

# X-Linked Disorders

Inheritance • mosaicism • disease mechanisms

Core principles

Clinical examples

Pedigree reasoning

**Dr Abu Suraih Sakhri**

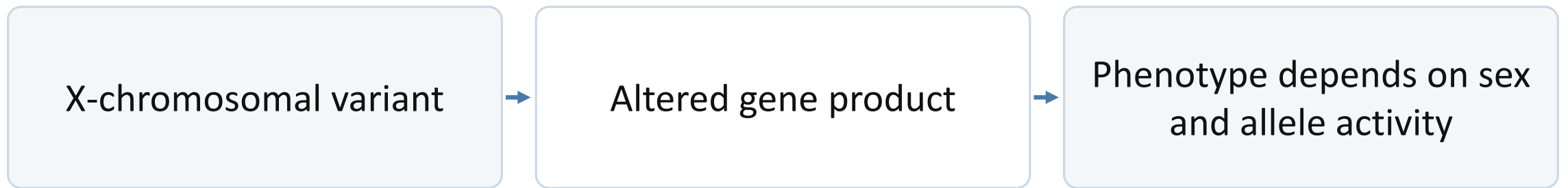
MBBS, MD (Pathology)

[www.abusuraihsakhri.com](http://www.abusuraihsakhri.com)

# Learning objectives

- Identify characteristic X-linked recessive and dominant pedigrees.
- Predict offspring genotypes using parental sex chromosomes.
- Explain how X-inactivation creates phenotypic mosaicism.
- Relate representative gene defects to their clinical manifestations.
- Recognize exceptions to simplified inheritance rules.

## The affected gene lies on the X chromosome



**X-linked describes locus; Recessive versus dominant describes expression and transmission.**

# The X and Y chromosomes are not equivalent

## X chromosome

Many genes have no functional counterpart on Y.

Pathogenic X variants may be unopposed in XY individuals.

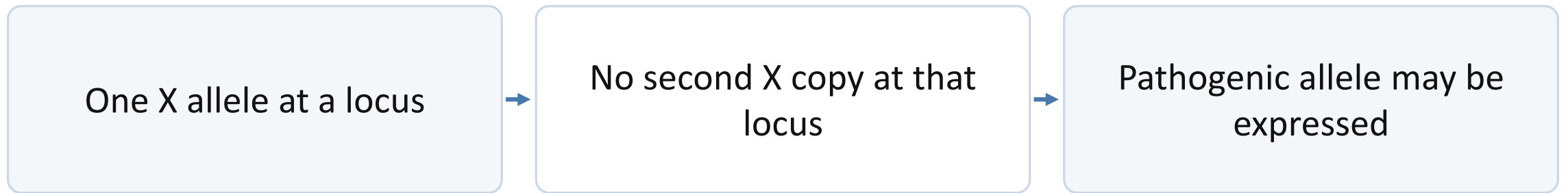
## Y chromosome

Its male-specific region encodes fewer genes.

Many Y-linked genes relate to spermatogenesis.

**The pseudoautosomal regions are an important exception.**

# Hemizyosity explains male vulnerability



*Hemizygous means one allele copy at a locus, not two identical mutant alleles.*

# Sex chromosome origin determines paternal transmission

Father: X / Y



Father gives Y to sons

Mother: X / X



Father gives X to daughters

**An X-linked allele is not passed directly from father to son.**

## Pseudoautosomal regions: A boundary to the rule

### Not every gene on X lacks a corresponding copy on Y

- Some genes occur in homologous pseudoautosomal regions of both sex chromosomes.
- The classic hemizygous-X model applies most directly outside these regions.
- Rare pathogenic variants in pseudoautosomal genes may show different transmission.

# What makes X-linked recessive disease “recessive”?

Carrier XX individual: A normal allele often compensates



XY individual: Pathogenic allele is unopposed



Clinical expression depends on the gene and cellular context

*“Recessive” does not mean every heterozygous female is symptom-free.*

# Carrier mother: Four equally likely chromosome combinations

Assume  $X^N X^m$  mother and  $X^N Y$  father

Mother  $X^N X^m$

×

Father  $X^N Y$

$X^N X^N$  daughter

$X^N X^m$  daughter

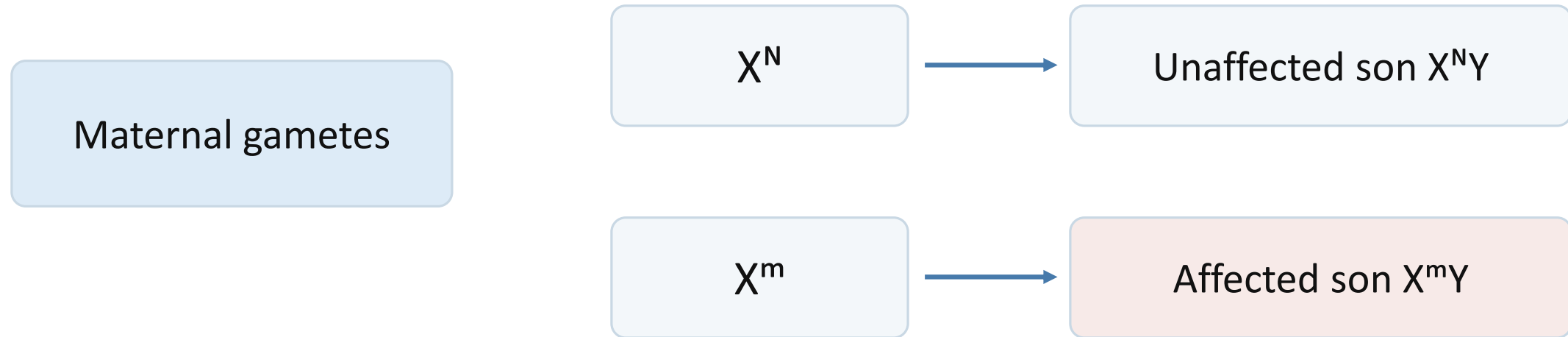
$X^N Y$  son

$X^m Y$  son

Among sons: 1 in 2 affected; Among daughters: 1 in 2 carriers.

# Risk to a son of a heterozygous mother

A son receives his single X chromosome from his mother



Each son independently has a 50% chance of inheriting the maternal variant.

## Risk to a daughter of a heterozygous mother

Each daughter receives paternal  $X^N$  plus one maternal X

Maternal  $X^N$



$X^N X^N$  noncarrier

Maternal  $X^m$



$X^N X^m$  carrier

One in two daughters inherit the pathogenic X allele.

## Affected father with an unaffected mother

Assume  $X^mY$  father and  $X^N X^N$  mother

Father  $X^mY$

×

Mother  $X^N X^N$

$X^N X^m$  daughter

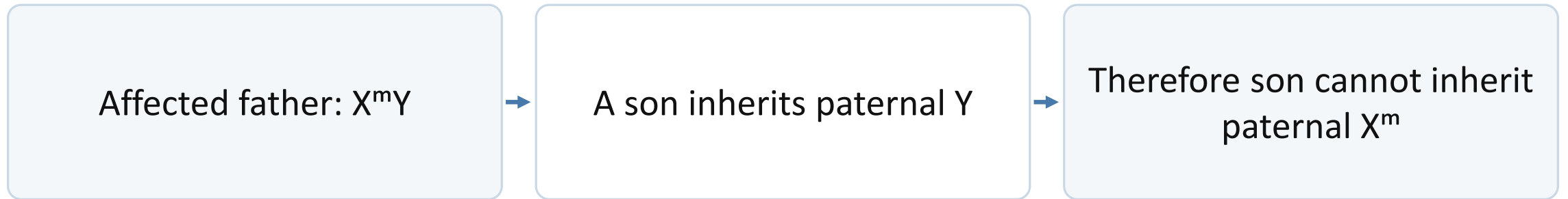
$X^N X^m$  daughter

$X^N Y$  son

$X^N Y$  son

All daughters inherit  $X^m$ ; No sons inherit their father's  $X^m$ .

## Why father-to-son transmission is absent



*This excludes direct paternal transmission of the X variant; A son may still be affected via his mother.*

# Why daughters of an affected man are obligate carriers

Father passes  $X^m$  to every daughter



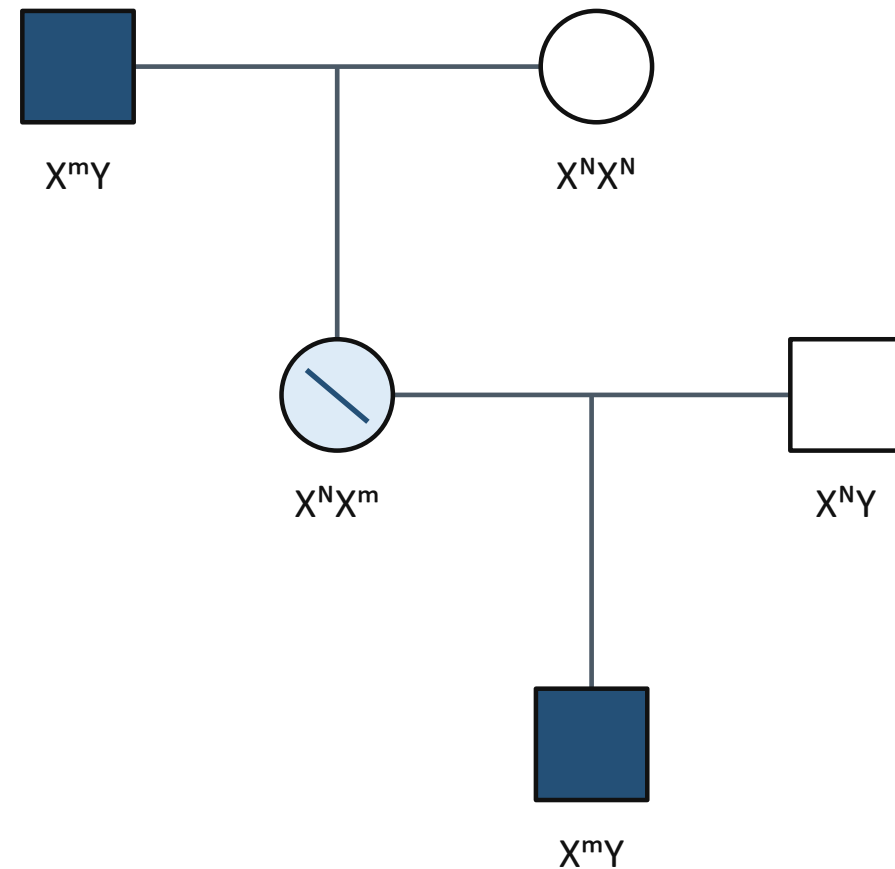
Unaffected mother passes  $X^N$



Every daughter is  $X^N X^m$

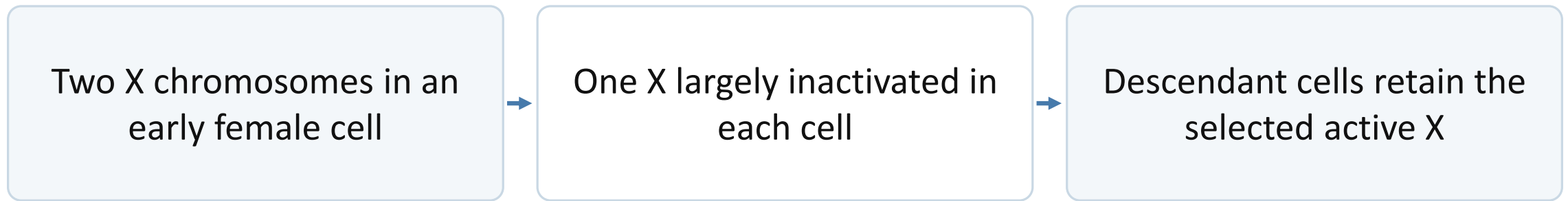
*Assumes a classic X-linked recessive allele and unaffected, noncarrier mother.*

# An X-linked recessive pedigree can skip generations



Filled square = affected male Slashed circle = carrier female Open symbol = unaffected

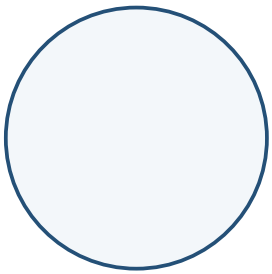
## X-inactivation: One X is transcriptionally silenced



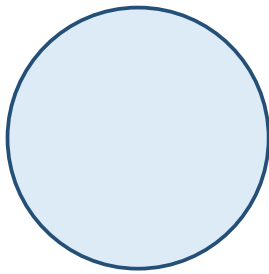
*This dosage-compensation process creates cellular mosaicism in heterozygotes.*

# Random X-inactivation produces two cell populations

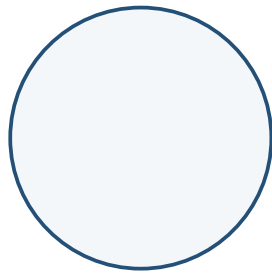
**Heterozygous  $X^N X^m$  individual**



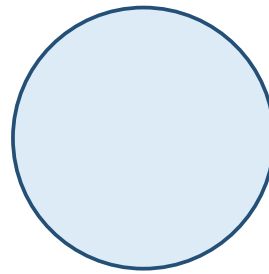
$X^N$  active



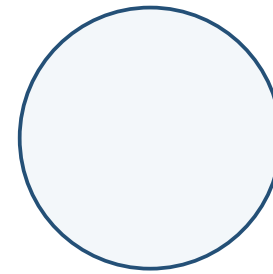
$X^m$  active



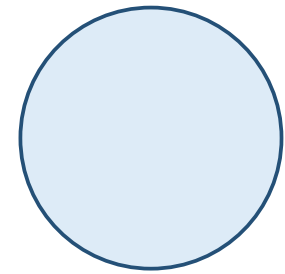
$X^N$  active



$X^m$  active



$X^N$  active



$X^m$  active

**A tissue may contain mixtures of cells expressing different X alleles.**

# Skewed X-inactivation changes phenotypic expression

## Relatively balanced activation

Cells expressing  $X^N$  and  $X^m$  coexist.

Clinical effect may be attenuated.

## Skewed activation

One X is active in more cells.

Phenotype shifts toward the active allele.

**Skewing can modify heterozygous female manifestations.**

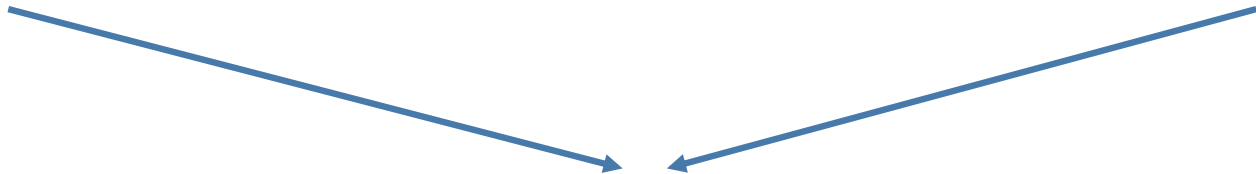
## A carrier state does not guarantee an absent phenotype

- Heterozygous females often retain enough normal gene product to be unaffected.
- X-inactivation may leave a functionally important fraction of cells expressing the mutant allele.
- Skewing can increase or decrease disease expression.
- Consequently, family history alone cannot define clinical severity.

## Red-cell mosaicism gives a measurable example

Normal-G6PD erythroid clones

Deficient-G6PD erythroid clones

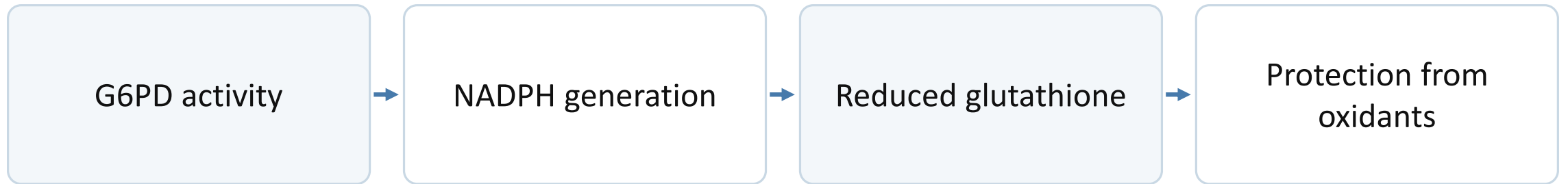


```
graph TD; A[Normal-G6PD erythroid clones] --> C[Mixed population of circulating erythrocytes]; B[Deficient-G6PD erythroid clones] --> C;
```

Mixed population of circulating erythrocytes

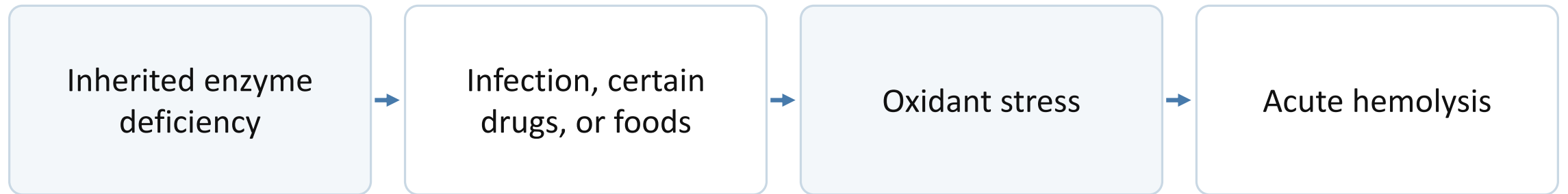
**Only the enzyme-deficient fraction is especially vulnerable to oxidant stress.**

# G6PD: The biochemical defense against oxidants



**Enzyme deficiency weakens erythrocyte protection from oxidative injury.**

## G6PD deficiency is often unmasked by exposure



*A molecular defect can remain clinically silent until an environmental trigger.*

## Why older G6PD-deficient erythrocytes are vulnerable

- Mature red cells cannot synthesize new proteins.
- Some G6PD variants yield enzyme with reduced stability.
- With erythrocyte aging, protective enzyme activity may decline.
- Oxidative challenge preferentially injures insufficiently protected cells.

# G6PD heterozygotes: Disease risk is not all-or-none

## Hemizygous affected male

All erythroid precursors carry the pathogenic X allele.

Many red cells share the enzymatic vulnerability.

## Heterozygous female

Two erythrocyte populations may coexist.

Clinical hemolysis remains possible.

**The proportion of susceptible red cells reflects X-inactivation.**

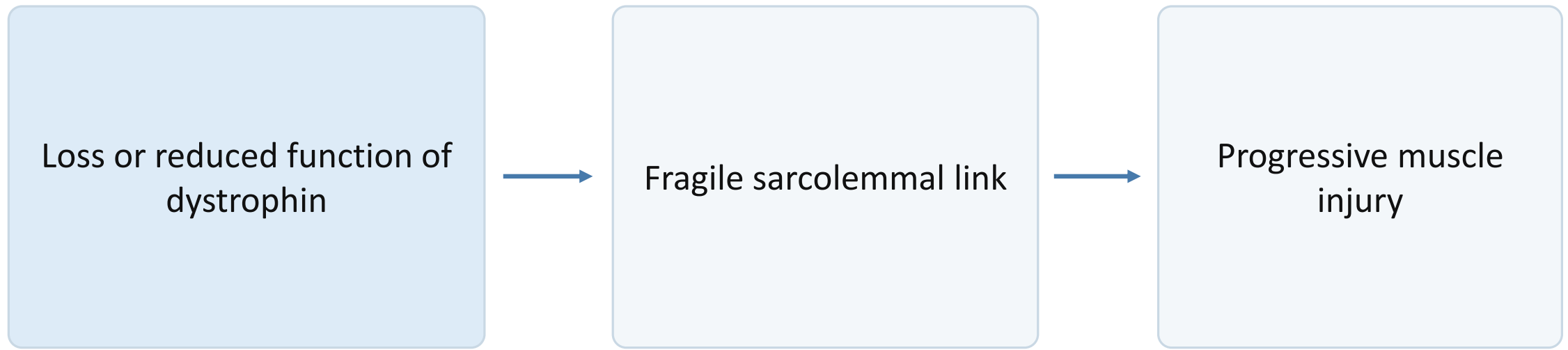
## Robbins groups X-linked disorders across organ systems

| System          | Examples in Table 5.3                          |
|-----------------|------------------------------------------------|
| Musculoskeletal | Duchenne muscular dystrophy                    |
| Hematopoietic   | Hemophilia A/B; CGD; G6PD deficiency           |
| Immune          | Agammaglobulinemia; Wiskott–Aldrich            |
| Metabolic       | Diabetes insipidus; Lesch–Nyhan                |
| Nervous         | Fragile X syndrome (inheritance is nonclassic) |

*Table groupings follow Robbins; They are not substitutes for gene-specific classification.*

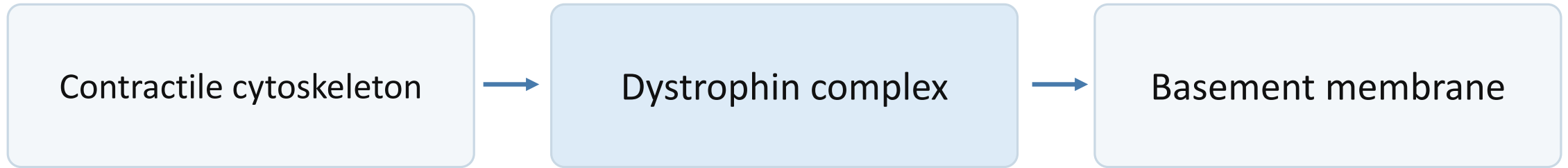
# Dystrophinopathy: X-linked structural-protein disease

## DMD gene variant



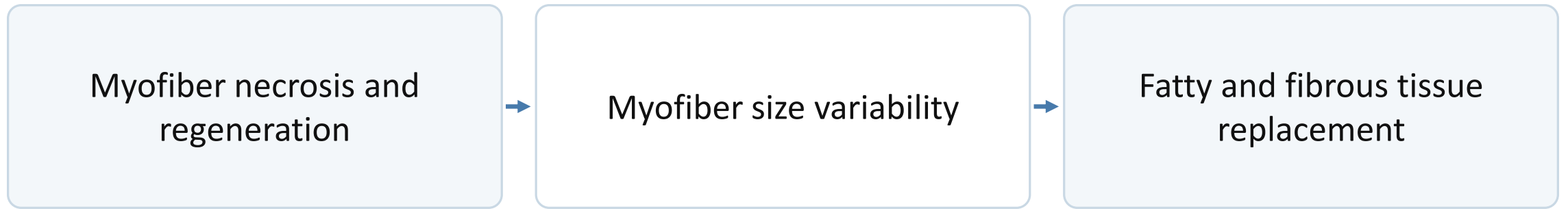
# Dystrophin links muscle cytoskeleton to matrix

## Simplified membrane-support schematic



Membrane fragility → calcium influx → necrosis

# Muscle pathology evolves from damage to replacement



*Morphologic progression is Ch. 27; This is a schematic, not a histology image.*

# Clinical consequences of Duchenne muscular dystrophy

- Early childhood proximal weakness, initially affecting pelvic-girdle muscles.
- Calf pseudohypertrophy reflects apparent enlargement despite weakness.
- Progressive respiratory and cardiac involvement follows muscle disease.
- Clinical severity correlates with near-total dystrophin loss.

# Duchenne and Becker differ in residual dystrophin

## Duchenne phenotype

Mutations typically prevent effective dystrophin production.

Usually early onset and more severe progression.

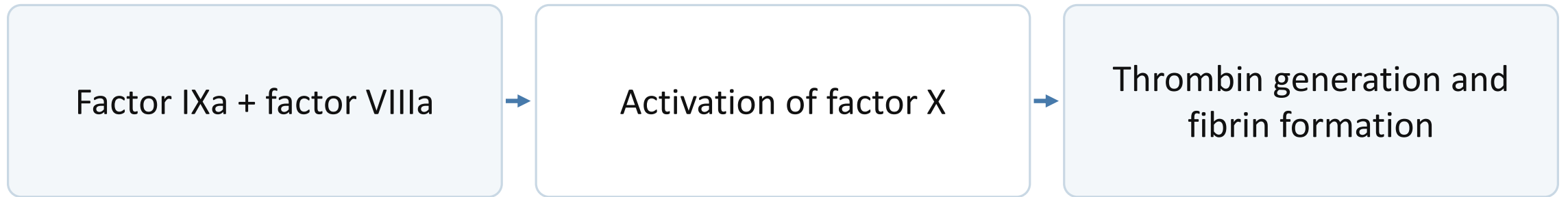
## Becker phenotype

Some truncated dystrophin retains partial function.

Usually later onset and milder progression.

**Both are X-linked dystrophinopathies, but protein consequences differ.**

## Hemophilia A and B disrupt the same coagulation step



**Hemophilia A: Factor VIII deficiency; Hemophilia B: Factor IX deficiency.**

## Bleeding phenotype reflects impaired secondary hemostasis

- Deep tissue hemorrhage and bleeding after trauma or surgery.
- Hemarthroses are particularly characteristic.
- Recurrent joint hemorrhage may produce progressive deformity.
- Petechiae are not a typical defining feature.

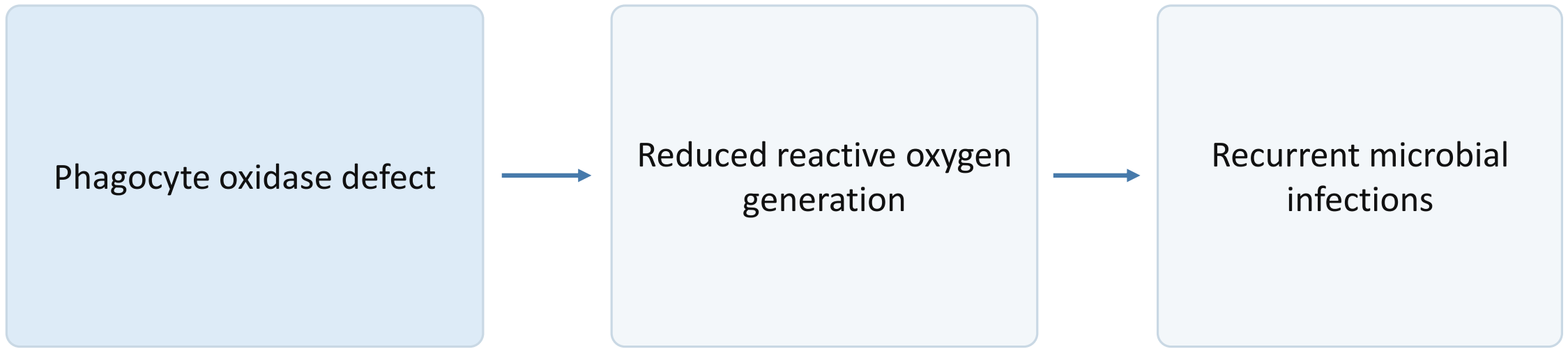
## Distinguishing hemophilia A from B

| Feature            | Hemophilia A               | Hemophilia B              |
|--------------------|----------------------------|---------------------------|
| Affected factor    | VIII                       | IX                        |
| Inheritance        | X-linked recessive         | X-linked recessive        |
| Coagulation screen | Prolonged aPTT; normal PT  | Prolonged aPTT; normal PT |
| Confirmation       | Factor VIII activity assay | Factor IX activity assay  |

*PT/aPTT alone do not distinguish the factor deficiency.*

# Chronic granulomatous disease: Defective oxidative killing

## Phagocyte microbicidal failure



# Not all chronic granulomatous disease is X-linked

## X-linked forms

Often involve gp91phox, a membrane component of oxidase.

Classic X-linked transmission can occur.

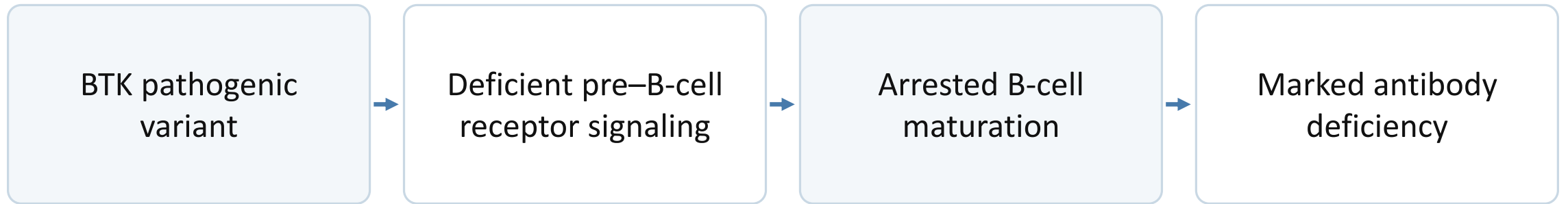
## Autosomal recessive forms

Can involve cytoplasmic oxidase components.

Both sexes can be similarly affected.

**A clinical syndrome may have multiple molecular inheritance patterns.**

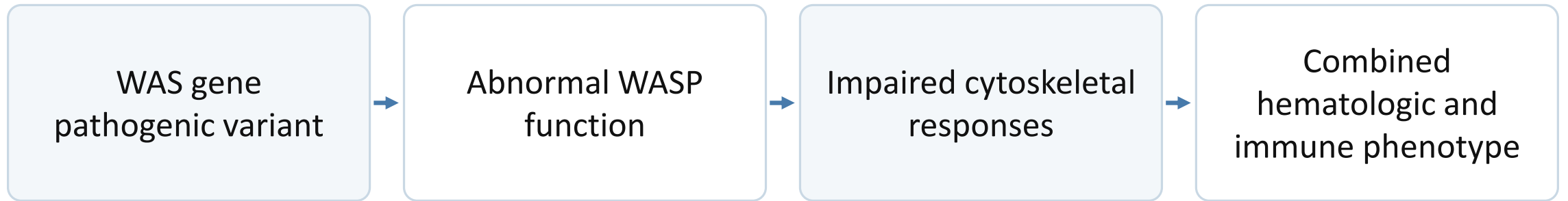
# BTK deficiency blocks B-lymphocyte maturation



## X-linked agammaglobulinemia: Clinical phenotype

- B-cell maturation fails, impairing immunoglobulin production.
- Maternal antibodies transiently protect young infants.
- Recurrent bacterial respiratory infections usually emerge after this protection wanes.
- Typical inheritance is X-linked; Distinguish phenocopies due to other genes.

# Wiskott–Aldrich: Disturbed cytoskeletal responses



# Wiskott–Aldrich: Three high-yield clinical features

**One X-linked disorder affects platelets and immune function.**

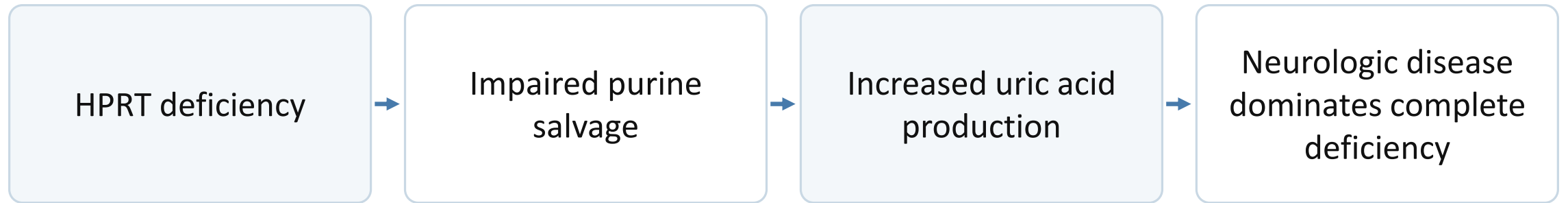
Thrombocytopenia

Eczema

Recurrent infection

*The classic triad is a recognition aid, not a replacement for molecular diagnosis.*

## Lesch–Nyhan: Defective purine salvage



# Hyperuricemia alone does not capture Lesch–Nyhan

## Partial HPRT deficiency

Increased uric acid production.

May contribute to gout through hyperuricemia.

## Complete HPRT deficiency

Marked neurologic phenotype characterizes Lesch–Nyhan.

Hyperuricemia is an associated biochemical feature.

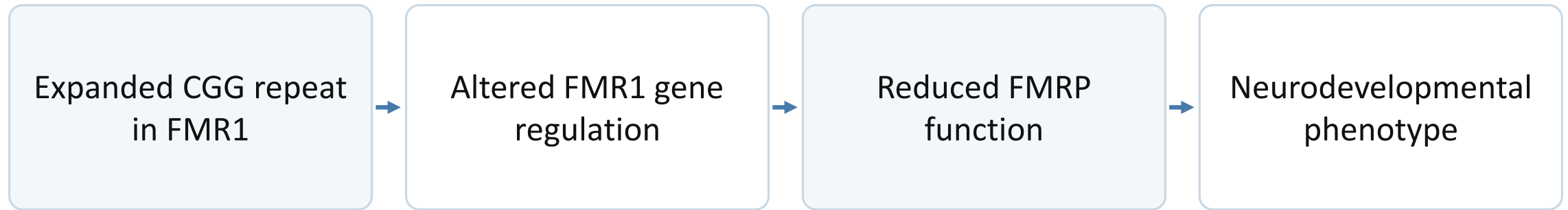
## “Diabetes insipidus” in the X-linked disorder list

### Interpret disease labels within a specific molecular context

- Robbins Table 5.3 lists diabetes insipidus among X-linked recessive conditions.
- The label alone does not identify the pathogenic gene or distinguish all DI etiologies.
- A phenotype-based name cannot establish inheritance without its molecular subtype.

**Do not treat every case of diabetes insipidus as X-linked.**

# Fragile X syndrome is associated with FMR1 CGG expansion



*Triplet-repeat expansion follows distinct mechanisms from a simple recessive point mutation.*

## Fragile X: Clinical and molecular clues

- Intellectual disability and developmental involvement predominate.
- Clinical features can include long face, large ears, and macroorchidism.
- Physical features are variable; Some may be subtle or absent.
- DNA-based repeat analysis replaced historical cytogenetic fragile-site testing.

# Why fragile X is not a simple Mendelian pedigree

## Robbins Table 5.3

Places fragile X in its historical X-linked recessive list.

Male predominance is a useful initial clue.

## Detailed Chapter 5 discussion

Explains unstable repeat expansions and nonclassic inheritance.

Premutation transmission can differ from fully affected states.

**Use gene- and repeat-specific counseling; Avoid oversimplified 50% “affected” labels.**

## X-linked dominant: One altered X may express disease

Pathogenic X-linked variant



Phenotype in heterozygous  
XX individual



Inheritance can occur  
through either parent

**X-linked dominant expression differs from the typical carrier phenotype.**

## X-linked dominant: Affected father

Assume affected  $X^D Y$  father and unaffected  $X^N X^N$  mother

Father  $X^D Y$

×

Mother  $X^N X^N$

$X^N X^D$  daughter

$X^N X^D$  daughter

$X^N Y$  son

$X^N Y$  son

All daughters inherit the variant; None of the sons receive the paternal X.

## X-linked dominant: Affected heterozygous mother

Assume affected  $X^D X^N$  mother and unaffected  $X^N Y$  father

Mother  $X^D X^N$

×

Father  $X^N Y$

$X^N X^N$  daughter

$X^D X^N$  daughter

$X^N Y$  son

$X^D Y$  son

50% risk of inheriting the variant within either offspring sex.

# Rett syndrome: MECP2-related neurodevelopmental disease

MECP2 loss of function



Altered methyl-CpG–  
dependent gene regulation



Neurodevelopmental  
stagnation or regression

## Rett: Characteristic clinical evolution

- Often recognized after apparently normal early development.
- Progressive loss of acquired speech and purposeful hand movements.
- Stereotyped hand movements, ataxia, seizures, and breathing disturbances may appear.
- Phenotypic variability reflects broader effects of MECP2 dysfunction.

# MECP2 disorders in males: Avoid an absolute rule

## Earlier simplified description

Rett-associated variants were described as lethal in hemizygous males.

A classic teaching heuristic.

## Expanded Robbins discussion

Male survivors with MECP2 variants are recognized.

Outcomes range from severe encephalopathy to intellectual disability.

**“Always male-lethal” is not a scientifically defensible blanket statement.**

# Other X-linked dominant examples require subtype precision

## Vitamin D–resistant rickets

Some forms as X-linked dominant.

The inherited molecular subtype determines its pedigree.

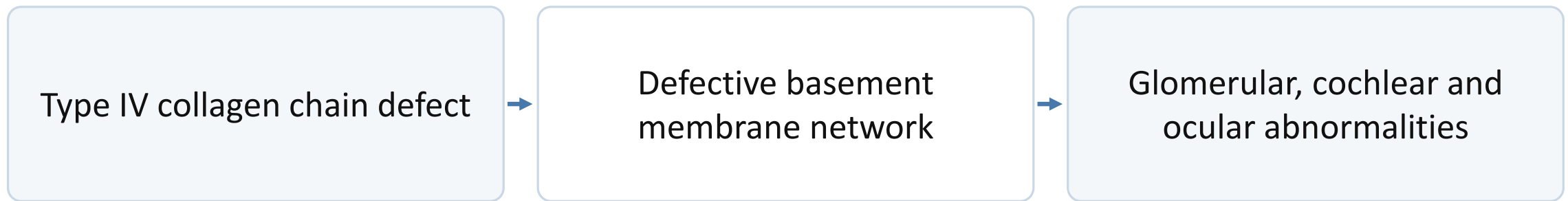
## Alport syndrome

X-linked disease occurs in a major subset.

Autosomal recessive and dominant forms also exist.

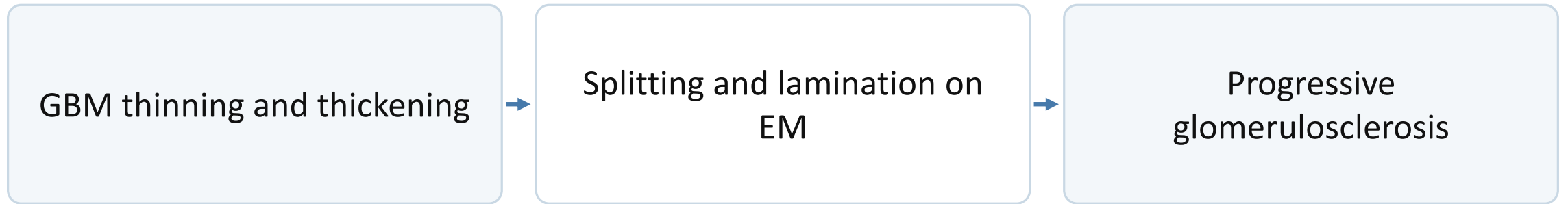
**A disease name may refer to more than one genetic mechanism.**

# Alport syndrome: Basement-membrane collagen defect



*COL4A5 is implicated in X-linked Alport; Other collagen IV genes yield autosomal forms.*

# Alport: Morphology predicts progressive renal disease



*Schematic of pathological progression; The “basket-weave” appearance is an actual described EM finding, not pictured here.*

## Alport demonstrates inheritance heterogeneity

| Inheritance form    | Typical genetic context      | Key interpretive point                                         |
|---------------------|------------------------------|----------------------------------------------------------------|
| X-linked            | COL4A5                       | Males often more severely affected; females may have hematuria |
| Autosomal recessive | Other type IV collagen genes | Both sexes can express full disease                            |
| Autosomal dominant  | Other type IV collagen genes | Vertical transmission may occur in either sex                  |

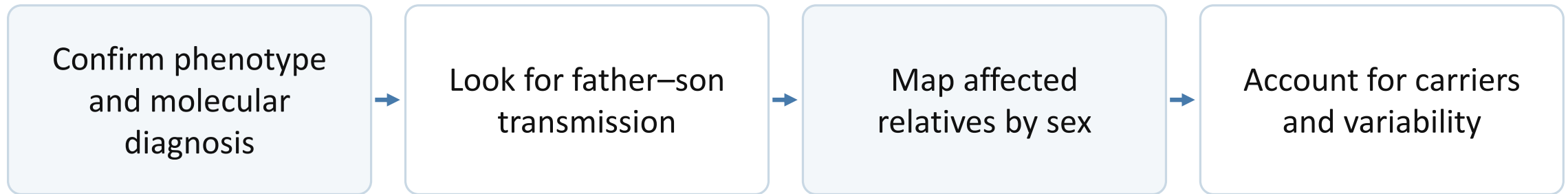
## X-linked recessive versus X-linked dominant

| Feature                     | X-linked recessive                     | X-linked dominant                           |
|-----------------------------|----------------------------------------|---------------------------------------------|
| Typical affected group      | Hemizygous XY individuals              | Either XX or XY individuals                 |
| Heterozygous XX phenotype   | Often unaffected; may manifest         | Often affected; severity variable           |
| Affected father → sons      | No paternal X transmission             | No paternal X transmission                  |
| Affected father → daughters | Obligate carriers if mother unaffected | All inherit paternal variant                |
| Heterozygous mother         | Half sons may be affected              | Half children of either sex inherit variant |

## Compare X-linked with autosomal inheritance

| <b>Pedigree feature</b>     | <b>X-linked</b>                | <b>Autosomal</b>               |
|-----------------------------|--------------------------------|--------------------------------|
| Father-to-son transmission  | Absent for paternal X variants | Possible                       |
| Sex distribution            | Often asymmetric               | Frequently similar by sex      |
| Carrier females             | Common in X-linked recessive   | Common in autosomal recessive  |
| Affected father → daughters | All inherit his X variant      | Not obligatorily all daughters |

# Pedigree analysis: A reproducible sequence



**A pedigree suggests a model; The gene-level diagnosis determines the final classification.**

## Consider female manifestations explicitly

- Symptoms in a heterozygous woman do not exclude X-linked recessive inheritance.
- Mosaic X-inactivation can produce tissue-dependent clinical effects.
- X-linked dominant disorders may manifest in heterozygous women by definition.
- Phenocopies and alternative genetic mechanisms should remain in the differential.

# Clinical pattern recognition before molecular confirmation

| Clinical presentation                     | Illustrative X-linked mechanism         |
|-------------------------------------------|-----------------------------------------|
| Proximal weakness with muscle replacement | Dystrophin deficiency                   |
| Hemarthroses, prolonged aPTT              | Factor VIII or IX deficiency            |
| Oxidant-triggered acute hemolysis         | G6PD deficiency                         |
| Early recurrent bacterial infections      | BTK-associated B-cell maturation arrest |
| Eczema, thrombocytopenia, infections      | WASP dysfunction                        |
| Hematuria, deafness, renal injury         | Type IV collagen abnormality            |

## Worked case: Maternal transmission of hemophilia

**An unaffected woman has an affected brother and an affected son.**

- What mode of inheritance is suggested?
- Why is her normal clinical examination insufficient to exclude carriage?
- Would the affected son pass the pathogenic X to his sons?

## Case analysis: What the pedigree establishes

Affected males through  
maternal line



X-linked recessive is a strong  
hypothesis



Carrier status requires  
appropriate assessment

**An affected father passes Y—not his mutant X—to every son.**

## Worked case: Episodic hemolysis in a woman

**A heterozygous woman develops hemolysis after an oxidant exposure.**

- Does symptomatic disease exclude a classic X-linked trait?
- Which erythrocyte population is susceptible to oxidant injury?
- What mechanism creates different susceptibility among her red cells?

## Case analysis: Mosaicism explains the hemolysis

Heterozygous X-linked G6PD variant



Different active X alleles  
among erythroid clones



Variable oxidant-induced  
hemolysis

**Carrier females are not necessarily protected from an X-linked phenotype.**

## Five interpretive traps in X-linked genetics

- Equating X-linked with exclusively male disease.
- Calling every heterozygous woman completely asymptomatic.
- Ignoring de novo variants or genes with nonclassic repeat expansion.
- Equating a syndrome name with only one inheritance pattern.
- Using a pedigree as a substitute for gene-level diagnosis.

# Integrative synthesis: Locus, transmission, expression

Locus: Variant resides on X



Transmission: Parental X/Y  
segregation



Expression: Gene effect and  
X-inactivation

**These three variables must be considered separately in every case.**

# Primary sources and cross-chapter reading

## Primary textbook

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

## Source sections

- Chapter 5: Genes and Human Diseases — X-Linked Disorders, pp. 126–127.
- Chapter 5: Epigenetic machinery and nonclassic repeat disorders.
- Chapters 6, 14, 20, 26, and 27: selected disease mechanisms.