

## Turner Syndrome: Toward Early Recognition and Improved Outcomes

Faculty and Disclosures

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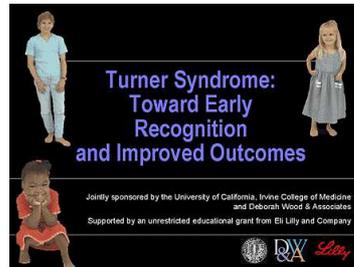
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### TURNER SYNDROME: TOWARD EARLY RECOGNITION AND IMPROVED OUTCOMES

#### Turner Syndrome: Definition, Epidemiology, and Clinical Features

This educational activity will discuss the genetic characteristics of Turner syndrome, and how particular genetic deficiencies may be responsible for some of the physical characteristics; explain how to recognize the physical features of Turner syndrome to enhance early identification and patient outcomes; describe treatment strategies; and provide some resources for information and support that you may wish to share with your colleagues or patients.



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The history of Turner syndrome began in 1938, when Henry Turner described 7 patients between the ages of 15 and 23, who were referred to him for dwarfism and lack of sexual development. He treated them with pituitary extracts, but they were ineffective. <sup>[1]</sup>

Since then, many studies have evaluated Turner syndrome in greater detail and added to our knowledge base. An international multidisciplinary workshop was convened in March 2000, in Naples, Italy, in conjunction with the Fifth International Symposium on Turner Syndrome, to update the comprehensive recommendations on the diagnosis of Turner syndrome that were originally published in 1994.

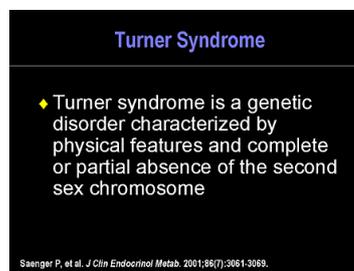
Turner syndrome, also referred to as Ullrich-Turner syndrome, is a genetic disorder in which an X chromosome is missing or structurally abnormal and is not caused by a growth hormone deficiency.

Most reports of Turner syndrome cite its incidence as 1 in 2000- to 2500 live female births. <sup>[2-4]</sup> Although short stature is the most common feature of Turner syndrome, many other recognizable characteristics may also exist. Girls with Turner syndrome are at increased risk for several disorders that do not manifest as obvious physical features during childhood. An example of 1 characteristic that commonly occurs in these patients is ovarian failure.

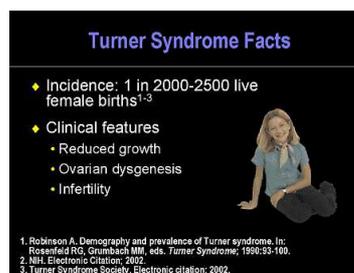
#### Diagnosis and Genetics

Because Turner syndrome is a genetic disorder, its diagnosis is made by testing an individual's genetic makeup. Human chromosomes contain all of an individual's genetic material. The process of determining an individual's chromosomal pattern is called karyotyping, and this is achieved through a blood test. Diagnosis can also be established prenatally by amniocentesis.

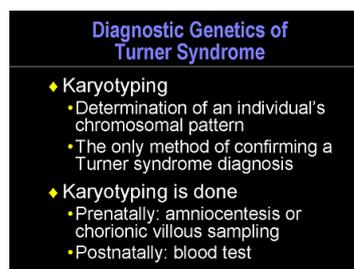
The following is a quick review of the distinction between karyotype, genotype, and phenotype. Karyotype refers to an individual's chromosomal pattern. It is a photographic enlargement of the chromosomes after they have been arranged according to size and



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numbered. Shown here is the Turner syndrome karyotype 45, X. Genotype refers to an individual's entire genetic constitution, including the specific genes an individual has for certain traits. For example, an individual might have the genes for blood types A and O or the gene for tongue-rolling. Phenotype (from the Greek *phainein*, "to show") refers to the observable physical, biochemical, and physiological expression of an individual's genotype or one's manifestation of various environmental influences. For example, a person's natural hair color and blood type are phenotypic expressions of genetically determined traits. (An individual's altered hair color is a phenotypic expression of an environmental influence).

In summary, "normal" individuals have 23 pairs of chromosomes, or 46 total (this includes a pair of sex chromosomes). A normal female karyotype is designated as 46, XX. The XX indicates the normal composition of sex chromosomes for a female. This is represented in the picture. A normal male karyotype would be indicated as 46, XY.

Turner syndrome, like many other human disorders and malformations, is a direct result of missing, broken, or extra chromosomes.

Three separate chromosomal patterns or karyotypes are recognized as representing Turner syndrome (see slide):

1. Absence of X chromosome: The individual missing an entire X chromosome. This accounts for about 60% of all diagnosed Turner syndrome cases and is referred to as 45, X. These girls are the most seriously affected.
2. Chromosome structural abnormalities: These patterns are also called partial X deletions. For example, one arm of the X chromosome may be missing or malformed.
3. Chromosomal mosaicism: This pattern occurs when different cells within an individual, who has developed from a single fertilized egg, have a different chromosomal makeup. Most commonly, there will be some cells with the typical ("normal") number of chromosomes (46 chromosomes) and other cells with an altered number (45 chromosomes).

Recently, the first gene for Turner syndrome was identified. It is the gene that is responsible for at least part of the short stature in patients with Turner syndrome and is known as the SHOX = Short Stature HomeobOX (SHOX)-Containing gene.

The SHOX gene is contained on the distal ends of the short arms of the X and Y chromosomes (pseudoautosomal part of the gene). The SHOX gene encodes a protein, which is a transcription factor. A transcription factor is a type of protein that enhances the expression of other genes involved in various developmental processes. This transcription factor contains a homeo domain, a special protein sequence that is able to bind to DNA and is involved in the regulation of multiple genes. Two active copies of the SHOX gene are needed for full expression of the protein. Deficiency of one copy of SHOX is associated with short stature in some patients.

Growth occurs through the extension of the ends of the long bones at the growth plates — the epiphyses — which are comprised of cartilage. When the cartilage cells in this area increase and subsequently become ossified, growth occurs.

### Karyotype vs Genotype vs Phenotype

- ♦ **Karyotype**
  - Chromosomal pattern
- ♦ **Genotype**
  - Entire genetic constitution
- ♦ **Phenotype**
  - Physical and physiological makeup
  - e.g., short stature, infertility, osteoporosis

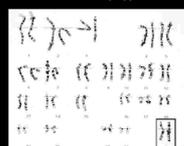


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### Normal Chromosomal Patterns

- ♦ "Normal" individual has 22 pairs of autosomal chromosomes and a pair of sex chromosomes
- Female karyotype: 46, XX
- Male karyotype: 46, XY

**Female Karyotype<sup>1</sup>**



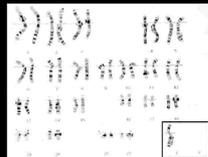
1. NH, Electronic Citation; 2002.

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### Turner Syndrome Sex Chromosomal Patterns

- ♦ Complete absence of X (45, X)
- ♦ Structural abnormalities
  - Partial X deletion
- ♦ Mosaicism (mixture of 2 cell lines)

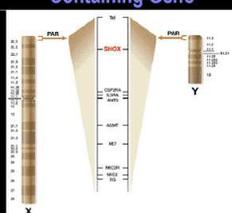
**Turner Syndrome Karyotype (45, X)<sup>1</sup>**



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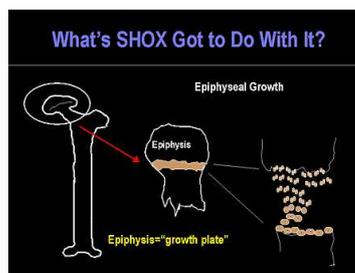
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### Short Stature HomeobOX (SHOX)-Containing Gene



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The current hypothesis is that the SHOX protein, which is expressed by these cells, may be playing a role in chondrogenesis, the formation of cartilage. If SHOX is playing a significant role in how cartilage is formed, then it is likely that it also plays an important role in long-bone growth. One reason for short stature in Turner syndrome is that when an entire X chromosome or a large portion of an X chromosome is missing, the required 2 active SHOX genes are not present.



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### Turner Syndrome: Affect on Body Systems

Turner syndrome may affect many body systems. Therefore, girls should be observed for any of the possible characteristics suggestive of Turner syndrome so that it is both recognized and managed in an integrated, multidisciplinary fashion.



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This is a quick overview of the incidence rates for some of the more common phenotypes associated with Turner syndrome. Despite these statistics, many girls with Turner syndrome do not display the classic visual signs of the syndrome.

Phenotype	Incidence
♦ Short stature	100%
♦ Infertility	98%
♦ Primary gonadal failure	95%
♦ Osteoporosis	50%
♦ Cubitus valgus	45%
♦ Low posterior hairline	40%
♦ Carbohydrate intolerance	30-40%
♦ High blood pressure	25-40%
♦ Short metacarpals	35%
♦ High arched palate	35%
♦ Structural abnormalities in kidney	35%
♦ Hypothyroidism (Hashimoto thyroiditis)	35%

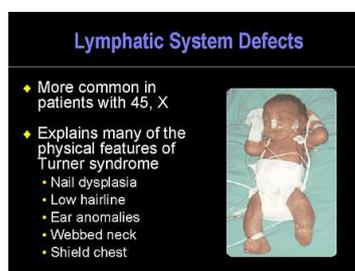
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### Lymphatic System Defects

There is growing evidence that abnormal lymphatic development, including lymphedema and consequent cell-migration abnormalities, is important in the pathogenesis of a number of the physical stigmata and other clinical manifestations of Turner syndrome.

This is a photograph of an infant with 45, X Turner syndrome diagnosed in utero, with a cystic hygroma discovered during a routine prenatal ultrasound. Labor was induced at 36 weeks' gestation because of evidence of fetal distress, and the infant was born prematurely.



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Peripheral lymphedema, present dorsally on the hands and feet; it may be the initial presenting sign of Turner syndrome and is found in approximately one-third of affected infants. For example, there is usually a crease across the ankle joint. Although lymphedema in girls with Turner syndrome is occasionally severe or permanent, it tends to improve with age.



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Nail dysplasia is found in approximately 70% of patients with Turner syndrome.<sup>[5]</sup> Peripheral lymphedema is most likely responsible for developmental abnormalities of the nails, which may be small, narrow, hyperconvex, and deeply inserted at an acute angle. Nail dysplasia may be particularly marked in the feet, with some patients having a complete absence of toenails.

Note the comparison between normal and index fingernails of individuals with and without Turner syndrome. A normal finger is on the left, and the finger of a girl with Turner syndrome is on the right.



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A webbed neck occurs in 25% of girls with Turner syndrome.<sup>[3]</sup> This condition is secondary to lymphatic problems. It develops prenatally when the jugular lymph sacs accumulate lymph and enlarge, forming a distended sac known as a cystic hygroma, in the posterior and lateral neck regions. During late gestation, the lymph collection resolves, leaving loose, redundant skin that forms the webbed neck. The photo on the far right shows an extreme case of webbed neck. Plastic surgery may be able to improve the situation.



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Shortness of the neck is also common, occurring in about 40% of patients.

<sup>[6]</sup> It may be due to a skeletal abnormality such as hypoplasia of the cervical vertebrae.

A low posterior hairline occurs in 40% of girls with Turner syndrome,<sup>[3]</sup> whereby hair extends onto the back of the neck. In this girl, her posterior hairline reaches lower than normal. This develops secondarily to lymphedema and cell migration abnormalities. It is thought to be affected by stretching of the skin by the underlying cystic hygroma (a distended sac of accumulated lymph) at around 10 to 12 weeks' gestation. At this time the hair follicles grow downward into the underlying mesenchyme.

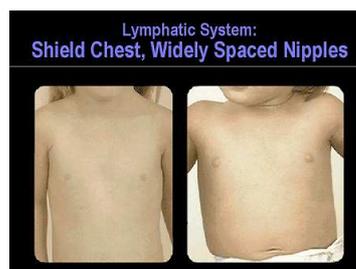


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The frequent occurrence of bushy eyebrows in girls with Turner syndrome also could relate to altered tension on the skin during this period of development.

Low-set ears may be present and are also a result of lymphedema and cell-migration abnormalities.

Stretching of the thoracic cage as a result of fetal edema may contribute to the "shield chest" and widely spaced nipples sometimes seen in girls with Turner syndrome.



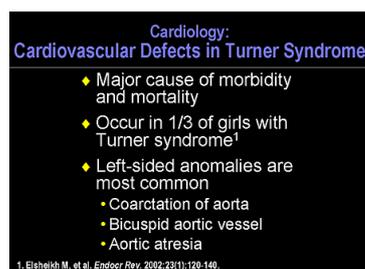
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### Other Anomalies Associated With Turner Syndrome

Cardiovascular defects also may be the result of a defective lymphatic system and are a major cause of morbidity in Turner syndrome. In fact, cardiovascular abnormalities represent the single highest cause of death in these patients. Management of these problems is therefore a vital aspect of comprehensive patient care.

Cardiovascular anomalies are a common feature of Turner syndrome at all ages and are present in more than one-third of patients.<sup>[6]</sup> The most frequent defects are left-sided anomalies, including coarctation of the aorta, bicuspid aortic valve, and aortic atresia.

It is important, therefore, for cardiac specialists to be on the alert for girls with these cardiac defects and to consider referral for evaluation of possible Turner syndrome.



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At least one-third of girls with Turner syndrome have some type of renal anomaly.<sup>[3]</sup> The basis for the high frequency of renal anomalies in Turner syndrome is not known. While most of these defects are of limited clinical importance and generally do not affect renal function, a number of them may predispose individuals to urinary tract infections.

The most common defects are of 3 primary types and are related to the stage of development at which the defect occurs:

1. Defects of the collecting system occur earliest in gestation - within the first 5 weeks - and include partial or complete duplications. Renal duplications are generally not of clinical importance.
2. Defects related to the position of the kidneys occur during the period from 5 to 9 weeks' gestation. Such defects include "horseshoe kidney" and ectopic or malrotated kidneys. Horseshoe kidney is one of the hallmark renal anomalies of Turner syndrome, occurring in about 10% of these patients. Renal function is generally normal; however, because the ureters run anterior to the fused portion of the kidney, urine flow may be impeded and ureteric obstruction and/or secondary urinary tract infection may develop.
3. Defects involved with variations in the number and position of the renal arteries develop late in the first trimester. While accessory arteries are usually clinically insignificant, obstruction of the ureters may occur, causing secondary hydronephrosis and/or urinary tract infection.

A variety of ocular findings have been reported in patients with Turner syndrome, including strabismus and ptosis (drooping of the eyelid). The most common form of strabismus is esotropia, or inward turning of one eye, while the less common form is exotropia, or outward turning of the eye. Strabismus usually occurs between the ages of 6 months and 7 years but is most often first noted around two-and-a-half years of age.

Strabismus can be detected by shining a light into the eyes to assess the position of the corneal light reflex. Asymmetry of the position of this reflex suggests the presence of strabismus, as shown in the child in the lower left photo who has marked esotropia of the right eye.

Patients with Turner syndrome have a very high incidence of ear and hearing disorders. These problems may have a major impact on quality of life for both girls and women. At least three-quarters of patients with Turner syndrome have a history of recurrent, acute otitis media starting in infancy or early childhood. This finding may be crucial to the diagnosis of Turner syndrome in a short girl without other obvious physical stigmata.

The very high incidence of severe, recurrent, or chronic otitis media in girls with Turner syndrome seems to result from a disturbed relationship between the middle ear and the eustachian tube and is compounded by anatomical abnormalities of the pharynx and palate.

When considering the characteristic of multiple nevi in girls with Turner syndrome, we need to remember that nevi are not the same as freckles. Nevi, also commonly called moles, are often raised and palpable. These nevi have generally been reported as benign-appearing melanocytic nevi, such as the one shown here at the top right.

As with the general population, nevi increase in size and number throughout childhood and particularly during adolescence. Several recent studies have shown that increased numbers of melanocytic nevi are a risk factor for melanoma. Although girls with Turner syndrome can develop melanoma, it is generally felt that the rate of malignant transformation in nevi is not increased in these patients. Any dysplastic nevi, such as the

**Nephrology:  
Renal Anomalies**

- ◆ Occur in 1/3 of girls with Turner syndrome<sup>1</sup>
- ◆ Most abnormalities are benign
- ◆ Risk of urinary tract infections
- ◆ Most common
  - Defect in collection system
    - Partial or complete duplication
  - Position of kidney
    - Horseshoe
    - Ectopic or malrotated
  - Renal vascular abnormalities

1. NH. Electronic Citation; 2002.

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**Ophthalmology:  
Eye Findings**

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**Otolaryngology:  
Ear Findings**

- ◆ Recurrent otitis media
- ◆ Structural defects

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**Dermatology**

**Multiple Nevi**

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one shown at the bottom right, should be followed closely by a dermatologist.

### Orthopedic Abnormalities

In parallel with the slow, delayed growth pattern, skeletal maturation is significantly delayed in most girls with Turner syndrome. The degree of delay is not uniform among the bones.

A number of the most readily recognizable features of Turner syndrome are detectable on examination of the arms and hands. These are worth looking for, as they may serve as helpful clues for diagnosing Turner syndrome in patients with otherwise less obvious clinical features.

A standard radiograph of the left hand and wrist for bone age is a helpful tool in the diagnosis of Turner syndrome. Apart from the assessment of skeletal maturation, the bone age film provides valuable clues, such as metacarpal shortening. In this radiograph of a 9-year-old girl with Turner syndrome, small bone size is apparent.

Rarely, a wrist deformity called Madelung deformity is detected. This skeletal abnormality is associated with wedging of the carpal bones and bowing of the radius and ulna.

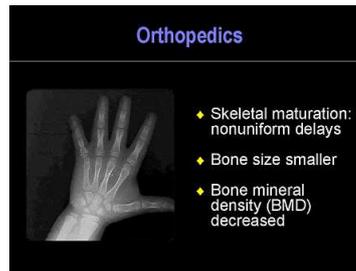
Shortening of the fourth and sometimes the fifth metacarpal, which is present in 35% of patients,<sup>[3]</sup> is the most notable anomaly of the hands in Turner syndrome. When the fourth metacarpal is abnormally small, a depression instead of the normal protrusion of the fourth knuckle is present when the patient makes a fist, as shown here. This shortening can be easily detected by using a flat edge, such as a ruler, and placing it across the third and fifth knuckles. If the abnormality is present, the flat edge will not touch the fourth metacarpal head.

Knee abnormalities have been reported in up to 60% of patients with Turner syndrome.<sup>[5]</sup> An example of this orthopedic abnormality is knock-knees and is shown in the photo on the left.

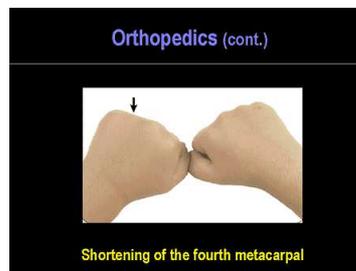
Scoliosis is reported in only 12% of girls with Turner syndrome, but this is substantially greater than the 2% to 3% incidence observed in the general population.<sup>[7]</sup> In addition, when compared with girls in the general population, girls with Turner syndrome may develop scoliosis much earlier, with its initial occurrence in early childhood and subsequent progression with any growth spurts, including those induced by therapies. Scoliosis in patients with Turner syndrome, therefore, must be carefully evaluated and treated.

Micrognathia refers to the relative smallness of the chin. This abnormality occurs in 60% of girls with Turner syndrome.<sup>[6]</sup> As shown in the picture, the chin sits farther back than its normal position.

Cubitus valgus occurs in about 45% of girls with Turner syndrome.<sup>[3]</sup> It refers to the deviation of the extended forearms to bend away from the body when the arms are at rest and is also described as an increased carrying angle. The carrying angle refers to the angle between the long axis of the upper arm and the axis of the supinated forearm. In the general female population, this angle averages about 12 degrees.



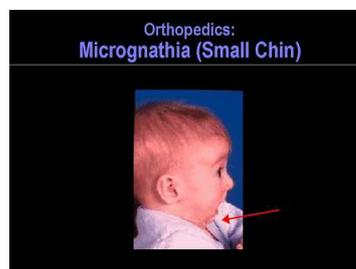
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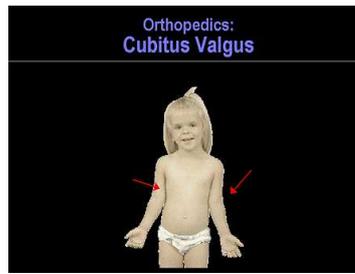
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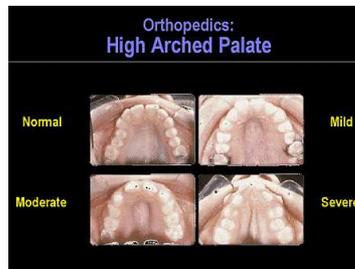
Although the carrying angle may change with age, when cubitus valgus is present, it is usually readily detectable in early childhood, as seen in this 3-year-old girl, whose carrying angle is about 25 to 30 degrees.

Cubitus valgus is caused by developmental abnormalities in the trochlea of the humerus. Alteration in the shape of the trochlea changes the angle of articulation with the ulna, resulting in increased elbow angulation.



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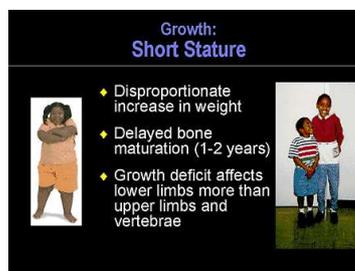
Another skeletal abnormality is high-arched palate, which occurs in 35% of girls with Turner syndrome.<sup>[3]</sup> These pictures represent the various severities of a high-arched palate. Rather than a gentle curve, the high-arched palate is V- or U-shaped. The 10-year-old patient shown in the last photograph has a severely narrow and high palate, with marked dental crowding. This type of palate is sometimes referred to as a "cathedral" palate.



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### Growth Deficits

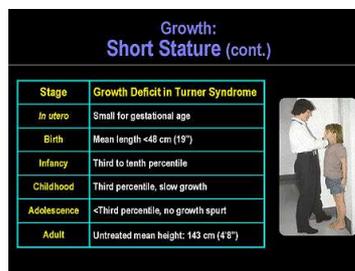
Short stature is a hallmark of Turner syndrome and occurs in almost 100% of cases.<sup>[3]</sup> Short stature often includes a disproportionate increase in weight, thereby placing these girls at increased risk for health issues associated with being overweight. In Turner syndrome, the growth deficit typically affects the lower limbs more than the upper limbs resulting in legs that are disproportionately shorter than the trunk. These 9-year-old twin sisters clearly demonstrate the growth deficit in a girl with Turner syndrome.



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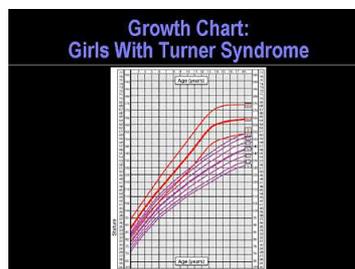
Growth retardation in Turner syndrome can be detected based on the deficits listed in this table. Since short stature may be the only obvious feature of Turner syndrome, tracking growth on a standard growth chart will identify the lack of progress and always warrants further evaluation.

Although the timing of growth failure is more variable with certain karyotypes, early growth failure occurs with all karyotypes of Turner syndrome. Fifty percent of girls with Turner syndrome fall below the fifth percentile by 1.5-years-old and 75% are below the fifth percentile before age 4. On average, height is below the fifth percentile for 5 years before the diagnosis of Turner syndrome is made.<sup>[8]</sup>



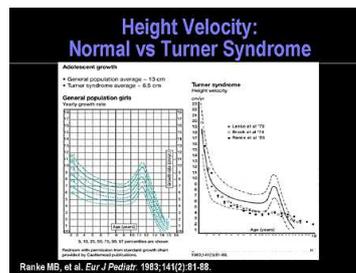
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It is important, therefore, to look at a number of different values of height and weight plotted on a standard growth chart over time to determine a child's rate of growth. The red lines in this chart represent percentile norms for stature (height) in the general population of girls from ages 3 to 18. The purple lines represent the height of girls with Turner syndrome.



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How quickly or slowly the child has been growing can be more important than her percentile. Children at or below the fifth percentile for height may be normal if their height velocity, or the rate at which they are growing, is normal. Normally, the height-velocity curve is somewhat L-shaped due to the decrease in growth velocity after age 2 and the subsequent growth spurt during puberty. In contrast, girls with Turner syndrome exhibit a different growth-velocity curve with values below normal and no growth spurt during puberty.



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### Other Physiological and Psychosocial Issues

Growth hormone (GH) secretion in girls with Turner syndrome by stage of maturity (age) is as follows:

- Childhood: spontaneous growth hormone (GH) secretion is normal in girls with Turner syndrome (see dots in left section).
- Puberty: GH secretion in girls with Turner syndrome is below that of age-matched controls (see dots below right gray section).

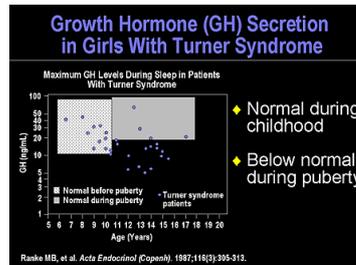
However, GH secretion in these girls is normal when accounting for variables such as pubertal status, bone age, fat-free mass, and physical fitness. Similar findings are reported for GH responses to provocative stimuli. Given the usual finding of normal GH secretion and the relatively large doses of GH required to stimulate growth in these patients, the concept of reduced sensitivity to GH in Turner syndrome has arisen. If present, this is probably localized to specific tissues - presumably the cartilage and bone matrix, and perhaps other components of the linear growth response.

Since girls with Turner syndrome are not GH-deficient and may be somewhat GH-resistant, therapy for Turner syndrome uses greater doses (up to 0.375 mg/kg/week) of GH than those used for children with GH deficiency that is not associated with Turner syndrome.

Ovarian dysgenesis refers to abnormal development of the ovary and affects about 95% of girls with Turner syndrome.<sup>[3]</sup> This results in delayed or absent sexual development at the time when other girls are going through puberty. The overall incidence of spontaneous puberty in girls with Turner syndrome is 12%.<sup>[6]</sup> Primary amenorrhea (no menstrual periods ever) is common. Some girls will enter and go partly through puberty with some breast development but not begin to menstruate (achieve menarche). Others may achieve menarche and then have gonadal failure in which the ovaries stop working. Estrogen production ceases and the result is infertility. Girls with spontaneous pubertal development also are at risk for premature menopause.

It is important that any psychosocial deficits be detected early, to allow for timely intervention and to minimize the potentially negative impact on learning and socialization. Psychosocial issues associated with Turner syndrome include:

- Slightly lower than average IQ scores that, in part, reflect lower scores on performance than on verbal tasks, suggesting a non-verbal type of learning disability.
- Deficits in memory, attention, and visual processing. Several tests can be used to demonstrate psychosocial deficits, including the Block Design subtest of the Wechsler Intelligence Scale for Children (WISC), and the Judgement of Line Orientation task.
- Difficulties in school with mathematics and geometry that can lead to trouble reading maps and following directions, which may pose a significant challenge for daily life.



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### Ovarian Dysgenesis

- ◆ 95% incidence<sup>1</sup>
- ◆ Abnormal development of the ovary
- ◆ Delayed or absent pubertal development
- ◆ Infertility
- ◆ Premature menopause

1. NIH. Electronic Citation; 2002.

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### Psychosocial Issues

- ◆ Performance IQ mildly reduced (verbal IQ normal)
- ◆ Deficits and adaptation problems
  - Memory, attention, visual processing
  - Mathematics and geometry
  - Young girls: increased activity, concentration difficulties
  - Older girls: anxiety, depression, social isolation, less likely to marry
- ◆ Evaluation and management
  - Ask parents if child is having trouble in school
  - For girls with Turner syndrome, specialists conduct baseline evaluation of development/behavior with regular reviews
  - Coping strategies

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- Predisposition to age-specific problems with psychosocial adaptation.

All newly-diagnosed children with Turner syndrome should undergo a baseline evaluation of developmental and behavioral status by a specialist, as well as a regular review of progress. Any child who is not achieving adequate developmental or educational milestones deserves regular follow-up and perhaps appropriate intervention. Academic tutoring, occupational therapy, and training in problem-solving strategies can help girls and women with Turner syndrome cope with their visual-spatial and cognitive challenges. Individual psychotherapy can address the social and emotional difficulties. Although the cause of the psychosocial problems associated with Turner syndrome remains unknown, it seems likely that genes in the pseudoautosomal regions of the sex chromosomes play important roles in this area. With respect to coping strategies, many patients and their families have benefited significantly from support group programs.

### Referral, Testing, and Treatment

Not all girls with Turner syndrome present with obvious signs of the condition. If a girl or woman presents with short stature or any of the features or abnormalities described, the need for a karyotype and referral to a specialist should be considered.

The physical stigmata of Turner syndrome may be subtle and left unrecognized unless specifically sought. It is essential to recognize such features, since early diagnosis is necessary to prevent associated morbidities and to maximize the growth and development of girls with Turner syndrome.<sup>[5]</sup>

For those girls who are not diagnosed in prenatal life or infancy, one study found that they were not diagnosed until a mean age of 9 years, despite growth failure and the presence of other features of Turner syndrome.<sup>[9]</sup> This results in delaying initiating treatment until the age of 12, on average.<sup>[10]</sup>

Upon referral to a specialist, the following steps will be performed:

- Assessing growth, physical features, and abnormalities.
- Performing a karyotype to confirm a diagnosis of Turner syndrome.
- Conducting additional tests to identify other organ abnormalities (ie, thyroid levels, renal ultrasound, and echocardiogram) that may need monitoring or treatment.

Once diagnosed, most girls with Turner syndrome will regularly see a pediatric endocrinologist who will monitor the appropriate organ systems and provide timely treatment and other management. Treatment for Turner syndrome consists of GH therapy, followed by estrogen replacement therapy. The timing of estrogen therapy relative to GH therapy is important. Initiation of GH therapy should take place as soon as possible since once the epiphyses are closed, linear growth is completed and GH therapy is no longer effective. Referral for GH therapy at an early age could increase the chances of maximizing its benefits on linear growth while allowing more age-appropriate timing of estrogen

#### Indications for Referral and Testing

- ◆ Short stature
- ◆ Renal anomaly
- ◆ Heart defect
- ◆ Hearing loss
- ◆ Physical features
- ◆ Delayed puberty or menstruation

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#### Referral: Necessary for Diagnosis and Treatment

- ◆ Girls with Turner syndrome are not receiving the care they need
  - Average age at diagnosis (for those who present after infancy): 9 years<sup>1</sup>
  - Average age at start of treatment: 12 years<sup>2</sup>
- ◆ Referral to a pediatric endocrinologist is essential for the girl with growth delay or other characteristics of Turner syndrome

1. Sivendahl L, Dunneport ML. J Pediatr. 2000;137(4):455-459.  
2. Data on file, Eli Lilly and Company.

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#### Evaluation by a Specialist

- ◆ Assessment
  - Growth
  - Physical features
  - Abnormalities
- ◆ Karyotype leads to diagnosis
- ◆ Test for other organ abnormalities
  - Thyroid levels
  - Renal ultrasound
  - Echocardiogram

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#### Management and Treatment for Girls With Turner Syndrome

- ◆ Specialty follow-up
- ◆ Growth hormone therapy should be initiated early
  - Maximize benefits on linear growth
- ◆ Estrogen replacement therapy needs to be initiated
  - Feminization
  - Prevention of bone degeneration

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replacement. Generally, adult height gain is greater in the studies in which GH was started earlier and estrogen started later.

The timing of estrogen therapy initiation is considered on an individual basis and takes into account age-appropriate pubertal development and further growth potential. Although estrogen therapy is often delayed until age 14 or 15 — since it contributes to the closure of the epiphyses — using very low doses of estrogen may permit replacement at an earlier age. If GH therapy has been initiated early and sufficient exposure has occurred, it is possible to initiate estrogen replacement therapy to start the feminization process at an earlier age (an age during which the child's peers are undergoing feminization). In addition to estrogen's role in the feminization process, it is also needed for prevention of osteoporosis.

Results of GH clinical trials vary depending upon a number of factors, including age at the start of therapy, GH dose, duration of therapy, use of concomitant anabolic steroids, timing of estrogen replacement, and probably, undefined intrinsic or extrinsic factors.

Pretreatment height velocities average around 4 centimeters per year. The reported height velocities in the first year of GH treatment range from about 5 to 8 centimeters per year. After the first year of treatment, height velocities generally decline, as seen in this graph, but they remain greater than pretreatment velocities in most patients.

The average untreated adult height of patients with Turner syndrome in the United States is 143 centimeters (4 feet, 8 inches). Growth hormone therapy increases average adult height by up to 10 centimeters (4 inches), depending on study conditions. Consequently, even with treatment, adult height remains at least 10 centimeters below the average height of healthy females. This means that GH treatment, according to current regimens, corrects only about 50% of the adult height deficit. A number of large-scale studies evaluating the final height effect of GH remain ongoing around the world.

### Patient Management

Turner syndrome is not only a growth problem, but also involves all body systems and should be treated in a multidisciplinary fashion.

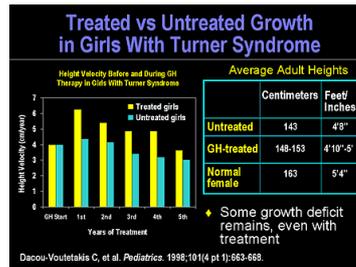
Many chronic or long-term problems can be associated with Turner syndrome, thus re-emphasizing the importance of early recognition, referral, diagnosis, therapy, and continued monitoring/management.

Health professionals caring for women with Turner syndrome must be up-to-date on appropriate monitoring strategies to identify potential long-term problems in these women.

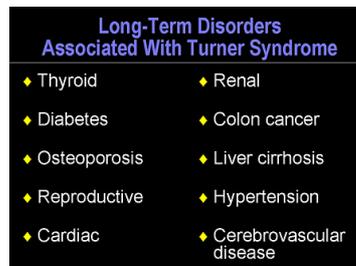
Patients with Turner syndrome have a variety of potential endocrine and metabolic problems in addition to their growth disorder and ovarian failure that require monitoring and sometimes therapy. These include thyroid dysfunction and diabetes.

Autoimmune hypothyroidism (Hashimoto thyroiditis) may develop insidiously, with or without goiter. It occurs in up to 35% of patients<sup>[11]</sup> and increases in frequency with age. When present, it may impair further growth. There may be a modest increase in the incidence of Graves' disease (hyperthyroidism). Care should be taken to monitor thyroid size and function and to avoid over-replacement with thyroxine.

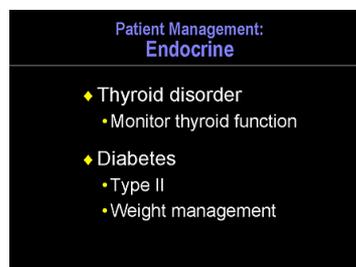
Diabetes is an important cause of potential morbidity in girls and women with Turner syndrome. These individuals have twice the risk of the general population for developing type II diabetes.<sup>[11]</sup> (Studies have provided conflicting results regarding the risk of type I diabetes in these patients). Since obesity increases the risk for insulin resistance, patients should be



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encouraged to maintain their weight within an appropriate range for their height. This is especially important for girls with Turner syndrome who are predisposed to a disproportionate increase in weight.

The risk of developing osteoporosis in women with Turner syndrome is 10-fold greater than that of the general population.<sup>[12]</sup> Two studies have reported higher rates of fracture in adults with Turner syndrome at typical osteoporotic sites.<sup>[13, 14]</sup> In addition, Ross and colleagues<sup>[15]</sup> found an almost 3-fold higher rate of wrist fracture in girls with Turner syndrome between ages 9 and 13, despite normal bone density at that site. This finding raises the question of factors, other than hormonal status, that may underlie increased fractures in girls with Turner syndrome.

Hormonal status contributes substantially to bone mineral status. After linear growth is completed (ages 14 to 15), estrogen is needed for maintenance of bone, since without it, bone will degenerate. In girls with Turner syndrome, an underlying developmental defect of bone might also be important as may problems with spatial orientation that might lead to increased falls.

Since hormone replacement therapy is often delayed until late adolescence, older women may receive inadequate replacement therapy. Estrogen deficiency in adulthood is an important factor that contributes to osteopenia in women with Turner syndrome. This is supported by the findings of a study in middle-aged women that the duration of hormone replacement therapy was the strongest positive predictor of bone mineralization.<sup>[16]</sup>

Although almost all women with Turner syndrome fail to enter puberty and, therefore, are infertile, the degree of ovarian function in these patients ranges from complete pubertal failure to normal pubertal development and, rarely, fertility.

Normally, the process of ovarian degeneration that usually spans at least 40 years in a normal female is compressed in girls with Turner syndrome to just a few months in the latter stages of embryogenesis. Although often only a fibrous streak of ovary remains at birth, the uterus, fallopian tubes, vagina, and external genitalia develop normally.

Fewer than 5% of patients with Turner syndrome will maintain enough ovarian function for ovulatory menses to occur and pregnancy has rarely been reported. Women with Turner syndrome who do achieve pregnancy have a substantially higher risk for abnormal pregnancies.

Infertility has a major psychological and lifestyle impact. For most couples who are infertile due to Turner syndrome, adoption is the most practical method of having children. This young woman with Turner syndrome and her husband adopted a girl with Turner syndrome.

Other reproductive options for women with Turner syndrome continue to improve and pregnancy through related or anonymous ovum donation has been successful in a number of these women.

### Patient Monitoring

Turner syndrome is associated with significant morbidity and mortality that have a negative impact on a patient's quality of life. Therefore, both girls and women with Turner syndrome should incorporate management strategies that include careful monitoring and early intervention and prophylaxis.

#### Patient Management: Osteoporosis

- ◆ Increased risks of osteoporosis and fracture in girls and women with Turner syndrome
- ◆ Risk may be due to hormonal and other factors
- ◆ Therapy for osteoporosis prevention and treatment
  - Hormone replacement therapy
  - Other

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#### Patient Management: Reproductive Issues

- ◆ Almost all women with Turner syndrome are infertile
- ◆ Adoption is the method of choice for most
- ◆ Assisted reproductive technology is also an option



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#### Monitoring of Girls and Women With Turner Syndrome

- ◆ Women with Turner syndrome require careful follow-up
- ◆ Early intervention and prophylaxis may decrease morbidity and mortality and improve the quality of life

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Saenger and colleagues<sup>[17]</sup> recently outlined detailed recommendations for the diagnosis and management of Turner syndrome. In summary, pediatric monitoring includes all of these areas, which obviously requires a multidisciplinary management approach. These monitoring strategies will most likely be carried out by a pediatric endocrinologist as well as a team of other specialists, as needed.

### Pediatric Monitoring

- ◆ Short stature
- ◆ Puberty
- ◆ Cardiac
- ◆ Renal
- ◆ Blood pressure
- ◆ Thyroid
- ◆ Hearing/ear
- ◆ Speech
- ◆ Vision
- ◆ Orthopedic
- ◆ Orthodontic
- ◆ Weight
- ◆ Lymphedema
- ◆ Glucose intolerance
- ◆ Need for plastic surgery

Saenger P, et al. J Clin Endocrinol Metab. 2001;88(7):3061-3069.

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At adulthood, some women with Turner syndrome will return to a general practice physician, who must be up-to-date on appropriate management strategies in order to identify potential long-term problems in these patients. Adult monitoring includes comprehensive medical evaluations and follow-up of any medical problems that were present during childhood.

### Adult Monitoring

- ◆ Annual medical history and general physical evaluation
  - Blood pressure
  - Heart auscultation
  - Thyroid size/function
  - Breast exam
  - Pap smear
- ◆ Otological exam and hearing evaluation
- ◆ Weight management
- ◆ Cardiovascular monitoring
- ◆ Lab tests
  - Hemoglobin
  - Renal function
  - Fasting blood glucose
  - Lipid profile
  - Liver enzymes
  - Thyroid stimulating hormone (TSH)
- ◆ Bone density/fractures
- ◆ Estrogen therapy
- ◆ Fertility/family planning
- ◆ Psychological/educational issues

Saenger P, et al. J Clin Endocrinol Metab. 2001;88(7):3061-3069.

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### Resources and Conclusions

In addition to referring your patients to a specialist, you may offer these helpful resources to girls with Turner syndrome and their parents for information and support.

MAGIC is the acronym for Major Aspects of Growth In Children.

### Patient, Family, and Professional Resources

- ◆ Genetic counseling
- ◆ Turner Syndrome Society
  - [www.turner-syndrome-us.org](http://www.turner-syndrome-us.org)
- ◆ MAGIC Foundation
  - [www.magicfoundation.org/turners.html](http://www.magicfoundation.org/turners.html)
- ◆ Human Growth Foundation
  - [www.hgfound.org](http://www.hgfound.org)

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Early diagnosis and referral of girls with Turner syndrome will lead to earlier initiation of treatment and improved outcomes.

### Thank You for Helping to Recognize the Many Faces of Turner Syndrome



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### References

#### Turner Syndrome: Toward Early Recognition and Improved Outcomes

1. Turner Syndrome: Toward Early Recognition and Improved Outcomes

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