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Overgrowth Disorders Associated with Tall Stature

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During the past several years there has been an increased interest in overgrowth, new disorders have been described, and a number of responsible genes and genotype-phenotype correlations have been identified. The observations in overgrowth disorders complement those obtained in patients with short stature and illustrate the complexity of human growth and the remarkable number of genes and factors needed to attain normal and proportional growth.

In the context of this review, a number of disorders of overgrowth characterized by tall stature, defined as a height of more than 2 standard deviations (2 SD) or excessive growth velocity, prenatally or postnatally, will be reviewed. The disorders that are addressed extensively in other publications will be mentioned only briefly. The height varies substantially among various populations, and to establish the diagnosis of tall stature the knowledge of the height of each population is needed.

Recognition of overgrowth and the diagnosis are important for medical management, genetic counseling, and surveillance for possible tumor development.

DIAGNOSTIC EVALUATION OF TALL STATURE

The clinical manifestations of a number of overgrowth disorders may overlap, diagnosis may be difficult, and confirmation by DNA studies may be needed. An algorithm to aid in the diagnostic evaluation of patients with tall stature is depicted in Fig. 1.

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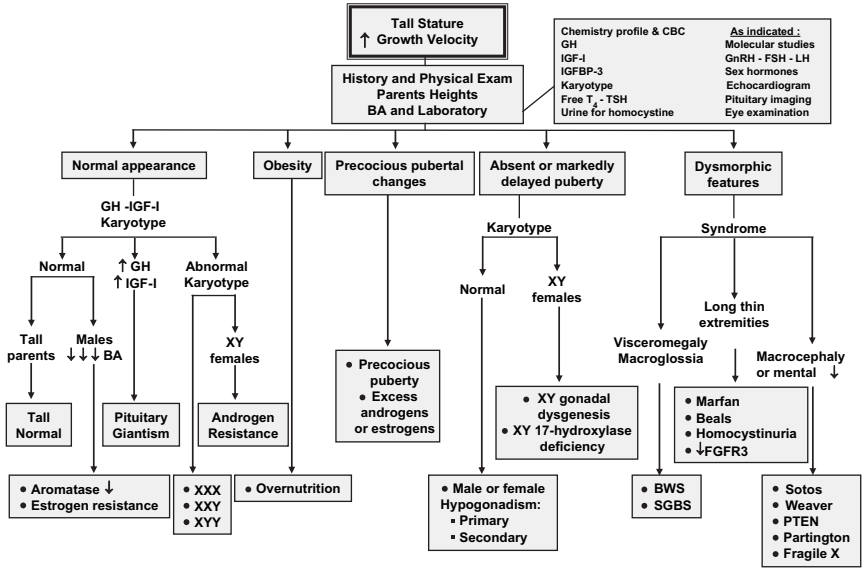

Fig. 1. Algorithm of tall stature. BA, bone age; GH, growth hormone; IGF-I, insulin-like growth factor I; IGFPB-3, insulin-like growth factor binding protein 3; T4, thyroxine; TSH, thyroid-stimulating hormone; GNRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicular stimulating hormone; BWS, Beckwith-Wiedemann syndrome; SGBS, Simpson-Golabi-Behmel syndrome; FGFR3, fibroblast growth factor receptor 3; PTEN, phosphatase tensin homolog in chromosome 10; ↓, decreased, deficiency, or delayed; ↑, increased; ↓↓↓, markedly delayed.

As always, the history and physical findings are most important. Analysis of the growth chart, growth velocity, and weight, as well as parental heights is invaluable. A bone age and prediction of adult height should be obtained.

A chemistry profile is quite helpful to exclude metabolic abnormalities and organ dysfunction. Serum growth hormone (GH) and insulin-like growth factor (IGF)-I should be obtained to screen for GH excess. Serum IGF-II levels may be helpful for some disorders. Since trisomy X (XXX female) and XYY males may have tall stature as the only manifestation, a karyotype is needed to detect these disorders. Serum (and urine) homocystine is advisable in patients with mental retardation, central nervous system (CNS) abnormalities, or Marfanoid features, and is mandatory in tall girls before estrogen treatment. Because of the high incidence of mental retardation in fragile X, particularly in males, DNA testing for fragile X should be performed. Other determinations would depend on the presenting symptoms and signs, such as an echocardiogram with aortic root dimensions in patients suspected of Marfan syndrome; serum gonadotropins and sex hormones in patients with an abnormality in pubertal development; MRI of the brain in patients suspected to have a hypothalamic/pituitary tumor; and molecular studies in some cases.

A patient with dysmorphic features and other abnormalities (mental retardation) is most likely affected with a syndrome. A patient with absent or markedly delayed puberty may have primary or secondary hypogonadism or XY-gonadal dysgenesis. Patients with precocious pubertal changes may be affected with central or peripheral precocious puberty, as a result of excess of androgens or estrogens. It may also be a patient with Klinefelter with a germinoma in the mediastinum secreting human chorionic gonadotropin. In an obese patient with no other abnormal physical findings, overnutrition would be the likely cause of tall stature. On the other hand, a patient with markedly absent subcutaneous tissue may be affected with lipodystrophy.

A tall patient in good health without abnormal physical findings and of tall parents, most likely has genetic tall stature, a normal variant. He or she also could be affected with aromatase deficiency or estrogen resistance, beginning pituitary giantism, androgen resistance, or chromosomal abnormality. To distinguish among the different possibilities, serum GH and IGF-1 and a karyotype are needed.

For patients with mental retardation and dysmorphic features with normal karyotypes, there are now powerful methods for whole genome analysis, such as array High Resolution Comparative Genome Hybridization (array-HR-CGH) and Multiplex Ligation Probe Amplification (MLPA) to find DNA chromosome imbalances (microdeletions–duplications) and new chromosome regions and candidate genes for specific phenotypes [1,2]. These methods could be useful for the evaluation of patients.

ETIOPATHOGENESIS AND MOLECULAR BASIS OF OVERGROWTH DISORDERS

Recent findings have disclosed a number of genes and factors important for linear and proportional growth [3]. It is of interest that when the observations available are analyzed, a pattern in the pathogenesis of the seemingly diverse overgrowth disorders is emerging (Table 1).

1. An excess of a growth gene, SHOX (for short stature *ho*meobox–containing gene), in the extra X chromosome, as in Klinefelter syndrome and trisomy X. *SHOX* is a gene in the pseudoautosomal region (PAR1) of the human sex chromosomes (X and Y). Also, from an excess of the Y-specific growth control gene mapped to the long arm of the Y chromosome (GCY), as in XYY males.
2. An excess of GH secretion as in pituitary giantism, McCune-Albright syndrome (20q12-q13.2), Multiple Endocrine Neoplasia Type I (MEN I) (11q13), and Carney complex type II (2p16).
3. An excess or modulation of growth factors (IGF-II, IGF-I, insulin).

- Overexpression of IGF-II in Beckwith Wiedemann syndrome (BWS) (*H19* gene, 11p15.5) and in somatic overgrowth observed with H-19 abnormal methylation and silencing (11p15.5); or, IGF-II modulation in Simpson-Golabi-Behmel syndrome (SGBS) (defect in glypican 3 gene, Xq26) and SGBS type II (Xp22).

Table 1
Molecular basis and etiopathogenesis of overgrowth (established or suggested)

Extra growth genes		Molecular basis
• Klinefelter (47,XXY)	Extra growth gene *SHOX*	Extra X
• Trisomy X (47,XXX)	Extra growth gene *SHOX*	Extra X
• Males 47,XYY	Extra Y specific growth control gene	Extra Y
Excessive GH secretion (Pituitary tumors)		
• Sporadic		
Gigantism/Acromegaly	Mutations in Gs α protein gene	20q12-q13.2
	LOH (allelic loss) of (no mutations of *MEN1* gene)	11q13
	Overexpression of *PTTG*	
McCune-Albright	Mutations in Gs α protein gene	20q12-q13.2
• Familial		
MEN-1	*MEN1* gene mutations and LOH of 11q.13	11q13
Acromegaly/Gigantism	LOH (allelic loss) of (no mutations of *MEN-1* gene)	11q13
Extra growth factors		
• IGF-II		
Beckwith-Wiedemann	Overexpression of *IGF2*	11p15.5
H19-silencing	Overexpression of *IGF2*	11p15.5
Simpson-Golabi-Behmel, type 1	Deficiency of glypican-3—*GPC3* gene	Xq26
Simpson-Golabi-Behmel, type 2	Mutation in the *CXORF5* gene	Xp22
• IGF-I-Insulin		
Obesity	Hyperinsulinism—Free IGF-I	Several
Lipodystrophy	Hyperinsulinism	Several
Infant of diabetic mother	Hyperinsulinism	
Infant Giants with neonatal hypoglycemia	Hyperinsulinism	Several
Growth factors—receptors		
• Trisomy of IGF-1R	Extra IGF-IR	Duplication 15q
• CATSHL syndrome	Inactivating mutation of *FGFR3*	4p16.3
• Partington	Extra *FGFR3* gene**?**	Duplication 4p16.3
Deficiency of factors needed to arrest growth		
• Aromatase deficiency	Estrogen deficiency - Mutations - *Cyp19* gene	15q21.1
• Estrogen receptor deficiency	Estrogen deficiency - Mutations - *estrogen receptor* α gene	6q25.1
• Hypogonadism	Estrogen deficiency (Secondary)	Several
Deficiency of factors needed to prevent elongation of bones		
• Marfan I (MFS1)	Defective fibrillin gene (*FBN1*)	15q21.1
• Marfan II (MFS2)	Mutations in *TGFBR2*	3p24.1
• Fibrillinopathies	Mutation of fibrillin gene (*FBN1*)	15q21.1
• Beals (CCA)	Mutation in *FBN2*	5q23-31
• Homocystinuria type 1	Mutations of *CBS* gene	21q23

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Table 1
(continued)

Alterations of genes involved in regulation of cell cycle, growth, and tumor suppression		
• PTEN hamartoma syndrome	*PTEN* gene mutations	10q23
Bannayan-Riley-Ruvalcaba	*PTEN* gene mutations	10q23
Cowden disease	*PTEN* gene mutations	10q23
Lhermitte-Duclos disease	*PTEN* gene mutations	10q23
• Sotos syndrome	*NSD1* gene mutations	5q35
• Neurofibromatosis type 1	Defective *NF1* gene	17q11.2

Abbreviations: CBS, cystathionine-beta-synthase; CCA, congenital contractural arachnodactyly; Cyp19, cytochrome P450, 19, aromatase; *FBN1* or *FBN2*, fibrillin gene 1 or 2; *FGFR-3*, fibroblast growth factor receptor 3; *GPC3*, glypican 3; Gs α, guanine nucleotide-binding protein, 1 stimulatory, alpha chain; IGF-I or -II, insulin like growth factor I or II; LOH, loss of heterozygosity; MEN1, Multiple endocrine neoplasia type 1; NF1, neurofibromatosis type 1; *NSD1,* nuclear receptor binding SET (SET = su(var), enhancer-of-zeste and trithorax) domain protein 1; *PTEN*, phosphatase and tensin homolog in chromosome 10; *PTTG,* pituitary tumor transforming gene; *SHOX,* short stature homeobox containing gene; *TGFBR2,* transforming growth factor-beta receptor 2.

- Excess of insulin (and free IGF-I) in obesity, and excess of insulin in lipodystrophy, infants of diabetic mothers, and infant giants with hyperinsulinemia. Among the neonatal hyperinsulinemia syndromes, five genetic forms have been described recently, including autosomal recessive homozygous mutations in the *KCNJ11* and *ABCC8* genes, which encode the pancreatic β-cell K_{ATP} channel subunits Kir6.2 and SUR1, respectively, adjacent on the same chromosome (11p15.1); autosomal dominant activating mutation in the glucokinase gene (*GCK)* (7p15-p13); autosomal dominant hyperinsulinism-hyperammonemia syndrome (function activating mutations of the glutamate dehydrogenase gene (*GLUD1*) (10q23.3) and the mitochondrial enzyme short chain 3-hydroxy-acyl-CoA dehydrogenase gene that catalyzes fatty acid oxidation [4]. Focal abnormalities in the growth and functioning of pancreatic β cells due to the loss of the short arm of the maternal chromosome 11 with the loss of the *ABCC8/KCNJ11* genes and other imprinted growth suppressor genes may cause also hyperinsulinism.

4. An excess or mutations of receptors for growth factors: trisomy of IGF1R, in trisomy of 15q; inactivating mutation of the fibroblast growth factor receptor-3 (*FGFR3* at 4p16.3.); and in Partington syndrome (trisomy of 4p16.3).
5. A deficiency of factors needed to arrest growth such as estrogen in aromatase deficiency (15q21.1), estrogen receptor deficiency (6q25.1), and hypogonadism.
6. A deficiency of factors needed to prevent elongation of the bones and dysmorphic proportions, such as in Marfan syndrome I (MFS1) (defective fibrillin gene, *FBN1* on 15q21.1); Marfan syndrome II (MFS2) (defective *TGFBR2* on 3p22); fibrillinopathies (defective *FBN1*, on 15q21.1) without classical Marfan; Beals syndrome (mutation in the second gene for fibrillin, *FBN2*, 5q23-31), and homocystinuria type 1 (deficiency of cystathionine β-synthase, *CBS*, 21q22.3).
7. Alterations in genes involved in cell cycle, proliferation, and growth and tumor suppression, such as in PTEN hamartoma syndrome (defective *PTEN* gene, 10q23.31), which includes Bannayan-Riley-Ruvalcaba syndrome,

Cowden disease, and Lhermitte-Duclos disease, all being allelic disorders; in Sotos syndrome (defective *NSD1* gene, 5q35); and neurofibromatosis type 1 (defective *NF1* gene, 17q11.2).

NUTRITION—OVERNUTRITION (OBESITY)

Obese children tend to have increased height velocity, to be taller than their lean peers, and to have advanced skeletal maturation. In several studies, the obese subjects were taller than average, by about 1 SD, from the age of 6 to 9 years, with 29% of the girls and 25% of the boys above the 90th percentile for height. The girls had early puberty and menarche. The rate of sexual maturation was variable in boys. Although prepubertal children who are obese are taller than their peers, they do not seem to attain a tall or excessive adult height. Growth charts for obese children showing that obese boys up to the age of 13 years and girls up to age of 12.5 are taller than their normal-weight peers have been reported [5]. Obese children had advanced skeletal maturation, a blunted pubertal growth spurt, when compared with lean subjects, and normal adult heights.

Obese girls had excess muscle mass and lean tissue for height in addition to excess body fat.

Gene abnormalities in the adipocyte axis, leptin, leptin receptor, and proopiomelanocortin/melanocyte-stimulating hormone/melanocortin-4 receptor are rare. The genetic influence in weight has been well established by the study of identical twins.

The tall stature and increased growth velocity associated with obesity are probably mediated by insulin and IGF-I. Obese children have variable but usually normal to elevated plasma IGF-I concentration, despite suppressed GH secretion, compared with normal-weight individuals. Hyperinsulinemia is a consistent finding in obesity and insulin can activate the IGF type 1 receptor resulting in increased height velocity. In addition insulin is the main regulator of IGFBP-1. Hyperinsulinemia decreases IGFBP-1, and as a result there is an increase in free IGF-I. Recent studies of patients with moderate and severe obesity and controls clearly showed the increase in insulin in males and females, the decrease in the IGFBP-1 and the increase in the free IGF-I [6,7]. Thus, the increased growth velocity of obese children is most likely the result of hyperinsulinemia and increased free IGF-I.

HORMONAL

Excessive growth hormone secretion

Giantism is characterized by excessive height and body proportions and acromegaly by the disproportional enlargement of acral parts, hands, and feet, and coarsening of facial features with enlargement of supraorbital ridges, nose, ears, and chin, thick lips, and exaggerated nasolabial folds. Both giantism and acromegaly result from the excessive secretion of GH, arising from an eosinophilic or chromophobe adenoma or hyperplasia of the anterior pituitary. Excessive

production of GH could be caused by the adenoma or by ectopic secretion of GH-releasing hormone (GHRH) centrally, by hypothalamic tumors (gangliocytomas) or peripherally (pancreatic and carcinoid tumors and bronchial adenomas) [8,9]. Pituitary somatotrophs often display a somatic gain of function mutation in *GNAS* (OMIM 139320) in adenomas and in patients with McCune-Albright (OMIM 174800) [10]. In patients with Carney complex, there are heterozygous loss-of-function germline mutations in *PRKAR1A* (OMIM 188830). Patients with multiple endocrine neoplasia type I (MEN1) (OMIM 131100) have mutations in the *MEN1* gene, encoding the 613 amino acid tumor suppressor menin.

The diagnosis is based on the demonstration of excessive secretion of GH as well as the presence of a pituitary adenoma or pituitary hyperplasia with enlargement of the sella [9,11]. McCune-Albright syndrome comprises, presently, approximately 20% of the patients reported with giantism. The definitive test for the diagnosis of excessive GH secretion is the failure of the serum GH to decrease to less than 1 ng/mL after an oral glucose load (1.75 gm/Kg–maximum 75 or 100 g). Normal-weight individuals decrease the serum GH concentration to less than 1 ng/mL. Serum IGF-I concentration is a sensitive screening test and is elevated approximately 4- to 10-fold above normal.

Transsphenoidal surgery by a neurosurgeon experienced in this technology is the treatment of choice. If GH secretion is not normalized by surgery, the options include pituitary radiation and medical therapy with octreotide (a long-acting somatostatin analog [SMS201-995]) or bromocriptine or both. Octreotide preoperatively could be useful to decrease the size of the adenoma [12]. A new mode of therapy is the use of pegvisomant, a GH receptor antagonist that competes with native GH for the GH receptor [9]. Pegvisomant normalizes serum IGF-I concentrations in more than 90% of patients, such that in terms of serum IGF-I normalization, pegvisomant now represents the most effective medical treatment for acromegaly. The long-term safety needs to be determined regarding pituitary tumor growth and liver toxicity.

Acromegaloidism

This rare heterogeneous group of disorders affecting children and adults is characterized by tall stature, excessive growth, and features of acromegaly, without excessive GH or IGF-I production and without pituitary adenoma or hyperplasia.

The clinical manifestations resemble those of patients with pituitary gigantism and acromegaly with excessive GH secretion. The manifestations include tall stature and rapid growth in children, as well as acral enlargement, acromegalic facies, headache, fatigue, hyperhidrosis, arthralgias, and hypertension in more than 50% of the cases. Other less frequent manifestations include hypertrichosis, paresthesia, oily odorous skin, and dysphonia.

A number of patients and kindred without GH excess and acromegaloidism have been described, indicating heterogeneity of this group of disorders [13,14].

Growth factor receptors

Trisomy of IGF-I receptor

Trisomy of the IGF-I receptor has been reported in a few children and is frequently associated with tall stature and mental retardation. In 2002, Faivre and colleagues [15] reported four children from two unrelated families presenting with overgrowth and a terminal duplication of the long arm of chromosome 15. In both cases, chromosome analysis of the parents showed a balanced translocation involving 15q26.1-qter. Molecular and cytogenetic studies showed three copies of the *IGF1R* gene, suggesting that the overgrowth observed in these patients might be causally related to a dosage effect of the *IGF1R* gene, in contrast to severe growth retardation observed in patients with terminal deletion of 15q. These patients had a specific phenotype with macrosomia at birth, overgrowth, macrocephaly, craniosynostosis in some, and mild developmental delay being the major clinical features. Additional cases have been reported [16–18].

Skin fibroblasts from a patient with three copies of the *IGF1R* showed accelerated growth, whereas cells from a subject with only one copy of the *IGF1R* showed slower growth, when compared with controls. The child with three copies of the *IGF1R* gene was tall. These findings and aforementioned reports are consistent with the concept that IGF1R gene copy number is of functional and clinical importance in humans and responsible for the overgrowth [17].

Impaired FGFR3–CATSHL syndrome

Fibroblast growth factor receptor 3 (FGFR3) is one of five distinct membrane-spanning tyrosine kinases and a negative regulator of endochondral bone growth.

Activating mutations of *FGFR3* are well known to cause a variety of short-limbed bone dysplasias and craniosynostosis syndromes including achondroplasia, hypochondroplasia, thanatophoric dysplasia I and II, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAM) syndrome, and lacrimo-auriculo-dental-digital (LADD) syndrome.

Abnormal FGFR3 signaling can cause human anomalies by promoting as well as inhibiting endochondral bone growth.

Recently, Toydemir and colleagues [19] reported a novel mutation inactivating the *FGFR3*, causing a syndrome characterized by camptodactyly (90%), tall stature (100%), scoliosis, and hearing loss (85%) (CATSHL syndrome). They evaluated a large pedigree in which 27 living affected family members spanning four generations were affected with a dominantly inherited disorder. Adult males had a mean height of 195 cm (77 inches) and females of 178 cm (70 inches). Several of them had microcephaly and 60% had development delay and/or mental retardation. Radiographic findings included tall vertebral bodies with irregular borders and broad femoral metaphyses with long tubular shafts. They had bilateral sensorineural hearing loss that was congenital or developed in early infancy and progressed, variably, in early childhood and ranged from mild to severe.

A heterozygous missense mutation of the *FGFR3* that was predicted to cause a partial loss of FGFR3 function was identified in 20 of the 20 affected members

tested. The observation suggested that the haploinsufficiency caused loss of *FGFR3* function by a dominant negative mechanism [19].

The anomalies observed in these family members recapitulated the defects identified in mice lacking *fgfr3* (*fgfr3*$^{-/-}$). The skeletal phenotype of these mice is characterized by elongated long bones, particularly the femur, and long vertebral bodies, that predispose the animals to thoracic kyphoscoliosis. Only bones formed by endochondrial ossification were affected in the mice and in the patients with this syndrome and the bones most notably affected were the long bones and vertebral bodies. The mice also exhibited profound sensory neural deafness, which was caused by cochlear defects.

Hyperthyroidism

Tall stature, increased linear growth, and bone maturation have been observed in many children with thyrotoxicosis. Whether the thyroid hormone works synergistically with IGF-I to stimulate growth is not known, but this is a possibility.

There is no need for concern or treatment in regard to the tall stature and transitory increased linear growth. The growth rate normalizes with treatment of the thyrotoxicosis.

Lipodystrophy

Lipodystrophy includes a rare group of disorders characterized by generalized or partial absence of adipose tissue depots, insulin resistance, hyperinsulinemia, hyperlipidemia, and nonketotic diabetes mellitus. Some causative gene mutations have been identified in the congenital autosomal recessive generalized form of lipodystrophy, known as Berardinelli-Seip (BSCL1) in the gene on 9q34.3, which encodes 1-acylglycerol-3-phosphate 0-acyltransferase 2 (*AGPAT2*), and in a gene on 11q13 (BSCL2) that encodes seipin; in familial partial lipodystrophy (Dunnigan type)–gene encoding nuclear envelope protein, lamin A (*LMNA*) (1q21.2); and in familial partial lipodystrophy variant (limbs, face, and neck) in the peroxisome proliferators activator receptor γ (*PPAR*$_\gamma$) gene. Recent observations in transgenic mice and in humans have demonstrated that the insulin resistance, hyperinsulinemia and diabetes result from the lack of fat and consequent deficiency of leptin and adiponectin, peptides (adipocytokines) that may influence insulin sensitivity and energy balance. Leptin plays a pivotal role in regulating food intake, energy expenditure, and neuroendocrine function.

Patients with *congenital autosomal recessive generalized lipodystrophy* (BSCL) have gigantism; increased growth velocity; acromegaloid features; large hands, feet, and ears; prominent mandible; and advanced bone maturation. (Fig. 2) They may have macrosomia at birth or postnatal gigantism. Hyperinsulinemia could be responsible for muscular hypertrophy, polycystic ovary syndrome, and increased linear growth. GH secretion is normal or low. Insulin can activate the IGF-I receptor, and bring forth accelerated growth, acromegaloid changes, and abundant curly hair. It is of interest that abundant curly hair is seen in patients with GH resistance after treatment with IGF-I.

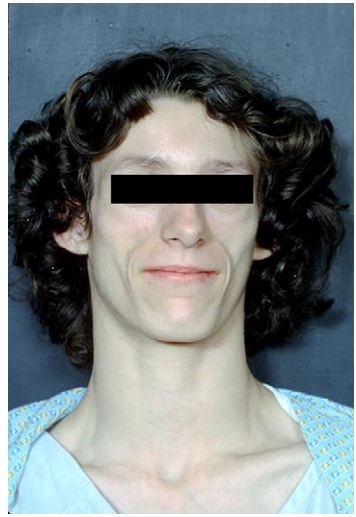

Fig. 2. A 15-year-old girl with total lipodystrophy with markedly decreased subcutaneous tissue over the face, trunk, and limbs: xanthomas, hyperlipidemia (10,000 mg/dL triglycerides), lipemia retinalis, hyperinsulinemia, insulin-resistant diabetes. She was given 8 units of regular insulin per kg, intravenously, over 24 hours; blood glucose levels remained 200 to 300 mg/dL. She had marked muscular hypertrophy, particularly of the calf muscles. She was the champion track runner of her high school.

In the absence of adipose tissue depots, excess lipid accumulates in nonadipose tissues (fat in the wrong place), such as in the liver cells, skeletal and cardiac muscle cells, and the islet β cells. These cells are designed to store fat for use as energy during hard times. The intramyocellular triglycerides and hepatosteatosis are associated with insulin resistance by means related to impaired fatty acid oxidation.

All patients with lipodystrophy have low levels of leptin and adiponectin and varying degrees of insulin resistance. Yamauchi and colleagues [20] reported that insulin resistance in mice with general lipodystrophy was completely reversed by the systemic administration of the combination of adiponectin and leptin, but only partially by either adiponectin or leptin alone.

Equally in humans, Oral and colleagues [21] reported dramatic improvements in glycemic control, hypertriglyceridemia, and hepatic steatosis in patients treated with recombinant leptin (0.04 to 0.08 mg/kg/day) for 4 months. The improvement, although dramatic, was not total. It may be that for complete reversal of the metabolic abnormalities a combination of leptin and adiponectin, as in the experimental mice, is needed.

Prepubertal sex hormone excess

Prepubertal secretion of androgens or estrogens, regardless of etiology, is probably the most frequent cause of excessive growth velocity and tall stature in

childhood. It is well known that *precocious puberty* (complete or incomplete, isosexual precocity), a *prepubertal increase in androgen secretion* by adrenals (congenital adrenal hyperplasia, nonclassical congenital adrenal hyperplasia, peripheral resistance to glucocorticoids, tumors) or testes (Leydig cell tumor), or an *increase of estrogen secretion* by adrenals or ovaries (cyst or tumors) accelerate linear growth and skeletal development and induce sexual development.

Although unusually tall during early childhood, because of the advanced skeletal maturation out of proportion of the advanced height, the eventual adult stature can be and usually is less than normal if the condition remains untreated.

The *clinical manifestations* of this group of disorders are distinctive. A comprehensive discussion of diagnostic approach, treatment, and of other aspects of these disorders is available elsewhere [22].

Sex hormone deficiency or resistance

Permanent deficiency of testosterone in the male and of estrogen in the female will result in delayed skeletal maturation, prolonged period of growth, tall stature, and eunuchoid proportions, with long legs and low upper lower segment ratio. This is, of course, with the provision that there is no GH deficiency, Turner syndrome, or any other disorder affecting linear growth.

Testosterone deficiency in the male could be the result of gonadotropin deficiency from various causes, defective production owing to enzymatic abnormalities in the synthesis of testosterone, Leydig cell deficiency, or anorchia. Estrogen deficiency in the female could be the result of gonadotropin deficiency, defective production owing to enzymatic abnormalities in the synthesis of estrogen (ie, 17-alpha-hydroxylase deficiency, aromatase deficiency), or lack of ovaries.

In males with testosterone deficiency, to prevent the lack of pubertal development, psychologic problems, and eunuchoid proportions, treatment with testosterone should be started after the patient has attained a bone age of 11 or 12 years. Injectable depot preparations of testosterone esters (enanthate or cypionate) are preferred. There are different regimens that can be used. The overall goal of the treatment is to attain full pubertal development within a 4- or 5-year period, at the same age as peers, and to attain the genetic growth potential, without tall stature and eunuchoid proportions.

Transdermal formulations of testosterone in the form of a patch or a gel are now available. These preparations have not been evaluated in children younger than 15 years of age. More information is needed regarding the concentrations of testosterone obtained with the 2.5-mg patch or gel in young adolescents and the effect on bone maturation and pubertal changes, before recommendations can be given.

In females with estrogen deficiency, estrogen substitution therapy should be provided after a bone age of 10 or 11 has been attained. A small dose of ethinyl estradiol (100 ng/kg daily) could be given at the beginning to permit better breast development than with full estrogen replacement doses. Again, the

goal is to attain full pubertal development within a period of 4 to 5 years, attain normal rate of growth and fuse the epiphyses, and to prevent tall stature and eunuchoid proportions.

Aromatase deficiency—estrogen resistance

Recently a few male and female patients with estrogen deficiency, as a result of deficiency of aromatase, by mutations in the *CYP19* gene or estrogen resistance, as a result of a mutation of the estrogen receptor gene α (*ER*α), have been described [23–26].

Aromatase deficiency is rare in humans. Aromatase is the enzyme that catalyzes conversion of androgens into estrogens. Affected individuals cannot synthesize endogenous estrogens. If the fetus lacks aromatase activity, dehydroepiandrosterone sulfate produced by the fetal adrenal glands cannot be converted to estrogens by the placenta, so it is converted to testosterone peripherally and results in virilization of both fetus and mother. Virilization manifests as pseudohermaphroditism in female infants and hirsutism and acne in the mother. The manifestations in the mother resolve following delivery. To date, only seven males and seven females with aromatase deficiency have been reported. Affected females are typically diagnosed at birth because of the pseudohermaphroditism. Cystic ovaries and delayed bone maturation can occur during childhood and adolescence. They present at puberty with tall stature, primary amenorrhea, failure of breast development, virilization, and hypergonadotropic hypogonadism [23]. Affected males do not present with obvious defects at birth and are diagnosed much later in life. The clinical symptoms include tall stature, delayed skeletal maturation, delayed epiphyseal closure, bone pain, eunuchoid body proportions, and excess adiposity. There is impairment of lipid and insulin metabolism. Morishima and colleagues [24] reported a 24-year-old male 204 cm (6 ft 8 inches) tall and still growing, with a bone age of 14 years despite normal puberty and full virilization at the proper age. Bone mineral density was markedly decreased. He was affected with severe aromatase deficiency, homozygous for a novel mutation of the *CYP 19* gene encoding P-450 aromatase. Plasma androgen and gonadotropins were elevated and estrogens were undetected. Estrogen replacement therapy reverses the symptoms in male and female patients [25].

As a result of the lack of estrogen or estrogen effect, the closure of the epiphyses is markedly delayed, the growth period is prolonged, and the patients reach excessive tall stature. Smith and colleagues [26] reported the first case of estrogen resistance, a 28-year-old male, 204 cm (6 ft 8 inches) in height, who underwent pubertal development at the proper age, was shaving regularly at the age of 17 to 18 years, had normal adult testosterone concentrations, normal adult-size genitalia and spermatogenesis, unfused epiphyses, and a bone age of 15 years. The bone mineral density was markedly decreased. His estrogen resistance was caused by a disruptive mutation in the *ER*α gene. Plasma estrogen levels and gonadotropins were elevated.

This case, as well as the cases with aromatase deficiency, has clearly demonstrated the major and critical role of estrogen in epiphyseal maturation, the pubertal spurt, gonadotropin regulation, and bone mineralization.

Other conditions

There are a few other disorders that need some mention. Some form of intervention to prevent unusual tall stature may be needed in patients with complete or incomplete androgen resistance (XY females), and XY gonadal dysgenesis (Swyer syndrome).

Since they are genetically male, their adult height would be that expected for a male. Depending of the genetic potential, the adult height may exceed the 2 SD for females. To prevent tall stature, if desired, treatment similar to that used to curtail adult height in tall, healthy girls, could be given.

Patients with 17-alpha-hydroxylase deficiency are genetically males (XY) and could be phenotypically females, may have no secretion of androgens or estrogens, and no pubertal changes. The bone age is delayed and the period of growth prolonged. They need estrogen to provide pubertal changes and prevent excessive tall stature.

Familial glucocorticoid deficiency

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder of adrenal unresponsiveness to ACTH, which has long been recognized as a clinical entity. Tall stature and advanced bone age are frequent findings. This condition is characterized by glucocorticoid deficiency in the presence of elevated circulating ACTH levels, but normal mineralocorticoid production, except, occasionally, at a time of stress [27]. Patients usually present in infancy or early childhood with hyperpigmentation, normal serum electrolytes, hypoglycemic episodes, vomiting, failure to thrive, or/and unusually severe responses to infections or stress. Age of onset of symptoms and clinical severity of the disease vary between cases, suggesting a heterogeneous genetic origin. Among over 50 described patients, 18 died as a result of the disease.

Clark and colleagues [28] reported a point mutation in the coding region of the ACTH melanocortin 2 receptor (*MC2R*) gene (chromosome 18p11.2) in a family with this condition. Some patients are homozygous for the same point mutation and others are compound heterozygous [29].

Approximately 25% to 40% of patients with FGD have a loss of function mutation in the *MC2R* gene, encoding the ACTH-G protein-coupled receptor (FGD type 1: OMIM 202200).

Loss of function mutations in a gene (chromosome 21q22.1) that encodes MC2R accessory protein (*MRAP*), have also been found (FGD type 2) [30]. *MRAP* aids in the processing and trafficking of the ACTH receptor from the endoplasmic reticulum to the plasma membranes of glucocorticoid-producing cells in the zona fasciculata of the adrenal cortex.

A third chromosome site (8q11.2-q13.2) has been detected in other subjects with FGD and designated FGD type 3 (OMIM 609197). The mutated gene has

not been identified but probably encodes a product that is involved with the function of the ACTH receptor.

Basal serum cortisol levels may be normal in some patients and low in others, but the response to ACTH stimulation is abnormally low.

Patients with point mutations in the *ACTH receptor* gene are usually noted to be of tall stature. Birth weight and length may be over the 75th and 97th percentile and height during infancy and childhood may be +4.0 to +5.6 SD. There is no evidence of excessive GH secretion and serum levels of IFG-I and IGFBP-1 are normal. The bone age is advanced.

The cause of the tall stature is not clearly known. It may be because of a lack of the growth-inhibiting effect of cortisol or because of the absence of adrenal androgens and their effect on the cartilage growth plate. Others have suggested that it may be related to increased levels of ACTH.

CHROMOSOME DISORDERS

Extra growth genes

Trisomy X (47,XXX females)

Patients with trisomy X tend to be tall. Forty-two percent of girls between the ages of 6 and 13 years are over the 90th percentile. Adolescent and adult 47,XXX females are tall with heights generally at or above the 90th percentile (171 cm; 67.32 in.). Long legs are present before puberty. Most of the patients have a normal phenotype, affected children are not recognized, and the condition is underdiagnosed. Trisomy X is the most frequent X chromosomal abnormality occurring in 1 of 1000 newborn females. Some patients may have minimal dysmorphic features (clinodactyly, syndactyly). Most of the patients have normal sexual development, menarche, and ovarian function, but some may have secondary amenorrhea and premature ovarian failure. Primary amenorrhea and ovarian dysgenesis have been reported. The IQ may range from 55 to 115 and approximately one half to two thirds may be slightly below normal [31].

The cause for the tendency to tall stature is probably the extra X chromosome. Many observations have clearly indicated that the absence of one X (45,XO) and Xp deletions, particularly the lack of the tip of Xp, leads to short stature and that additional X chromosomes can compensate for that loss. Rao and colleagues [32] isolated a homeobox-containing gene in the pseudoautosomal region (PAR1) of the human sex chromosomes X and Y that they named SHOX (for *s*hort stature *ho*meobo*x*–containing gene). The evidence suggests that deletions of the tip of Xp with the absence of SHOX could result in short stature and additional inactivated X chromosomes, with active growth genes (SHOX) escaping inactivation, could cause tall stature, such as in Klinefelter syndrome and trisomy X [33].

The presence of long legs in trisomy X as well as in Klinefelter syndrome, before puberty, suggests that they are related to the extra X chromosome and to the extra growth gene *SHOX*, with the effect on bone growth. The effect of *SHOX* on bone growth is well known. *SHOX* mutations resulting in *SHOX*

haploinsufficiency have been identified in approximately 60% of patients with dyschondrosteosis (Leri-Weill syndrome [LWS]), an autosomal dominant form of mesomelic dysplasia, with deformity of the forearm (Madelung deformity), metaphysical changes, severe short stature, short arms, and short legs. Recently, a novel class of pseudoautosomal region 1 deletions downstream of SHOX were identified in approximately 15% of LWS [34]. Haploinsufficiency of *SH0X* is found in some cases of idiopathic short stature and homozygous loss of *SH0X* results in the more severe Langer mesomelic dysplasia (LMD).

The possibility of 47,XXX should be suspected in girls of normal or tall stature with secondary amenorrhea, premature ovarian failure, or learning difficulties. A karyotype would seem advisable in the evaluation of tall girls.

Many of the patients are normal and need no treatment. For patients with excessive tall stature, treatment similar to that described for tall girls could be provided [35,36].

Klinefelter syndrome XXY

This syndrome was first described by Klinefelter, Reifenstein, and Albright [37] in 1942 with the characteristic features that became evident at adolescence of gynecomastia, tallness, variable degree of eunuchoidism, imperfect virilization, small firm testes with hyalinization of the seminiferous tubules and aggregation or clumping of the Leydig cells, small penis, tendency to dull mentality and increased urinary excretion of gonadotropins (Fig. 3). In 1959, a 47,XXY sex chromosome constitution in patients with this disorder was first reported. All the variants have in common the presence of at least 2 X chromosomes and

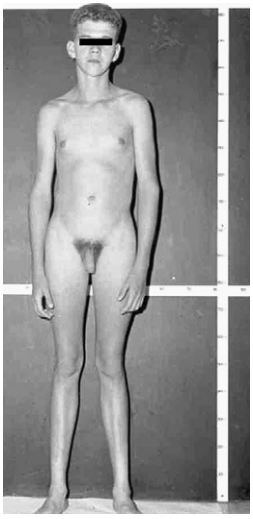

Fig. 3. A tall boy, 15 years 10 months old, with Klinefelter syndrome: karyotype XXY, small firm testes, gynecomastia, and long legs. Height 185 cm (6 ft 0.75 in).

a Y, except for the rare patients who have only a 46,XX complement (XX males SRY positive).

They are on the average 10 cm (3.9 in) taller than XY males. Tall stature is usually present before puberty, as is the disproportionate leg length, which suggests that this feature is not related to androgen deficiency and may be determined by the extra X chromosome (extra *SHOX*) as in trisomy X. The arm span is not increased and is equal to or less than the height. Affected children may be immature, excessively shy, anxious, aggressive, and may engage in antisocial acts, such as fire setting, theft, and cruelty to animals. The full-scale IQ is usually normal. Severe retardation is uncommon.

The active genes escaping inactivation in the second inactivated X chromosome may be responsible for the abnormalities found in Klinefelter syndrome and, particularly, the extra growth gene, *SHOX*, responsible for the tall stature. Patients with Klinefelter syndrome with an isochromosome Xq (47,XiXqY), lacking the extra short arm of the second X chromosome and consequently the extra SHOX gene, show all typical manifestations of Klinefelter syndrome except tall stature. Moreover, patients who have only a 46,XX complement (SRY positive) with 2 SHOX but no long arm of the Y are not tall and have a height similar to females [38].

Chromosome surveys at birth show an incidence of approximately 1:500 to 1:1000. Less than 10% of the estimated number of affected fetuses are detected perinatally and 75% of patients go through life undetected. Diagnosis of the syndrome in patients after puberty is not difficult, by the findings of the typical phenotype of tall stature, incomplete virilization, small firm testes, and elevated serum gonadotropin levels [39]. The diagnosis can be confirmed by the karyotype.

With the onset of puberty, testosterone synthesis is impaired, gonadotropin levels are elevated, and degeneration of seminiferous tubules occur [40,41]. Osteoporosis occurs in 25% of the patients. To prevent the physical and psychologic complications of hypogonadism, testosterone treatment is recommended.

Psychologically disturbing or persisting gynecomastia should be corrected by reduction mammoplasty. Early intervention for learning and behavioral disorders may be beneficial.

47,XYY males

47,XYY males are known to have excessive height [42]. The first report of an XYY male was made in 1961, when an essentially normal, fertile male of average intelligence was studied because he had a daughter with Down syndrome. Subsequently, an increased prevalence of the XYY karyotype (20/1000 versus 1/1000 in the general population) was found among tall, mentally retarded incarcerated males and created a stereotype of affected individuals as having deviant behavior, marked by physical aggressiveness and violence (1% risk versus 0.1% risk in 46,XY males). This impression is not applicable to all the patients. The only consistent physical feature of the syndrome is excessive height, with 50% of the patients being above the 90th percentile of normal.

Forty percent to 50% have learning difficulties [42]. Adults with this syndrome are tall, have nodular cystic acne, have large deciduous and permanent teeth, some neurologic abnormalities such as intention tremor, incoordination, and, frequently, radio-ulnar synostosis.

There is no evidence of any endocrine abnormality. XYY males are taller than XY males; XY females are taller than XX females; and patients with XY gonadal dysgenesis are taller than patients with XX gonadal dysgenesis. A region that has a great influence in growth and in tooth size was mapped by different investigators to the most proximal portion of the long arm of the Y, close to the centromere, and is called Growth Control in the Y (*GCY*) or Y-specific growth gene [43]. Possible candidate genes are not yet identified [44]. The *GCY* may be the gene responsible for the difference in height and tooth size between males and females. Eight unselected XYY boys were followed longitudinally. They were taller than controls during childhood and at the onset of puberty. The adult height was 188.1 cm (6 ft 2 in ± 1.5 in), which is twice the mean male-female difference in height (163.8 cm for the female, 176.5 cm for the male, and 188 cm for the XYY males). The observations suggest that tall stature in 47,XYY males is related to extra growth genes in the additional Y chromosome, *SHOX,* and *GCY* or Y-specific growth gene.

As with trisomy X and Klinefelter, XYY males go unrecognized, because of the lack of marked phenotypic changes. To detect them, a karyotype needs to be obtained in any patient with tall stature whose cause is unknown. The disorder should be suspected in tall males with nodular cystic acne who exhibit antisocial behavior.

The offspring of this category of patients may be at higher risk of chromosomal abnormalities and therefore preimplantation genetic diagnosis can be suggested to these patients.

Fragile X syndrome

The fragile X syndrome is the most common form of inherited mental retardation with prevalence estimated to be approximately 1:1250 males and 1:2500 females. In 1991, the gene that when disrupted results in the fragile X site in Xq27.3 was isolated and characterized. The DNA segment shows a peculiar stretch of trinucleotide repeats (cytidine, guanosine, guanosine [CGG]) in the fragile X mental retardation gene 1 (*FMR1*) that increases the size of the specific DNA fragment of the X chromosome in Xq27.3. The fragile X syndrome may also arise in patients with deletions and point mutations of the *FMR1* gene without CGG amplification [45,46].

In young fragile X–positive girls, the two most common and most important findings were the overgrowth, present from birth on, and behavioral features, including severe attention problems and extreme shyness and anxiety. In males, the most typical features are mental retardation, tall stature, large ears, and macroorchidism, with approximately half of the patients having an ear length above the 90th percentile for normal. Testicular volumes after puberty in healthy males range from 10 to 25 mL and in the patients range

from 25 to 70 mL. Overgrowth and macrocephaly are seen in females. Females function in the borderline to mildly retarded range. Intelligence assessment showed an IQ of less than 70 in 25% and of less than 85 in 53% of the girls with positive fragile X chromosome, by cytogenetic studies.

Fragile X–associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder occurring in male and rarely in female carriers of a premutation expansion (55 to 200 CGG repeats) of the *FMR1* gene. Females had less reduction in cerebellar volume and a lower incidence of involvement of the middle cerebellar peduncles (13% compared with affected males 58%) [47]. The cause of the overgrowth is not known.

The possibility of fragile X syndrome should be suspected in males and females with mental retardation and the phenotypic changes, late-onset ataxia, action tremor, or neuropathy, particularly in those with a family history of mental retardation, and the diagnosis confirmed by DNA testing. No treatment is known except for supportive measures for the psychologic and behavioral disorders. No treatment is, usually, needed for the overgrowth.

Chromosome 22q13.3 deletion syndrome (OMIM #606232)

A number of patients have been described with a terminal deletion of 22q13.3. The terminal 22q13.3 deletion syndrome is characterized by neonatal hypotonia, global developmental delay, normal to accelerated growth, absent to severely delayed speech, autistic behavior, and minor dysmorphic features.

Although patients with simple 22q13 terminal deletion had a general tendency to overgrowth, the patients with a ring 22 often showed growth failure.

The cause of the overgrowth is not known.

SYNDROMES AND OTHERS

Marfan syndrome—type 1 and type 2 (MFS1, MFS2)

Marfan syndrome is an inherited disorder of connective tissue affecting the skeletal, cardiovascular, and ocular systems, as well as the dural ectasia of the lumbosacral spinal canal. It is estimated to affect 2 to 3 in 10,000 people.

The clinical manifestations relating to the skeleton include tall stature, long and thin arms and legs (dolichostenomelia) (Fig. 4), arachnodactyly (spidery fingers), pectus excavatum (hollow chest) or carinatum (pigeon breast), narrow facies with narrow palate, and scoliosis and kyphosis in 60% to 100% of the patients. Joint laxity and inguinal, femoral, and diaphragmatic hernias are other consequences of the abnormal connective tissue. The ocular manifestations include upward subluxation of the lenses, as a result of the defect of the suspensory ligament, increased axial globe length with myopia, and retinal detachment. Dural ectasia of the lumbosacral spinal canal is one of the major manifestations. The most life-threatening complications are those of the cardiovascular system, with dilatation of the ascending aorta with or without dissecting aneurysm, and less commonly of the thoracic or abdominal aorta or pulmonary artery. As a consequence of the dilatation of the aorta there is secondary aortic regurgitation. Mitral valve prolapse is very common also.

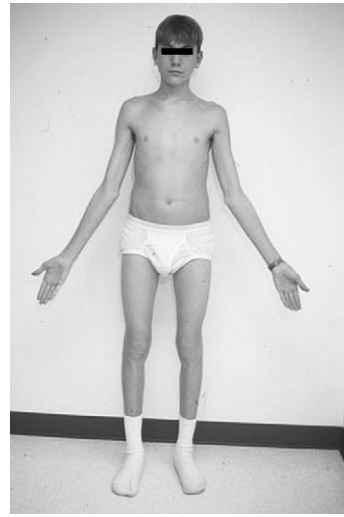

Fig. 4. A boy, 14 years 2 months old, with Marfan syndrome showing dolichomorphism, slender extremities, and long limbs. Arm span is 10.2 cm more than height. He has cardiovascular changes with dilatation of aortic root.

Without treatment for the cardiovascular complications, particularly the aortic dilatation, the mean age of death is in the mid-40s, from aortic dissection and rupture [31].

Patients with Marfan syndrome are mentally normal, but neuropsychologic impairment, including learning disability and attention deficit disorder, occurs in approximately 40% of the patients.

This is an inherited disorder, transmitted in an autosomal dominant fashion. Approximately 85% of the patients have a positive family history and 15% of the patients have a sporadic presentation. The basic defect in Marfan syndrome (MFS type 1) was traced in 1991 to a defective fibrillin gene (*FBN1*) mapped to chromosome 15 (15q21.1). Fibrillin is a connective tissue protein found in microfibrils, a constituent of elastic tissue and abundant in tissues affected in Marfan syndrome, including the aorta, the suspensory ligament of the lens, and periosteum. The latter suggests the possibility that normal elastic/connective tissue in the periosteum is needed to prevent elongation of the bones.

There is a remarkable degree of clinical variability, both within and between families for which there is no clear explanation. New insights regarding the pathogenesis of Marfan syndrome have developed from investigation of murine models of this disorder. Fibrillin-1 deficiency is associated with excess signaling of transforming growth factor beta (TGF-beta). Inhibition of TGF-beta attenuates the clinical manifestations of the disease. TGF-beta antagonists (angiotensin II receptor blocker, losartan) have shown great success in improving or preventing several manifestations of Marfan syndrome in these mice,

including aortic aneurysm [48,49]. The loss of fibrillin 1 protein by any of several mechanisms and increased bioavailability of TGF-beta may be very relevant in the development of Marfan syndrome [50].

In a minority of cases of MFS phenotypes, no mutations in the FBN1 gene are identified. In 2004, mutations in the *TGFBR2* gene were identified in patients with MFS (MFS type 2) and may be responsible for 10% of the cases [49]. Autosomal dominant inheritance has been observed in some families with a variety of *TGFBR2* mutations. The identification of *TGFBR2* mutations in MFS type 2 provided direct evidence of the relation of FBN1 and TGF-beta in humans. More than 500 FBN1 mutations have been found in Marfan syndrome [51]. *TGFBR2* mutations are still limited.

For the clinical diagnosis, the revised criteria of 1996 (Ghent Nosology) [52] is followed. This is based on four major diagnostic findings: (1) the skeletal, (2) ocular, and (3) cardiovascular systems and (4) dural ectasia of the lumbosacral spinal canal.

The diagnosis of Marfan syndrome can be made in an index case–when there is a major involvement in two different organ systems and a minor involvement in a third system or when there is a mutation in the *FBN1* gene, a major involvement of one system, and a minor involvement of a second system.

For a relative of an index case, the diagnosis can be made when there is a major criterion provided by family history and one major criterion in an organ system and involvement of a second organ system.

In a patient with no family history, in whom mutations of the fibrillin 1 have been detected, two major manifestations in separate organ systems will be required for the diagnosis of Marfan syndrome. Otherwise, the patient may be affected with a so-called fibrillinopathy, without Marfan syndrome.

Female and male patients with Marfan syndrome may attain an excessively tall height. Treatment to curtail final height may be indicated [36]. In addition, since scoliosis and kyphosis might develop in 60% to 100% of patients with Marfan syndrome, the arrest of growth may be beneficial. Attention is most important to the possible development, prevention, and treatment of life-threatening cardiovascular abnormalities. Propranolol, to reduce the pounding of the ventricular ejection on the ascending aorta, is now routinely used in patients who are beginning to have dilatation of the aortic root. By the experience in MFS models in mice, an angiotensin II receptor blocker should prove useful. A composite graft operation to replace the ascending aorta and aortic valve for the most life-threatening manifestation, aortic root aneurysm, has led to a nearly normal lifespan for affected individuals who are appropriately recognized and treated [48].

Beals syndrome (congenital contractural arachnodactyly)

The skeletal features of Beals syndrome are similar to those for Marfan syndrome with long slender limbs (dolichostenomelia) and arachnodactyly. There is camptodactyly of the fingers. The difference with Marfan syndrome is that there are joint contractures, rather than looseness of the joints, and previously

it was thought that the eye and the aorta were not affected. The helixes of the ears are folded and the ears have a wrinkled appearance. Kyphosis, scoliosis, or kyphoscoliosis occur in 50% of the patients who are more severely affected. Other manifestations are micrognathia and atrial and ventricular septal defects. Since the original report, several patients have been found to have mitral valve prolapse [53], structural cardiac anomalies, occasionally aortic root dilatation similar to those seen in Marfan syndrome, and ectopia lentis [54]. These reports underscore the need for periodic eye and echocardiographic evaluations of all patients with congenital contractural arachnodactyly (CCA).

This is an inherited disorder segregating in an autosomal dominant fashion caused by a mutation in a second fibrillin gene (*FBN2*) mapped to chromosome 5q23-31.

Diagnosis is based on clinical grounds. Although rare, at least 33 pedigrees with CCA have been described. These patients can have tall stature, but there are no reports of excessive height and treatment for it.

Fibrillinopathies

There is a remarkable degree of clinical variability both within and between families with Marfan syndrome as well as in individuals with related disorders of connective tissue.

The term fibrillinopathies is applied for clinical entities associated with abnormalities of fibrillin 1 or fibrillin 2. It includes the previously defined disorders, Marfan syndrome (MFS1), and CCA (FBN2), and several other related connective tissue disorders caused by mutations in the *FBN1* gene that do not meet the criteria of Marfan syndrome [55], such as dominant ectopia lentis, familial ascending aortic aneurysms [56], isolated skeletal features of Marfan syndrome without ocular or cardiovascular manifestations [57], and the Marfanoid craniosynostosis (Shprintzen-Goldberg) syndrome [58]. Mutations of the fibrillin gene are spread throughout the gene and, with the exception of neonatal Marfan syndrome, show no obvious clustering or phenotypic association.

Mutations in the fibrillin 1 gene that disrupt the profibrillin processing may result in isolated skeletal features of the Marfan syndrome in some families. In one report, six other individuals in the proband's family had the fibrillin 1 gene mutation that segregated with tall stature. None of the affected individuals had cardiac or ocular manifestations. The authors suggested that the fibrillin 1 gene is one of the genes that determines height in the general population [57].

One needs to consider that some tall individuals may have *FBN1* gene mutations.

Homocystinuria type 1

Homocystinuria is an inherited inborn error of metabolism of methionine, due to a deficiency of the enzyme cystathionine beta-synthase (CBS), originally reported by Carson and Neill [59] and Gerritsen and Vaughn [60] in 1963. CBS converts homocysteine to cystathionine, a reaction needing pyridoxal phosphate (vitamin B6) as a cofactor. The prevalence is estimated at 1:200,000

live births. In Ireland it is more frequent, 1:40,000 live births. Approximately 40% of the patients respond to high doses of vitamin B6 (pyridoxine) and, usually, have milder clinical manifestations, delay in the onset, or a lower rate of complications than those who do not respond to vitamin B6 therapy [61]. Some patients may not respond to vitamin B_6 because of folate depletion. Thus, folic acid 1 to 5 mg per 24 hours should be added to the regimen.

Cystathionine β synthase deficiency is inherited as a recessive trait, but there is considerable genetic heterogeneity in known patients. The gene for cystathionine beta-synthase (*CBS*) has been mapped to chromosome 21q21.

The clinical manifestations are similar to those for Marfan syndrome with some differences [62]. Major involvement relates to four different organ systems: the ocular, the skeletal, vascular, and central nervous system. Ectopia lentis or subluxation of the lens downward, contrary to the upward dislocation in Marfan syndrome, is the most consistent finding. The skeletal abnormalities impart a phenotype similar to Marfan syndrome, with dolichostenomelia (elongated and thin arms and legs), arachnodactyly, and tall stature often with eunuchoid proportions. Among the most consistent skeletal abnormalities is osteoporosis. Scoliosis and kyphosis occur frequently. Other abnormalities include genu valgum and pectus carinatum or excavatum. The most frequent central nervous system manifestation is mental retardation, which may occur in as many as 50%, with an IQ ranging from 30 to 75. Thromboembolic episodes involving the large and small vessels are life threatening, particularly those in the brain, are common and may occur at any age, and could occur in approximately 6% of patients undergoing surgery.

The sulfhydryl groups of homocysteine interfere with collagen cross-linking and cause collagen abnormalities. In view of the similarities of many of the clinical features of homocystinuria and Marfan syndrome, it is likely that many of the manifestations and tall stature are related to qualitative changes of fibrillin. Sulfhydryl groups may contribute also to the disruption of vascular endothelium and as a result thrombosis.

Beckwith-Wiedemann syndrome

This syndrome was initially described independently by Beckwith [63] and Wiedemann [64] in 1963. It is associated with prenatal and postnatal overgrowth with the most characteristic features occurring at birth: omphalocele or umbilical defects, macroglossia, and gigantism (Fig. 5). Thirty percent to 50% of the affected children may have severe, persistent hypoglycemia beginning in the first days of life from hyperinsulinism, as a result of pancreatic islet cell hyperplasia. The hypoglycemia usually subsides by 4 months of age. There is visceromegaly with enlargement of the liver, kidneys, and pancreas and at times cardiomegaly; renal medullary dysplasia; consistently, fetal adrenal cortical cytomegaly; and interstitial cell hypoplasia of the gonads. Hemihypertrophy is present in 12.5% of cases [65,66].

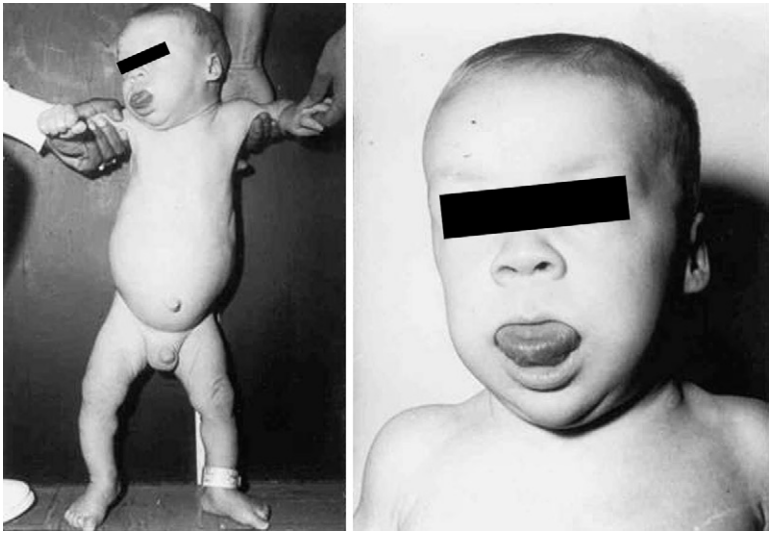

Fig. 5. A 15-month-old with Beckwith-Wiedemann syndrome; height 87.5 cm (34.5 in) and weight 14.6 kg (both >95th percentile). Macroglossia still evident. He did not have hypoglycemia.

There is an increased incidence of malignant tumors (7.4% to 10%), the most frequent being Wilms' tumors and adrenal cortical carcinoma. Other tumors could be nephroblastoma, hepatoblastoma, and rhabdomyosarcoma [67].

Children with Beckwith-Wiedemann syndrome (BWS) are large at birth. Growth velocity is usually above the 90th percentile until 4 to 6 years of age and normal thereafter. They reach an average height of 2.5 standard deviation score at or after puberty with weights between the 75th and 95th percentiles.

The prevalence is estimated to be approximately 1 in 14,000 persons. Approximately 85% of the cases are sporadic and 15% inherited, suggesting autosomal dominant inheritance with incomplete penetrance.

BWS is a complex and heterogeneous genetic disorder resulting from alterations of the expression of imprinted genes, involved in growth and cell cycle control, in the 11p15 chromosomal region [68,69]. Clustered imprinted genes are regulated by differentially methylated imprinting control regions (ICRs) or domains that affect gene activity. The primary imprint signal for each of these clusters is DNA methylation [70].

There are two imprinted centers or domains on chromosome 11p15. The imprinted center or domain 1 (IC1) is near its telomere and harbors two imprinted genes–*IGF2* and *H19,* a maternally expressed, paternally imprinted gene that may serve as a tumor suppressor. Normally, paternal *H19* is methylated and silenced, permitting paternal expression of adjacent *IGF2,* and the maternal *H19* is expressed and *IGF2* silenced. When maternal *H19* is

methylated, its expression is inhibited while expression of *IGF2* is no longer repressed, resulting in its biallelic expression [71].

The loss of imprinting of the maternal *IGF2* gene, with resulting biallelic expression, is one of the most common molecular defects found in patients with Beckwith-Wiedemann syndrome without chromosomal abnormalities. Over expression of *IGF2* can also result from paternal uniparental disomy (UPD) of chromosome 11 or from duplications of the paternal 11p15 region associated with trisomy of 11p.

The imprinted center or domain 2 (IC2) is centromeric to imprinted domain 1 and it houses a number of imprinted genes. *CDKN1C* is a maternally expressed paternally imprinted gene. Approximately 5% to 10% of the sporadic patients and 40% of the familial cases with BWS harbor loss of function mutations in *CDKN1C*, resulting in biallelic expression of *CDKN1C*. *KCNQ10T1* is a paternally expressed, maternally imprinted gene. Loss of methylation of maternal *KCNQ10T1* with biallelic expression of *KCNQ10T1* is seen in 50% to 60% of sporadic cases.

IGF-II is an important growth factor for fetal growth. Transgenic experiments in mice have shown that loss of the functional paternal *igf2* allele results in 40% prenatal growth retardation [72]. Overexpression of *igf2* can result in most of the symptoms of BWS [73,74] and targeted disruption of the igf2r, which is involved in degradation of IGF-II, results in overgrowth and elevated levels of IGF-II [75]. The overgrowth in Beckwith-Wiedemann is in organs rich in IGF-II. The IGF-IR is activated by IGF-I and IGF-II, both major regulators of somatic growth and cellular proliferation. The overexpression of *IGF2* results in overgrowth prenatally and postnatally. In addition, *IGF2* imprinting is lost in sporadic Wilms' tumors suggesting that *IGF2* overexpression is responsible for overgrowth and development of tumors [76].

The diagnosis is based on the clinical manifestations that have been described. Some of the phenotypic changes are somewhat similar to those of infants of diabetic mothers and Simpson-Golabi-Behmel syndrome (SGBS).

Detection and treatment of hypoglycemia are most important for survival and to prevent neurologic damage. Regular follow-up for possible tumor development is needed and routine ultrasonography of the kidneys is mandatory (every 3 months for the first 6 years recommended) because Wilms' tumor and adrenocortical carcinoma are the most frequent neoplasms.

Patients with hemihypertrophy and uniparental disomy have a high frequency of tumors (hepatoblastomas and Wilms' tumors).

Somatic overgrowth (H19 methylation and silencing)

As we discussed previously in relation to Beckwith-Wiedemann syndrome, the *H19* gene, with locus in the chromosome 11p15 region, is closely related to *IGF2* in the imprinted center 1. These two genes are oppositely imprinted. The differentially methylated region (DMR) controls the allele-specific expression of both the *H19* tumor-suppressor gene and the *IGF2* growth factor. *H19* is paternally imprinted and maternally expressed in most tissues. Biallelic

expression or *igf2* by disruption of maternal *igf2* imprinting has been shown in mice, as a result of a maternally inherited targeted *H19* gene. Also, biallelic expression of *IGF2*, associated with methylation and silencing of the maternal normally expressed *H19* gene, has been found in BWS and Wilms' tumors.

Morison and colleagues [77] examined *H19* methylation and *IGF2* expression in children with overgrowth, without diagnostic features of BWS or abnormalities suggesting any particular syndrome. In three of the six children with somatic overgrowth, there was abnormal methylation and silencing of *H19* and overexpression of *IGF2*. This observation has important implications for the evaluation of children with overgrowth without other manifestations suggestive of a syndrome.

Simpson-Golabi-Behmel syndrome, types 1 and 2

Simpson-Golabi-Behmel syndrome was originally described by Simpson in 1975 [78], and by Golabi and Behmel, independently, in 1984 [79,80]. The gene was identified by Pilia and colleagues in 1996 [81].

This syndrome is an X-linked recessive disorder characterized by prenatal and postnatal overgrowth, unusual facial appearance (described in the past as bulldog syndrome), and digital and other anomalies. Female carriers sometimes can have some facial changes.

Affected male patients may attain adult heights of 192 to 210 cm (6 ft 4 in to 6 ft 11 in). They have macrosomia, macroglossia, visceromegaly, omphalocele, renal dysplasia, earlobe creases, neonatal hypoglycemia as a result of islet cell hyperplasia, and a risk of embryonal tumors, including Wilms' tumor, neuroblastoma, and hepatocellular carcinoma during early childhood, features similar to the BWS. Perinatal and infant mortality is high [82,83].

The most prominent features of the disorder consist of overgrowth, characteristic facial changes (large protruding jaw, widened nasal bridge, upturned nasal tip, broad nose, wide mouth, large tongue, thick lips), high arched or cleft palate, large head, hypoplastic or absent index fingernails, and inguinal hernia. The bone age is advanced. Intelligence is usually normal or only mildly retarded in some cases. Hypotonia is common.

This syndrome results from different mutations or microdeletions of the glypican-3 (*GPC3*) gene in Xq26 (SGBS1), suggesting that SGBS is caused by a nonfunctional GPC-3 protein. GPC-3, a membrane-bound protein, is selectively expressed in embryonic mesodermal tissues where it interacts with IGF-II and may be important in the modulation of *IGF2*. Glypican is thought to control the growth of mesodermal embryonic tissue acting in concert with *IGF2*. Studies of double mutant mice indicated that the GPC-3 protein did not sequester IGF-II or IGF-I but suggested that the effects of GPC-3 protein and IGF on cell proliferation and somatic growth converge at a common downstream site. Inactivation mutations of GPC3 lead to excessive growth, inferring that the normal function of GPC-3 is to restrain cell proliferation. The *gpc3*-deficient mice exhibited abnormalities typical of SGBS. The overgrowth of the *gpc3*-deficient mice was similar to that of mice deficient in IGF receptor type II

(igf2r), a negative regulator of IGF-II [84]. Theoretically, GPC-3 protein could facilitate degradation of IGF-II through a further interaction with the IGF-II receptor. The loss of function of GPC-3 and decreased IGF-II binding would lead to an increase in the level of IGF-II that could activate the IGF type I receptor.

Patients with SGBS have many overlapping features with patients affected with BWS and in some cases molecular studies will be needed to assign a proper diagnosis. The clinical overlap with BWS may be owing to overexpression of IGF-II.

A gene located at chromosome Xp22 has been associated with SGBS type 2. Brzustowicz and colleagues [85] mapped the locus for the disorder to a 6-Mb region on chromosome Xp22. The findings excluded involvement of the *GPC3* gene. The protein may interact above or below the site of GPC-3 action.

Phosphatase tensin homolog in chromosome 10 hamartoma syndrome

Phosphatase tensin homolog in chromosome 10 (PTEN) hamartoma syndrome, an autosomal dominant disorder, includes Bannayan-Riley-Ruvalcaba syndrome (BRRS), Cowden disease, and Lhermitte-Duclos disease (LDD), previously thought to be separate disorders [86].

PTEN encodes a protein with tumor-suppressing activity that dephosphorylates both lipid and protein substrates, and negatively regulates the signaling pathway stimulated by cell growth factors such as IGF-I and thus indirectly controls the cell cycle and apoptosis [87]. *PTEN* has been shown recently to play a big role in human malignancy. Somatic *PTEN* deletions and mutations have been observed in sporadic breast, brain, prostate, and kidney cancer cell lines and in several primary tumors, such as endometrial carcinomas, malignant melanoma, and thyroid tumors.

Germline mutations of *PTEN* have been identified in 60% of patients with BRRS and in 80% of patients with Cowden disease and in patients with LDD (OMIM 158350). Presently, it is thought that the three disorders are heterozygotic allelic disorders and the same condition. Patients may have distinctive features of one or the other syndrome with identical mutations of *PTEN*. Members of the same family have been described with manifestations consistent with BRRS and Cowden disease or Cowden disease and LDD. Some patients with BRRS may develop characteristics of Cowden disease as they age [88].

The BRRS is characterized by macrocephaly, multiple hamartomas (lipomas, hemangiomas, lymphangiomas, intestinal polyps) and other tumors (seminoma, germinoma), macrosomia at birth, pigmented spots in the glans and shaft of the penis, and pseudopapilledema [65,88].

Cowden disease has been described mainly in adults. It is an autosomal dominant condition characterized by macrocephaly, multiple hamartomatous lesions, especially of the skin and mucous membranes, with verrucous skin lesions of the face and limbs, and cobblestone-like papules of the gingiva and

buccal mucosa, but also involving hamartomas and neoplasms of internal organs, most commonly in the thyroid, breast, and ovary [65,88].

Progressive macrocephaly, scrotal tongue, and mild to moderate mental retardation are important signs of Cowden syndrome in young children. Trichilemmomas in the nasolabial folds and palmar and plantar hyperkeratotic pits usually become evident later in childhood. They are often accompanied by the appearance of subcutaneous lipomas and cutaneous hemangiomas.

LDD or dysplastic gangliocytoma of the cerebellum, previously referred to as cerebello parenchymal disorder VI (OMIM #601728), is a rare cerebellar lesion, which may occur sporadically or in association with Cowden disease [89,90]. Adult-onset LDD is now considered pathognomonic for Cowden disease. Approximately 220 cases of LDD have been reported. MRI in patients with LDD is often diagnostic [90]. It is characterized by macrocephaly that may be progressive, developmental delay, seizures, cerebellar signs (tremors, dysdiadochokinesia), and, in some cases, increased intracranial pressure, as the result of herniation of cerebellar tonsils. There is a global hypertrophy of the cerebellum, coarse gyri, inverted cortex pattern, and hamartomatous overgrowth of hypertrophic ganglion cells, which replace the granular layer and Purkinje cells of the cerebellum.

PTEN mutations are also found in up to 20% of Proteus syndrome and approximately 50% of Proteus-like syndrome [86].

Because of the variety of hamartomas and tumors that could occur in patients with BRRS, Cowden disease, and LDD, presenting variably at different ages [88], long-term follow-up and appropriate cancer screening of affected patients are needed. The treatment depends on the type of hamartoma or tumor.

Partington syndrome

In 1997, Partington and colleagues [91] reported three families with 11 members, male and female, showing a new overgrowth syndrome. The syndrome is characterized by generalized overgrowth, mild to moderate mental handicap, and duplication of 4p16.3. The soft tissues are involved with thickening and coarsening of the face. The head hair is abundant and the eyebrows are bushy. Bony overgrowth leads, primarily, to a heavy body frame with a large head circumference, prominent supraorbital ridges, and a square jaw, but a rather small, upturned nose. The hands and feet are big. The degree of mental handicap varies from moderate to mild with no specific behavioral characteristics. Considerable variation is seen in the manifestations of this syndrome between various members of the same family.

The height was well above average. Although physical overgrowth was detectable in childhood, it became most obvious in late adolescence (all >75th percentile) and early adult life. The average adult height for the males was 187.75 cm (6 ft 2 in) with a range of 181 cm to 197 cm (5 ft 11 in to 6 ft 5.5 in) and for the adult females was 171.1 cm (5 ft 7.4 in) with a range of 166 cm to 179 cm (5 ft 5.4 in to 5 ft 10.5 in). Patients with overgrowth are big people with large body frames.

The 4p16 region contains many genes, some of them responsible for well-known disorders such as Huntington disease, achondroplasia, thanatophoric dysplasia, and hypochondroplasia.

The three families reported by Partington and colleagues [91] had different translocations. All four subjects with overgrowth studied received an unbalanced translocation with three copies of 4p16.3 and one member receiving one copy of 4p16.3 had growth failure. The authors suggested that *FGFR3* could be a candidate gene for the growth abnormalities in the overgrowth syndrome (three doses leading to overgrowth) and a single dose leading to growth failure (Pitt-Rogers-Danks syndrome).

The suggestion that additional doses of the *FGFR3* are responsible for the overgrowth has been questioned, because present evidence would suggest that *FGFR3* is a negative regulator of bone growth. Whether the overgrowth syndrome described by Partington and colleagues [91] is the result of overdosage of the *FGFR3* gene, inactivating mutations of the gene, or other genes in 4p16.3 remains to be determined by further studies.

Sotos syndrome

This syndrome was described in 1964 [92]. The major diagnostic features are a distinctive facial configuration, large dolichocephalic head, excessive growth, and a nonprogressive neurologic disorder with mental retardation (Figs. 6 and 7).

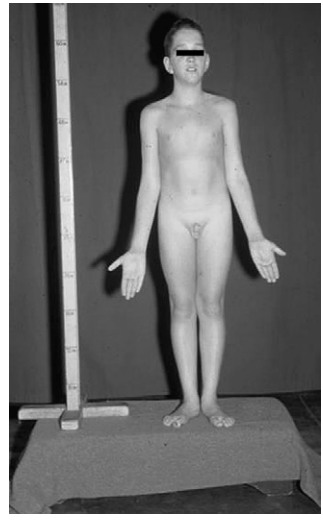

Fig. 6. The original patient with Sotos syndrome. A boy, 10 years 3 months old, with a height (156 cm) equal to an average 14.5-year-old boy, arm span of 173 cm, long hands and feet (12.8% and 18.0% of height), dolicocephalic large head (59 cm circumference), frontal bossing, downslanting of eyes, large ears, prominent jaw, mild dorsal scoliosis, beginning puberty (G-2), and developmental delay (IQ of 70).

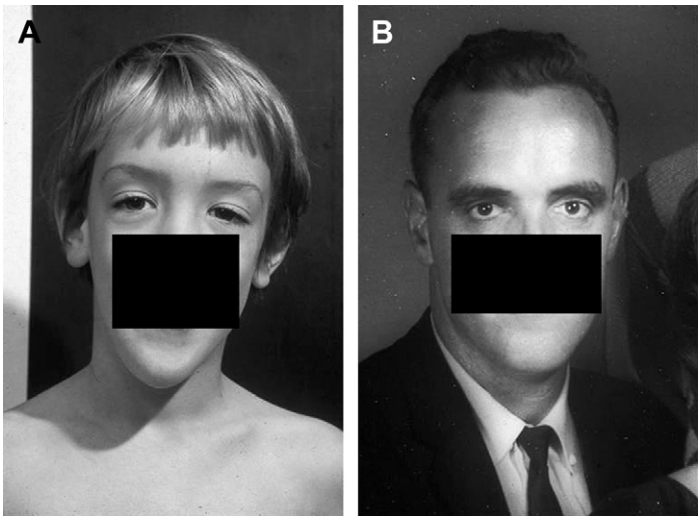

Fig. 7. (*A*) A girl, 4 years 8 months old, with Sotos syndrome. Height was 124 cm (4 ft 0.75 in, height age 7 years 7 months) and weight was 35.2 kg (weight age 7 years 9 months). Bone age was 4 years 10 months. Her adult height is 188 cm (6 ft 2 in). Her father (*B*) (height 198 cm, 6 ft 6 in) and her half sister from a different mother are also affected. Note the characteristic features: large head, frontal bossing, hypertelorism, downslanting of palpebral fissures, pointed chin, and large ears.

The prevalence is not known, but it is, probably, one of the most frequent overgrowth syndromes after BWS and Marfan syndrome. Males and females are affected equally.

One of the main clinical finding is prenatal and postnatal overgrowth. The growth velocity is particularly excessive in the first 3 to 4 years of life and subsequently proceeds at the normal rate, but in the high percentiles. Adult heights exceed, usually, the 50th percentile of normal and are on the average 1.8 SDS for males (186.0 $\pm$ 5.7 cm [1 SD]) and females (173.1 $\pm$ 7.7 cm) [93]. Some individuals may reach excessive adult heights; males of 193 cm to 203 cm (6 ft 4 in to 6 ft 8 in) and females up to 188 cm (6 ft 2 in) are known.

The craniofacial configuration is most characteristic, with a prominent forehead, receding fronto-parietal hairline, dolichocephalic large head, hypertelorism, downslanting of the palpebral fissures, and high narrow palate, with prominent palatine ridges and pointed chin. Premature eruption of teeth occurs in 60% to 80% and advanced bone age in 75% to 84% of the cases. CNS manifestations are frequent. Delay in the attainment of milestones of development, walking and talking and in particular speech, is almost always present and clumsiness is frequent (60% to 80%), as is hypotonia and lax joints. Mental deficiency is present in 85% to 100% of the patients, with an average IQ of 75 and a range from 40 to borderline mildly retarded. Ten percent to 15% may be normal mentally. Seizures may occur in 30% of the cases. There is

an increased incidence of tumor development (~2.2% to 3.9%). Mildly enlarged ventricles and increased subarachnoid spaces may be present in some patients. Other abnormalities have been described: cardiac (septal defects, patent ductus arteriosus), musculoskeletal (kyphoscoliosis), urogenital (hydronephrosis, hypoplastic kidneys, renal agenesis, dilatation of the renal pelvis), inguinal hernias, ophthalomologic (strabismus, refractive errors, retinal or optic nerve anomalies), endocrinological (primary hypothyroidism), and others [31,94].

No endocrine abnormalities have been found to explain the rapid growth.

A genetic cause was suspected for a long time. Several families with members affected in two or three generations were reported, suggesting autosomal dominant inheritance [95]. Most of the cases are sporadic (85%), but could be a result of new mutations, most frequently in the paternal chromosome. Kurotaki and colleagues [96] in 2002 identified deletions or point mutations of a single gene, nuclear receptor binding SET domain protein 1 (*NSD1*), located at chromosome 5q35 in 75% of sporadic cases, indicating that haploinsufficiency of NSD1 is the major cause of Sotos syndrome. The finding that all the *NSD1* mutations identified were either heterozygous or hemizygous is consistent with an autosomal dominant condition. There is a difference in the spectrum of *NSD1* aberrations reported so far between the Japanese and non-Japanese patients. The incidence of deletions is higher in the Japanese patients and intragenic mutations higher in non-Japanese patients. Patients with microdeletions have more severe learning disabilities than patients with mutations [97].

The human *NSD1* gene is expressed in the human fetal brain, which could explain the large brain and mental deficiency. It is also expressed in skeletal muscle, kidney, spleen, peripheral leukocytes, and thymus. The NSD1 protein interacts with the ligand-binding domain of nuclear hormone receptors and may act as a corepressor or coactivator. The finding that haploinsufficiency of *NSD1* induces overgrowth in Sotos syndrome implies that *NSD1* acts as a corepressor of genes that promote growth. A patient with a duplication of 5q35.2,q35.3 had microcephaly and short stature, suggesting that a dosage effect of the NSD1 gene causes a reverse phenotype from Sotos syndrome [98].

The NSD1 is a member of a protein family that includes NSD2 and NSD3, with similar functional domains and 70% to 75% sequence identity with NSD1. No truncating mutation or gene deletions in *NDS2* and *NSD3* were identified in either gene in patients with overgrowth phenotypes [99].

Genotype-phenotype correlations were studied in 266 patients with *NSD1* alterations [97]. Ninety-three percent of the patients who had been clinically diagnosed with Sotos syndrome had NSD1 abnormalities, of which 83% were intragenic mutations and 10% microdeletions. It is possible that 7% of the patients harbored mutations that were not detected. The characteristic facial configuration was almost universally present (99%), learning disability affected 97% of the patients (could be less because bias in the referral of patients with mental retardation), and overgrowth was common, with 90% of individuals having height and/or head circumference of at least 2 SD above the mean.

Advanced bone age was present in 76% of affected individuals in whom it was measured. These main features and other abnormalities were identified in similar proportion of individuals with microdeletions and intragenic mutations.

Other genotype-phenotype correlations found, with minor variations, that the craniofacial configuration, overgrowth, and mental deficiency (and advanced bone age) were the main characteristics [100–103].

The molecular studies have confirmed the original observations reported 43 years ago [92] of a syndrome with the main characteristics of a large dolicocephalic head, distinctive facial configuration, excessive growth, and a nonprogressive neurologic disorder with mental retardation.

There is no biochemical marker for the disease. The diagnosis is based on clinical grounds. The most characteristic manifestations are the craniofacial configuration, the excessive growth, and developmental delay. The diagnosis can be confirmed by DNA studies. Some of the diagnostic tests, such as fragile X by DNA analysis, a karyotype, serum GH, and IGF-I, are mainly to exclude other possibilities. MRI of the brain, showing mildly enlarged ventricles and increased subarachnoid spaces in some patients, is helpful, but not diagnostic.

For management, one of the important concerns is the mental deficiency. Girls with an excessive height with a predicted ultimate height in excess of 178 cm (5 ft 10 in) may benefit from treatment with high doses of estrogen to curtail linear growth, as for tall healthy girls [35,36]. Social and behavioral problems, during childhood and immaturity in adulthood, may benefit from psychologic counsel. Other important concerns are the possibility of tumor development (2.2% to 3.9%) and the risk of transmission. Because the evidence indicates that this is an autosomal dominant disorder, the affected individual has a 50% risk of having affected children. In sporadic cases, the risk to the healthy parents of having another affected child is low, less than 1%. Affected individuals are fertile. There is no evidence, presently, that life span is shortened.

Weaver syndrome

This syndrome, described in 1974 [104], is characterized by excessive growth, prenatally or postnatally, unusual facies, advanced skeletal maturation, and camptodactyly.

Some males have attained an adult height of 194.2 cm (6 ft 4.5 in), a weight of 102.2 kg, and a head circumference of 61 cm (24.0 in), and some females an adult height of 176.3 cm (69.4 in), a weight of 87.6 kg, and a head circumference of 59.5 cm (23.4 in).

The excessive growth is present at birth or has its onset during infancy. Eighty percent of the patients are developmentally delayed or have mental retardation. Mental retardation can range from mild to severe. Many of the features resemble Sotos syndrome [105]. The craniofacial characteristics, although somewhat similar, are in some points different. Patients with Weaver syndrome have hypertelorism, large ears, depressed nasal bridge, and downslanting palpebral features, but the skull, in many cases, is not dolichocephalic,

the occiput is often flat, patients do not have a prominent chin, and the face is broad. Another distinctive finding is that in many cases there is hypertonia rather than hypotonia. No consistent endocrinological abnormality has been found. Striking is the advanced skeletal maturation, with the carpal age much higher than the maturation of the hand. The long bones are widened or splayed and camptodactyly is frequent.

Most of the cases have been sporadic. Parent-to-child transmission has been reported, suggesting autosomal dominant inheritance. *NSD1* mutations were described in 2003 in three patients thought to have Weaver syndrome, suggesting that Sotos and Weaver syndromes were probably allelic [106]. In subsequent analysis in 2005, these three patients had Sotos syndrome and none of the patients with classic Weaver syndrome had *NSD1* mutations. The authors suggested that diagnosis of Weaver syndrome should be given only if the presence of *NSD1* abnormalities has been excluded [97]. The cause remains to be determined.

Neurofibromatosis type I—OMIM 162200

Neurofibromatosis was originally described by von Recklinghausen [107]. Neurofibromatosis type I (NF1) is a common disorder that predisposes to neoplasia in tissues derived from the embryonic neural crest. Several variations of neurofibromatosis have been described. The classic von Recklinghausen type has been designated type I, NF1.

Although NF1 often is only of cosmetic concern, serious and often lethal complications may occur. It is not possible to predict which symptoms will develop in any affected individual. The age-specific prevalence of most manifestations on NF1 increases with age [108].

NF1 is caused by mutations of the *NF1* gene on chromosome 17q11.2, encoding neurofibromin, a protein involved in the regulation of cell differentiation and proliferation. Neurofibromin has been associated with microtubules in some cell types and functions in other cell types as a negative regulator of the proto-oncogene RAS, which is a critical molecule in many intracellular signaling pathways and transduces both growth-promoting and growth-arrest signals [109].

NF1 comprises approximately 90% of all the cases of neurofibromatosis. It is one of the most common autosomal dominant disorders with a frequency of one case per 3000 births. Nearly 50% of the cases are sporadic.

Short stature and microcephaly are not uncommon. Macrocephaly may be present in 25% to 50% of cases. Some patients (2% to 4%) are excessively tall and slender and the possibility of neurofibromatosis has to be considered in patients with overgrowth [110]. A few may have central precocious puberty with increased linear growth. In some cases gigantism could be the result of excessive GH secretion from an optic nerve glyoma or hypothalamic tumor. Excessive GH production may be the consequence of loss of somatostatinergic inhibition of GH secretion by tumor encroachment upon hypothalamic neurons [110]. In some patients, tall stature occurs without excessive GH secretion.

Individuals with microdeletions are typically taller than individuals with intragenic *NF1* mutations, suggesting that deletion of a neighboring gene might promote human growth. Mutations in *RNF135*, which is within the NF1 microdeletion region in six families characterized by overgrowth, learning disability, and dysmorphic features, were identified, demonstrating that *RNF135* haploinsufficiency contributes to the phenotype of NF1 microdeletion cases [111].

A National Institutes of Health [112] consensus development conference identified seven important components for the diagnosis of NF1: (1) six or more cafe-au-lait spots 5 mm or greater in diameter in prepubertal patients and over 15 mm in diameter in postpubertal individuals; (2) two or more neurofibromas of peripheral nerves of any type or one plexiform neurofibroma; (3) freckling in the axillary or inguinal region; (4) optic glioma; (5) two or more Lisch nodules (hamartomas of the iris); (6) a distinctive bony lesion such as dysplasia of the sphenoid, at the base of the skull, or pseudoarthrosis or thinning of long bone cortex, with or without complete interruption of the bone; and (7) a first-degree relative with NF1, according to the preceding criteria. Two or more of these components must be present to make a diagnosis of NF1.

If potential excessive height represents a problem, the treatment approach would be similar to that described for tall girls and tall boys.

Nevo syndrome

Nevo syndrome is a rare autosomal recessive disorder characterized by increased birth length, kyphosis, muscular hypotonia, and joint laxity. Only a few cases have been reported. Some of these patients present clinical features similar to those in the kyphoscoliotic type of Ehlers-Danlos syndrome type VI-A (EDS VIA), an inherited connective tissue disorder characterized by a deficiency of lysyl hydroxylase because of mutations in *PLOD1*. The authors reported findings in seven patients with Nevo syndrome. Six patients were homozygous for a point mutation in exon 9 of *PLOD1* causing a nonsense mutation, while one patient was homozygous for a large deletion comprising exon 17 of *PLOD1*. These findings suggest that the Nevo syndrome is allelic to and clinically indistinguishable from EDS VIA [113].

Elejalde syndrome (OMIM 200995)

Elejalde syndrome, also known as acrocephalopolydactylous dysplasia, was reported by Elejalde and colleagues [114] in 1977. They described an unusual and fortunately rare, prenatal gigantism with craniosynostosis and polydactyly, in dysmorphic fetuses, still births, and newborns. The main characteristic is gigantism with birth weights in two patients reported at 4.3 and 7.5 kg. They have a rounded, globular body, omphalocele, short limbs, craniosynostosis, and redundant skin all over the body but most noted on the neck. The craniosynostosis produces turricephaly. Patients have hypertelorism,

Table 2
Characteristics at birth of disorders with prenatal overgrowth (macrosomia)

Disorder	Abnormalities	Head size	Hypoglycemia	Inheritance	Other
Infant of Diabetic Mother	↑ fat and muscle mass Respiratory distress Hyperbilirubinemia Renal vein thrombosis Polycythemia	Normal	Early: 75% transient	—	Cardiomegaly Subaortic stenosis Left colon syndrome Lumbosacral agenesis
Infant giants	None	Small	Severe-persistent (hyperinsulinism)	Most sporadic Others AR or AD	—
Beckwith-Wiedemann syndrome	Macroglossia Omphalocele Prominent eyes Visceromegaly Ear lobe creases	Small	Severe-persistent (hyperinsulinism)	Sporadic 85% Familial 15%	Renal dysplasia Hemihypertrophy Cytomegaly of adrenal cortex Tumors: Wilms
Simpson-Golabi-Behmel syndrome	Macroglossia Visceromegaly Hypertelorism Ear lobe creases Unusual facies Hypotonia	Macrocephaly	Severe-persistent (hyperinsulinism)	X-linked recessive	Heart defect Hypoplastic index finger nails
Perlman syndrome	Distended abdomen Receding hairline Inverted V-shaped upper lip Micrognathia	Normal	Severe (hyperplasia β cell)	Autosomal recessive	Renal dysplasia Wilms tumor Visceromegaly: Kidneys-Liver
Sotos syndrome	Prominent forehead Hypertelorism Pointed chin Hypotonia	Macrocephaly Dolichocephaly	Not	Autosomal dominant or Sporadic	Feeding problems Respiratory difficulty Advanced bone age

Weaver syndrome	Prominent forehead Hypertelorism	Macrocephaly (flat occiput)	Not	Sporadic or Autosomal dominant	Markedly advanced bone age
Nevo syndrome	Dorsiflexion of feet Edema	Macrocephaly Dolichocephaly	Not	Autosomal recessive	Advanced bone age High arched palate
Marfan syndrome, neonatal, severe	Long-thin body, arms, and legs	Normal size Dolichocephaly	Not	Sporadic or Autosomal dominant	Pulmonary emphysema
Lipodystrophy	Decreased subcutaneous fat Large hands, feet, and ears	Normal	Not	Autosomal recessive	Advanced bone age
Elejalde syndrome	Dysmorphic fetuses and newborns Rounded globular body Polydactyly	Craniosynostosis (turricephaly)	Not	Autosomal recessive?	Excessive connective tissue Polycystic kidneys Pulmonary hypoplasia
Marshall-Smith syndrome	Prominent forehead, eyes Markedly advanced bone age Broad metacarpals, proximal and middle phalanges	Macrocephaly (dolichocephaly)	Not	Sporadic	Severe respiratory difficulties

AD, autosomal dominant; AR, autosomal recessive; —, not applicable.

epicanthal folds, and downslanting palpebral features [115]. The gigantism can be detected early in pregnancy by sonographic examination.

One of the most remarkable findings in these patients is the striking, excessive amount of connective tissue in the kidneys, pancreas, lungs, and skin, resulting in damage to the glomeruli, obstruction and dilatation of the renal tubules, cystic kidney disease, severe pulmonary hypoplasia, and pancreatic insufficiency.

The other characteristic is the overgrowth of the perivascular nerve fibers in many of the tissues.

A few cases have been described in consanguineous families, suggesting autosomal recessive inheritance. It has been hypothesized that this syndrome may be associated with an inactivating mutation of the *FGFR* gene [116].

The prognosis depends on the severity of the renal dysplasia and pulmonary hypoplasia, which, when severe, is incompatible with survival. It is possible there are mild forms that are not recognized. This syndrome should be considered in the diagnosis of fetuses affected with bilateral polycystic kidney disease. Mild cases may not be recognized during the neonatal period or early childhood [115].

PRENATAL OVERGROWTH

There are a number of disorders associated with prenatal overgrowth. A number of them have already been described. Some of the characteristics at birth of the different disorders are indicated in Table 2.

Infants of diabetic mothers are typically large, with birth weights greater than 2 SDS for gestational age and often weighing more than 4 kg (8 lb 13 oz). The size of the infant is related to the degree of hyperglycemia in the mother and a reflection of the fetal hyperglycemia and hyperinsulinemia.

Infant giants from normal-size mothers, without history of maternal diabetes or maternal glucose intolerance, have birth weights varying from approximately 3.8 kg (8 lb 6 oz) to well over 5 kg (11 lb). The affected infants have neonatal severe intractable hypoglycemia as a result of hyperinsulinism, referred in the past as nesidioblastosis or β-cell dysmaturation syndrome. These infants do not have associated malformations.

Most of the cases have been sporadic. The possibility that some cases are genetic variations of the Beckwith-Wiedemann syndrome cannot be excluded. Cases of Beckwith-Wiedemann syndrome with overgrowth without malformations have been observed.

Some may be affected by single or multiple islet cell adenomas, a somewhat uncommon cause of hyperinsulinemic hypoglycemia in neonates and infants. The other possibility is that some infant giants are affected by one of the five genetic forms of congenital hyperinsulinism that have been previously mentioned [4].

Perlman syndrome has to be considered in the differential diagnosis of prenatal overgrowth. It is characterized by gigantism and renal hamartomas.

References

[1] Krepischi-Santos AC, Vianna-Morgante AM, Jehee FS, et al. Whole-genome array-CGH screening in undiagnosed syndromic patients: old syndromes revisited and new alterations. Cytogenet Genome Res 2006;115(3-4):254–61.

[2] Kirchhoff M, Bisgaard AM, Bryndorf T, et al. MLPA analysis for a panel of syndromes with mental retardation reveals imbalances in 5.8% of patients with mental retardation and dysmorphic features, including duplications of the Sotos syndrome and Williams-Beuren syndrome regions. Eur J Med Genet 2007;50(1):33–42.

[3] Argente J, Pérez-Jurado LA, Sotos JF. Molecular bases of pathological growth. J Endocr Genet 2000;1(4):179–210.

[4] De León DD, Stanley CA. Mechanisms of disease: advances in diagnosis and treatment of hyperinsulinism in neonates. Nat Clin Pract Endocrinol Metab 2007;3(1):57–68.

[5] De Simone M, Farello G, Palumbo M, et al. Growth charts, growth velocity and bone development in childhood obesity. Int J Obes 1995;19(12):851–7.

[6] Ballerini MG, Ropelato MG, Domené HM, et al. Differential impact of simple childhood obesity on the components of the growth hormone-insulin-like growth factor (IGF)-IGF binding proteins axis. J Pediatr Endocrinol Metab 2004;17(5):749–57.

[7] Argente J, Caballo N, Barrios V, et al. Multiple endocrine abnormalities of the growth hormone and insulin-like growth factor axis in prepubertal children with exogenous obesity; effect of short-and long-term weight reduction. J Clin Endocrinol Metab 1997;82(7): 2076–83.

[8] Sotos JF. Overgrowth—section II hormonal causes. Clin Pediatr 1996;35(11):579–90.

[9] Melmed S. Medical progress: acromegaly. N Engl J Med 2006;355(24):2558–73, Erratum in: N Engl J Med 356(8):879, 2007.

[10] Online Mendelian Inheritance in Man OMIM (TM). McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) World Wide Web URL, Available at: http://www.ncbi.nlm.nih.gov/omim. Accessed December 15, 2007.

[11] Katznelson L. Diagnosis and treatment of acromegaly. Growth Horm IGF Res 2005;15 (Suppl A):S31–5.

[12] Bowden SA, Sotos JF, Stratakis CA, et al. Successful treatment of an invasive growth hormone-secreting pituitary macroadenoma in an 8-year-old boy. J Pediatr Endocrinol Metab 2007;20(5):643–7.

[13] Stratakis CA, Turner ML, Laffety A, et al. A syndrome of overgrowth and acromegaloidism with normal growth hormone secretion is associated with chromosome 11 pericentric inversion. J Med Genet 2001;38(5):338–43.

[14] Alvarez-Vázquez P, Rivera A, Figueroa I, et al. Acromegaloidism with normal growth hormone secretion associated with X-Tetrasomy. Pituitary 2006;9(2):145–9.

[15] Faivre L, Gosset P, Cormier-Daire V, et al. Overgrowth and trisomy 15q26.1-qter including the IGF1 receptor gene: report of two families and review of the literature. Eur J Hum Genet 2002;10(11):699–706.

[16] Nagai T, Shimokawa O, Harada N, et al. Postnatal overgrowth by 15q-trisomy and intrauterine growth retardation by 15q-monosomy due to familial translocation t(13;15): dosage effect of IGF1R? Am J Med Genet 2002;113(2):173–7.

[17] Okubo Y, Siddle K, Firth H, et al. Cell proliferation activities on skin fibroblasts from a short child with absence of one copy of the type 1 insulin-like growth factor receptor (IGF1R) gene and a tall child with three copies of the IGF1R gene. J Clin Endocrinol Metab 2003;88(12):5981–8.

[18] Kant SG, Kriek M, Walenkamp MJ, et al. Tall stature and duplication of the insulin-like growth factor I receptor gene. Eur J Med Genet 2007;50(1):1–10.

[19] 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(5):935–41.

[20] Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Genet 2001;*7*(8):941–6.
[21] Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. N Engl J Med 2002;346(8):570–8.
[22] Grumbach MM, Styne DM. Puberty: ontogeny, neuroendocrinology, physiology, and disorders. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, editors. Williams textbook of endocrinology. 9th edition. Philadelphia: WB Saunders Co.; 2003. p. 1115–286.
[23] Conte FA, Grumbach MM, Ito Y, et al. A syndrome of female pseudohermaphrodism, hypergonadotropic hypogonadism, and multicystic ovaries associated with missense mutations in the gene encoding aromatase (P450-arom). J Clin Endocrinol Metab 1994;*78*(6):1287–92.
[24] Morishima A, Grumbach MM, Simpson ER, et al. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 1995;80:3689–98.
[25] Jones ME, Boon WC, McInnes K, et al. Recognizing rare disorders: aromatase deficiency. Nat Clin Pract Endocrinol Metab 2007;3(5):414–21.
[26] 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.
[27] Lin L, Hindmarsh PC, Metherell LA, et al. Severe loss-of-function mutations in the adrenocorticotropin receptor (ACTHR, MC2R) can be found in patients diagnosed with salt-losing adrenal hypoplasia. Clin Endocrinol (Oxf) 2007;66(2):205–10.
[28] Clark AJ, McLoughlin L, Grossman A. Familial glucocorticoid deficiency associated with point mutation in the adrenocorticotropin receptor. Lancet 1993;341:461–2.
[29] Matsuura H, Shiohara M, Yamano M, et al. Novel compound heterozygous mutation of the MC2R gene in a patient with familial glucocorticoid deficiency. J Pediatr Endocrinol Metab 2006;19(9):1167–70.
[30] Metherell LA, Chapple JP, Cooray S, et al. Mutations in MRAP, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2. Nat Genet 2005;*37*:166–70.
[31] Sotos JF, Argente J. Postnatal non-endocrine overgrowth. In: Martini L, editor, Encyclopedia of endocrinology and endocrine diseases, Vol. 4. San Diego (CA): Academic Press; 2004. p. 7–24.
[32] Rao E, Weiss B, Fukami M, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet 1997;16(1):54–63.
[33] Kanaka-Gantenbein C, Kitsiou S, Mavrou A, et al. Tall stature, insulin resistance, and disturbed behavior in a girl with the triple X syndrome harboring three SHOX genes: offspring of a father with mosaic Klinefelter syndrome but with two maternal X chromosomes. Horm Res 2004;61(5):205–10.
[34] Benito-Sanz S, Thomas NS, Huber C, et al. A novel class of Pseudoautosomal region 1 deletions downstream of SHOX is associated with Leri-Weill dyschondrosteosis. Am J Hum Genet 2005;*77*(4):533–44.
[35] Drop SL, DeWaal WJ, De Munick Keizer-Schrama SM. Sex steroid treatment of constitutionally tall stature. Endocr Rev 1998;19(5):540–58.
[36] Sotos JF. Overgrowth—section I overgrowth disorders. Clin Pediatr 1996;*35*(10): 517–29.
[37] Klinefleter HF, Reifenstein EC Jr, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis with a Leydigism and increased excretion of follicle-stimulation hormone. J Clin Endocrinol Metab 1942;2:615–27.
[38] Vorona E, Zitzmann M, Gromoll J, et al. Clinical, endocrinological, and epigenetic features of the 46,XX male syndrome, compared with 47,XXY Klinefelter patients. J Clin Endocrinol Metab 2007;92(9):3458–65.

[39] Aksglaede L, Andersson AM, Jørgensen N, et al. Primary testicular failure in Klinefelter's syndrome: the use of bivariate luteinizing hormone-testosterone reference charts. Clin Endocrinol (Oxf) 2007;66(2):276–81.
[40] Bastida MG, Rey RA, Bergadá I, et al. Establishment of testicular endocrine function impairment during childhood and puberty in boys with Klinefelter syndrome. Clin Endocrinol (Oxf) 2007 Jul 20; [Epub ahead of print] PMID: 17645574.
[41] Wikström AM, Hoei-Hansen CE, Dunkel L, et al. Immunoexpression of androgen receptor and nine markers of maturation in the testes of adolescent boys with Klinefelter syndrome: evidence for degeneration of germ cells at the onset of meiosis. J Clin Endocrinol Metab 2007;92(2):714–9.
[42] Geerts M, Steyaert J, Fryns JP. The XYY syndrome: a follow-up study on 38 boys. Genet Couns 2003;14(3):267–79.
[43] Salo P, Kääriäinen H, Page DC, et al. Deletion mapping of stature determinants on the long arm of the Y chromosome. Hum Genet 1995;95:283–6.
[44] Kirsch S, Weiss B, Zumbach K, et al. Molecular and evolutionary analysis of the growth-controlling region on the human Y chromosome. Hum Genet 2004;114(2):173–81.
[45] Mandel JL, Biancalana V. Fragile X mental retardation syndrome: from pathogenesis to diagnostic issues. Growth Horm IGF Res 2004;14(Suppl A):S158–65.
[46] Willemsen R, Oostra BA, Bassell GJ, et al. The fragile X syndrome: from molecular genetics to neurobiology. Ment Retard Dev Disabil Res Rev 2004;10(1):60–7.
[47] Adams JS, Adams PE, Nguyen D, et al. Volumetric brain changes in females with fragile X-associated tremor/ataxia syndrome (FXTAS). Neurology 2007;69(9):851–9.
[48] Judge DP, Dietz HC. Therapy of Marfan syndrome. Annu Rev Med 2007 Sep 10; [Epub ahead of print] PMID: 17845137.
[49] Mizuguchi T, Matsumoto N. Recent progress in genetics of Marfan syndrome and Marfan-associated disorders. J Hum Genet 2007;52(1):1–12.
[50] Byers PH. Determination of the molecular basis of Marfan syndrome: a growth industry. J Clin Invest 2004;114(2):161–3.
[51] Faivre L, Collod-Beroud G, Loeys BL, et al. Effect of mutation type and location on clinical outcome in 1,013 probands with Marfan syndrome or related phenotypes and FBN1 mutations: an international study. Am J Hum Genet 2007;81(3):454–66.
[52] De Paepe A, Devereux RB, Dietz HC, et al. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996;62(4):417–26.
[53] Anderson RA, Koch S, Camerini-Otero RD. Cardiovascular findings in congenital contractural arachnodactyly: report of an affected kindred. Am J Med Genet 1984;18(2):265–71.
[54] Bawle E, Quigg MH. Ectopia lentis and aortic root dilatation in congenital contractural arachnodactyly. Am J Med Genet 1992;42(1):19–21.
[55] Hayward C, Brock DJ. Fibrillin-1 mutations in Marfan syndrome and other type-1 fibrillinopathies. Hum Mutat 1997;10(6):415–23.
[56] Milewicz DM, Michael K, Fisher N, et al. Fibrillin-1 (FBN1) mutations in patients with thoracic aortic aneurysms. Circulation 1996;94(11):2708–11.
[57] Milewicz DM, Grossfield J, Cao SN, et al. A mutation in FBN1 disrupts profibrillin processing and results in isolated skeletal features of the Marfan syndrome. J Clin Invest 1995;95(5):2373–8.
[58] Sood S, Eldadah ZA, Krause WL, et al. Mutation in fibrillin-1 and the Marfanoid-craniosynostosis (Shprintzen-Goldberg) syndrome. Nat Genet 1996;12(2):209–11.
[59] Carson NA, Neill DW. Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland. Arch Dis Child 1962;37:505–13.
[60] Gerritsen T, Vaughn JG, Waisman HA. The identification of homocystine in the urine. Biochem Biophys Res Commun 1962;19(9):493–6.
[61] Mudd SH, Levy HL, Kraus J. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, et al, editors. 7th edition, The metabolic basis of inherited disease, Vol 2. New York: McGraw-Hill; 2001. p. 2007–56.

[62] Sotos JF. Overgrowth—section V syndromes and other disorders associated with overgrowth. Clin Pediatr 1997;36(2):91–103.
[63] Beckwith JB . Macroglossia, omphalocele, adrenal cytomegaly, gigantism, and hyperplastic visceromegaly. Birth Defects Orig. Art. Ser 1969;(2):188–96.
[64] Wiedemann HR. Familial malformation complex with umbilical hernia and macroglossia—A ''new syndrome.'' J Genet Hum 1964;(13):223–32 [Article in French].
[65] Sotos JF. Overgrowth—section VI genetic syndromes and other disorders associated with overgrowth. Clin Pediatr 1997;36(3):157–70.
[66] Sotos JF, Argente J. Beckwith-Wiedemann syndrome. In: Martini L, editor, Encyclopedia of endocrinology and endocrine diseases, Vol. 1. SanDiego (CA): Academic Press; 2004. p. 336–40.
[67] Gracia Bouthelier R, Lapunzina P. Follow-up and risk of tumors in overgrowth syndromes. J Pediatr Endocrinol Metab 2005;1(18 Suppl):1227–35.
[68] Enklaar T, Zabel BU, Prawitt D. Beckwith-Wiedemann syndrome: multiple molecular mechanisms. Expert Rev Mol Med 2006;8(17):1–19.
[69] Sparago A, Russo S, Cerrato F, et al. Mechanisms causing imprinting defects in familial Beckwith-Wiedemann syndrome with Wilms' tumour. Hum Mol Genet 2007;16(3):254–64.
[70] Edwards CA, Ferguson-Smith AC. Mechanisms regulating imprinted genes in clusters. Curr Opin Cell Biol 2007;19(3):281–9.
[71] Weksberg R, Shuman C, Smith AC. Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet 2005;137(1):12–23.
[72] DeChiara TM, Robertson EJ, Efstratiadis A. Parental imprinting of the mouse insulin-like growth factor II gene. Cell 1991;64:849–59.
[73] Eggenschwiler J, Ludwig T, Fisher P, et al. Mouse mutant embryos overexpressing IGF-II exhibit phenotypic features of the Beckwith-Wiedemann and Simpson-Golabi-Behmel syndromes. Genes Dev 1997;11(23):3128–42.
[74] Sun FL, Dean WL, Kelsey G, et al. Transactivation of IGF2 in a mouse model of Beckwith-Wiedemann syndrome. Nature 1997;389(6653):809–15.
[75] Lau MM, Stewart CE, Liu Z, et al. Loss of the imprinted IGF2/cation-independent mannose 6-phosphate receptor results in fetal overgrowth and perinatal lethality. Genes Dev 1994;8(24):2953–63.
[76] Ogawa O, Eccles MR, Szeto J, et al. Relaxation of insulin-like growth factor II gene imprinting implicated in Wilm's tumour. Nature 1993;22(6422):749–51.
[77] Morison IM, Becroft DM, Taniguchi T, et al. Somatic overgrowth associated with overexpression of insulin-like growth factor II. Nat Med 1996;2(3):311–6.
[78] Simpson JL, Landey S, New M, et al. A previously unrecognized X-linked syndrome of dysmorphia. Birth Defects Orig. Art Ser 1975;XI(2):18–24.
[79] Golabi M, Rosen L. A new X-linked mental retardation-overgrowth syndrome. Am J Med Genet 1984;17(1):345–58.
[80] Behmel A , Plöchl E, Rosenkranz W. A new X-linked dysplasia gigantism syndrome: identical with the Simpson dysplasia syndrome? Hum Genet 1984;67(4):409–13.
[81] Pilia G, Hughes-Benzie RM, MacKenzie A, et al. Mutations in GPC3, a glypican gene, cause the Simpson-Golabi-Behmel overgrowth syndrome. Nat Genet 1996;12(3):241–7.
[82] 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(2):129–35.
[83] Terespolsky D, Farrell SA, Siegel-Bartelt J, et al. Infantile lethal variant of Simpson-Golabi-Behmel syndrome associated with hydrops fetalis. Am J Med Genet 1995;59(3):329–33.
[84] Cano-Gauci DF, Song HH, Yang H, et al. Glypican-3-deficient mice exhibit developmental overgrowth and some of the abnormalities typical of Simpson-Golabi-Behmel syndrome. J Cell Biol 1999;146(1):255–64.
[85] Brzustowicz LM, Farrell S, Khan MB, et al. Mapping of a new SGBS locus to chromosome Xp22 in a family with a severe form of Simpson-Golabi-Behmel syndrome. Am J Hum Genet 1999;65(3):779–83.

[86] Eng C. PTEN: one gene, many syndromes. Hum Mutat 2003;22(3):183–98.
[87] Waite KA, Eng C. Protean PTEN: form and function. Am J Hum Genet 2002;70(4): 829–44.
[88] Lachlan KL, Lucassen AM, Bunyan D, et al. Cowden syndrome and Bannayan Riley Ruvalcaba syndrome represent one condition with variable expression and age-related penetrance: results of a clinical study of PTEN mutation carriers. J Med Genet 2007;44(9): 579–85.
[89] Tan TC, Ho LC. Lhermitte-Duclos disease associated with Cowden syndrome. J Clin Neurosci 2007;14(8):801–5.
[90] Robinson S, Cohen AR. Cowden disease and Lhermitte-Duclos disease: an update. Case report and review of the literature. Neurosurg Focus 2006;20(1):E6.
[91] Partington MW, Fagan K, Soubjaki V, et al. Translocations involving 4p16.3 in three families: deletion causing the Pitt-Rogers-Danks syndrome and duplication resulting in a new overgrowth syndrome. J Med Genet 1997;34(9):719–28.
[92] Sotos JF, Dodge PR, Muirhead D, et al. Cerebral gigantism in childhood: a syndrome of excessively rapid growth and acromegalic features and a nonprogressive neural disorder. N Engl J Med 1964;271:109–16.
[93] Cole TR, Hughes HE. Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet 1994;31(1):20–32.
[94] Root AW, Diamond FB. The Sotos syndrome—NSD1 haploinsufficiency: cerebral gigantism update. Growth, Genetics, & Hormones 2006;22(3):33–48.
[95] Zonana J, Sotos JF, Romshe CA, et al. Dominant inheritance of cerebral gigantism. J Pediatr 1977;91(2):251–6.
[96] Kurotaki N, Imaizumi K, Harada N, et al. Haploinsufficiency of NSD1 causes Sotos syndrome. Nat Genet 2002;30(4):365–6.
[97] Tatton-Brown K, Douglas J, Coleman K, et alChildhood Overgrowth Collaboration. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. Am J Hum Genet 2005;77(2):193–204.
[98] Chen CP, Lin SP, Lin CC, et al. Molecular cytogenetic analysis of de novo dup (5)(q35.2q35.3) and review of the literature of pure partial trisomy 5q. Am J Med Genet A 2006;140(14):1594–600.
[99] Douglas J, Coleman K, Tatton-Brown K, et alChildhood Overgrowth Collaboration. Evaluation of NSD2 and NSD3 in overgrowth syndromes. Eur J Hum Genet 2005;13(2):150–3.
[100] Rio M, Clech L, Amiel J, et al. Spectrum of NSD1 mutations in Sotos and Weaver syndromes. J Med Genet 2003;40(6):436–40.
[101] Cecconi M, Forzano F, Milani D, et al. Mutation analysis of the NSD1 gene in a group of 59 patients with congenital overgrowth. Am J Med Genet A 2005;134(3):247–53.
[102] Türkmen S, Gillessen-Kaesbach G, Meinecke P, et al. Mutations in NSD1 are responsible for Sotos syndrome, but are not a frequent finding in other overgrowth phenotypes. Eur J Hum Genet 2003;11(11):858–65.
[103] de Boer L, Kant SG, Karperien M, et al. Genotype-phenotype correlation in patients suspected of having Sotos syndrome. Horm Res 2004;62(4):197–207.
[104] Weaver DD, Graham CB, Thomas IT, et al. A new overgrowth syndrome with accelerated skeletal maturation, unusual facies, and camptodactyly. J Pediatr 1974;84:547–52.
[105] Opitz JM, Weaver DW, Reynolds Jr JF. The syndromes of Sotos and Weaver: reports and review. Am J Med Genet 1998;79(4):294–304.
[106] Douglas J, Hanks S, Temple IK, et al. NSD1 mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. Am J Hum Genet 2003;72(1):132–43.
[107] von Recklinghausen F. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin: August Hirschwald; 1882. [In German].
[108] Friedman JM, Birch PH. Type 1 neurofibromatosis: a descriptive analysis of the disorder in 1,728 patients. Am J Med Genet 1997;70(2):138–43.

[109] Gutmann DH. Recent insights into neurofibromatosis type 1: clear genetic progress. Arch Neurol 1998;55(6):778–80.
[110] Karantza M, Geffner M. Growth and growth hormone in children with neurofibromatosis type 1. Growth Genet Horm 2005;21:33–8.
[111] Douglas J, Cilliers D, Coleman K, et alChildhood Overgrowth Collaboration. Mutations in RNF135, a gene within the NF1 microdeletion region, cause phenotypic abnormalities including overgrowth. Nat Genet 2007;39(8):963–5.
[112] National Institutes of Health. Neurofibromatosis. National Institutes consensus development conference statement. Bethesda (MD): The Institute; 1987. p. 6.
[113] Giunta C, Randolph A, Al-Gazali LI, et al. Nevo syndrome is allelic to the kyphoscoliotic type of the Ehlers-Danlos syndrome (EDS VIA). Am J Med Genet A 2005;133(2):158–64.
[114] Elejalde BR, Giraldo C, Jimenez R, et al. Acro-cephalopolydactylous dysplasias. Birth Defects Orig Artic Ser 1977;13(3B):53–67.
[115] Elejalde BR, Elejalde MM, Iafolla AK. Acrocephalopoly-dactylous dysplasia. In: Buyse ML, editor, Birth defects encyclopedia, Vol. I. Cambridge (MA): Blackwell; 1990. p. 35.
[116] Silhánová E, Plevová P, Curík R, et al. Elejalde syndrome—a case report. Am J Med Genet A 2006;140(20):2223–6.