

Autosomal Dominant Disorders

Inheritance • penetrance • molecular pathogenesis • clinicopathologic examples

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Learning objectives

- Interpret pedigrees and Mendelian recurrence risk for dominant alleles.
- Distinguish de novo mutation, penetrance, expressivity, and delayed onset.
- Explain haploinsufficiency, dominant-negative effects, and gain of function.
- Connect molecular lesions to familial hypercholesterolemia, Marfan syndrome, and EDS.

Single-gene disorders: Transmission patterns

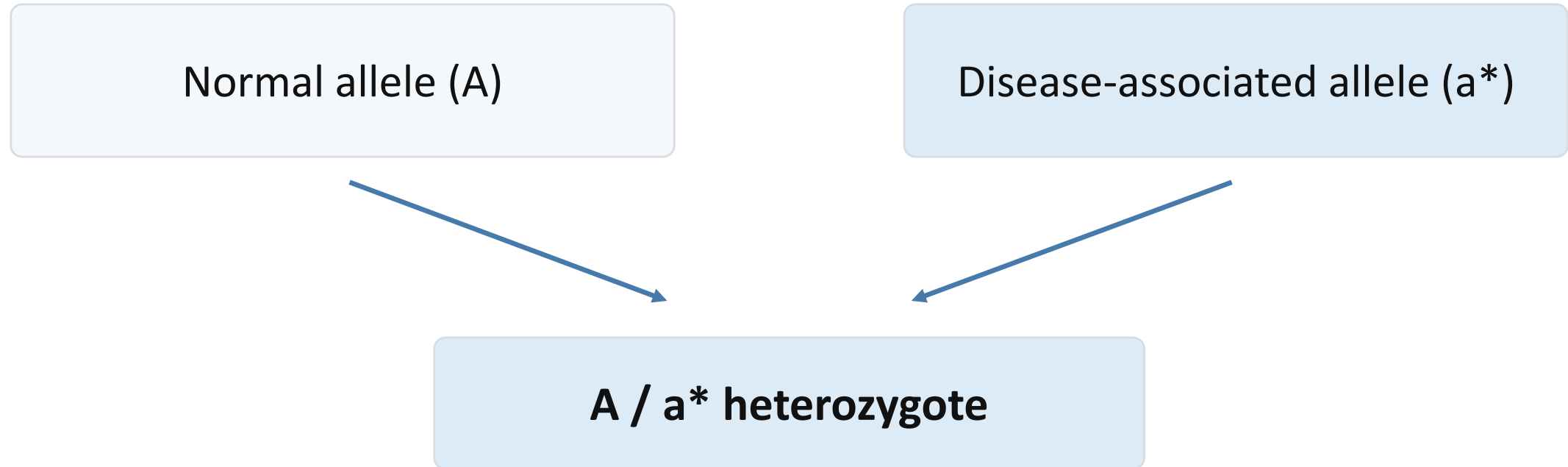
Autosomal dominant

Autosomal recessive

X-linked

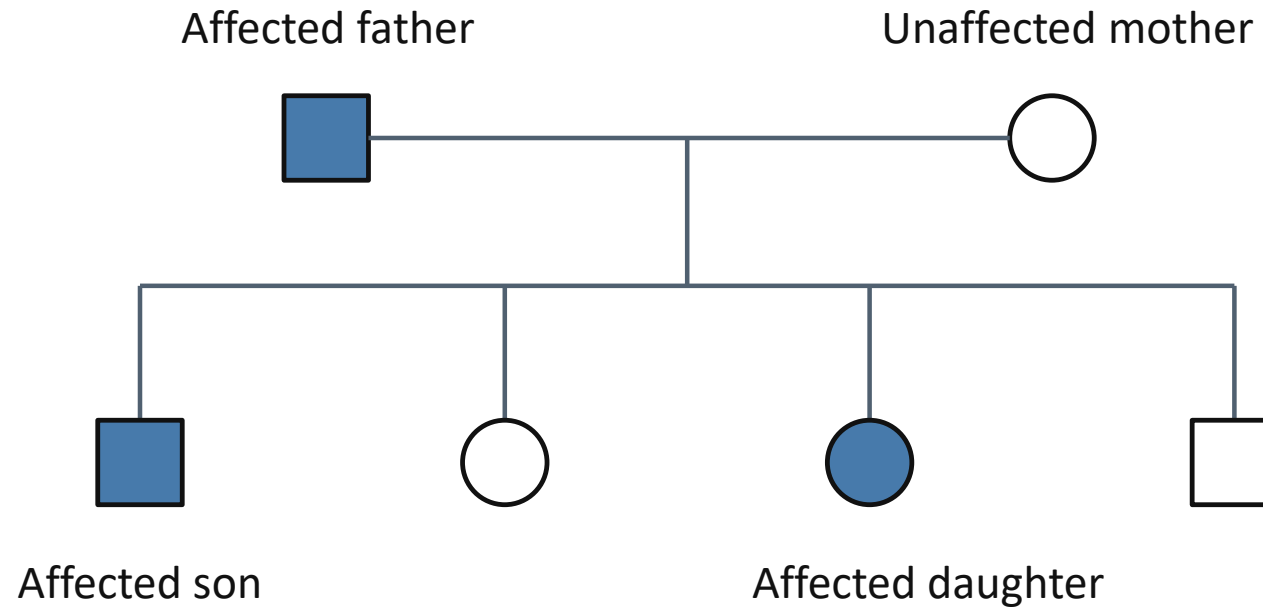
These are distinct Mendelian transmission patterns, not sequential stages.

Dominant phenotype in a heterozygote



A single altered autosomal allele can be sufficient to produce disease.

Both sexes can inherit and transmit



Schematic pedigree: Illustrates sex-independent transmission, not an observed family.

The canonical 1-in-2 transmission risk

Affected heterozygous parent (A / a*)

	A	A*
A	A/A	A/a*
A	A/A	A/a*

Each pregnancy has a 50% chance of inheriting the disease-associated allele.

Recurrence risk applies to each pregnancy

Pregnancy 1

50% allele inherited

50% allele not inherited

Pregnancy 2

50% allele inherited

50% allele not inherited

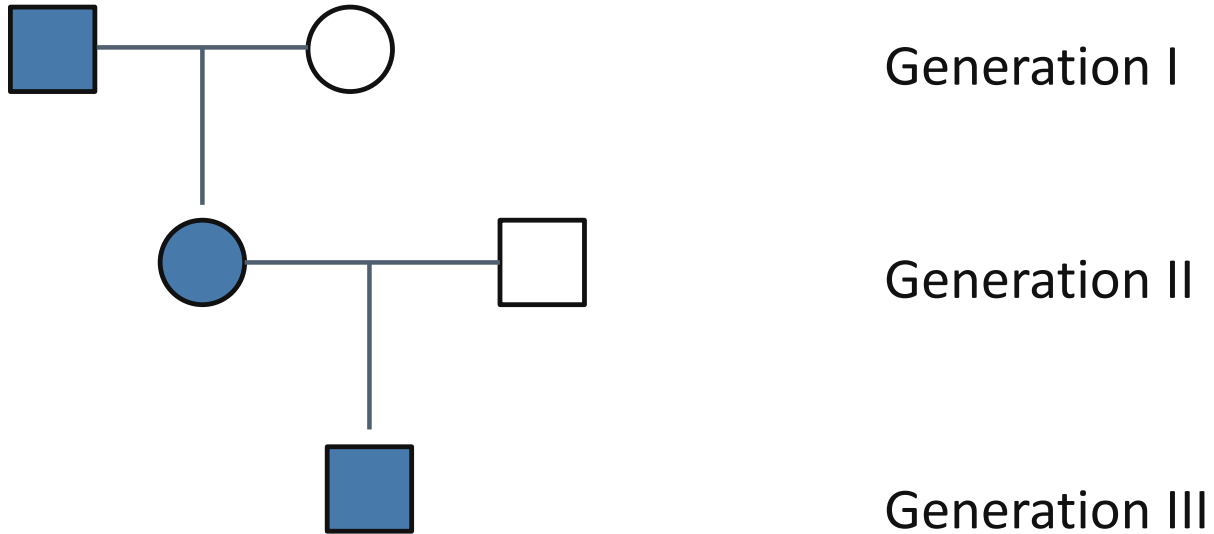
Pregnancy 3

50% allele inherited

50% allele not inherited

The outcome of one pregnancy does not alter the Mendelian allele risk of the next.

Pedigree clue: Vertical transmission

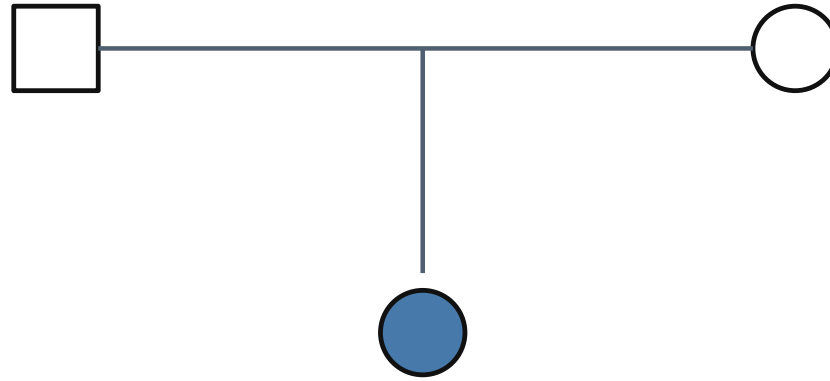


Affected individuals in successive generations support, but do not prove, dominance.

A negative family history does not exclude dominance

- A pathogenic variant may arise de novo in the proband.
- An affected parent may appear healthy because penetrance is incomplete.
- An inherited disorder may present after the parent's current age.
- The degree of disease expression may be subtle in relatives.

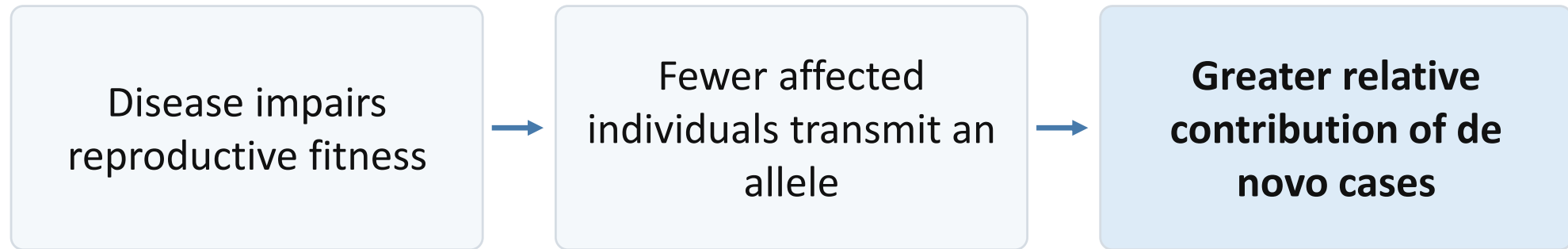
De novo mutation: A new germline event



New mutation arising in a parental germ cell

A sporadic presentation can still have an autosomal dominant molecular cause.

Reproductive fitness shapes observed pedigrees



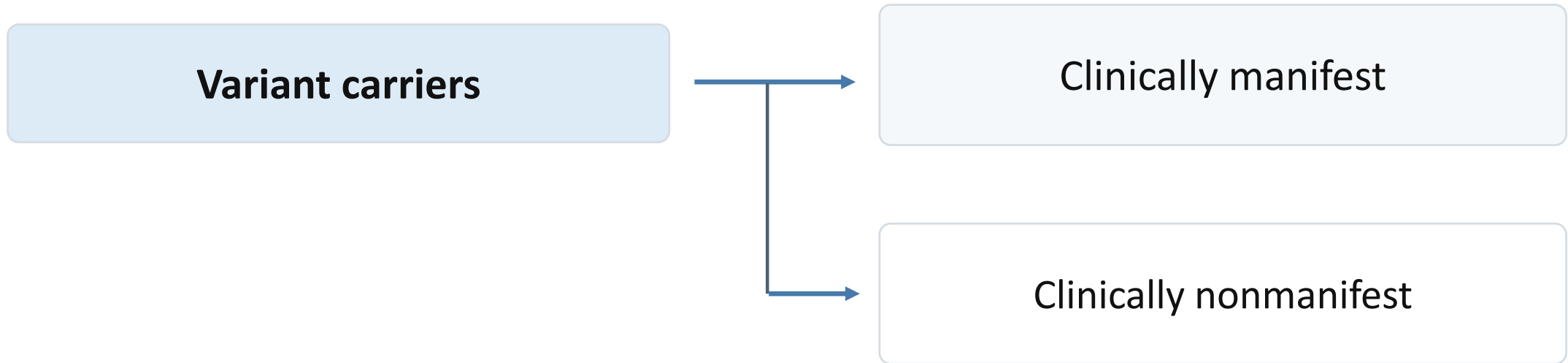
This relationship describes case origins, not a fixed mutation rate.

Paternal-age association in selected syndromes



Some RTK–RAS–MAPK pathway mutations with increased paternal age.

Penetrance: Whether the phenotype appears



Incomplete penetrance: Some genotype-positive individuals lack the defined trait.

Penetrance is a population proportion

Penetrance

=

Carriers expressing the phenotype

All carriers of the variant

50% penetrance to mean expression in half of variant carriers.

Expressivity: How severe or extensive disease becomes



Variable expressivity concerns phenotype intensity, not the presence of a variant.

Penetrance and expressivity are different

Dimension	Incomplete penetrance	Variable expressivity
Question	Is the trait present?	How strongly is it expressed?
Carrier status	Variant present	Variant present
Phenotype	May be absent	Present, but variable
Clinical implication	Apparently unaffected relative	Relatives differ in manifestations

Neurofibromatosis type 1: Phenotype spectrum

Pigmented skin macules

Multiple cutaneous tumors

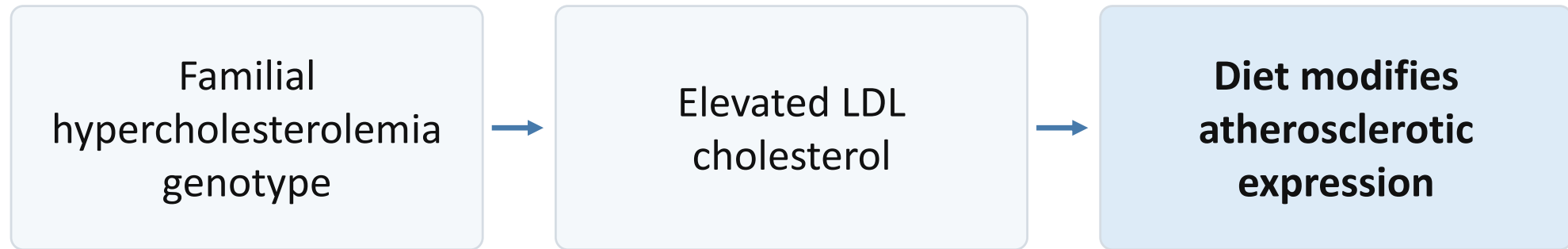
Skeletal abnormalities

Examples across an expressivity spectrum; This is not a temporal sequence.

Why can relatives express one allele differently?

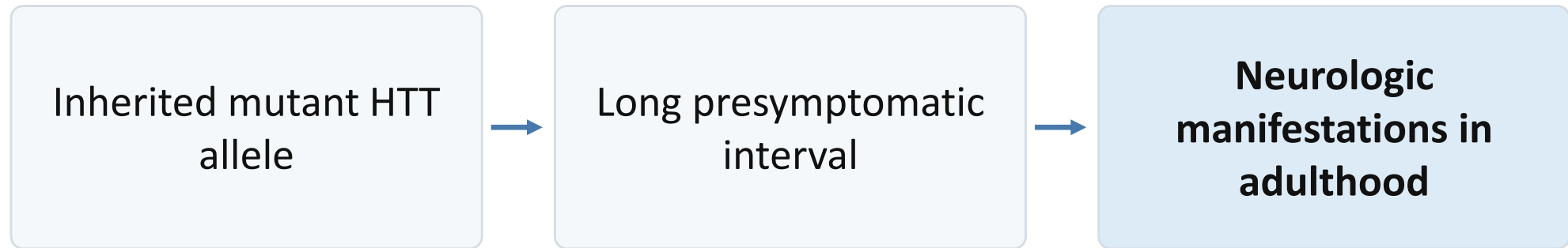
- Other inherited loci may modify the phenotypic effect.
- Environmental exposures may amplify or attenuate consequences.
- Different tissues can show different clinical manifestations.
- The full basis of incomplete penetrance and expressivity is not settled.

Environmental modifier: LDL burden in FH



The allele contributes susceptibility; Exposures modify clinical outcome.

Age-dependent onset: Huntington disease



A young carrier may have no clinical manifestations despite the genotype.

Family-history interpretation requires three questions

Is the mutation de novo?

Could an inherited allele have incomplete penetrance?

Is onset delayed?

Is expression subtle or heterogeneous?

Three molecular routes to autosomal dominance

Haploinsufficiency
Too little functional protein

Dominant-negative action
Mutant product impairs normal product

Gain of function
Excess or new pathological activity

Loss of function does not always mean dominance

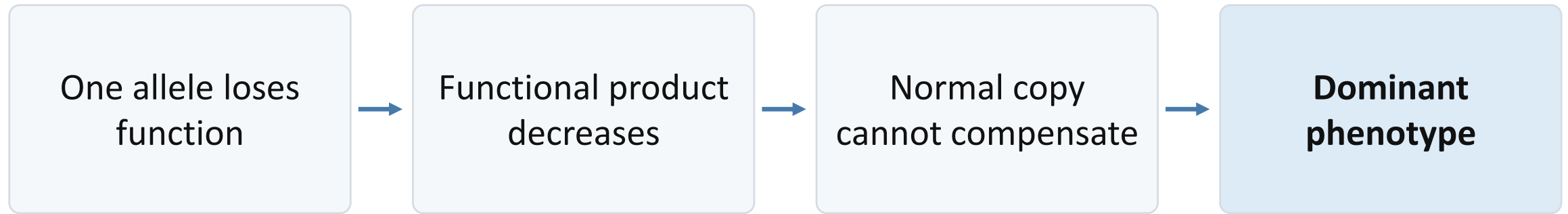
Adequate compensation

- One normal allele produces enough active product.
- The heterozygote can be phenotypically normal.

Inadequate compensation

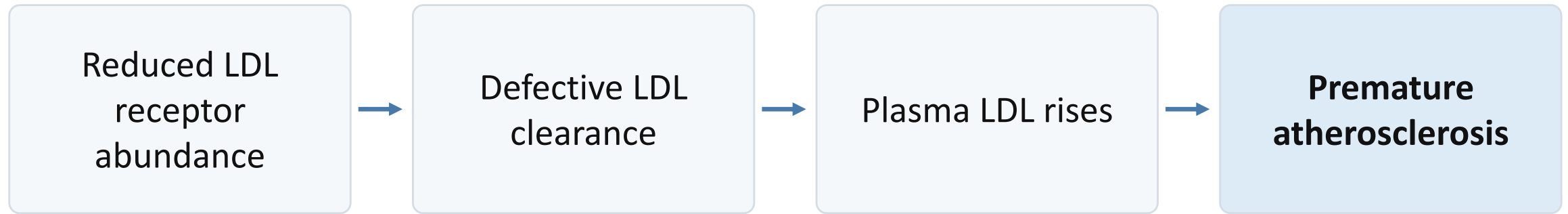
- One normal allele cannot meet functional demand.
- A heterozygote manifests disease.

Haploinsufficiency: One normal allele is insufficient



Disease follows insufficient total functional gene product.

LDLR loss of function: Pathophysiologic chain



Familial hypercholesterolemia illustrates haploinsufficiency in heterozygotes.

Gene dosage matters, but mechanism matters more

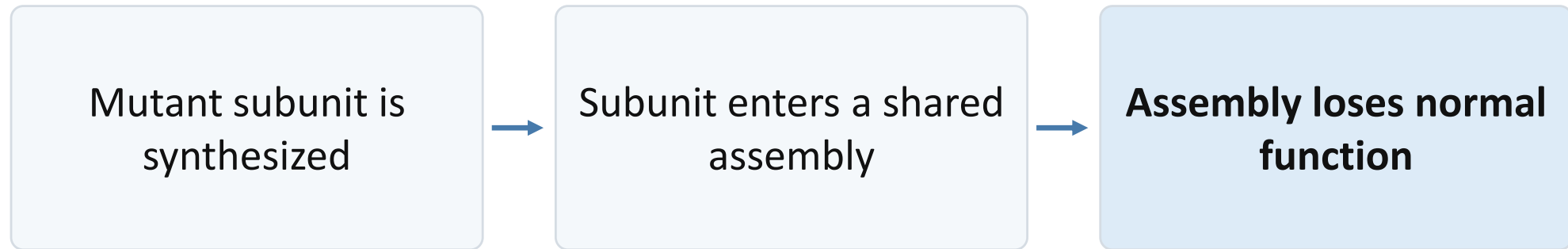
Molecular observation

- An allele can yield less normal protein.
- A mutant polypeptide may still be synthesized.

Functional consequence

- Too little total functional protein:
Haploinsufficiency.
- Disruption of normal complexes:
Dominant-negative effect.

Dominant-negative action: Protein interference



The mutant protein affects products from the normal allele.

Collagen trimer assembly illustrates interference

Normal chain

Normal chain

Mutant chain



Composite collagen trimer

Abnormal subunit compromises the complex

Osteogenesis imperfecta: A structural-protein model

- Some variants involve defective collagen chains in multimeric assemblies.
- A mutant chain can destabilize otherwise normal collagen molecules.
- The resulting collagen deficiency or dysfunction produces skeletal fragility.
- The same clinical grouping can encompass distinct molecular mechanisms.

Gain of function: An altered protein acquires activity

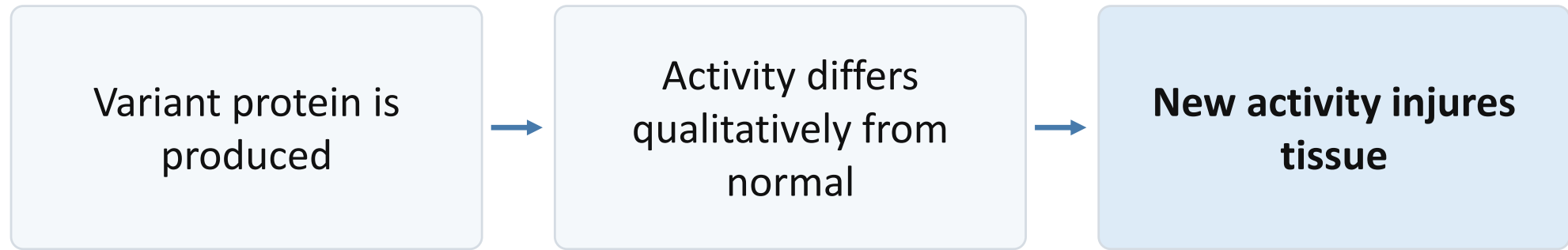
Increased normal activity

- A pre-existing function becomes overactive.
- Signaling or enzymatic output can be excessive.

Novel pathological activity

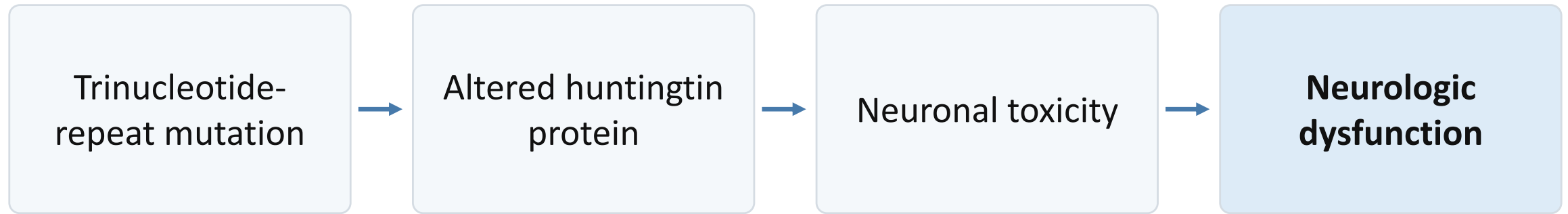
- A mutation may impart a new protein behavior.
- The new activity can be toxic to cells.

Neomorphic alleles create a new functional effect



A neomorphic effect differs from simple loss of the wild-type activity.

Huntington disease: Pathogenic protein toxicity



Huntington disease as a dominant gain-of-function example.

Mechanism comparison: Three distinct lesions

Mechanism	Core defect	Illustrative condition
Haploinsufficiency	Insufficient normal product	Familial hypercholesterolemia
Dominant negative	Mutant product impairs an assembly	Some osteogenesis imperfecta
Gain of function	Increased/new harmful activity	Huntington disease

Predict the mechanism from the molecular lesion

Half of receptor supply cannot clear sufficient ligand

Mutant collagen chain destabilizes an assembled trimer

A toxic mutant protein injures neurons

The clinical dominance alone does not define the mechanism

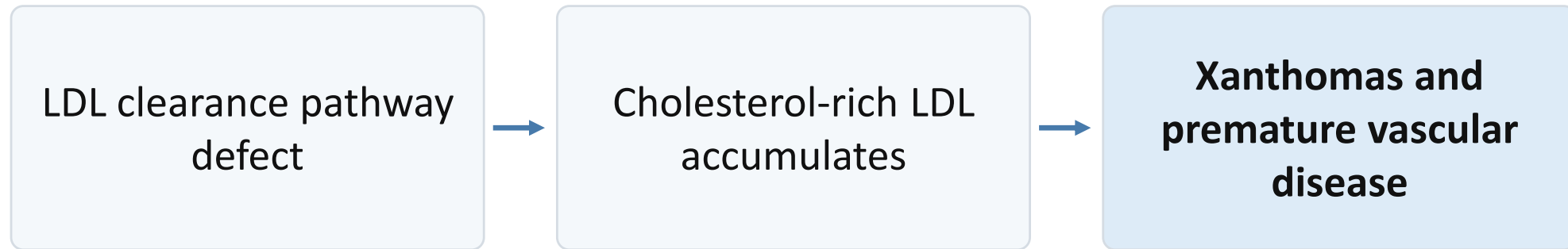
Autosomal dominant disorders affect many systems

System	Textbook examples
Nervous	Huntington disease; neurofibromatosis; myotonic dystrophy; tuberous sclerosis
Urinary	Polycystic kidney disease
Gastrointestinal	Familial polyposis coli
Hematopoietic	Hereditary spherocytosis; von Willebrand disease
Skeletal	Marfan; some EDS; osteogenesis imperfecta; achondroplasia
Metabolic	Familial hypercholesterolemia; acute intermittent porphyria

Disorder names alone do not identify inheritance

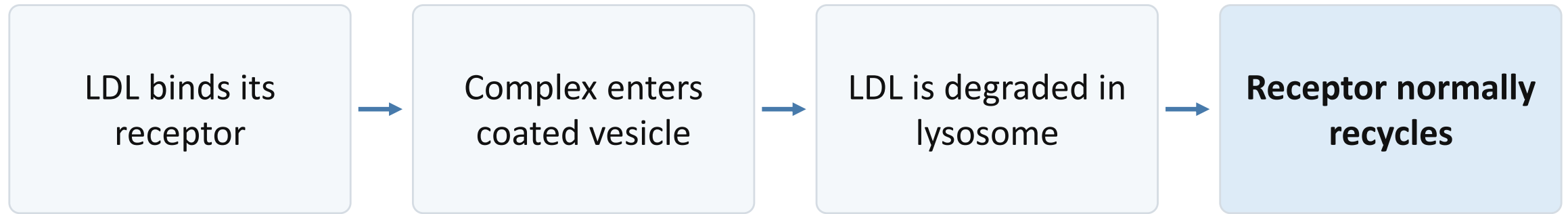
- Some disease groups contain both dominant and recessive genetic subtypes.
- Ehlers–Danlos syndromes illustrate molecular and inheritance heterogeneity.
- A pedigree must be interpreted together with phenotype and genotype.
- Do not assume every patient bearing a syndrome label has the same molecular lesion.

Familial hypercholesterolemia: Clearance failure



The dominant phenotype is expressed through impaired hepatic LDL removal.

Normal LDL uptake: Receptor-mediated endocytosis



This trafficking pathway controls LDL residence time in plasma.

PCSK9 controls LDL receptor recycling

Without excess PCSK9 action

- LDL receptor is retrieved after internalization.
- Recycling sustains cell-surface receptor supply.

With activating PCSK9 mutation

- More internalized receptors are degraded.
- Cell-surface LDL receptors decline.

Three molecular entry points to FH

Gene	Affected step	Consequence
LDLR	Receptor synthesis, binding, trafficking	Less hepatic LDL clearance
APOB	LDL ligand binds receptor poorly	Reduced receptor-mediated uptake
PCSK9	Enhanced receptor degradation (activating variants)	Reduced surface LDL receptors

Heterozygous LDLR loss shows gene dosage

Two functioning alleles



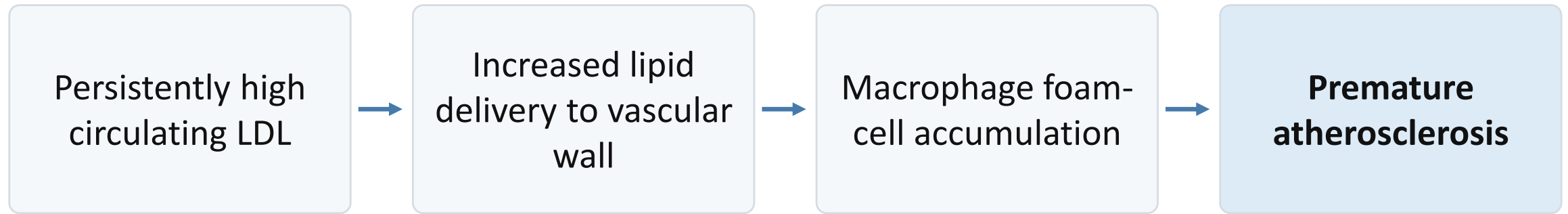
Normal LDL receptor supply

One functioning allele



Reduced receptor supply → LDL
accumulation

Why LDL accumulation damages arteries



The vascular phenotype arises downstream of a defective clearance receptor.

Heterozygous and biallelic FH are not equivalent

Finding	Heterozygous LDLR variant	Biallelic severe LDLR variants
Receptor function	Reduced	Much more severely reduced
Plasma cholesterol	Increased from birth	Markedly increased
Manifestations	Xanthomas; premature atherosclerosis	Potential very early vascular disease
Interpretation	Classic dominant expression	More severe gene-dosage phenotype

Familial hypercholesterolemia: Clinical reasoning

- A family history of premature coronary disease strengthens suspicion.
- Tendon xanthomas can reflect chronically elevated circulating LDL.
- Recognize that multiple gene products can converge on the same pathway.
- A phenotype alone does not resolve LDLR, APOB, and PCSK9 mechanisms.

Marfan syndrome: A connective-tissue disorder

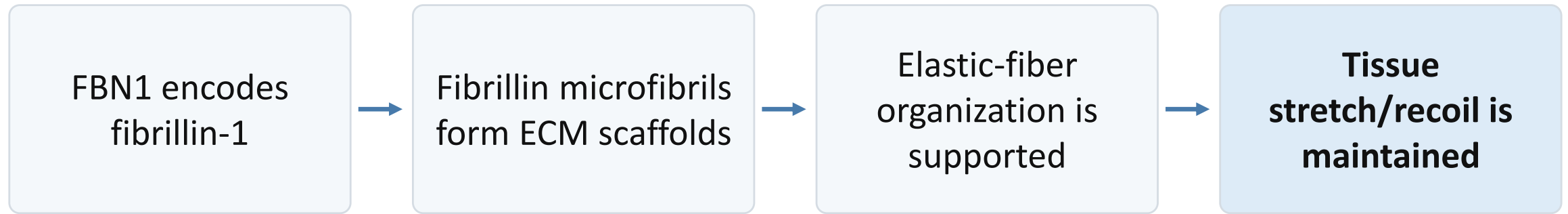
Skeleton: Disproportionate growth and skeletal features

Eye: Lens-support abnormality

Cardiovascular: Aortic and valvular disease

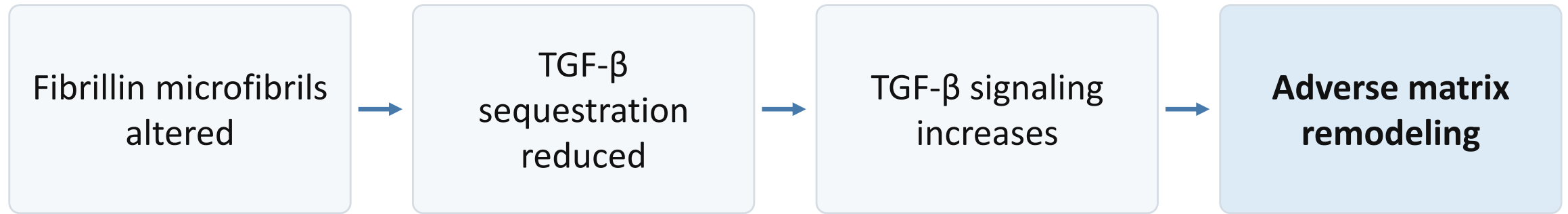
Core molecular defect: Fibrillin-1

Fibrillin-1 provides structural support



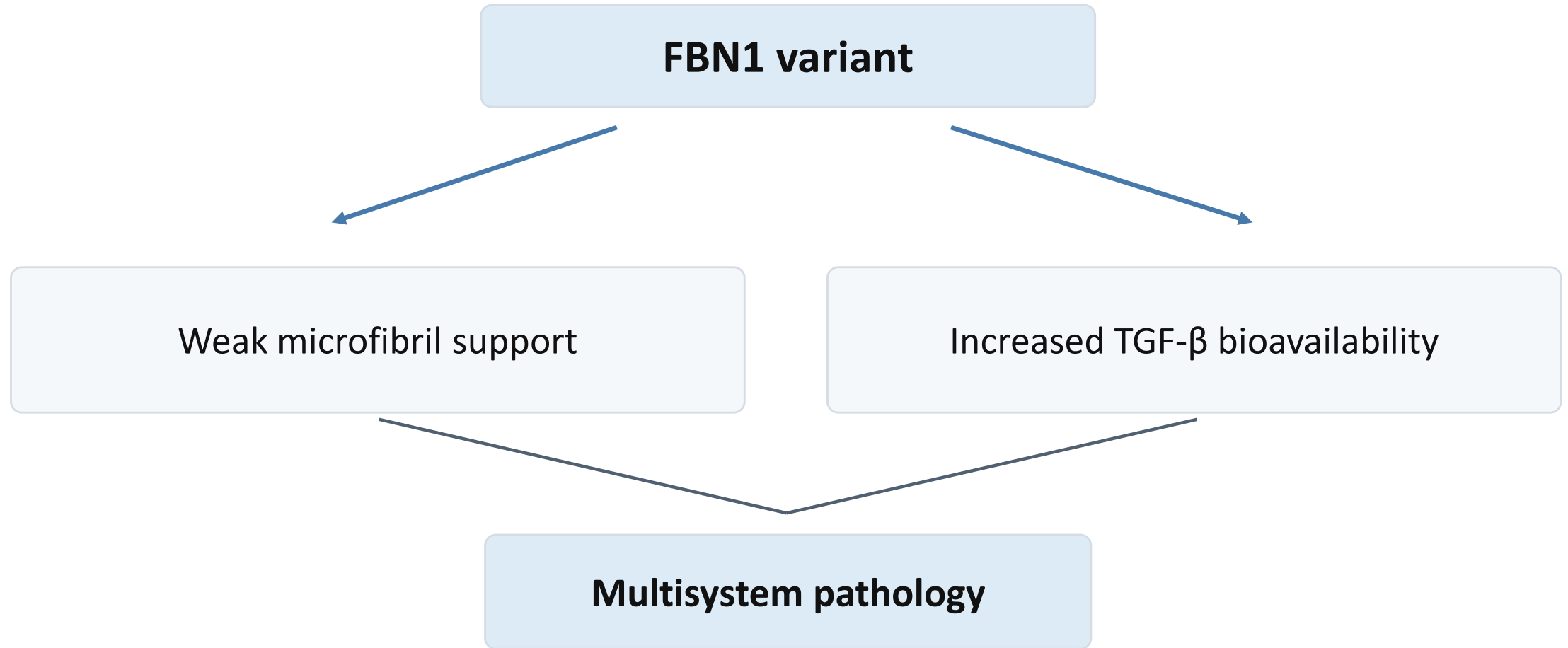
Aorta, ciliary zonules, and ligamentous tissue are especially dependent on support.

Marfan syndrome: Excess TGF- β signaling



Dysregulated signaling adds to the mechanical consequences of ECM failure.

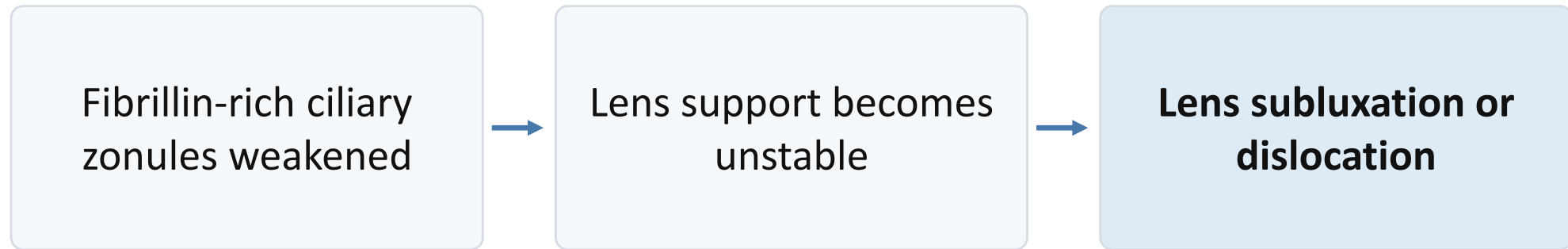
Two pathogenic pathways converge in Marfan



Marfan skeletal features reflect connective-tissue weakness

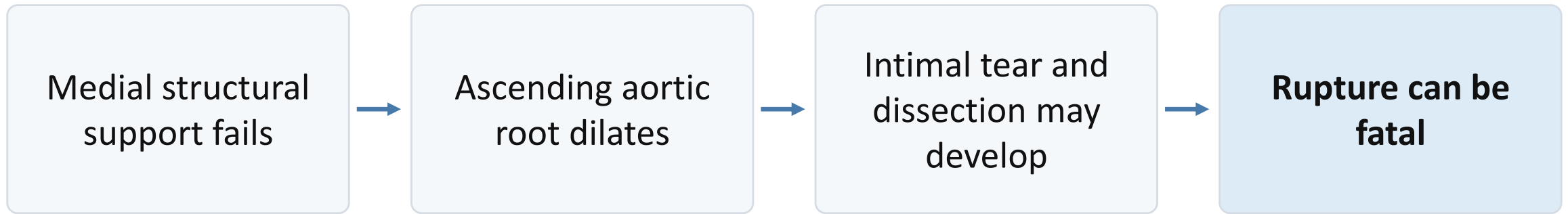
- Tall habitus and long extremities may be prominent.
- Long, tapering digits and ligamentous laxity affect the hands and feet.
- Spinal curvature and chest-wall deformities can accompany the phenotype.
- Skeletal findings vary; They are not required to be equally prominent.

Ectopia lentis localizes a structural defect



Bilateral ectopia lentis is a characteristic ocular clue in Marfan syndrome.

Aortic medial degeneration is the life-threatening lesion



Aortic pathology is more consequential than the visible skeletal phenotype.

Marfan syndrome varies across and within families

Predominantly skeletal presentation

- Tall habitus and ligamentous changes.
- Little clinically evident eye disease may coexist.

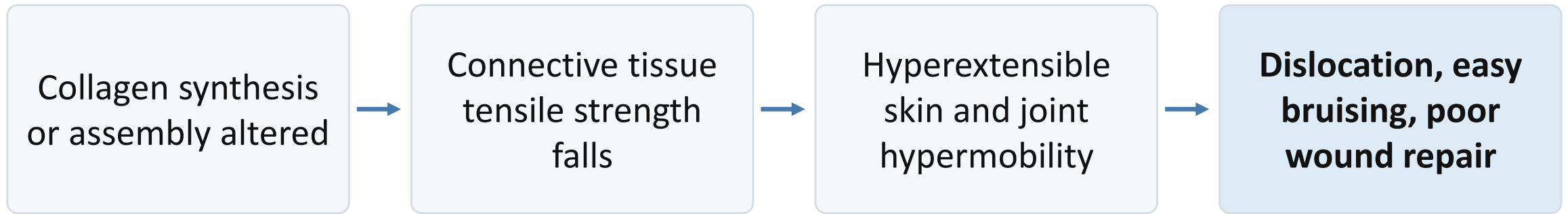
Cardiovascular/ocular presentation

- Aortic pathology or ectopia lentis may dominate.
- Skeletal abnormalities may be subtle.

EDS: A heterogeneous set of collagen disorders

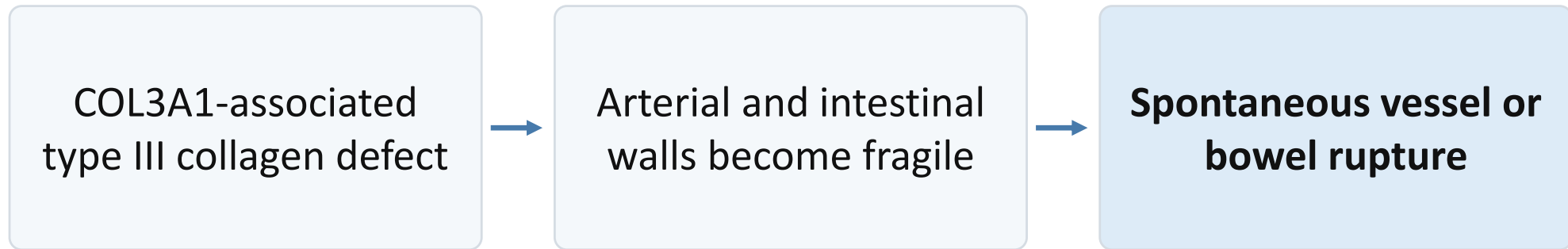
- EDS encompasses defects in collagen chains, collagen-processing enzymes, and ECM-associated proteins.
- Affected subtypes may be autosomal dominant or autosomal recessive.
- Clinical variability reflects differences in the protein and pathway affected.
- Skin, joints, vessels, and hollow viscera are variably vulnerable.

EDS skin and joint findings follow reduced tensile strength



Clinical manifestations follow the tissue distribution of the affected collagen system.

Vascular EDS: Type III collagen fragility



Skin hyperextensibility may be less prominent than in other EDS subtypes.

EDS inheritance depends on the affected pathway

Illustrative subtype	Genetic lesion (textbook example)	Inheritance
Classical EDS	Type V collagen genes	Autosomal dominant
Vascular EDS	COL3A1, type III collagen	Autosomal dominant
Kyphoscoliotic EDS	PLOD1, lysyl hydroxylase	Autosomal recessive

Dominant and recessive pedigrees differ

Clue	Autosomal dominant	Autosomal recessive
Typical family history	Multiple generations may be affected	Parents often clinically unaffected
Affected × unaffected	50% mutant-allele transmission if heterozygous	Risk depends on partner carrier status
Heterozygote	May have phenotype	Usually clinically unaffected for classic loss of function
Exceptions	De novo, incomplete penetrance, late onset	Consanguinity, compound heterozygosity

Case 1: The apparently sporadic disorder

A child has achondroplasia. Both parents have no clinical skeletal abnormality.

Question: Does an unaffected parental phenotype rule out autosomal dominant disease?

Case 1: Interpret the genetic event

- No: A de novo pathogenic germline mutation can cause a dominant disorder.
- Some FGFR3-associated achondroplasia cases to paternal-age-related mutation occurrence.
- A sporadic presentation and a dominantly acting variant are compatible.

Case 2: Opposite clinical severity in one pedigree

A parent has a few pigmented skin macules; Their affected child has multiple neurofibromas and skeletal changes.

Question: Which concept best explains the different intensity of manifestations?

Case 2: Variable expressivity, not penetrance

- Both relatives express a recognizable disease phenotype.
- The clinical spectrum differs in extent and severity.
- Variable expressivity describes this pattern; Incomplete penetrance would refer to a carrier with no phenotype.

Case 3: Match the lesion to the mechanism

A heterozygous variant yields an abnormal protein that enters a multimeric ECM complex and disrupts its organization.

Question: Haploinsufficiency, dominant-negative interference, or gain of function?

Case 3: Dominant-negative interference

- The mutant polypeptide enters a complex with other protein subunits.
- The abnormal component impairs assembly or stability of the shared structure.
- This is a dominant-negative mechanism, distinct from merely producing less protein.

Integrating inheritance with molecular pathology

50% allele transmission per pregnancy
(heterozygous affected × unaffected)

Penetrance = whether; Expressivity = how much

Haploinsufficiency / dominant negative / gain of function

Mechanism explains phenotype and guides family interpretation

Source and scope of this lecture

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 5: Genes and Human Diseases — section Autosomal Dominant Disorders.
- Related source sections: transmission patterns; structural and receptor protein disorders; Marfan syndrome; EDS; familial hypercholesterolemia.
- All schematics and teaching cases are original educational compositions based on those sections.