



The aetiology of extreme tall stature in a screened Finnish paediatric population

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ABSTRACT

Background: Extremely tall children (defined as height SDS (HSDS) $\geq +3$) are frequently referred to specialized healthcare for diagnostic work-up. However, no systematic studies focusing on such children currently exist. We investigated the aetiology, clinical features, and auxological clues indicative of syndromic tall stature in extremely tall children subject to population-wide growth monitoring and screening rules.

Methods: Subjects with HSDS $\geq +3$ after three years of age born between 1990 and 2010 were identified from the Helsinki University Hospital district growth database. We comprehensively reviewed their medical records up to December 2020 and recorded underlying diagnoses, auxological data, and clinical features.

Findings: We identified 424 subjects (214 girls and 210 boys) who fulfilled the inclusion criteria. Underlying growth disorder was diagnosed in 61 (14%) patients, in 36 (17%) girls and 25 (12%) boys, respectively ($P=0.15$). Secondary causes were diagnosed in 42 (10%) patients and the two most frequent secondary diagnoses, premature adrenarche, and central precocious puberty were more frequent in girls. Primary disorder, mainly Marfan or Sotos syndrome, was diagnosed in 19 (4%) patients. Molecular genetic studies were used as a part of diagnostic work-up in 120 subjects. However, array CGH or next-generation sequencing studies were seldom used. Idiopathic tall stature (ITS) was diagnosed in 363 (86%) subjects, and it was considered familial in two-thirds. Dysmorphic features or a neurodevelopmental disorder were recorded in 104 (29%) children with ITS. The probability of a monogenic primary growth disorder increased with the degree of tall stature and deviation from target height.

Interpretation: A considerable proportion of extremely tall children have an underlying primary or secondary growth disorder, and their risk is associated with auxological parameters. Clinical features related to syndromic tall stature were surprisingly frequent in subjects with ITS, supporting the view that syndromic growth disorders with mild phenotypes may be underdiagnosed in extremely tall children. Our results lend support to comprehensive diagnostic work-up of extremely tall children.

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1. Introduction

Tall stature is a common reason for paediatric endocrinologist or clinical geneticist consultation that aims at early detection and treatment of possible underlying primary or secondary pathological causes [1]. Several guidelines on the diagnostic approach to tall stature and accelerated growth have been published [1–6]. The

guidelines suggest that children over three years with either height SDS (HSDS) $\geq +2.5$ [1,2,7] or height deviation from target height (HSDS-THSDS) $\geq +2$ SDS [3,5,6], should be evaluated in specialized healthcare. Additionally, the most comprehensive guideline on tall stature, the Dutch national guideline [1], recommends that molecular genetic studies including whole-exome sequencing (WES) could be considered as a part of the comprehensive diagnostic evaluation in extremely tall children, defined as HSDS $\geq +3$ from the age and sex specific population mean (i.e. corresponding to 99.9th centile) or HSDS-THSDS $\geq +2.5$.

The aetiology of tall stature has previously been described in only five notable cohort studies with diverse inclusion criteria and varying

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Research in context

Evidence before this study

The aetiology of tall stature in children is poorly characterized. Furthermore, no systematic studies describing aetiology and clinical features of extremely tall children, defined as height SDS $\geq +3$, currently exist. However, most comprehensive guidelines suggest that extremely tall children should be referred to specialized healthcare for comprehensive diagnostic work-up, despite the tenuous evidence-base. We carried out a search in PubMed using the terms: 'tall stature' AND 'etiology' up to the date 29 June 2021, and identified 386 publications in addition to our previously gathered reports on the topic. Only five of these were original studies and reported the aetiology of tall stature.

Added value of this study

To the best of our knowledge, we are reporting the first study describing the aetiology, comorbidities, and physical features of extremely tall children. Our results are based on a large cohort from a screened paediatric population with an equal number of girls and boys. We show that a considerable proportion of extremely tall children, independent of sex, have an underlying primary or secondary growth disorder. Additionally, our data suggest that, in addition to clinical features, auxological features are related to the risk of a syndromic underlying cause. Thus, auxological data could be used to target molecular genetic studies that may increase diagnostic yield. Though sex chromosome aneuploidy was rare among extremely tall children, monogenic syndromes were relatively frequent, particularly in the tallest subjects. Thus, suggesting next-generation sequencing as a first-line molecular genetic study.

Implications of all the available evidence

Primary and secondary growth disorders are frequent in extremely tall children. In aggregate, our study and previous reports on the subject lend support to comprehensive diagnostic work-up of extremely tall children. The threshold of performing molecular genetic studies to rule out syndromic causes should be low in those with no apparent features of a secondary growth disorder. Future studies should elucidate the prevalence of syndromic causes underlying childhood extremely tall stature and clarify the added benefit of combining clinical and auxological features, including longitudinal childhood growth, in differentiating those with primary or secondary growth disorders from children with idiopathic tall stature.

preventive healthcare produces population-level auxological data, which can be used for the development of evidence-based screening and diagnostic practices [15–17]. We report the first study on the aetiology of extreme tall stature (HSDS $\geq +3$ after the age of three years) from a screened population of children examined in a large tertiary centre that serves as the primary referral centre for child health clinic and school healthcare services. We describe auxological clues and physical features related to underlying pathology and report comorbidities of extreme tall stature.

2. Methods

2.1. Patients, methods, and centre

This retrospective study was conducted at the Children's Hospital, Helsinki University Hospital (HUU). The extremely tall subjects and their auxological data were gathered from the growth database PEDIATOR® (Tilator Oy). The growth database has been used systematically since 1999 to store and evaluate growth measurements in secondary healthcare in the HUU catchment area, which comprises the municipalities of Helsinki, Espoo, Vantaa, Kirkkonummi, Kerava, and Kauniainen. The growth database includes auxological measurements performed by trained nurses in child health clinics and school healthcare services in primary healthcare and measurements performed in secondary healthcare. The auxological data are routinely transferred and saved to the growth database before the first evaluation in paediatric specialized healthcare. At the time of auxological data retrieval (2015), the database included measurements from more than 123 600 children. In 2017 the HUU catchment area, in which the yearly birth rate is approximately 13 500, covered a population of 1.22 million, i.e. more than 23% of the Finnish population [21]. Recently updated (2010) Finnish reference material, obtained from the same district, was employed in growth evaluation [16]. The study adheres to the RECORD guidelines [22].

The inclusion criteria of the study were: at least two independent height measurements with at least three standard deviation scores (SDS) above the age and sex specific population mean after the age of three years; born in 1990 or later to include patients with adequate history in electronic medical records; and place of residence, verified by the Population Register Centre, in the HUU catchment area. We assessed all available clinical, laboratory, genetic (up to December 2020), and auxological data (up to December 2017) from the electronic medical records (Uranus by CGI Inc.) and PEDIATOR®. The auxological data were evaluated and clear erroneous measurements were excluded. Based on the review of medical records the subjects were allocated to diagnostic groups: primary growth disorders, secondary growth disorders, and idiopathic tall stature, according to the *International Classification of Pediatric Endocrine Diagnoses* (ICPED) for tall stature [23]. In those with self-evident diagnoses set by paediatric subspecialists or paediatricians based on adept workup, the classification was recorded by the first author (J.K.). The rest were classified based on a joint decision with an experienced paediatric endocrinologist (M.H.) following a thorough review of all available data. Physical features were noted and other reported diagnosis set in specialized healthcare.

Klinefelter syndrome was diagnosed based on the presence of supernumerary X-chromosome(s), including mosaicism, in a boy's karyotype. Marfan syndrome was genetically confirmed in all except one patient, in whom the diagnosis was set based on clinical features [24]. Sotos syndrome was genetically confirmed in all but one patient, in whom the diagnosis was set based on clinical features [25]. Premature adrenarche was diagnosed if a history of androgenic signs (i.e. adult-type body odour, oily hair, comedones or acne, or appearance of pubic or axillary hair), elevated serum dehydroepiandrosterone sulfate (DHEAS) ($\geq 1 \mu\text{mol/l}$) (data were available in 15/16 patients) [26], and an increase in HSDS was found before the age of 8 years in a

reported rates of detected pathology [8–12]. However, the few previous studies have been affected by apparent selection bias [8–12], and importantly, included a minimal number of extremely tall subjects [8–10,12]. Thus, the available guidelines rely on a shallow evidence base, and a clear knowledge gap exists regarding the aetiology, associated clinical features, and comorbidities of tall, and in particular, extreme tall stature. Therefore, systematic and representative reports on the frequency, underlying aetiology, and risk factors of pathological underlying conditions are needed to refine the diagnostic and referral practices of tall and extremely tall children.

In Finland, population-wide height screening has been practiced for decades and more than 99% of children participate in child health clinic and school healthcare services [13]. Each child is measured at least once a year until the child reaches adult height [14] and the auxological data are subjected to growth screening rules and referral practices [15–20]. Therefore, in Finland, growth monitoring in

prepubertal girl or 9 years in a prepubertal boy. Central precocious puberty (CPP) was diagnosed if clinical signs of puberty, i.e. breast stage 2 in girls or genital stage 2 in boys, were noted prior to age 8 and 9 years, respectively, and serum luteinizing hormone was in the pubertal range, i.e. serum LH ≥ 5 IU/L in a GnRH stimulation test or basal serum LH was ≥ 0.3 IU/L ($n=9$) [27]. Additionally, two patients were diagnosed with CPP at a later age based on puberty nomogram [28]. Growth hormone (GH) excess was diagnosed in subjects with accelerated growth, failure to suppress GH to below 1 ng/ml in an oral glucose tolerance test [29] and the GH suppression was interpreted as abnormal by the treating endocrinologist ($n=2$), or in one patient based on substantially elevated serum IGF-I, neurofibromatosis type I, and bilateral optic pathway gliomas. Hyperthyroidism caused by Graves' disease was diagnosed based on suppressed TSH and concomitantly elevated T4 or T3 and presence of TSH-R-antibodies. Congenital adrenal hyperplasia (CAH) was diagnosed based on growth acceleration, significantly advancing bone, and abnormally elevated serum 17-hydroxyprogesterone [30]. Biallelic *CYP21A2* mutations were verified in 2 of 3 patients. Obesity was considered to cause the tall stature if, in the absence of other causal factors, a substantial increase in weight-for-height coincided with an increase in HSDS [2,3]. Subjects were classified as having idiopathic tall stature (ITS) when no specific cause for tall stature was diagnosed by the physician in charge [2]. Further sub-classification to familial ITS was set for subjects with parental HSDS $\geq +2$ in either parent; or target height (TH) $\geq +1.6$ SDS from the sex-specific population mean; or the subject was diagnosed as having familial tall stature by the treating physician, based on a similar pattern of growth in either parent(s).

2.2. Auxological data

The availability and summary of auxological data are shown in Table 1. In short, 8105 height measurements were available for the study cohort. Over 90% of the subjects had ten or more measurements available with a mean of 19 measurements per subject. For calculation of SD scores, the most recent Finnish [16,31,32] and Dutch [33] reference data were used (Table 1). Formulas used to calculate TH are shown in Supplementary Table 1. HSDS-THSDS was calculated by comparing the greatest HSDS after 3 years of age and TH. Measurements of height for bone age, sitting height to height, and head circumference at the oldest age were used in analyses. For secondary causes, growth acceleration prior to diagnosis was determined (Table 1). For patients with primary causes and subjects with ITS, growth acceleration at the mean age at diagnosis for the patients with a secondary disorder was calculated (Table 1).

2.3. Statistical analyses

We performed all statistical analyses with SPSS® statistical software for Windows, version 25.0 (SPSS®, Chicago, IL, USA). P-value < 0.05 was considered to denote statistical significance. The results are presented as mean (SD) unless otherwise stated. Chi-square tests were used to analyse between-sex differences in diagnostic classifications. Receiver operating characteristic (ROC) curves and the AUC with 95% CI were used to evaluate the diagnostic performance of key auxological measurements. Based on the ROC curves, the cut-off values maximizing sensitivity and specificity were determined, prioritizing sensitivity of at least 80%. For a between-group comparison of growth acceleration, the Kruskal-Wallis test was used.

2.4. Ethics

The study was approved by the Ethics Committee of Helsinki University Hospital.

2.5. Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

3.1. Overview of the aetiology of extreme tall stature

A total of 841 subjects (433 females, 408 males) fulfilled the auxological criteria of the study, i.e. two or more HSDS measurements $\geq +3$ after the age of three years. After exclusion of subjects with erroneous personal information, the year of birth before 1990, place of residence outside the HUH catchment area, inclusion based on apparent measurement error or erroneously documented age, and subjects without diagnostic evaluation for tall stature in specialized healthcare, we identified 424 subjects (214 females, 210 males) who comprised the final study cohort (Figure 1).

Extreme tall stature was equally frequent in girls and boys (Figure 2). A comprehensive overview of the study cohort is shown in Tables 1–3. ITS, primary, and secondary causes were equally frequent in girls and boys (χ^2 (2, $N=424$) = 3.6, $P=0.17$. $\phi_c=0.092$). Pathological condition (primary or secondary growth disorder) was diagnosed in 61 (14%) patients, including 36 (17%) females and 25 (12%) males; (χ^2 (1, $N=424$) = 2.1, $P=0.15$. $\phi_c=0.070$, Figure 2). A primary growth disorder was diagnosed in 19 (4%) patients (nine females, ten males) and a secondary growth disorder in 42 (10%) (27 females, 15 males). Idiopathic tall stature was diagnosed in 363 subjects (86%) (178 females, 185 males).

3.2. Diagnostic Studies

Diagnostic studies and height-reducing treatments are shown in Table 2. Bone age was examined in 381 (90%) subjects and any laboratory studies to rule out hormone excess in 370 (87%). The diagnosis was set based on abnormal laboratory results in 31 (7%) patients. Oral glucose tolerance test with GH sampling was examined in 15 (4%) subjects and abnormal GH suppression after hyperglycaemia was observed in two patients. Other imaging studies (brain or aortic MRI, cardiac or abdominal ultrasound scan) were performed in 195 (46%) subjects. Brain MRI revealed abnormal findings underlying tall stature in five patients: pituitary GH-producing adenoma ($n=1$), bilateral optic pathway gliomas ($n=1$), parahippocampal glioma ($n=1$), and hamartoma ($n=2$). Brain MRI was reported normal in others ($n=87$). Abdominal US was performed in 94 subjects without any reported findings explaining growth acceleration or tall stature. Cardiac US or aortic MRI revealed abnormal findings in five patients and was reported normal by paediatric cardiologists in others ($n=68$). The patients with abnormal cardiac findings all had Marfan or Marfan-like syndrome; dilated aorta was noted in five patients and additional mitral valve prolapse in two.

Genetic studies were employed in 120 subjects (29% of the study cohort) and a genetic diagnosis was achieved in 20 (5% of the study cohort) patients (Table 2). Of these, karyotype was examined in 98 (23%; 19 females, 79 males) and sex chromosome aneuploidy was noted in only three patients. Chromosomal microarray was applied in eight (2%; four females, four males) and a gene panel in four (1%; four females) subjects with no molecular genetic confirmation of underlying cause. Single-gene sequencing was performed in 39 (9%; 15 females, 24 males) and a pathological variant was noted in 17 patients. A pathogenic variant in *FBN1* was detected in nine of out 14 subjects studied and a pathogenic *NSD1* variant in four of the 21 subjects. Other pathogenic variants were detected in *CYP21A2* ($n=2$), *NF1* ($n=1$), and *TGF β 3* ($n=1$). Molecular genetic studies without molecular genetic confirmation for clinical suspicion were in Fragile X ($n=17$), *AIP* ($n=2$), *MEN1* ($n=1$), *PTEN* ($n=1$), and *MC4R* ($n=1$) (Table 2).

Table 1
Key auxological measurements and data availability

	Primary Growth disorders	Marfan and Marfan-like syndrome	Sotos syndrome	Syndromes with sex chromosome anomaly, including aneuploidy	Secondary Growth disorders	Premature adrenarche	Precocious puberty	Growth hormone excess	Congenital adrenal hyperplasia	Other secondary causes; specified*	Idiopathic Tall stature (ITS)	Familial ITS with a tall parent **or TH above 1.6	Familial ITS without a tall parent	Non-Familial ITS	Study cohort
n of subjects (female %)	19 (47)	11 (55)	5 (40)	3 (33)	42 (64)	16 (75)	11 (82)	3 (33)	3 (0)	9 (56)	363 (49)	141 (53)	100 (47)	122 (46)	424 (50)
Greatest height SDS
Greatest height SDS at more than 3 years of age (SDS): median (IQR)	4.0 (1.1)	4.0 (1.0)	4.0 (2.2)	3.4	3.5 (0.5)	3.3 (0.4)	3.6 (0.3)	4.4	3.5	3.4 (0.4)	3.6 (0.6)	3.6 (0.6)	3.6 (0.5)	3.5 (0.6)	3.6 (0.6)
Age at the greatest height SDS measurement (years): mean (SD)	8.9 (5.0)	10.1 (5.8)	6.1 (2.7)	9.4 (3.1)	7.9 (2.7)	7.7 (1.6)	8.2 (2.1)	10.4 (5.4)	4.1 (1.3)	8.3 (3.3)	8.0 (3.5)	8.2 (3.7)	7.2 (3.1)	8.4 (3.4)	8.0 (3.5)
Target height (TH) ***
TH data availability: n (%)	15 (79)	9 (82)	3 (60)	3 (100)	41 (98)	15 (94)	11 (100)	3 (100)	3 (100)	9 (100)	352 (97)	141 (100)	98 (98)	113 (93)	408 (96)
TH (SDS): median (IQR)	0.6 (0.9)	0.5 (1.3)	0.4	0.9	0.4 (1.1)	0.1 (0.8)	0.0 (2.1)	1.2	0.4	0.8 (1.2)	1.0 (0.9)	1.5 (0.6)	0.8 (0.8)	0.6 (0.8)	1.0 (1.0)
TH above 1.6 SDS or parental height above 2 SDS in either parent: n (%)	6 (32)	2 (18)	1 (20)	3 (100)	9 (21)	4 (25)	1 (9)	2 (67)	1 (33)	1 (11)	141 (39)	141 (100)	0	0	156 (37)
Height deviation from TH (SDS): median (IQR)	3.2 (1.4)	3.7 (1.5)	3.6	2.5	3.2 (1.2)	3.2 (0.8)	3.5 (1.7)	3.1	3.1	2.8 (1.5)	2.6 (1.0)	2.1 (0.7)	2.8 (0.8)	3.0 (0.9)	2.7 (1.0)
Birth Length†
Birth length data availability: n (%)	15 (79)	7 (64)	5 (100)	3 (100)	34 (81)	15 (94)	8 (73)	2 (67)	3 (100)	6 (67)	301 (83)	119 (84)	83 (83)	99 (81)	350 (83)
Birth length (cm): median (IQR)	54 (4.0)	51 (5.0)	55 (4.0)	51	51 (2.1)	51 (2.0)	51 (3.5)	50	49	51 (1.5)	52 (3.0)	53 (3.0)	52 (3.0)	52 (2.5)	52 (3.0)
Head Circumference††
Head circumference; age more than 6 months data availability: n (%)	7 (37)	3 (27)	4 (80)	0	24 (57)	11 (69)	5 (45)	2 (67)	1 (33)	5 (56)	228 (63)	86 (61)	66 (66)	76 (62)	259 (61)
Head circumference; most recent measurement (SDS): mean (SD)	1.8 (1.3)	1.6 (0.8)	1.9 (1.7)	..	1.1 (1.3)	1.0 (0.7)	0.8 (0.7)	2.5 (0.3)	-2.1	1.5 (2.1)	1.2 (1.2)	1.4 (1.1)	1.0 (1.2)	1.2 (1.2)	1.2 (1.2)
Height SDS for bone age
Bone age; age more than 3 years data availability: n (%)	9 (47)	5 (45)	1 (20)	3 (100)	35 (83)	16 (100)	11 (100)	2 (67)	3 (100)	3 (33)	280 (77)	105 (74)	79 (79)	96 (79)	324 (76)
Height SDS for bone age (SDS): mean (SD)	2.7 (1.0)	2.6 (0.6)	4.8	2.1 (1.0)	0.6 (1.1)	0.7 (0.6)	0.4 (0.7)	2.1 (2.9)	-1.0 (0.8)	1.0 (1.9)	1.6 (1.0)	2.0 (1.0)	1.5 (1.0)	1.3 (1.0)	1.5 (1.1)
Age at most recent bone age measurement	11.7 (2.4)	12.4 (1.4)	11.9	10.4 (4.0)	9.4 (2.2)	8.4 (1.6)	9.7 (1.5)	11.4 (5.0)	11.7 (3.9)	9.8 (2.2)	9.1 (2.9)	9.3 (3.1)	8.3 (2.9)	9.5 (2.6)	9.2 (2.8)

(continued on next page)

Table 1 (Continued)

	Primary Growth disorders	Marfan and Marfan-like syndrome	Sotos syndrome	Syndromes with sex chromosome anomaly, including aneuploidy	Secondary Growth disorders	Premature adrenarche	Precocious puberty	Growth hormone excess	Congenital adrenal hyperplasia	Other secondary causes; specified*	Idiopathic Tall stature (ITS)	Familial ITS with a tall parent **or TH above 1.6	Familial ITS without a tall parent	Non-Familial ITS	Study cohort
(years): mean (SD)
Sitting height to height †††
Sitting height; age more than 3 years data availability: n (%)	11 (58)	7 (64)	2 (40)	2 (67)	26 (62)	11 (69)	9 (82)	1 (33)	3 (100)	2 (22)	130 (36)	53 (38)	33 (33)	44 (36)	167 (39)
Sitting height to height Z-score (SDS): mean (SD)	-0.9 (1.4)	-1.7 (1.1)	-0.1 (0.7)	0.9 (0.5)	-0.4 (1.3)	-0.4 (1.0)	-1.0 (1.0)	-2.4	1.6 (1.3)	0.4 (0.6)	-0.7 (1.0)	-0.9 (1.0)	-0.7 (1.0)	-0.6 (1.1)	-0.7 (1.1)
Age at the most recent sitting height measurement (years): mean (SD)	14.4 (2.0)	15.1 (2.0)	12.5 (1.7)	13.5 (1.5)	9.8 (2.4)	8.8 (1.1)	9.7 (1.6)	16.1	10.8 (5.0)	11.3 (1.3)	9.1 (3.3)	9.6 (3.8)	8.3 (3.0)	8.9 (2.9)	9.5 (3.4)
Age at diagnosis §
Age at diagnosis data availability: n	16	9	4	3	35	16	11	3	3	2
Age at diagnosis (years): mean (SD)	8.3 (5.9)	11.5 (5.3)	1.5 (1.0)	7.6 (3.2)	7.4 (2.2)	7.3 (1.1)	7.5 (2.1)	10.8 (3.5)	3.9 (1.2)	8.5 (3.2)
Growth acceleration §§
Growth acceleration data availability: n	13	33	16	11	2	3	1	222
Growth acceleration (delta HSDS per year): median (IQR)	-0.1 (0.4)	1.0 (0.6)	0.2 (0.4)	0.5 (0.3)	0.5	1.2	0.7	0.1 (0.3)

*Other secondary causes: Graves' hyperthyroidism (n=1); parahippocampal glioma with normal GH and IGF-1 in a prepubertal patient (n=1); obesity (n=7).

**Parental height ≥ 2 SDS.

***Formulas used to calculate TH are shown in Supplementary Table 1.

†Gestational ages were not available for the study cohort.

††Head circumference SDS was calculated using the Finnish reference data [30].

†††Sitting height to height Z-score was calculated using Finnish reference data in subjects aged 8 years or more (n=114) [31] and the Dutch reference data for measurements at a younger age (n=53) [32].

§The age at diagnosis was calculated for patients with primary or secondary causes, excluding subjects with obesity.

§§Growth acceleration prior to diagnosis was calculated for secondary causes. The age difference between measurements used to calculate growth acceleration was set between 6 months to two years for all subjects. For patients with primary causes and subjects with ITS, the measurement at the older age had to be between the ages of 6.9 to 8 years.

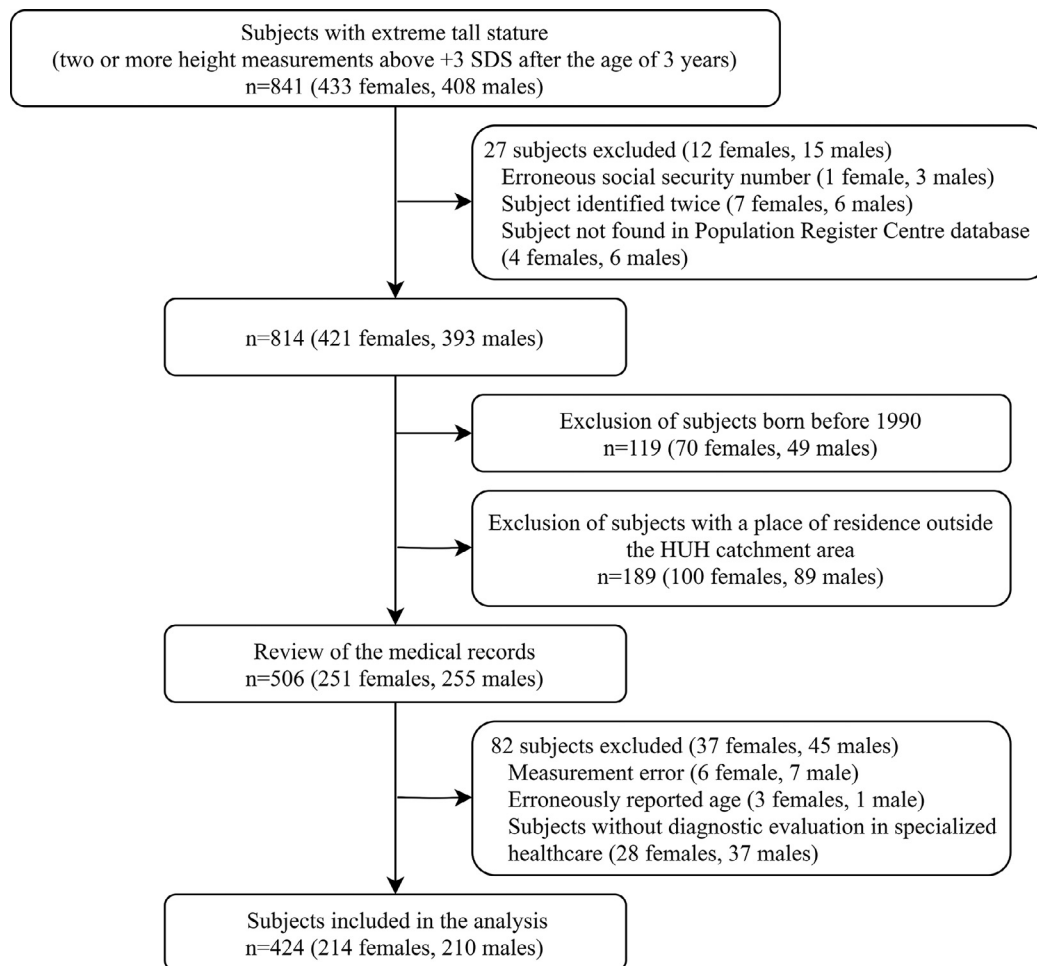


Figure 1. A flowchart depicting the formation of the study cohort of extremely tall statured children.

3.3. Primary and secondary causes

The most common primary growth disorder (clinically defined syndrome) for both sexes was Marfan syndrome (six girls, four boys), followed by Sotos syndrome (two girls, three boys) and Loey-Dietz syndrome (one boy). Molecular genetic confirmation was conducted for nine patients with Marfan syndrome, for four patients with Sotos syndrome, and for the patient with Loey-Dietz syndrome. All patients with Marfan syndrome ($n=10$) or Marfan-like syndrome (Loey-Dietz syndrome; $n=1$) underwent both cardiac imaging and ophthalmologic consultation and pathologic cardiac or aortic findings were noted in five (45%) patients and lens luxation in two (18%). The mean age at the first abnormal cardiac US finding was 7.6 (2.6 SD) years ($n=4$). The mean systemic score [24] for patients with Marfan syndrome at the time of diagnosis was 4 (1.9) ($n=7$). Sex chromosome aneuploidy underlying extreme tall stature was rare. Klinefelter syndrome was diagnosed in one patient and sex chromosome mosaicism in two: 46XY/47XYY in a boy and 46XX/47XXY in a girl, respectively. The mean age at the diagnosis was 11.5 (5.3), 1.5 (1.0), and 7.6 (3.2) years, for Marfan and Marfan-like syndromes, Sotos syndrome, and sex chromosome aneuploidy, respectively (Table 1).

The two most frequent secondary causes (endocrine causes), premature adrenarche (12 girls, four boys) and central precocious puberty (CPP) (nine girls, two boys), were more frequent in girls, whereas congenital adrenal hyperplasia (CAH) was diagnosed only in boys ($n=3$). Growth hormone (GH) excess was diagnosed in one girl and two boys. In patients with GH excess, a pathogenic variant in *NFI* was noted in one and pathogenic variants in *AIP* excluded in others

($n=2$). All patients with CPP or GH excess underwent brain MRI. Hamartoma was noted in two patients with CPP (18%) and a GH adenoma ($n=1$) and bilateral optic pathway gliomas ($n=1$) in two patients with GH excess. Other secondary causes included hyperthyroidism caused by Graves' disease ($n=1$) and a parahippocampal glioma with normal GH and IGF-1 in a prepubertal patient ($n=1$). Obesity and weight gain as growth accelerating causes were diagnosed in seven subjects. The mean age at diagnosis for a secondary disorder was 7.4 (2.2) years ($n=35$), age at diagnosis data is shown in detail in Table 1.

3.4. Idiopathic tall stature

Idiopathic tall stature (ITS) (i.e. no pathological cause for tall stature was evident) was diagnosed in 363 (178 girls, 185 boys) subjects. Familial ITS was diagnosed in 241 (66% of the subjects with ITS), of whom 141 had a tall parent (parental HSDS $\geq +2$) or TH $\geq +1.6$ SDS. Non-familial ITS was diagnosed in 122 subjects (56 girls, 66 boys).

3.5. Adult height-reducing treatment

Adult height-reducing treatment was conducted in 13 (3%) subjects; in five boys and eight girls (Table 2). Nine of the treated patients had ITS. Epiphysiodesis of the distal femora and proximal tibiae was conducted in seven subjects, and high-dose sex steroid treatment in six girls. Additionally, metatarsal epiphysiodesis was performed for four patients (Table 2).

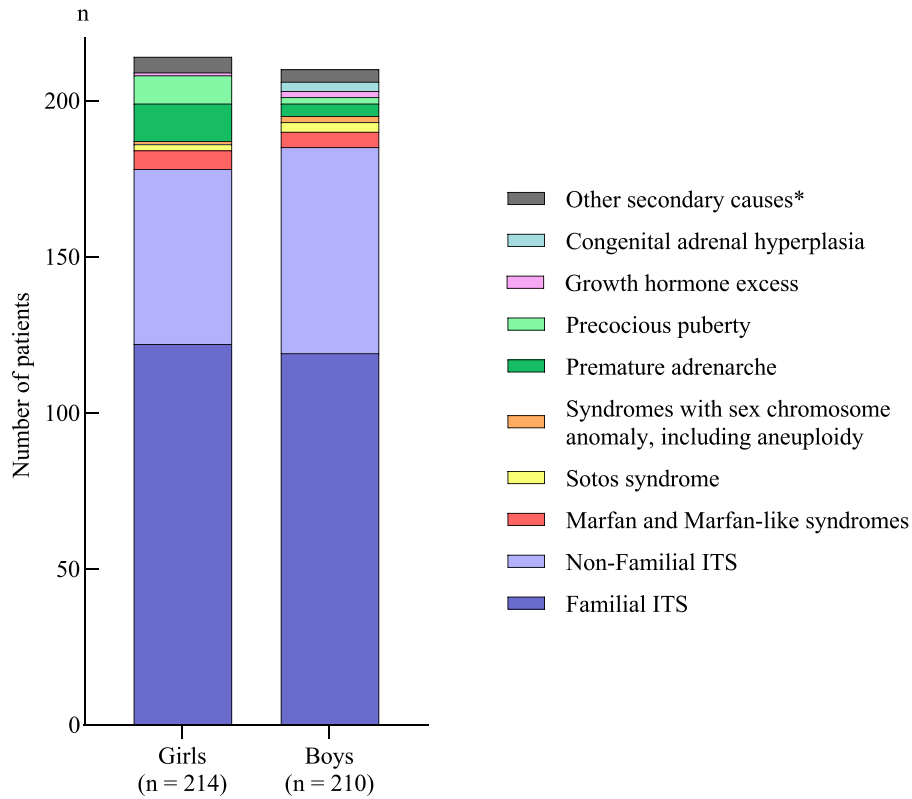


Figure 2. The aetiology of extremely tall stature, defined as height SDS of more than +3 after the age of three years, in children born 1990 or later with a place of residence in the HUH catchment area. *Other secondary causes: Graves' hyperthyroidism (n=1); parahippocampal glioma with normal GH and IGF-1 in a prepubertal patient (n=1); obesity (n=7).

3.6. Features associated with primary growth disorders

Physical features or a neurodevelopmental disorder i.e. features associated with primary growth disorders were noted in 128 (30%) subjects, shown in detail in Table 3. Any feature associated with primary growth disorders was documented in the majority of patients with Marfan and Marfan-like syndrome (n=10; 91%), in all patients with Sotos syndrome (n=5) or sex chromosome aneuploidy (n=3), i.e. in all except one patient with a primary growth disorder. Conversely, such a feature was noted in six (14%) patients with a secondary cause and 104 (29%) subjects with ITS.

In subjects with ITS, a physical feature associated with syndromic tall stature was noted in 71 (20%) subjects and a neurodevelopmental disorder in 55 (15%) (reported features and neurodevelopmental disorders are shown in detail in Table 3). The most common features were learning disabilities (including ADHD and ADD; n=47; 13%), followed by physical features of the extremities (n=43; 12%), head region (n=36; 10%), and thorax (n=18; 5%). Intellectual disability was diagnosed in five subjects with ITS. Autism spectrum disorder was diagnosed only in boys (n=11) and all except one had ITS. The most common physical feature among subjects with ITS was pes planus/planovalgus (n=18), followed by flexible joints (n=16), and high-arched palate (n=15). Subjects with ITS and a neurodevelopmental disorder underwent genetic studies relatively frequently: karyotype was examined in 32 subjects, array studies applied in six, Fragile X excluded in 12, and pathogenic variants in *NSD1* excluded in ten.

3.7. Auxology

Key auxological measurements were determined for each subject, Table 1. The cohort was then divided into quartiles based on the degree of tall stature (HSDS), Figure 3. The secondary growth disorders were more prevalent in subjects with HSDS <+3.6, i.e. in the

quartiles 1 and 2 (χ^2 (1, N=424) =6.8, P<0.01. ϕ_c =0.13). In contrast, with an increasing degree of tall stature, the frequency of primary causes increased, from less than 1% (n=1) in those with the HSDS <+3.3 to 10% (n=11) in those with the HSDS \geq +3.9 SDS (χ^2 (1, N=212) =8.8, P<0.005. ϕ_c =0.21). Over half of the patients with a primary cause had the greatest HSDS \geq +3.9. Moreover, in subjects with height in the tallest quartile, HSDS \geq +3.9, primary causes were more frequent than secondary causes (10% (n=11) vs 7% (n=7)). Molecular genetic studies were employed in 22, 22, 29, and 49 subjects in HSDS quartiles 1 to 4, respectively. Similarly, the risk of underlying growth disorders was influenced by the degree of height deviation from target height (HSDS-THSDS), shown in Supplementary Figure 1. With increasing HSDS-THSDS, the overall detected pathology increased from 5% (n=5) in those with HSDS-THSDS <2.2 to 25% (n=26) in those with HSDS-THSDS \geq 3.2 (χ^2 (1, N=204) =16.8, P<0.001. ϕ_c =0.29). Growth acceleration (delta HSDS per year) at the time of diagnosis in patients with a secondary growth disorder, and the respective measure in subjects with a primary disorder or ITS at the same mean age, is shown in Supplementary Figure 2 and Table 1. In a between-group analysis [H(2)=86.5, P<0.0001], those with a secondary disorder had significantly greater growth acceleration than those with ITS or primary disorder (Supplementary Figure 2).

Next, we evaluated whether key auxological measures assorted diagnostic groups using the ROC analysis. In a comparison of patients with a monogenic primary growth disorder and subjects with ITS, the HSDS cut-off of +3.7 SDS resulted in 81% sensitivity and 63% specificity in detecting a monogenic primary growth disorder with a positive likelihood ratio (+LR) of 2.18 and a negative likelihood ratio (-LR) of 0.30; HSDS-THSDS cut-off of +2.7 SDS differentiated the groups with 83% sensitivity and 51% specificity (+LR 1.72 and -LR 0.32) (Figure 4). Additionally, based on AUCs, HSDS for bone age assorted secondary causes from ITS and sitting height to height SDS and birth length assorted monogenic syndromes from ITS (Supplementary Table 2).

Table 2
Diagnostic studies and height-reducing treatments

	Primary Growth disorders	Marfan and Marfan-like syndrome	Sotos syndrome	Syndromes with sex chromosome anomaly, including aneuploidy	Secondary Growth disorders	Premature adrenarache	Precocious puberty	Growth hormone excess	Congenital adrenal hyperplasia	Other secondary causes; specified*	Idiopathic Tall stature (ITS)	Familial ITS with a tall parent ** or TH above 1.6	Familial ITS without a tall parent	Non-Familial ITS	Study cohort
n of subjects (female %)	19 (47)	11 (55)	5 (40)	3 (33)	42 (64)	16 (75)	11 (82)	3 (33)	3 (0)	9 (56)	363 (49)	141 (53)	100 (47)	122 (46)	424 (50)
DIAGNOSTIC STUDIES	**	**	**	**	**	**	**	**	**	**	**	**	**	**	**
Bone age; n (%)	11 (58)	5 (45)	3 (60)	3 (100)	40 (95)	16 (100)	11 (100)	3 (100)	3 (100)	7 (78)	330 (91)	128 (91)	89 (89)	113 (92)	381 (90)
Growth acceleration laboratory studies***; any; n (%)	17 (89)	9 (82)	5 (100)	3 (100)	42 (100)	16 (100)	11 (100)	3 (100)	3 (100)	9 (100)	311 (86)	112 (79)	85 (85)	114 (93)	370 (87)
Oral glucose tolerance test with GH sampling	1	1	0	0	3	1	0	2	0	0	11	3	3	5	15
Imaging studies other than bone age; any†	17 (89)	11 (100)	5 (100)	1 (33)	32 (76)	10 (63)	11 (100)	3 (100)	3 (100)	5 (71)	146 (40)	50 (35)	39 (39)	57 (46)	195 (46)
Brain MRI	4	3	1	0	23	6	11	3	1	2	65	23	12	30	92
Abdominal US	5	2	2	1	21	9	3	2	3	4	68	24	25	19	94
Cardiac echocardiogram, cardiac or aortic MRI	16	11	5	0	1	0	0	0	1	0	56	19	12	25	73
Genetic Studies	**	**	**	**	**	**	**	**	**	**	**	**	**	**	**
Molecular genetic studies; any; n (%)	17 (89)	10 (91)	4 (80)	3 (100)	12 (29)	4 (25)	0	3 (100)	2 (67)	3 (33)	91 (25)	22 (16)	25 (25)	44 (36)	120 (28)
Chromosome studies	8	3	2	3	8	4	0	0	1	3	82	20	22	40	98
Array studies	0	0	0	0	0	0	0	0	0	0	8	0	2	6	8
Fragile X	2	0	1	1	1	1	0	0	0	0	14	3	3	8	17
Single gene or gene panel	14	10	4	0	6	0	0	3	2	1	23	5	5	13	43
Gene panel	0	0	0	0	0	0	0	0	0	0	4	0	1	3	4
<i>FBN1</i> (single gene sequencing or as part of a gene panel)	9	9	0	0	0	0	0	0	0	0	5	0	1	4	14
<i>NSD1</i> (single gene sequencing or as part of a gene panel)	4	0	4	0	1	0	0	0	0	1	16	5	3	8	21
Other growth targeted single gene study; specified††	1	1	0	0	5	0	0	3	2	0	3	0	1	2	9
TREATMENT	**	**	**	**	**	**	**	**	**	**	**	**	**	**	**
Adult height suppressive treatment †††; n (%)	6 (32)	5 (45)	1 (20)	0	1 (2)	0	0	1 (33)	0	0	9 (2)	4 (3)	3 (3)	2 (2)	13 (3)
Epiphyseodesis of the distal femora and proximal tibiae	2	2	0	0	1	0	0	1	0	0	4	3	1	0	7
High-dose sex steroid treatment	1	1	0	0	0	0	0	0	0	0	5	1	2	2	6
Metatarsal epiphyseodesis	3	2	1	0	1	0	0	1	0	0	0	0	0	0	4

* Other secondary causes: Graves' hyperthyroidism (n=1); parahippocampal glioma with normal GH and IGF-1 in a prepubertal patient (n=1); obesity (n=7).

**Parental height ≥ 2 SDS.

***Thyroid function, DHEAS, GH, IGF-1, OGTT, testosterone, estradiol, FSH, LH.

†Brain or Aortic MRI, cardiac or abdominal ultrasound scan; any.

††Consists of *AIP* (n=2), *CYP21A1* (n=2), *NFI* (n=1), *TGFB3* (n=1), *MEN1* (n=1), *PTEN* (n=1), *MC4R* (n=1).

†††Epiphyseodesis of the distal femora and proximal tibiae or high-dose sex steroid treatment.

Table 3
Features associated with primary growth disorders

	Primary Growth disorders	Marfan and Marfan-like syndrome	Sotos syndrome	Syndromes with sex chromosome anomaly, including aneuploidy	Secondary Growth disorders	Premature adrenarche	Precocious puberty	Growth hormone excess	Congenital adrenal hyperplasia	Other secondary causes; specified*	Idiopathic Tall stature (ITS)	Familial ITS with a tall parent **or TH above 1.6	Familial ITS without a tall parent	Non-Familial ITS	Study cohort
n of subjects (female %)	19 (47)	11 (55)	5 (40)	3 (33)	42 (64)	16 (75)	11 (82)	3 (33)	3 (0)	9 (56)	363 (49)	141 (53)	100 (47)	122 (46)	424 (50)
DIAGNOSTIC STUDIES	**	**	**	**	**	**	**	**	**	**	**	**	**	**	**
Bone age: n (%)	11 (58)	5 (45)	3 (60)	3 (100)	40 (95)	16 (100)	11 (100)	3 (100)	3 (100)	7 (78)	330 (91)	128 (91)	89 (89)	113 (92)	381 (90)
Growth acceleration laboratory studies***; any: n (%)	17 (89)	9 (82)	5 (100)	3 (100)	42 (100)	16 (100)	11 (100)	3 (100)	3 (100)	9 (100)	311 (86)	112 (79)	85 (85)	114 (93)	370 (87)
Oral glucose tolerance test with GH sampling	1	1	0	0	3	1	0	2	0	0	11	3	3	5	15
Imaging studies other than bone age; any†	17 (89)	11 (100)	5 (100)	1 (33)	32 (76)	10 (63)	11 (100)	3 (100)	3 (100)	5 (71)	146 (40)	50 (35)	39 (39)	57 (46)	195 (46)
Brain MRI	4	3	1	0	23	6	11	3	1	2	65	23	12	30	92
Abdominal US	5	2	2	1	21	9	3	2	3	4	68	24	25	19	94
Cardiac echocardiogram, cardiac or aortic MRI	16	11	5	0	1	0	0	0	1	0	56	19	12	25	73
Genetic Studies	**	**	**	**	**	**	**	**	**	**	**	**	**	**	**
Molecular genetic studies; any: n (%)	17 (89)	10 (91)	4 (80)	3 (100)	12 (29)	4 (25)	0	3 (100)	2 (67)	3 (33)	91 (25)	22 (16)	25 (25)	44 (36)	120 (28)
Chromosome studies	8	3	2	3	8	4	0	0	1	3	82	20	22	40	98
Array studies	0	0	0	0	0	0	0	0	0	0	8	0	2	6	8
Fragile X	2	0	1	1	1	1	0	0	0	0	14	3	3	8	17
Single gene or gene panel	14	10	4	0	6	0	0	3	2	1	23	5	5	13	43
Gene panel	0	0	0	0	0	0	0	0	0	0	4	0	1	3	4
<i>FBN1</i> (single gene sequencing or as part of a gene panel)	9	9	0	0	0	0	0	0	0	0	5	0	1	4	14
<i>NSD1</i> (single gene sequencing or as part of a gene panel)	4	0	4	0	1	0	0	0	0	1	16	5	3	8	21
Other growth targeted single gene study; specified††	1	1	0	0	5	0	0	3	2	0	3	0	1	2	9
TREATMENT	**	**	**	**	**	**	**	**	**	**	**	**	**	**	**
Adult height suppressive treatment †††; n (%)	6 (32)	5 (45)	1 (20)	0	1 (2)	0	0	1 (33)	0	0	9 (2)	4 (3)	3 (3)	2 (2)	13 (3)
Epiphyseodesis of the distal femora and proximal tibiae	2	2	0	0	1	0	0	1	0	0	4	3	1	0	7
High-dose sex steroid treatment	1	1	0	0	0	0	0	0	0	0	5	1	2	2	6
Metatarsal epiphyseodesis	3	2	1	0	1	0	0	1	0	0	0	0	0	0	4

* Other secondary causes: Graves' hyperthyroidism (n=1); parahippocampal glioma with normal GH and IGF-1 in a prepubertal patient (n=1); obesity (n=7).

**Parental height ≥ 2 SDS.

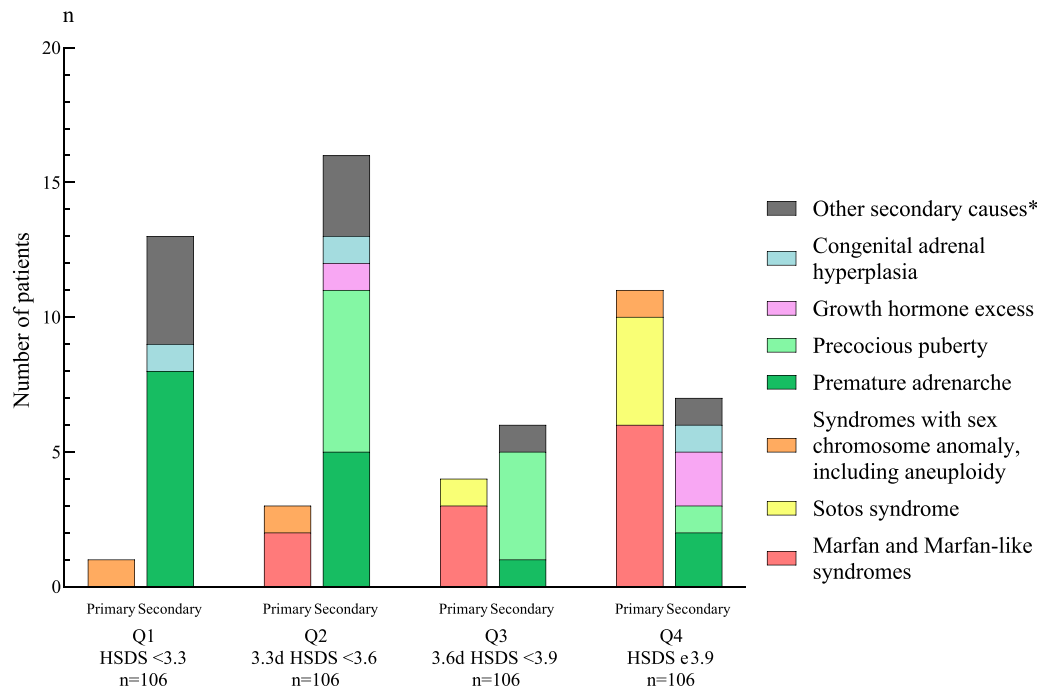


Figure 3. Distribution of the primary (syndromes with sex chromosome or autosomal or without known chromosomal anomaly) and secondary (overgrowth with increased/decreased hormone secretion or action) diagnoses according to the degree of tall stature. Classification to quartiles is based on the greatest HSDS after the age of three years. *Other secondary causes: Graves' hyperthyroidism (n=1); parahippocampal glioma with normal GH and IGF-1 in a prepubertal patient (n=1); obesity (n=7).

4. Discussion

We describe the underlying aetiology, associated clinical features, and auxological clues indicative of a primary disorder in the first study of extremely tall children subject to population-wide growth monitoring and screening rules. Our results are based on the largest cohort of extremely tall children reported to date, including 424 subjects, with an equal number of girls and boys, and comprehensive auxological data including more than 8000 height measurements. A primary or secondary growth disorder was diagnosed in 14% (n=61) of the subjects with slight female predominance among the secondary causes. The latter is in accordance with the reported sex

difference in the frequency of premature adrenarache and CPP [34,35]. In contrast to previous retrospective cohort studies on the aetiology of tall stature, however, we report a higher proportion of primary or secondary growth disorders (14% vs. 1.5% to 9%) [8-10]. This discrepancy is likely to be explained by diverse inclusion criteria, apparent selection bias as reflected by uneven sex distribution, and a minimal proportion of extremely tall subjects in previous studies [8-10].

Primary disorders, which may lack apparent physical stigmata other than tall stature, were diagnosed in 19 (4%) of the subjects. In accordance with previous reports, Marfan syndrome followed by Sotos syndrome were the most numerous monogenic syndromes and the monogenic syndromes were more frequent than sex chromosome aneuploidies [8,9]. Interestingly, only one patient with Marfan syndrome had a retrospectively estimated systemic score above the proposed cut-off for molecular genetic testing in adults [24], ≥ 7 . However, as the clinical signs develop over time, lower systemic score cut-offs for children have been suggested [1]. Indeed, a cut-off of $\geq 3-4$ for children was recently proposed [1] and this criterion was met in all but one of our patients with Marfan syndrome with phenotype data available. As the systemic scores were retrospectively determined, however, they may represent the minimum estimates of the true systemic scores.

Due to several reasons, however, we speculate that our reported proportion of primary growth disorders among extremely tall children is a minimum estimate of the true prevalence, particularly that of monogenic growth disorders. First, molecular genetic testing other than karyotyping was sparsely used. Moreover, *FBN1* gene test in particular had a high diagnostic yield as *FBN1* was tested in 14 subjects and a pathogenic variant was noted in nine. Second, a surprisingly large proportion of the subjects with ITS displayed features related to syndromic tall stature. In fact, a physical feature related to a syndromic cause of tall stature was noted in 21% and a neurodevelopmental disorder in 15% of the subjects with ITS. The latter was explained by the two-fold higher frequency of intellectual disability, autism spectrum disorders, and learning disabilities among the extremely tall children with ITS as compared with the Finnish reference population, whereas ADHD and ADD were equally frequent

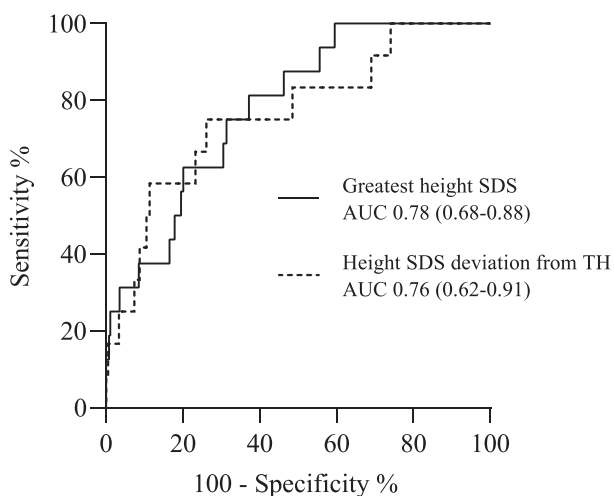


Figure 4. The performance of auxological parameters in differentiating monogenic primary growth disorders and idiopathic tall stature. ROC curves and AUCs with 95% CIs for greatest HSDS after the age of 3 years and height deviation from target height (HSDS-THSDS). The greatest measured HSDS was available for 16 patients with a monogenic syndrome, 363 subjects with idiopathic tall stature (ITS), and HSDS-THSDS for 12 patients with monogenic syndrome and 352 subjects with ITS.

[36]. Third, the few studies that have assessed the diagnostic benefit of next-generation sequencing (NGS) studies in selected cohorts of tall subjects have shown significant additional diagnostic yield [11,12]. Indeed, in tall patients with syndromic features, a molecular genetic assessment that included NGS resulted in a genetic diagnosis in 43% of the patients; the proportion was 8% in those without additional clinical features [11]. In another setting, in subjects with overgrowth and intellectual disability (OGID), a causal mutation in one of 14 epigenetic regulatory genes (including *NSD1*) was detected in half of the subjects by using WES [12]. Thus, NGS studies seem to provide additional diagnostic yield particularly in those tall subjects with additional clinical features. Conversely, in our cohort and those of previous retrospective studies, karyotyping appears to be much less useful [8,9]. In fact, in our study karyotype was normal in over 96% of the subjects. Thus, karyotyping could be reserved for those extremely tall children with additional features related to sex chromosome aneuploidy. On a similar note, testing for Fragile X had a low diagnostic yield, and general indications for molecular genetic testing should be applied for diagnosing/ruling out this syndrome in extremely tall children. Most patients with a primary growth disorder had either Marfan or Sotos syndrome and concurrently the most frequent syndromic features in the ITS cohort were related to neurologic development and connective tissue findings. Therefore, our data suggest that Marfan and Marfan-like syndromes and the Sotos syndrome spectrum are important target conditions for molecular genetic testing in extremely tall children. The latter is also supported by the urgency to diagnose Marfan syndrome early due to the risk of vascular complications as noted in the Dutch guideline [1].

Taken together, based on previous reports [11,12,37] and our results we propose a more active diagnostic approach to extreme tall stature: an NGS panel, with an option to expand to WES, as a first-line molecular genetic study to those children with extreme tall stature and no clues for a secondary growth disorder. Such a panel should include, at a minimum, genes related to Marfan, Marfan-like, and Sotos spectrum syndromes, but preferably all known genes related to exceptional tall stature [11,12]. With this approach, diagnostic yield is expected to be high particularly in subjects with syndromic features [11] or intellectual disability [12]. Depending on the clinical scenario and syndromic features, however, chromosomal microarray, single-gene studies, or MLPA may be appropriate first-line studies.

Overgrowth in children can be defined with three indicators of growth: tall stature (HSDS), height deviation from target height (HSDS-THSDS), and growth acceleration (delta HSDS per year) and each parameter can be used to guide the diagnostic work-up. Indeed, we found that auxological features significantly influence the risk of a secondary and syndromic growth disorder and thus, provide evidence that auxological data can be used for targeting molecular genetic testing¹. Subjects in the tallest quartile (HSDS $\geq +3.9$) had a ten-fold higher frequency of a primary growth disorder than subjects in the shortest quartile (HSDS $< +3.3$) and similarly subjects with HSDS-THSDS $\geq +3.2$ had a five-fold higher frequency of primary or secondary growth disorder compared to subjects with HSDS-THSDS $< +2.2$. Indeed, based on the AUCs, greatest HSDS and HSDS-THSDS emerged as auxological cues that could aid in differentiating monogenic syndromes from ITS. For secondary causes, in turn, growth acceleration at the time of diagnosis appears to differentiate secondary causes from primary causes and ITS in extremely tall children. Additionally, HSDS for bone age, sitting height to height, and birth length may each add diagnostic benefits in differentiating secondary causes or monogenic syndromes from ITS. Based on likelihood ratios, however, the performance of a single auxological parameter was limited. We expect that a combination of auxological, physical, and neurodevelopmental features would provide a more efficient predictive tool for differentiating those with a primary or secondary growth disorder from those with ITS. Of note, patients with Klinefelter

syndrome were infrequent in our cohort supporting the view that applying HSDS criteria alone would have a low diagnostic yield, as previously noted [1]. For patients with Klinefelter syndrome, the median height is increased around 1 SDS compared to the reference population, resulting in height that frequently overlaps with the general population [38].

A natural limitation of our study is incomplete data and the retrospective study design. NGS studies were seldom used in our study cohort and this may have affected the results regarding primary disorders. Additionally, the phenotyping of subjects was not conducted systematically (Tables 1–3). The strengths of our study, in turn, are the large background population of the HUH catchment area (population of 1.22 million), population-wide growth monitoring, comprehensive screening and referral rules [15–20], and the large cohort size with equal sex distribution. Taken together, we estimate that our results and study population represent the general population well.

In conclusion, we show that a considerable proportion, 14% in our study cohort, of extremely tall children (i.e. HSDS $\geq +3$), independent of sex, have an underlying primary or secondary growth disorder. Primary growth disorders were more frequent among the tallest subjects and in subjects with comorbidities or physical features related to syndromic tall stature. High prevalence of the physical features and neurodevelopmental diagnoses in subjects with ITS supports the view that syndromic tall stature was underdiagnosed in our cohort. Our results lend support to a comprehensive diagnostic work-up of extremely tall children and the use of auxological data in estimating the risk of primary and secondary growth disorders. Future studies should address the diagnostic yield of NGS studies in extremely tall subjects and clarify the value of auxological, physical, and neurodevelopmental features in efficient targeting of molecular genetic studies.

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Contributors

M.H. designed the study with the support of T.R. and P.M. Clinical and auxological data were collected by J.K. and E.S. and allocation of patients into diagnostic groups was done by J.K. and M.H. The manuscript was written by J.K., E.S., P.M., T.R., and M.H. All authors critically revised the manuscript and approved the manuscript and the journal prior the first submission. M.H. and J.K. coordinated the study. All authors had full access to all data. The underlying data and analysis have been verified by J.K. and M.H.

Data sharing statement

Study data are not publicly available owing to data privacy issues, but access to the anonymized data can be obtained from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101208.

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