

Cytogenetic Disorders Involving Sex Chromosomes

From dosage compensation to gonadal and somatic phenotypes

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Learning objectives

- Explain why sex-chromosome imbalance is more tolerable than autosomal imbalance.
- Describe random X inactivation, XIST, and clonally stable mosaicism.
- Relate escape genes, PAR, SHOX, and SRY to phenotype.
- Compare mechanisms and clinical effects of Klinefelter and Turner syndromes.

Sex-chromosome aneuploidy: A distinctive category

- Extra or missing X or Y chromosomes may be compatible with survival.
- Phenotypic consequences concentrate in growth, sexual development, and fertility.
- Compensation is substantial, but incomplete.

Two blue X chromosomes are shown side-by-side.

46,XX

A blue X chromosome and a red Y chromosome are shown side-by-side.

46,XY

Two blue X chromosomes and one red Y chromosome are shown side-by-side.

47,XXY

A single blue X chromosome is shown.

45,X

Sex-chromosome versus autosomal imbalance

Feature	Sex chromosomes	Autosomes
Survival	Numerical imbalance often tolerated	Monosomy generally incompatible with survival
Compensation	X inactivation reduces active X dosage	No equivalent chromosome-wide system
Y contribution	Relatively limited gene content	Most autosomes carry many essential genes
Typical effects	Gonadal, fertility and somatic features	Often widespread developmental effects

Why tolerance is possible

**Most X-linked genes
Are inactivated**



**The Y chromosome
Carries limited genes**



**Residual active dosage
Still matters**

Tolerance of chromosome imbalance does not imply a normal phenotype.

Four reference complements

- 46,XX and 46,XY are typical human complements.
- 47,XXY demonstrates an additional X chromosome.
- 45,X demonstrates absence of a second sex chromosome.

Two blue 'X' chromosomes are shown side-by-side.

46,XX

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Two blue 'X' chromosomes and one red 'Y' chromosome are shown side-by-side.

47,XXY

A single blue 'X' chromosome is shown.

45,X

The X-dosage problem

**XX cells contain
Two X chromosomes**



**XY cells contain
One X chromosome**



**Dosage compensation
Equalizes many active
genes**

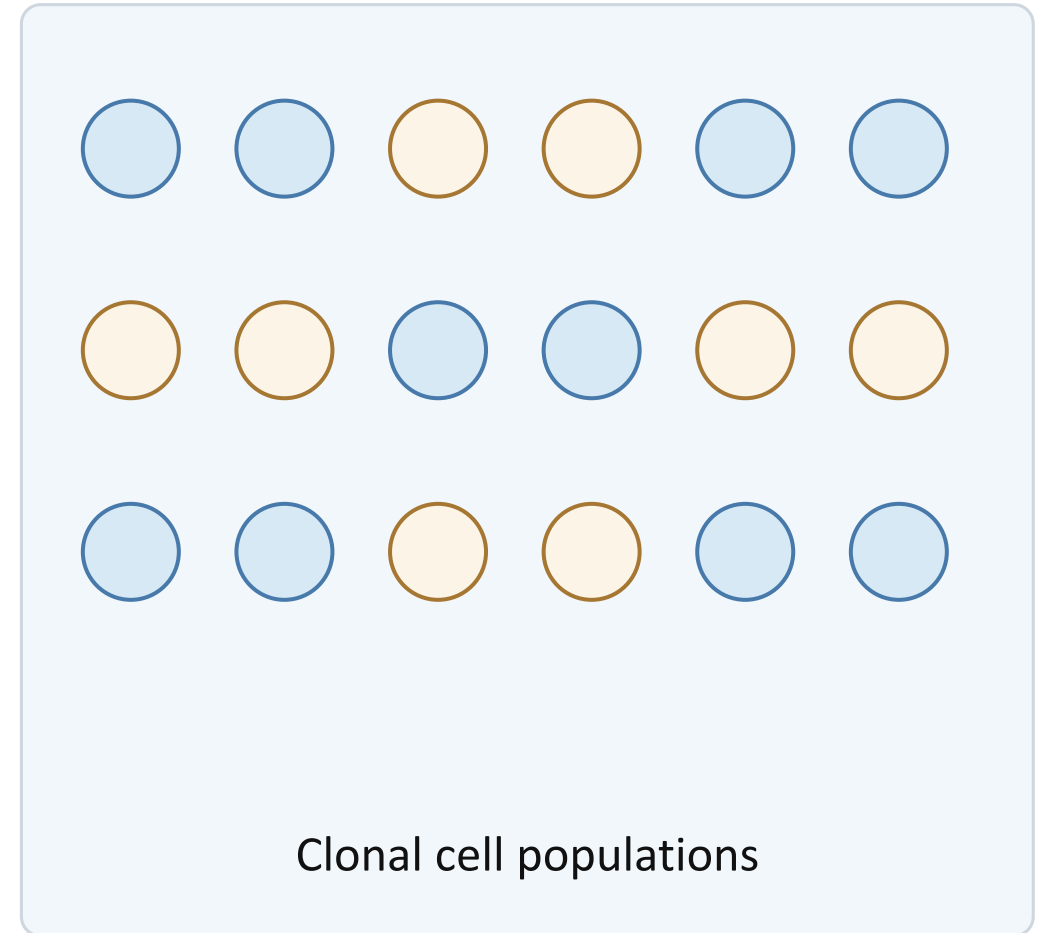
Without inactivation, many X-linked genes would be expressed at different doses.

The Lyon hypothesis: Four organizing principles

- Only one X chromosome remains broadly active in each somatic cell.
- Either the maternal or paternal X can be inactivated.
- The initial choice occurs early in embryogenesis and is random.
- The same X remains inactive in descendants of that cell.

Random choice occurs early in development

- Different embryonic precursor cells may silence different parental X copies.
- This creates an initial mixture of cellular X-inactivation states.
- The outcome is a characteristic cellular mosaic.



X inactivation is clonally maintained

**Cell selects
Maternal or paternal X**



**Chosen X becomes
Epigenetically silent**

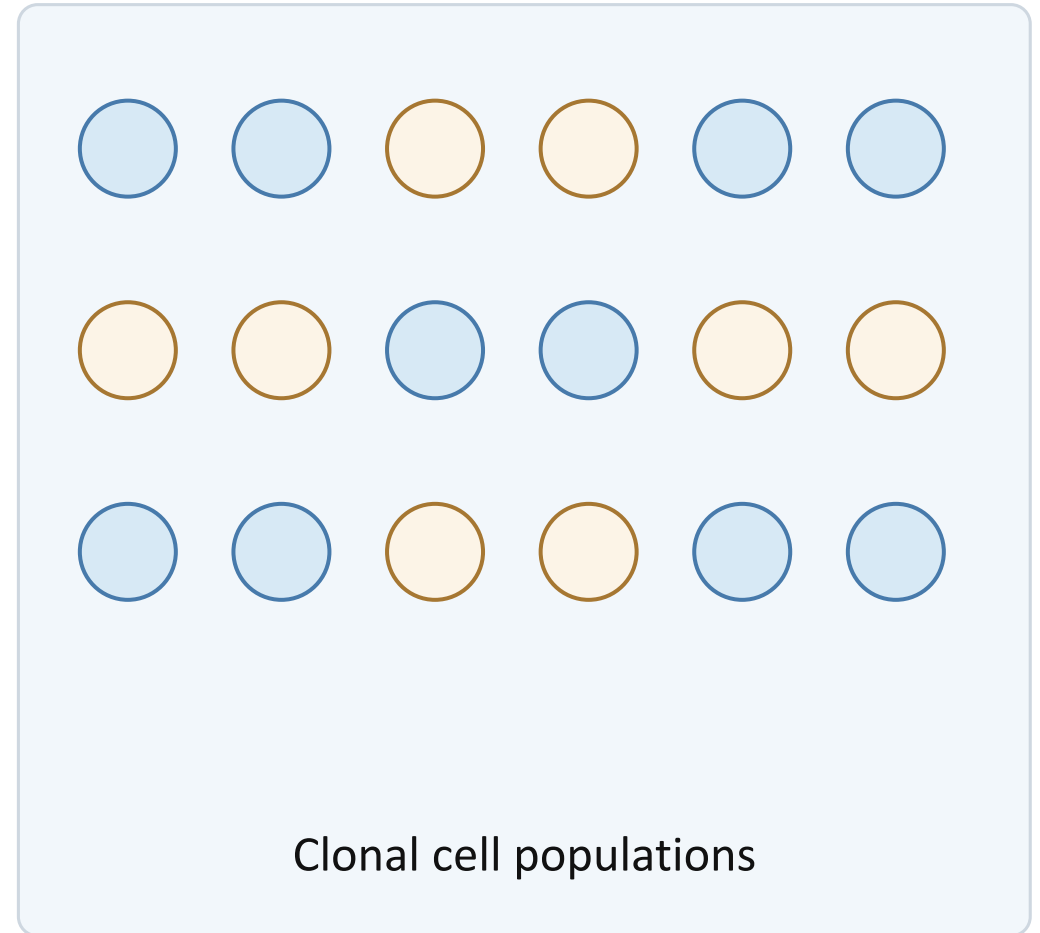


**Daughter cells inherit
The same inactive X**

The pattern persists across somatic cell divisions.

A normal XX individual is a cellular mosaic

- One cell lineage predominantly expresses genes from maternal X.
- Another expresses genes from paternal X.
- The tissue is genetically XX throughout but differs in active parental X.

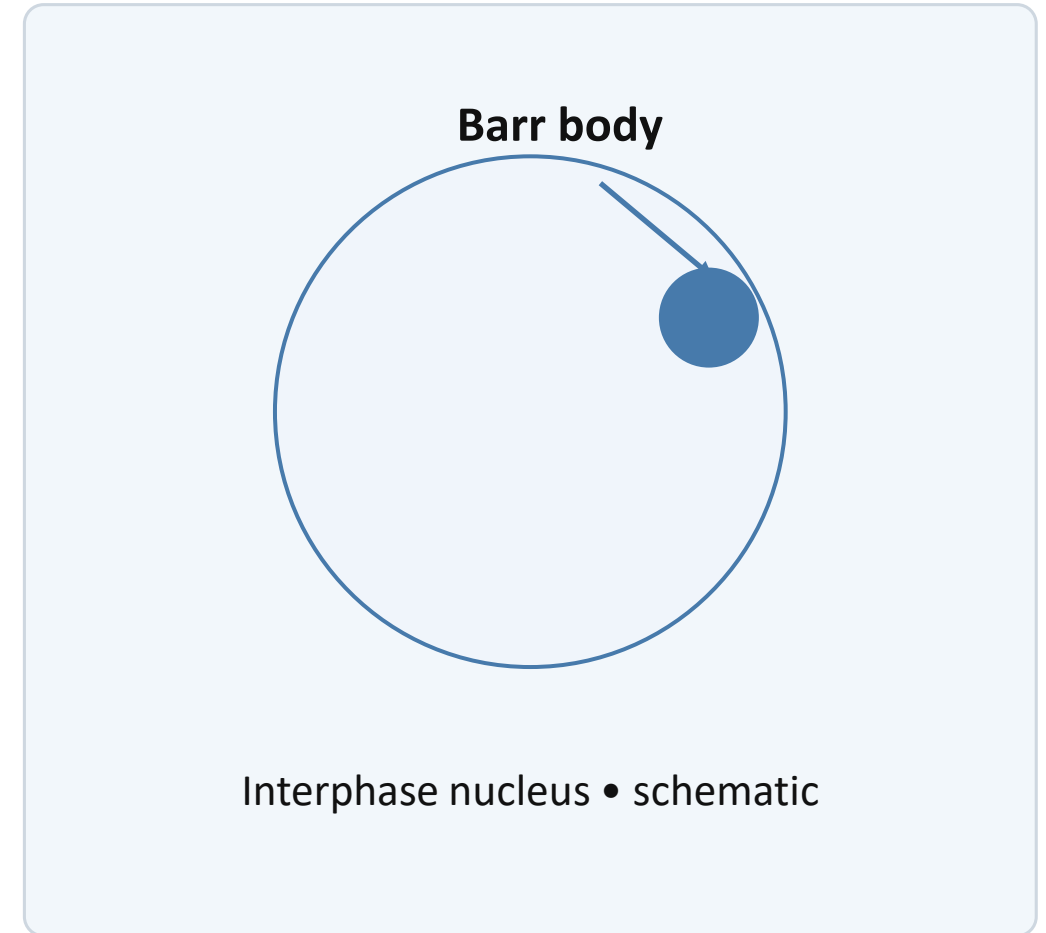


Chromosomal mosaicism is not X-inactivation mosaicism

Property	X-inactivation mosaicism	Chromosomal mosaicism
Karyotype	Usually same 46,XX in cells	Different karyotypic cell lines
Origin	Random epigenetic X choice	Postzygotic chromosome error
Inheritance	State maintained in clones	Cell-line karyotype maintained
Clinical impact	Dosage compensation pattern	Proportion and tissues of abnormal cells

The Barr body: Inactive X in interphase nuclei

- Condensed inactive X appears as a small, dense nuclear chromatin mass.
- It is usually located near the nuclear membrane.
- Barr body presence reflects an inactive X, not complete genetic silence.



Barr bodies reflect X inactivation

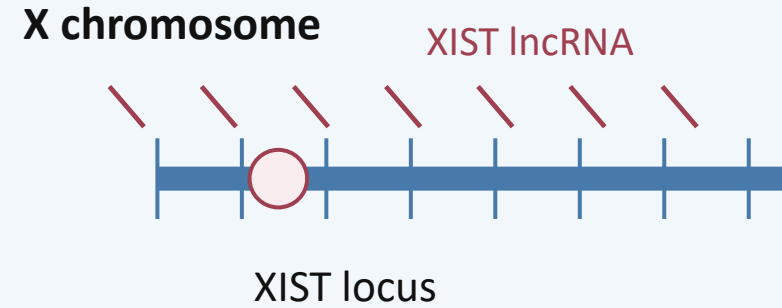
Complement	Expected inactive X copies	Interpretation
46,XY	0	One X is active
46,XX	1	One X inactive
47,XXY	1	Additional X is inactive
47,XXX	2	Two X chromosomes inactive
45,X	0	No second X to inactivate

Barr body counting has limitations

- It reflects condensed X chromatin, not precise genotype by itself.
- X-inactivation escape genes remain functionally relevant.
- Mosaic cell lines may yield variable nuclear findings.
- Full cytogenetic interpretation requires chromosome-level assessment.

XIST initiates chromosome-wide silencing

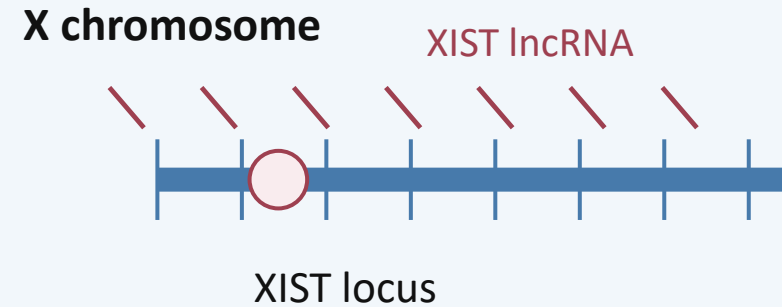
- XIST is a long noncoding RNA transcribed from the future inactive X.
- The RNA remains nuclear and coats the chromosome of origin.
- XIST expression is suppressed on the active X.



Schematic

XIST coating precedes chromatin repression

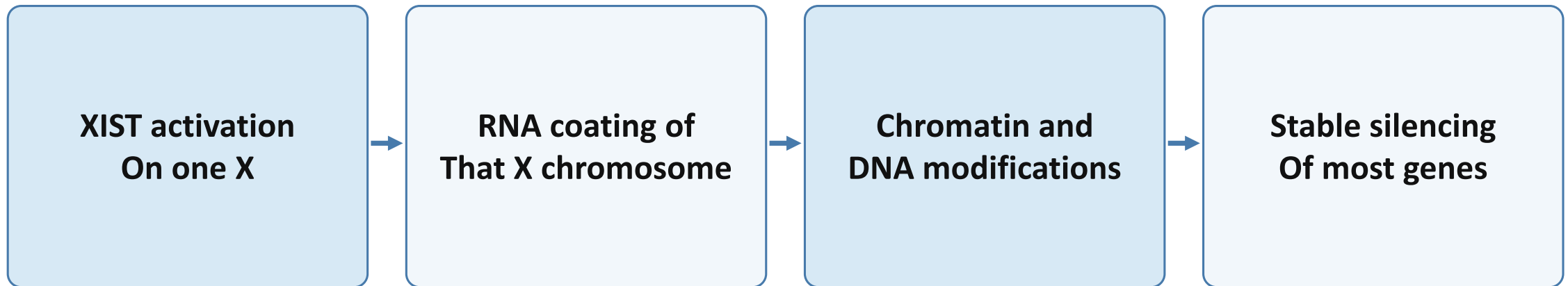
- The XIST transcript spreads along the chromosome that produces it.
- It helps recruit chromatin-modifying and DNA-methylation processes.
- The result is a relatively inactive X chromosome.



**Chromatin silencing • DNA
methylation**

Schematic

Sequence of dosage compensation



The X chromosome is broadly, but not completely, silenced.

Active X and inactive X: Molecular contrast

Characteristic	Active X	Inactive X
XIST expression	Suppressed	Expressed
Chromatin status	Relatively permissive	Condensed / repressed
Most X genes	Transcribed	Silenced
Escape loci	Transcribed	Remain expressed in subset

Dosage compensation is not complete

- Some X-linked loci retain expression despite X inactivation.
- Escaping genes create persistent sensitivity to X copy number.
- Both extra copies and loss of copies can alter development.

Escape from inactivation differs by X arm

- The source identifies more escape genes on Xp than on Xq.
- This helps explain why partial X deletions may have different phenotypes.
- Escape loci provide a mechanism for the effect of X aneuploidy.

X chromosome • conceptual gene map

Xp: More escape loci



Xq: Fewer escape loci

Gene dosage drives both deficiency and excess

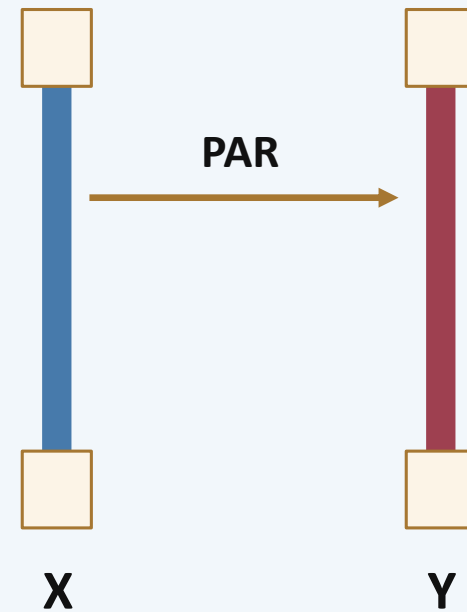


The same principle works in the opposite direction when an extra chromosome is present.

Pseudoautosomal regions link X and Y

- The tips of X and Y carry homologous regions.
- These pseudoautosomal regions (PARs) recombine in meiosis.
- Their genes escape typical X dosage compensation.

Shared homologous terminal segments



Pseudoautosomal dosage is usually balanced

**X and Y share
Homologous PAR genes**



**Typical XX and XY cells
Carry two copies**



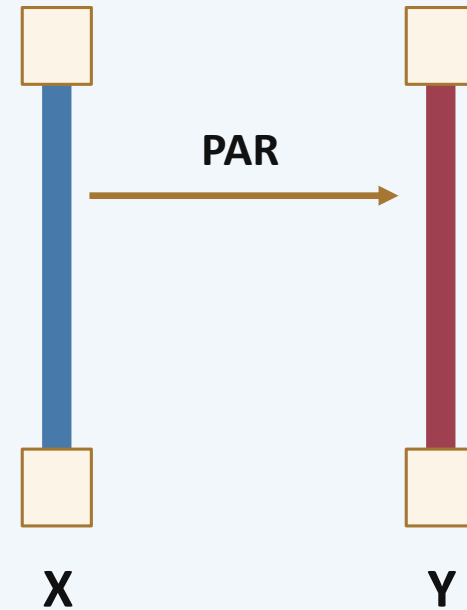
**Dosage differences emerge
With aneuploidy**

Shared copies on X and Y help equalize dosage between chromosomal sexes.

SHOX: An instructive escape gene

- SHOX lies in the pseudoautosomal region at Xp22.33.
- It contributes to growth-plate development and skeletal growth.
- Its effective dose varies with the number of intact sex chromosomes.

Shared homologous terminal segments



SHOX dosage and linear growth

- Turner syndrome may reduce functional SHOX copies to one.
- Typical XX and XY complements have two copies.
- Klinefelter syndrome may provide a third copy, associated with tall stature.

45,X 

SHOX reduction

**46,XX or
46,XY** 

Reference dosage

47,XXY 

SHOX excess

A single gene illustrates opposite phenotypes

Setting	SHOX dosage	Growth phenotype
45,X Turner	Reduced	Short stature
46,XX or 46,XY	Typical	Reference growth regulation
47,XXY Klinefelter	Increased	Relatively tall stature / long legs

Why one active X does not make 45,X normal

- X escape genes need dosage from more than one sex chromosome.
- Both X chromosomes contribute to aspects of normal female growth.
- Oogenesis has developmental requirements beyond somatic X dosage compensation.

Special rule in the female germline

**Somatic cells
Inactivate one X**



**Oogonia reactivate
The inactive X**



**Both X chromosomes
Support oogenesis**

Somatic X inactivation and germline X activity must not be conflated.

The Y chromosome: Fewer genes, targeted functions

- The Y carries substantially less coding material than the X.
- Its genes include regulators of testicular development.
- Additional Y genes participate in spermatogenesis.

Relative gene content, not a physical scale drawing

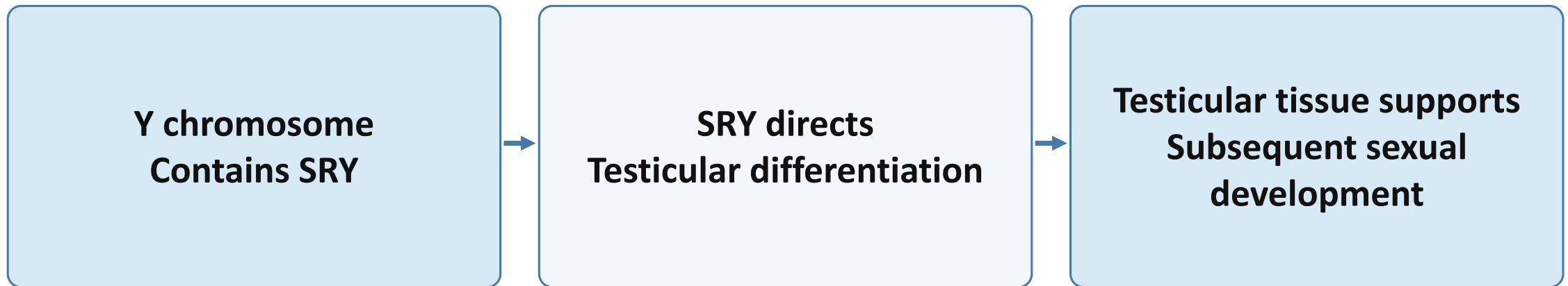


X



Y

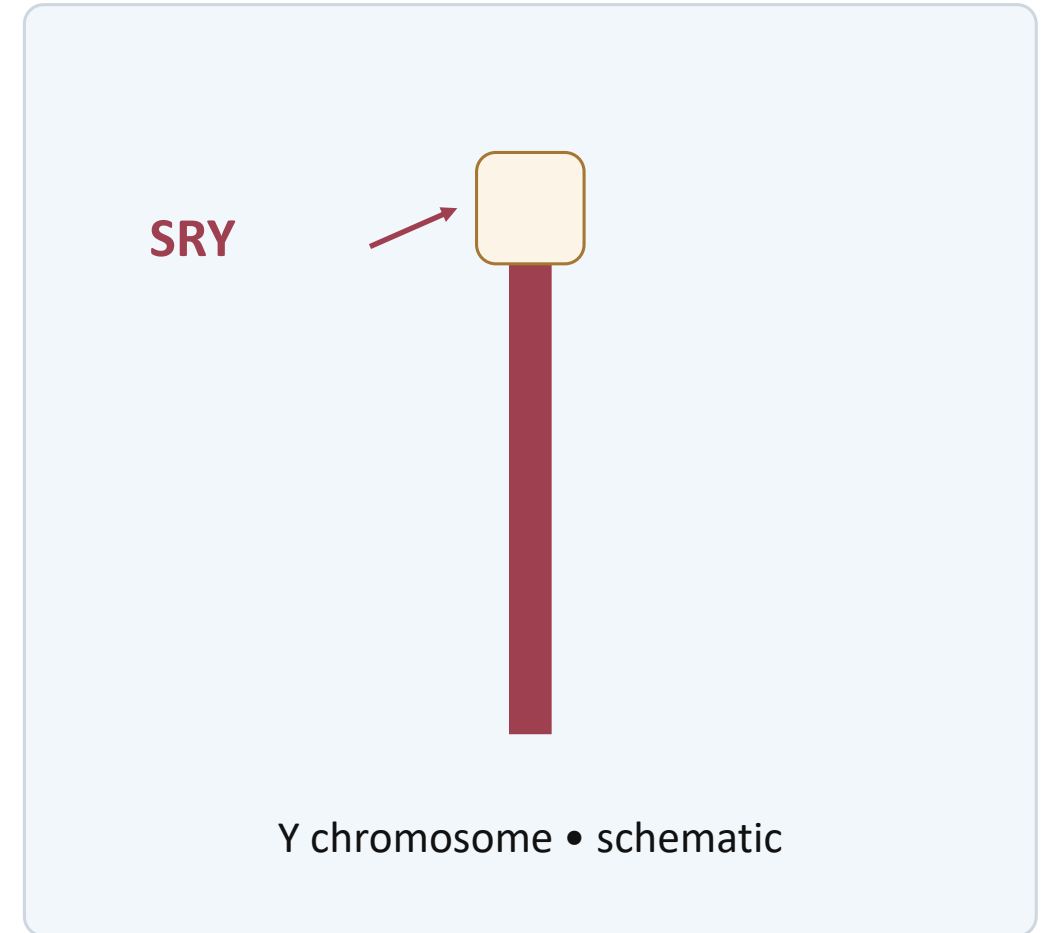
SRY initiates the testicular developmental program



This is the typical developmental pathway; Chromosomal, gonadal and external phenotypes must be distinguished.

SRY location and meaning

- The source locates SRY on the distal short arm of Y.
- SRY is the principal chromosome-linked testis-determining gene.
- The presence of Y material is biologically important beyond karyotype notation.



Genes beyond SRY matter for the Y phenotype

- The male-specific region of Y contains additional protein-coding genes.
- Several are expressed predominantly in the testis.
- Disruption of Y-associated spermatogenesis genes can impair sperm production.

Sex-chromosome number changes: Nondisjunction

**Segregation error
During meiosis**



**Gamete has extra
Or absent chromosome**



**Zygote acquires
Aneuploid complement**

The source describes nondisjunction and anaphase lag as major causes of aneuploidy.

Mitotic error can generate mosaic karyotypes

**Initially uniform
Zygote**



**Postzygotic
Segregation error**

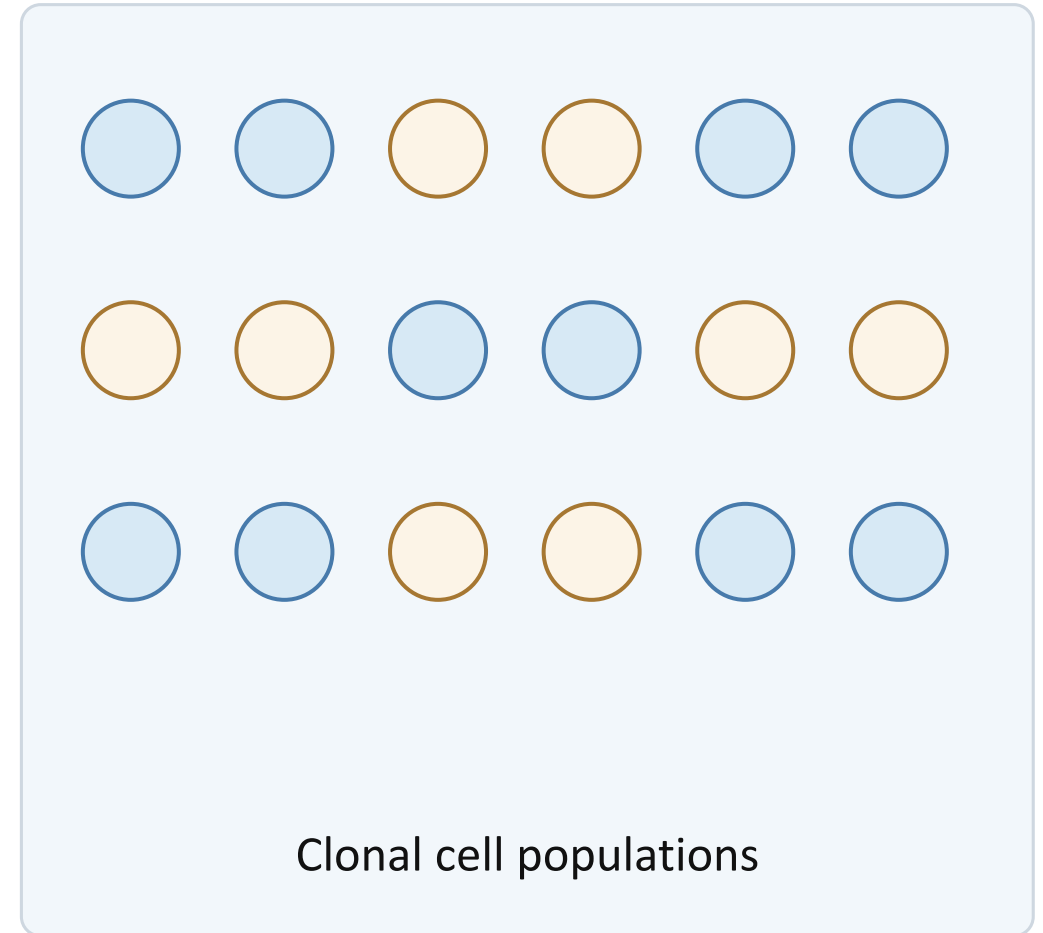


**Two cell lines
With different karyotypes**

Clinical expression depends in part on tissue distribution and proportion of abnormal cell lines.

Mosaicism creates variable phenotypic severity

- Mosaic lines can include 45,X/46,XX or 46,XY/47,XXY.
- The proportion of abnormal cells may differ by tissue.
- A peripheral blood karyotype samples only one cellular compartment.



Three principal cytogenetic mechanisms

Mechanism	Chromosome-level event	Illustrative setting
Meiotic nondisjunction	Abnormal gamete complement	Nonmosaic 47,XXY
Postzygotic mitotic error	Different cell lines arise	45,X/46,XX mosaic
Structural X abnormality	Loss or rearrangement of X segments	Xq isochromosome; Ring X

Sex-chromosome disorders may emerge at puberty

- Congenital karyotypic change may be present without obvious neonatal signs.
- Hypogonadism becomes more apparent as puberty should progress.
- Infertility or amenorrhea may prompt later cytogenetic testing.

Sex-chromosome disorders: Broad clinical themes

Domain	Underlying cause	Representative clinical expression
Growth	Altered escape-gene dosage	Short or tall stature
Gonadal function	Disrupted gonadal development	Hypogonadism
Fertility	Impaired germ-cell maintenance	Reduced gametogenesis
Learning	Variable chromosome-dosage effects	Selected cognitive-domain differences

Klinefelter syndrome: The extra-X example

- Defined by male hypogonadism with at least two X chromosomes and Y material.
- The characteristic complement is 47,XXY.
- Clinical manifestations reflect extra X dosage plus gonadal failure.



46,XX



46,XY



47,XXY



45,X

47,XXY formation and molecular consequence

**Nondisjunction
In parental meiosis**



**Additional X in
47,XXY cells**



**Escape-gene dosage
Is increased**

Inactivation silences most genes on one X but does not remove all dosage effects.

Klinefelter phenotype reflects gonadal failure

- Small, atrophic testes are a consistent pathological feature.
- Secondary male sexual features may be reduced.
- Gynecomastia and a relatively tall, long-legged habitus may be present.

45,X 

SHOX reduction

**46,XX or
46,XY** 

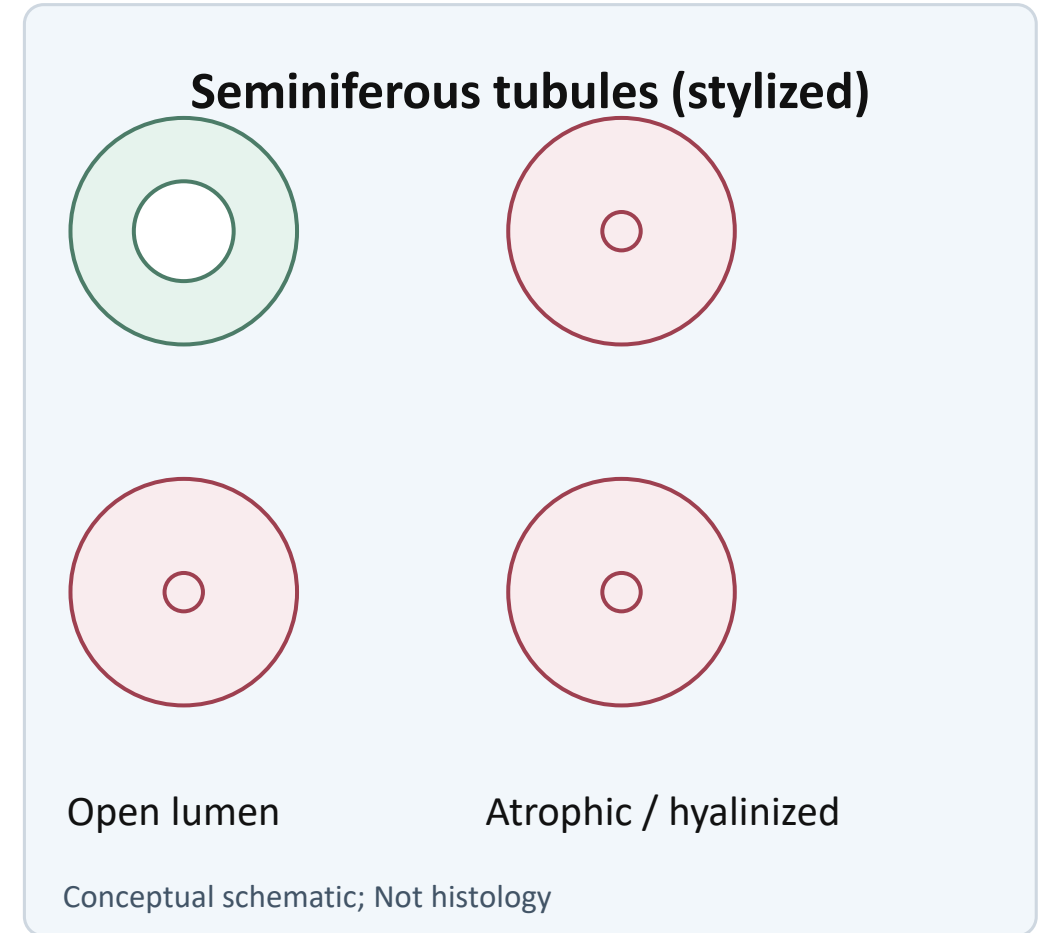
Reference dosage

47,XXY 

SHOX excess

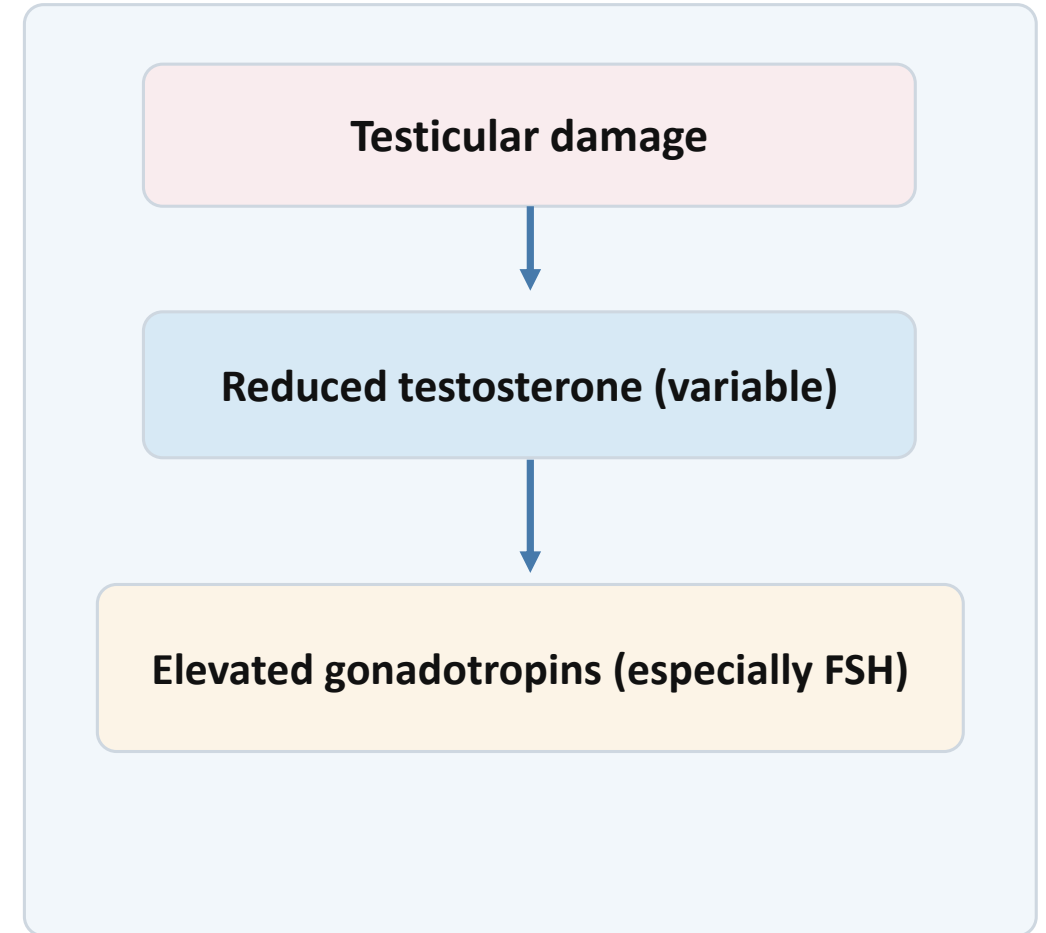
Seminiferous tubular changes explain infertility

- Seminiferous tubules may be severely atrophic and hyalinized.
- Some testes contain a mixture of preserved and atrophic tubules.
- Spermatogenesis is reduced or absent in affected tubules.



Endocrine consequence of primary testicular damage

- Follicle-stimulating hormone is consistently elevated in the source.
- Testosterone is variably reduced.
- Elevated estradiol-to-testosterone balance influences feminization.



Klinefelter syndrome: Clinical burden beyond the testes

- Insulin resistance, type 2 diabetes, and metabolic syndrome are reported.
- Osteoporosis and fracture susceptibility relate to sex hormone imbalance.
- The source also describes increased risks for selected tumors and autoimmune disease.

Klinefelter: Mechanistic explanations

Change	Mechanism	Phenotypic link
Extra active escape genes	Incomplete X silencing	Gonadal and somatic effects
Additional SHOX copy	Growth-gene excess	Tall stature and long legs
Androgen receptor variation	CAG repeat-dependent sensitivity	Variable androgen response
Testicular degeneration	Impaired endocrine / germ-cell function	Hypogonadism; Infertility

Turner syndrome: The missing-X example

- Turner syndrome involves complete or partial X monosomy.
- 45,X is the canonical complement, but mosaic and structural forms occur.
- The classic phenotype includes short stature and ovarian insufficiency.



46,XX



46,XY



47,XXY



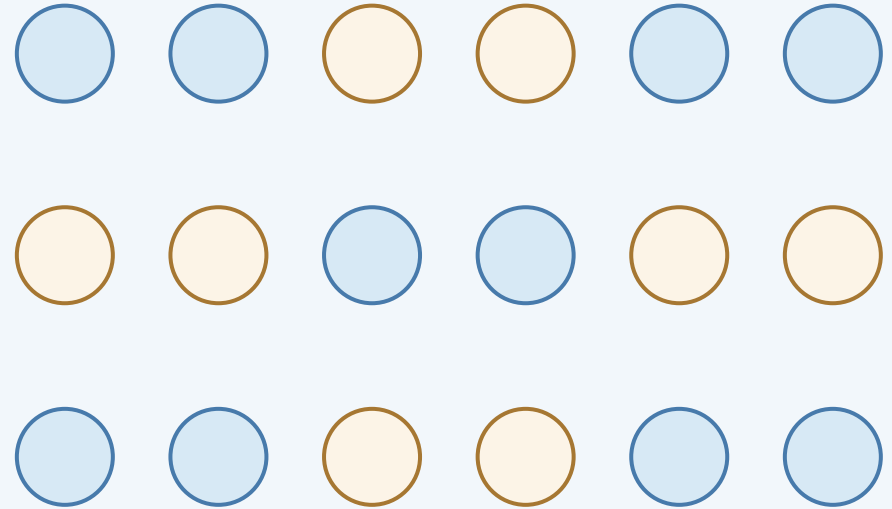
45,X

Turner syndrome includes multiple karyotypic forms

Category	Examples	Common genetic feature
Complete monosomy	45,X	Only one complete X
Structural abnormalities	l(Xq), r(X), del(X)	Functional partial X monosomy
Mosaicism	45,X/46,XX; 45,X/46,XY	Variable proportion of 45,X cells

Turner mosaicism modifies severity

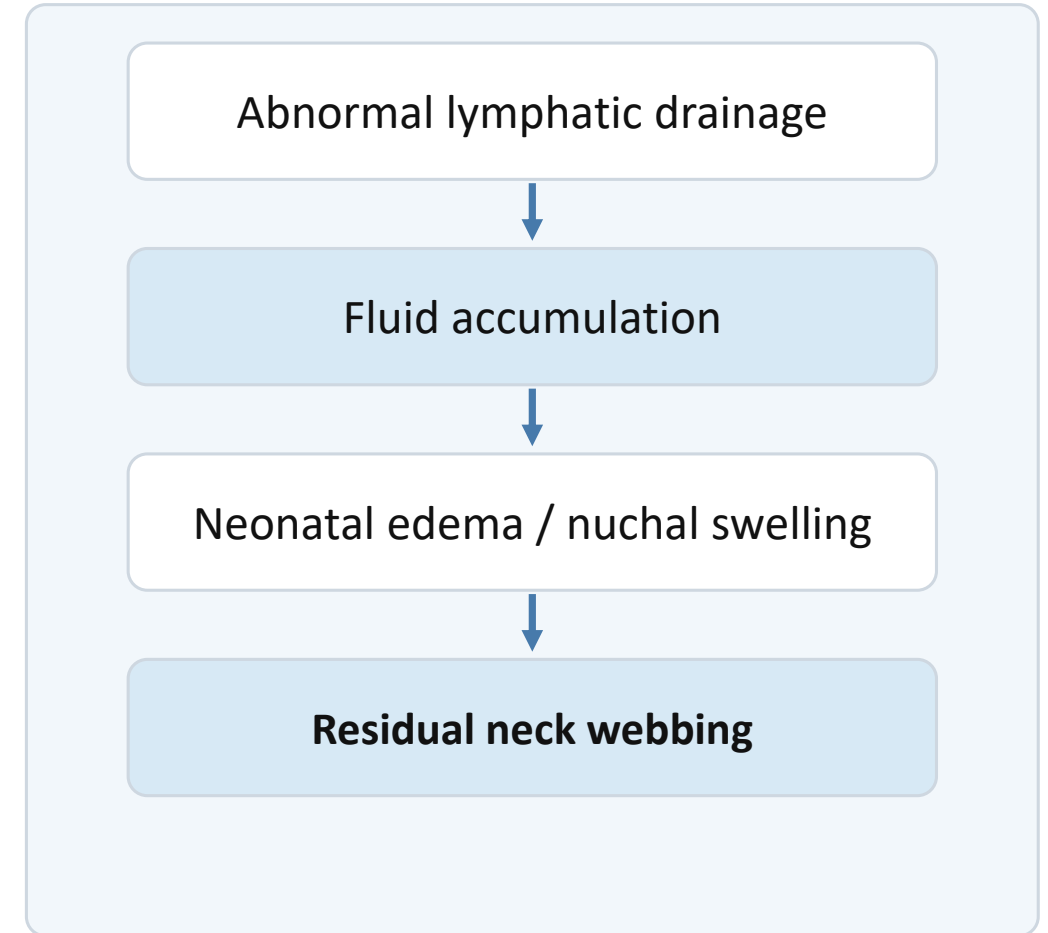
- Mosaic individuals may have attenuated somatic findings.
- A higher proportion of 45,X cells may correlate with more severe features.
- The source notes that sensitive methods detect mosaicism missed by routine testing.



Clonal cell populations

Early Turner manifestations reflect lymphatic dysfunction

- Neonatal edema can involve the dorsum of the hands and feet.
- Nuchal fluid accumulation may manifest as cystic hygroma.
- Subsequent neck webbing reflects residual tissue changes.

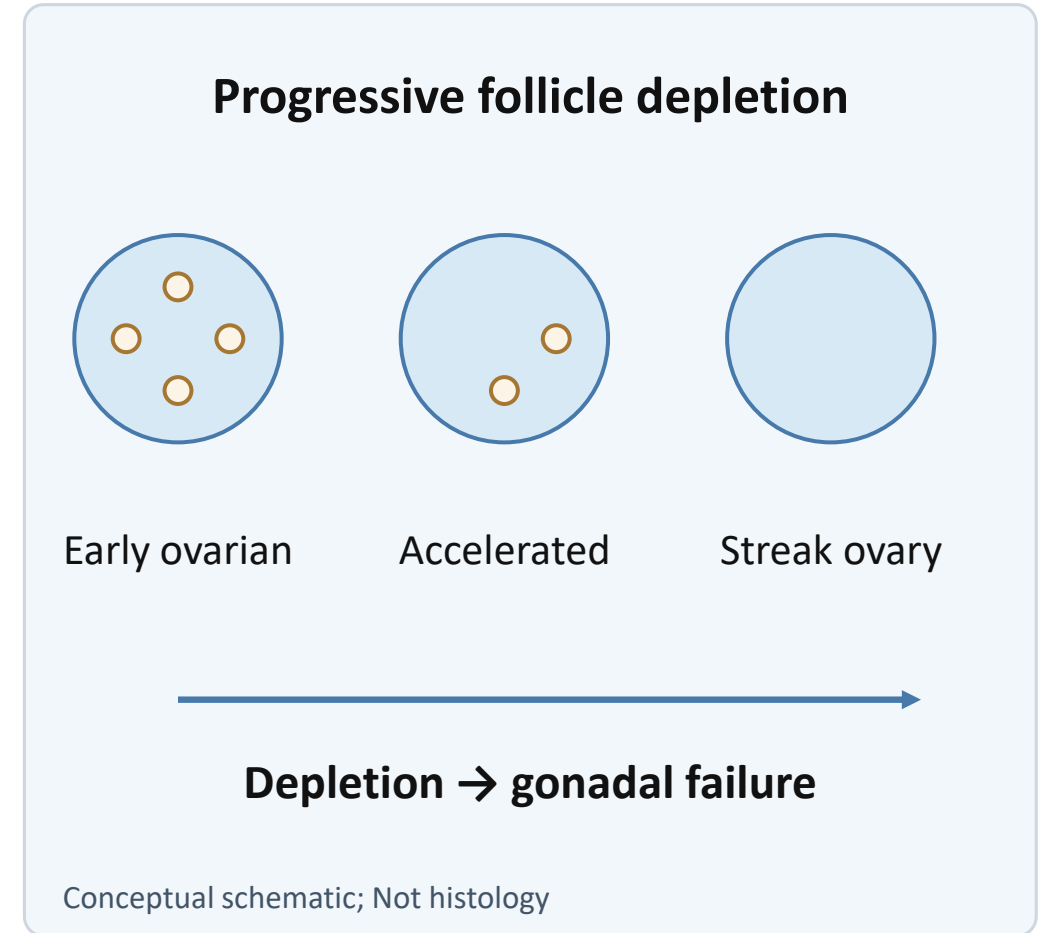


Cardiovascular defects are major Turner complications

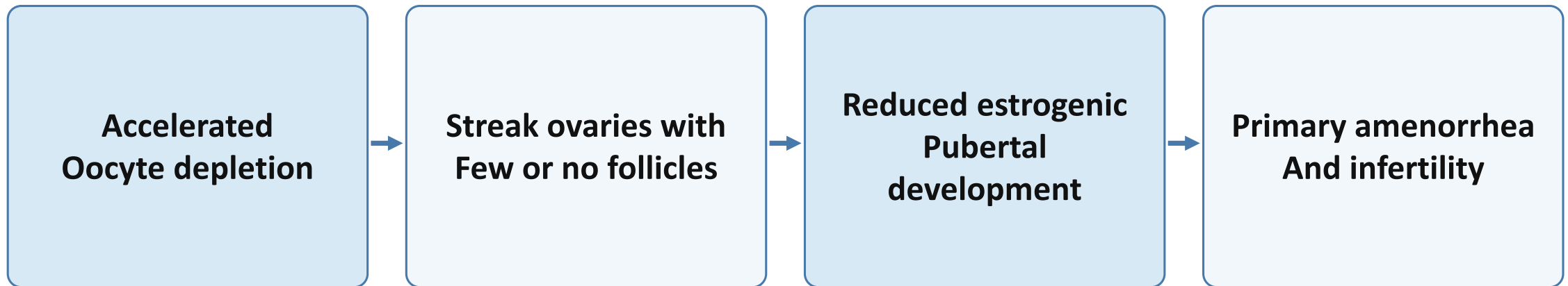
- Coarctation of the aorta and bicuspid aortic valve are characteristic.
- Aortic root dilatation and dissection risk are highlighted in the source.
- Cardiovascular abnormalities are a major contributor to excess mortality.

Ovarian failure begins with accelerated follicle loss

- Early fetal ovarian development may initially be near normal.
- Oocyte loss accelerates without the second X chromosome.
- The resulting gonads become fibrous, follicle-depleted streak ovaries.



Gonadal failure explains the reproductive phenotype



Severe ovarian depletion and resulting hypergonadotropic ovarian insufficiency.

Turner: SHOX haploinsufficiency and height

- Loss of one SHOX copy contributes to short stature.
- This locus maps to the pseudoautosomal region of Xp.
- SHOX alone does not account for the cardiac or metabolic phenotype.

45,X 
SHOX reduction

**46,XX or
46,XY** 
Reference dosage

47,XXY 
SHOX excess

Additional Turner clinical findings

- Secondary sexual development may be reduced or absent.
- Thyroid autoimmunity and clinical hypothyroidism occur in some individuals.
- Glucose intolerance, insulin resistance, and fatty liver are noted in a subset.

Y-derived material in Turner warrants attention

- Some patients carry a 45,X/46,XY mosaic complement or Y fragments.
- The source associates Y sequences with increased gonadoblastoma risk.
- Karyotype and molecular findings influence interpretation of gonadal risk.

45,X cell line

46,XY or Y-derived fragments

Mosaic / structural findings

Klinefelter and Turner: Essential differences

Feature	Klinefelter	Turner
Typical complement	47,XXY	45,X
Core gonadal finding	Testicular atrophy	Streak ovaries
Growth tendency	Tall / long legs	Short stature
Pubertal dysfunction	Male hypogonadism	Ovarian insufficiency
Fertility	Reduced spermatogenesis	Oocyte depletion
Dosage mechanism	Escape gene excess	Escape gene deficiency

Clinical presentation by age: Compare mechanisms

Stage	Typical signal	Diagnostic thinking
Neonatal	Lymphedema; Neck webbing	Consider Turner syndrome
Childhood	Disproportionate short growth	Investigate sex-chromosome dosage
Puberty	Hypogonadism; Amenorrhea	Consider XXY or X monosomy
Adulthood	Infertility; Endocrine deficits	Consider missed sex-chromosome disorder

Cytogenetic diagnosis: Questions to answer

- Is the chromosome complement numerically abnormal?
- Is there a structural X alteration?
- Is more than one cell line present?
- Is Y chromosomal material detectable in a relevant clinical setting?

Diagnostic consideration: A single cell sample can miss mosaicism

- The tissue sampled may not match the distribution in other organs.
- Mosaicism may be less evident with limited cell counts.
- A normal-appearing phenotype does not exclude a cytogenetic disorder.

Applied case: Delayed puberty and infertility

A young adult with small testes, reduced facial hair, and long legs presents for infertility evaluation. The clinical findings suggest primary testicular failure.

Which sex-chromosome complement is most characteristic?

Case interpretation: The additional X explains the syndrome

- 47,XXY is the characteristic Klinefelter complement.
- Escape-gene overdosage persists despite X inactivation.
- Atrophic seminiferous tubules help explain infertility.

Applied case: Short stature and primary amenorrhea

An adolescent with short stature and absent spontaneous menstruation is found to have a congenital left-sided cardiovascular defect.

What common chromosome abnormality links these findings?

Case interpretation: X monosomy links multiple organs

- 45,X is the classic Turner complement.
- SHOX deficiency explains an important component of short stature.
- Accelerated oocyte loss explains ovarian failure; Cardiac defects involve additional loci.

Applied case: Mosaic result with Y material

Chromosome analysis in a patient with Turner-associated findings identifies 45,X/46,XY mosaicism.

What additional gonadal risk is emphasized?

Case interpretation: Y material and gonadoblastoma

- Turner syndrome can include cell lines containing Y material.
- Y-chromosome sequences with increased gonadoblastoma risk.
- Mosaic karyotypes require interpretation beyond the headline diagnosis.

Synthesis: From chromosome to clinic

Chromosome event	Molecular consequence	Clinical correlate
Additional X	Escape-gene excess	XXY-associated hypogonadism
Missing / partial X	Escape-gene deficiency	Turner-associated growth and ovarian defects
Mosaic cell lines	Tissue-variable dosage	Variable phenotypic severity
Y material	SRY and other Y genes	Testicular differentiation / fertility pathways

Five mechanisms to retain

- Sex-chromosome imbalance is partially tolerated because most X genes are inactivated.
- XIST initiates stable silencing; Inactive X can appear as a Barr body.
- Escape and PAR genes preserve clinically relevant copy-number effects.
- SRY and other Y genes influence gonadal development and spermatogenesis.
- Extra or missing X dosage provides a mechanistic bridge to XXY and Turner phenotypes.

Core reference and source boundaries

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

Chapter 5: Genes and Human Diseases, pp. 149–152.

Primary heading: Cytogenetic Disorders Involving Sex Chromosomes.

Adjacent examples: Klinefelter Syndrome and Turner Syndrome.