

Trisomy 21

(Down syndrome)

Chromosomal basis, developmental consequences and clinicopathologic correlations

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Learning objectives

- Interpret trisomy 21, Robertsonian translocation and mosaic cytogenetic patterns.
- Connect extra chromosome 21 dosage to selected molecular and organ-system effects.
- Explain major congenital, hematologic, neurologic and immune associations.
- Distinguish prenatal screening from diagnostic confirmation.

Down syndrome is a chromosomal disorder

- The phenotype results from an extra dosage of chromosome 21 genetic material.
- It is the most common chromosomal disorder and a major cause of intellectual disability.
- Different cytogenetic routes converge on increased chromosome 21 dosage.

One syndrome can arise through distinct chromosomal mechanisms.

Newborn frequency in the United States

United States

~1 in 700 newborns

Type of estimate

Live-birth frequency

- About one affected newborn in 700 in the United States.
- This is an approximate textbook incidence, not an independently verified 2026 surveillance estimate.
- It expresses live-birth frequency, not the risk for a particular pregnancy.

Normal human chromosome complement

Chromosome 21 in a normal diploid cell



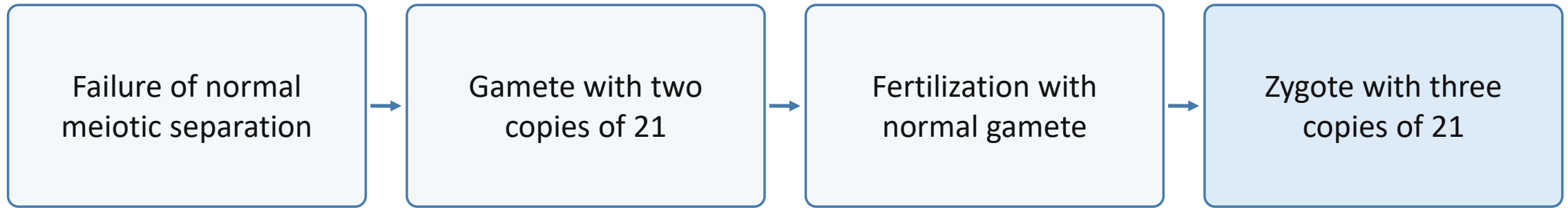
Two homologues

- Human somatic cells normally contain 46 chromosomes: 22 autosomal pairs and a sex-chromosome pair.
- Karyotyping arranges metaphase chromosomes by homologous pairs.
- G-banding allows recognition of whole-chromosome gains and large rearrangements.

Euploidy versus aneuploidy

Term	Definition	Relevance here
Euploid	Exact multiple of the haploid set (23)	Normal diploid cells: 46
Aneuploid	Chromosome count not an exact multiple of 23	Trisomy 21: 47
Trisomy	A third copy of a particular chromosome	Extra genetic material from chromosome 21

How a trisomic zygote can arise



- Nondisjunction produces gametes with an extra chromosome or with a missing chromosome.
- Fertilization involving a gamete with two copies of chromosome 21 can yield three copies in the zygote.

The 47-chromosome constitution

Chromosome 21 in typical free trisomy

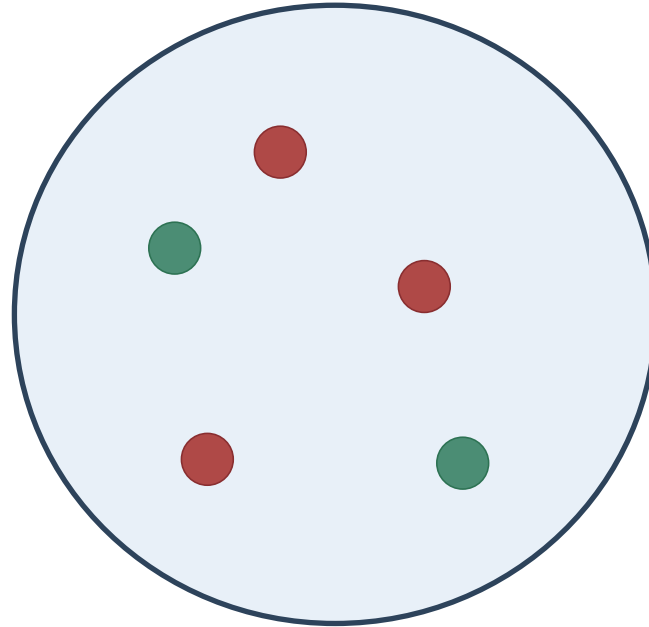


Three separate homologues

- Typical free trisomy 21 contains three separate copies of chromosome 21.
- Affected individuals usually have 47 chromosomes rather than 46.
- Sex chromosomes are designated separately (for example, 47,XX,+21).

FISH can demonstrate three chromosome 21 signals

3 × chromosome 21 probe signals

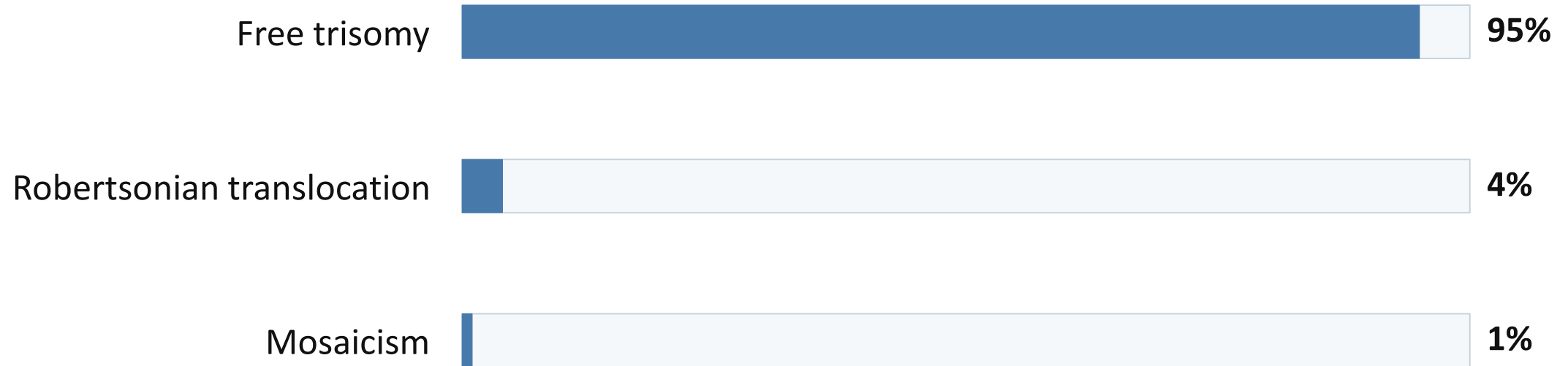


2 × chromosome 13 probe signals

Schematic (not observed FISH)

- Chromosome 21–specific probes identify its copy number in an interphase nucleus.
- The source example shows three chromosome 21 signals and two chromosome 13 control signals.

Three cytogenetic mechanisms underlie the phenotype



Proportion of Down syndrome cases (%)

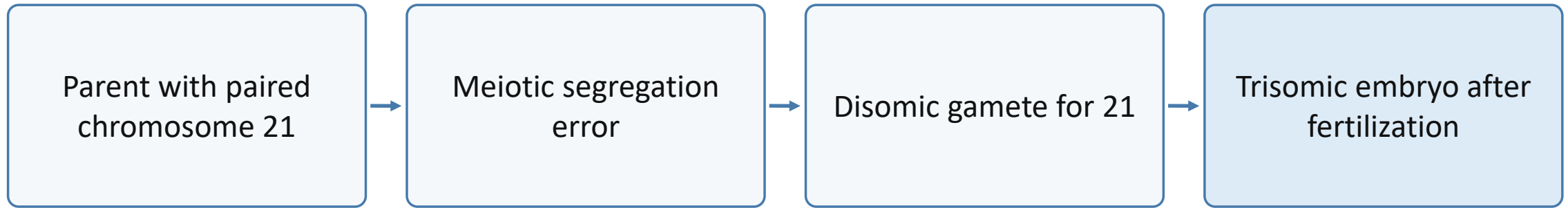
- The source estimates approximately 95% free trisomy, 4% Robertsonian translocation and 1% mosaicism.
- These are proportions among Down syndrome cases, not population prevalence.

Meiotic nondisjunction is the predominant route

- Failure of normal chromosomal separation occurs during gametogenesis.
- The common result is a conceptus with an additional entire chromosome 21.
- Parents of children with free trisomy 21 generally have normal constitutional karyotypes.

Aneuploidy in the child need not reflect an abnormal parental karyotype.

Nondisjunction: The conceptual sequence



- The error occurs before fertilization in the classical meiotic form.
- The chromosome imbalance is then carried into subsequent embryonic cell divisions.

The extra chromosome is usually maternally derived

- DNA polymorphism analyses traced the extra chromosome 21 to the maternal parent in about 95% of cases.
- This observation supports an important role for errors arising in the ovum.
- It does not imply maternal causation through behavior or a controllable exposure.

Maternal age strongly modifies live-birth frequency

Maternal age <20

1 in 1,550 live births

Maternal age >45

1 in 25 live births

- Approximately 1 in 1,550 live births for mothers younger than 20.
- For mothers older than 45, the corresponding figure is about 1 in 25.
- These two reported groups are endpoints, not a continuous risk model.

The age association does not fully explain nondisjunction

- The maternal-age correlation indicates that meiotic chromosome segregation is age-sensitive.
- Multiple hypotheses have been proposed.
- The precise reason for greater susceptibility to nondisjunction is not established in the source.

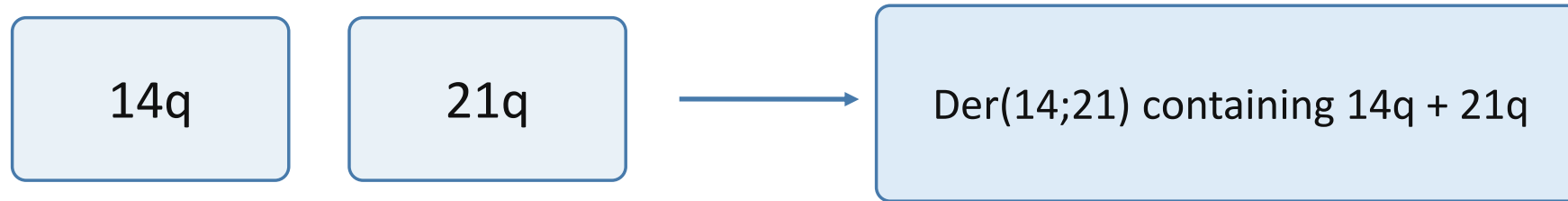
Association is well established; A single definitive causal mechanism is not.

Free trisomy and translocation are not synonymous

Dimension	Free trisomy 21	Robertsonian-associated Down syndrome
Chromosome complement	Usually 47	May contain 46 chromosomes
Additional material	Independent chromosome 21	Additional 21q material on a derivative chromosome
Typical mechanism	Meiotic nondisjunction	Centric fusion involving acrocentric chromosomes
Parental status	Usually normal karyotypes	Can involve a balanced carrier

Robertsonian translocation joins long arms

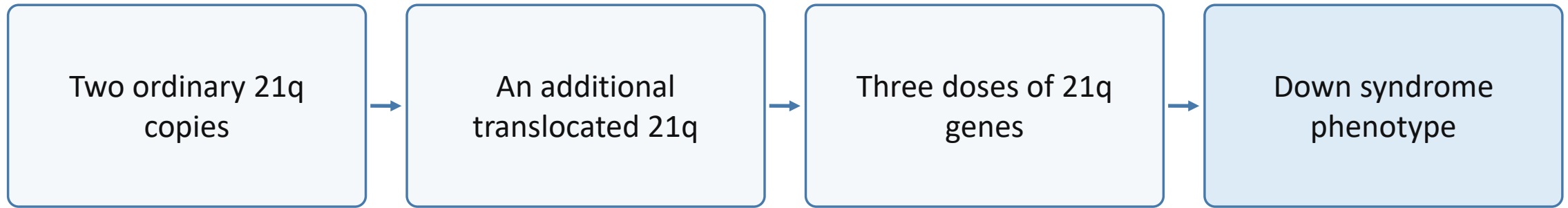
Conceptual chromosome-arm arrangement



Schematic; No physical chromosome scale implied

- A Robertsonian rearrangement involves centric fusion of acrocentric chromosomes.
- Chromosome 21q can be translocated to another acrocentric chromosome.
- Clinical significance depends on the net dosage of chromosome 21 material.

An extra 21q copy causes dosage imbalance



- Two ordinary chromosome 21 copies plus a translocated 21q copy supply three doses of 21q.
- The resulting gene dosage can produce the Down syndrome phenotype despite a different chromosome count.

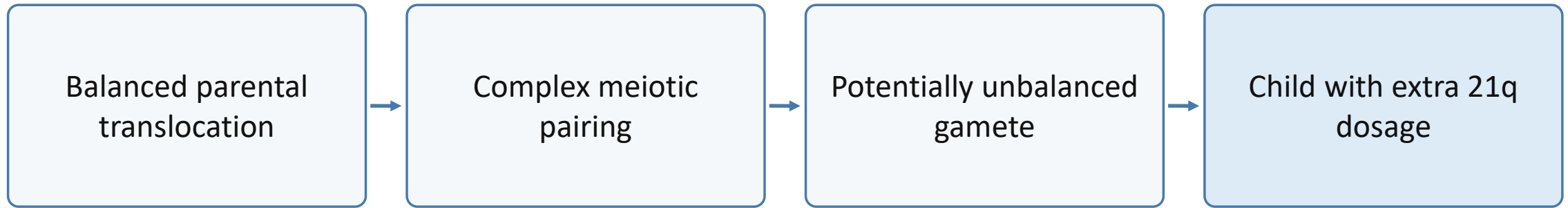
Chromosomes 14 and 22 are illustrative partners

- Chromosome 21 material attached to another acrocentric chromosome, such as 14 or 22.
- The rearrangement changes chromosome structure, not merely chromosome count.
- Conventional karyotyping is important for classifying the rearrangement.

Balanced carrier versus affected conceptus

Feature	Balanced Robertsonian carrier	Down syndrome from translocation
Genetic dosage	Essential long-arm complement remains balanced	Chromosome 21 dosage is increased
Chromosome count	Often 45	Often 46 for rob(14;21)-associated cases
Clinical phenotype	Carrier may be unaffected	Down syndrome phenotype
Reproductive relevance	Unbalanced gametes may form	May recur in a family

Why carrier parents can produce unbalanced gametes

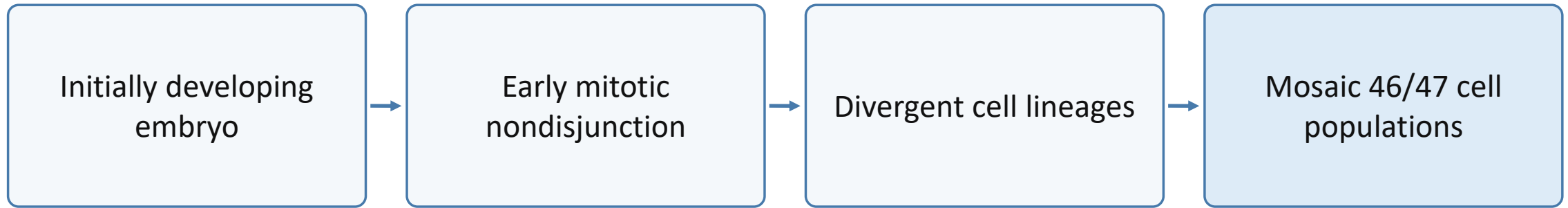


- Rearranged and normal homologues must pair and segregate during meiosis.
- This segregation can yield gametes with unbalanced chromosomal content.
- Consequently, a translocation-associated case may have a familial origin.

Translocation status changes genetic evaluation

- About 4% of Down syndrome cases are attributed to Robertsonian translocation.
- Some of these rearrangements are inherited; Others are not.
- Characterizing the child's karyotype can indicate whether parental chromosomal evaluation is relevant.

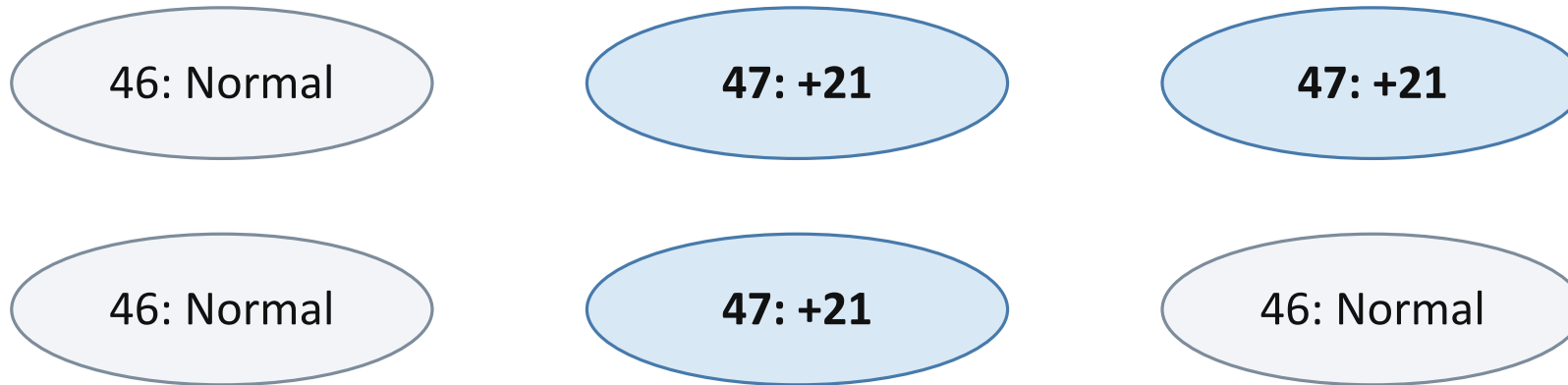
Mosaicism originates after fertilization



- An early mitotic segregation error can create genetically distinct cell populations.
- The viable mosaic typically contains both 46-chromosome and 47-chromosome cell lines.
- Different tissues may contain different proportions of affected cells.

Mosaic Down syndrome contains distinct cell lines

Coexisting cell lines



Cells shown in illustrative proportions only

- The classic designation uses 46- and 47-chromosome cell populations.
- The textbook estimates approximately 1% of individuals with Down syndrome are mosaics.
- Tissue distribution is important; One sample does not fully capture all cell lineages.

Mosaic phenotype is variable

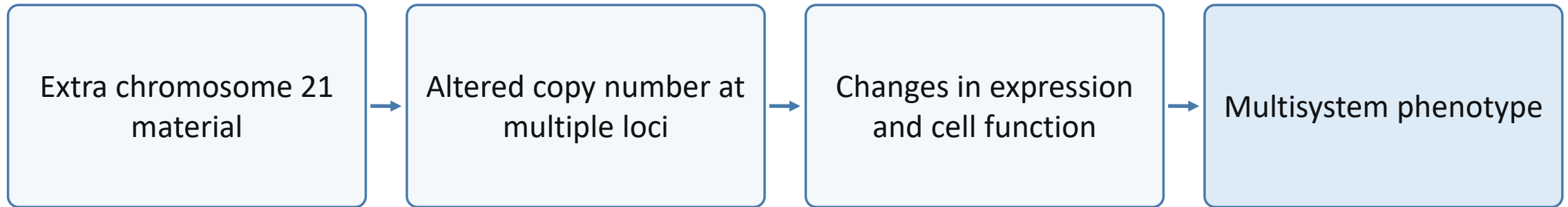
- The presence and distribution of trisomic cells influence clinical expression.
- Some affected individuals show milder phenotypic features.
- The source notes that some mosaics can have normal or near-normal intellectual functioning.

A mosaic karyotype does not determine an individual's phenotype with certainty.

Three routes: Origin and diagnostic implications

Mechanism	When it arises	Key cytogenetic concept
Free trisomy	Usually meiotic error	Three separate chromosome 21 copies
Robertsonian translocation	Chromosomal rearrangement; Sometimes inherited	Extra chromosome 21 long-arm material
Mosaicism	Early postzygotic mitotic error	Two or more cell lines

Gene dosage is the unifying pathogenic principle



- The phenotype reflects dosage imbalance across many loci on chromosome 21.
- An additional chromosome or chromosome segment can increase expression of relevant genes.
- Robbins does not attribute the full syndrome to one causal gene.

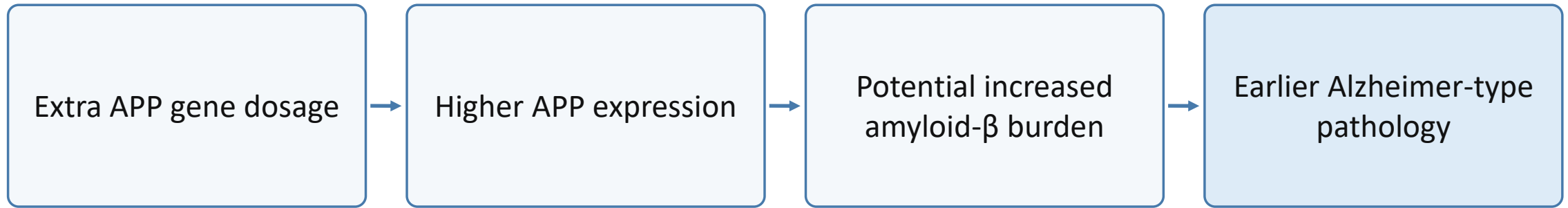
Most chromosome 21 protein-coding genes are overexpressed

- The source describes overexpression of most protein-coding genes located on chromosome 21.
- Increased gene dosage affects many pathways simultaneously.
- The relationships among dosage, pathway responses and individual features remain complex.

Dosage alteration differs from single-gene disease

Dimension	Trisomy 21	Simplified single-gene model
Genetic origin	Additional chromosomal material	Pathogenic change at a specific gene
Molecular consequence	Many gene products may change	A principal protein or pathway may dominate
Phenotypic explanation	Distributed dosage effects	Often focused gene–phenotype chain

APP is one chromosome 21 dosage-sensitive gene

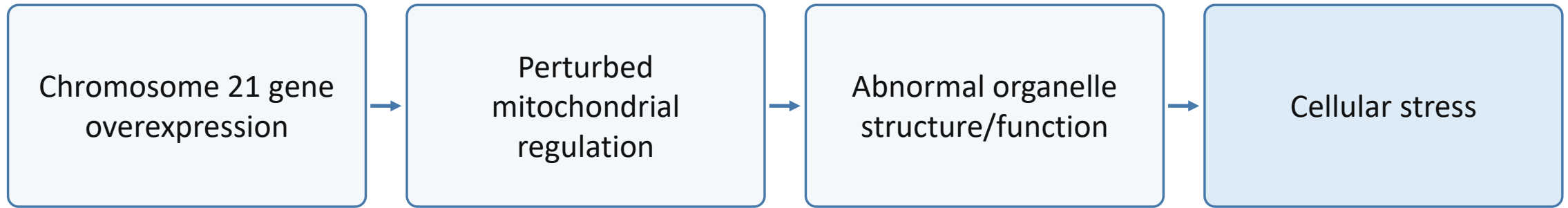


- The gene encoding amyloid- β precursor protein (APP) is on chromosome 21.
- Increased APP dosage is a plausible contributor to amyloid-related neuropathology.
- This as one component of a wider phenotype.

Amyloid- β accumulation offers a neuropathologic link

- Amyloid- β aggregation as a potential initiating event in Alzheimer disease.
- Extra APP dosage in trisomy 21 may contribute to earlier amyloid pathology.
- The molecular association should not be treated as an explanation for all cognitive features.

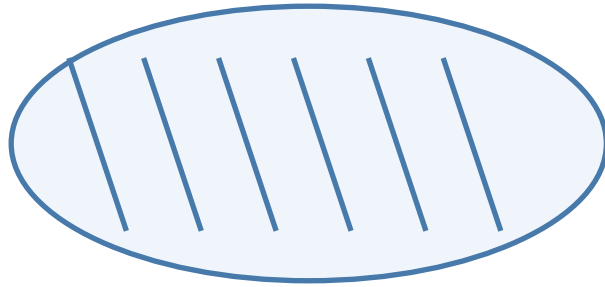
Chromosome 21 dosage also affects mitochondria



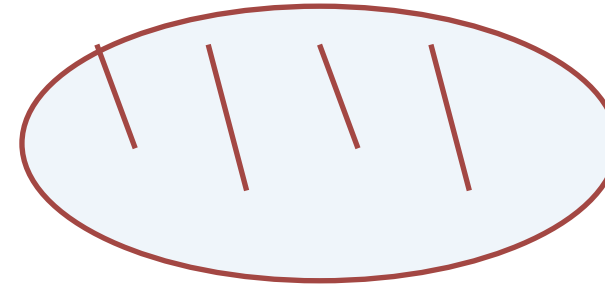
- Approximately 10% of the genes overexpressed in Down syndrome are involved directly or indirectly in mitochondrial regulation.
- The source reports abnormalities in mitochondrial morphology and function.

Mitochondrial cristae may be swollen or disrupted

Simplified mitochondrial ultrastructure



Illustrative intact folds

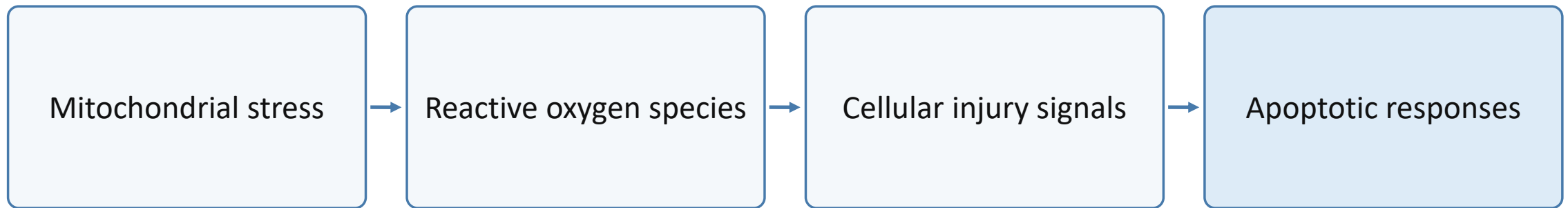


Illustrative swollen / disrupted folds

Schematic; Not an electron micrograph

- Broken or swollen cristae are described in several tissues.
- Altered mitochondrial structure accompanies broader functional stress.

Oxidative stress may amplify cellular injury



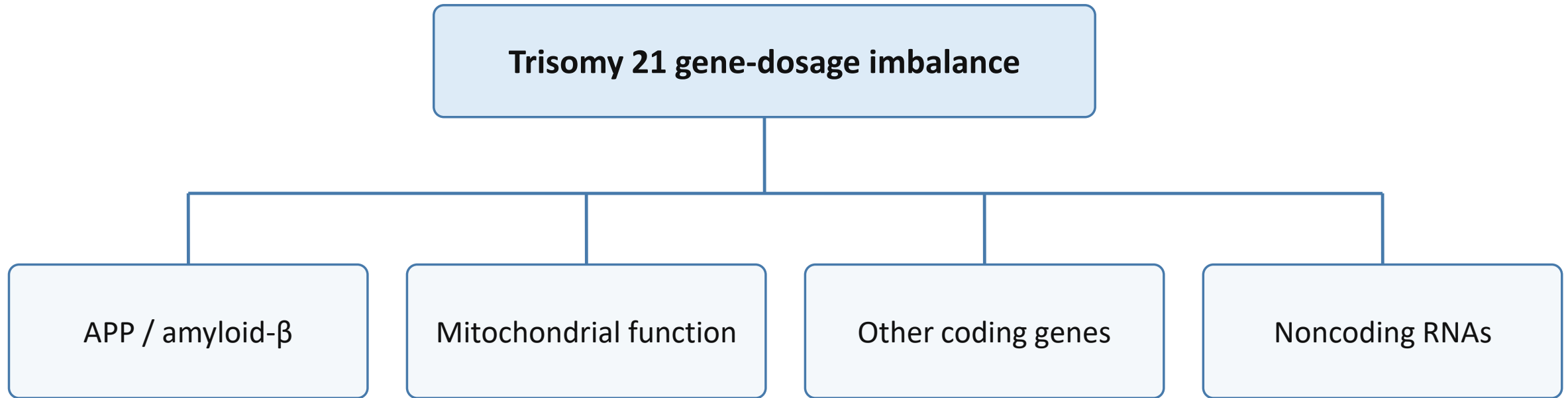
- Mitochondrial stress is linked in the source to generation of reactive oxygen species.
- Activation of apoptosis is also reported.
- These changes provide candidate mechanisms for tissue dysfunction without fully specifying organ-level causation.

Noncoding RNA contributions remain uncertain

- Chromosome 21 has a high density of long noncoding RNAs.
- The biological functions of most of these transcripts remain unknown in the source.
- Their quantitative contribution to the phenotype requires further study.

Do not assign unverified downstream effects to individual lncRNAs.

Molecular disease model: Interacting contributors



- Gene dosage is central; APP-related amyloid biology and mitochondrial stress are examples.
- Noncoding RNA biology remains a potential additional layer.
- The magnitude of each pathway's contribution differs across features and is incompletely resolved.

The clinical phenotype can be recognized at birth

- The source highlights a recognizable constellation of facial features.
- Clinical examination may prompt cytogenetic assessment.
- No single physical feature is sufficient to establish a chromosomal diagnosis.

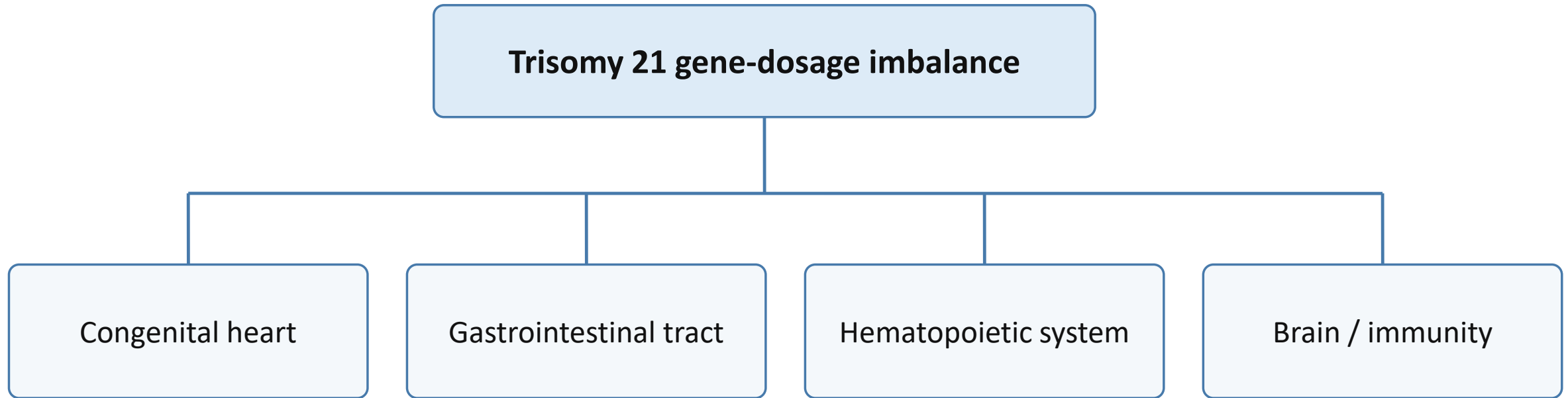
Characteristic facial findings

Finding	Description	Diagnostic interpretation
Flat facial profile	Reduced prominence of the midface/profile	Recognizable component of the pattern
Oblique palpebral fissures	Slanting ocular openings	One feature among several
Epicanthic folds	Skin folds near the medial canthi	Supportive, not diagnostic alone

Intellectual disability is a central association

- Down syndrome is a major cause of intellectual disability.
- Neurodevelopmental outcomes span a spectrum of functional abilities.
- Mosaic individuals may show particularly variable outcomes.

The syndrome affects multiple organ systems



- Congenital cardiac and gastrointestinal anomalies.
- Leukemia risk, neurodegenerative pathology and immune dysregulation are important associations.
- Clinical manifestations arise from the same chromosomal diagnosis but differ by system.

Congenital heart disease affects many patients

Congenital heart disease

~40%

Without reported congenital heart
disease

~60%

- Approximately 40% of individuals with Down syndrome have congenital heart disease in the source.
- Cardiac abnormalities are a major determinant of infant and early-childhood morbidity.

Atrioventricular septal defects predominate

- The source describes atrioventricular septal defects as the most frequent congenital cardiac lesion.
- They account for 43% of the listed congenital heart defects among affected patients.
- The name identifies abnormal septation involving the atrioventricular junction.

Ventricular septal defects are also common

- Ventricular septal defects account for 32% of the cardiac defects tabulated.
- They represent a communication across the interventricular septum.
- This category should be distinguished from complete atrioventricular septal defects.

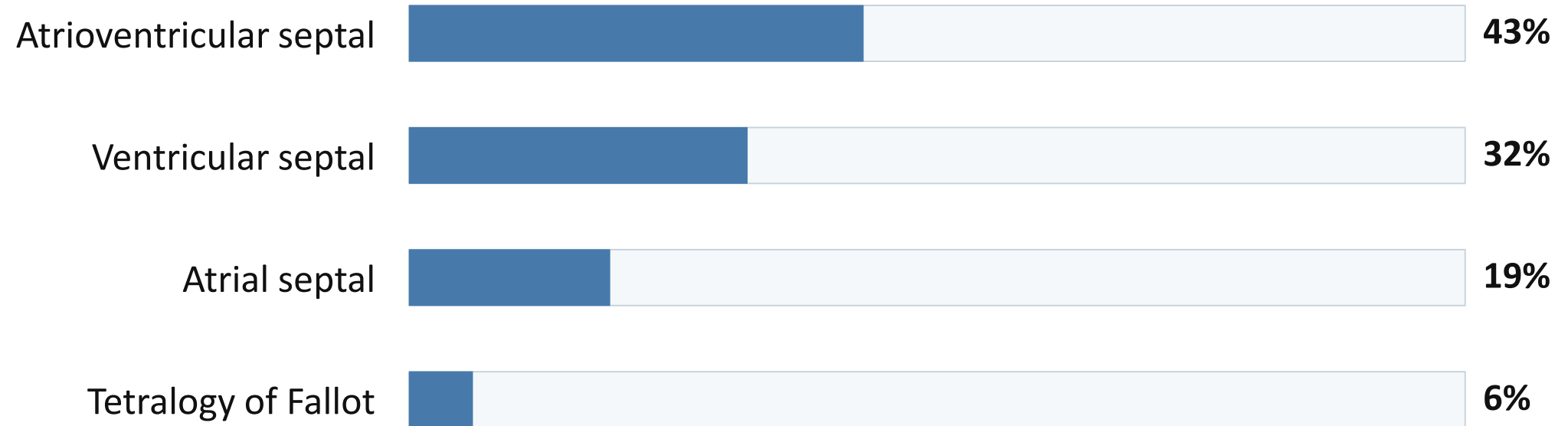
Atrial septal defects form another major category

- Atrial septal defects account for 19% of the listed lesions.
- They involve abnormal communication across the interatrial septum.
- Defect classification informs the anatomical interpretation of congenital heart disease.

Tetralogy of Fallot is less frequent

- Tetralogy of Fallot in 6% of its congenital cardiac breakdown.
- Its presence is an important reminder that the cardiac phenotype is not limited to septal defects.
- The cited percentages apply to the specified cardiac-defect distribution.

Congenital heart defect distribution



Share of reported congenital heart defects (%)

- Percentages are categories of congenital heart disease reported in the source.
- They must not be interpreted as percentages among all individuals with Down syndrome.

Congenital heart disease drives early mortality

- Cardiac problems are described as responsible for most deaths during infancy and early childhood.
- This association provides the clinical rationale for early attention to congenital heart disease.
- It is a historical/source statement, not a current age-specific mortality estimate.

Anatomic diagnosis matters because cardiac lesions contribute materially to prognosis.

Gastrointestinal atresias are additional malformations

- Esophageal and small-bowel atresias among associated congenital anomalies.
- Atresia denotes interruption or absence of a normal luminal passage.
- These are developmental structural abnormalities, not consequences of leukemia or later dementia.

Cardiac versus gastrointestinal malformations

System	Examples in the source	Pathologic category
Cardiovascular	AVSD, VSD, ASD, tetralogy of Fallot	Congenital defects of cardiac structure
Gastrointestinal	Esophageal atresia; Small-bowel atresia	Congenital interruption of a hollow viscus

Hematopoietic malignancy risk is elevated

- Children with trisomy 21 have an increased likelihood of developing leukemia.
- Both precursor B-cell acute lymphoblastic leukemia and acute myeloid leukemia.
- The reported relative-risk increases differ substantially by leukemia category.

Precursor B-ALL: Approximately 20-fold relative risk

Precursor B-cell ALL

~20-fold higher risk

Metric type

Relative risk increase

- An approximately 20-fold increased risk for precursor B-cell acute lymphoblastic leukemia.
- A relative-risk multiplier is not an absolute probability of developing leukemia.
- Disease-specific numerical claims are retained in their textbook context.

Acute myeloid leukemia: Approximately 500-fold risk

Acute myeloid leukemia

~500-fold higher risk

Metric type

Relative risk increase

- The source reports an approximately 500-fold increase in acute myeloid leukemias.
- This is a relative-risk comparison with the general population, not lifetime incidence.
- The cited statement does not subdivide AML into molecular subtypes.

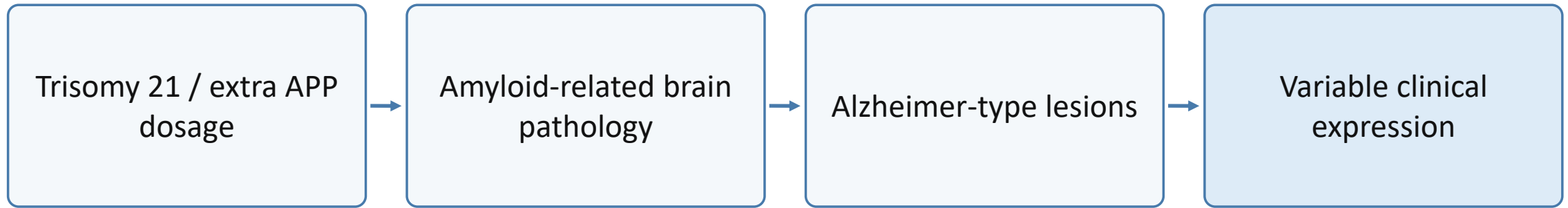
The two leukemia risk statements are distinct

Leukemia category	Reported increase	Interpretation
Precursor B-cell ALL	20-fold	Marked increase in relative risk
Acute myeloid leukemias	500-fold	Even larger relative increase
Both categories	No absolute rates stated	Do not infer absolute incidence from fold change

Alzheimer-type neuropathology develops early

- The source states that virtually all people with trisomy 21 beyond age 40 develop neuropathologic changes characteristic of Alzheimer disease.
- This is a statement about neuropathologic changes, not a claim that every individual has symptomatic dementia.
- The APP dosage pathway provides one mechanistic link.

Distinguish Alzheimer pathology from clinical dementia

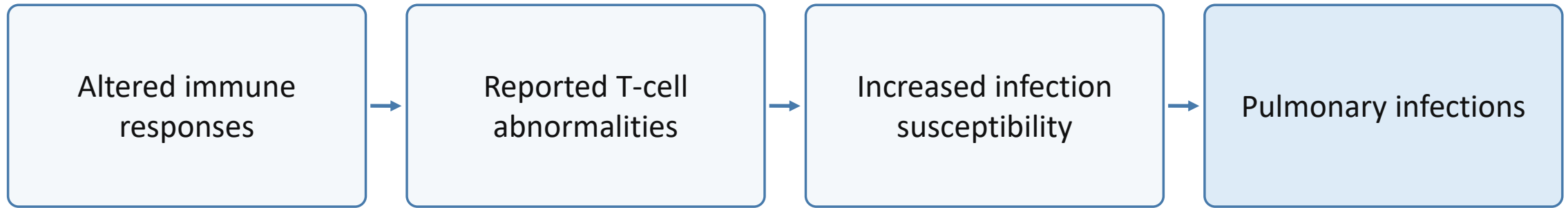


- The appearance of neuropathologic lesions and the manifestation of dementia are different outcomes.
- The textbook's near-universal statement concerns microscopic neuropathology over age 40.

Immune disturbances increase infection susceptibility

- Down syndrome is associated with abnormal immune responses.
- The source identifies serious infections, especially in the lungs, as an important consequence.
- It describes reported abnormalities affecting predominantly T-cell functions.

Immunologic disturbance: Clinical consequences



- The precise immunologic basis is not fully defined in the source.
- The relationship to respiratory infection is established clinically, though not explained by a single pathway.

Thyroid autoimmunity is another immune association

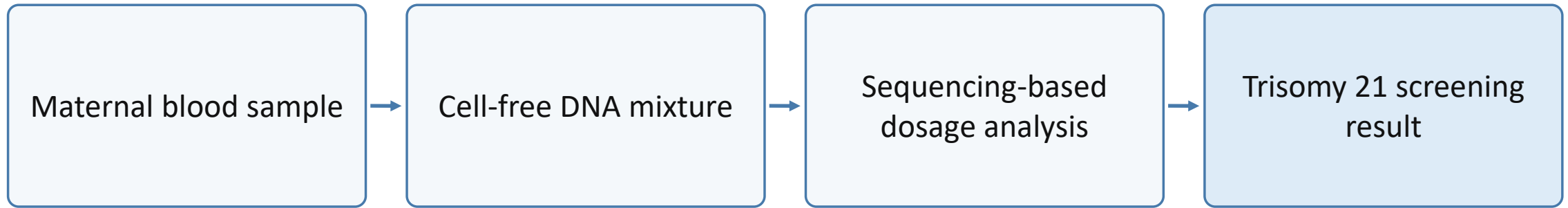
- The textbook specifically mentions predisposition to thyroid autoimmunity.
- The immune phenotype encompasses more than susceptibility to infection.
- The source does not specify the frequency or detailed autoantibody profile.

Medical care has changed survival

- Increased longevity to improvements in medical care.
- The text provides historical median age-at-death figures (25 years in 1983 and 47 years at a later reporting point).
- These figures should not be used as validated contemporary survival estimates without independent updating.

Survival statistics depend strongly on era, population and clinical care.

Prenatal screening analyzes fetal-derived DNA



- Maternal blood contains a cell-free DNA mixture with a fetal-derived component.
- The fetal-derived component as the basis of chromosome-dosage screening.
- The assay assesses relative chromosome 21 representation rather than a physical karyogram.

Fetal-derived cell-free DNA fraction in the source

Fetal-derived fraction

~5–10%

Specimen

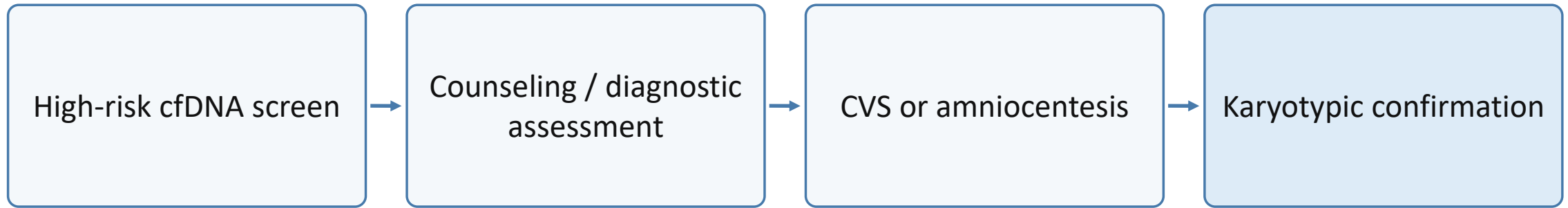
Maternal blood

- That approximately 5–10% of circulating cell-free DNA in maternal blood is fetal-derived.
- The reported percentage is an illustrative source range rather than a universal result for every specimen.
- Polymorphic markers can help distinguish fetal-derived material.

Sequencing detects relative chromosome 21 dosage

- The source describes next-generation sequencing analysis of chromosome-linked DNA abundance.
- An excess representation of chromosome 21 sequences generates a high-risk screening signal.
- Screening is noninvasive but does not independently establish a fetal karyotype.

A positive screen requires diagnostic evaluation



- Cell-free DNA testing is framed as screening.
- The source notes that positive screens are generally confirmed with conventional cytogenetic testing.
- Chorionic-villus sampling or amniocentesis can provide fetal-derived cells for analysis.

Screening versus diagnostic cytogenetics

Approach	Material/target	Question answered
Maternal cfDNA screen	Cell-free DNA in maternal plasma	Is trisomy 21 likely?
FISH	Chromosome-specific signals in cells	Are three 21-linked signals present?
Conventional karyotype	Cultured or prepared cells/chromosomes	What is the chromosomal constitution and structural pattern?

Sampling route and assay should not be conflated

- Chorionic-villus sampling and amniocentesis are methods of obtaining fetal-related material.
- Karyotyping and FISH are laboratory methods applied to collected cells.
- A sampling procedure is not itself a chromosomal result.

Recognizing free trisomy, translocation and mosaicism

Cytogenetic pattern	What is seen	Interpretive caution
Free trisomy 21	Extra independent chromosome 21	Parents commonly have normal karyotypes
Translocation form	Additional 21q on a derivative chromosome	Consider balanced familial rearrangement
Mosaic form	46- and 47-chromosome lineages	Proportions differ by sampled tissue

Clinical appearance is not molecular classification

- Similar phenotypic features can arise from different chromosomal mechanisms.
- Clinical features prompt diagnosis; Cytogenetic analysis classifies the underlying abnormality.
- Translocation detection is especially important for understanding possible familial origins.

Trisomy 21 versus trisomy 13/18

Dimension	Trisomy 21	Trisomy 13 or 18
Common pathway	Usually nondisjunction	Usually nondisjunction
Maternal age	Strong association	Also associated with advanced maternal age
Malformations	Multisystem abnormalities	Generally more severe and widespread
Infant survival	Substantial survival possible	Early death far more frequent

Case application: Newborn with suggestive features

A newborn has a flat facial profile, oblique palpebral fissures and epicanthic folds.

Question: What type of investigation can establish the chromosomal constitution?

Answer: Cytogenetic testing, with a karyotype to classify free trisomy versus rearrangement.

Morphology supports clinical recognition; Cytogenetics defines the mechanism.

Case application: Chromosome 21 material on chromosome 14

An affected child has extra 21q material attached to an acrocentric chromosome.

Question: Why might examination of parental chromosomes matter?

Answer: A balanced Robertsonian carrier parent is possible in some cases.

Familial inheritance is possible, not obligatory, in translocation-associated cases.

Case application: Distinct 46- and 47-cell populations

Cytogenetic examination identifies both normal-count and trisomy 21 cell lines.

Question: Which early developmental event can account for this pattern?

Answer: Postzygotic mitotic nondisjunction during embryogenesis.

Phenotypic expression depends partly on cell-line representation and distribution.

Integrated clinicopathologic synthesis

- Three cytogenetic routes lead to extra chromosome 21 dosage: Free trisomy, Robertsonian translocation and mosaicism.
- Effects span neurodevelopment, congenital heart disease, gastrointestinal malformations, leukemia risk, neurodegeneration and immunity.
- Gene dosage is polygenic; APP and mitochondrial pathways are examples, not complete explanations.
- Prenatal cfDNA is a screening modality; Cytogenetic testing defines the chromosomal pattern.

Primary reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter: Genes and Human Diseases — Chromosomal Disorders.
- Teaching scope: Trisomy 21 (Down Syndrome) and directly relevant cytogenetic background.
- All factual quantitative estimates in this lecture reflect the supplied textbook excerpt; they have not been independently updated.