

Klinefelter syndrome

Sex-chromosome aneuploidy, mechanisms, testicular pathology, and clinical effects

Robbins-based pathology lecture

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Learning objectives

- Relate a supernumerary X chromosome to a variable male phenotype.
- Explain X-inactivation escape, SHOX dosage, and androgen receptor effects.
- Recognize characteristic testicular changes and gonadotropin patterns.
- Connect infertility and systemic associations to clinicopathologic findings.

Core definition: Extra X and male hypogonadism

- Klinefelter syndrome is a sex-chromosome disorder affecting individuals with a Y chromosome and at least two X chromosomes.
- Male hypogonadism is a defining pathophysiologic feature.
- The classic chromosome complement is 47,XXY.
- Phenotype varies substantially among affected individuals.

Genotype is not the same as phenotype

Chromosomal description

- Supernumerary X chromosome in the presence of a Y chromosome.
- Classic 47,XXY or a mosaic cell population.

Clinical expression

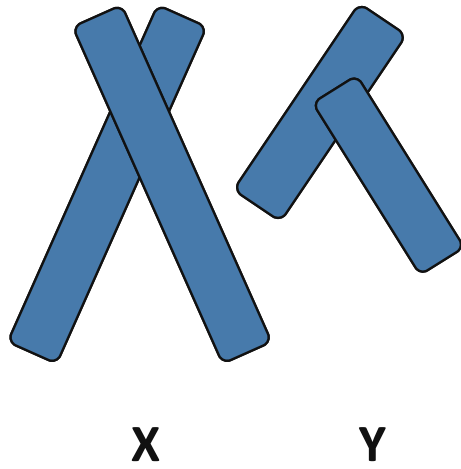
- Hypogonadism and impaired spermatogenesis are central.
- Body habitus, secondary sexual characteristics, and comorbidity vary.

Why sex-chromosome imbalances are relatively tolerated

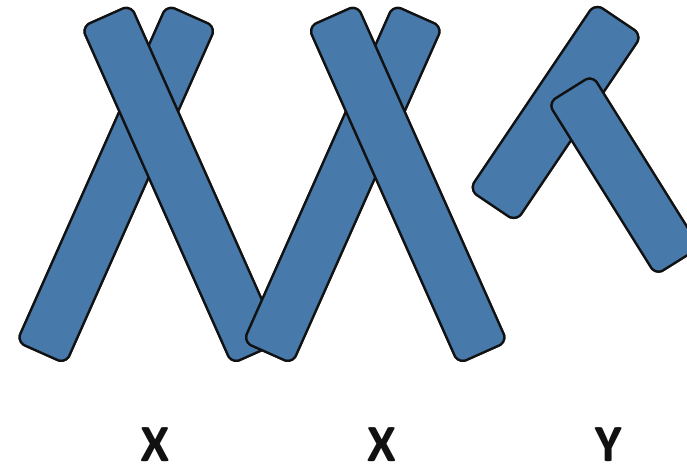
- Most genes on all but one X chromosome are inactivated.
- The Y chromosome contains less genetic material than an autosome.
- Nevertheless, genes that escape X-inactivation produce residual dosage effects.
- Reproductive development and fertility remain particularly vulnerable.

Normal male versus classic Klinefelter complement

Usual male: 46,XY



Klinefelter: 47,XXY

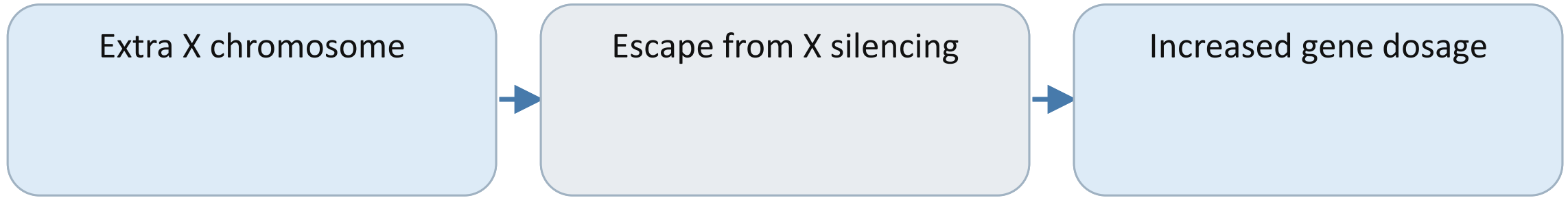


The additional X chromosome is the cytogenetic distinction illustrated here.

Y chromosome: Determinant of testicular development

- The presence of a Y chromosome generally drives male sex determination.
- SRY is located on the short arm of the Y chromosome.
- The Y chromosome also carries genes relevant to spermatogenesis.
- An additional X modifies development despite the Y chromosome.

Two interacting pathogenetic axes



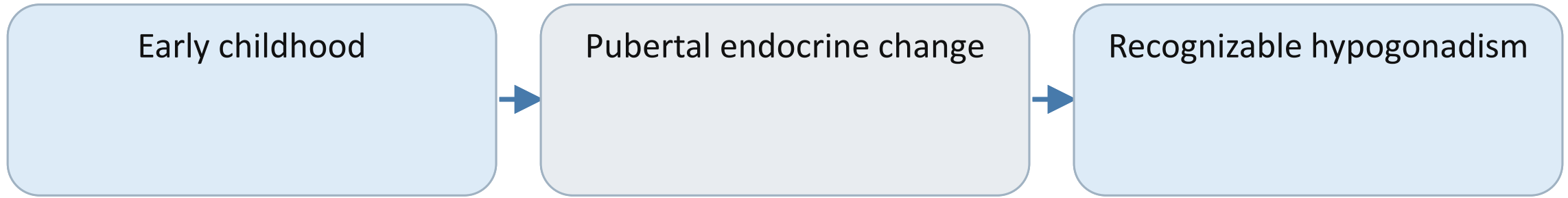
Gene-dosage effects act alongside testicular dysfunction to produce the clinical phenotype.

Hypogonadism is a second major axis, not simply a synonym for extra X dosage.

Frequency and underrecognition

- An incidence of approximately 1 in 660 live male births.
- This as an underestimate.
- Mild phenotypes may not lead to clinical assessment.
- Ascertainment therefore favors individuals with more conspicuous manifestations.

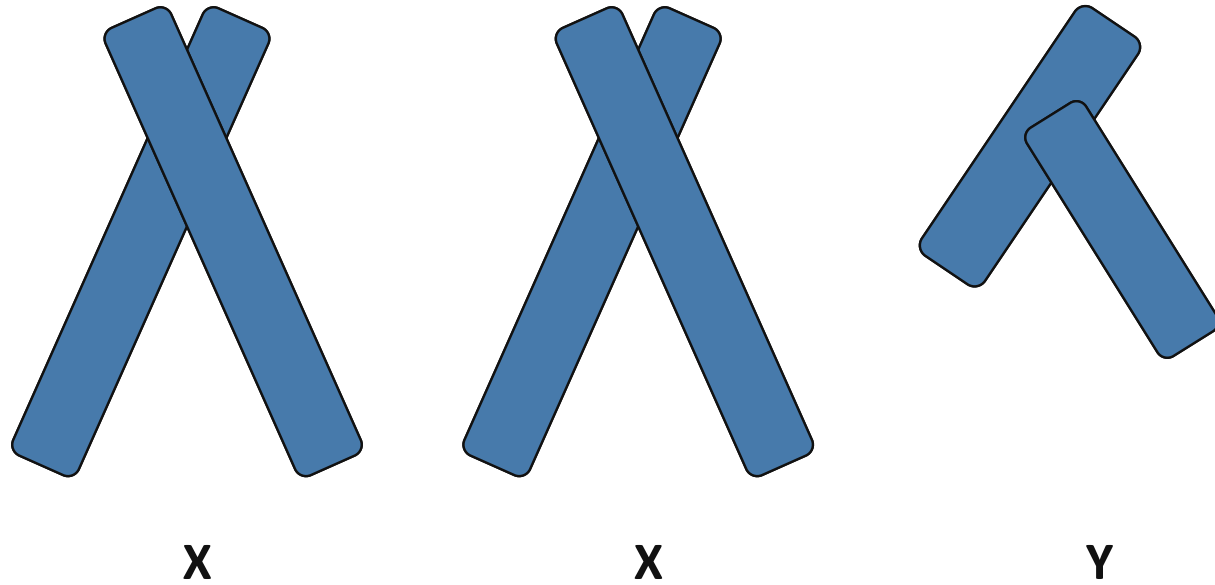
Why diagnosis commonly occurs after childhood



Before puberty, characteristic androgen-dependent clinical signs may be absent or subtle.

Clinical recognition and the presence of the genetic condition are separate issues.

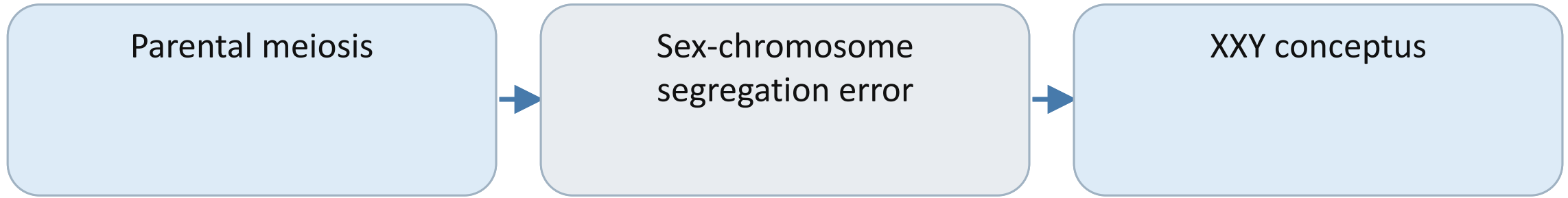
Classic karyotype: 47,XXY



47,XXY

Schematic representation: Two X chromosomes and one Y chromosome

Meiotic nondisjunction produces an extra X



Abnormal chromosome segregation during gamete formation yields the classic complement.

Maternal and paternal origins

Maternal contribution

- A segregation error in oogenesis may transmit the supernumerary X.
- The parental origin does not create a reliably distinct phenotype.

Paternal contribution

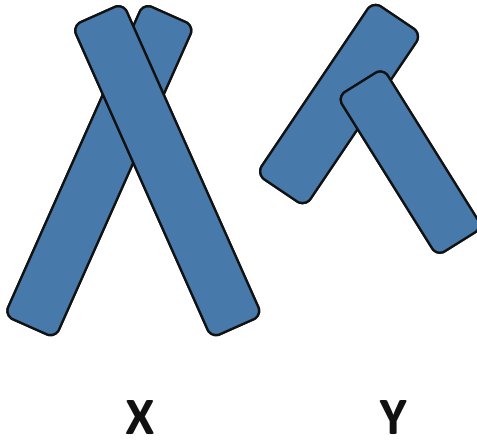
- A segregation error in spermatogenesis may likewise produce 47,XXY.
- First-meiotic-division errors from both parents.

Maternal age as a risk factor

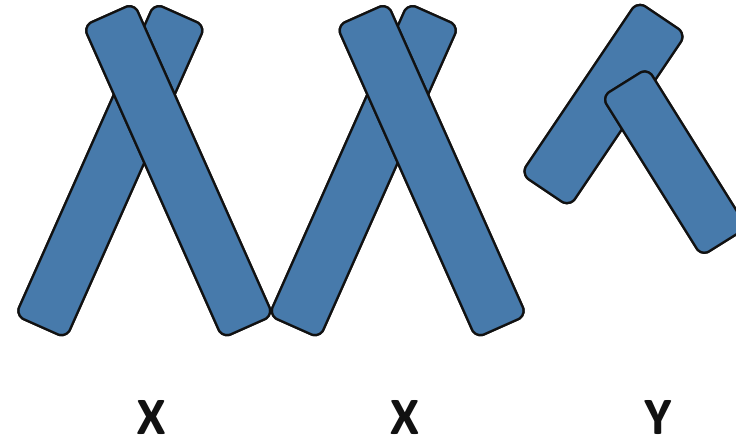
- Advanced maternal age is listed as a risk factor in the Robbins section.
- This association concerns nondisjunction risk, not a distinct subtype of the disease.
- The genetic outcome is an extra sex chromosome; Phenotype still varies afterward.

Mosaic form: 46,XY / 47,XXY

Cell line A



Cell line B



Mosaicism refers to more than one chromosomal cell population

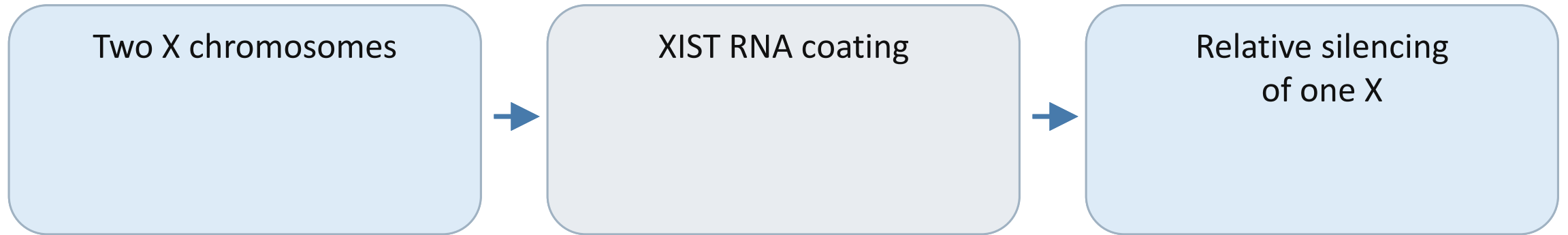
Mosaicism modifies chromosomal composition

- Mosaic patients contain distinct cell populations with different complements.
- A frequent reported pattern combines 46,XY and 47,XXY cells.
- The tested tissue and its cell populations matter when interpreting mosaicism.
- Karyotypic heterogeneity is one contributor to overall clinical variability.

Structural-X variants beyond simple XXY

- The textbook also describes rare cell lines bearing structurally abnormal X chromosomes.
- An isochromosome involving the X long arm is given as an example.
- These are chromosomal variants, not evidence that all cases are simple 47,XXY.
- Karyotype interpretation should distinguish number from structure.

Lyonization: One X largely remains active

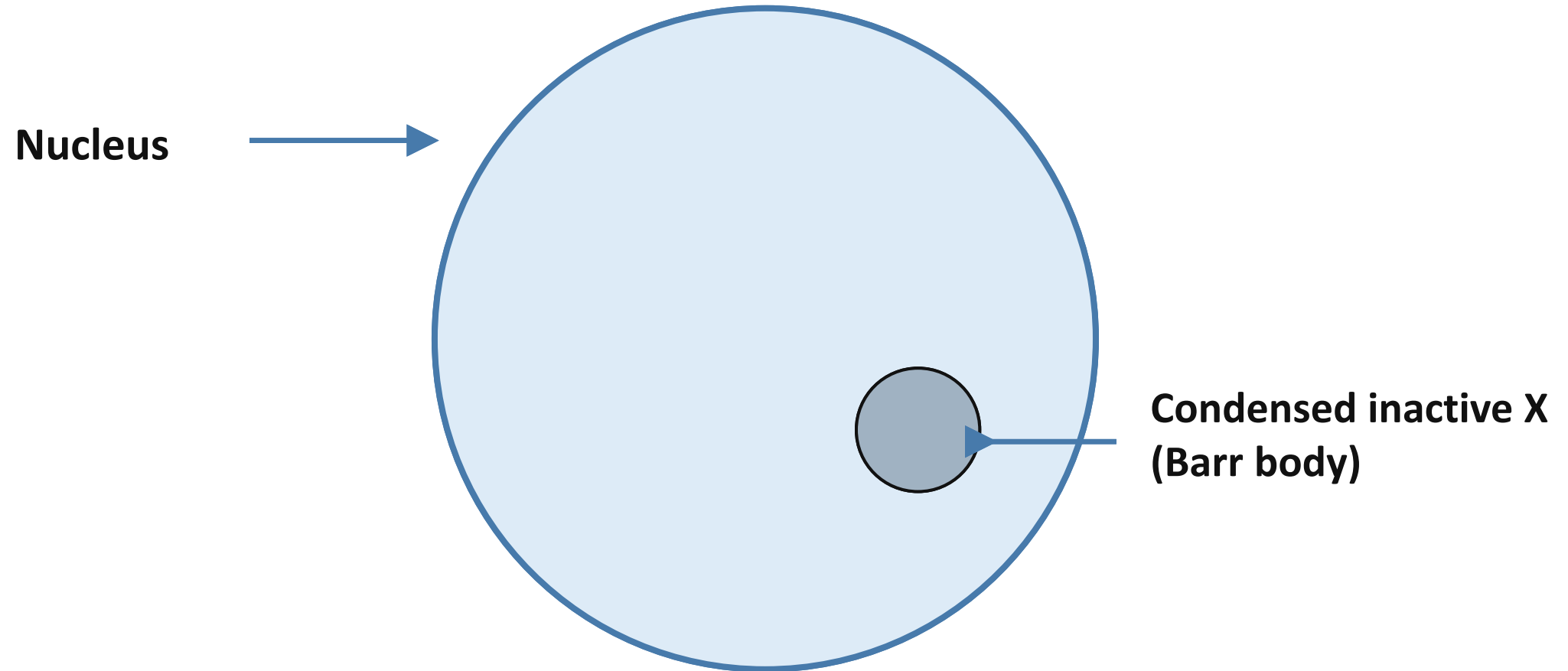


Some loci escape inactivation, so dosage compensation is incomplete.

X-inactivation provides partial dosage compensation

- In cells with multiple X chromosomes, all but one undergo X-inactivation.
- Silencing occurs early in embryogenesis and is maintained in descendant cells.
- This produces a functional mosaic of maternal-X and paternal-X activity.
- Silencing is incomplete at some loci, explaining persistent dosage effects.

Barr body: The inactive X chromosome

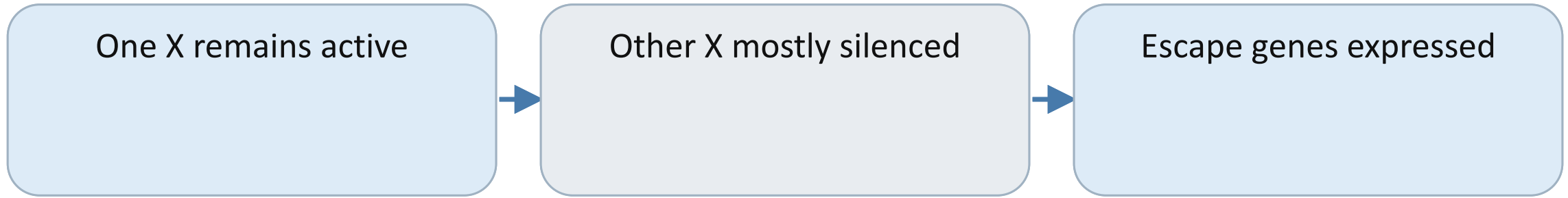


Schematic: Condensed nuclear chromatin, not a diagnostic micrograph

XIST is a noncoding RNA with a silencing role

- XIST is transcribed at the X-inactivation center.
- The RNA coats the chromosome from which it is expressed.
- Chromatin changes and DNA methylation contribute to silencing.
- The active X does not express XIST in the same way.

X-inactivation does not silence every locus

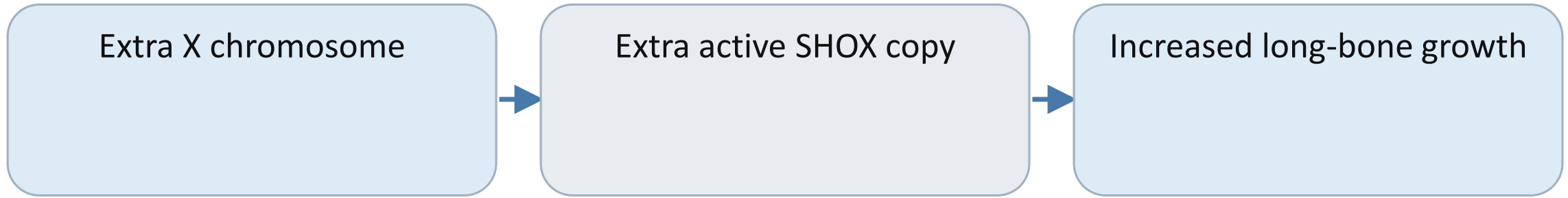


Genes that escape Lyonization can have increased copy-dependent output in XXY cells.

Pseudoautosomal regions escape silencing

- The ends of the X and Y chromosomes share homologous pseudoautosomal regions.
- These regions recombine during meiosis.
- Their genes commonly escape X-inactivation.
- Additional active copies can influence somatic development.

SHOX dosage helps explain tall stature



Additional SHOX dosage as a probable contributor to tall stature and long legs.

Proposed genotype–phenotype link; Body proportions are not universal.

Extra X alters more than X-linked transcription

- The source states that many upregulated transcripts lie outside the X chromosome.
- The supernumerary X can influence expression of autosomal genes indirectly.
- Gene-dosage effects therefore need not be restricted to X-linked proteins.
- This is a genomic regulatory effect, distinct from testicular hormone deficiency.

The androgen receptor is X-linked

- The androgen receptor gene is located on the X chromosome.
- The receptor mediates target-cell responses to testosterone.
- Polymorphic CAG trinucleotide repeats influence receptor activity.
- Hormone concentration alone may not capture the tissue androgen response.

CAG-repeat length and receptor sensitivity

Shorter androgen-receptor CAG repeat

Greater sensitivity to a given androgen dose

Potentially stronger receptor-mediated response

Source relationship: relative functional sensitivity

Longer androgen-receptor CAG repeat

Lower sensitivity to a given androgen dose

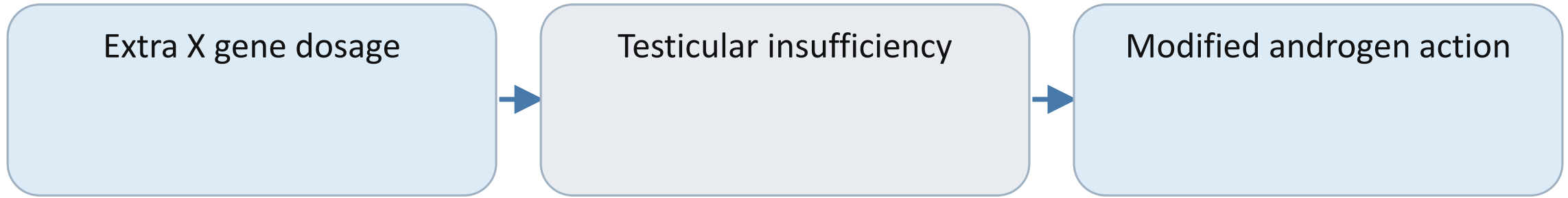
Potentially weaker receptor-mediated response

Repeat length is not itself a clinical diagnosis

Preferential inactivation may modify androgen effects

- Preferential inactivation of the X carrying the shorter CAG-repeat androgen receptor allele.
- The expressed receptor may therefore be comparatively less androgen-sensitive.
- At lower testosterone concentrations, this may amplify the hypogonadal phenotype.
- The textbook associates this model with some genital-development features.

Integrated molecular-to-hormonal phenotype



Gene dosage, gonadal impairment, and receptor sensitivity jointly contribute to variable findings.

Conceptual integration of textbook-described contributors.

Hypogonadism becomes clearer around puberty

- Puberty normally increases demand for testosterone-dependent development.
- Klinefelter syndrome may become conspicuous when androgen-dependent changes are inadequate.
- Presentation before puberty is less common.
- Timing of recognition does not determine the origin of the chromosome abnormality.

Body proportions and skeletal phenotype

Typical pattern

- Tall or elongated body habitus.
- Relatively long legs with increased sole-to-pubic-bone length.
- SHOX dosage is a proposed molecular explanation.

Interpretive caution

- Neither height nor limb length is diagnostic alone.
- Physical attributes vary substantially.
- Karyotype and gonadal phenotype are more informative together.

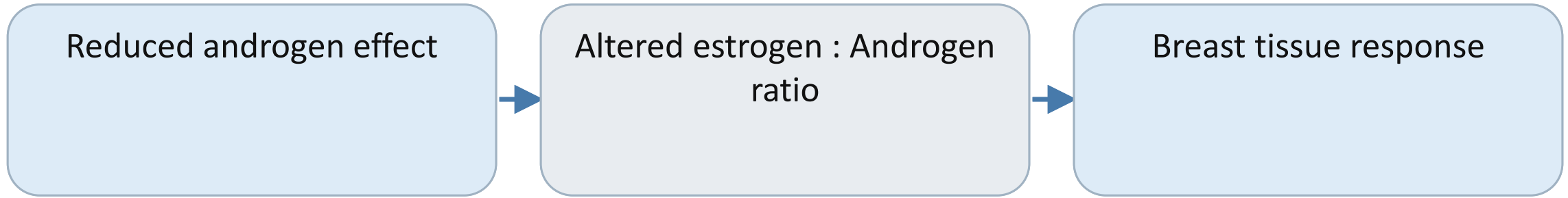
Small testes are a central morphological finding

- The source describes testes as small and atrophic.
- Atrophy reflects loss or failed maturation of the seminiferous tubular compartment.
- Testicular size connects cytogenetic disease with endocrine and reproductive failure.
- Other somatic characteristics may be inconspicuous despite gonadal pathology.

Incomplete masculinization of secondary characteristics

- Some patients lack the typical deepening of the voice.
- Beard development and male-pattern pubic hair may be reduced.
- The penis may be relatively small in affected individuals.
- These are examples of variable androgen-dependent features, not universal signs.

Gynecomastia reflects hormonal balance



Estradiol levels may be higher while testosterone is variably reduced; The balance influences feminization.

The precise mechanism responsible for higher estradiol is described as unknown.

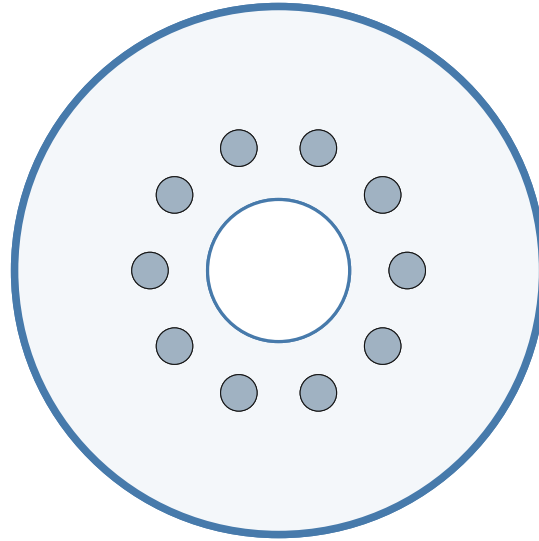
Cognitive phenotype: Avoid overgeneralization

- Cognitive performance ranges from average to below average description.
- Modest difficulties may involve verbal skills.
- Reading and language comprehension are specifically mentioned.
- The chromosomal diagnosis does not predict uniform intellectual impairment.

Phenotypic variability is fundamental

- An individual may not show the complete traditional constellation of findings.
- Degree of hypogonadism differs between affected persons.
- X-inactivation patterns, mosaicism, and receptor variation offer plausible modifiers.
- The source emphasizes hypogonadism as the most consistent feature.

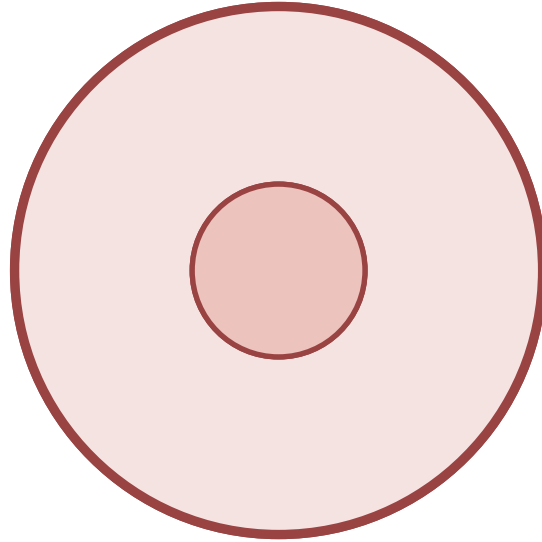
Normal-appearing seminiferous tubule: Conceptual reference



**Patent lumen with
cellular rim**

Schematic only: Provides architectural context for the abnormal patterns.

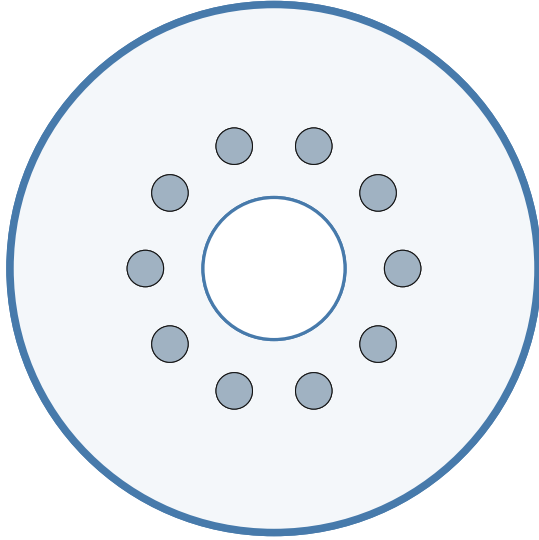
Atrophic tubule with hyaline replacement



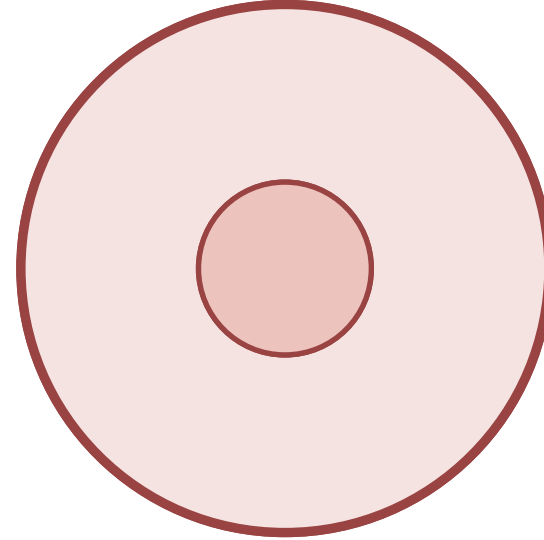
Hyalinized tubular ghost

The source describes pink, hyaline, collagenous remnants when atrophy is advanced.

Mixed preservation and atrophy



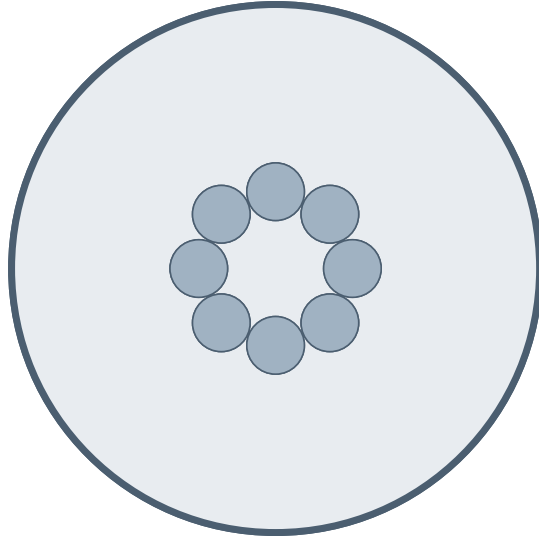
Relatively preserved



Atrophic / hyalinized

Apparently normal tubules interspersed with atrophic tubules in some patients.

Primitive tubules may fail to form a lumen



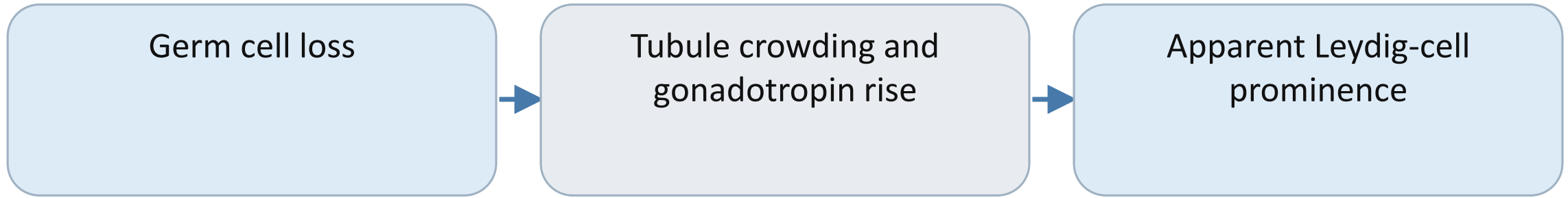
**Primitive solid cellular
cord**

Embryonic-appearing cords may remain without lumen formation or mature spermatogenesis.

Tubular pathology can be heterogeneous

- Complete tubular loss with hyaline ghosts is one described pattern.
- Patchy preserved and atrophic tubules represent another pattern.
- Primitive, non-lumen-forming cords are also reported.
- These patterns converge on diminished mature sperm production.

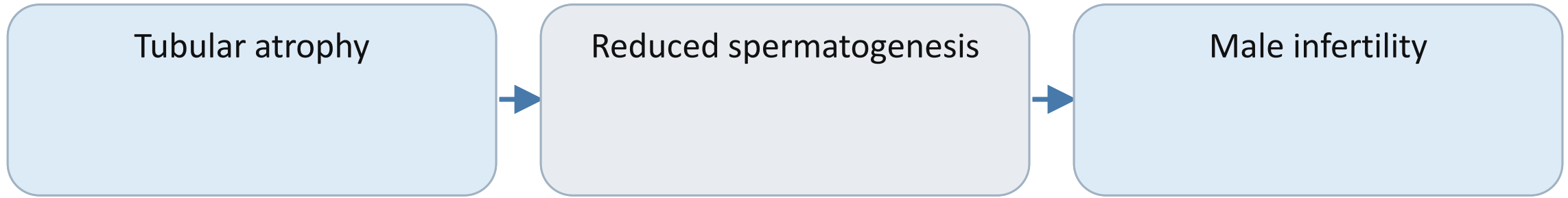
Leydig cells may appear relatively prominent



The textbook attributes prominence partly to the reduction of surrounding tubular components.

This does not establish that increased Leydig-cell function compensates effectively.

How testicular changes impair fertility



The principal reproductive consequence is reduced production of mature sperm.

Infertility is a major route to recognition

- Klinefelter syndrome is an important genetic cause of male infertility.
- Testicular damage can impair spermatogenesis even when somatic signs are subtle.
- The degree of tubular preservation may vary histologically.
- A fertility presentation should prompt integration of gonadal and chromosomal findings.

Gonadotropins are characteristically elevated

- The source describes elevated plasma gonadotropin concentrations.
- Follicle-stimulating hormone (FSH) is particularly consistently increased.
- The endocrine pattern accompanies testicular dysfunction.
- Klinefelter syndrome is therefore a form of primary gonadal failure.

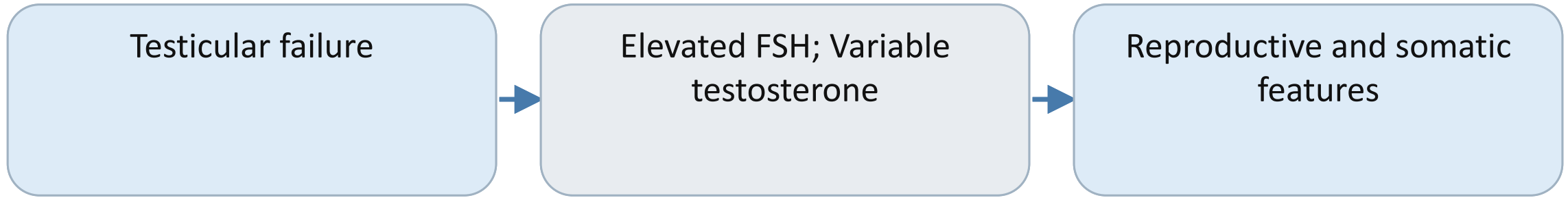
Testosterone is variably reduced

- Testosterone concentration is not uniformly low in all cases.
- The degree of androgen deficiency influences clinical expression.
- Some physical signs are consequences of reduced androgen action.
- The hormone profile must be interpreted alongside the testes and karyotype.

Estradiol and androgen balance

- Mean estradiol concentrations are reported as higher in affected individuals.
- The mechanism remains unknown.
- The estrogen-to-testosterone balance modifies the degree of feminization.
- Avoid attributing a single proven biochemical pathway without further evidence.

Endocrine, tissue, and clinical integration



Tubular atrophy, impaired spermatogenesis, and altered sexual characteristics are linked findings.

The endocrine flow is a conceptual causal synthesis, not a diagnostic cutoff algorithm.

Clinicopathologic connections

Finding	Source-based interpretation
Elevated FSH	Testicular dysfunction with a hypergonadotropic pattern
Small atrophic testes	Tubular impairment and reduced germ cell function
Variable testosterone	Heterogeneous androgen-dependent manifestations
Reduced spermatogenesis	Potential infertility
Gynecomastia	Altered sex-steroid balance

Metabolic associations

- Increased type 2 diabetes frequency.
- Metabolic syndrome and insulin resistance are also described.
- These are comorbid associations rather than defining diagnostic criteria.
- Clinical assessment should not focus exclusively on infertility.

Skeletal complications reflect sex-steroid imbalance

- Osteoporosis is more frequent account.
- Fracture risk is correspondingly increased.
- Sex-hormonal imbalance is the suggested contributing mechanism.
- Skeletal consequences illustrate the systemic impact of hypogonadism.

Cardiovascular associations reported by Robbins

- Congenital heart disease is reported more often.
- Mitral valve prolapse is highlighted.
- Atrial and ventricular septal defects are also mentioned.
- These associations are not required to recognize the syndrome.

Extragonadal germ-cell tumor association

- An increased risk of extragonadal germ-cell tumors.
- The mediastinum is the emphasized site.
- Mediastinal teratoma is given as an example.
- This is an important neoplastic association, not a diagnostic requirement.

Additional breast and autoimmune associations

- The source describes a higher frequency of breast cancer.
- Autoimmune disorders, particularly systemic lupus erythematosus, are also reported more often.
- These associations should be separated from the direct gonadal histopathology.
- Risk associations do not mean each patient will develop these conditions.

Typical manifestations: Direct effects and associations

Core disease expressions

Small atrophic testes; reduced spermatogenesis

Elevated FSH; variable testosterone

Variable virilization; long legs; gynecomastia

Infertility

Systemic associations

Type 2 diabetes / metabolic syndrome

Osteoporosis and fractures

Congenital cardiac abnormalities

Mediastinal germ-cell tumors; breast cancer; autoimmunity

Application case: Puberty and hypogonadism

A male adolescent has disproportionately long legs, small testes, and incomplete development of secondary sexual characteristics.

Which chromosomal complement would unify the phenotype?

Classic 47,XXY is a leading mechanistic possibility; Chromosomal testing would establish the complement.

Application case: Infertility and tubular atrophy

An adult with reduced sperm production is found to have small testes, increased FSH, and variable testosterone concentration.

What links the reproductive and endocrine findings?

Primary testicular dysfunction with seminiferous tubular impairment links these observations.

Application case: Interpreting testicular architecture

A conceptual pathology drawing shows seminiferous structures replaced by hyaline collagenous remnants; Other tubules are better preserved.

Why can different tubules have different appearances?

Heterogeneous tubular atrophy, ranging from patchy preservation to hyaline ghosts.

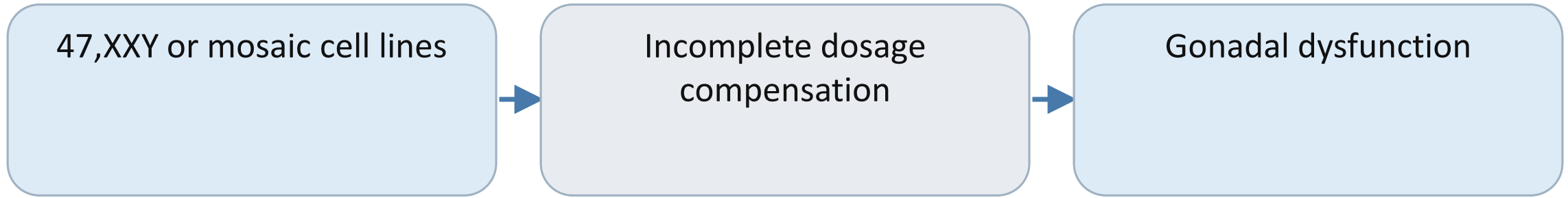
Klinefelter and Turner: Sex-chromosome contrast

Feature	Klinefelter syndrome	Turner syndrome
Representative karyotype	47,XXY	45,X
Gonadal phenotype	Male hypogonadism	Female hypogonadism
Sex-chromosome imbalance	Supernumerary X	Loss of all or part of an X
Common theme	Abnormal gene dosage and fertility	Abnormal gene dosage and fertility

Pitfalls in interpreting phenotype

- Do not exclude an extra X chromosome solely because body habitus appears typical.
- Do not assume severe cognitive impairment from karyotype alone.
- Do not equate a variable testosterone level with absence of testicular pathology.
- Do not infer the complete karyotype from a single clinical feature.

Synthesis: From chromosome complement to tissue changes



The characteristic outcome is hypogonadism, with broad variation in somatic manifestations.

Reduced spermatogenesis, elevated FSH, and tubular atrophy link mechanism to pathology.

Major clinicopathologic conclusions

- An additional X chromosome acts through incompletely silenced genes and altered regulation.
- SHOX dosage contributes to body proportions; Androgen-receptor variation can modify response.
- Testicular tubular pathology underlies impaired sperm formation and a hypergonadotropic pattern.
- Clinical expression and systemic associations are heterogeneous.

Source and limits of this lecture

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 5, “Genes and Human Diseases”: sex-chromosome disorders and Klinefelter syndrome.
- Figures in this lecture are original, simplified editable schematics; no histological specimen images are reproduced.
- Diagnostic algorithms, treatment recommendations, and changing practice guidelines were outside the supplied excerpt.