

Gonadal Mosaicism

Germ-cell lineage mutations, unexpected recurrence, and
comparison with somatic mosaicism

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Learning outcomes

- Explain why phenotypically normal parents may have more than one affected child.
- Trace the postzygotic origin of gonadal mosaicism and its transmission through gametes.
- Distinguish germ-lineage mosaicism from the regional overgrowth of somatic mosaicism.
- Interpret the examples of osteogenesis imperfecta and paternal-age–associated mutations.

The usual autosomal dominant pedigree



- A pathogenic heterozygous variant often produces disease in the carrier.
- Typically, an affected parent can transmit that variant to a child.

Normal parents do not exclude dominant disease

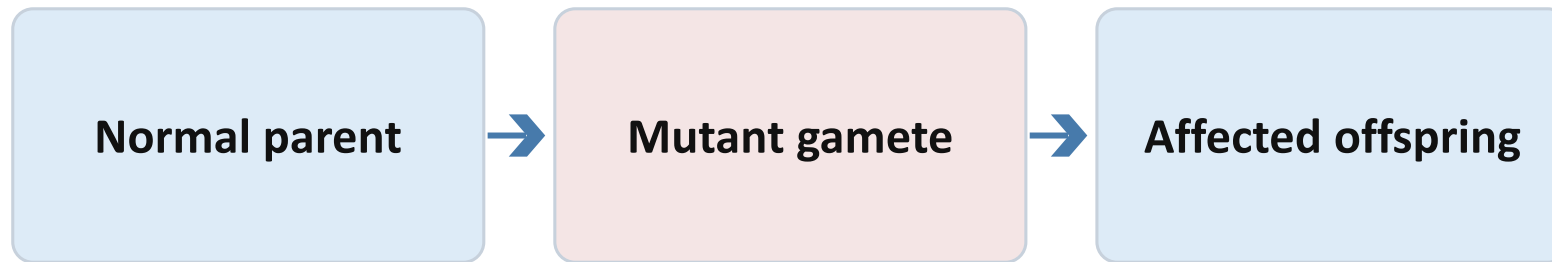
Phenotype observed

One child may carry a new pathogenic variant despite unaffected parents.

Genotype transmitted

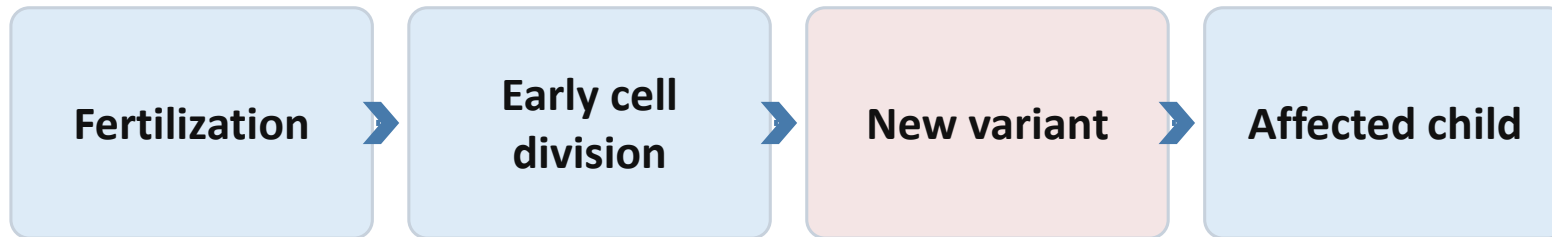
Unaffected parental phenotype is not a complete statement about germ cells.

A new variant may begin in a single gamete



- The mutation originates in the egg or sperm contributing to conception.
- The child may have a dominant disorder even though neither parent is clinically affected.

A mutation may occur shortly after fertilization



- The textbook also describes very early embryonic mutation as an origin of apparently sporadic disease.
- The affected child need not have inherited a pre-existing parental mutation.

Why a single sporadic case can look straightforward

Single-child event

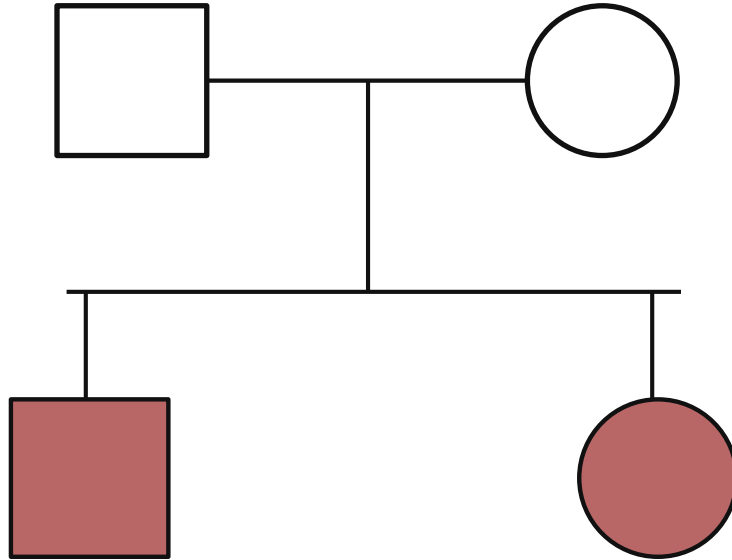
One de novo event may explain the first affected child.

Parental germ-lineage clone

The ordinary sporadic-case model does not itself require a parent with mutant germ cells.

A second affected sibling poses a new question

Phenotypically normal parents



Two affected children

Conceptual pedigree — affected/unaffected symbols only

- Two affected offspring born to phenotypically normal parents prompt reconsideration.
- A single independent mutation in the first child does not explain recurrence.

Osteogenesis imperfecta illustrates the exception

- Osteogenesis imperfecta as an autosomal dominant example.
- An apparently unaffected couple can have more than one affected child.
- Gonadal mosaicism offers a mechanistic explanation for such a pedigree.

Mendelian transmission is not abolished

Allele effect in child

A mutant allele can still act dominantly in an offspring.

Distribution in parent

The unusual feature is its nonuniform presence in the germ cells of an unaffected parent.

Gonadal mosaicism: The defining feature

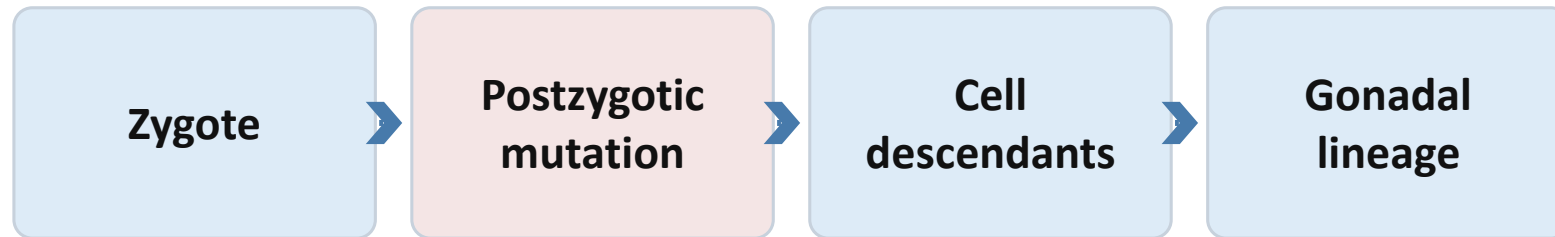
Mutant germ-cell lineage

A pathogenic mutation occupies some germ-cell precursors or gametes.

Clinically normal soma

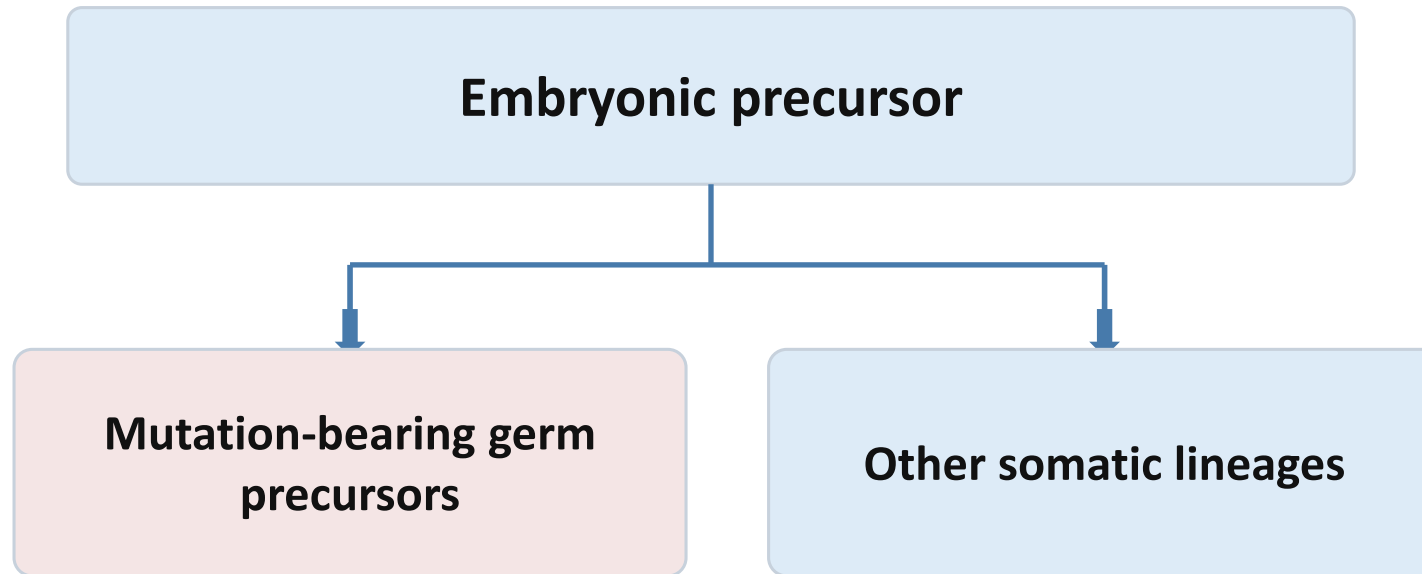
The parent's somatic tissues may be unaffected, leaving no overt phenotype.

The initiating event is postzygotic



- The mutation occurs after fertilization during the parent's early embryogenesis.
- Its descendants form a lineage rather than replacing every cell of the parent.

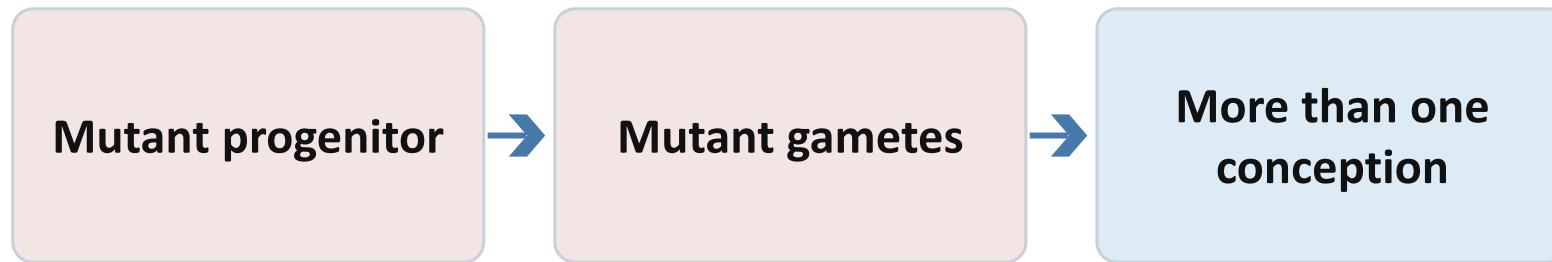
Developmental lineage determines the outcome



Schematic: Descendant-cell distribution

- A postzygotic event is propagated only to descendants of the mutant cell.
- If descendants enter germ-cell precursors, mutant gametes can be produced.

The germ-cell precursor is the critical compartment



- Mutation in a progenitor can produce multiple genetically related gametes.
- This is why the same pathogenic variant may recur in siblings.

The somatic phenotype may remain normal

Somatic tissues: Normal

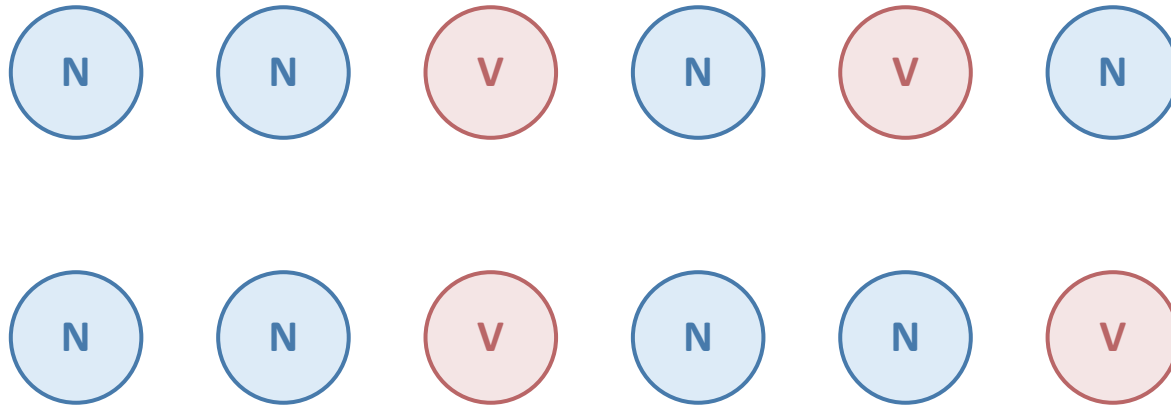
The parent's clinically examined body tissues may lack the mutation.

Some germ cells: Mutant

Absence of a visible disorder therefore does not eliminate a germ-lineage mechanism.

A mosaic gonad makes nonidentical gametes

Gamete population (illustrative, not quantitative)



N: No modeled variant V: Modeled variant

- Both variant-bearing and variant-free gametes may arise.
- The illustrated mixture is conceptual and does not encode a measured proportion.

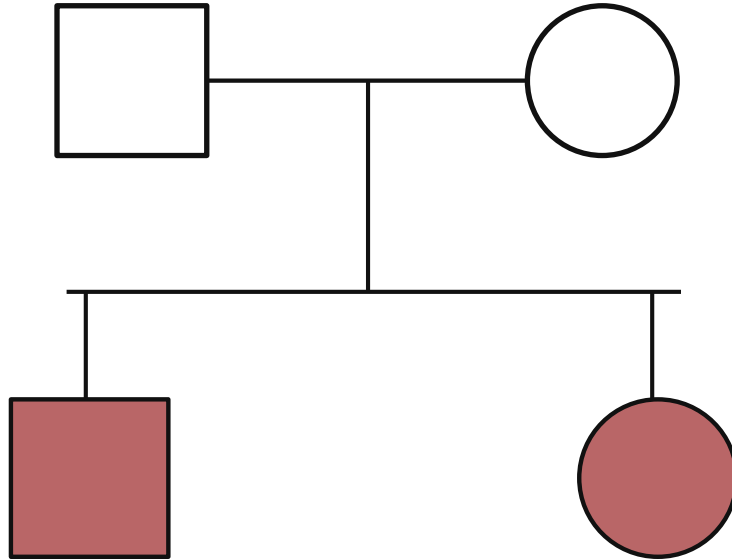
A mutant gamete can initiate an affected child



- A variant-bearing sperm or egg participates in fertilization.
- The resulting child can manifest the autosomal dominant phenotype.

One parental lineage can yield repeated transmission

Phenotypically normal parents



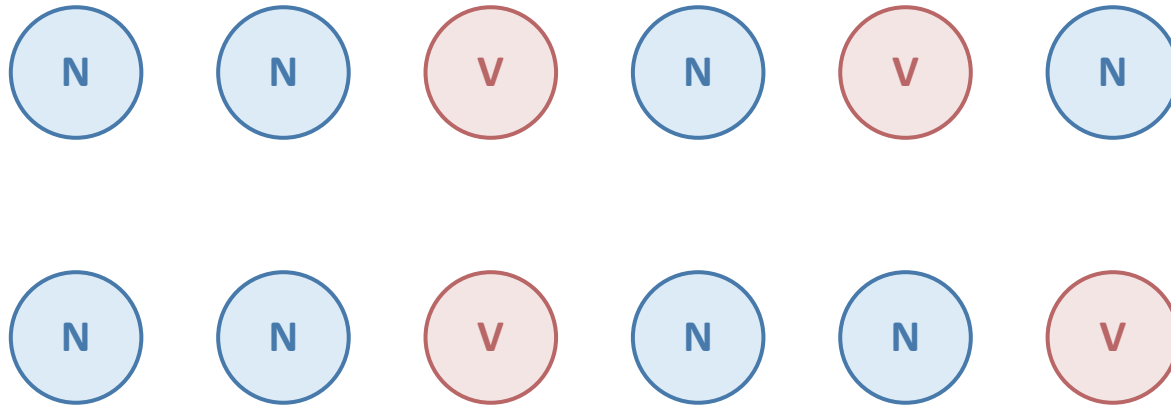
Two affected children

Conceptual pedigree — affected/unaffected symbols only

- Multiple offspring may receive variant-bearing gametes from the same parent.
- This is recurrence through the parental germ-cell population, not transmission between siblings.

The fraction of mutant gametes matters

Gamete population (illustrative, not quantitative)



N: No modeled variant V: Modeled variant

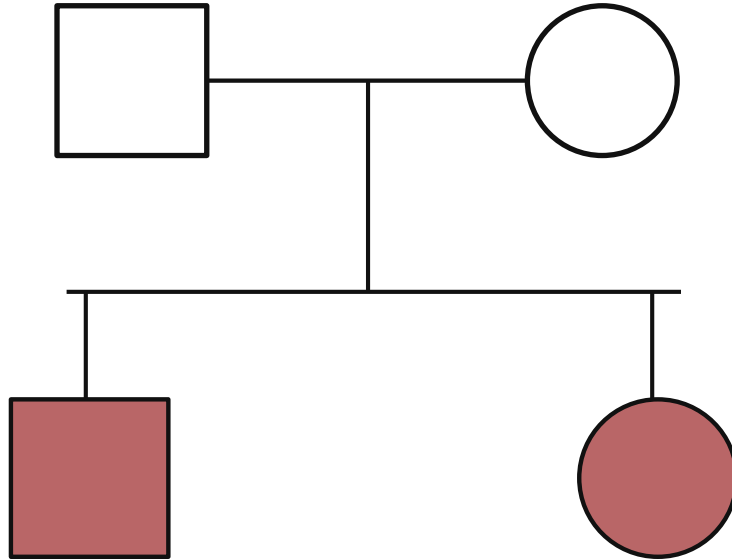
- Recurrence likelihood to the proportion of germ cells carrying the mutation.
- Without measuring or otherwise characterizing that proportion, a specific family risk cannot be inferred here.

A standard 50% rule cannot simply be copied

Situation	Transmission interpretation
Constitutionally heterozygous parent	Classic dominant model: each conception can inherit one of two alleles.
Gonadal mosaic parent	Gametes arise from mixed mutant and nonmutant precursors; proportion is uncertain.

The pedigree may hide the causal mosaicism

Phenotypically normal parents



Two affected children

Conceptual pedigree — affected/unaffected symbols only

- The parent appears unaffected because phenotype tracks somatic distribution.
- Siblings reveal a transmitted pathogenic variant, suggesting a parental germ-cell source.

Which cells carry the variant is more informative than appearance

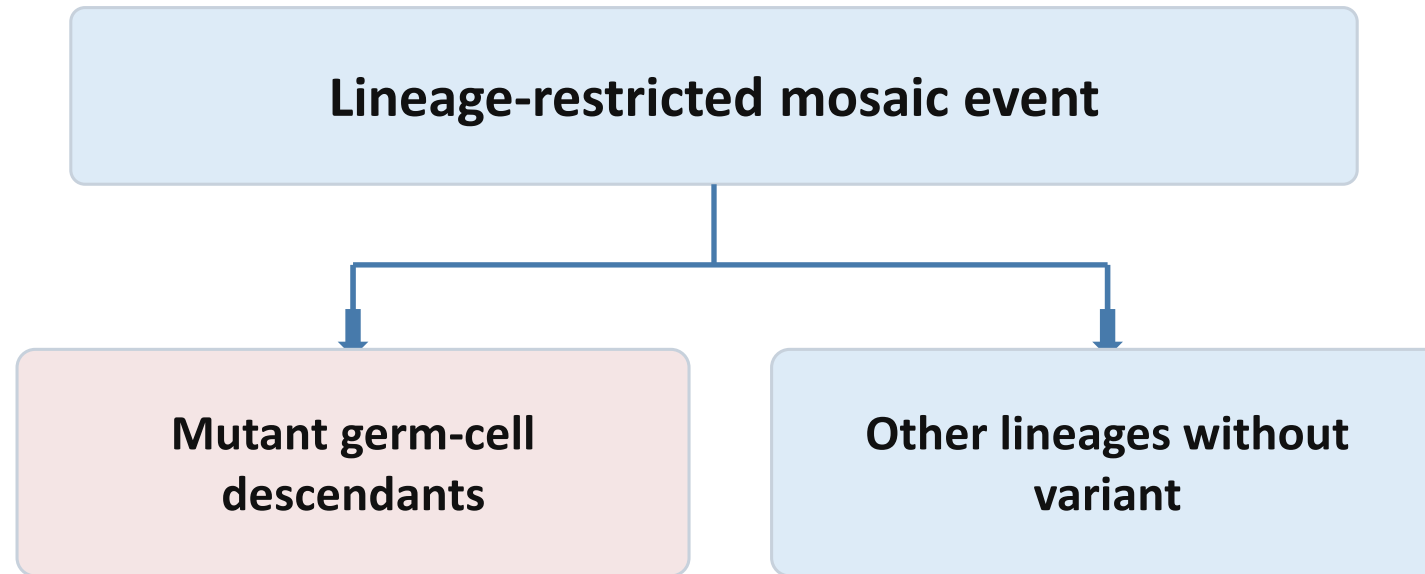
Observed phenotype

Phenotype describes what is observed in the person.

Cellular genotype distribution

Mosaic distribution describes which cell lineages carry the mutation.

Mutation timing affects cellular distribution



Schematic: Descendant-cell distribution

- A postzygotic mutation may populate only selected descendant lineages.
- The text specifically identifies gonad-directed mutant lineages as the source of transmission.

Germline-restricted and somatic mosaicism differ

Feature	Gonadal mosaicism	Somatic mosaicism
Cell population	Germ-cell lineage / gametes	A subset of body tissues
Immediate clue	Unexpected recurrence in siblings	Regional or asymmetric phenotype
Transmission emphasis	May transmit mutant gametes	Tissue growth or function in carrier

An unaffected parent's somatic test has limits

Sampled somatic cells

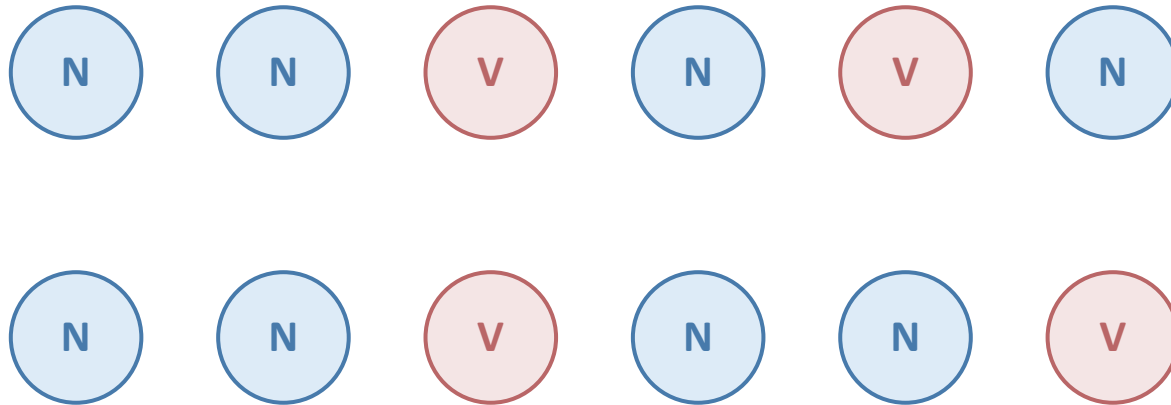
Testing a somatic specimen addresses variants present in that specimen.

Unsampled germ cells

A variant restricted to germ-cell precursors could be absent from that sample.

An illustrative germ-cell model is not a risk estimate

Gamete population (illustrative, not quantitative)



N: No modeled variant V: Modeled variant

- The relative numbers of circles are for mechanism teaching only.
- Robbins provides no universal numeric recurrence percentage for gonadal mosaicism.

Reproductive recurrence is a lineage property



- Embryonic mutant progenitor → mutant gametes → possible affected offspring.
- A repeated event need not imply two independent, identical de novo mutations.

Osteogenesis imperfecta: Interpreting family history

HYPOTHETICAL TEACHING CASE

Hypothetical: Two children show a clinically recognized dominant skeletal disorder; Both parents appear unaffected.

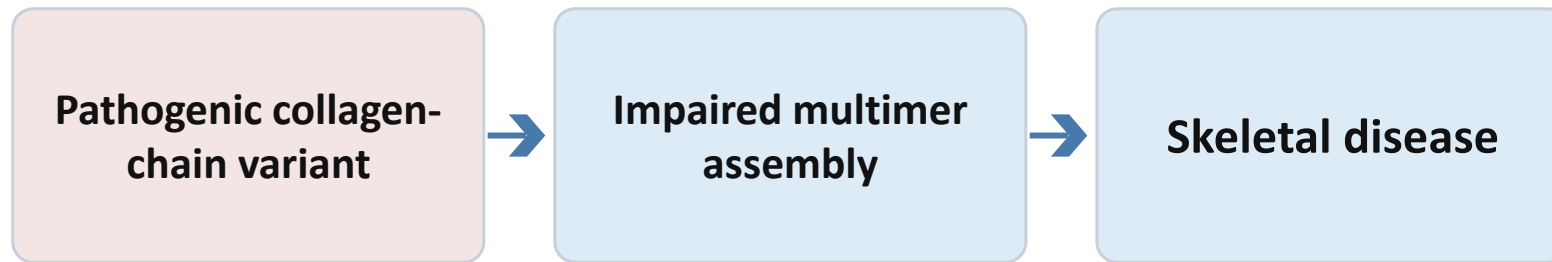
Question: Which biological compartment in a parent can explain repeated transmission?

Case mechanism: Parental germ-cell mosaicism

Mechanistic interpretation

- A postzygotic parental mutation can populate gamete precursors.
- More than one mutant gamete can produce affected children despite a normal parental phenotype.

Dominant collagen disorders add a mechanistic layer



- Some osteogenesis imperfecta variants as dominant-negative collagen defects.
- A variant inherited by the child can impair normal collagen multimer assembly.

Mutation origin and molecular effect are distinct

Lineage-level question

Origin: When and in which parental cell lineage did the mutation arise?

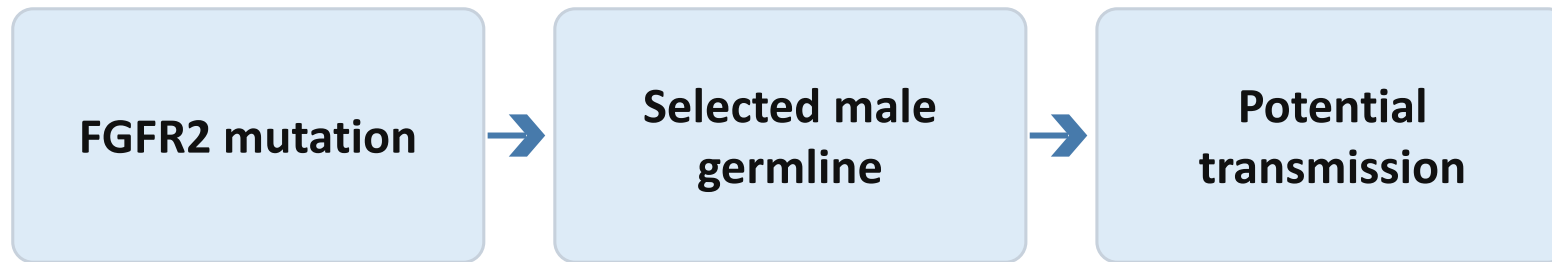
Molecular-level question

Effect: What does the inherited variant do to the child's protein or phenotype?

Paternal age is relevant to a restricted subset

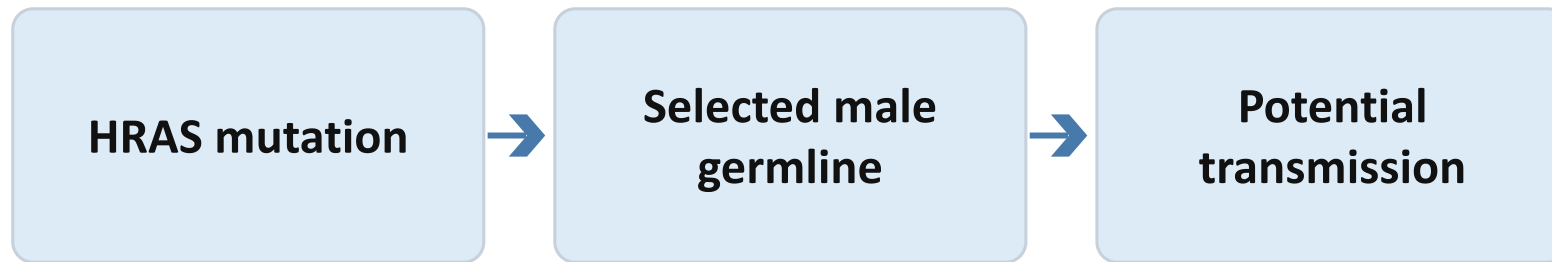
- Increased paternal-age association for certain mutations.
- This must not be generalized to all mosaic disorders or all autosomal dominant diseases.
- The described mechanism involves positive selection in the male germline.

Apert syndrome is an FGFR2 example



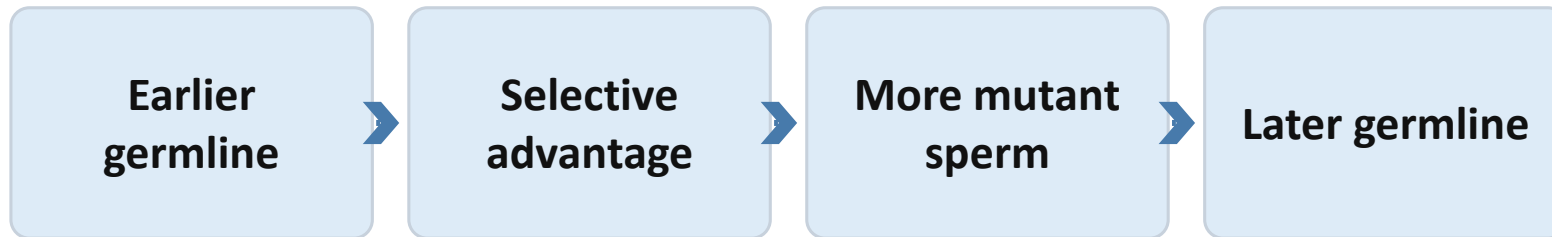
- Apert syndrome is cited with pathogenic FGFR2 mutations.
- It among disorders showing a paternal-age-associated increase.

Costello syndrome is an HRAS example



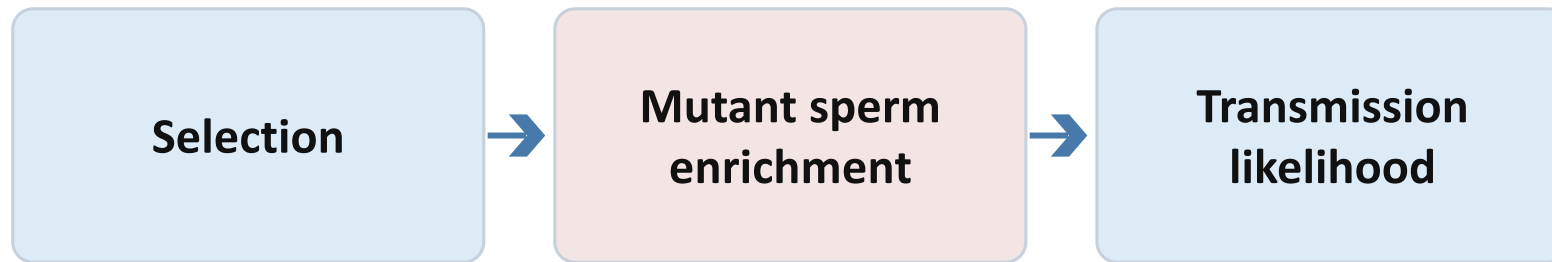
- Costello syndrome is cited with HRAS mutations.
- Its inclusion illustrates a similar male-germline selection phenomenon.

Positive selection changes clonal representation



- Some mutations favor expansion or persistence of mutant sperm-forming lineages.
- Their relative representation can increase during a father's reproductive lifespan.

Representation and transmission risk are linked



- Mutant sperm representation can increase with age for these examples.
- A greater relative presence among sperm can increase the likelihood of passing on that mutation.

Aging and mosaicism are not interchangeable

Question	Ordinary gonadal mosaicism	Selected male germline
Why mutant gametes exist	Postzygotic mutant precursor lineage	Mutant lineage with positive selection
What determines transmission	Mutant germ-cell fraction	Representation may change with paternal age
Applies to	The germline mosaicism mechanism	Specified mutation classes only

The paternal-age model is mutation-specific

- The textbook examples are FGFR2-associated Apert and HRAS-associated Costello syndromes.
- The selective advantage is a property of particular mutations and contexts.
- Do not infer the same time course for osteogenesis imperfecta or every autosomal dominant variant.

Somatic mosaicism concerns body-cell lineages

Somatic mutant clone

Mutation-bearing cells form a subset of the individual's somatic tissues.

Tissue-restricted phenotype

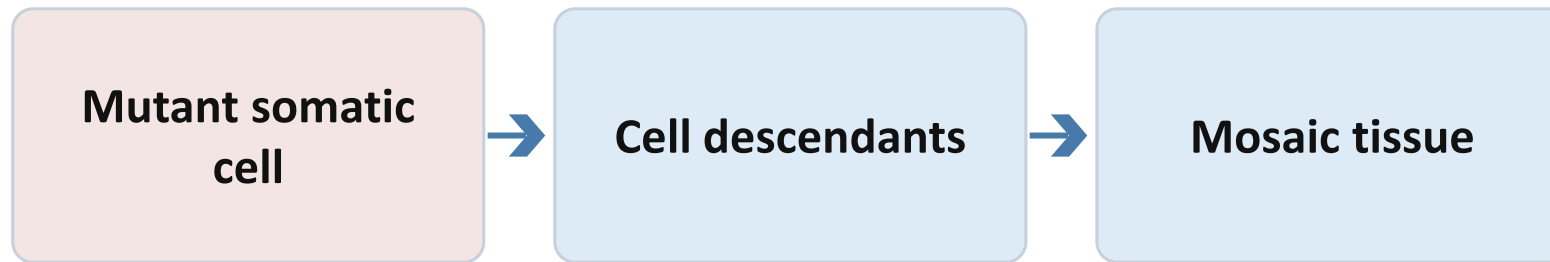
Clinical consequences follow the distribution and activity of those cells.

Somatic mutations arise during normal life



- Somatic changes across tissue growth, development and aging.
- A postzygotic mutation does not necessarily indicate inherited disease.

Clonal expansion is one possible fate



- A mutation in a cell may be propagated to numerous descendants.
- Sequencing studies reveal recurrent expanded mutant populations in normal tissues.

Potentially oncogenic does not mean cancer

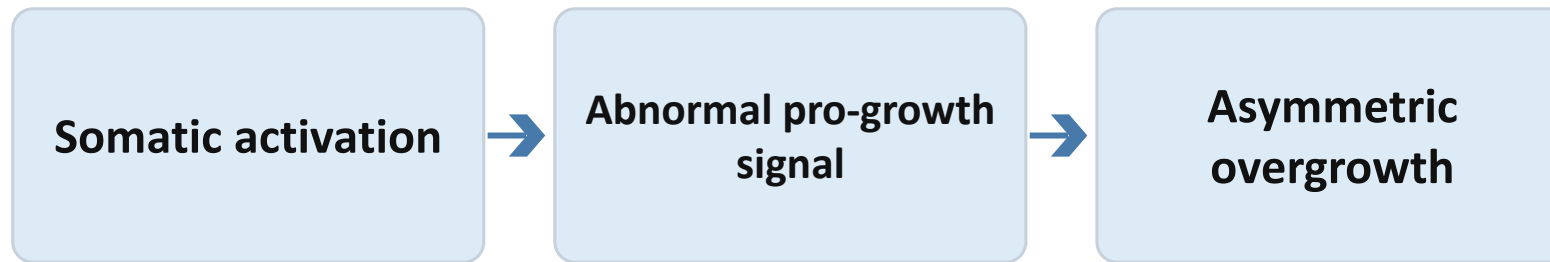
Potential driver activity

Some recurrent somatic changes are potentially oncogenic.

Not sufficient alone for cancer

In isolation, they can be insufficient to cause malignancy.

An important presentation is regional overgrowth



- Activating somatic mutations can produce local excess growth.
- The result can be asymmetry between affected and unaffected anatomical regions.

Several named phenotypes belong to the spectrum

- Proteus syndrome is listed among somatic overgrowth disorders.
- CLOVES syndrome encompasses congenital lipomatous overgrowth and malformation features.
- Robbins also names megalencephaly–polymicrogyria–polydactyly–hydrocephalus syndrome.

CLOVES is a multisystem acronym

Congenital, lipomatous overgrowth

Vascular malformations

Epidermal nevi

Spinal/skeletal anomalies or
scoliosis

PIK3CA–AKT–mTOR regulates growth signals



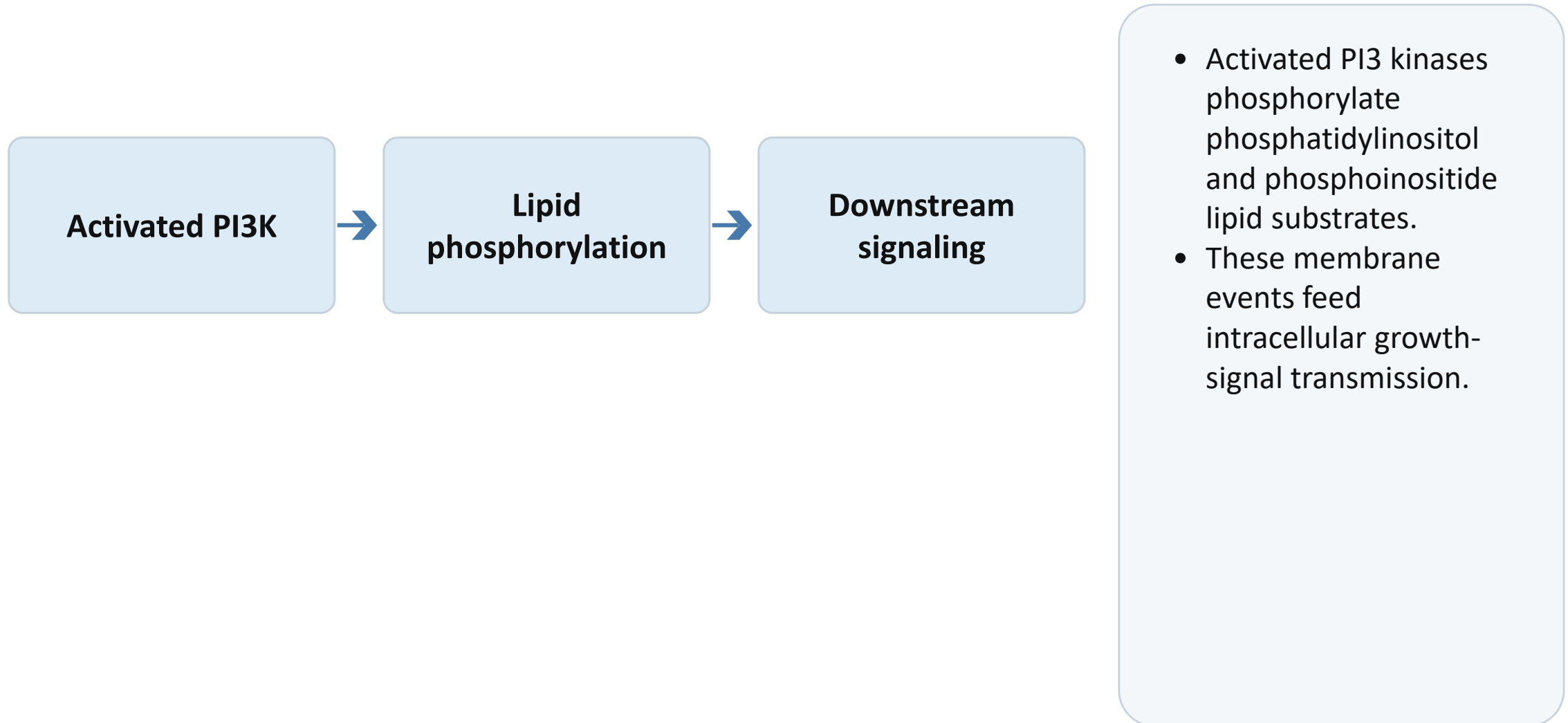
- Activating mutations in components of this signaling system.
- The pathway links extracellular growth-factor stimulation with intracellular pro-growth effects.

Growth factors normally engage surface receptors

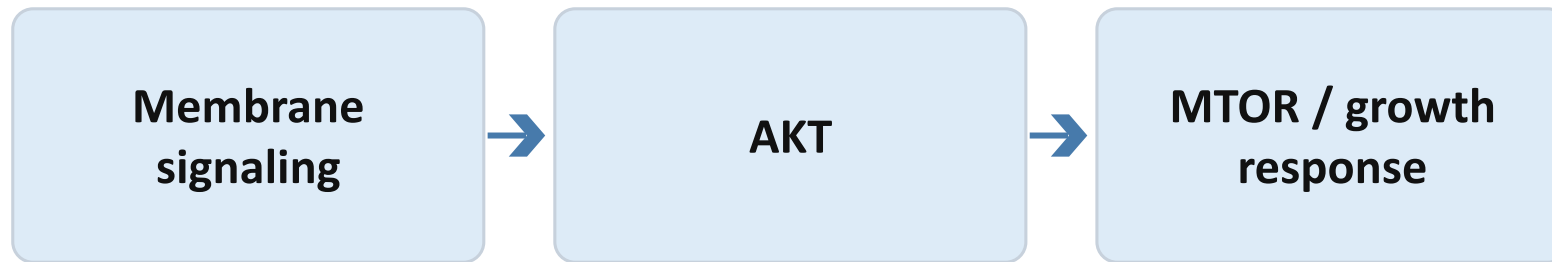


- Receptor tyrosine kinase activation recruits intracellular PI3 kinases.
- This creates a regulated link between outside signals and downstream growth pathways.

PI3K acts on membrane phosphoinositides



AKT and mTOR are downstream components



- AKT and mTOR relay and regulate growth-related cellular signaling.
- Their activation helps explain how a mutation alters tissue growth.

Activating variants uncouple growth from stimuli

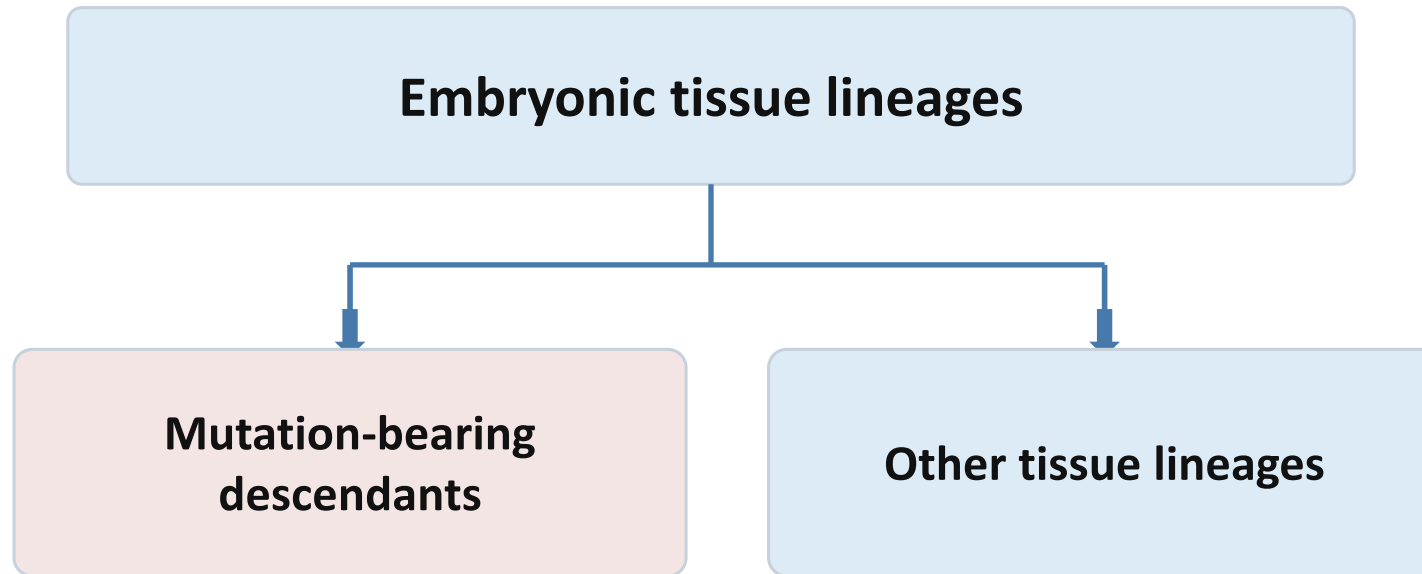
Regulated signaling

Ordinary signaling responds to external growth-factor activation.

Mutation-driven signaling

An activating missense mutation can sustain abnormal pro-growth signaling even without that input.

Cell distribution predicts anatomical distribution



Schematic: Descendant-cell distribution

- Somatic daughter cells retain the mutation and occupy particular tissues.
- The affected body regions depend on where the mutant lineage contributed during development.

Asymmetry reflects unequal lineage contribution

Affected region

A mosaic clone can be concentrated in only part of the body.

Less affected region

Bone, skin or other affected structures may therefore grow at different rates.

Different tissue types may share a growth phenotype

Bone: Regional overgrowth

Skin: Regional overgrowth

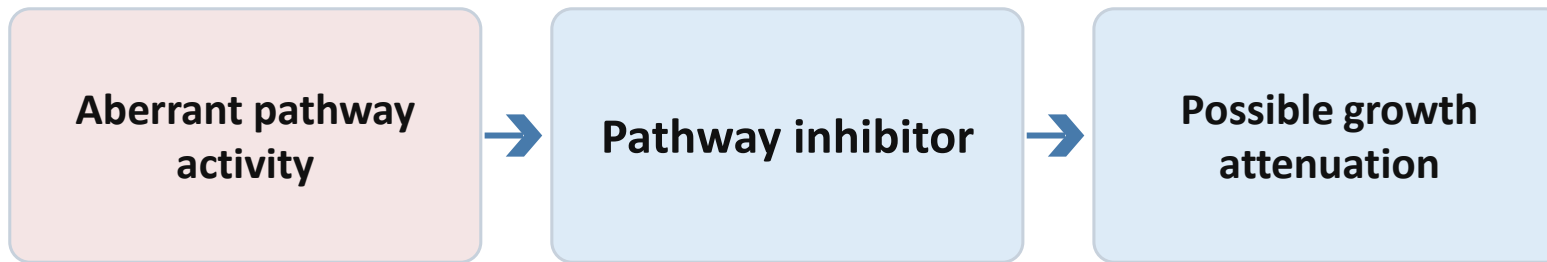
Other organs: Variable involvement

Final pattern: Anatomical
asymmetry

Distribution—not a single universal lesion—is central

- Mosaic overgrowth can distort discrete central or distal anatomical regions.
- Clinical appearance varies with the specific tissues and their mutant-cell distribution.
- A general mechanism should not be mistaken for one fixed gross or histologic morphology.

Targeted pathway inhibition: Textbook perspective



- The source describes trials of PI3K/AKT/mTOR pathway inhibition.
- It reports that some interventions can attenuate progressive overgrowth in certain circumstances.
- No specific regimen or current approval status is asserted.

Gonadal versus somatic: The biological question

Dimension	Gonadal	Somatic
Mutation-bearing cells	Gamete progenitors / gametes	Selected body-cell clones
Key consequence	Potential transmission to offspring	Tissue-restricted phenotype
Typical clue in this lesson	Repeated affected siblings	Regionally asymmetric overgrowth
Important caution	Parent may be unaffected	Somatic mutation need not mean cancer

Constitutional mutation versus mosaic mutation

Broad cellular distribution

A constitutional variant is broadly present because it is established at or near conception.

Restricted descendant lineage

A mosaic variant exists in a subset of descendants because it arose after fertilization.

Recurrence and regional growth answer different questions

Family-level pattern

Recurrence asks whether a parent's germ cells can transmit the variant repeatedly.

Tissue-level pattern

Regional growth asks which tissues of an individual contain an activating somatic mutation.

Case: Normal examination, recurrent dominant disorder

HYPOTHETICAL TEACHING CASE

Hypothetical: Two siblings have an autosomal dominant condition. Neither parent has overt clinical manifestations.

Which two different genetic mechanisms can leave a parent phenotypically normal?

Case answer: Mosaicism versus incomplete penetrance

Mechanistic interpretation

- Gonadal mosaicism: A parent may carry the pathogenic variant in gamete precursors but not in examined somatic tissues.
- Incomplete penetrance: A person with a disease-associated constitutional variant may show no clinical phenotype.
- The two explanations should not be equated solely because the parent appears unaffected.

Case: Asymmetric overgrowth in one child

HYPOTHETICAL TEACHING CASE

Hypothetical: A child has progressively disproportionate growth limited to selected anatomical regions.

What is the key cell-distribution mechanism?

Case answer: Regionally restricted mutant cells

Mechanistic interpretation

- A somatic activating variant within the PI3K/AKT/mTOR pathway can drive local growth.
- Anatomical asymmetry follows where the mutant clone resides.
- This vignette alone does not establish a named syndrome or a molecular diagnosis.

An interpretation checklist for unusual pedigrees

- Establish whether the condition is considered autosomal dominant in the cited context.
- Determine whether the parents are clinically affected or apparently normal.
- Ask whether more than one offspring has the same phenotype.
- Distinguish a one-off de novo event from a possible parental germ-cell clone.

Four concepts that must remain separate

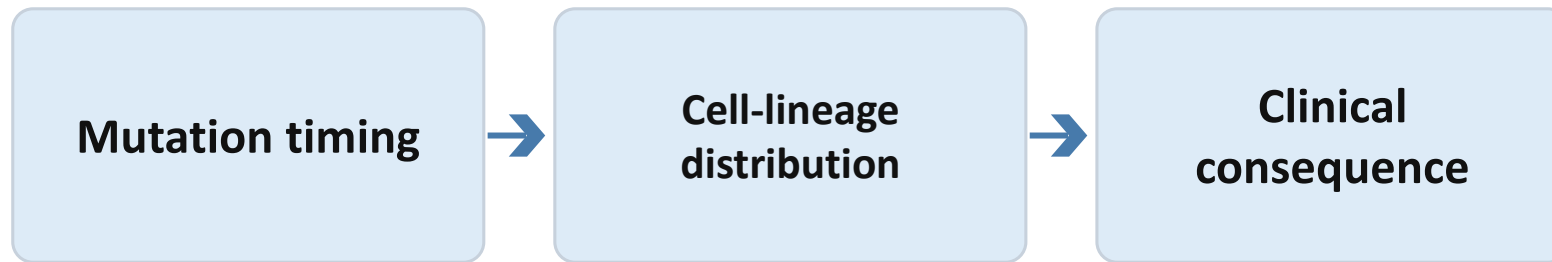
De novo: A new mutation event

Gonadal: Mutant germ-cell lineage

Somatic: Mutant body-cell lineage

Positive selection: Mutant sperm
enrichment in certain disorders

Mechanism determines clinical interpretation



- Timing determines descendant-cell distribution.
- Cell distribution determines whether the dominant signal is familial recurrence, regional overgrowth, or both.
- Phenotype alone may not disclose the genotype of every relevant lineage.

Core synthesis

- Gonadal mosaicism explains why a phenotypically normal parent can have more than one affected child.
- The likelihood of recurrence depends on mutant germ-cell representation, not a universal fixed percentage.
- Apert/FGFR2 and Costello/HRAS illustrate selected paternal-age associations.
- Somatic mosaicism can cause asymmetric overgrowth through activating PI3K/AKT/mTOR signaling.

Primary source

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- Chapter 5, Genes and Human Diseases: Autosomal Dominant Disorders (p. 125); Gonadal Mosaicism (pp. 158–159); Somatic Mosaicism (p. 159).
- Teaching diagrams and cases are original conceptual representations of the cited textbook material; not patient or laboratory evidence.