

Single-Gene Disorders

Mutational mechanisms • allelic effects • inheritance • phenotypes

Mutations → proteins → tissues → clinical phenotype

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

What this lecture explains

INTRODUCTION

- Recognize the molecular classes of mutations that alter gene function.
- Relate mutant-allele dosage and protein function to dominant or recessive phenotypes.
- Differentiate pleiotropism, genetic heterogeneity and codominance.
- Apply genotype–phenotype reasoning to representative Mendelian conditions.

Where monogenic disease fits

INTRODUCTION

Monogenic	Complex multigenic	Chromosomal
A major defect in one gene	Multiple variants plus environment	Numerical or structural chromosome change
Frequently Mendelian segregation	Often multifactorial susceptibility	May affect many genes
Examples: sickle cell disease, CF	Examples: common hypertension, diabetes	Examples: large deletions, trisomies

Germline versus somatic mutation

INTRODUCTION

Germline / inherited	Somatic / acquired
May be transmitted to offspring	Not transmitted through germ cells
May be present in many tissues	Restricted to a cell lineage
Relevant to inherited disease	Relevant to tumors and mosaicism

Hereditary, familial and congenital are not synonyms

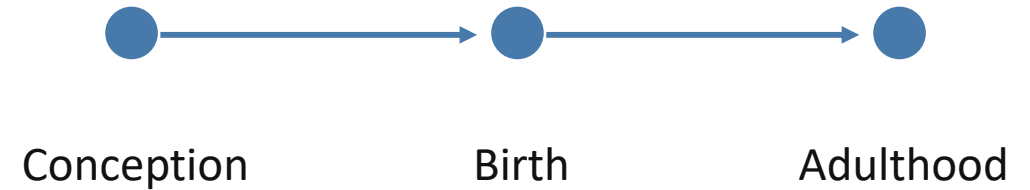
INTRODUCTION

Term	Meaning	Teaching implication
Hereditary	Transmitted via germ cells	May become symptomatic late in life
Familial	Occurs within relatives	Not sufficient alone to prove inheritance
Congenital	Present at birth	Can be non-genetic

Congenital does not necessarily mean genetic

INTRODUCTION

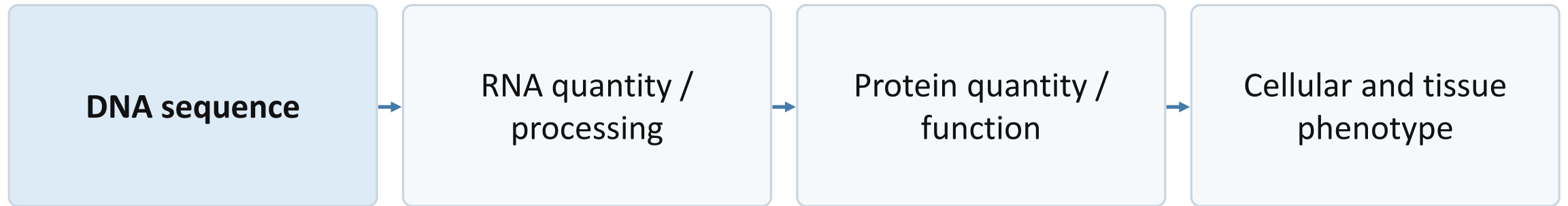
- Congenital refers to timing of presence, not the underlying cause.
- A hereditary variant can produce symptoms only in adult life.
- Huntington disease illustrates delayed onset of a genetic condition.



Genetic origin and clinical onset may occur at different times.

A single gene can influence multiple levels of function

INTRODUCTION



A mutation becomes clinically relevant through its effect on a gene product.

Mutation: The basic definition

INTRODUCTION

A mutation is a permanent change in DNA sequence.

- A germline mutation can be passed to descendants.
- A somatic mutation is acquired within the individual.
- The functional consequence depends on the location and nature of the change.

Mutation classes: Orient the problem

INTRODUCTION

Coding substitution

Missense or nonsense

Regulatory region

Altered transcription

Splice region

Abnormal RNA processing

Insertion or deletion

In-frame change or frameshift

Gene rearrangement

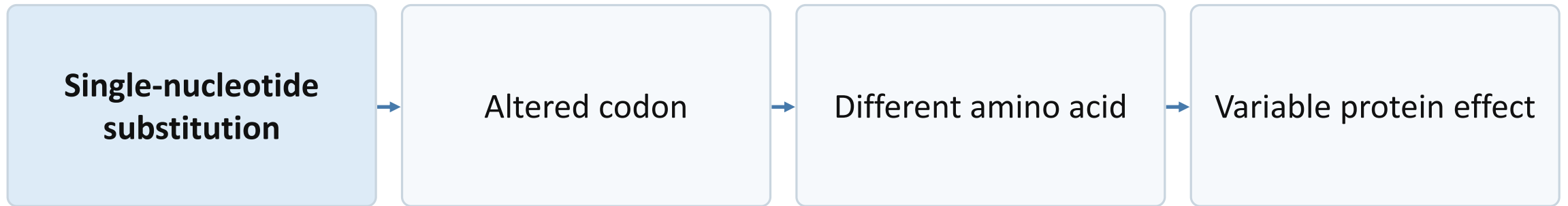
Altered copy number or
structure

Repeat expansion

Dynamic repeat-length change

Missense mutation changes an encoded amino acid

MUTATION MECHANISMS



The severity is determined by the biochemical and structural role of the substitution.

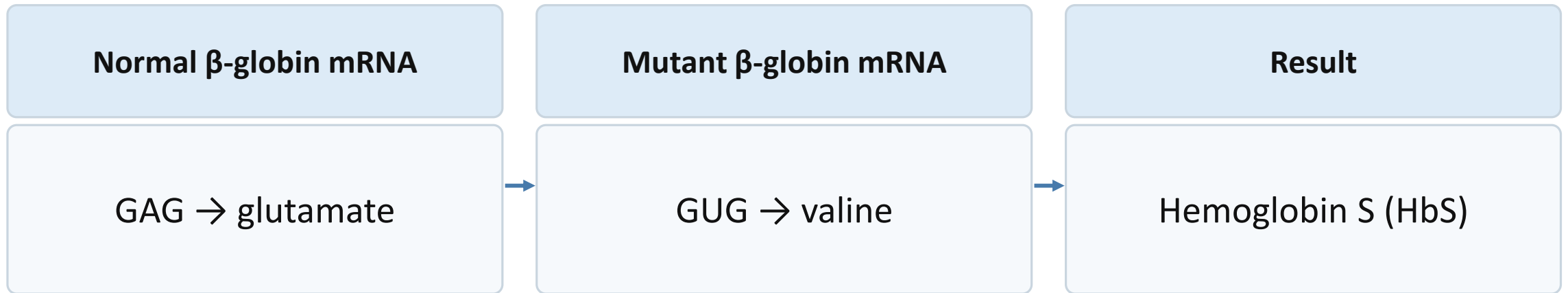
Conservative and nonconservative missense changes

MUTATION MECHANISMS

Conservative	Nonconservative
Biochemically similar amino acid	Biochemically dissimilar amino acid
May have little functional effect	More likely to perturb structure or function
Context still matters	Context still matters

Sickle cell disease: A coding substitution

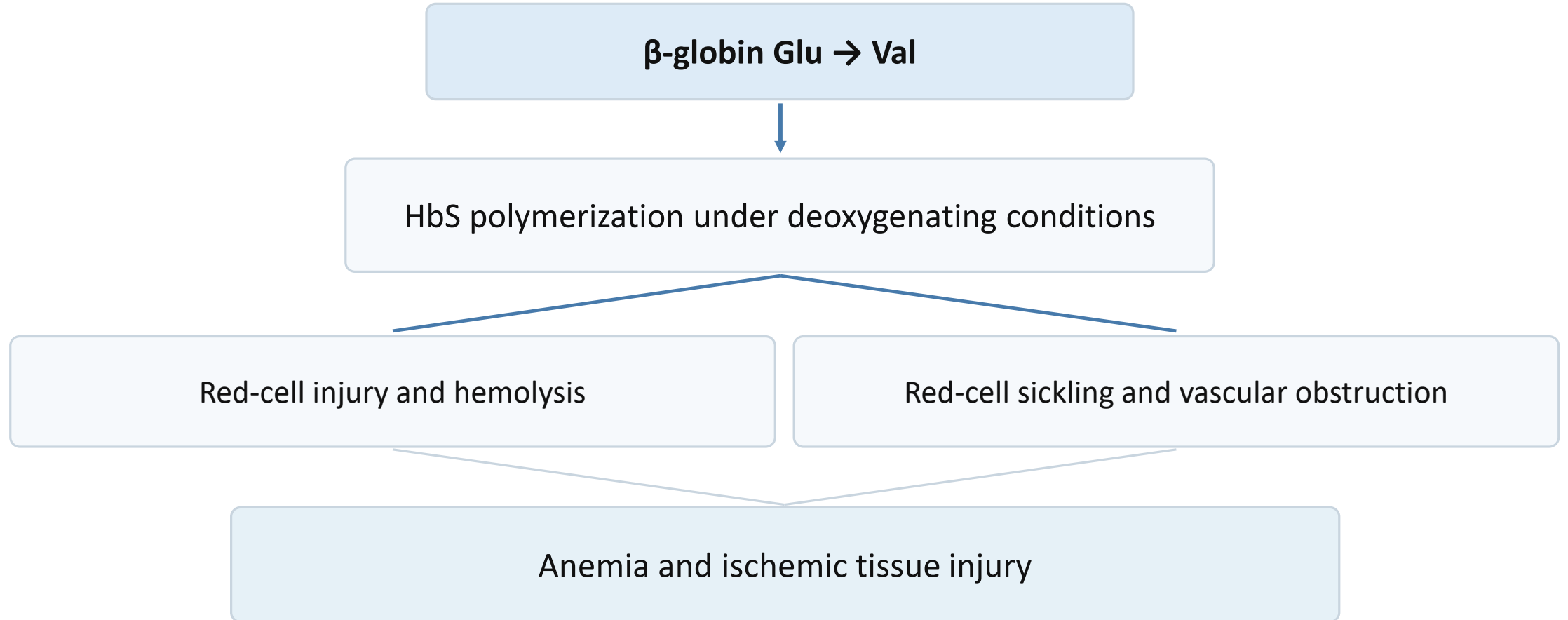
MUTATION MECHANISMS



The single amino acid change is glutamate → valine in the β -globin chain.

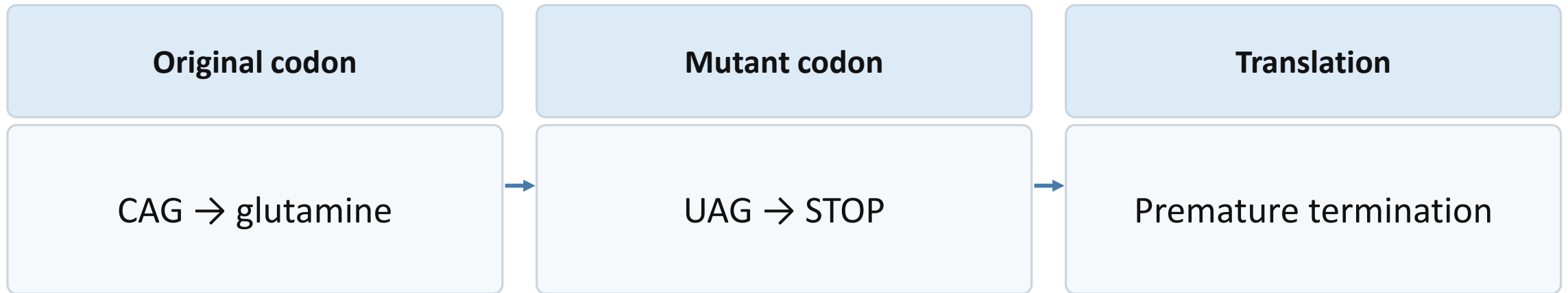
Why HbS changes red-cell behavior

MUTATION MECHANISMS



Nonsense mutation creates a premature stop

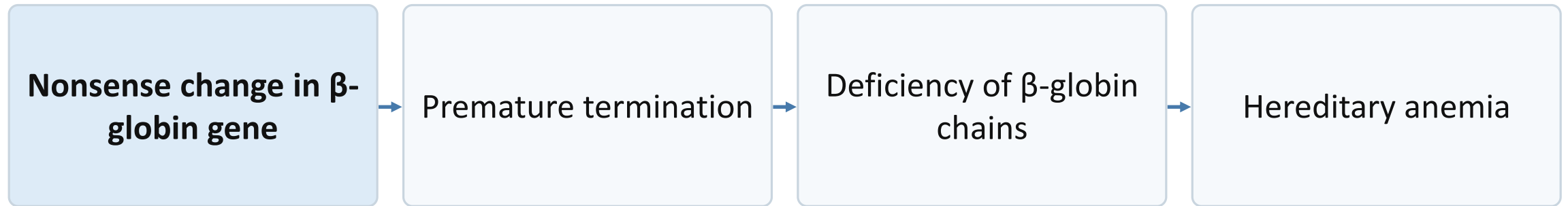
MUTATION MECHANISMS



Truncated proteins are frequently unstable or nonfunctional.

β -thalassemia: The nonsense example

MUTATION MECHANISMS



The phenotype results from reduced chain production, not an altered mature chain.

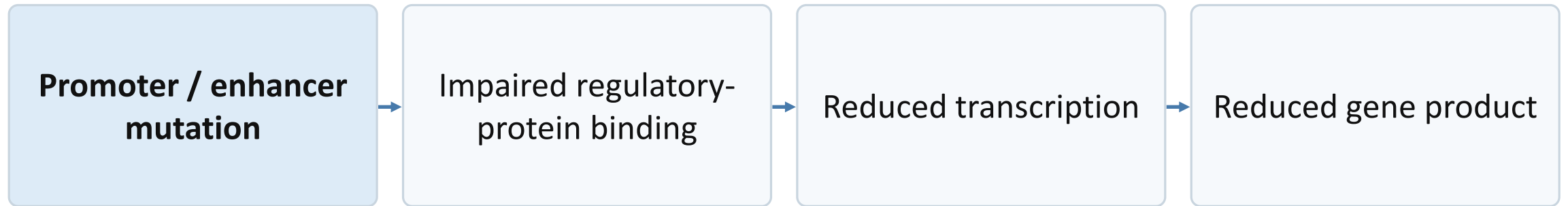
Missense and nonsense are not equivalent

MUTATION MECHANISMS

Missense	Nonsense
Codon specifies a different amino acid	Codon becomes a premature stop
Full-length protein may be produced	Protein may be truncated or absent
Sickle hemoglobin: altered behavior	Some β -thalassemias: deficient globin production

Regulatory mutations alter transcription

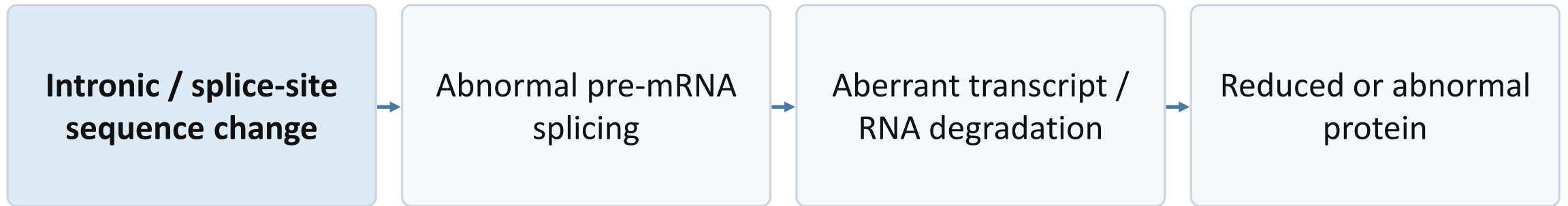
MUTATION MECHANISMS



Coding sequence can remain intact while protein production declines.

Splice-region mutations alter RNA maturation

MUTATION MECHANISMS



A gene can fail despite an apparently preserved coding exon sequence.

Insertions and deletions depend on their length

MUTATION MECHANISMS

- A coding insertion or deletion can preserve or disrupt the reading frame.
- A multiple of three nucleotides preserves triplet grouping.
- Other lengths shift downstream codons, usually with extensive effects.

ABC | DEF | GHI

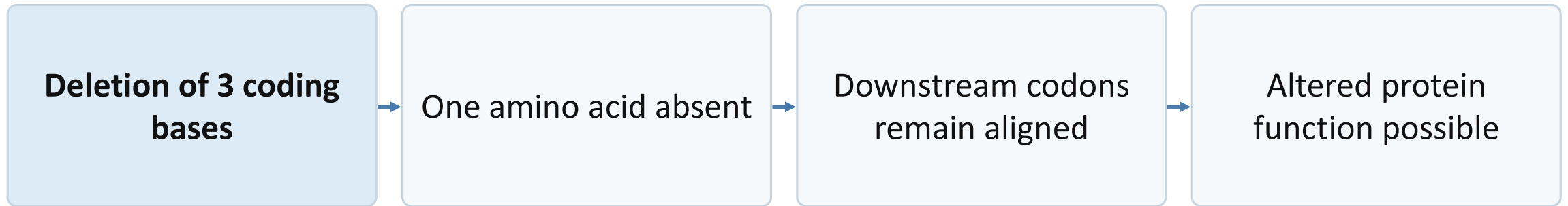
ABC | GHI

ABD | EFG | HI...

Simplified triplet schematic; Letters denote bases, not actual sequence.

In-frame deletion preserves the reading frame

MUTATION MECHANISMS



Loss of one amino acid is not synonymous with a frameshift.

CFTR Δ F508 illustrates an in-frame deletion

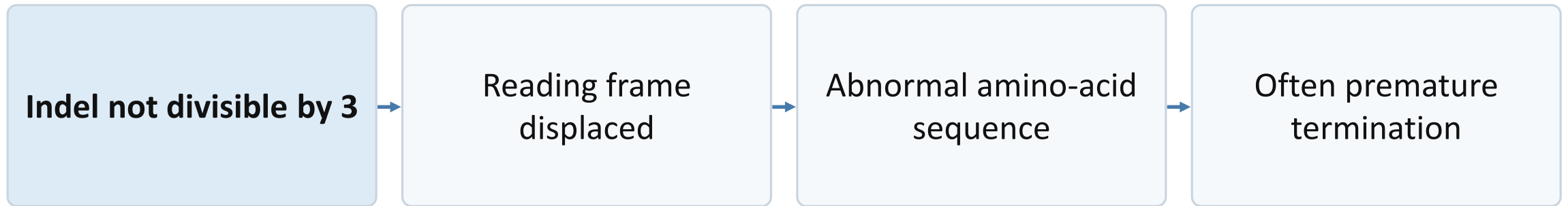
MUTATION MECHANISMS

A three-base deletion removes phenylalanine at position 508.

- The reading frame remains intact.
- The CFTR protein lacks this residue.
- The specific molecular defect is distinct from a frameshift mutation.

Frameshift changes downstream codons

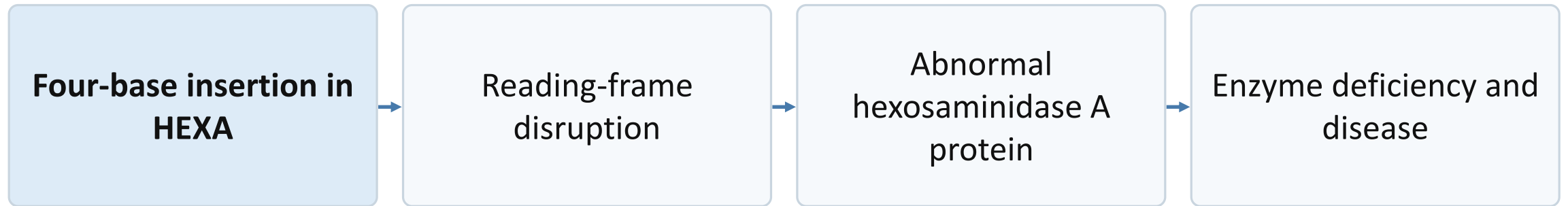
MUTATION MECHANISMS



The downstream consequence can be substantially larger than the original DNA change.

Tay–Sachs: An example of frameshift mutation

MUTATION MECHANISMS



A particular four-base insertion associated with Tay–Sachs disease.

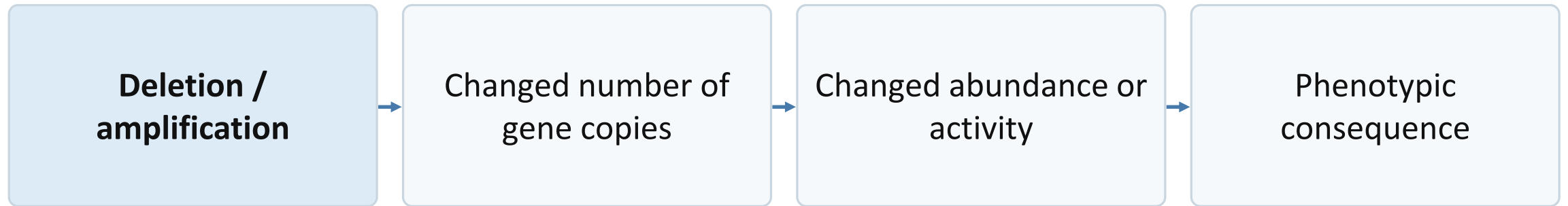
In-frame versus frameshift: Clinical reasoning

MUTATION MECHANISMS

In-frame indel	Frameshift indel
Length divisible by 3	Length not divisible by 3
Triplet grouping preserved	Triplet grouping altered
Selected residues added/removed	Downstream residues changed
May preserve substantial protein	Often introduces premature stop

Copy-number change can alter gene dosage

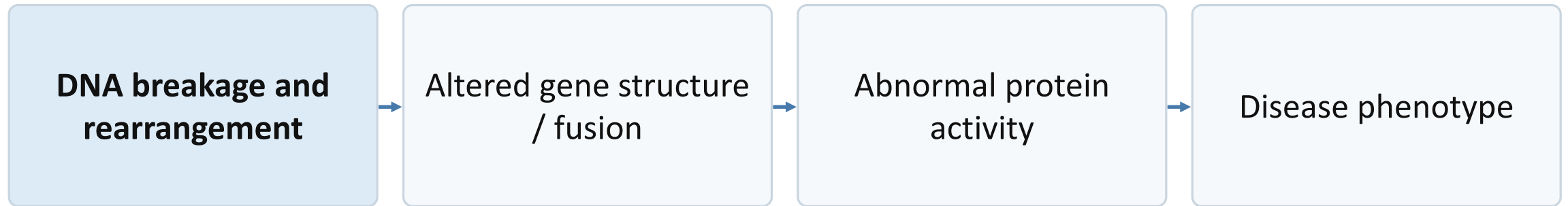
MUTATION MECHANISMS



Gene copy-number abnormalities may be germline or acquired in somatic tissues.

Gene rearrangements can create abnormal function

MUTATION MECHANISMS

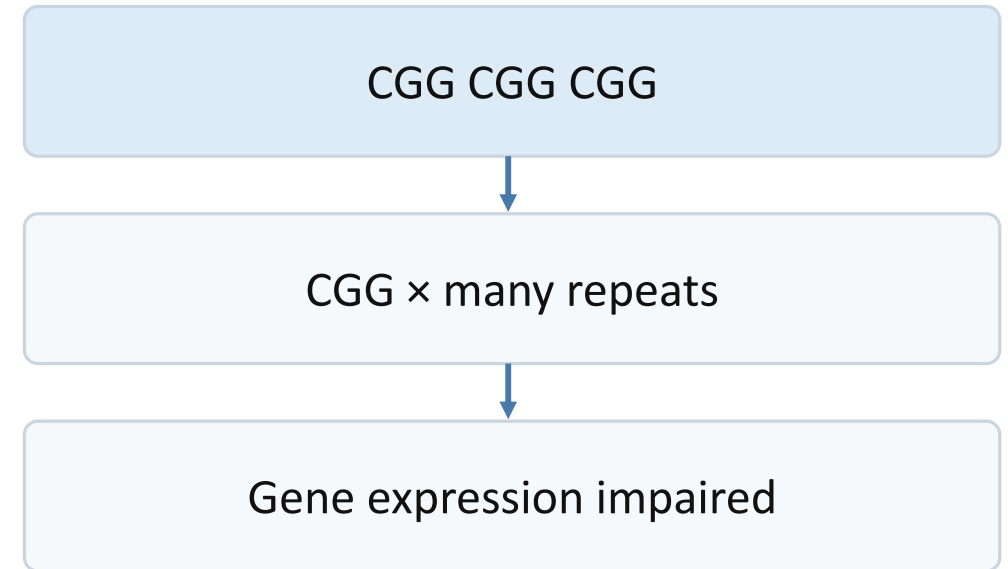


BCR–ABL rearrangement in chronic myeloid leukemia is a somatic example.

Repeat expansions behave differently

MUTATION MECHANISMS

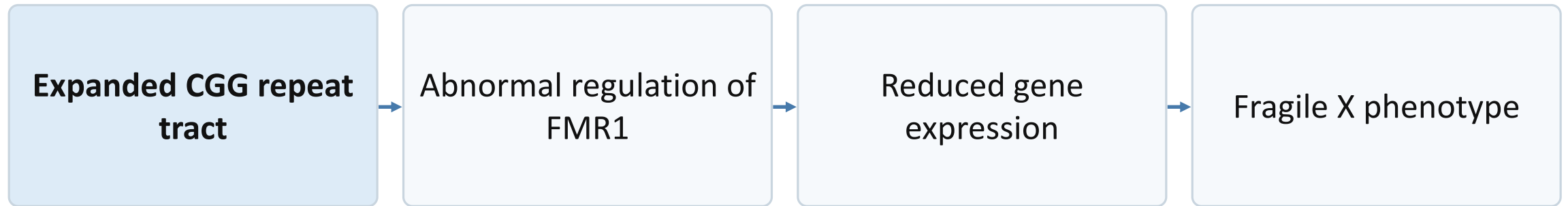
- Tandem trinucleotide sequences can expand markedly.
- Repeat length may be unstable between generations.
- The size and site of the expansion influence gene expression and phenotype.



Schematic repeat units; Not a patient sequence.

Fragile X: Expanded FMR1 CGG repeats

MUTATION MECHANISMS



FMR1 expansion as an example of a dynamic mutation.

One pathway, multiple points of disruption

MUTATION MECHANISMS

DNA



RNA



Protein



Phenotype

Coding mutation • promoter variant • deletion

Transcription loss • splice defect • premature-stop transcript

Reduced amount • truncated form • abnormal activity

Cellular failure • tissue pathology • clinical disease

What defines a monogenic disorder?

MONOGENIC DISEASE

A pathogenic mutation in one gene has a large functional effect.

- Disease often follows a recognizable Mendelian segregation pattern.
- Expression reflects both the mutant allele and the function of its gene product.
- A monogenic cause can still produce diverse clinical findings.

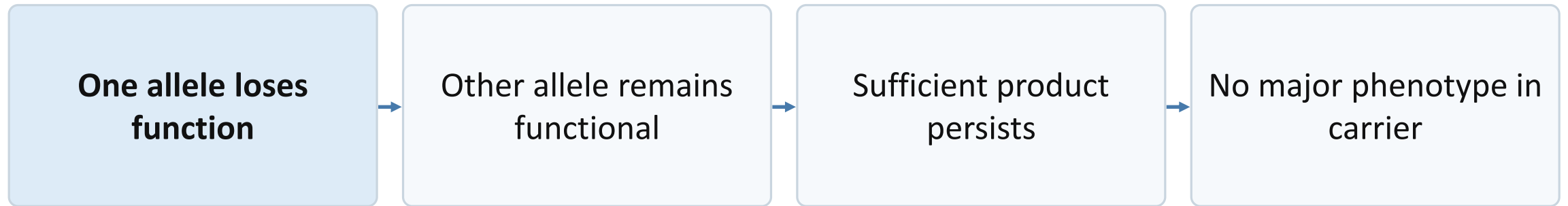
A single allele may or may not be enough

MONOGENIC DISEASE

Heterozygote	Homozygote / biallelic
One mutant copy, one functional copy	Both gene copies affected
May be asymptomatic for recessive traits	Typically manifests recessive loss of function
May manifest dominant traits	Severity depends on specific variants

Wild-type allele can compensate for loss of function

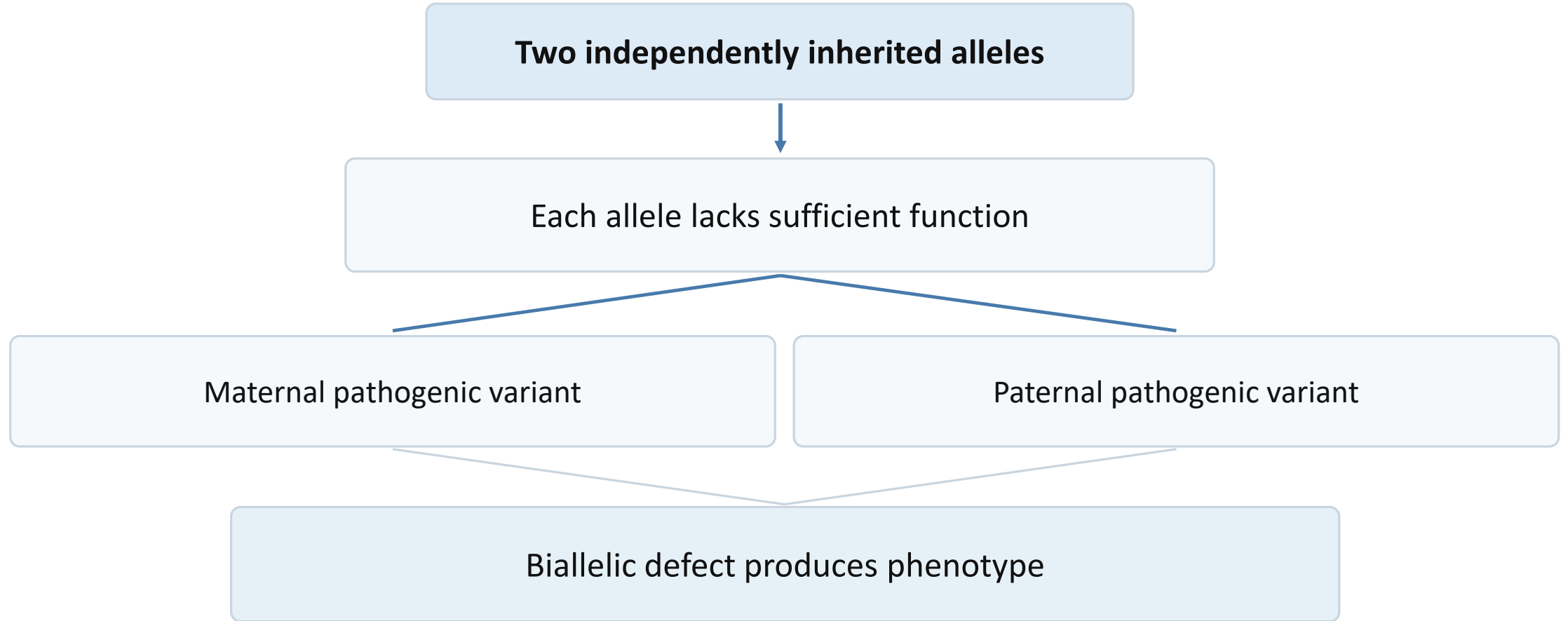
MONOGENIC DISEASE



This is a common explanation for asymptomatic heterozygous carriers.

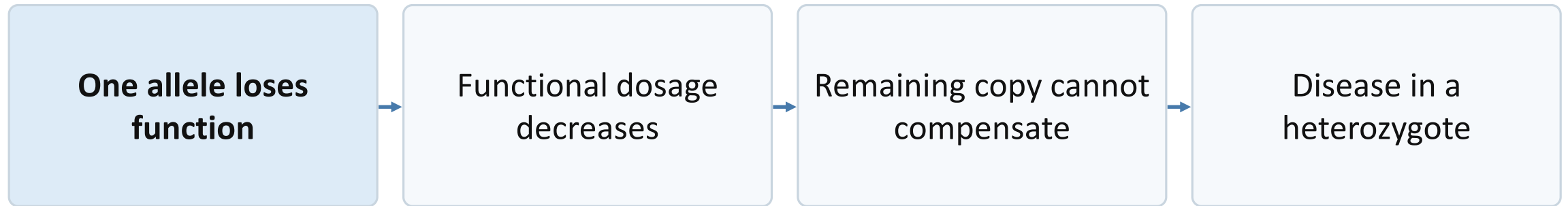
Recessive loss of function: Two hits in trans

MONOGENIC DISEASE



Haploinsufficiency: One normal copy is insufficient

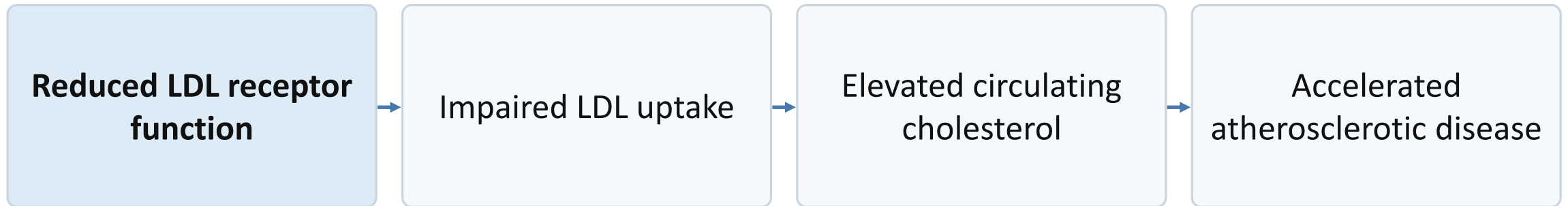
MONOGENIC DISEASE



This is one mechanism of autosomal dominant disease.

Familial hypercholesterolemia: Gene dosage matters

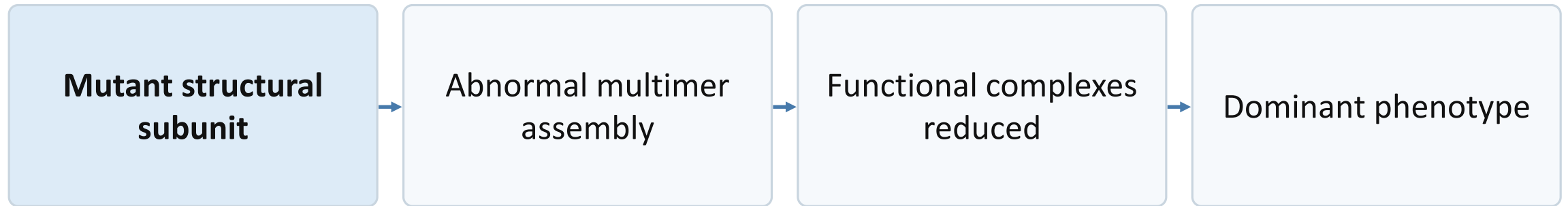
MONOGENIC DISEASE



LDL receptor haploinsufficiency in affected heterozygotes.

Dominant-negative proteins disrupt complexes

MONOGENIC DISEASE



Some collagen disorders exemplify this mechanism.

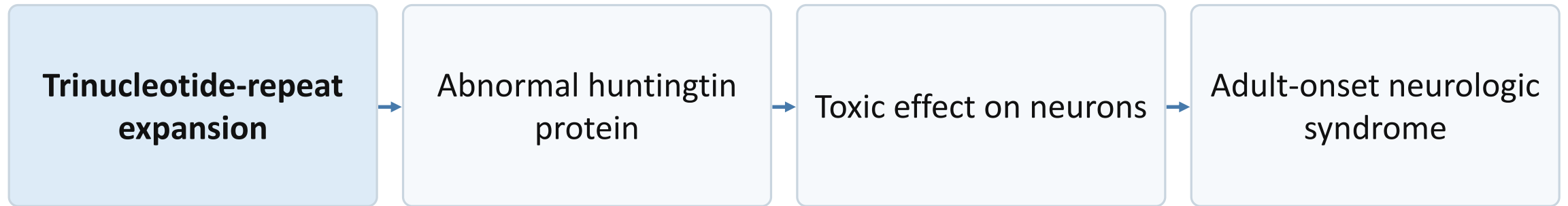
Gain of function creates excessive or new activity

MONOGENIC DISEASE

Hyperactive normal activity	New (neomorphic) activity
Protein performs its usual function excessively	Protein acquires a novel activity
Can cause disease in heterozygotes	Can cause disease in heterozygotes
Distinct from insufficient protein quantity	Distinct from classic loss of function

Huntington disease illustrates toxic protein gain

MONOGENIC DISEASE



This is not explained by simple loss of half the gene product.

Mechanism predicts more than mutation size

MONOGENIC DISEASE

Mechanism	Functional consequence	Typical pattern
Recessive loss	One normal copy sufficient	Autosomal recessive
Haploinsufficiency	One normal copy insufficient	Autosomal dominant
Dominant negative	Mutant protein impairs wild type	Often autosomal dominant
Gain of function	Abnormal or excessive activity	Often autosomal dominant

Classic transmission patterns

INHERITANCE

Autosomal dominant

Heterozygote phenotype

Autosomal recessive

Biallelic variants required

X-linked recessive

Hemizygous males often
manifest

Autosomal dominant transmission

INHERITANCE

	A	a
a	Aa	aa
a	Aa	aa

An affected heterozygote × unaffected homozygote: Each child has a 1-in-2 chance of inheriting the variant.

Autosomal dominant: The phenotype may skip recognition

INHERITANCE

- A de novo variant can occur without a previously affected parent.
- Incomplete penetrance may obscure vertical transmission.
- Some conditions manifest only after years of apparently normal health.

Autosomal recessive transmission

INHERITANCE

	A	a
A	AA	Aa
a	Aa	aa

Two heterozygous carriers: 1-in-4 affected, 1-in-2 carrier, 1-in-4 unaffected noncarrier per conception.

Compound heterozygosity is still biallelic disease

INHERITANCE

- A person can inherit two different pathogenic variants in the same gene.
- The variants reside on opposite copies (in trans).
- Neither allele supplies adequate functional product.

Maternal allele: Variant A

Paternal allele: Variant B

Two different pathogenic variants may produce recessive disease.

Autosomal recessive disorders often affect siblings

INHERITANCE

- Parents may be healthy heterozygotes.
- Brothers and sisters can be affected despite unaffected parents.
- Recurrence probability applies independently to each conception.
- Enzyme defects often exhibit this inheritance pattern.

X-linked recessive inheritance

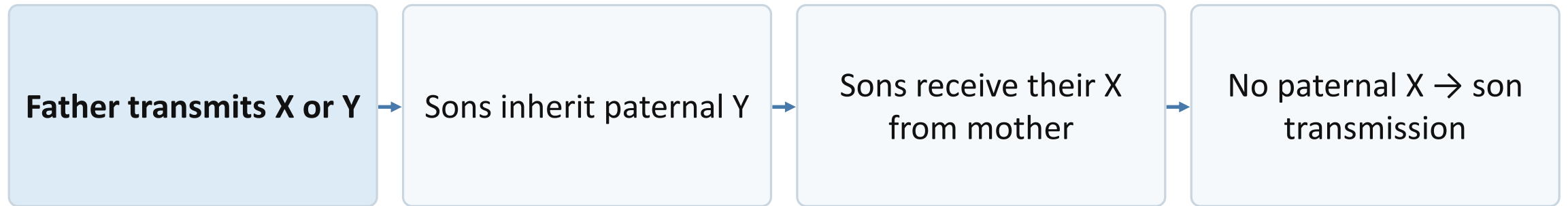
INHERITANCE

	X^N (father)	Y (father)
X^N (mother)	$X^N X^N$	$X^N Y$
X^m (mother)	$X^N X^m$	$X^m Y$

Carrier mother $\times$ unaffected father: Half of sons inherit the affected X; Half of daughters become carriers.

Why there is no father-to-son X-linked transmission

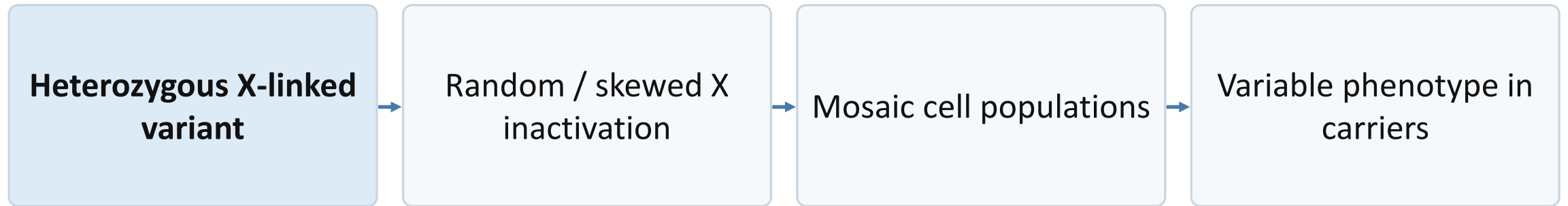
INHERITANCE



A father with an X-linked recessive variant passes his X chromosome to daughters.

X inactivation explains variable female expression

INHERITANCE



This using susceptibility to hemolysis in female G6PD carriers.

Codominance: Both alleles contribute to phenotype

GENOTYPE AND PHENOTYPE

Neither expressed allele is necessarily masked by the other.

- Both inherited alleles can contribute detectable products.
- AB blood-group antigens are a classic example.
- Histocompatibility antigens also exhibit codominant expression.

AB blood group: Two detectable antigen products

GENOTYPE AND PHENOTYPE

- The A and B alleles each contribute an expressed blood-group antigen.
- The AB phenotype demonstrates expression from both alleles.
- Codominance should not be confused with incomplete penetrance.

A allele → A antigen

B allele → B antigen

Two allelic products coexist in the same phenotype.

Penetrance asks whether a phenotype appears

GENOTYPE AND PHENOTYPE

Complete penetrance	Incomplete penetrance
All variant carriers express the trait	Only a fraction of carriers express it
Genotype predicts presence of disease	Apparently unaffected carrier may exist
Expression can still vary in severity	Nonexpression is not evidence of absent allele

Expressivity asks how strongly it appears

GENOTYPE AND PHENOTYPE

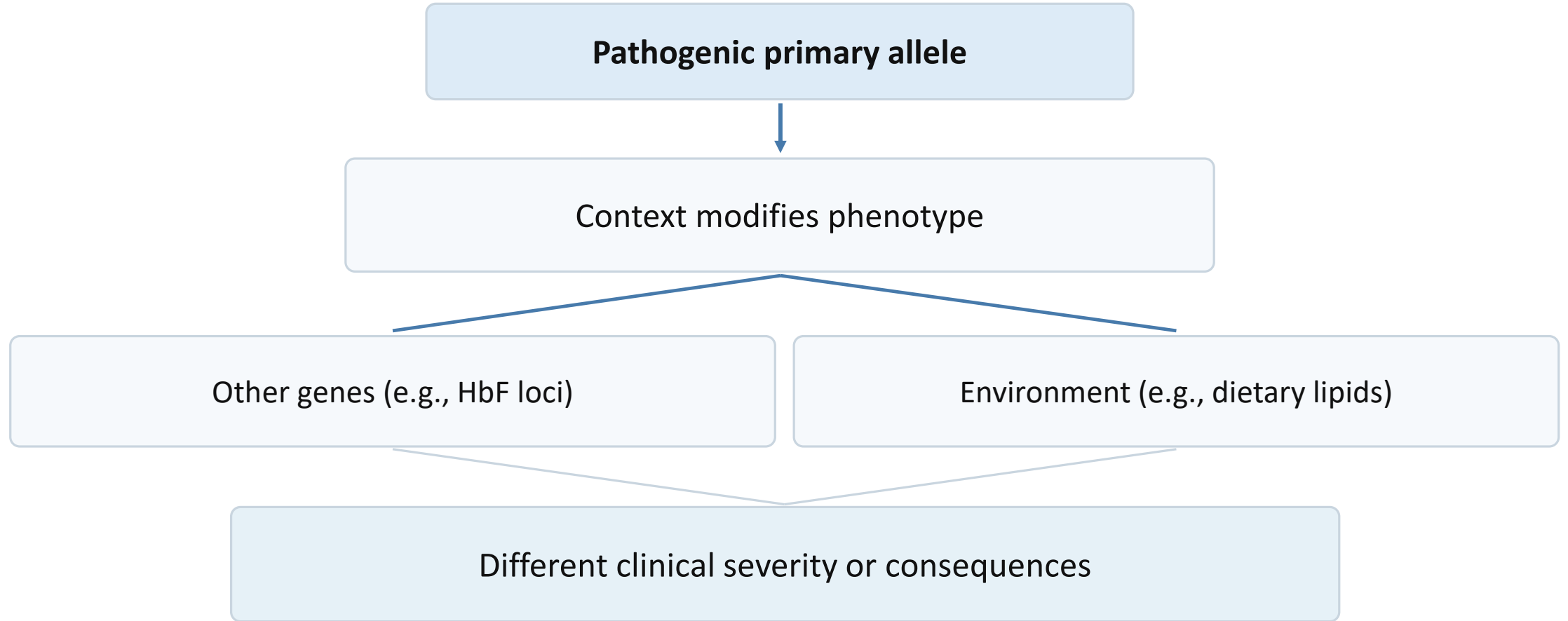
- Variable expressivity occurs among individuals who exhibit the trait.
- Phenotype can range from mild to severe even for one genetic condition.
- Neurofibromatosis type 1 to illustrate this range.



Illustrative spectrum, not measured severity data.

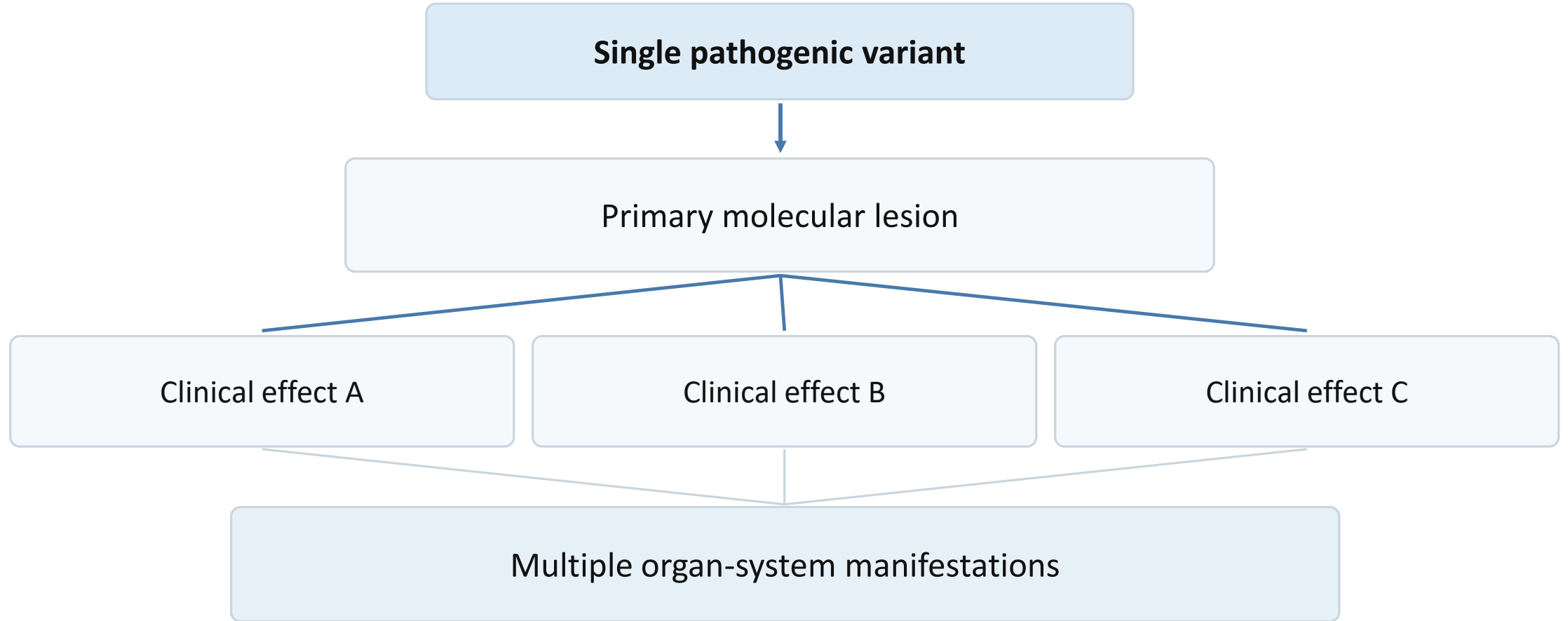
Modifier genes and environment influence expression

GENOTYPE AND PHENOTYPE



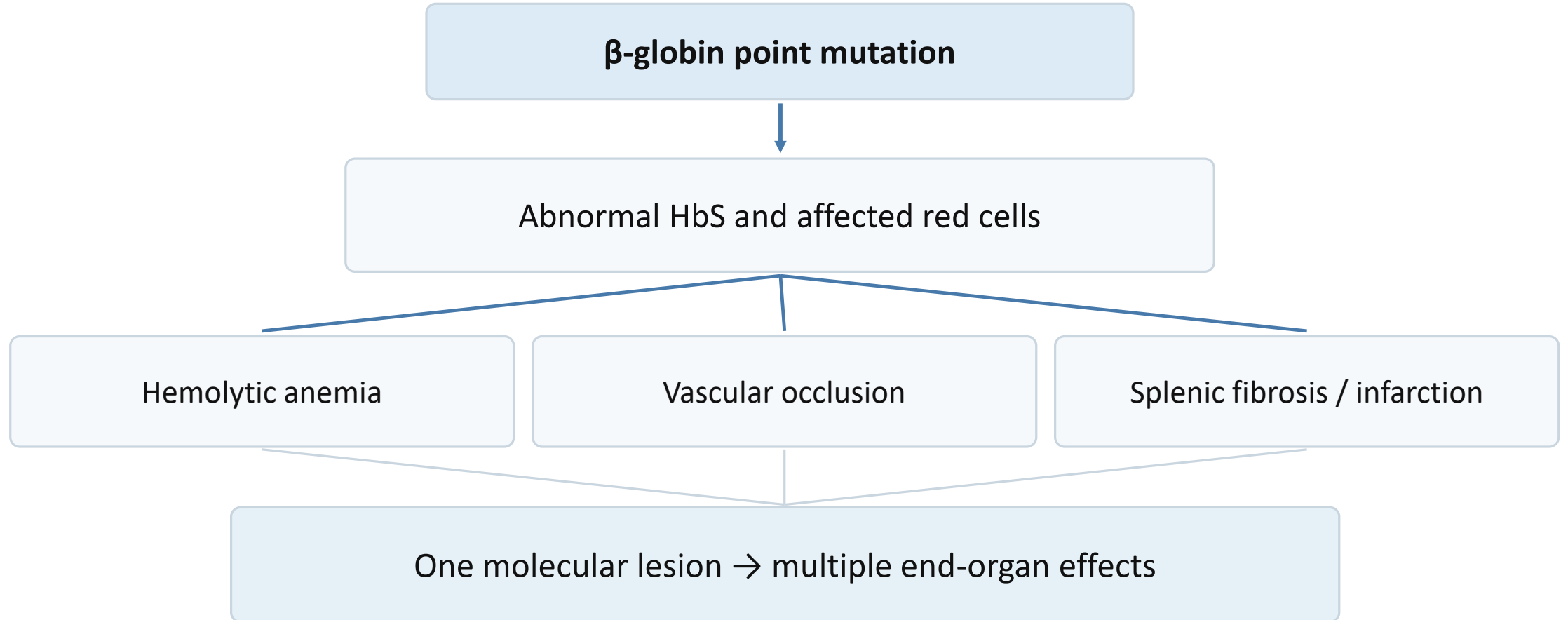
Pleiotropism: One mutation, many consequences

GENOTYPE AND PHENOTYPE



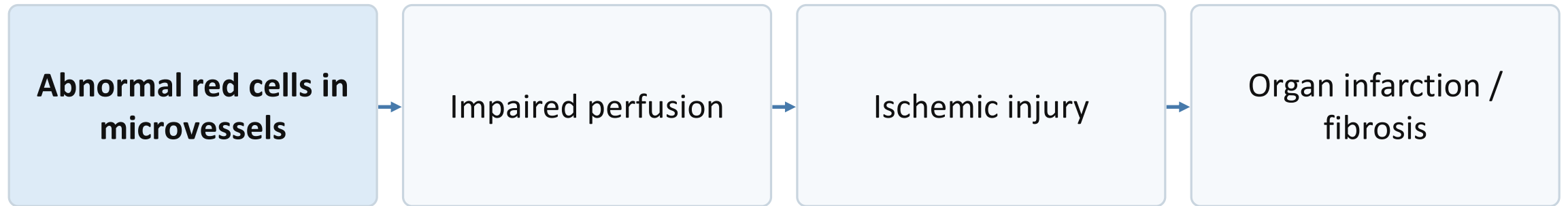
Sickle cell disease illustrates pleiotropism

GENOTYPE AND PHENOTYPE



From vascular obstruction to tissue damage

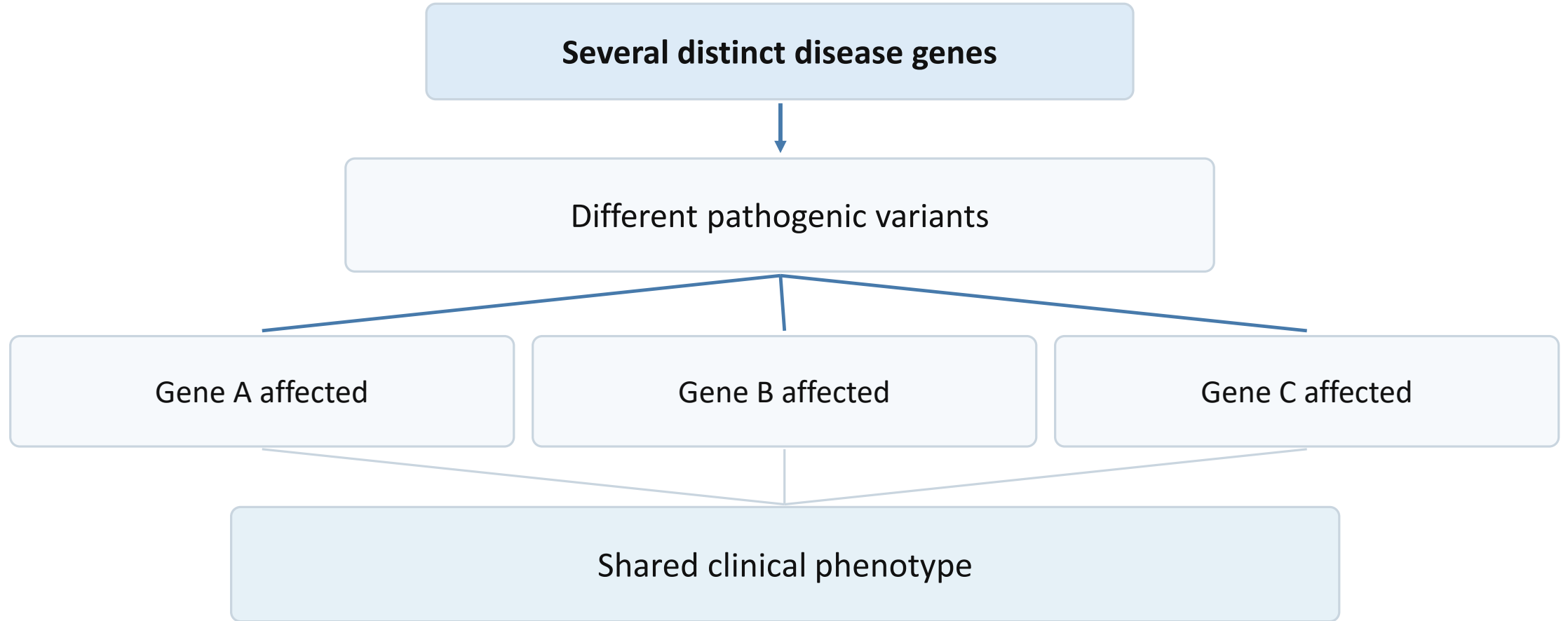
GENOTYPE AND PHENOTYPE



The tissue changes are consequences of the primary hemoglobin defect.

Genetic heterogeneity: Many genes, similar phenotype

GENOTYPE AND PHENOTYPE



Congenital deafness illustrates locus heterogeneity

GENOTYPE AND PHENOTYPE

An apparently homogeneous clinical phenotype may have multiple genetic causes.

- Profound congenital deafness as an example.
- Distinct autosomal recessive loci may cause similar hearing-loss phenotypes.
- Phenotype alone may not identify the causal gene.

Pleiotropism versus genetic heterogeneity

GENOTYPE AND PHENOTYPE

Pleiotropism	Genetic heterogeneity
One mutation	Different genetic loci
Many phenotypic effects	A similar phenotype
Sickle cell disease	Congenital deafness
One cause → many consequences	Many causes → similar consequence

Case: A healthy couple has an affected child

APPLICATION

Illustrative teaching case

Two unaffected parents have a child with a severe enzyme deficiency. Both parents carry a pathogenic variant in the same autosomal gene.

Which inheritance pattern fits, and what is the recurrence probability?

Answer and rationale are recorded in the speaker notes.

Case: One variant, multiple organ injuries

APPLICATION

Illustrative teaching case

A patient has a β -globin mutation, chronic hemolysis, and ischemic injury involving several organs.

Which genetic concept unifies these apparently different findings?

Answer and rationale are recorded in the speaker notes.

Case: One diagnosis, different genes

APPLICATION

Illustrative teaching case

Two unrelated families have profound congenital deafness but have pathogenic variants in different autosomal genes.

Which genetic principle explains the same clinical description?

Answer and rationale are recorded in the speaker notes.

An efficient approach to monogenic disease

APPLICATION

1. Define the variant

Coding • regulatory • splice • structural • repeat



2. Determine gene-product effect

Absent • reduced • altered • excessive • toxic



3. Infer allele behavior

Dominant • recessive • codominant



4. Explain phenotype

Tissue consequences • penetrance • expressivity

Major lessons from single-gene disorders

SYNTHESIS

- Monogenic disease is defined by a large-effect alteration in one gene.
- The biochemical effect of the allele determines much of the inheritance pattern.
- Pleiotropism links one mutation to multiple manifestations; Heterogeneity links multiple genes to one phenotype.
- Penetrance, expressivity, age of onset and modifying factors complicate prediction.

Source and interpretive scope

SYNTHESIS

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 5: Genes and Human Diseases, pp. 122–127.
- Central heading: “Single-Gene Disorders,” p. 124; adjacent sections: Mutations and Transmission Patterns of Single-Gene Disorders.
- Original conceptual schematics and practice vignettes; no reproduced pathology figures or generated specimens.