

Structural Abnormalities of Chromosomes

Chromosomal mechanisms, cytogenetic nomenclature, and
clinicopathologic consequences

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Learning objectives

- Distinguish chromosome number abnormalities from structural rearrangements.
- Explain how breakage, loss, fusion, and inversion alter chromosomes.
- Interpret core translocation, deletion, ring, and isochromosome notation.
- Connect balanced or unbalanced architecture to phenotype and reproductive risk.

Two categories of cytogenetic disorder

- A numerical abnormality changes chromosome complement.
- A structural abnormality alters one or more chromosomal segments.
- Both may influence survival, development, and clinical phenotype.

Numerical changes
Change in chromosome count

Structural changes
Rearrangement or loss of chromosome segments

The normal human chromosome complement

- Chromosome complements are conventionally stated as 46,XX or 46,XY.
- The chromosome count alone does not establish structural normality.
- Band-level notation identifies rearranged arms and breakpoints.

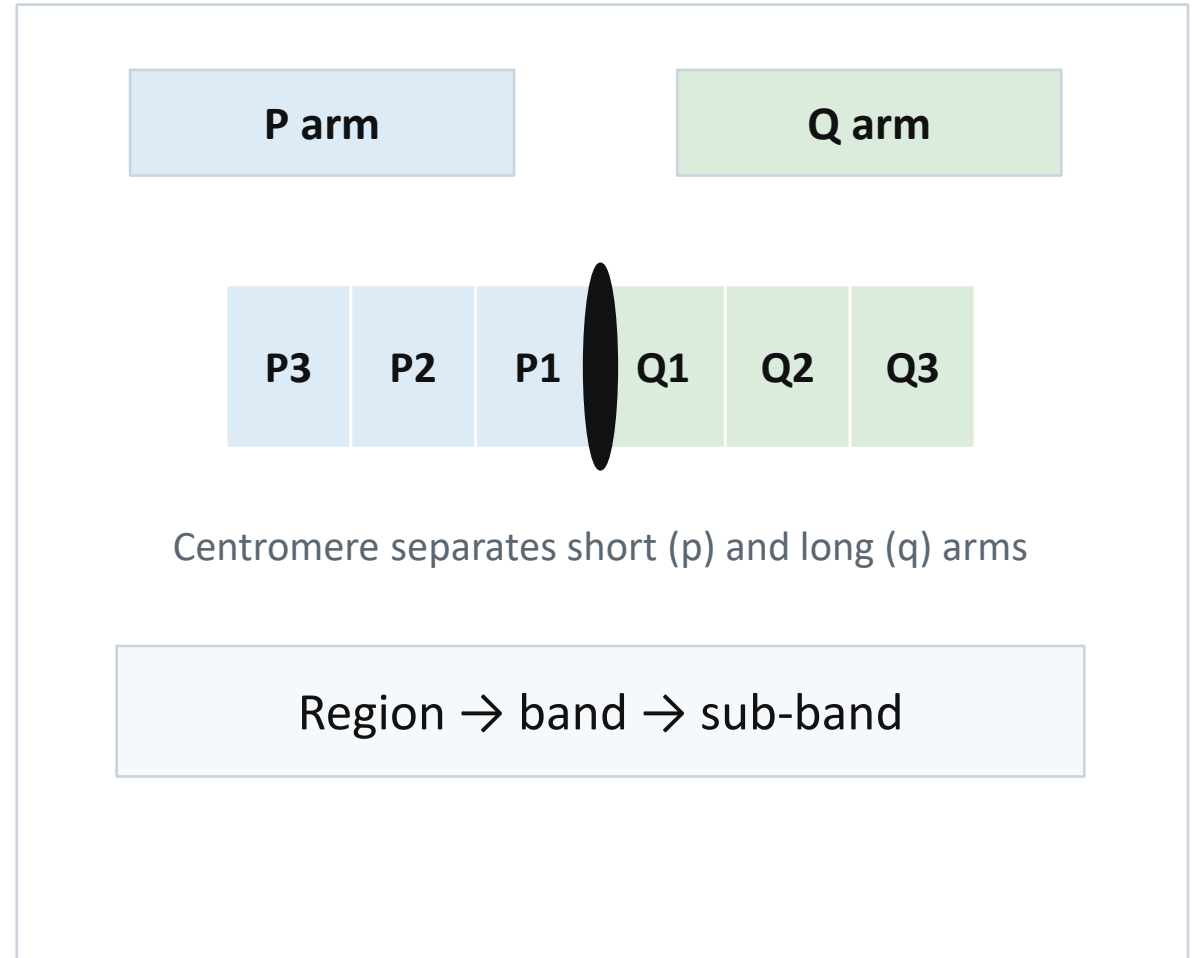
46,XX or 46,XY

46,XX,t(2;5)(q31;p14)

The total count can remain unchanged despite rearrangement

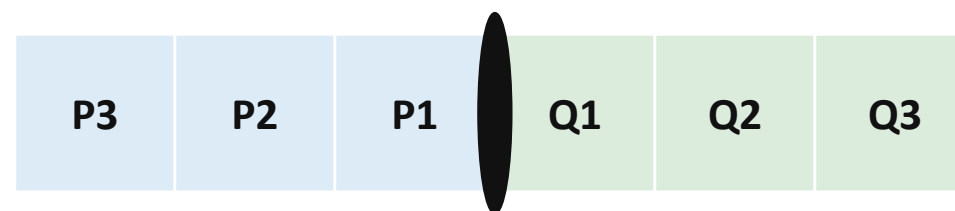
Reading a chromosome: P arm and q arm

- P denotes the short arm; Q denotes the long arm.
- The centromere is the reference point for numbering regions.
- Regions, bands, and sub-bands are numbered outward from it.



Interpreting a cytogenetic address

- Xp21.2 identifies a specific segment on the X chromosome.
- The address gives arm, region, band, then sub-band.
- Precise breakpoint descriptions localize structural changes.



X p 2 1 . 2

Chromosome X • short arm • region 2 • band 1 • sub-band 2

Routine banding has finite resolution

- Routine banding requires an alteration of approximately 2–4 Mb to be visible.
- A visually normal karyotype cannot exclude smaller structural changes.
- Fluorescence in situ hybridization can resolve selected kilobase-scale targets.

Banded karyotype

Large changes (~2–4 Mb) visible in routine banding

Fluorescence in situ hybridization

Selected loci: Changes detectable at kilobase scale

Genomic test choice depends on the question

- Karyotyping demonstrates chromosome counts and large rearrangements.
- FISH interrogates selected loci at higher resolution.
- Sequencing and emerging methods can identify structural changes not resolved by banding.

Chromosomal count and gross pattern

Locus-specific rearrangement or loss

Higher-resolution sequence-level analysis

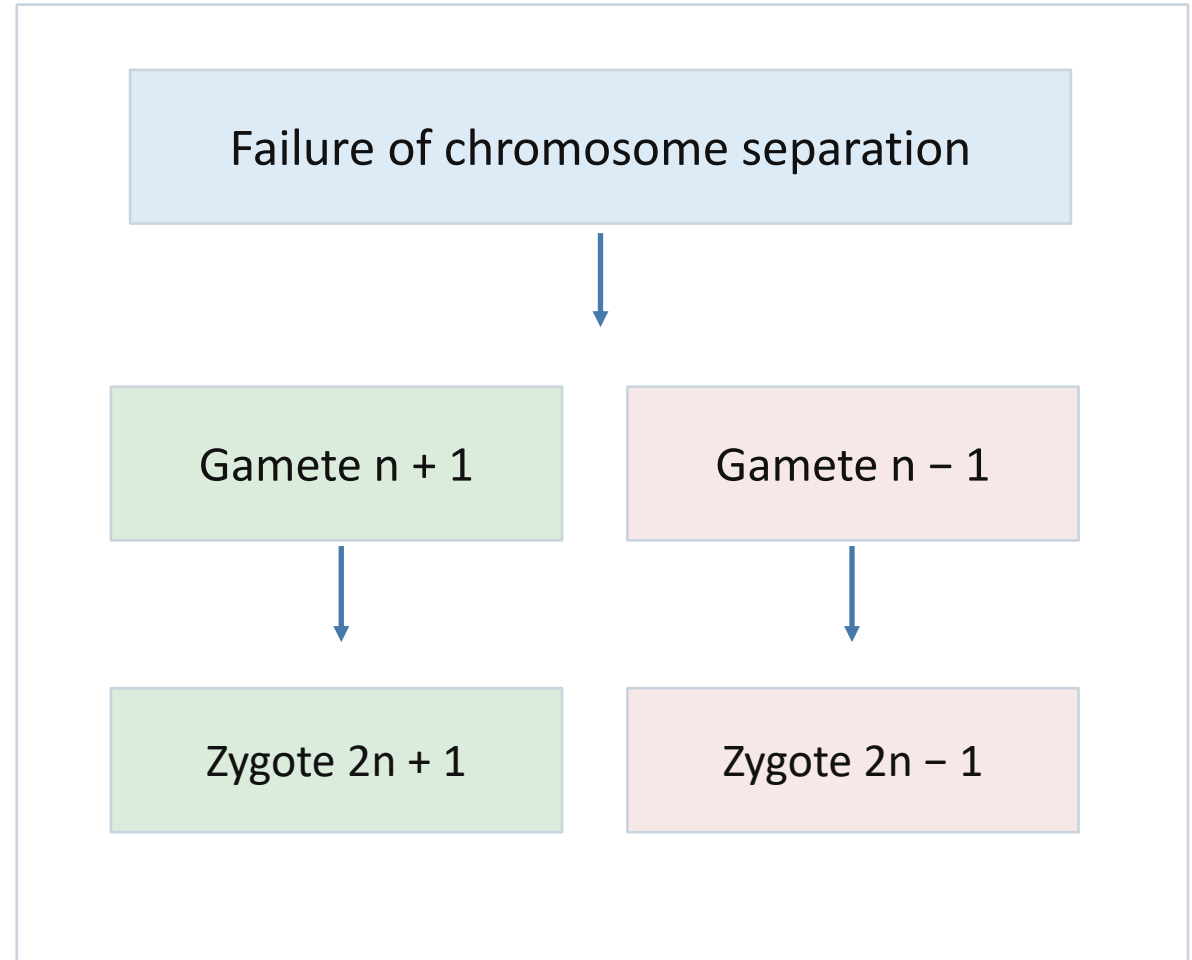
Euploidy and aneuploidy

Copy number is distinct from rearrangement.

- Euploid: An exact multiple of the haploid chromosome number (23).
- Aneuploid: A complement that is not an exact multiple of 23.
- A structural rearrangement may be present with a count of 46.

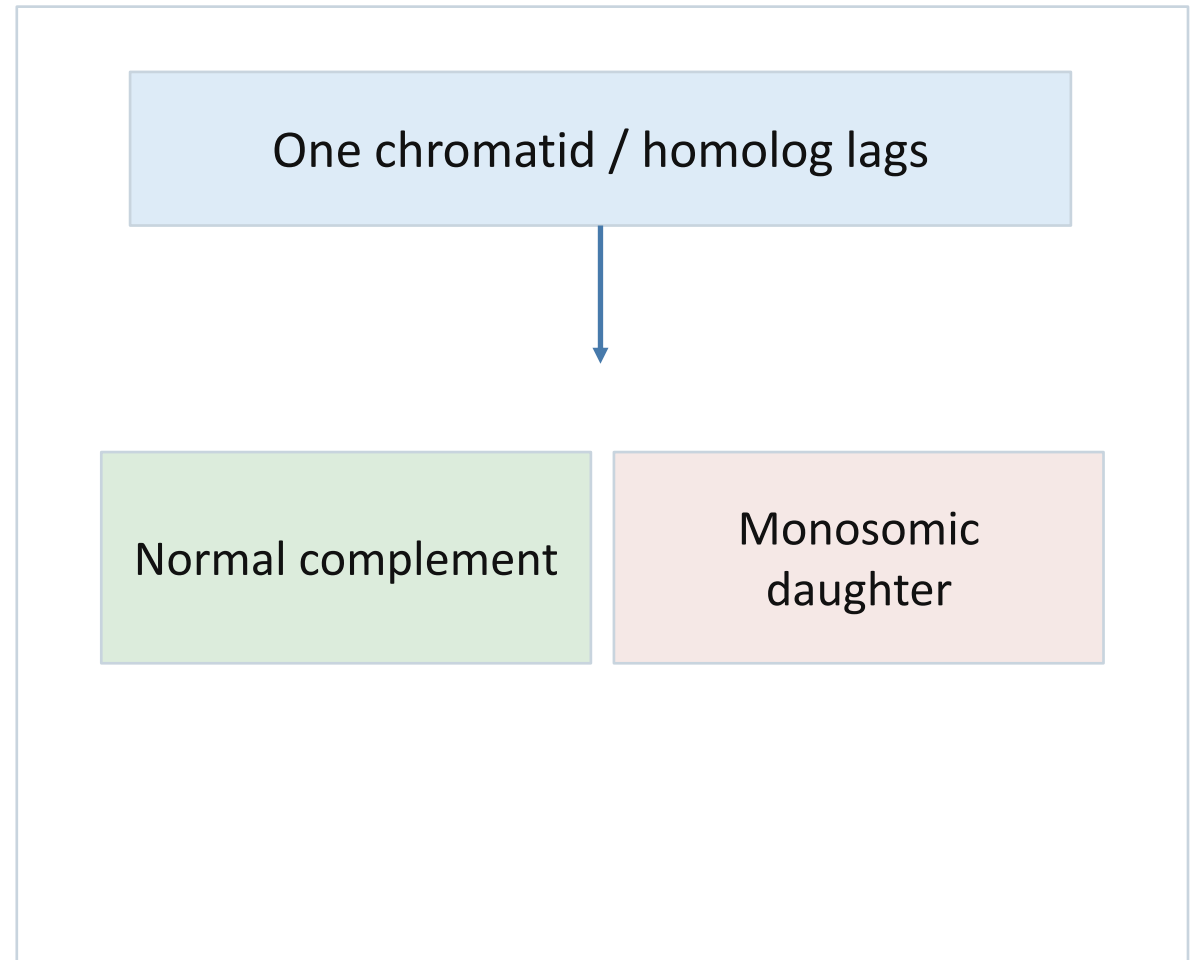
Nondisjunction creates abnormal gametes

- Failed separation during gametogenesis creates $n + 1$ and $n - 1$ gametes.
- With a normal gamete, fertilization can yield trisomy or monosomy.
- This numerical mechanism provides context for chromosomal disorders.



Anaphase lag differs from nondisjunction

- A homolog or chromatid lags behind during cell division.
- It may be excluded from the daughter nucleus.
- The result may be one normal cell and one monosomic cell.



Chromosomal dosage influences viability

- Autosomal monosomy generally removes too much genetic information for survival.
- Some autosomal trisomies permit live birth but cause major abnormalities.
- Sex-chromosome aneuploidies can have variable, compatible-with-life phenotypes.

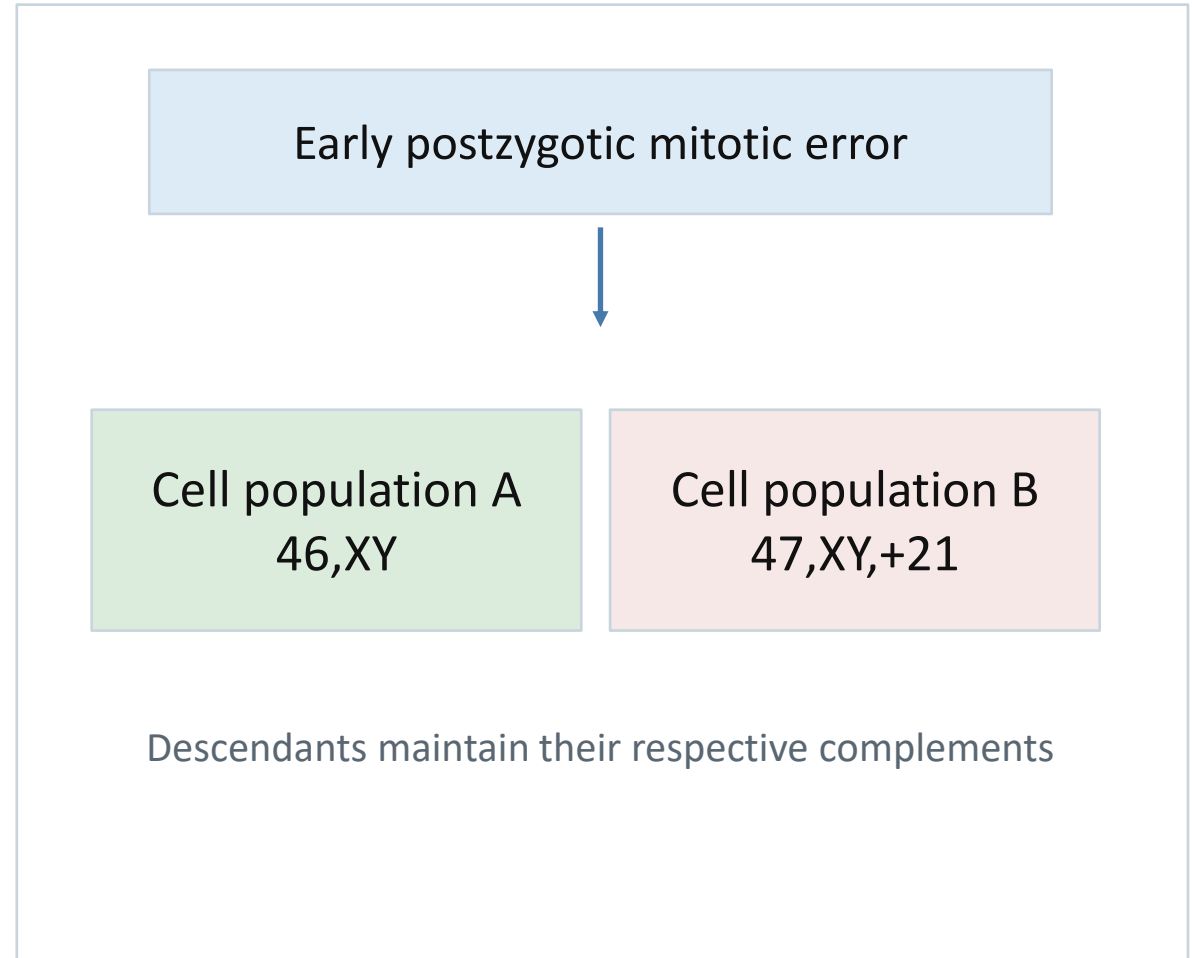
Autosomal monosomy

Usually incompatible with live birth /
embryogenesis

Selected autosomal trisomies

Mosaicism: Two chromosome complements

- A mitotic error after fertilization can create distinct cell populations.
- Each population contributes descendants to developing tissues.
- Phenotypic expression depends in part on which cells and tissues are affected.



Sex chromosome mosaicism as an example

45,X/47,XXX is a postzygotic numerical mosaic.

- A division error can produce descendants with one or three X chromosomes.
- The populations coexist in a single individual.
- The distribution of 45,X cells influences Turner-spectrum expression.

Mosaic trisomy 21 as an example

46,XY/47,XY,+21

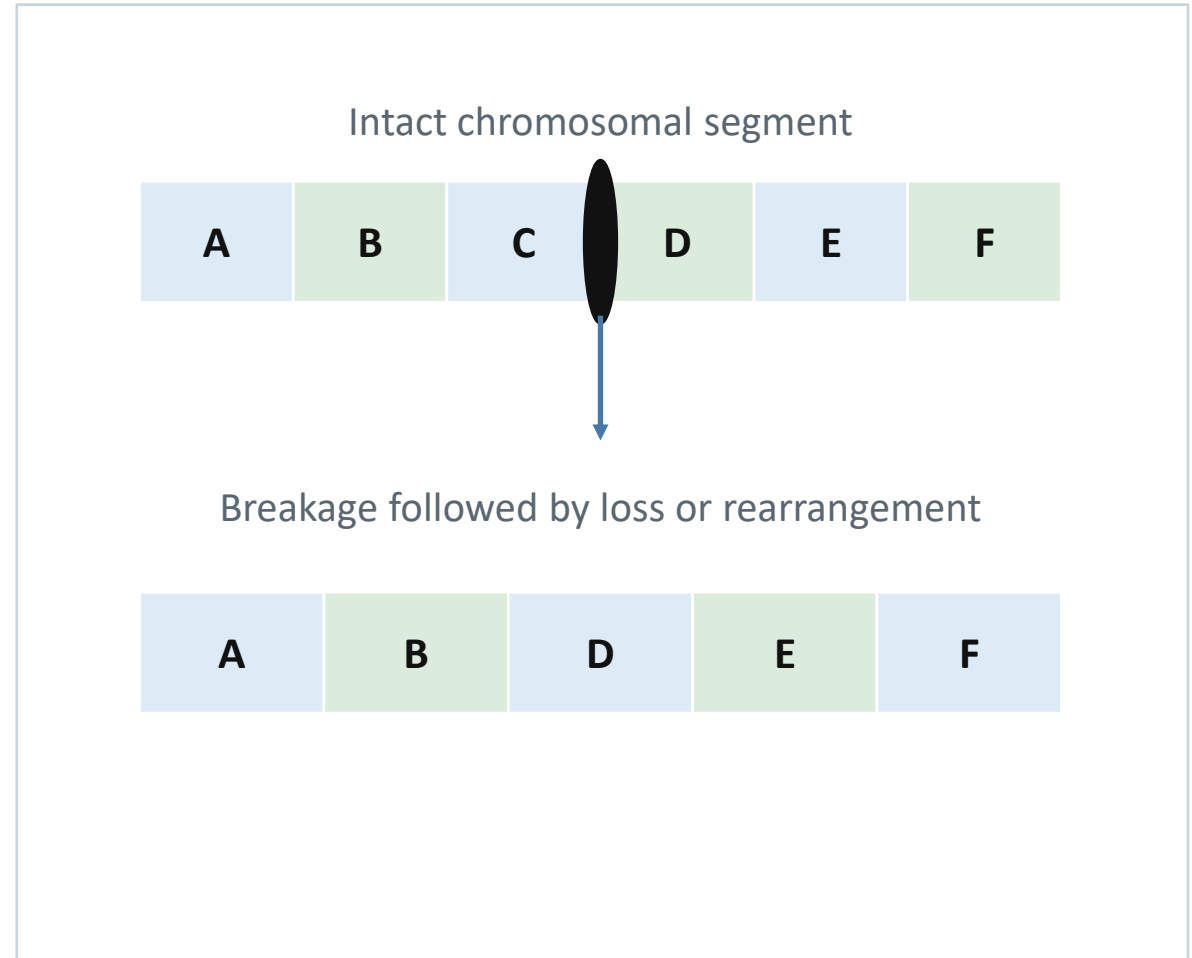
- Early mitotic error may create a trisomic and a normal cell population.
- A monosomic lineage may be nonviable and disappear during development.
- Down-syndrome expression varies with the proportion of trisomic cells.

Timing matters in postzygotic mosaicism

- An early event can affect a broader descendant cell population.
- The lineage and tissue distribution shape clinical expression.
- Somatic chromosome change can also occur later in life.
- Loss of Y is described as a common acquired event in older males.

Structural chromosome abnormalities arise after breakage

- Chromosome breaks may be followed by loss of DNA.
- Broken segments can also be rejoined in a different configuration.
- The type of rearrangement determines gene dosage and genomic architecture.



Structural rearrangements: Main families

Rearrangement	Defining structural event
Reciprocal translocation	Exchange between chromosomes
Robertsonian translocation	Centric fusion of acrocentrics
Isochromosome	One arm lost; remaining arm duplicated
Inversion	Reinsertion of an inverted interval
Deletion	Loss of an interval or terminal segment
Ring chromosome	Fusion of broken chromosome ends

Balanced and unbalanced are not synonyms for benign and harmful

- Balanced rearrangement: Usually no or very little net DNA loss.
- Unbalanced rearrangement: Missing or extra chromosomal material.
- Balanced carriers can still have reproductive risk or breakpoint-related effects.

Rearrangement with no major DNA loss

Loss, duplication, or breakpoint disruption

Balanced rearrangements can change chromosome morphology

- Balanced reciprocal translocations can retain a total count of 46.
- A karyotype can disclose rearranged derivative chromosomes.
- Chromosome number and chromosome organization must be evaluated separately.

46,XX or 46,XY

46,XX,t(2;5)(q31;p14)

The total count can remain unchanged despite rearrangement

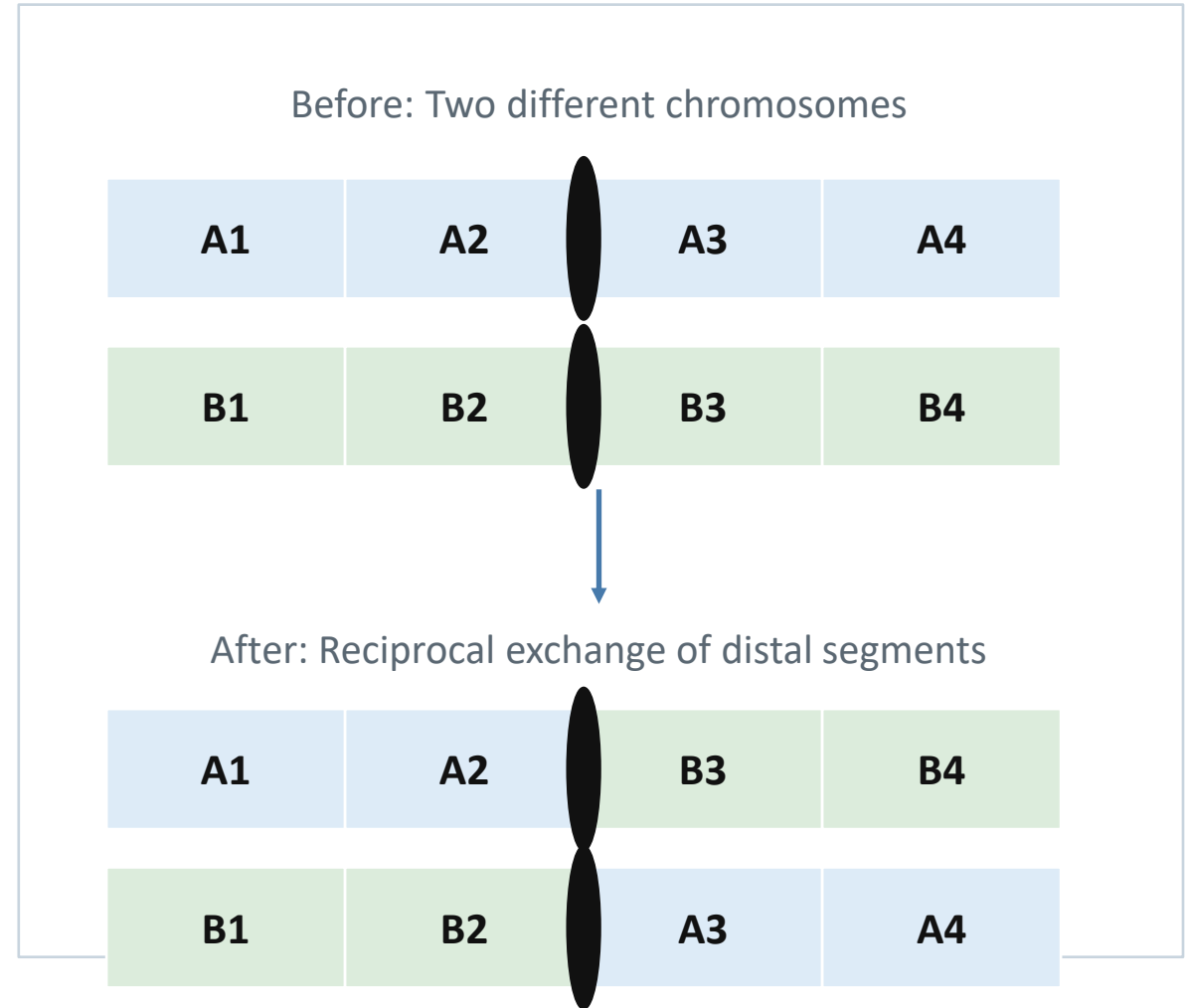
A structural breakpoint may interrupt a gene

Copy-neutral does not guarantee no biological effect.

- Inversions usually preserve DNA copy number.
- Exception: A breakpoint interrupts a critical gene.
- Phenotype depends on what is disrupted as well as the overall DNA amount.

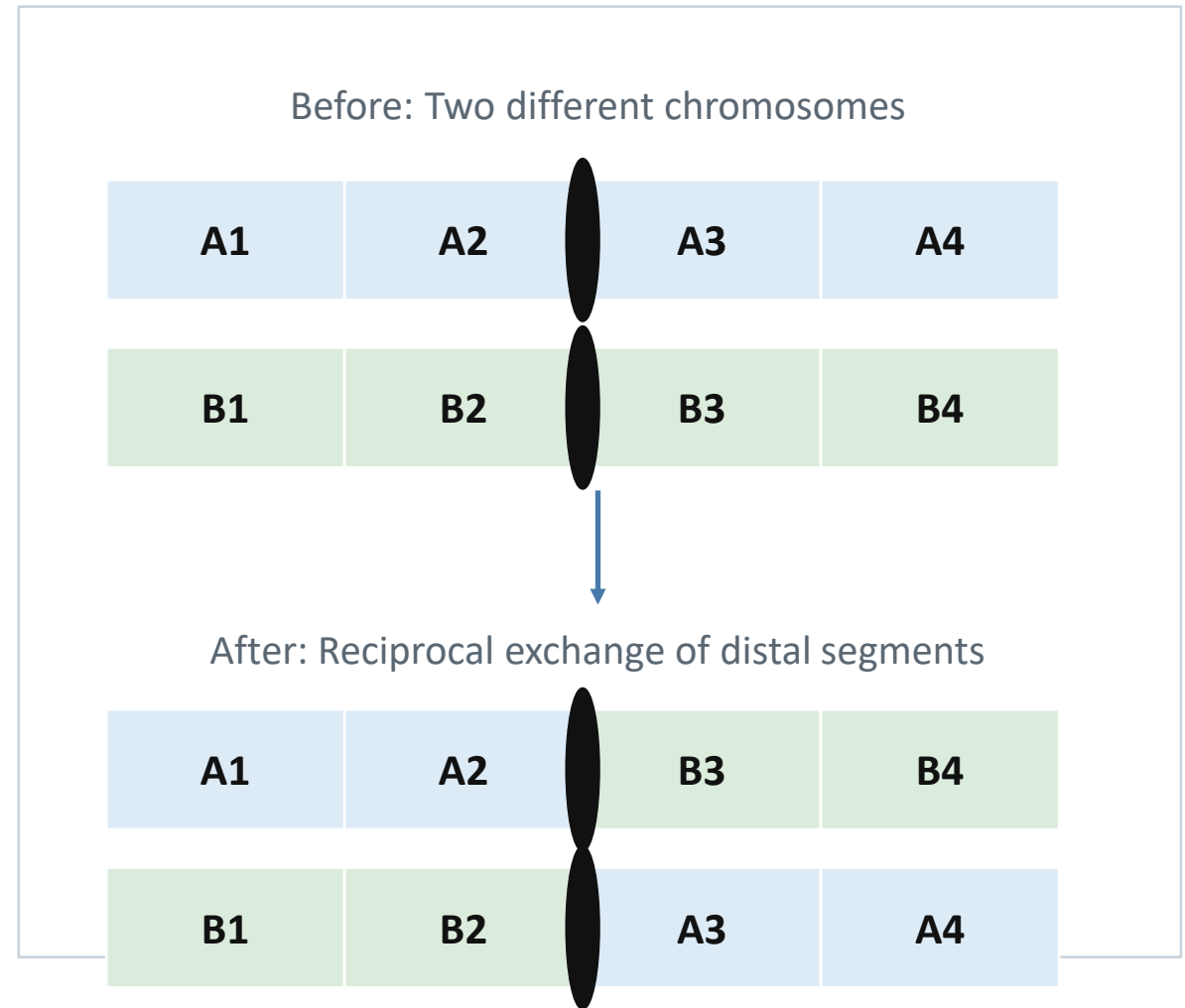
Translocation means transfer between chromosomes

- A segment from one chromosome becomes attached to another.
- Reciprocal exchange is one important form.
- The chromosome products can be cytogenetically identifiable.



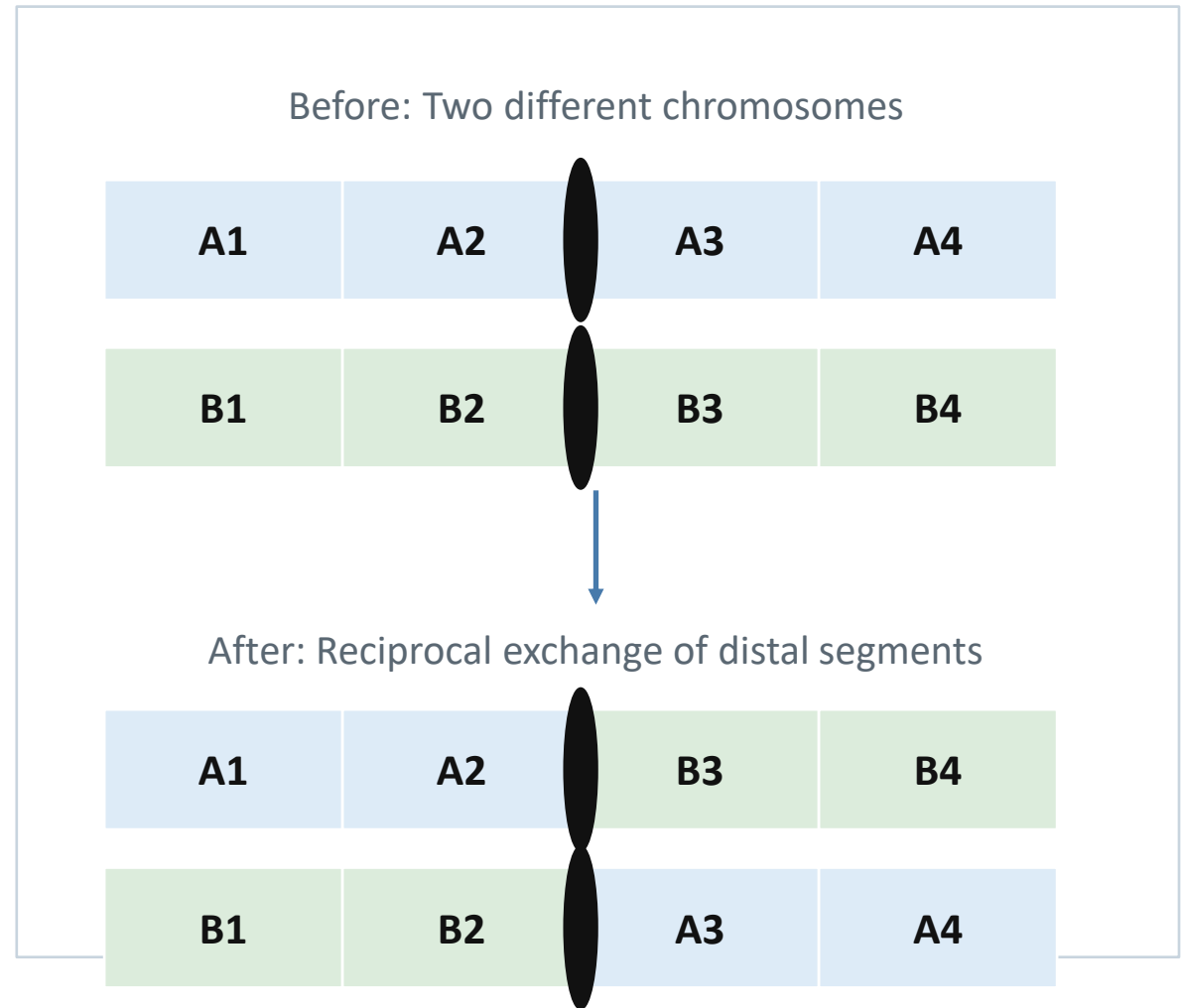
Reciprocal translocation: Two chromosome breaks

- A break occurs in each of two different chromosomes.
- The resulting chromosome segments exchange partners.
- Two derivative chromosomes may be produced.



Balanced reciprocal translocation preserves most DNA

- Exchange typically causes no or very little genetic material loss.
- Many carriers are phenotypically normal.
- Rearranged chromosome structure still influences meiotic segregation.



Reciprocal translocation notation is structured

- 46,XX,t(2;5)(q31;p14) describes a balanced exchange.
- T(2;5) identifies the participating chromosomes.
- Q31 and p14 specify the breakpoint bands on chromosomes 2 and 5.

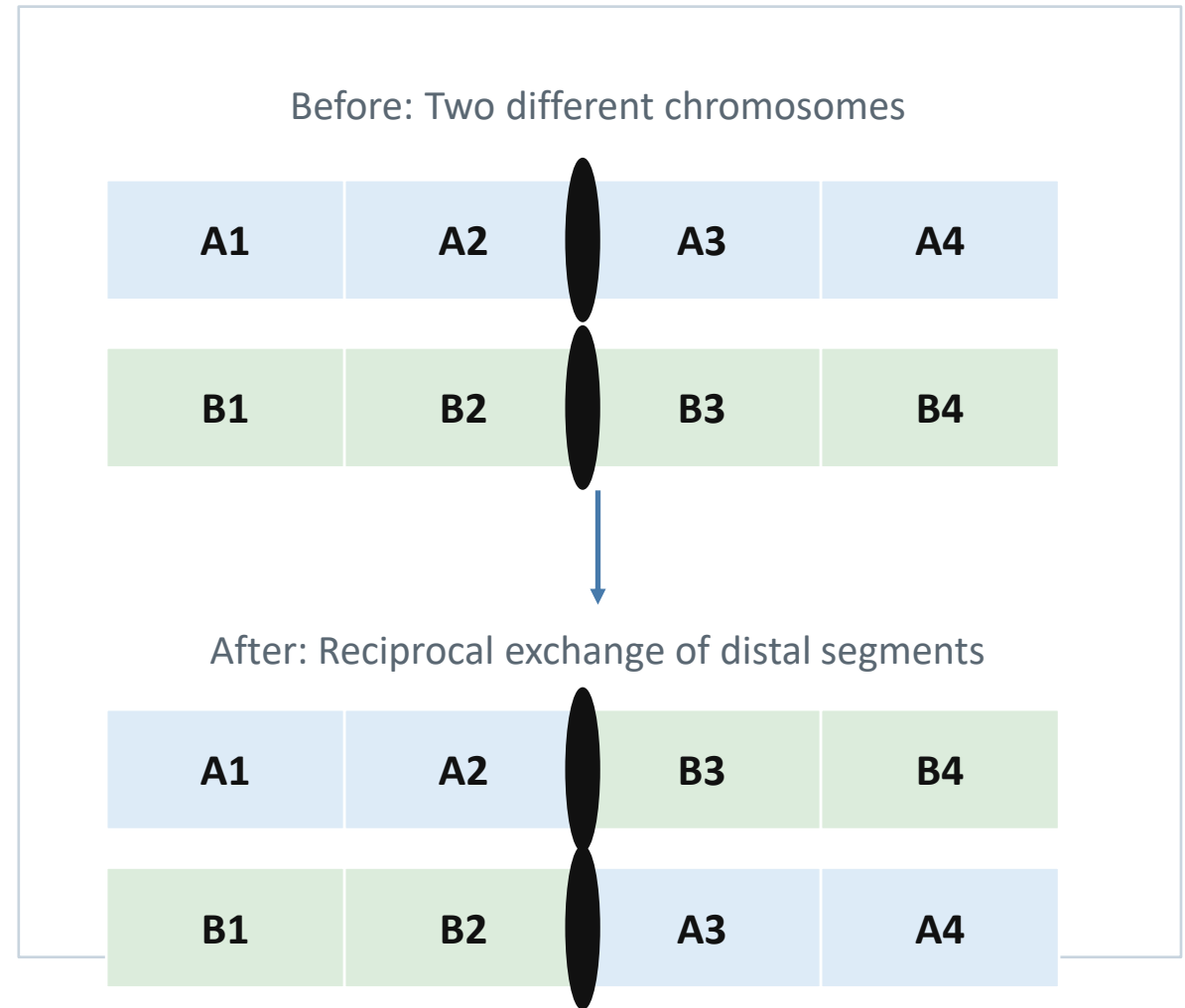
46,XX or 46,XY

46,XX,t(2;5)(q31;p14)

The total count can remain unchanged despite rearrangement

Derivative chromosomes are not identical to normal homologs

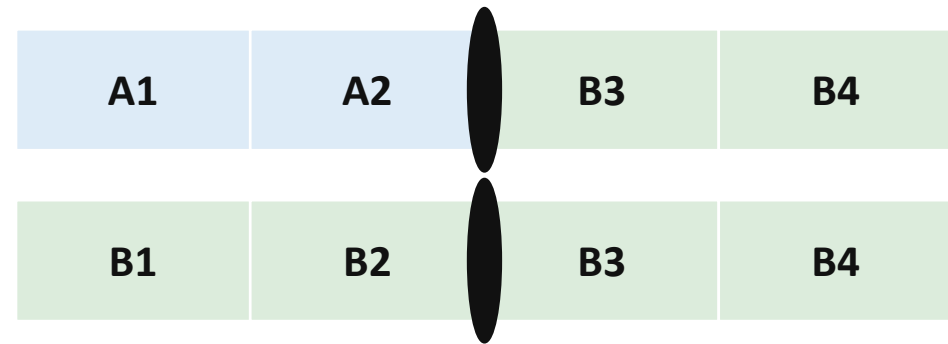
- One rearranged chromosome contains material from chromosome 2 and chromosome 5.
- Its reciprocal partner contains the exchanged complementary material.
- The two derivatives together may preserve the overall DNA complement.



Meiosis creates risk for unbalanced gametes

- A carrier may produce a gamete with a normal chromosome and the wrong derivative.
- That gamete may gain some sequences and lack others.
- Balanced somatic phenotype therefore does not remove reproductive risk.

Translocation carrier — simplified chromosome products

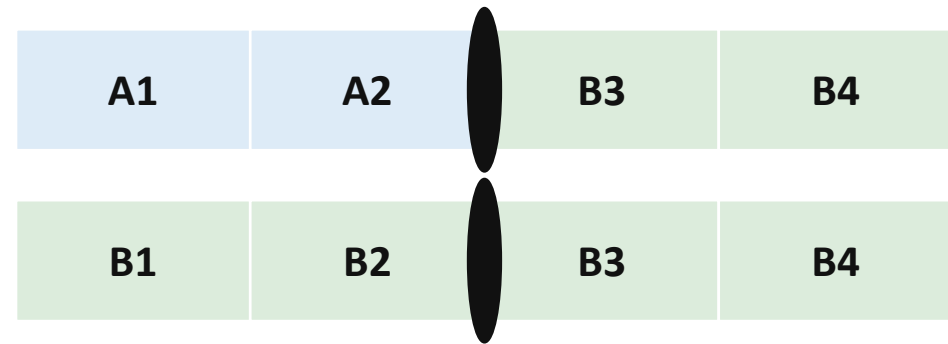


Unbalanced gamete: Duplicated B material
And missing part of A

An unbalanced zygote has abnormal gene dosage

- Fertilization of an unbalanced gamete produces an unbalanced conceptus.
- The missing and duplicated regions alter genetic dosage.
- Possible outcomes include pregnancy loss or birth of an affected child.

Translocation carrier — simplified chromosome products



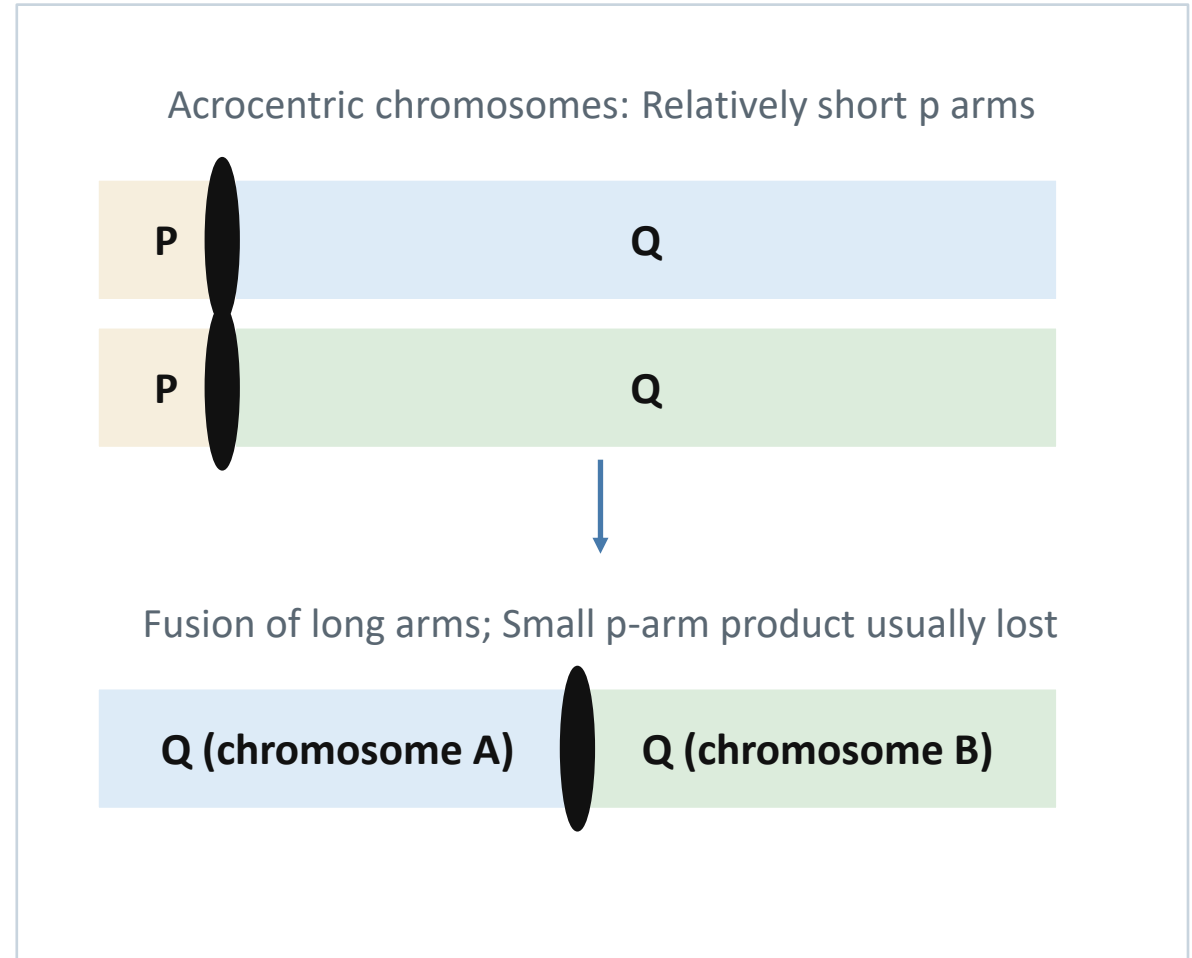
Unbalanced gamete: Duplicated B material
And missing part of A

Carrier phenotype and offspring risk are different questions

Question	Balanced carrier	Possible unbalanced offspring
Net gene dosage	Usually preserved	Extra and/or missing segments
Typical phenotype	Often clinically normal	May have developmental malformations
Main assessment	Carrier structural karyotype	Specific segmental imbalance

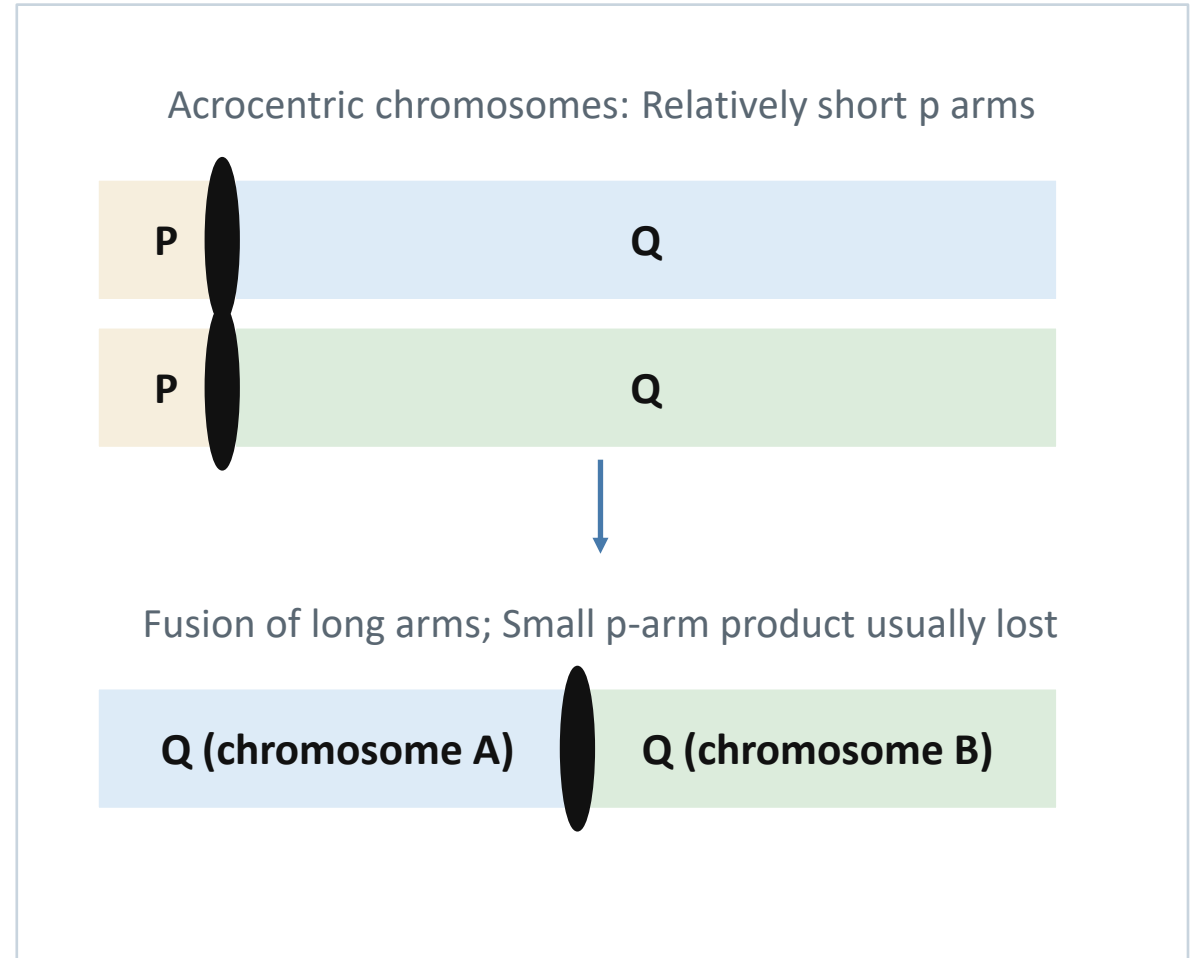
Robertsonian translocations involve acrocentrics

- Applicable human acrocentric chromosomes: 13, 14, 15, 21, and 22.
- Breaks occur near their centromeres.
- The long arms can become united in a centric fusion.



Robertsonian translocation: Centric fusion

- Long arms from two acrocentric chromosomes form one large product.
- A small product containing the short arms is often lost.
- The retained fused chromosome contains two q arms.



Why loss of acrocentric short arms can be tolerated

Some material is genomically redundant.

- The small p-arm product can carry redundant sequences.
- Examples include genes encoding ribosomal RNA.
- Its loss may be compatible with an apparently normal phenotype.

Balanced Robertsonian carriers: Clinical context

- Robertsonian translocations occur in approximately 1 in 1000 apparently normal individuals.
- The person may be phenotypically normal despite altered chromosome architecture.
- The principal concern is the possible production of abnormal progeny.

Robertsonian translocation and trisomy 21 risk

Segment dosage in offspring is the clinically important issue.

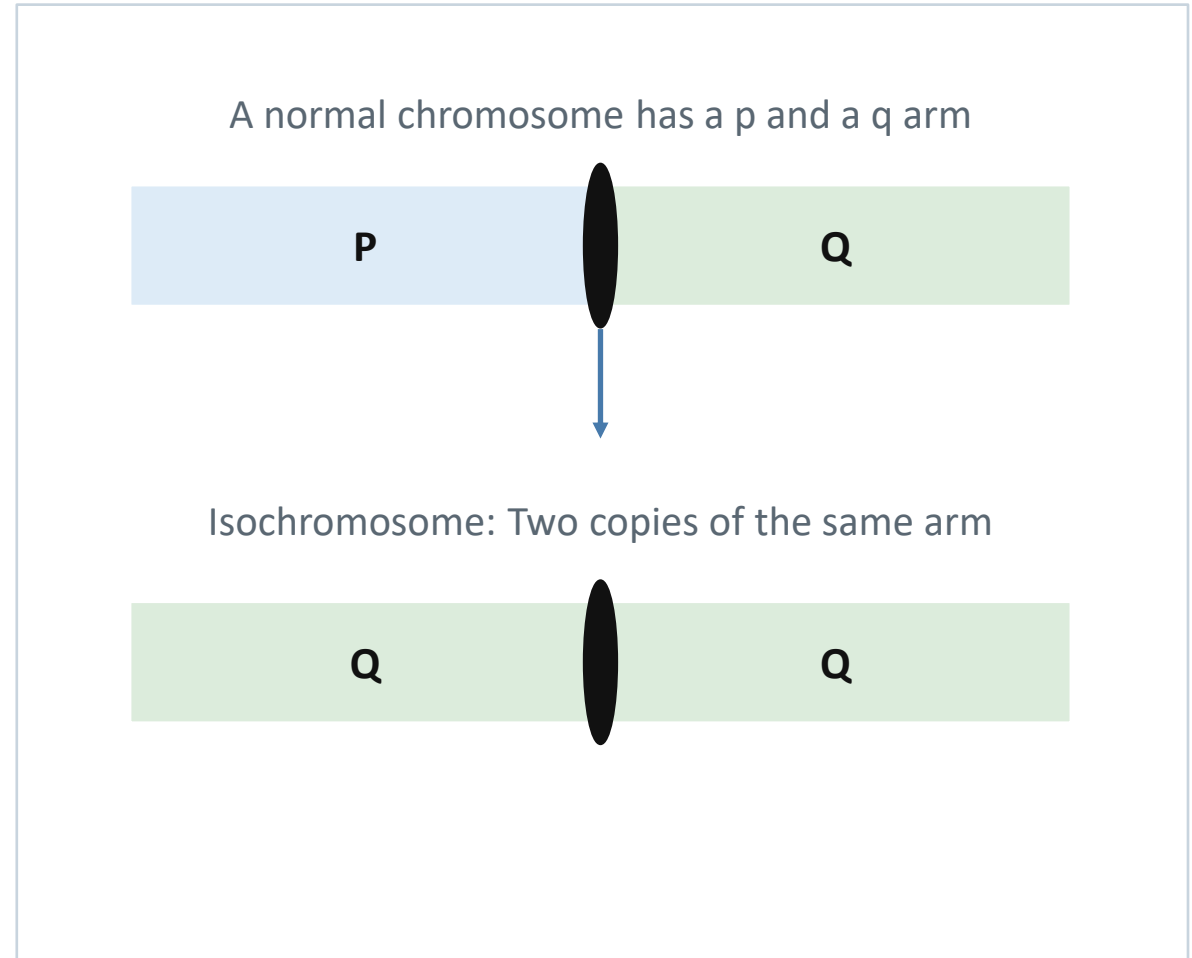
- A translocation involving chromosome 21 can produce gametes with extra 21q material.
- A resulting child may have translocation-associated Down syndrome.
- Distinguish an affected child from the phenotype of a balanced parental carrier.

Reciprocal versus Robertsonian translocations

Property	Reciprocal	Robertsonian
Chromosome partners	Two chromosomes	Two acrocentric chromosomes
Main event	Segment exchange	Fusion of two long arms
Material lost	Often little or none	Small p-arm product often lost
Carrier issue	Unbalanced gametes	Unbalanced gametes

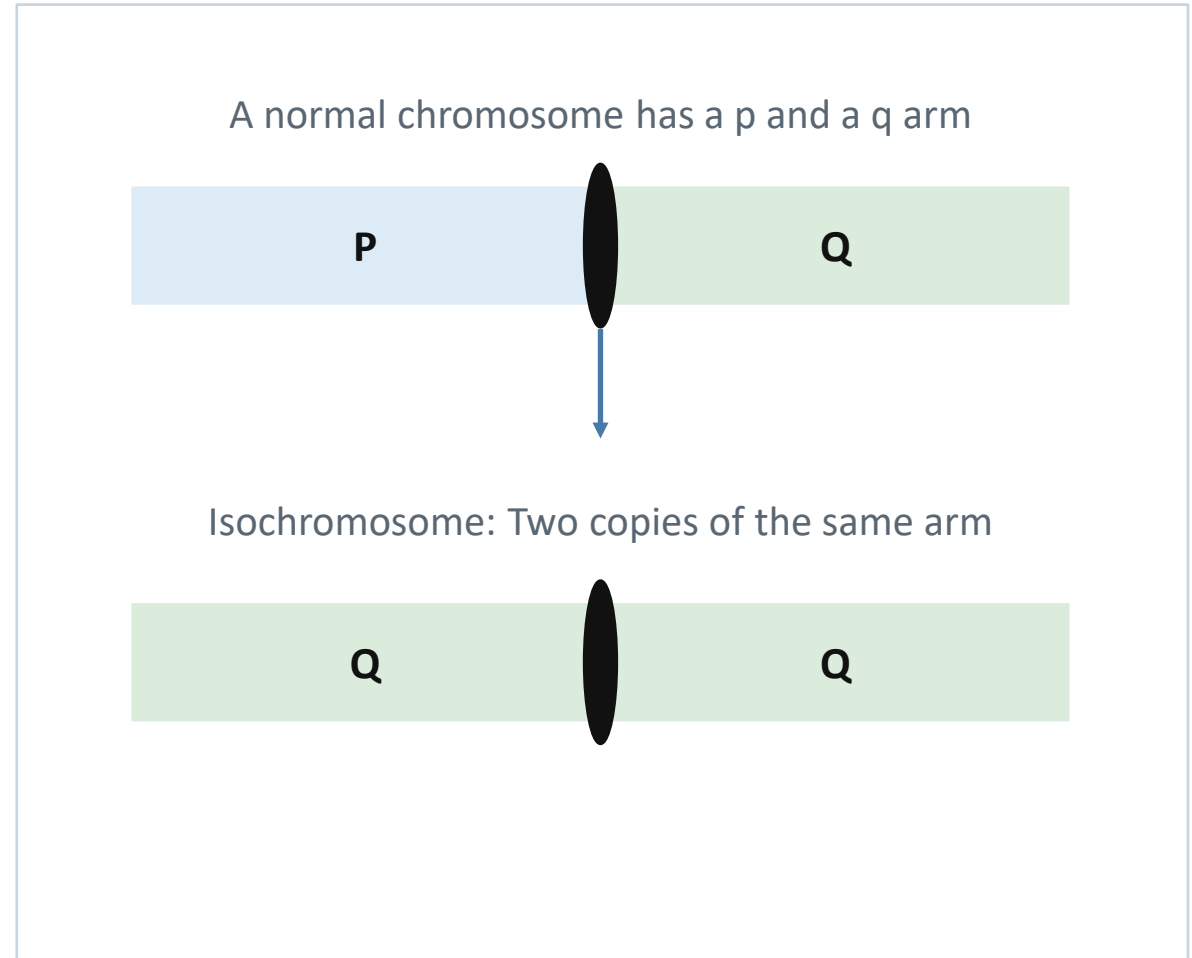
Isochromosomes duplicate one chromosome arm

- One chromosome arm is lost.
- The remaining arm is duplicated.
- The abnormal chromosome contains two copies of the same arm.



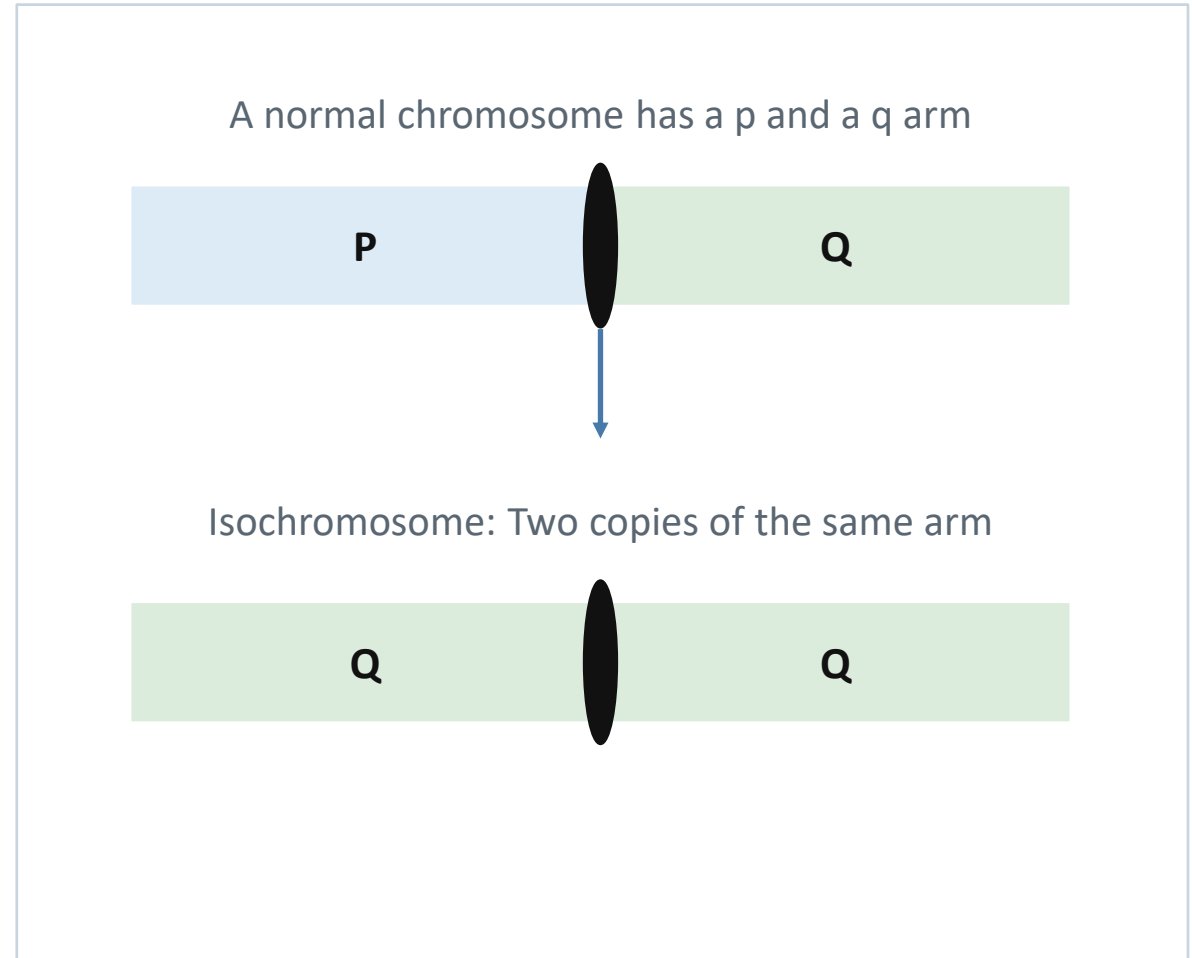
Isochromosome structure changes regional dosage

- The two arms have the same gene complement.
- Sequences on the lost arm are deficient.
- Sequences on the duplicated arm are present in excess.



An Xq isochromosome is a characteristic example

- I(X)(q10) as the commonest isochromosome seen in live births.
- The rearranged X carries two long arms.
- Its cytogenetic shorthand specifies an X chromosome and q-arm duplication.



Dosage effect of i(X)(q10)

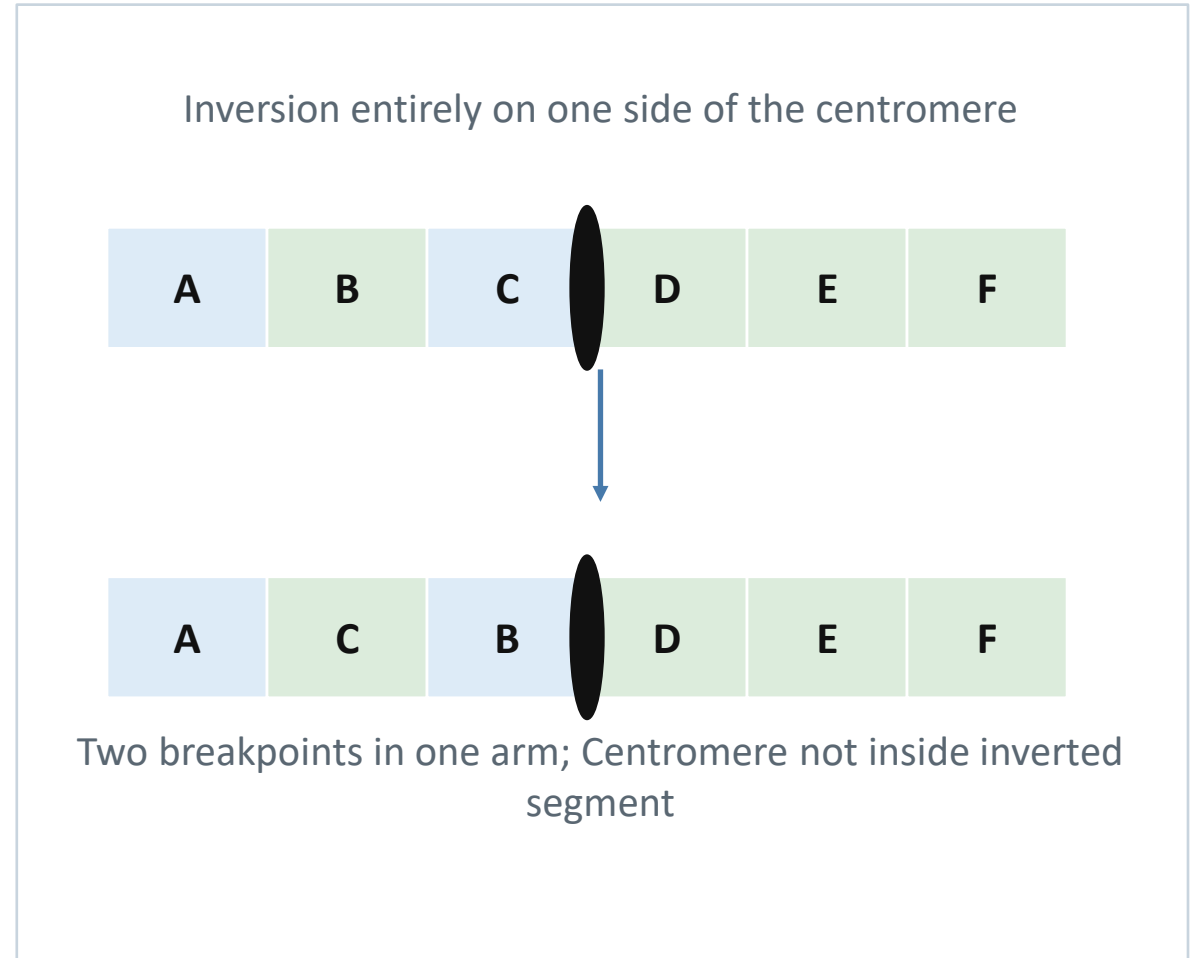
- Loss of the original Xp contributes monosomy of Xp genes.
- Duplication of Xq creates a trisomic dosage for Xq genes across the complement.
- The phenotype reflects this asymmetric gene dosage.

Rearrangement with no major DNA loss

Loss, duplication, or breakpoint disruption

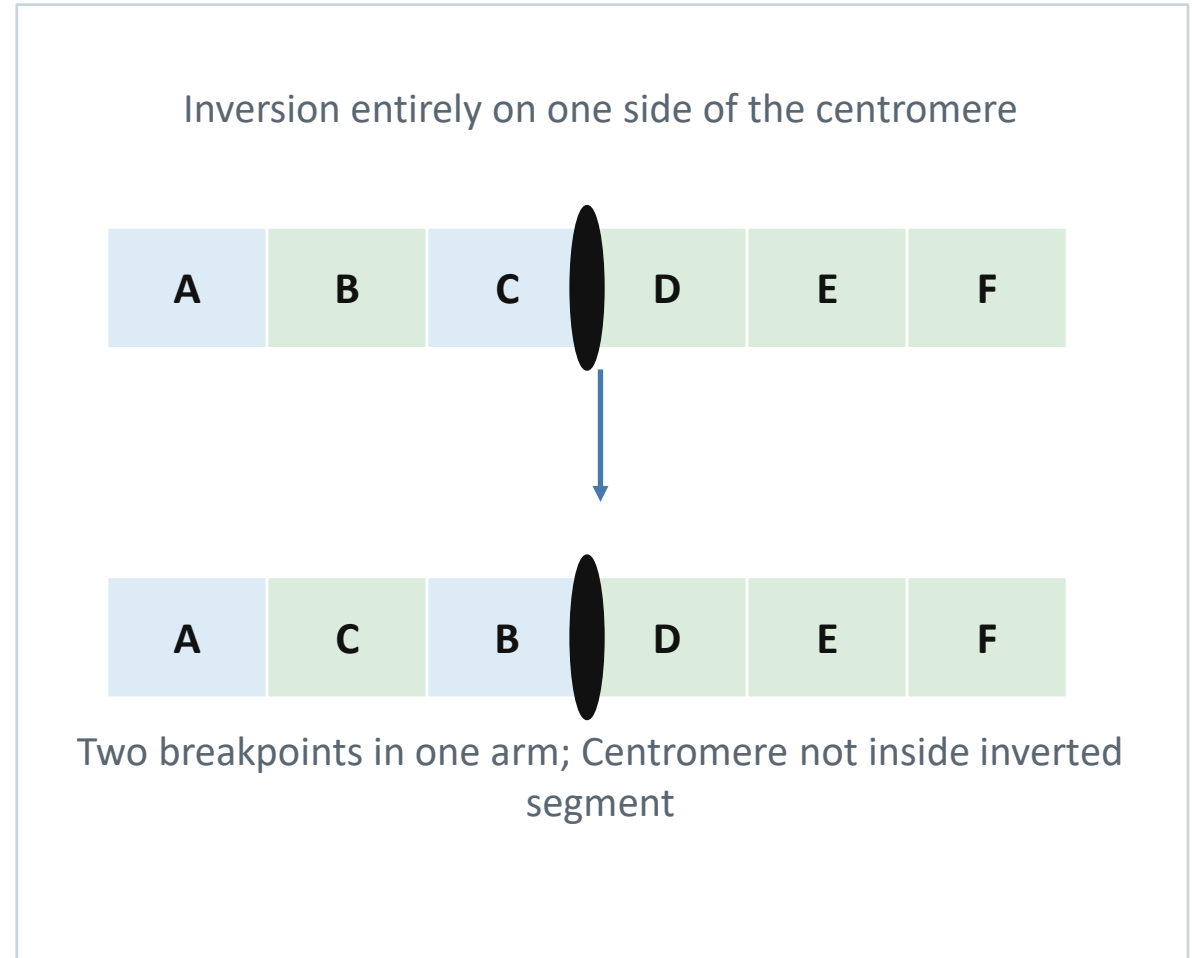
Inversion reverses an intrachromosomal segment

- Two breaks occur within a single chromosome.
- The intervening segment is reinserted in reverse orientation.
- No DNA copy-number change is required to form an inversion.



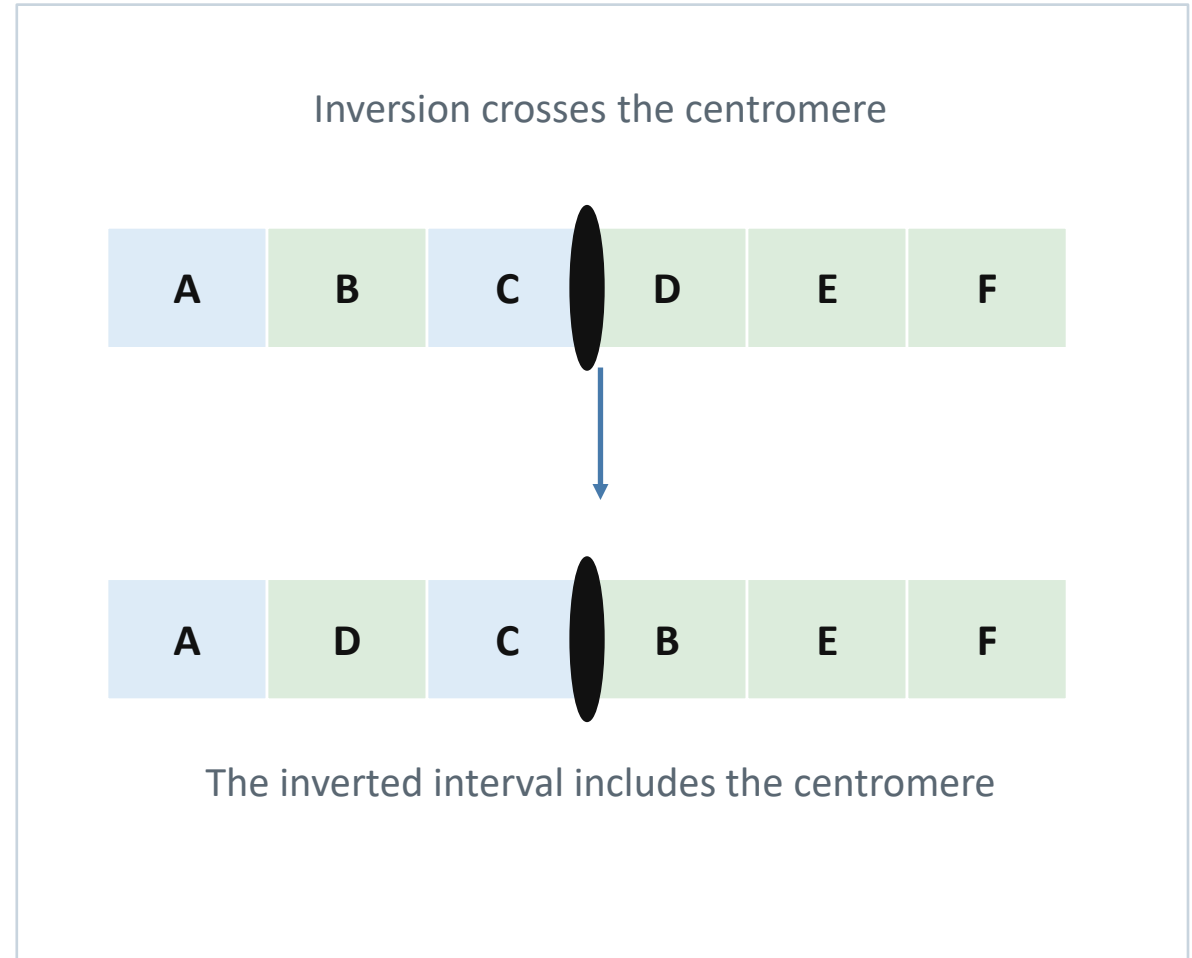
Paracentric inversion excludes the centromere

- Both breakpoints lie within one chromosome arm.
- The inverted segment does not contain the centromere.
- Orientation changes; Total segment dosage may be preserved.



Pericentric inversion includes the centromere

- Breakpoints occur on opposite sides of the centromere.
- The inverted interval includes the centromere.
- The p–q arm configuration is altered by the reversal.



Inversions are often compatible with normal development

- Many inversions retain the full chromosome complement.
- An unaffected phenotype is common when gene function is preserved.
- Breakpoints interrupting essential genes are clinically important exceptions.

Rearrangement with no major DNA loss

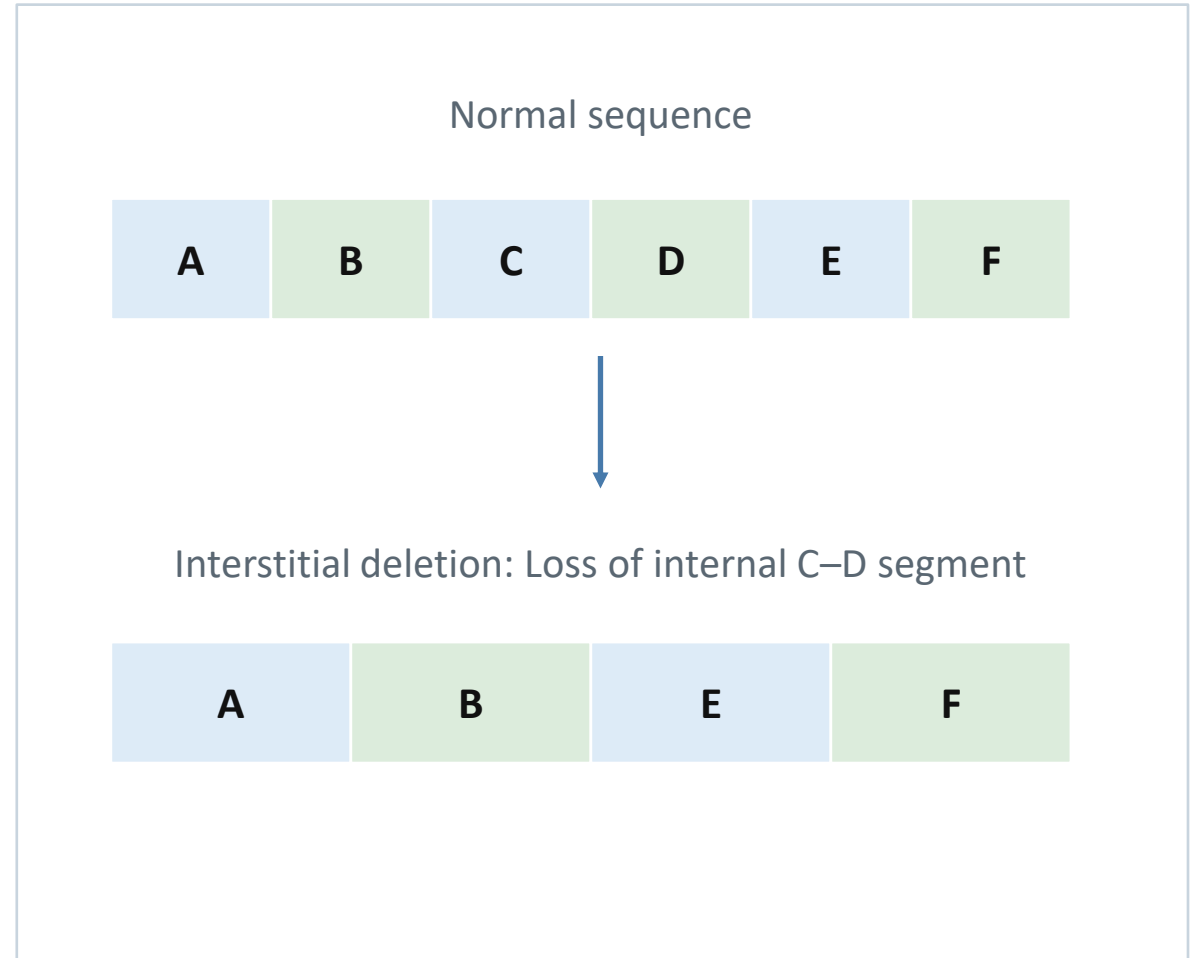
Loss, duplication, or breakpoint disruption

Paracentric and pericentric inversion compared

Feature	Paracentric	Pericentric
Break locations	Within one arm	On opposite arms
Centromere within inversion	No	Yes
DNA copy number	Often unchanged	Often unchanged
Major distinction	Position of reversed interval	Centromere included in interval

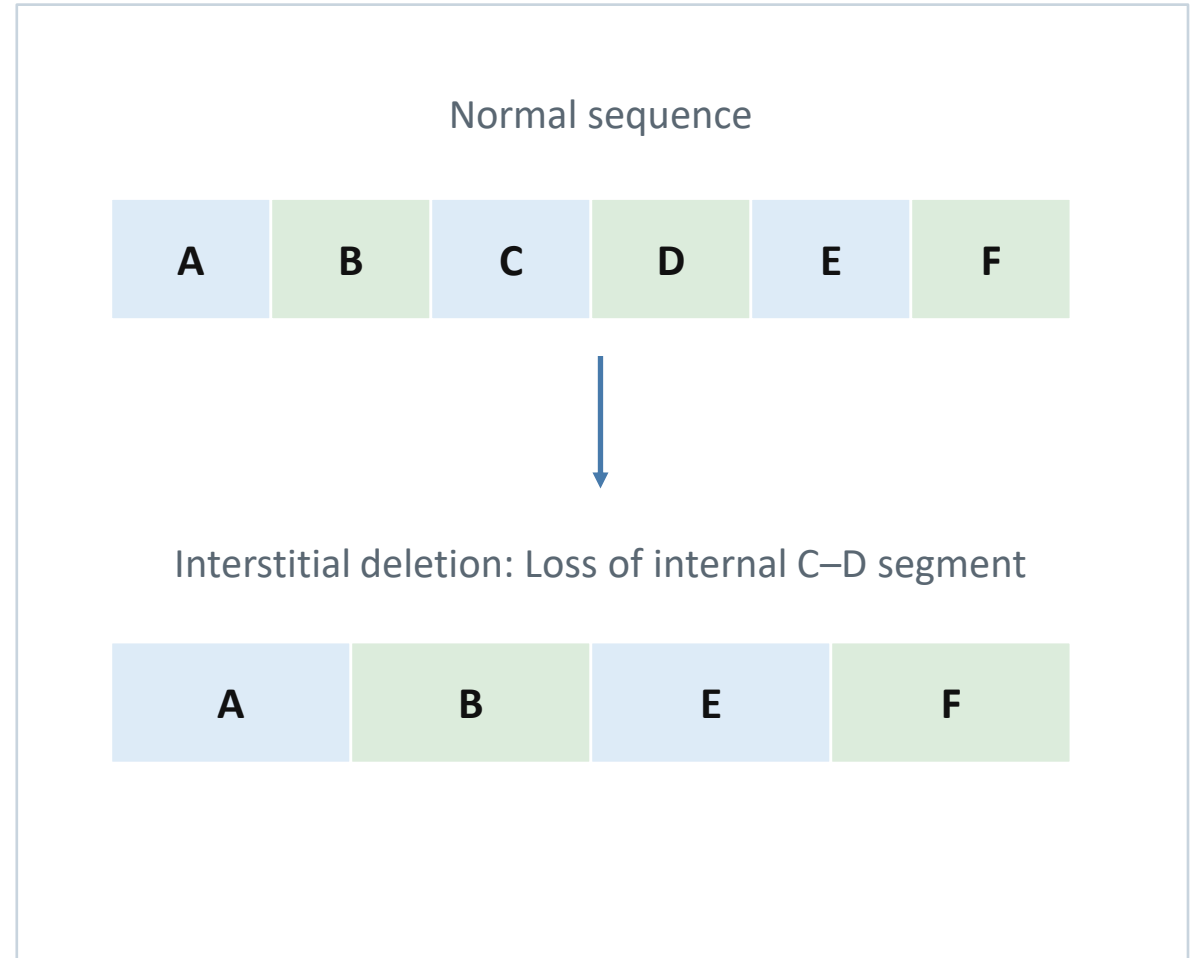
Deletion removes chromosomal DNA

- A chromosome loses a segment of genetic material.
- Interstitial and terminal deletions are two principal types.
- Loss of segmental dosage can alter phenotype.



Interstitial deletion: Two breaks within an arm

- Two intrachromosomal breaks delimit an internal interval.
- The material between them is lost.
- Remaining proximal and distal ends rejoin.



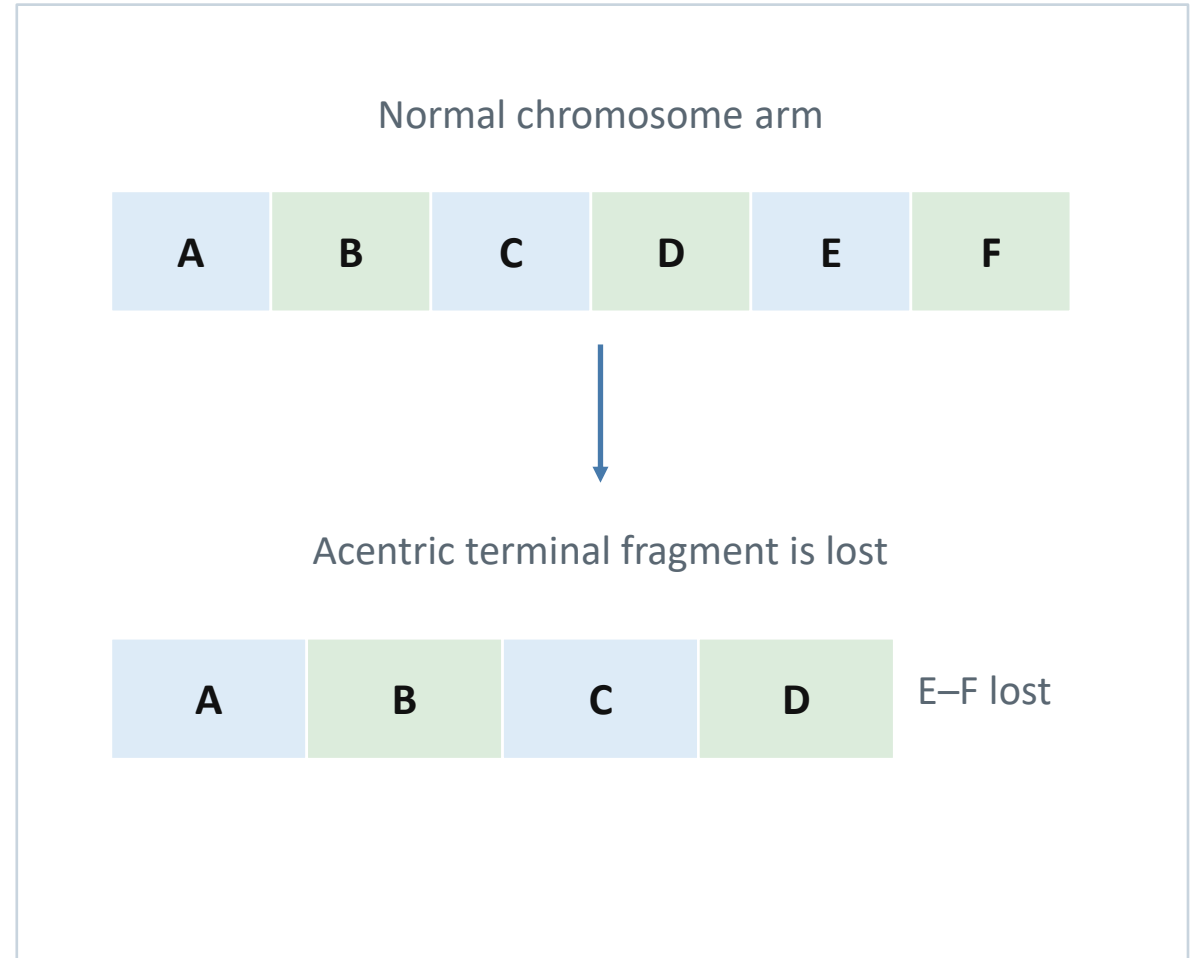
How to read a cytogenetic deletion

46,XY,del(16)(p11.2p13.1)

- 46,XY specifies the remaining overall chromosome count and sex complement.
- Del(16) identifies the chromosome carrying the deletion.
- P11.2 and p13.1 specify the short-arm breakpoint bands.
- The chromosomal material between the breakpoints is missing.

Terminal deletion: Loss from a chromosome end

- A break produces a distal, acentric fragment.
- The fragment is lost at a subsequent cell division.
- The retained chromosome now has an exposed broken end.



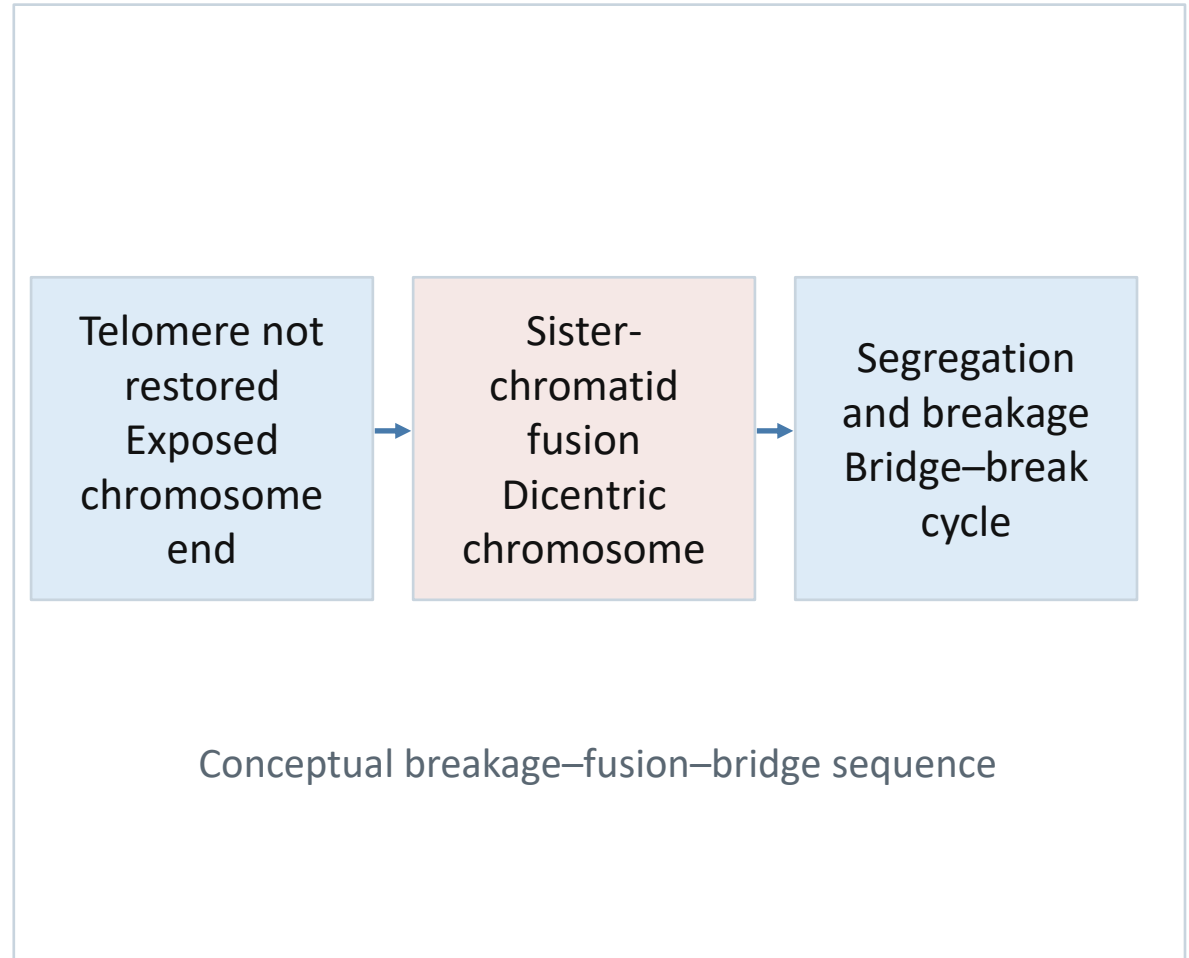
Terminal deletions require end protection

Telomeric protection stabilizes a broken chromosome end.

- The retained shortened chromosome must acquire protective telomeric sequences.
- Without effective end protection, sister chromatids may fuse after replication.
- Such fusion may initiate a breakage–fusion–bridge process.

Breakage–fusion–bridge cycle

- Unprotected sister chromatid ends can join to form a dicentric chromosome.
- Segregation may produce chromosomal bridging and breakage.
- Repeated cycles can perpetuate structural instability.



Interstitial versus terminal deletion

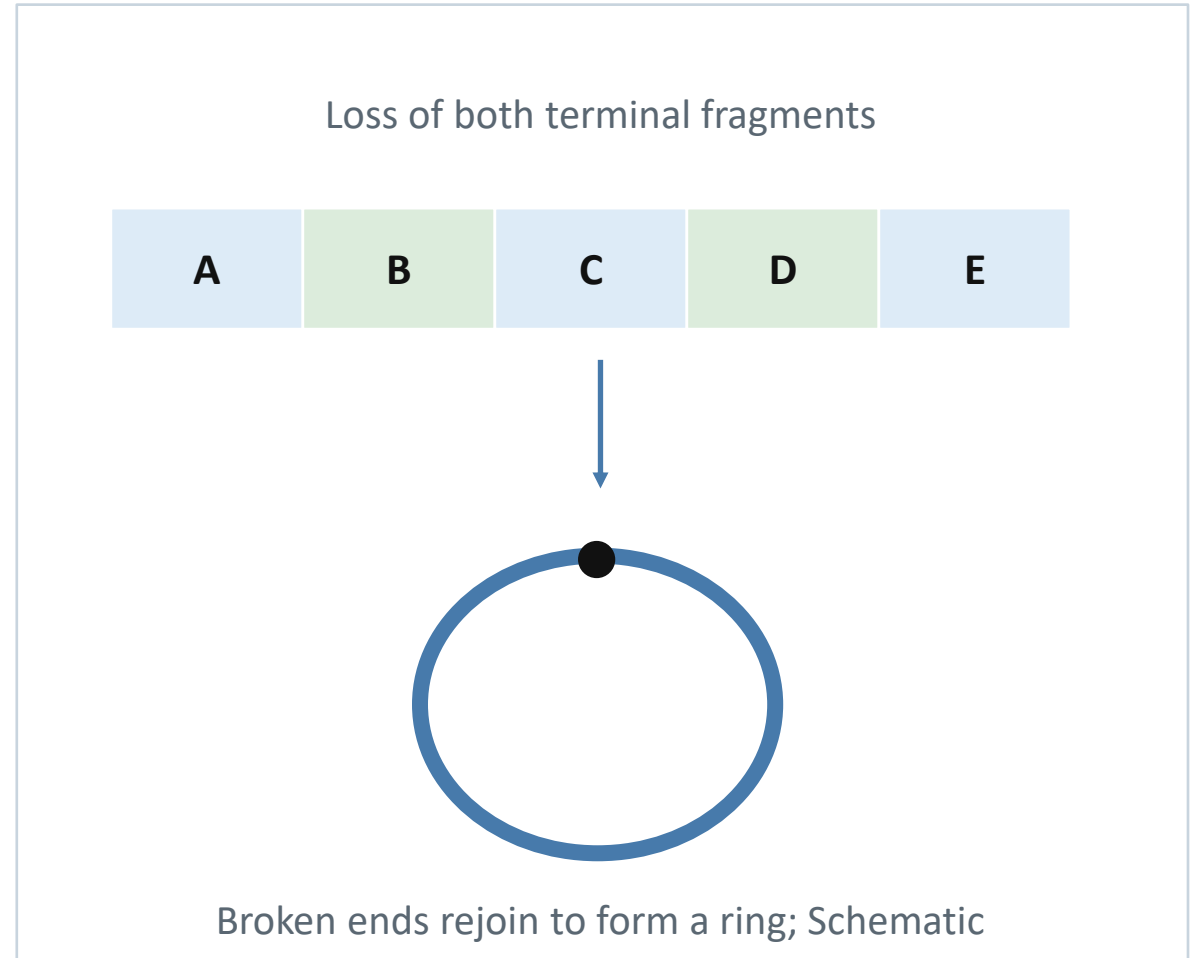
Property	Interstitial	Terminal
Typical breaks	Two in one chromosome arm	One within the chromosome arm
Lost material	Internal interval	Distal arm fragment
Broken-end issue	Flanking ends rejoin	New terminal end needs protection
Consequence	Segmental deletion	Deletion with possible end instability

Deletion consequences depend on the missing interval

- Loss can encompass multiple genes and regulatory regions.
- The extent and genomic content of the deletion determine the dosage deficit.
- Banding may miss deletions below its approximately 2–4 Mb resolution.
- Targeted FISH can identify selected smaller deletions.

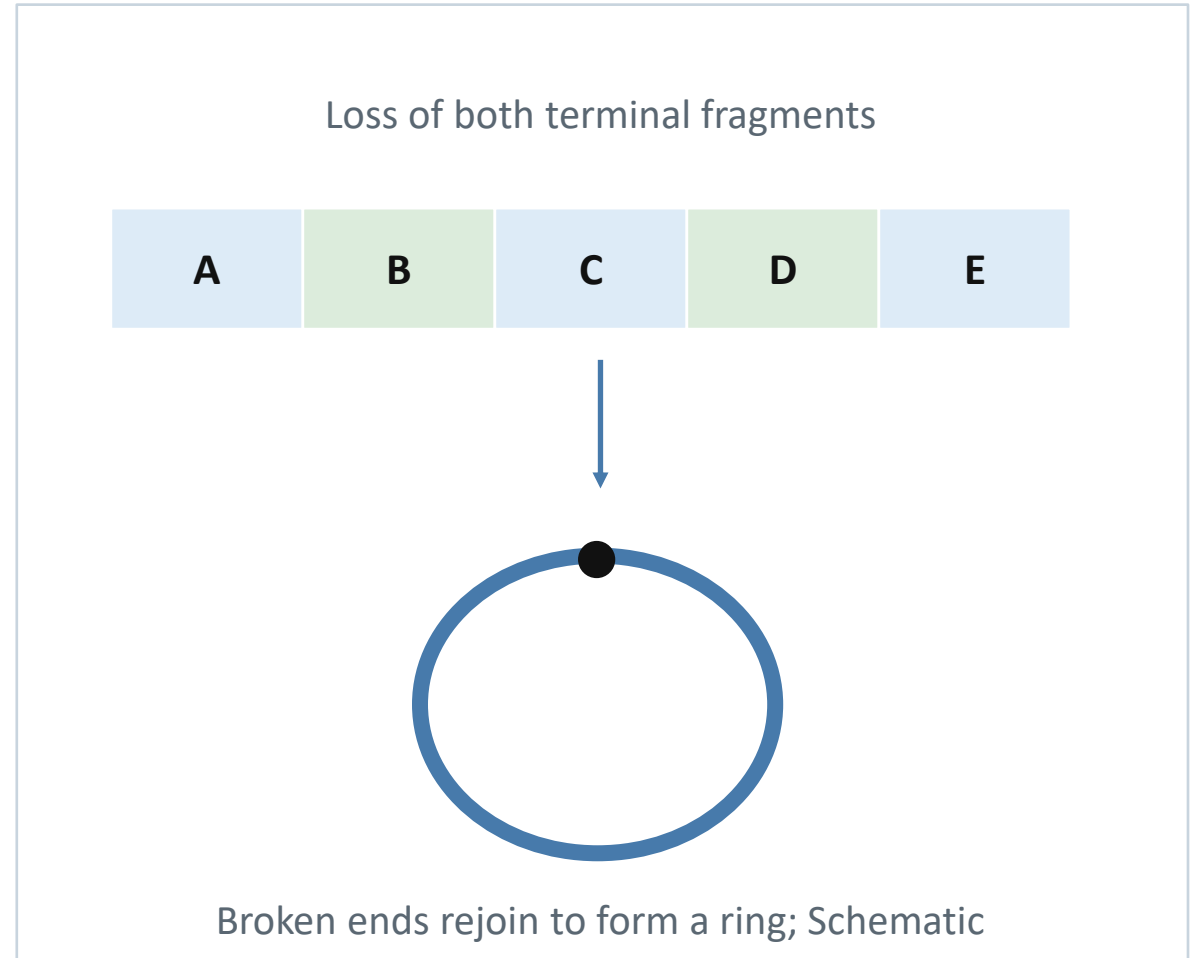
Ring chromosomes result from end-to-end fusion

- Breaks occur near both chromosome ends.
- Terminal fragments are lost.
- The broken chromosome ends fuse into a ring structure.



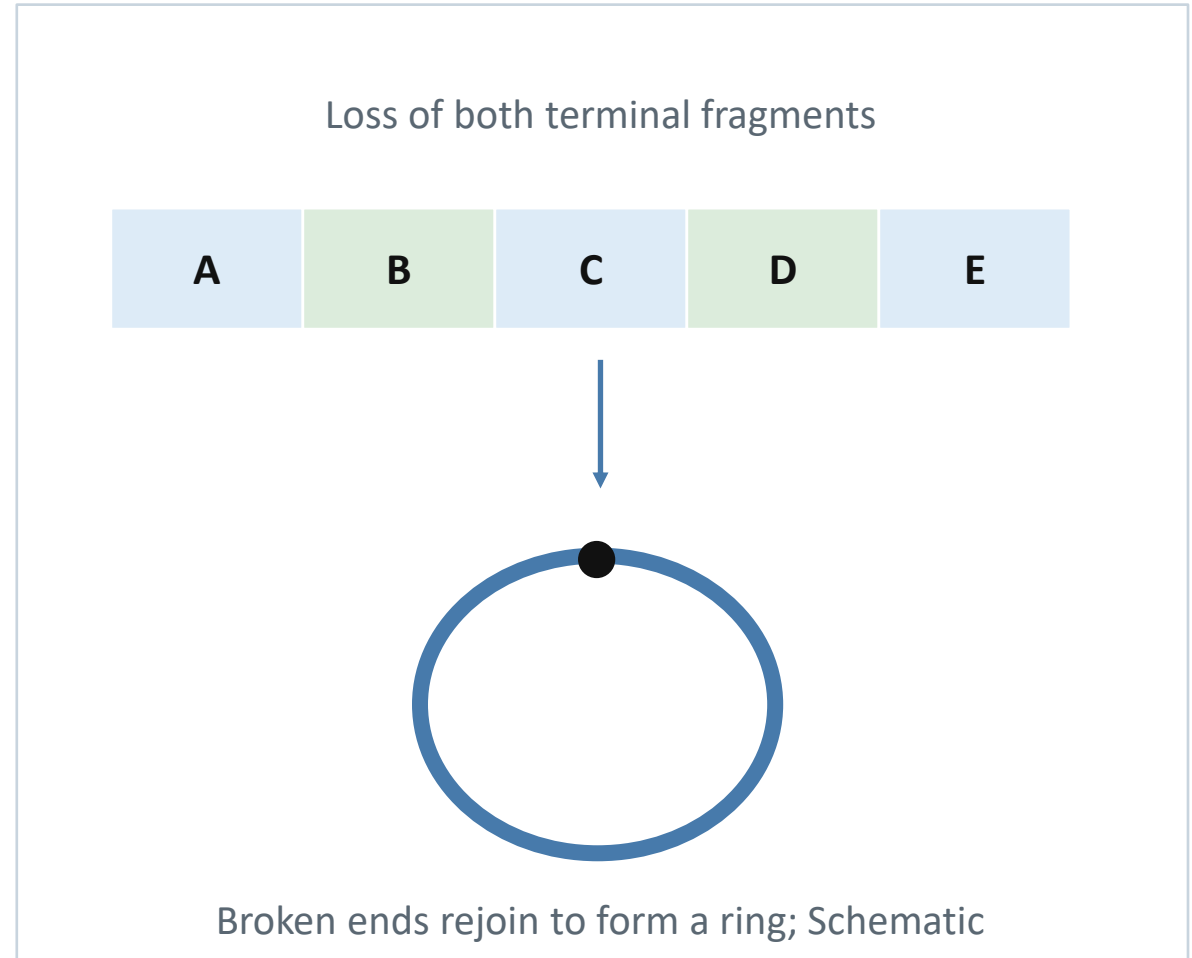
Ring chromosomes may be clinically consequential

- Loss of clinically important terminal DNA can create an abnormal phenotype.
- Ring chromosomes may behave abnormally during cell division.
- Robbins characterizes their consequences as usually serious.



Chromosome ring notation

- 46,XY,r(14) indicates a ring involving chromosome 14.
- The chromosome count and sex complement precede the rearrangement.
- The r identifies ring formation; Chromosome 14 is in parentheses.



Structural alterations: Dosage and architecture

Class	Primary architectural effect	Dosage status
Reciprocal translocation	Exchange between chromosomes	Can be balanced
Robertsonian translocation	Fusion of acrocentric long arms	Often balanced in carrier
Isochromosome	Duplication of one arm	Arm-specific imbalance
Inversion	Reversal within chromosome	Often copy-neutral
Deletion	Loss of chromosomal segment	Deficit
Ring chromosome	Fusion of damaged ends	Often terminal loss

Chromosome notation: Fast recognition

Notation	Interpretation
46,XX,t(2;5)(q31;p14)	Reciprocal translocation involving chromosomes 2 and 5
i(X)(q10)	Isochromosome consisting of X long arms
46,XY,del(16)(p11.2p13.1)	Deletion of the specified interval on 16p
46,XY,r(14)	Ring chromosome 14

What a conventional karyotype can show

- Total chromosome number and sex-chromosome complement.
- Large translocations, inversions, deletions, and ring forms.
- Chromosome arm and cytoband locations of visible changes.
- Not necessarily small, sub-band-scale rearrangements.

FISH improves locus-specific detection

- Fluorescent probes identify specific chromosome sequences.
- FISH can detect changes as small as kilobases.
- It is particularly useful when the clinically suspected region is known.

Banded karyotype

Large changes (~2–4 Mb) visible in routine banding

Fluorescence in situ hybridization

Selected loci: Changes detectable at kilobase scale

Sequencing can reveal additional structural change

Molecular resolution complements cytogenetic morphology.

- DNA sequencing and newer genomic approaches can identify rearrangements.
- Choice of method depends on the genomic question and diagnostic context.
- A structurally normal banded karyotype does not establish DNA-level normality.

Structural chromosome results need two interpretations

Cytogenetic interpretation	Clinical interpretation
What is rearranged?	Is genetic material missing or extra?
Where are the breakpoints?	Could a critical gene be disrupted?
Is the carrier balanced?	What is the potential offspring risk?
What assay resolved the change?	What are the limits of that assay?

Chromosomal abnormalities are selected against in development

- The textbook estimates chromosome abnormalities in approximately 7.5% of conceptions.
- Most of those conceptions do not survive to live birth.
- An estimated 0.5%–1.0% of live-born infants have chromosomal abnormalities.
- These figures cover chromosome disorders broadly, not only structural rearrangements.

Case: Normal carrier with an abnormal offspring risk

A phenotypically normal adult has 46,XX,t(2;5)(q31;p14).

Why can a balanced carrier have a child with chromosomal imbalance?

- Reciprocal translocation changes chromosome structure without necessarily changing total dosage.
- Meiotic segregation can transmit one derivative without its complementary partner.
- The conceptus may have missing and duplicated chromosome segments.

Case: Interpret a deleted chromosome segment

A karyotype is reported as 46,XY,del(16)(p11.2p13.1).

Which chromosome and arm are involved, and what is missing?

- Chromosome 16 carries the deletion; P specifies the short arm.
- The lost interval lies between the reported p-arm breakpoints.
- The chromosome count alone does not quantify the lost DNA.

Case: Distinguish inversion types

Two chromosome breaks occur on opposite sides of a centromere; The interval reinserts in reverse orientation.

What type of inversion is described?

- Pericentric inversion.
- The inverted segment includes the centromere.
- Copy-number neutrality does not exclude breakpoint disruption.

Case: A chromosome with two identical long arms

A chromosome is identified with two long arms derived from the X chromosome.

Name the structural lesion and predict dosage changes.

- I(X)(q10) is the Xq isochromosome.
- Genes on Xp are deficient; Genes on Xq are represented in excess.
- This is different from a copy-neutral inversion.

Case: Terminal deletion without telomere restoration

A terminal chromosome break leaves an unprotected end after distal-fragment loss.

What cell-cycle process can sustain chromosome instability?

- Sister chromatids can fuse after replication.
- The fusion forms a dicentric chromosome.
- Segregation and breakage can repeat as a breakage–fusion–bridge cycle.

Core distinctions for pathology practice

Chromosome architecture and DNA dosage both matter.

- Reciprocal and Robertsonian translocations can be balanced in a carrier but reproductive-risk relevant.
- Isochromosomes, deletions, and many rings alter regional gene dosage.
- Inversions are often copy-neutral but may disrupt critical genes.
- Karyotype, FISH, and sequence-level methods address different resolution scales.

References

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026). Chapter 5: Genes and Human Diseases, pp. 145–146.
- Structural Abnormalities of Chromosomes: chromosomal breakage, rearrangement, and cytogenetic notation.
- Related context in the same chapter: cytogenetic disorders and Trisomy 21, pp. 145–147.