Causes of short stature

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INTRODUCTION — Short stature is a term applied to a child whose height is 2 standard deviations (SD) or more below the mean for children of that sex and chronologic age (and ideally of the same racial-ethnic group). This corresponds to a height that is below the 2.3rd percentile. Short stature may be either a variant of normal growth or caused by a disease.

The most common causes of short stature beyond the first year or two of life are familial (genetic) short stature and delayed (constitutional) growth, which are normal non-pathologic variants of growth. The goal of the evaluation of a child with short stature is to identify the subset of children with pathologic causes (such as Turner syndrome, inflammatory bowel disease or other underlying systemic disease, or growth hormone deficiency). The evaluation also assesses the severity of the short stature and likely growth trajectory, to facilitate decisions about intervention, if appropriate.

This topic will review the main causes of short stature. The diagnostic approach to children with short stature is discussed separately. (See "Diagnostic approach to children and adolescents with short stature".)

NORMAL VARIANTS OF GROWTH

Familial short stature — Familial or genetic short stature is most often a normal variant, termed familial or genetic short stature (figure 1). These individuals usually have low-normal growth velocity throughout life. The otherwise normal growth velocity generally distinguishes these children from those with pathologic causes of short stature. Their bone age is consistent with their chronological age, which helps distinguish them from children with constitutional delay of growth (table 1). (See 'Constitutional delay of growth and puberty' below.)

Constitutional delay of growth and puberty — Constitutional delay of growth and puberty (CDGP, sometimes called constitutional short stature for prepubertal children) results in childhood short stature but relatively normal adult height. Children with CDGP are usually of normal size at birth. However, a downward shift in growth rate begins at three to six months of age that is parallel to that seen in most normally growing children in this age group, but tends to be more severe and prolonged. By three or four years of age, children with CDGP usually are growing at a low-normal rate (eg, about 4 to 5 cm/year in preadolescent girls, and 3.5 to 4.5 cm/year in preadolescent boys). The result is a growth curve that remains below, but parallel to, the third percentile for height. In addition to a low preadolescent growth rate, they tend to have delayed pubertal development. This leads to a marked height discrepancy during the early teenage years compared with their peers, but is followed by catch-up growth when they do enter puberty (figure 2).

The hallmark of CDGP is delayed skeletal age; it is more closely related to the height age (age at which one's height would be average) than the chronologic age (table 1). For these patients, height data should be interpreted according to bone age rather than chronological age to accurately reflect height potential. Because the bone age is delayed, growth typically continues longer than normal, often resulting in normal adult stature. In many cases, there is a family history of delayed growth and puberty in one or both parents (sometimes described as being a "late bloomer").

Idiopathic short stature — A practical definition of idiopathic short stature (ISS) is a height below 2 standard deviations (SD) of the mean for age, in the absence of any endocrine, metabolic, or other diagnosis. These children have normal (often at the lower limit) growth velocity and no biochemical or other evidence for a specific growth retarding condition, which implies normal results for endocrine screening tests, including those for growth hormone deficiency. Genome-wide studies indicate that the majority of the variation in adult height is explained by several hundred genetic variations, each with a small effect [1]. However, in a small proportion of the population, short stature is caused by specific genetic variations with large effect. As an example, emerging evidence suggests that mutations in the **S**hort Stature **HO**meobo**X** (SHOX) gene are responsible for 1 to 4 percent of individuals who would otherwise have been classified as having "idiopathic" short stature (see 'SHOX mutations' below). In addition to these genetic contributors to ISS, it appears that **epigenetic** changes may play a role in some cases of ISS. In one study, ISS is associated was increased methylation of two promoter regions for the insulin-like growth factor I (IGF-I) gene; these epigenetic changes are predicted to reduce the individual's sensitivity to growth hormone [2]. (See "Growth hormone insensitivity syndromes", section on 'Impaired IGF-I promoter function'.)

Growth hormone therapy is approved in the United States for children with ISS, which is defined for this purpose by a more stringent threshold for height (below -2.25 SD of the mean, and a predicted adult height is <63 inches for males and <59 inches for girls). However, the use of growth hormone for this group of patients remains controversial. Studies have shown that consumer preferences (family concern) and physician attitudes are important drivers of treatment decisions, independent of patient characteristics [3]. Treatment indications and efficacy are discussed in detail separately. (See "Growth hormone treatment for idiopathic short stature".)

ISS is a diagnosis of exclusion. The child's height percentile is below the range predicted by the midparental height and the bone age is not delayed, but there is no evidence of underlying genetic, systemic, or endocrine disease [4]. Although this may be a variant of normal growth, patients with this growth pattern warrant monitoring for the possibility of unrecognized underlying disease.

There is ongoing controversy about the nomenclature of ISS. Here, we use the term to refer to nonfamilial cases (ie, those without patterns of familial short stature). Others consider familial short stature and CDGP to be subcategories of ISS [4,5].

Small for gestational age infants with catch-up growth — Most infants born small for gestational age (SGA) experience catch-up growth by two years of age, sufficient to be within the normal range (length above -2 SD, ie, >2.3rd percentile). Catch-up growth may be delayed in infants who are born preterm in addition to SGA, but often continues into childhood to approach the range predicted by the family's height. SGA can be caused by maternal, placental, or fetal factors. In many cases these factors (such as intrauterine constraint from a small uterus) are transient and are followed by vigorous catch-up growth during infancy. (See "Infants with fetal (intrauterine) growth restriction".)

About 10 percent of SGA infants, particularly those born with more severe SGA, do not experience catch-up growth to reach the normal range by two years of age. This group of SGA infants can be considered to have a pathologic pattern of growth, so they are discussed later in this topic review. (See 'Other causes of short stature that may be pathologic' below.)

PATHOLOGIC CAUSES OF GROWTH FAILURE

Systemic disorders with secondary effects on growth — Almost any serious disease can cause growth failure (table 2). The abnormalities of growth and development that occur in children with acute or chronic illnesses may result from the primary disease process because of increased energy needs or nutritional deprivation (eg, decreased intake or malabsorption). Growth also may be affected by treatments, such as radiation therapy (a permanent effect), glucocorticoids, stimulants used for attention deficit disorder (ADD), or chemotherapy (mostly transient effects, but may have a small permanent effect if treatment is prolonged [6-9]). Some diseases may cause secondary derangements of the hormones that affect growth.

Diseases or processes that are particularly important causes of growth failure are outlined below. Other disorders that can cause growth failure with weight loss are outlined in a separate topic review. (See "Evaluation of weight loss in infants over six months of age, children, and adolescents", section on 'Differential diagnosis'.)

Undernutrition — Insufficient nutrition tends to lead to short stature with a delayed pattern of growth. Under-nutrition can be isolated (eg, caused by inadequate food supply or self-imposed restriction, such as fear of obesity [10]), or it may be a component of an underlying systemic disease that interferes with food intake or absorption, or increases energy needs. The hallmark of under-nutrition is low weight-for-height.

Glucocorticoid therapy — Since glucocorticoids are used for treatment of a variety of diseases, they are a common cause of growth failure in children. The growth failure can develop with or without other symptoms of glucocorticoid excess, known as Cushing's syndrome (see 'Cushing's syndrome' below). They suppress growth through several different mechanisms, including interference with endogenous growth hormone secretion and action, bone formation, nitrogen retention, and collagen formation [11]. The growth effects of glucocorticoids are related to the type, dose, and duration of the exposure. If glucocorticoids are discontinued, children usually experience some catch-up growth.

The relative effects of different glucocorticoids on growth are similar, but not identical, to the relative potencies for hypothalamic-pituitary-adrenal axis suppression [12]. Growth impairment is more pronounced with agents with a longer duration of action (eg, dexamethasone > prednisone > hydrocortisone). It is most pronounced when glucocorticoids are administered daily as compared with an alternate-day regimen [11]. Some inhibition of linear growth occurs even at the doses that are used for physiological replacement (ie, prednisone doses of 3 to 5 mg/m^2 per day; approximately 0.075 to 0.125 mg/kg per day), and progressive growth impairment is seen with increasing doses [13]. As an example, in a large series of children with growth failure due to chronic treatment with glucocorticoids for a systemic disease, the mean prednisone-equivalent dose was 0.5 ± 0.6 mg/kg per day [13]. Growth impairment can even occur with prolonged administration of inhaled glucocorticoids during childhood, although the overall effect of these agents on adult height appears to be small [14,15]. (See "Pharmacologic use of glucocorticoids", section on 'Dose' and "Major side effects of inhaled glucocorticoids", section on 'Growth deceleration'.)

Prolonged treatment with systemic glucocorticoids may have persistent effects on growth after therapy is discontinued. In a study of 224 children with cystic fibrosis who previously had been treated for up to four years with either alternate-day prednisone or placebo, mean height after age 18 years (on average six to seven years after cessation of therapy) was significantly lower in boys who had received either high- or low-dose prednisone (170.5 and 170.7 versus 174.6 cm with placebo; p = 0.03) [16]. This effect was most pronounced in boys who had started taking prednisone at six to eight years of age. In contrast, there was no persistent growth impairment in girls treated similarly.

Gastrointestinal disease — Children with growth failure resulting from gastrointestinal disease tend to have a greater deficit in weight than height (ie, they are underweight-for-height) in contrast to those with endocrine disorders, who are often overweight-for-height (see below).

Up to 50 percent of children with Crohn disease have a decrease in height velocity before the onset of gastrointestinal symptoms [17], and about 10 percent of children with Crohn disease have short stature when the Crohn disease is diagnosed [17]. The growth failure is closely related to the inflammatory disease process (mediated by proinflammatory cytokines), as well as decreased food intake, malabsorption, and/or high-dose glucocorticoids if used for treatment (see "Growth failure and poor weight gain in children with inflammatory bowel disease"). Similarly, celiac disease can present with growth failure, especially in younger children [18]. Both of these disorders are important considerations in the evaluation of a child whose linear growth has slowed, particularly if there are gastrointestinal symptoms and/or slow weight gain. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children".)

Rheumatologic disease — Childhood rheumatologic diseases, especially systemic juvenile idiopathic arthritis (JIA), are frequently associated with growth retardation. This may be a consequence of the proinflammatory cytokines associated with disease activity and is also caused by the high-dose glucocorticoids that are often used for treatment [19,20]. Common presenting symptoms in JIA are fever, arthralgias, rash, and lymphadenopathy, in addition to growth failure. (See "Systemic juvenile idiopathic arthritis: Course, prognosis, and complications", section on 'Growth retardation'.)

Renal disease — Growth failure is seen in at least one-third of children with chronic kidney disease. The primary causes of growth failure in children with chronic kidney disease are disturbances of growth hormone metabolism and its main mediator, insulin-like growth factor-I (IGF-I). Other factors may include metabolic acidosis, uremia, poor nutrition secondary to dietary restrictions, anorexia of chronic illness, anemia, calcium and phosphorus imbalance, renal osteodystrophy, or use of high-dose glucocorticoids if used for treatment. Affected patients are candidates for growth hormone therapy until renal transplantation, and some of these patients may also benefit from growth hormone therapy after transplantation. (See "Pathogenesis, evaluation and diagnosis of growth impairment in children with chronic kidney disease" and "Growth hormone treatment in children with chronic kidney disease and postrenal transplantation".)

Metabolic acidosis alone can also impair growth, as occurs in children with renal tubular acidosis [21]. Alkali therapy may lead to attainment and maintenance of normal stature [21]. (See "Etiology and clinical manifestations of renal tubular acidosis in infants and children".)

Cancer — Children with cancer may grow poorly before diagnosis because of poor food intake, nausea, vomiting, and increased caloric utilization. After diagnosis, anorexia, nausea, and vomiting induced by chemotherapy and radiotherapy also can contribute to impaired growth.

These effects often subside within one to two years of initiating treatment, and some children then have catch-up growth [22,23].

Late growth failure is common in children who received cranial radiotherapy because it can damage the hypothalamus and cause insufficiency of one or more hormones from the pituitary, including growth hormone, gonadotropins, and thyroid stimulating hormone (TSH) [24-28]. In younger children, especially girls, cranial radiotherapy can cause precocious puberty and adult short stature. Primary hypothyroidism also can occur if the thyroid gland was in the radiation field. Spinal irradiation may result in slow growth of the spine with relative preservation of normal limb growth. (See "Bone problems in childhood cancer patients", section on 'Altered epiphyseal growth'.)

Pulmonary disease — Cystic fibrosis is both a pulmonary and gastrointestinal disease. Growth failure in this disorder may be caused by multiple mechanisms, including poor food intake, maldigestion or malabsorption, chronic infection, and increased energy requirements (work of breathing) [29]. (See"Cystic fibrosis: Clinical manifestations and diagnosis" and "Cystic fibrosis: Nutritional issues".)

Immune deficiencies also may present with pulmonary symptoms and/or growth failure. (See "Causes of bronchiectasis in children".)

Asthma has been associated with a deceleration of growth velocity, which is most pronounced with severe disease. Growth failure in children with asthma is more often due to treatment with glucocorticoids. (See 'Glucocorticoid therapy' above.)

Cardiac disease — Growth failure is common in children with severe heart disease of any cause. The major pathogenetic factors are thought to be anorexia and increased basal energy requirements [30]. Occasionally, growth failure is the presenting feature of the heart disease. (See "Suspected heart disease in infants and children: Criteria for referral".)

Immunologic disease — Human immunodeficiency virus (HIV) infection is associated with growth failure. Mechanisms include anorexia, malabsorption, diarrhea, severe infections, and failure of one or more organ systems [31]. (See "Pediatric HIV infection: Classification, clinical manifestations, and outcome", section on 'Wasting syndrome'.)

Growth failure also can occur with other immunological deficiencies such as common variable immunodeficiency or severe combined immunodeficiency syndrome. As with HIV infection, multiple factors are probably involved. (See "Common variable immunodeficiency in children" and "Severe combined immunodeficiency (SCID): An overview".)

Metabolic diseases — Growth failure is common in children and adolescents with many of the inborn disorders of metabolism. Among acquired metabolic diseases, the most common is type 1 diabetes mellitus. In the past, type 1 diabetes mellitus was an important cause of short stature and attenuated growth because of caloric deficit resulting from severe glucosuria [32]. However, it is now rare because of improvements in therapy. Children with type 1 diabetes have some decrease in IGF-1 production or action, and there is a negative correlation between hemoglobin A1C (as an index of metabolic control) and adult height [33,34]. Nonetheless, in children with fair to good metabolic control, growth and adult height are usually within normal ranges. Occasionally, children with diabetes and very poor glycemic control develop Mauriac syndrome, characterized by attenuated linear growth, delayed puberty, hepatomegaly, and Cushingoid features. (See "Complications and screening in children and adolescents with type 1 diabetes mellitus", section on 'Growth'.)

Any disorder associated with vitamin D deficiency or decreased vitamin D action can cause hypophosphatemia and rickets; rickets is characterized by abnormal epiphyseal development, bowing of the extremities, and diminished growth. Vitamin D deficiency in the absence of rickets does not seem to affect linear growth. (See "Overview of rickets in children" and "Hereditary hypophosphatemic rickets and tumor-induced osteomalacia".)

Endocrine causes of growth failure — Primary endocrine disorders with effects on growth are uncommon but are important to identify because they can be treated (table 2). In general, these disorders are characterized by excessive weight for height. They should be considered in any child with markedly reduced height velocity, and especially in those with other pituitary disorders, brain tumors, septo-optic dysplasia (also known as optic nerve hypoplasia), midline brain and facial defects, neonatal hypoglycemia, history of cranial irradiation, or a familial pattern of growth hormone deficiency [35]. Any patient with an abnormality of one pituitary hormone (central hypothyroidism, Cushing's disease, or growth hormone deficiency) should be evaluated for other pituitary hormone deficiencies.

Cushing's syndrome — Cushing's syndrome is caused by excessive glucocorticoids and is characterized by the combination of weight gain and growth retardation, resulting in excessive weight-for-height (figure 3) [36-38].

Endogenous Cushing's syndrome (caused by excessive endogenous production of cortisol) is rare in children. The most common cause is a corticotropin (ACTH)-secreting pituitary adenoma (Cushing's disease) [36,38,39]. The syndrome also may be caused by an adrenal adenoma, especially in younger children. In one series of children with endogenous Cushing's syndrome, growth retardation was common (83 percent), but most patients had bone age within normal limits at diagnosis [36]. Other key clinical features are central obesity, suprascapular fat pad ("buffalo hump"), abdominal striae, hirsutism, acne, and neuropsychological symptoms [38]. The best tests to establish the diagnosis are a 24-hour urine collection for free cortisol (and creatinine), or a dexamethasone suppression test. Measurements of serum cortisol are not reliable screening tests, unless performed late at night. (See "Epidemiology and clinical manifestations of Cushing's syndrome" and "Establishing the diagnosis of Cushing's syndrome".)

Exogenous sources of glucocorticoids (eg, due to glucocorticoid therapy for asthma or inflammatory bowel disease) are a more common cause of Cushing's syndrome. (See 'Glucocorticoid therapy' above.)

Hypothyroidism — Growth failure is a well-recognized consequence of hypothyroidism during childhood and may be the presenting feature. The bone age is usually delayed; as a result, many children with hypothyroidism have a reasonably normal growth potential once the disorder is identified and treated. The evaluation should include measurements of both TSH and free thyroxine to allow detection of both primary and central hypothyroidism. Measurement of serum TSH alone will not detect central hypothyroidism as it can be low, normal, or even slightly elevated. (See "Acquired hypothyroidism in childhood and adolescence".)

Growth hormone deficiency — Growth hormone deficiency usually results from deficiency of growth hormone-releasing hormone (GHRH). It can also be caused by sellar and parasellar tumors (eg, craniopharyngioma [40]) that destroy the pituitary gland itself, in which case there may be deficiencies of multiple hormones produced by the anterior pituitary (see "Clinical manifestations of hypopituitarism"). Children with growth hormone deficiency can have striking catch-up growth during growth hormone replacement therapy [41]. Children with a sellar or parasellar tumor that causes growth hormone deficiency occasionally experience rapid catch-up growth after surgical resection of the tumor without growth hormone treatment; this phenomenon

is known as "growth without growth hormone" and is not fully understood [42,43]. A rare cause of growth hormone deficiency is an inactivating mutation of the GHRH receptor that is inherited in an autosomally recessive manner [44].

If growth hormone deficiency is congenital and complete, the diagnosis is relatively easy to confirm. Affected children present with severe postnatal growth failure, delayed bone age, and very low serum concentrations of growth hormone, IGF-I, and IGF-binding protein-3 (IGFBP-3, the major circulating binding protein for IGF-I) [35]. Additional findings are hypoglycemia, prolonged jaundice, and micropenis, especially if gonadotropins are deficient as well.

In children with less severe growth failure, whose height may still be within the normal range for age, the decision to undertake detailed testing should be based on strict auxological criteria. It is therefore mandatory to obtain accurate serial measurements of height. Any evidence of central nervous system disease or other anterior pituitary hormone deficiencies should lead to measurement of IGF-I and provocative testing of growth hormone (growth hormone stimulation tests). These provocative tests are not definitive but can be a valuable diagnostic tool when combined with auxological and bone age data and measurements of IGF-I and IGFBP-3. (See "Diagnosis of growth hormone deficiency in children".)

Congenital growth hormone insensitivity is a very rare disorder characterized by high serum growth hormone concentrations with low serum IGF-I and IGF binding-protein-3 concentrations [35]. In its complete form, this condition is called Laron-type dwarfism (complete growth hormone insensitivity) [45]. (See"Growth hormone insensitivity syndromes".)

Sexual precocity — Several conditions are associated with increased secretion of gonadal steroids (estradiol in girls and testosterone in boys), which have two consequences. One is sexual precocity. The other is accelerated epiphyseal development, which causes rapid childhood growth but more rapid advancement of bone age. As a result, height age is advanced compared with chronologic age, but it lags behind the markedly accelerated bone age. If their growth is not halted, these tall children will be short adults because early epiphyseal closure stops linear growth prematurely.

There are two types of sexual precocity:

- Gonadotropin-dependent precocious puberty (GDPP), also known as central (or true) precocious puberty, refers to the early occurrence of normal puberty. Precocious puberty historically had been defined as sexual development in girls before the age of eight years and in boys before the age of nine years; however, data for girls, particularly black girls, indicate that the age of onset of normal puberty is younger [46-48]. The hallmarks of precocious puberty are accelerated growth and advanced bone age, plus breast development in girls and penile enlargement and sexual hair growth in boys [49]. The pattern of secretion of pituitary gonadotropins and gonadal sex steroids is normal but early. (See "Definition, etiology, and evaluation of precocious puberty", section on 'Causes of central precocious puberty (CPP)'.)
- Gonadotropin-independent precocious puberty (GIPP), also known as peripheral precocious puberty, refers to sexual precocity due to adrenal or gonadal disorders (or rarely tumor production of human chorionic gonadotropin in boys). This pattern also may be seen in the setting of McCune-Albright syndrome or exposure to exogenous sex steroids. The clinical manifestations are similar to those of GDPP, except that the sexual development may be that of the opposite sex, eg, androgen effects in girls with congenital adrenal hyperplasia. (See "Definition, etiology, and evaluation of precocious puberty", section on 'Causes of peripheral precocity'.)

Children with untreated chronic hyperthyroidism may rarely have a similar pattern with rapid growth accompanied by early epiphysial maturation [50,51]. Pubertal timing is generally normal. (See "Clinical manifestations and diagnosis of hyperthyroidism in children and adolescents", section on 'Growth'.)

Genetic diseases with primary effects on growth — Several genetic disorders have prominent effects on growth. These disorders occasionally present with short stature as the initial clinical manifestation. Many other genetic disorders, such as Down syndrome, include short stature but are not listed here because stature is not a primary identifying characteristic.

Turner syndrome — Turner syndrome is an important consideration in girls with short stature and especially growth failure, because shortness may be the presenting feature of the syndrome; other physical abnormalities are variably expressed (table 3). Virtually all girls with Turner syndrome have short stature, with an average adult height about 20 cm shorter than predicted by the midparental height. In addition, affected patients usually have absent or very delayed pubertal development and may have a square "shield" chest, webbed neck, cubitus valgus (increased carrying angle of the arm), genu valgum (inward tilting knees), shortened fourth metacarpals, and Madelung deformity of the forearm (picture 1 and image 1). A Madelung deformity is a growth disturbance in the distal radial epiphysis that results in volar and ulnar tilted distal radial articular surface, volar translation of the hand and wrist, and a dorsally prominent distal ulna and wrist pain; this condition is sometimes termed "bayonet wrist". Prompt diagnosis of Turner Syndrome is important because of associated cardiovascular, renal, and endocrine abnormalities, which may require treatment, including growth hormone therapy. (See "Clinical manifestations and diagnosis of Turner syndrome".)

SHOX mutations — Mutations in the **S**hort Stature **HO**meobo**X** (SHOX)-containing gene on the X chromosome cause a syndrome in which the primary manifestation is short stature, which tends to be more severe in girls (MIM #300582). In addition to short stature, individuals with this mutation tend to have shorter forearms and lower legs (with reductions in arm span and leg length compared with trunk), Madelung deformity of the forearm (focal dysplasia of the distal radial physis) (picture 1 and image 1), cubitus valgus (increased carrying angle of the arm), high arched palate, and muscular hypertrophy (reflected as a short, stocky appearance), as compared with those with idiopathic short stature but no SHOX mutation [52]. These skeletal abnormalities are similar to those seen in many patients with Turner syndrome. (See "Sex chromosome abnormalities", section on 'Xp22 SHOX deletions'.)

SHOX mutations are present in approximately 1 to 4 percent of patients who would otherwise have been classified as having "idiopathic" short stature [52-54]. The SHOX gene is found in the pseudoautosomal region of the X and Y chromosomes and also is responsible for the short stature and skeletal deformities associated with Turner syndrome and Leri-Weill dyschondrosteosis [53,55-58]. Growth hormone treatment is effective in increasing linear growth in patients with isolated SHOX deficiency [59-61]. (See "Growth hormone treatment for idiopathic short stature".)

Prader-Willi syndrome — Prader-Willi syndrome (PWS) is the most common syndromic form of obesity. Obesity and hyperphagia typically develop during early childhood and can be severe. Other common clinical characteristics are hypotonia and feeding problems during infancy, developmental delay, and hypogonadism. Short stature is common but may not develop until late childhood when the child fails to undergo a pubertal growth spurt. Treatment with growth hormone improves linear growth and body composition. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome".)

Noonan syndrome — Noonan syndrome (MIM #163950) is a relatively common autosomal dominant disorder with an estimated incidence of one in 1000 to 2500 live births. Approximately 50 percent of children with Noonan syndrome have a mutation in the PTPN11 gene, mapped to chromosome 12q24.1, which encodes the non-receptor protein tyrosine phosphatase SHP2 [62-64]. Children with mutations in *PTPN11* have mild growth hormone resistance [65]. Less common mutations have been described in *KRAS*, *SOS1*, and *NRAS* (which, like *PTPN11* mutations, result in upregulation of the RAS-MAP kinase pathway [66-71]), as well as mutations in *RAF1* and *BRAS* [65,72]. Mutations in one these genes are found in approximately 70 percent of individuals with Noonan syndrome. Noonan syndrome and neurofibromatosis type 1 may occur together in patients with certain *NF1* mutations [73-75] (see "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis"). Some patients with *PTPN11* mutations also have a syndrome that includes giant cell lesions of bone or soft tissues. (See "Giant cell tumor of bone".)

Noonan syndrome is characterized by minor facial dysmorphism (hypertelorism, downward eye slant, and low-set ears), proportionate short stature, and heart disease, most often pulmonic stenosis and hypertrophic cardiomyopathy [62,76,77]. Other common findings include a short webbed neck, chest deformity (pectus excavatum), cryptorchidism, intellectual disability (mental retardation), bleeding diathesis, and lymphedema [62,77,78]. There appears to be a modest association between Noonan syndrome and several types of cancer, including neuroblastoma, acute leukemia, low grade glioma, and embryonic rhabdomyosarcoma [79,80].

The cardiac manifestations were assessed in an echocardiographic study of 118 patients with Noonan syndrome [76]. A dysplastic pulmonary valve was present in eight patients (7 percent), six of whom had significant stenosis. Among the 110 patients without valve dysplasia, significant pulmonic stenosis was present in 22 (20 percent). Other abnormalities included secundum atrial septal defects, localized anterior septal hypertrophy, and diffuse hypertrophy.

Short stature associated with Noonan syndrome can be treated effectively with growth hormone and is an approved indication by the US Food and Drug Administration (FDA). (See "Treatment of growth hormone deficiency in children".)

Russell-Silver syndrome — Russell-Silver syndrome (MIM #180860, also known as Silver-Russell syndrome and Russell-Silver dwarfism) is characterized by severe intrauterine growth restriction and postnatal growth retardation with a prominent forehead, triangular face, downturned corners of the mouth, and body asymmetry (hemihypertrophy) [81,82]. The facial features tend to become less obvious with age. The majority of infants have feeding difficulties, and mild developmental delay is seen in about one-third of subjects [83]. In about 60 percent of subjects, the syndrome is associated with epigenetic alterations involving either hypomethylation of an imprinting control region that regulates expression of the insulin-like growth factor-2 (IGF-2) gene and others on chromosome 11p15.5. IGF-2 is known to have important effects on growth, especially during fetal development. About 10 percent of cases are caused by maternal uniparental disomy of chromosome 7 [84]. Accordingly, one study describes severe pre- and post-natal growth restriction in four members of the same family with clinical features of Russell-Silver syndrome, due to a paternally-inherited mutation in the IGF-2 gene [85].

A few reports describe growth hormone treatment of individuals with Russell-Silver syndrome (which was given based on the indication of growth hormone therapy for individuals born small for gestational age) [85-87]. These individuals had a modest growth response to growth hormone. When growth hormone was started at a young age, the mean adult height in treated subjects was -1.3 SD, compared with an adult height of -3.6 to -2.9 SD in untreated subjects with this disorder

[86]. Of note, individuals with the hypomethylation defect tend to have inappropriately high levels of IGF-1 and IGFBP-3, suggesting a reduced sensitivity to IGF-1 [83,88].

Skeletal dysplasias — Skeletal dysplasias associated with short stature are caused by inherited defects in bone development and are often associated with disproportionate short stature (with limbs disproportionately short for the trunk, or vice versa). These include:

- Achondroplasia – Achondroplasia (MIM #100800) is the most common form of short-limbed dwarfism. It is characterized by short arms and legs (rhizomelia, preferentially involving the proximal limb segments), and midface hypoplasia, with macrocephaly [89]. It is caused by a heterozygous mutation in fibroblast growth factor receptor-3 (FGFR3; usually c.1138G>A or G>C) [90]. In its full form, achondroplasia is usually identified in infancy or early childhood. Complications include craniocervical junction compression, sleep apnea, and spinal stenosis. (See "Macrocephaly in infants and children: Etiology and evaluation", section on 'Anatomic megalencephaly'.)
- Hypochondroplasia – Hypochondroplasia (MIM #146000) is similar to achondroplasia in that it is characterized by disproportionately short limbs, lumbar lordosis, short and broad bones, and narrowing of the interpediculate distance of the lumbar spine, sometimes associated with macrocephaly, intellectual disability, and/or epilepsy. There is a wide range of clinical severity ranging from a phenotype similar to achondroplasia with severe short stature, to mild skeletal abnormalities [91]. The majority of cases are associated with mutations in FGFR3 (usually c.1620C>A or C>G), transmitted in an autosomal dominant fashion [92,93].
- Spondyloepiphysial dysplasia – This is a heterogenous group of dysplasias that primarily affect the epiphyses and vertebral bodies. Most forms are characterized by preferential shortening of the trunk as compared with the limbs (short-trunk dwarfism), complicated by spinal deformities, osteoarthritis, and sometimes by spinal cord compression due to subluxation of the cervical spine [94,95]. An x-linked form, usually associated with mutations of *TRAPPC2*, presents in boys in late childhood [96]. A congenital form is caused by mutations of *COL2A1*, the gene encoding type II collagen. This form usually is evident at birth and associated with midline cleft palate, with or without hearing loss, myopia, and retinal detachment [97,98].
- Osteogenesis imperfecta – Osteogenesis imperfecta encompasses a series of inherited connective tissue disorder characterized by bone fragility. There is a wide range of phenotypes ranging from severe disease and death in the neonatal period to premature osteoporosis. Children with moderate to severe disease are usually recognized by recurrent fractures but also develop short stature. Because bones are equally affected, the short stature tends to be proportionate (generalized). (See "Osteogenesis imperfecta: Clinical features and diagnosis".)
- More subtle skeletal dysplasias, categorized as dyschondrosteosis and hypochondroplasia, are common among children with apparent idiopathic short stature (ISS) or those born small for gestational age (SGA), and especially among those with parents who are very short [99].

Other causes of short stature that may be pathologic — Some individuals with apparent ISS may have underlying disorders that are pathologic but not diagnosed during a standard evaluation. If the short stature is severe, these patients warrant a detailed evaluation and ongoing monitoring for the possibility of subclinical underlying systemic disease. These patients also are candidates for growth hormone therapy. (See 'Idiopathic short stature' above and "Diagnostic

approach to children and adolescents with short stature" and "Growth hormone treatment for idiopathic short stature".)

About 10 percent of infants born SGA fail to experience catch-up growth sufficient to be within the normal range by two years of age. This growth pattern is more likely in those with severe SGA and can be considered pathologic, although the underlying mechanisms are unclear and likely vary. Depending on the extent of their catch-up growth during childhood and adolescence, these children may also benefit from growth hormone therapy. (See "Growth hormone treatment for children born small for gestational age".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: My child is short (The Basics)")

SUMMARY

- Short stature is defined as height that is 2 standard deviations (SD) or more below the mean height for children of that sex and chronological age in a given population. This translates to a height that is below the 2.3rd percentile. (See 'Introduction' above.)
- The two most common causes of short stature are familial (genetic) short stature and constitutional delay of growth and puberty (CDGP), which are normal variants of growth. These growth patterns often can be distinguished from one another, but some children have features of both (table 1). (See'Normal variants of growth' above.)
- Almost any serious systemic disease can cause growth failure (table 2). Systemic disorders or processes that may present with growth failure and/ordelayed puberty include undernutrition, glucocorticoid therapy, gastrointestinal disease (especially Crohn disease and celiac disease), and renal disease. (See 'Systemic disorders with secondary effects on growth' above.)
- A variety of genetic syndromes and congenital malformations are associated with short stature. Turner syndrome is particularly important because shortness and/or absent pubertal development may be the presenting feature, with or without other characteristic clinical features (see 'Turner syndrome' above). Most of these syndromes can be recognized by characteristic clinical features. These include Noonan, Russell-Silver, and Down syndromes. (See 'Genetic diseases with primary effects on growth' above.)

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