
Turner Syndrome

Cytogenetics • Pathogenesis • Clinicopathologic correlation

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Learning objectives

1

Interpret the karyotype

Explain complete X monosomy, structural X variants, and mosaicism.

2

Relate genes to phenotype

Connect X escape genes and SHOX dosage to the phenotype.

3

Explain ovarian pathology

Trace rapid oocyte loss to streak ovaries and hypogonadism.

4

Recognize clinical risk

Link characteristic features to cardiovascular and endocrine complications.

Turner syndrome: The defining abnormality

Complete or partial monosomy of X-chromosome material.

Occurs in phenotypic females and is characterized by hypogonadism.

The clinical phenotype varies with the chromosomal lesion and tissue mosaicism.

Central concept

Loss of gene dosage—not merely the numerical karyotype—drives the phenotype.

Why sex-chromosome imbalance permits survival

Numerical imbalance of sex chromosomes is more compatible with life than most autosomal monosomies.

One X chromosome undergoes inactivation in normal 46,XX development.

However, a subset of X genes escapes inactivation and requires normal dosage.

Normal 46,XX dosage versus 45,X

Typical 46,XX

Two X chromosomes are present.

Most genes on one X are inactivated in each cell.

Escape genes remain expressed from both X copies.

45,X

One X chromosome is absent.

Only one copy remains for many escape genes.

Dosage reduction contributes to somatic and gonadal disease.

X-inactivation is not complete

XIST expression

Long noncoding RNA coats the inactive X.



Chromatin silencing

Most genes on the coated chromosome are turned off.



Escape regions

Some X-linked genes remain transcriptionally active.

Illustrative mechanism—not a complete molecular pathway

Escape from X-inactivation is the key exception

Approximately 30% of Xp genes escape inactivation.

A smaller fraction of Xq genes (about 3%) also escape.

Functional consequences of losing these escape-gene copies help explain Turner syndrome.

Frequency of Turner syndrome

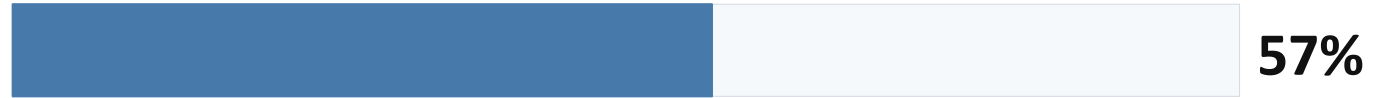
The main text reports approximately 1 in 2,000 live-born females.

The source figure captioned on the next page gives 1 in 3,000 female births.

These are discrepant textbook estimates; Neither is silently substituted for the other.

Three cytogenetic groups at routine analysis

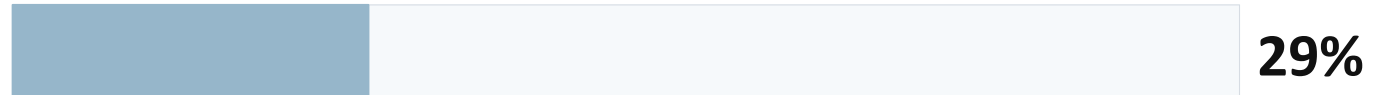
Entire X absent (45,X)



Structural X abnormalities



Mosaic cell populations



Approximate proportions reported by routine cytogenetic methods

Complete monosomy X: The largest group

Approximately 57% of affected individuals have a 45,X karyotype by routine cytogenetics.

The second sex chromosome is entirely absent.

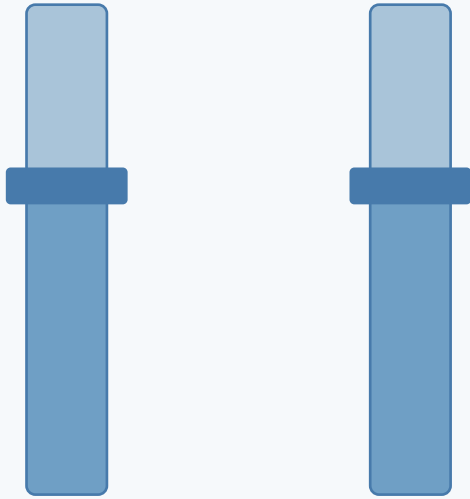
The resulting loss of X-linked gene dosage can produce a more pronounced phenotype.

Notation

45 = total chromosome count;
X = one X chromosome.

46,XX compared with classic 45,X

46,XX: Two X chromosomes



X

X

45,X: One X chromosome



X

One entire X copy is missing

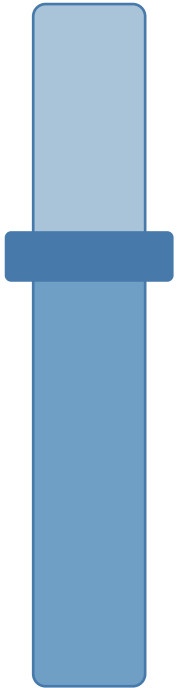
Structural X changes also cause Turner syndrome

Approximately 14% have structural changes in the X chromosome.

The common denominator is partial monosomy of X-chromosome material.

Loss may involve the short arm, long arm, or rearranged chromosome architecture.

Normal X, deletions and isochromosome



Normal X



Xp loss



Xq loss



Iso Xq

Isochromosome of the long arm: 46,X,i(X)(q10)

An isochromosome contains duplicated long-arm material around the centromere.

Formation of i(Xq) removes much of the normal X short arm.

The resulting Xp dosage deficiency contributes to the Turner phenotype.

Cytogenetic interpretation

The abnormal chromosome is structural—not a second intact X.

Ring X chromosome: 46,X,r(X)

Chromosome ends may be deleted and the chromosome circularized.

Formation of a ring can remove terminal sequences from both arms.

The phenotypic effect reflects the regions lost and possible mosaic cell populations.

Terminal or interstitial X-arm deletions

Loss of Xp or Xq material can be recorded as del(Xp) or del(Xq).

Deletion of Xp often removes genes governing somatic features.

Certain Xq regions are implicated in fertility and menstruation.

Mosaicism originates from distinct cell lines

Early cell-division error

A chromosomal error occurs in the developing conceptus.



Different descendant clones

Cells with different sex-chromosome complements persist.



Variable tissue distribution

The proportion and location of cell lines influence phenotype.

Mosaic karyotypes reported in Turner syndrome

45,X/46,XX: Monosomic and normal female cell populations.

45,X/46,XY: Monosomic and Y-bearing cell populations.

45,X/47,XXX or 45,X/46,X,i(X)(q10): Further documented combinations.

Mosaicism changes clinical severity

Higher 45,X fraction

Textbook associates a high fraction of 45,X cells with more severe manifestations.

Multiple tissues may carry monosomic cell populations.

Readily detectable 45,X/46,XX

Phenotype may be mild or nearly normal.

Amenorrhea may be the first reason for clinical evaluation.

Routine karyotyping may underestimate mosaicism

Conventional cytogenetic studies detect mosaicism in roughly 29–30% of patients in the cited series.

The source reports that more sensitive techniques increase estimated mosaic prevalence to as high as 75%.

Both testing approach and tissue representation matter when interpreting a result.

Residual ovarian function can occur

A small subset of patients is able to conceive.

Preserved function is consistent with the broad phenotypic range, particularly in mosaic disease.

Fertility is therefore not determined solely from the syndrome name.

Y-chromosome material changes tumor risk

Approximately 5–10% of patients carry Y sequences by the textbook estimate.

Y material may be present as a whole Y chromosome or translocated fragments.

Presence of Y material is associated with a higher risk of gonadoblastoma.

Interpretation

The risk pertains to Y-bearing gonadal tissue; No treatment protocol is specified by this source.

Why X loss affects the developing ovary

Normal oogenesis

Both X chromosomes are active in germ cells before meiosis.



Insufficient X dosage

Loss of a second X perturbs maintenance of the oocyte population.



Accelerated attrition

Germ cells disappear unusually early.



Streak ovaries

Gonads become fibrous and depleted of follicles.

Origin of the retained X chromosome

That the retained X is maternal in about 80% of cases.

This observation is consistent with an important role for paternal gametogenetic errors.

Parent-of-origin is not itself a sufficient explanation for all clinical manifestations.

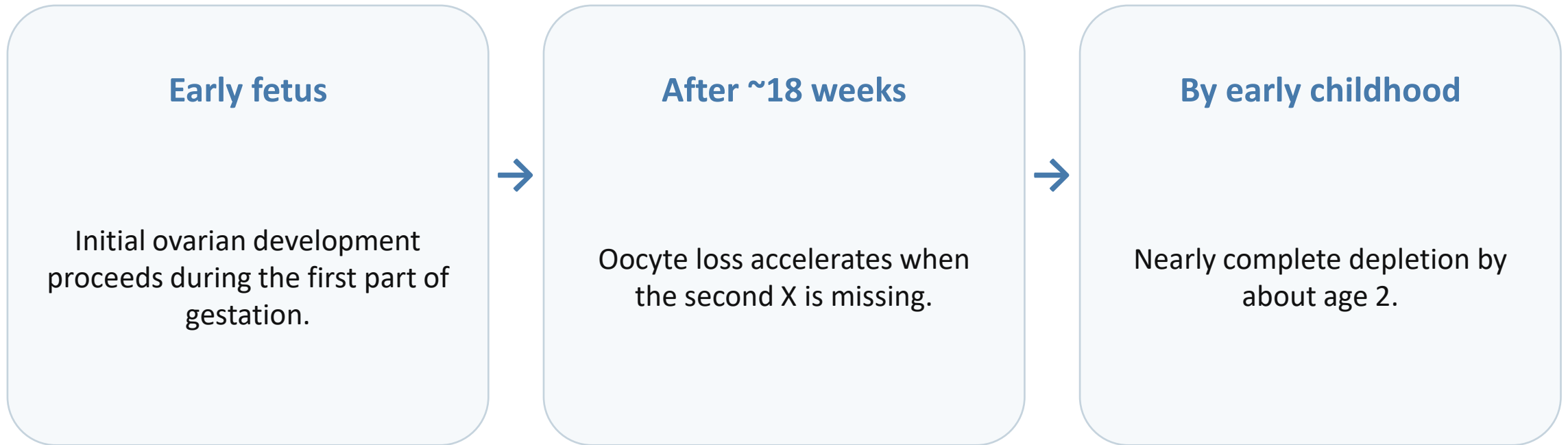
The normal ovarian germ-cell reserve

In normal fetal life, the ovaries can contain as many as 7 million oocytes.

Progressive physiological attrition reduces the reserve throughout development and adulthood.

This normal trajectory helps contextualize the greatly accelerated loss in Turner syndrome.

Oocyte loss in Turner syndrome



Approximate developmental stages as described

Streak ovaries: A pathologic endpoint

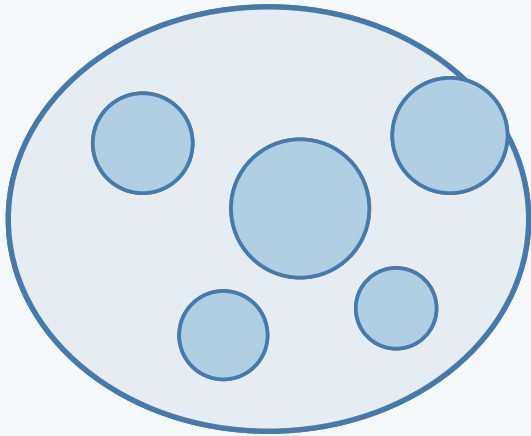
Gonads are reduced to atrophic fibrous strands.

Normal ova and follicles are absent or markedly depleted.

The lesion accounts for profound loss of ovarian hormone production and fertility.

Streak-ovary morphology as a conceptual model

Follicle-containing ovary



Streak ovary



Fibrous remnant

Schematic only: Not a histologic section or gross specimen

Ovarian failure precedes typical puberty

Accelerated oocyte attrition often finishes long before the expected age of menarche.

Primary amenorrhea and lack of normal secondary sex development follow ovarian failure.

This explains the textbook analogy: “menopause occurs before menarche.”

Pubertal signs of gonadal dysfunction

Typical puberty may fail to produce expected breast development.

Genital tissues can remain relatively infantile.

The source describes sparse pubic hair and absent menstruation.

Amenorrhea and infertility: Mechanism

Anatomic substrate

Streak ovaries contain very few or no functioning follicles.

Germ-cell loss precedes endocrine failure.

Clinical expression

Primary amenorrhea is a major diagnostic clue.

Infertility is common, though a small subset can conceive.

Primary amenorrhea is a sentinel presentation

Turner syndrome as the most important individual cause of primary amenorrhea.

It attributes approximately one-third of cases to Turner syndrome.

The combination with short stature substantially strengthens clinical suspicion.

SHOX: An X-linked growth-regulating gene

The SHOX locus lies at Xp22.33.

It belongs to the pseudoautosomal region shared by X and Y chromosomes.

Normal males and females usually carry two functional copies.

SHOX escapes ordinary X-inactivation

Pseudoautosomal position

SHOX maps to homologous X/Y chromosomal tips.



Biallelic expression

The locus escapes X-inactivation and retains two-copy dosage.



Turner syndrome

Loss of one functional copy creates haploinsufficiency.

SHOX insufficiency and short stature

Reduced SHOX dose

Only one functional copy remains
in classic X monosomy.



Growth-plate effects

The gene contributes to
longitudinal skeletal growth.



Reduced linear growth

Short stature becomes a key
clinical sign.

SHOX expression maps to the skeleton

The gene is expressed in fetal growth plates of several long bones.

Examples given: Radius, ulna, tibia, and fibula.

Dosage-dependent skeletal growth provides a mechanistic bridge from genotype to short stature.

Short stature: A diagnostic clue

Short stature is one of the most consistent somatic manifestations.

Adult height rarely exceeds 150 cm without context of modern treatment.

In a patient with primary amenorrhea, short stature points strongly toward X-chromosomal disease.

Different X regions influence different features

Xp alterations

Many characteristic somatic manifestations are associated with genes on Xp.

SHOX dosage provides a defined example.

Xq alterations

The textbook links multiple Xq regions to menstruation and fertility.

Ovarian function reflects more than the SHOX locus.

A single-gene explanation is insufficient

SHOX haploinsufficiency explains a substantial component of short stature.

It does not explain the characteristic cardiovascular abnormalities.

It also does not adequately explain the complex metabolic phenotype.

Mechanistic caution

The source does not identify a full set of causal genes for these additional features.

Earliest clinical signs: Peripheral lymphedema

Severely affected infants may have edema over the dorsum of hands and feet.

The underlying process is impaired lymphatic drainage or lymph stasis.

Edema may decrease over time even though the chromosomal condition persists.

Lymphatic abnormality explains the neck phenotype

Distended lymphatics

Abnormal lymphatic channels
allow fluid accumulation.



Nuchal swelling

Marked posterior cervical swelling
can form cystic hygroma.



Postnatal remodeling

Swelling subsides; Loose nuchal
skin and webbing can remain.

Cystic hygroma in the Turner phenotype

Cystic hygroma represents markedly distended lymphatic channels.

The source relates neck swelling to this process.

Persistent skin redundancy and webbing can be residual findings after fluid resolves.

Residual and musculoskeletal features

Neck webbing and low posterior hairline may persist.

Broad chest with widely spaced nipples is illustrated.

Cubitus valgus and pigmented nevi are also characteristic clinical clues.

Congenital cardiac disease is frequent

Cardiovascular malformations in 25–50% of patients.

Left-sided cardiac and aortic abnormalities predominate.

Cardiovascular disease is a principal determinant of serious clinical risk.

Two classic left-sided cardiovascular lesions

Coarctation of the aorta

An aortic narrowing lesion classically associated with Turner syndrome.

The source specifies preductal coarctation.

Bicuspid aortic valve

Abnormal aortic valve anatomy with two leaflets.

It is frequently identified among the syndrome's cardiac lesions.

Coarctation may disclose an undiagnosed syndrome

Coarctation is an important structural clue to an X-chromosomal disorder.

The textbook estimates Turner syndrome in about 5% of young females with coarctation.

Cardiac findings should be interpreted alongside stature, lymphatic and gonadal features.

Aortic-root dilation adds a separate risk domain

Aortic-root dilation in approximately 30% of cases.

This is distinct from the congenital defects of the aortic valve or arch.

The combination of multiple aortic pathologies increases clinical complexity.

Aortic dissection: A high-consequence complication

The source describes approximately 100-fold higher dissection risk.

Aortic involvement is clinically more consequential than cosmetic phenotypic markers.

Cardiovascular abnormalities are emphasized as the leading cause of excess mortality in affected children.

Why cardiovascular recognition matters

Recognition of syndrome

Phenotypic and cytogenetic clues identify Turner syndrome.



Identify structural risks

Evaluate coarctation, valve morphology, and aortic root.



Prevent missed hazards

Maintain vigilance for aortic complications.

Neurocognitive phenotype: An important distinction

Overall cognitive function is usually normal.

Some patients have subtle difficulty with nonverbal or visuospatial processing.

The disorder should not be equated with generalized intellectual disability.

Autoimmune thyroid involvement

Approximately half of patients develop thyroid-directed autoantibodies account.

Up to half of this antibody-positive group develops manifest hypothyroidism.

The mechanism for increased autoimmunity is noted as incompletely understood.

Metabolic manifestations are heterogeneous

Some individuals develop glucose intolerance, insulin resistance and obesity.

The source also lists nonalcoholic fatty liver disease and metabolic syndrome.

These abnormalities are not explained by SHOX haploinsufficiency alone.

Growth hormone and metabolic surveillance

Growth hormone is used to improve linear growth.

The textbook warns that GH therapy can exacerbate insulin resistance.

Clinical benefits therefore coexist with a metabolic consideration.

Estradiol replacement addresses gonadal failure

Estradiol among treatments for Turner syndrome.

Its mechanistic rationale follows from diminished ovarian estrogen production.

Its purpose is distinct from that of growth hormone, which targets stature.

Age-dependent diagnostic presentations

Age or setting	Prominent source-derived clues
Infancy	Edema of hands/feet, nuchal swelling, congenital cardiac lesions
Childhood	Short stature, residual neck webbing and skeletal findings
Puberty	Reduced breast development, absent menarche
Adulthood	Primary amenorrhea, infertility, possible mild mosaic phenotype

From phenotype to a chromosomal diagnosis

Clinical suspicion

Short stature, lymphedema,
primary amenorrhea or cardiac
lesion.



Cytogenetic study

Characterize 45,X, structural X
change, or mosaic cell lines.



Phenotype correlation

Interpret gonadal and somatic
findings with the chromosomal
result.

Genetic test results require phenotypic context

What a karyotype gives

Cellular sex-chromosome constitution.

Visible X-arm structural changes.

Cell lines sampled by conventional analysis.

What a karyotype cannot guarantee

Same phenotype in every individual.

Complete detection of low-level mosaicism.

A full account of tissue-specific cell-line distribution.

Y material creates a separate decision branch

Y-bearing sequences may exist even when much of the phenotype resembles typical Turner syndrome.

Y sequences carry a specific gonadoblastoma association.

This tumor risk should be distinguished from the more general risk of ovarian failure.

Clinical application: An infant

A newborn has swelling over the backs of both hands, edema of the feet, and a prominent nuchal swelling. A cardiac murmur is identified.

Which unifying syndrome and anatomic mechanism should be considered?

Infant case: An integrated explanation

Turner syndrome is a possible unifying diagnosis.

Lymph stasis explains the peripheral edema; Dilated lymphatic channels can produce nuchal cystic hygroma.

The cardiac finding raises concern for left-sided congenital disease.

Clinical application: Delayed puberty

A teenager has marked short stature, absent breast development, and primary amenorrhea. Cytogenetic examination identifies a 45,X cell population.

Connect the karyotype to both growth and gonadal findings.

Delayed puberty case: Two mechanistic links

SHOX haploinsufficiency contributes to reduced longitudinal growth.

Accelerated prenatal and childhood oocyte loss produces streak ovaries.

Loss of ovarian function explains the absent pubertal progression and menarche.

Clinical application: Mild mosaic phenotype

An adult of short stature presents with primary amenorrhea but lacks dramatic neck or chest findings. A karyotype identifies 45,X/46,XX mosaicism.

Why can the clinical phenotype be relatively mild?

Mosaic case: The proportion of affected cells matters

Mosaic individuals contain both monosomic and nonmonosomic cell populations.

The clinical manifestations can be attenuated when the 45,X cell population is less prominent.

Mild somatic features do not exclude clinically important gonadal dysfunction.

An integrated causal model of Turner syndrome

X gene dosage loss

Complete monosomy, structural loss or mosaicism.



Distinct tissue targets

SHOX-related growth; Ovarian germ cells; Lymphatic and cardiovascular development.



Characteristic disease

Short stature, streak ovaries, edema and congenital/aortic disease.

Connecting three findings to mechanisms

Finding	Pathogenetic explanation
Short stature	SHOX haploinsufficiency at Xp22.33
Primary amenorrhea	Accelerated oocyte loss and ovarian fibrosis
Neck webbing	Residual change after prenatal/postnatal lymphatic swelling
Cardiovascular lesions	Strong syndrome association; precise multi-gene mechanism incompletely understood

Five conclusions to retain

Turner syndrome results from partial or complete loss of X-chromosome material.

45,X, structural X abnormalities and mosaicism produce variable phenotypes.

SHOX insufficiency explains short stature; Oocyte depletion explains streak ovaries.

Lymphatic and cardiovascular lesions aid early recognition and determine risk.

Y-chromosome sequences specifically increase gonadoblastoma risk.

Primary source and interpretation limits

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).

Chapter 5, “Genes and Human Diseases,” pp. 149–153.

Turner syndrome section, Fig. 5.26 and preceding X-inactivation discussion.

The chapter text and Fig. 5.26 display discrepant birth-frequency estimates.