Sotos syndrome, Weaver syndrome, (pseudo)precocious puberty, hyperthyroidism and CAG) [14,33,34]. Bone age is usually assessed using the Greulich & Pyle method [35], and predicted adult height (PAH) via the Bayley & Pinneau (B&P) tables [36], either using the atlas or a computerized system [37]. For extensive reviews on bone age, the reader is referred to the review papers of Martin et al [38,39]. In fact, adult height prediction is a frequent reason for referring a tall child.

Further, the gestalt of the hand can suggest certain diagnoses, such as long slender phalanges in MFS, and bone age serves as the basis of adult height prediction in children above approximately 10 years.

**Further targeted diagnostic procedures**

In case of at least one clue for a primary growth disorder, and particularly if the initial assessment is suggestive for KS, MFS or other syndromes, genetic investigations are indicated.

Traditionally, a clinical suspicion of KS is confirmed by karyotyping, but in our laboratory we prefer an array analysis (SNP-array or CGH-array) as the first diagnostic step. The advantage of using a microarray is that it also allows for detection of copy number variants (CNVs, microdeletions and microduplications), for example a duplication of the SHOX gene. Triple SHOX gene copy syndrome is associated with very tall stature and relatively long legs [16]. It also enables the detection of uniparental disomy (UPD), for example Beckwith-Wiedemann syndrome [40]. However, one should note that a normal chromosomal microarray result does not always exclude UPD, as shown for UPDs in chromosome 15 [41]. Further, the difference in costs between the two diagnostic tools may play a role in the decision.

If MFS appears likely because of the compliance with the Revised Ghent criteria [20], a clinical geneticist (preferably affiliated to a Marfan expert clinic) may differentiate between MFS and several Marfan-like syndromes and perform genetic testing of *FBN1* and/or a panel of genes including *FBN1*. In case of a positive diagnosis, genetic counselling is offered to the patient and family.

In children with clinical features consistent with another primary growth disorder, further diagnostic workup by a clinical geneticist or paediatric endocrinologist may be warranted. Traditionally, a candidate gene approach is taken if clinical features are highly suggestive for a specific genetic syndrome, for example based on one of the established clinical scores. Presently, targeted gene panels are being increasingly used in such cases, (reviewed in [1]). In cases with an apparent novel form of syndromic TS, nontargeted trio exome sequencing may be indicated. This can indeed lead to unsuspected novel causes, such as an activating variant of *NPR2* [42] or an inactivating variant of *NPR3* [43].

If a secondary growth disorder appears likely, further diagnostic procedures depend on the specific clinical features. Obese children display an accelerated growth and an advanced bone age [44], which sometimes presents as HSDS > +2. However, pubertal and skeletal development are usually advanced and consequently adult height is within the normal range [45]. AG due to hyperthyroidism is very rare, and can easily be diagnosed by serum FT4 and TSH. Important diagnostic clues for familial glucocorticoid deficiency include hyperpigmentation, hypoglycaemia and seizures [13]. GH overproduction is extremely rare in the paediatric age range but should be excluded if the physical exam, growth charts and serially elevated IGF-1 levels are suggestive of this condition and no other cause be identified.

**Management of the tall child**

Obviously, management is primarily dependent on the underlying diagnosis. In most cases no pathologic cause can be found (ITS), and in some of them the predicted adult height is so tall that children and their parents may ask for a treatment to limit adult height. This request can also come from very tall syndromic children.

If the child and parents are indeed worried that adult height will become excessive, the estimated PAH plays an important role. Obviously, the accuracy of PAH increases by age, but at the same time the potential reduction of adult height by an intervention decreases. In the Netherlands, we advise to repeat a bone age and PAH estimation if the PAH is >2.3 SDS and if current height is 15 cm lower, so that a timely and informed decision can be made whether or not the patient and his or her family are seeking height-reducing treatment or not. For the tall population of the Netherlands, a PAH of 2.3 SDS equals 200 cm for boys and 185 cm for girls. When patients present at a later stage, epiphysiodesis is not effective anymore. If puberty starts late or shows a slow progression, one should be aware of the possibility that attained height may be substantially higher than predicted, so that more frequent bone age assessments may be indicated.

If the tall adolescent and the parents indeed consider an intervention to reduce adult height, it is the task of the paediatric endocrinologist to fully discuss the pros and cons of such intervention with them. In the past, high doses of sex hormones were prescribed in such cases, but the risk of later fertility problems in treated women has made this treatment obsolete [46,47]. At present, the only intervention we offer is percutaneous epiphysiodesis. In the discussion with the patient and

parents it is important to assess their perspective and coping abilities, and inform them about the predicted effect on adult height and about the possible adverse effects. The predicted effect is a loss of one third of the expected residual growth and the adverse events (e.g. complications of the operation) are usually mild [48-50]. Clearly, this is a personal decision from the part of the patient and his or her parents, based on their personal values, concerns and future outlook on life as an extremely tall adult. In our experience, only a subset of patients that are offered the option of epiphysiodesis, ultimately choose for surgical intervention and in cases of persistent doubt, we typically advise patients to refrain from any type of surgical therapy.

## Conclusion

Diagnosis and management of children and adolescents with TS/AG is a challenge because of the arbitrary definitions, large number of potential (mostly rare) causes and the nonspecific presentation of the most relevant disorders (KS and MFS), including a height within the reference range. Increased awareness of the clinical features of KS and MFS at all echelons of preventive and curative medicine is needed to increase the percentage of cases diagnosed in childhood. If KS is suspected, microarrays appear a more efficient tool than karyotyping if microarrays are readily available to the practitioner at a reasonable cost. Management is primarily dependent on the diagnosis, but also includes an accurate adult height prediction. In case of a tall predicted adult height, a balanced discussion with the child and parents is needed about pros and cons of surgical intervention.

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## Statement of Ethics

The authors have no ethical conflicts to disclose.

*Disclosure Statement*

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## Conflicts of interest

Authors declare no potential Conflicts of Interest.

## References

1. Lauffer P, Kamp GA, Menke LA, on behalf of the Dutch Working Group on T, et al. Towards a Rational and Efficient Diagnostic Approach in Children Referred for Tall Stature and/or Accelerated Growth to the General Paediatrician. Horm Res Paediatr. 2019;91(5):293-310.

2. van Dommelen P, van Zoonen R, Vlasblom E, Wit JM, Beltman M, Expert C. Guideline for referring short or tall children in preventive child health care. Acta Paediatr. 2021;110(4):1231-8.

3. Hermanussen M, Cole J. The calculation of target height reconsidered. Horm Res. 2003;59(4):180-3.

4. Quigley CA, Ranke MB. International Classification of Pediatric Endocrine Diagnoses Rotterdam: Growth Analyser; 2016 [cited 2018 2018 April 5]. Available from: http://www.icped.org.

5. Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. Arch Dis Child. 1999;80(2):192-5.

6. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab. 2003;88(2):622-6.

7. Aksglaede L, Link K, Giwercman A, Jorgensen N, Skakkebaek NE, Juul A. 47,XXY Klinefelter syndrome: clinical characteristics and age-specific recommendations for medical management. Am J Med Genet C Semin Med Genet. 2013;163C(1):55-63.

8. Chiu HH, Wu MH, Chen HC, Kao FY, Huang SK. Epidemiological profile of Marfan syndrome in a general population: a national database study. Mayo Clin Proc. 2014;89(1):34-42.

9. Groth KA, Stochholm K, Hove H, et al. Aortic events in a nationwide Marfan syndrome cohort. Clin Res Cardiol. 2017;106(2):105-12.

10. Redlich A, Lessel L, Petrou A, Mier P, Vorwerk P. Multiple endocrine neoplasia type 2B: Frequency of physical stigmata-Results of the GPOH-MET registry. Pediatr Blood Cancer. 2020;67(2):e28056.

11. Plamper M, Gohlke B, Schreiner F, Woelfle J. Phenotype-Driven Diagnostic of PTEN Hamartoma Tumor Syndrome: Macrocephaly, But Neither Height nor Weight Development, Is the Important Trait in Children. Cancers (Basel). 2019;11(7).

12. Leger J, Carel JC. Diagnosis and management of hyperthyroidism from prenatal life to adolescence. Best Pract Res Clin Endocrinol Metab. 2018;32(4):373-86.

13. Chung TT, Chan LF, Metherell LA, Clark AJ. Phenotypic characteristics of familial glucocorticoid deficiency (FGD) type 1 and 2. Clin Endocrinol (Oxf). 2010;72(5):589-94.

14. 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(10):4535-41.

15. Thomsett MJ. Referrals for tall stature in children: a 25-year personal experience. J Paediatr Child Health. 2009;45(1-2):58-63.

16. Upners EN, Jensen RB, Rajpert-De Meyts E, Duno M, Aksglaede L, Juul A. Short stature homeobox-containing gene duplications in 3.7% of girls with tall stature and normal karyotypes. Acta Paediatr. 2017;106(10):1651-7.

17. 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(4):260-7.

18. de Arriba Munoz A, Dominguez Cajal M, Rueda Caballero C, Labarta Aizpun JI, Mayayo Dehesa E, Ferrandez Longas A. Sitting height/standing height ratio in a Spanish population from birth to adulthood. Arch Argent Pediatr. 2013;111(4):309-14.

19. Turan S, Bereket A, Omar A, Berber M, Ozen A, Bekiroglu N. Upper segment/lower segment ratio and armspan-height difference in healthy Turkish children. Acta Paediatr. 2005;94(4):407-13.

20. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010;47(7):476-85.

21. Fredriks AM, Van Buuren S, van Heel WJ, Dijkman-Neerincx RH, Verloove-Vanhorick SP, Wit JM. Nationwide age references for sitting height, leg length, and sitting height/height ratio, and their diagnostic value for disproportionate growth disorders. Arch Dis Child. 2005;90(8):807-12.

22. Stheneur C, Tubach F, Jouneaux M, et al. Study of phenotype evolution during childhood in Marfan syndrome to improve clinical recognition. Genet Med. 2014;16(3):246-50.

23. Akutsu K, Morisaki H, Takeshita S, et al. Characteristics in phenotypic manifestations of genetically proved Marfan syndrome in a Japanese population. Am J Cardiol. 2009;103(8):1146-8.

24. Kwun Y, Kim SJ, Lee J, et al. Disease-specific Growth Charts of Marfan Syndrome Patients in Korea. J Korean Med Sci. 2015;30(7):911-6.

25. Quanjer PH, Capderou A, Mazicioglu MM, et al. All-age relationship between arm span and height in different ethnic groups. Eur Respir J. 2014;44(4):905-12.

26. Gerver WJM, Gkourogianni A, Dauber A, Nilsson O, Wit JM. Arm Span and Its Relation to Height in a 2- to 17-Year-Old Reference Population and Heterozygous Carriers of ACAN Variants. Horm Res Paediatr. 2020;93(3):164-72.

27. Smyth CM, Bremner WJ. Klinefelter syndrome. Arch Intern Med. 1998;158(12):1309-14.

28. Chang S, Skakkebaek A, Trolle C, Bojesen A, Hertz JM, Cohen A, et al. Anthropometry in Klinefelter syndrome--multifactorial influences due to CAG length, testosterone treatment and possibly intrauterine hypogonadism. J Clin Endocrinol Metab. 2015;100(3):E508-17.

29. Faivre L, Collod-Beroud G, Ades L, et al. The new Ghent criteria for Marfan syndrome: what do they change? Clin Genet. 2012;81(5):433-42.

30. Schibler D, Brook CGD, Kind HP, Zachmann M, Prader A. Growth and body proportions in 54 boys and men with Klinefelter's syndrome. Helv Paediat Acta. 1974;29(4):325-33.

31. Ratcliffe SG, Butler GE, Jones M. Edinburgh study of growth and development of children with sex chromosome abnormalities. IV. Birth Defects Orig Artic Ser. 1990;26(4):1-44.

32. Aksglaede L, Skakkebaek NE, Almstrup K, Juul A. Clinical and biological parameters in 166 boys, adolescents and adults with nonmosaic Klinefelter syndrome: a Copenhagen experience. Acta Paediatr. 2011;100(6):793-806.

33. Cole TR, Hughes HE. Sotos syndrome. J Med Genet. 1990;27(9):571-6.

34. Gibson WT, Hood RL, Zhan SH, et al. Mutations in EZH2 cause Weaver syndrome. Am J Hum Genet. 2012;90(1):110-8.

35. Greulich WW, Pyle SJ. Radiographic atlas of skeletal development of the hand and wrist. 2 ed. California: Stanford University Press; 1959.

36. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age. J Pediatr. 1952;40(4):423-41.

37. Thodberg HH, Jenni OG, Caflisch J, Ranke MB, Martin DD. Prediction of adult height based on automated determination of bone age. J Clin Endocrinol Metab. 2009;94(12):4868-74.

38. Martin DD, Wit JM, Hochberg Z, et al. The use of bone age in clinical practice - part 2. Horm Res Paediatr. 2011;76(1):10-6.

39. Martin DD, Wit JM, Hochberg Z, et al. The use of bone age in clinical practice - part 1. Horm Res Paediatr. 2011;76(1):1-9.

40. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2010;18(1):8-14.

41. Tucker T, Schlade-Bartusiak K, Eydoux P, Nelson TN, Brown L. Uniparental disomy: can SNP array data be used for diagnosis? Genet Med. 2013;14(8):753-6.

42. 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(12):E1988-E98.

43. Boudin E, de Jong TR, Prickett TCR, Let al. Bi-allelic Loss-of-Function Mutations in the NPR-C Receptor Result in Enhanced Growth and Connective Tissue Abnormalities. Am J Hum Genet. 2018;103(2):288-95.

44. de Groot CJ, van den Berg A, Ballieux B, et al. Determinants of Advanced Bone Age in Childhood Obesity. Horm Res Paediatr. 2017;87(4):254-63.

45. Johnson W, Stovitz SD, Choh AC, Czerwinski SA, Towne B, Demerath EW. Patterns of linear growth and skeletal maturation from birth to 18 years of age in overweight young adults. Int J Obes (Lond). 2012;36(4):535-41.

46. 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(12):5233-40.

47. Hendriks AE, Laven JS, Valkenburg O, et al. Fertility and ovarian function in high-dose estrogen-treated tall women. J Clin Endocrinol Metab. 2011;96(4):1098-105.

48. 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;2010:740629.

49. 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(3):219-23.

50. Hindmarsh PC. Long-term follow-up after bilateral percutaneous epiphysiodesis around the knee to reduce excessive predicted final height. Arch Dis Child. 2018;103(3):207-8.

51. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Fet al. CDC growth charts: United States. Adv Data. 2000(314):1-27.