

Chromosome 22q11.2

Deletion Syndrome

Genomic lesion • developmental mechanisms • multisystem phenotype

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

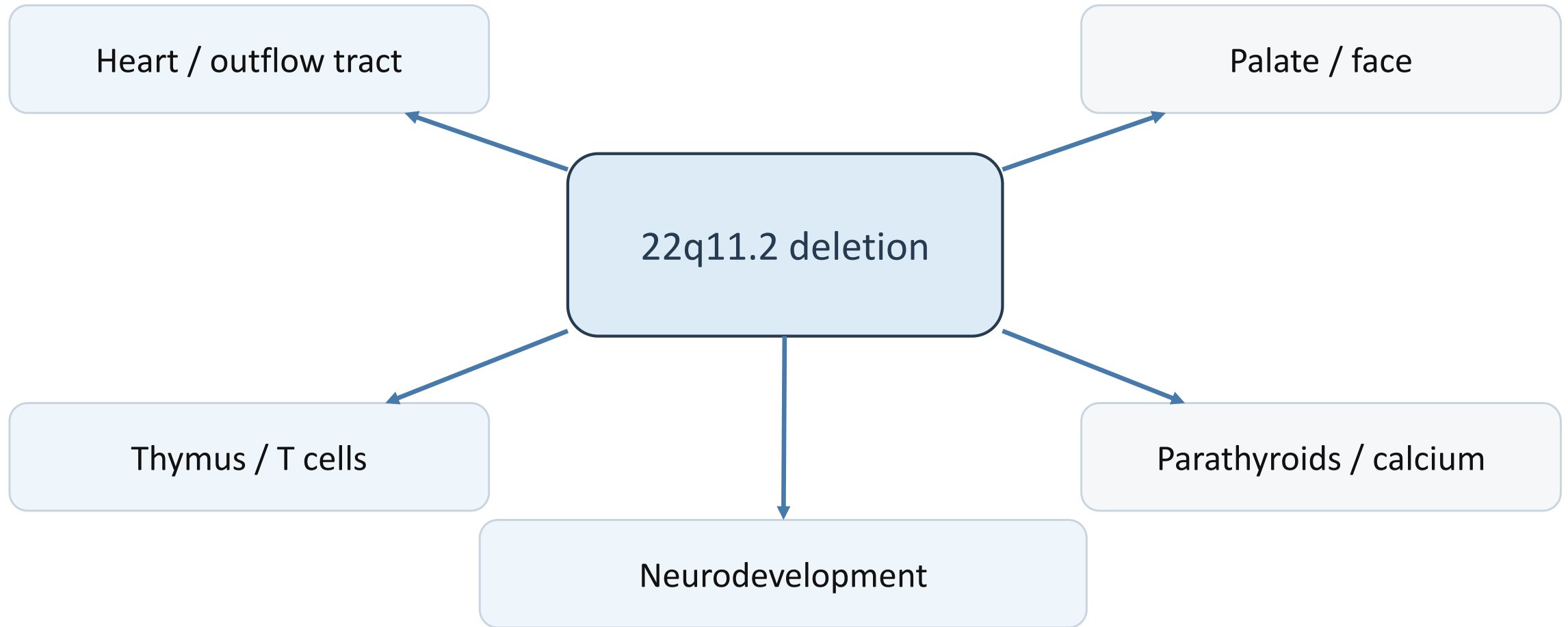
Learning objectives

- Locate chromosome band 22q11.2 and explain an interstitial deletion.
- Connect thymic, parathyroid, cardiac and palatal abnormalities to the syndrome.
- Interpret the DiGeorge–velocardiofacial clinical spectrum.
- Explain the TBX1/PAX9 developmental framework and FISH findings.

A deletion syndrome—not a single clinical presentation

- A small deletion on the long arm of chromosome 22 defines the disorder.
- Clinical expression spans congenital structural and functional abnormalities.
- A recognizable pattern may be incomplete in any one individual.

One genomic locus, multiple organ systems



Decoding the cytogenetic name

- 22 identifies the affected autosome.
- Q identifies the long chromosome arm; P denotes the short arm.
- 11.2 specifies region, band and sub-band along q.
- The locus designation is not the same as the amount of deleted DNA.

Numerical and structural chromosomal disorders

Numerical abnormality

Change in chromosome number

Example: Trisomy of a complete autosome

Overall chromosome dosage changes

Structural abnormality

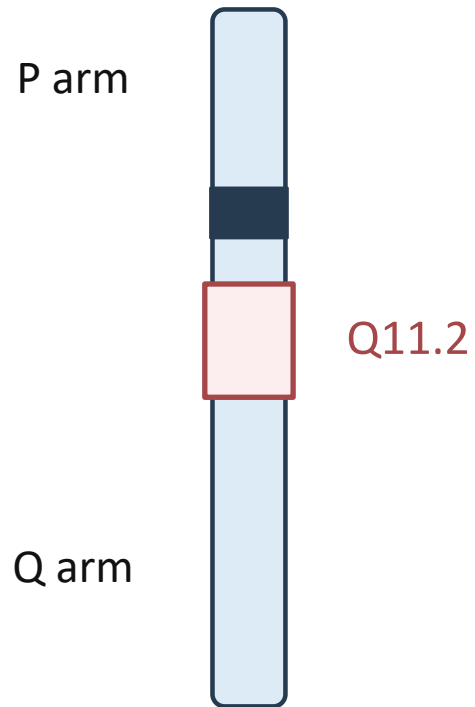
Chromosome number may remain 46

Loss, gain or rearrangement of a segment

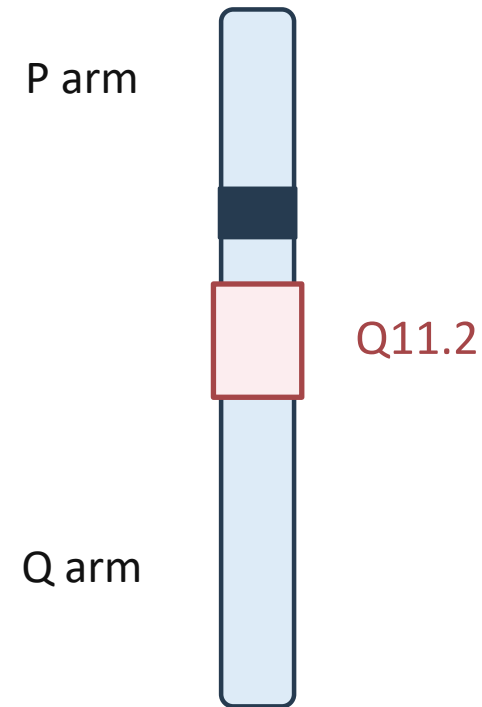
22q11.2 is a focal deletion

The 22q11.2 band on chromosome 22

Intact chromosome 22

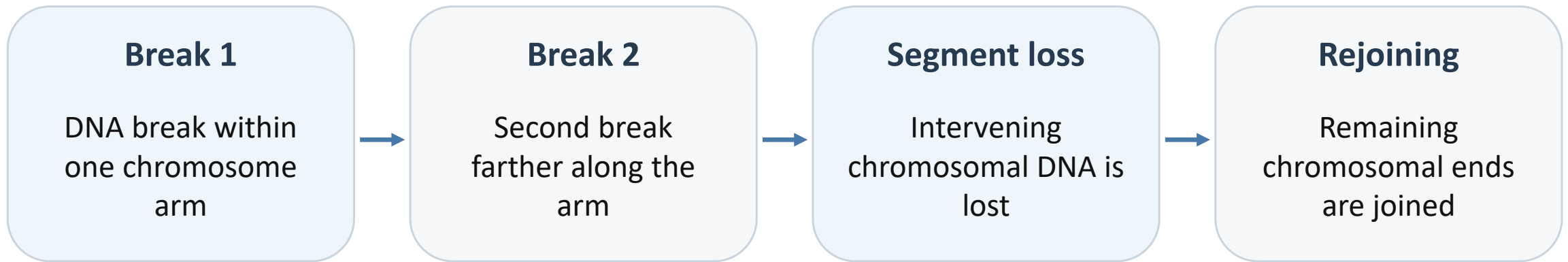


Intact chromosome 22



Two copies of the locus are present in this schematic normal cell.

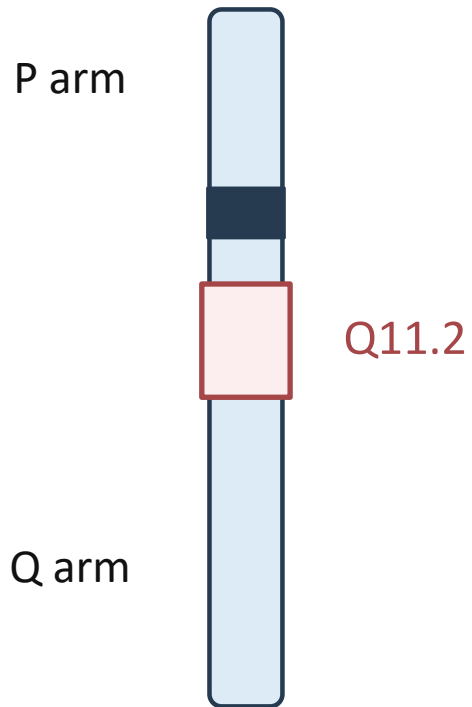
How an interstitial deletion can arise



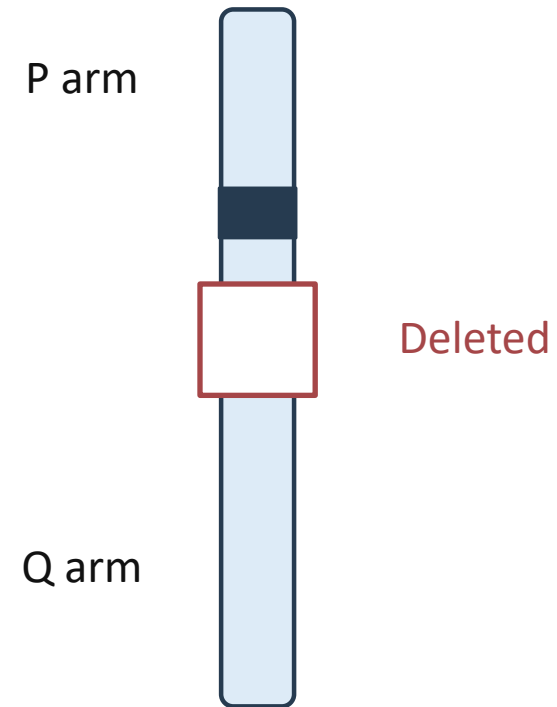
A general structural-deletion mechanism; Not an asserted patient-specific mechanism.

Interstitial loss on one homologue

Intact chromosome 22



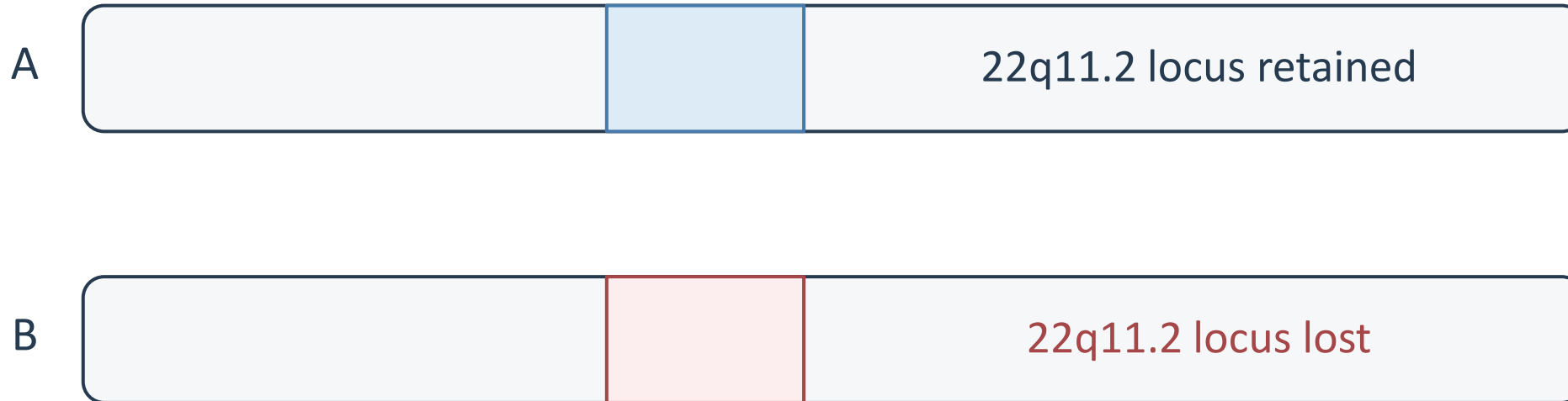
Chromosome 22 with
22q11.2 deletion



One chromosome 22 lacks the highlighted band: A copy-number loss, not a whole-chromosome loss.

A deletion produces regional gene-copy loss

Two homologous copies of chromosome 22



Loss of one copy changes local gene dosage. The diagram does not specify expression levels.

Why locus-level tests matter

Routine chromosome banding

Visible structural changes typically

Require $\approx 2\text{--}4$ million bp

Fluorescence in situ hybridization

Higher locus-level resolution

Can detect kilobase-scale changes

Robbins structural cytogenetics background; Detection depends on assay/probe design.

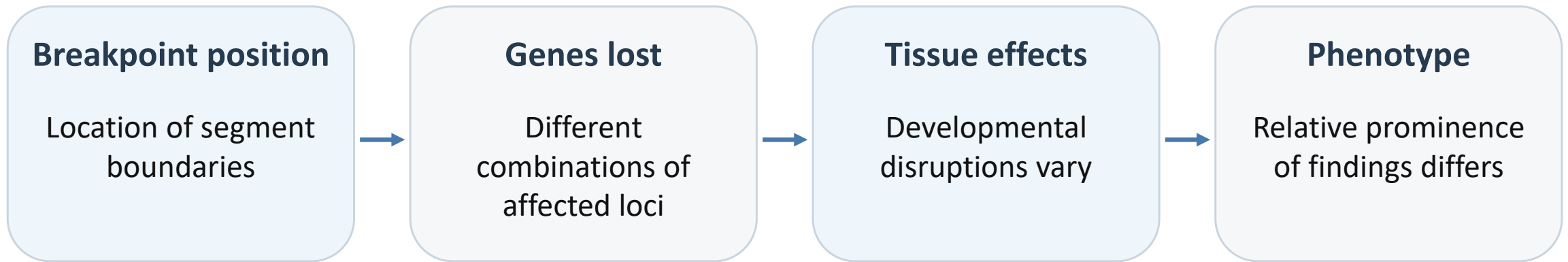
Size described for the deleted interval

≈1.5 Mb

A multigene chromosomal deletion.

The cited interval size is approximate; Deleted segments may differ.

Why deletion size matters



Variable deletion position/size as a probable contributor, not a complete explanation.

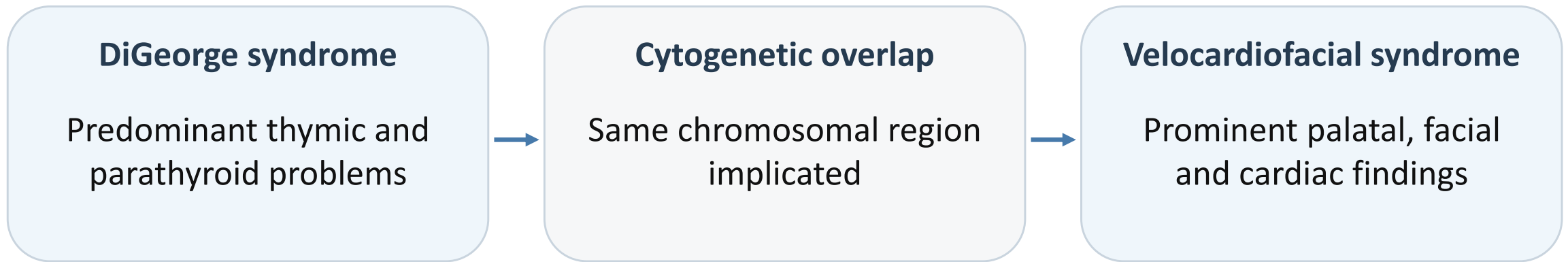
How often is the syndrome encountered?

Up to 1:4,000

Birth frequency quoted

Variable clinical features contribute to missed recognition.

From two historic labels to one spectrum



The shared molecular defect explains why older labels overlap clinically.

DiGeorge and velocardiofacial patterns

DiGeorge emphasis

Thymic hypoplasia

T-cell immunodeficiency

Parathyroid hypoplasia; Hypocalcemia

Cardiac outflow tract malformations

Velocardiofacial emphasis

Facial dysmorphism

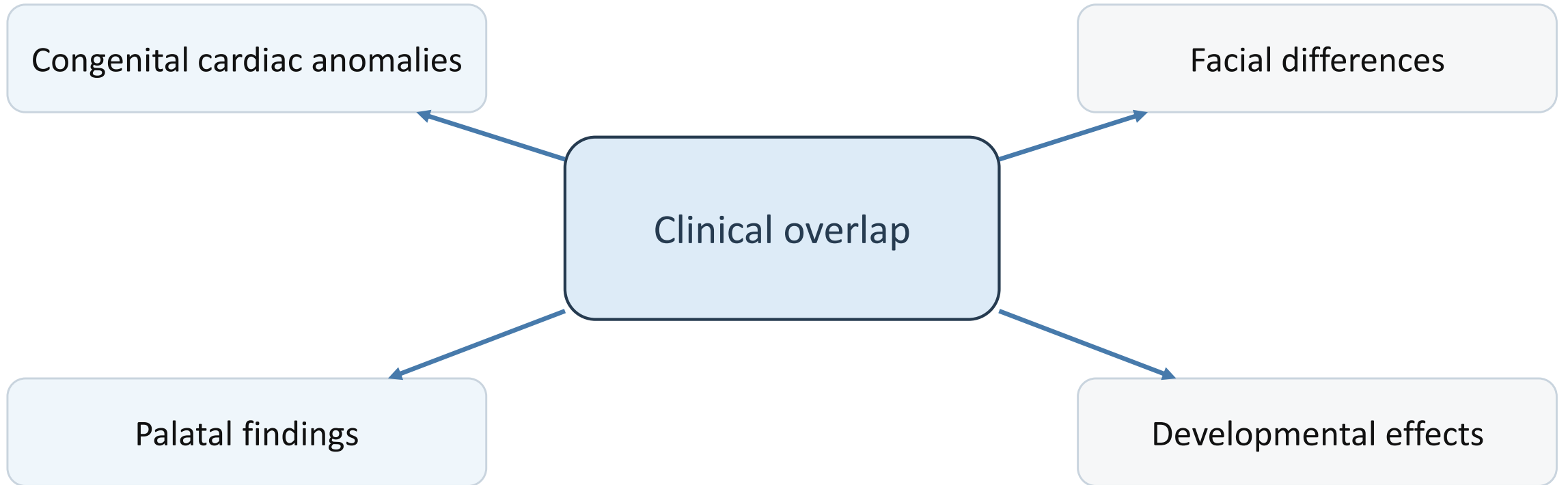
Cleft palate

Cardiovascular abnormalities

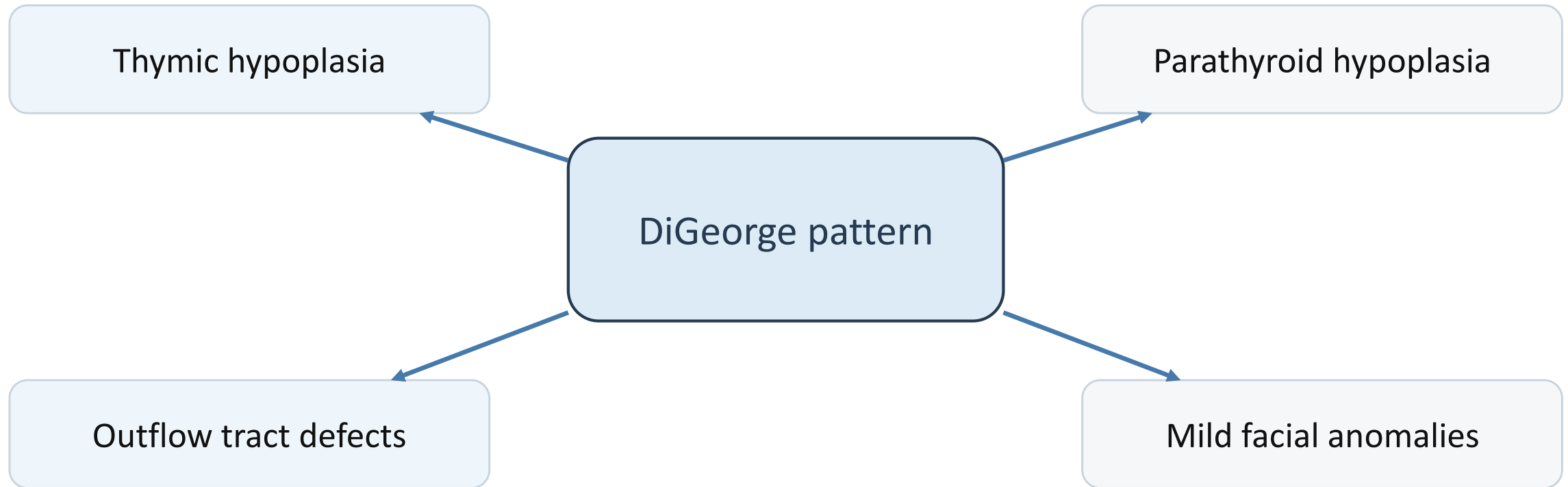
Learning disabilities

The labels describe predominant patterns within an overlapping syndrome.

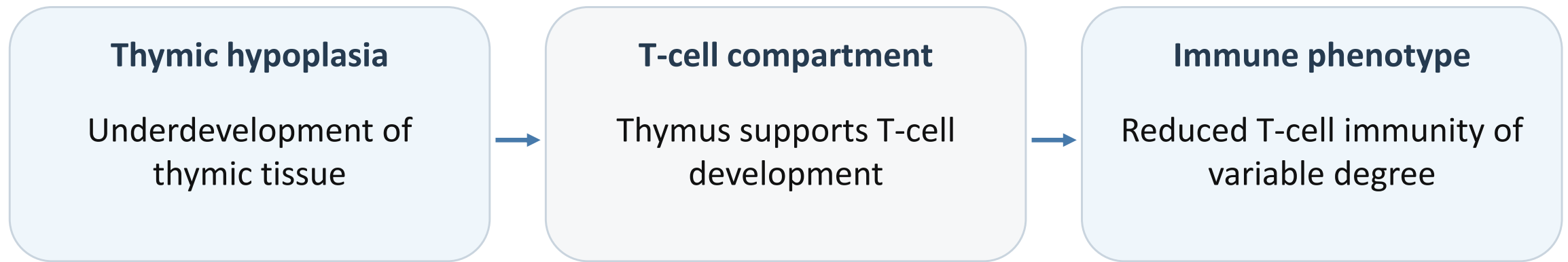
Shared features cross historic diagnoses



The DiGeorge phenotype: Linked developmental outcomes



Thymic hypoplasia explains T-cell immunodeficiency



Mechanistic sequence is a concise interpretation of the Robbins organ-function relationship.

Immune involvement is heterogeneous

- The degree of T-cell immunodeficiency varies across affected patients.
- Immunodeficiency is prominent in the DiGeorge presentation.
- It is less frequent in the classic velocardiofacial description.
- One apparently characteristic immune phenotype is not required in every case.

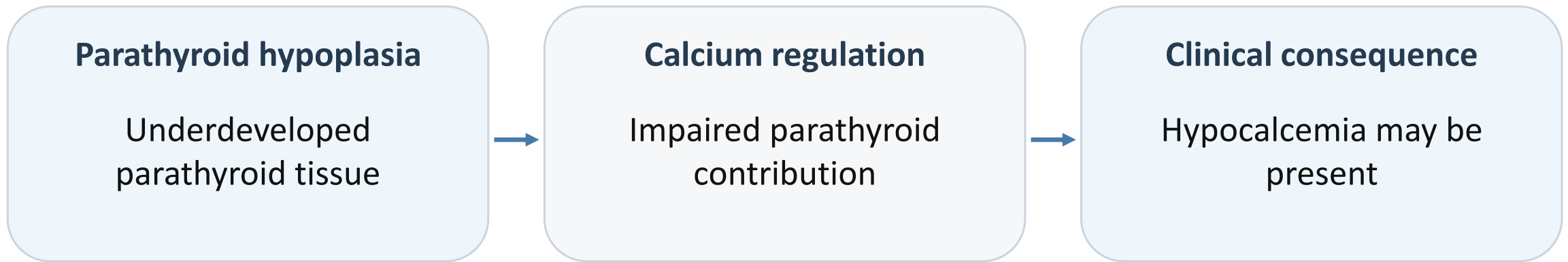
Atopic disease belongs to the clinical spectrum

- Atopic disorders may accompany the DiGeorge-pattern presentation.
- Robbins specifically mentions allergic rhinitis.
- Atopy and reduced T-cell immunity are not identical clinical phenomena.

Autoimmunity can coexist with immunodeficiency

- Autoimmune manifestations may occur in affected individuals.
- The source names autoimmune thrombocytopenia as an example.
- This reinforces that immune dysregulation is broader than infection susceptibility alone.

Parathyroid hypoplasia explains hypocalcemia



The calcium-regulation intermediate is functional reasoning; No laboratory cutoff is supplied.

Thymus and parathyroids: Two linked consequences

Thymus

Developmental hypoplasia

Functional correlate: T-cell immunity

Clinical category: Immunologic

Parathyroids

Developmental hypoplasia

Functional correlate: Calcium homeostasis

Clinical category: Endocrine

A shared embryologic region helps explain the co-occurrence; The organs have distinct functional outcomes.

Embryologic context of the classic phenotype

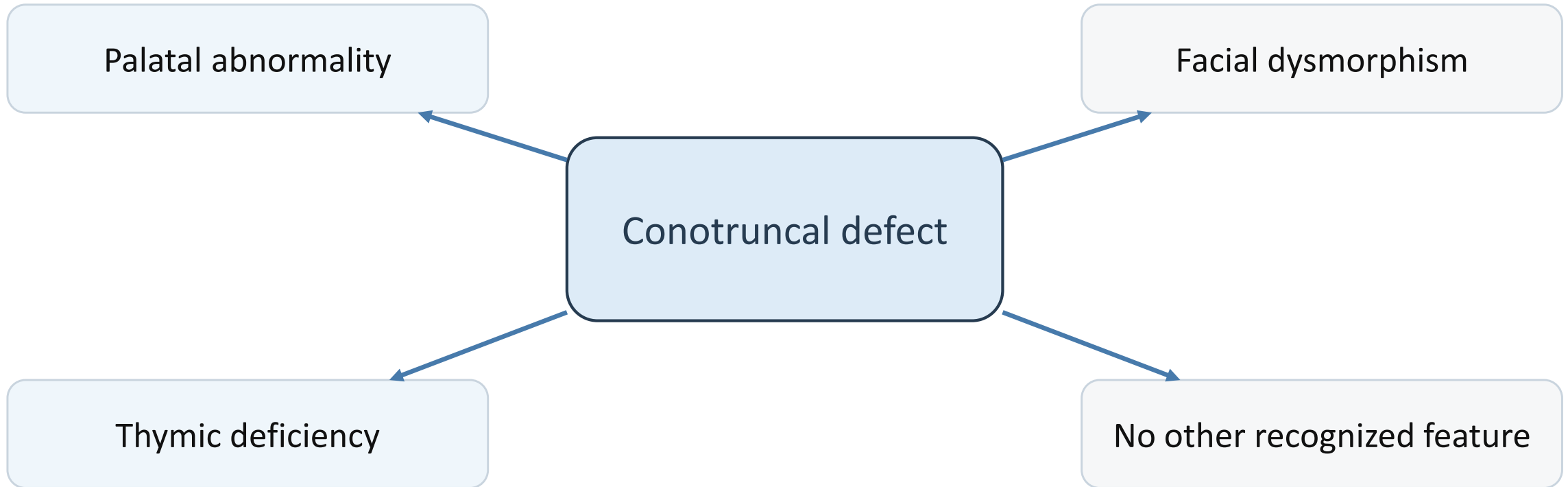


A schematic abstraction of the TBX1 expression/derivative relationship stated in the source.

Cardiac malformations prominently affect the outflow tract

- Outflow-tract defects are characteristic of the DiGeorge description.
- Cardiovascular anomalies also occur in velocardiofacial presentations.
- Congenital heart disease can be the dominant presenting feature.

Heart disease may appear with or without other findings



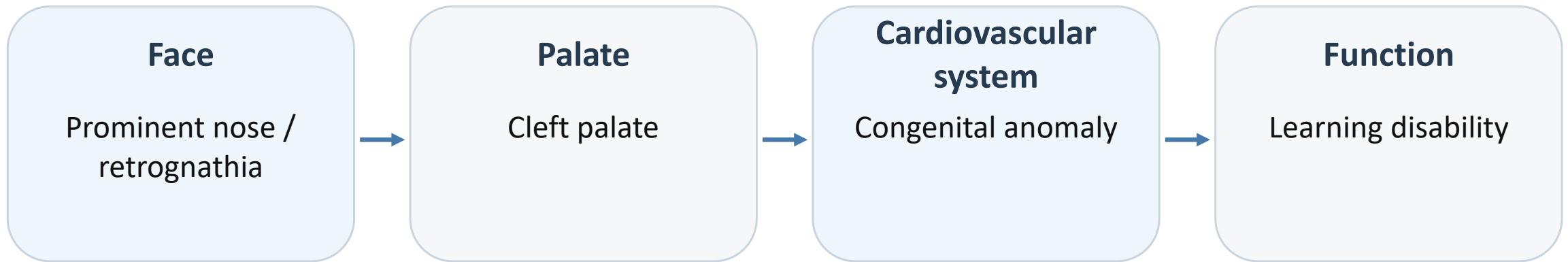
Palatal defects are part of the syndrome

- The source highlights abnormalities of the palate across the spectrum.
- Cleft palate is a classic velocardiofacial feature.
- The palatal phenotype connects structurally to the embryologic developmental network.

Facial dysmorphism has a characteristic description

- A prominent nose in velocardiofacial syndrome.
- Retrognathia is another cited feature.
- Facial abnormalities also occur, often mildly, with the DiGeorge phenotype.
- Clinical appearance alone does not establish a specific deletion.

Velocardiofacial features form a developmental constellation



Neurodevelopmental effects extend beyond physical malformations

- Developmental delay forms part of the broad syndrome definition.
- Learning disabilities are stressed in the velocardiofacial description.
- Structural and neurodevelopmental findings may coexist with different severity.

Developmental delay is not a specific organ lesion

Structural domain

Palate and craniofacial malformations

Cardiac outflow tract defects

Thymic / parathyroid hypoplasia

Functional domain

Learning disability

Developmental delay

Behavioral or psychiatric vulnerability

The deletion affects multiple developmental and clinical domains.

Psychiatric vulnerability is clinically important

- Increased risk of psychotic disorders.
- Schizophrenia and bipolar disorders are specifically mentioned.
- Psychiatric morbidity broadens the relevant phenotype beyond congenital malformations.

Schizophrenia risk reported in affected adults

≈25%

Adults with 22q11.2 deletion syndrome

Estimate quoted by Robbins; Not a current independently verified rate.

Attention-deficit/hyperactivity disorder

30–35%

Affected children in the source description

Textbook estimate; Population and ascertainment may matter.

Reverse association in childhood-onset schizophrenia

2–3%

Individuals reported to carry a deletion of this region

This is the reverse conditional association, not the individual risk of schizophrenia.

Risk in carriers versus deletion among cases

Carrier-to-outcome direction

Start with a 22q11.2 deletion

Ask whether schizophrenia develops

About 25% of adults

Case-to-genotype direction

Start with childhood-onset schizophrenia

Ask whether 22q11.2 is deleted

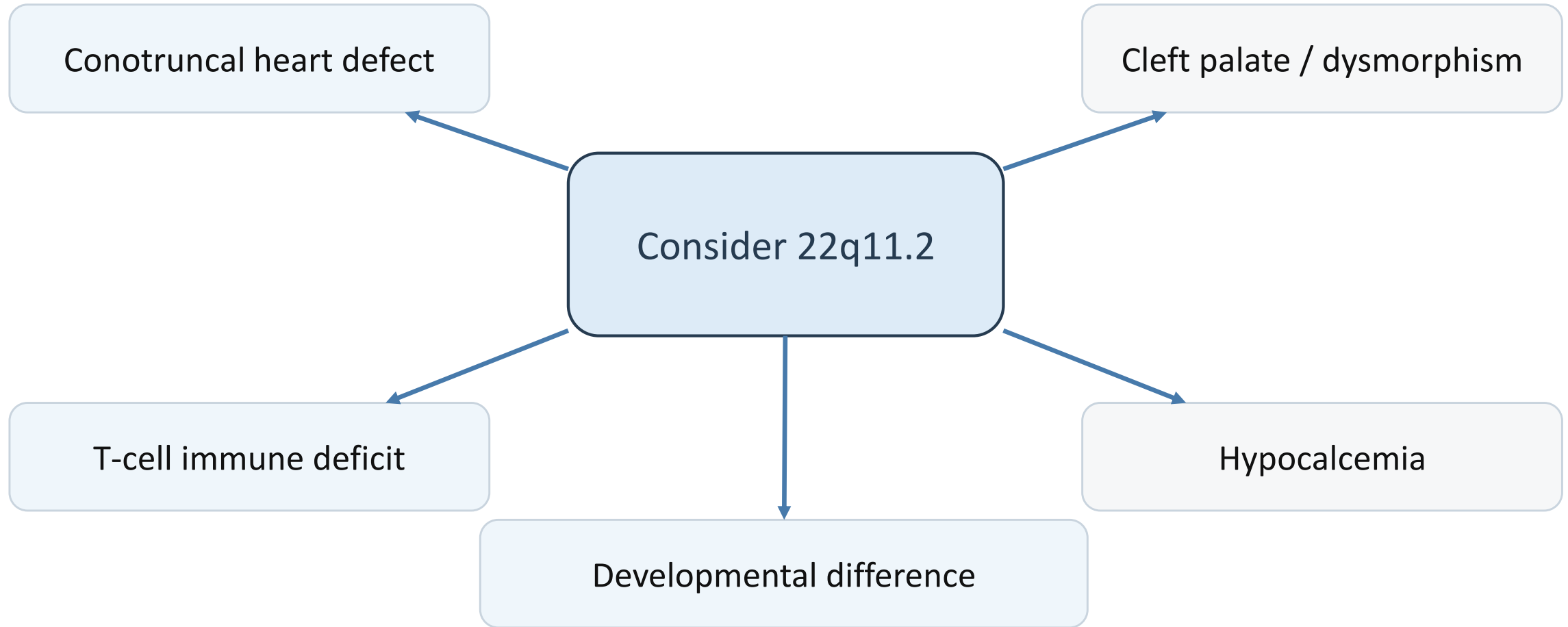
2–3%

The denominators differ: These figures must never be interchanged.

Not all components of the phenotype are explained

- The deleted interval contains numerous genes.
- TBX1 is closely linked to developmental malformations.
- The source does not identify the responsible gene(s) for behavioral and psychiatric effects.
- Avoid attributing all neuropsychiatric effects to TBX1 alone.

Clinical suspicion arises from combinations of findings



A similar phenotype may have another genomic cause

Typical molecular association

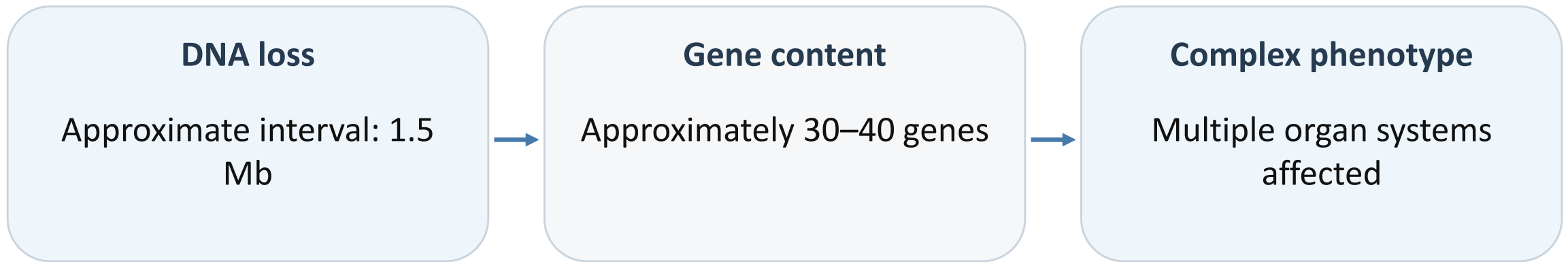
Deletion involving chromosome 22q11.2
Common genomic finding in the named
syndrome

Rare phenocopy described

Deletion involving chromosome 10p13–14
Small number of cases with a similar
phenotype

Phenotypic resemblance does not prove the same molecular lesion.

The deleted interval is a multigene region

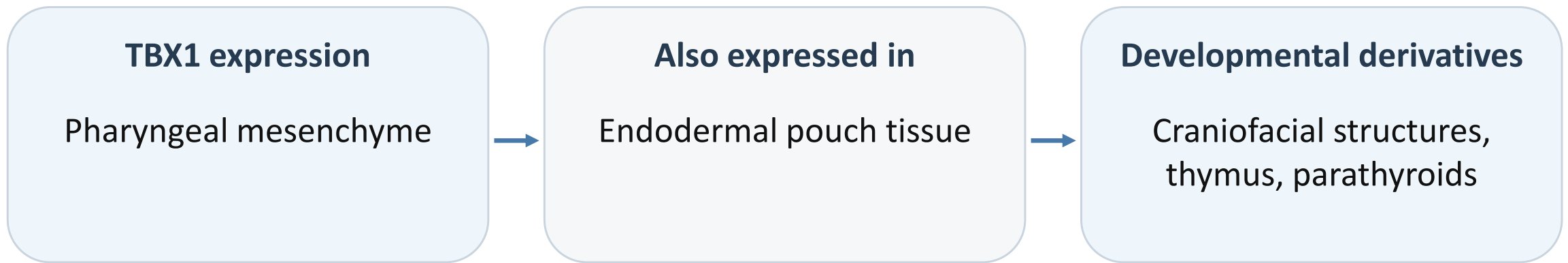


All quantities are quoted. The source later mentions ≈ 30 candidate genes, not a contradictory fixed gene count.

TBX1 is a central candidate gene

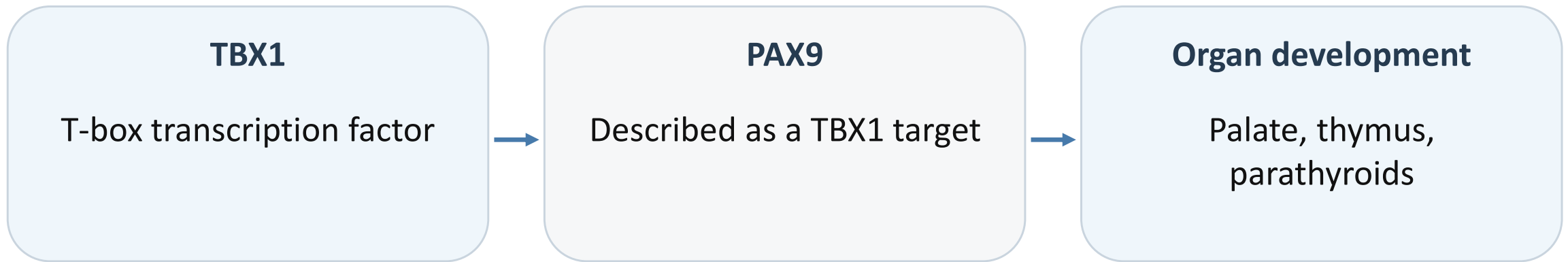
- TBX1 encodes a T-box transcription factor.
- It is most closely associated with phenotypic features.
- Its normal developmental expression is relevant to face, thymus and parathyroid formation.

Spatial expression of TBX1 helps explain tissue selectivity



This schematic is not a histologic reconstruction of embryonic anatomy.

TBX1 and PAX9: A developmental relationship

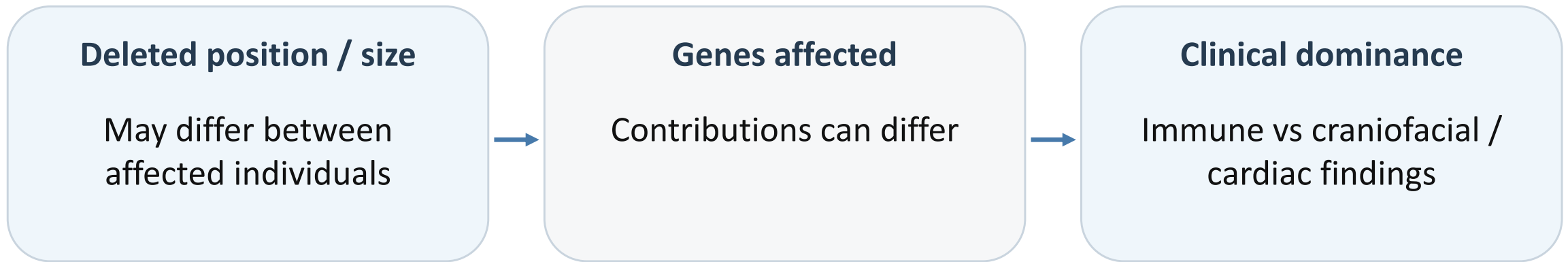


Do not interpret this simplified model as the only pathway or a complete regulatory network.

PAX9 expands the mechanistic explanation

- PAX9 is described as a target gene of TBX1.
- PAX9 to palatal, parathyroid and thymic development.
- The relationship offers a mechanistic bridge between genotype and organ malformations.

Why the phenotype varies even with a shared locus

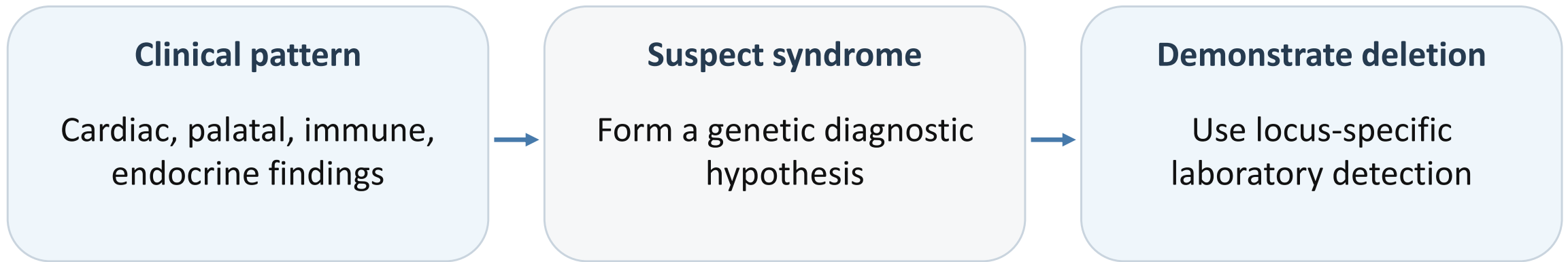


Robbins says this probably contributes to heterogeneity; Not an established one-to-one genotype map.

Causal interpretation has limits

- The molecular basis is explicitly described as incompletely understood.
- A multigene interval limits simple one-gene causal explanations.
- Unidentified contributors may underlie behavioral and psychiatric features.
- A phenotype–genotype association does not specify every intermediate mechanism.

Clinical suspicion is followed by genomic testing



FISH to establish the deletion; Contemporary algorithms are not covered by this source-only lecture.

FISH tests a chromosomal locus

- Fluorescence in situ hybridization uses fluorescent DNA probes.
- A probe targeted to 22q11.2 provides a locus-specific signal.
- A separate chromosome-22 control probe demonstrates the chromosome region remains present.

FISH signal schematic: A normal locus pattern

Chromosome 22: Homologue A



Red = 22q11.2 locus

Chromosome 22: Homologue B



Green = chromosome 22 control

Conceptual normal pattern: Both homologues retain the locus-specific and control signals.

FISH signal schematic: One deleted locus

Chromosome 22: Homologue A



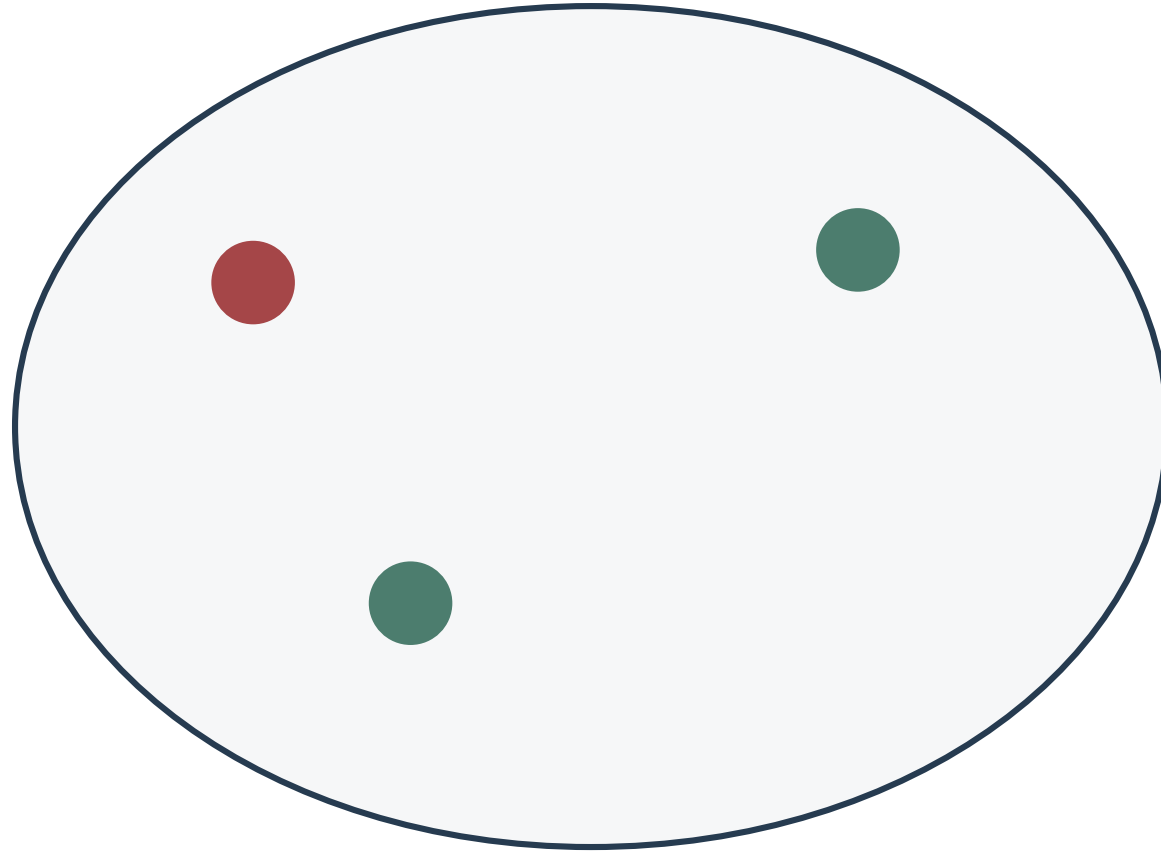
Red = 22q11.2 locus

Chromosome 22: Homologue B



Green = chromosome 22 control

Interphase FISH: Interpretation of deletion signals

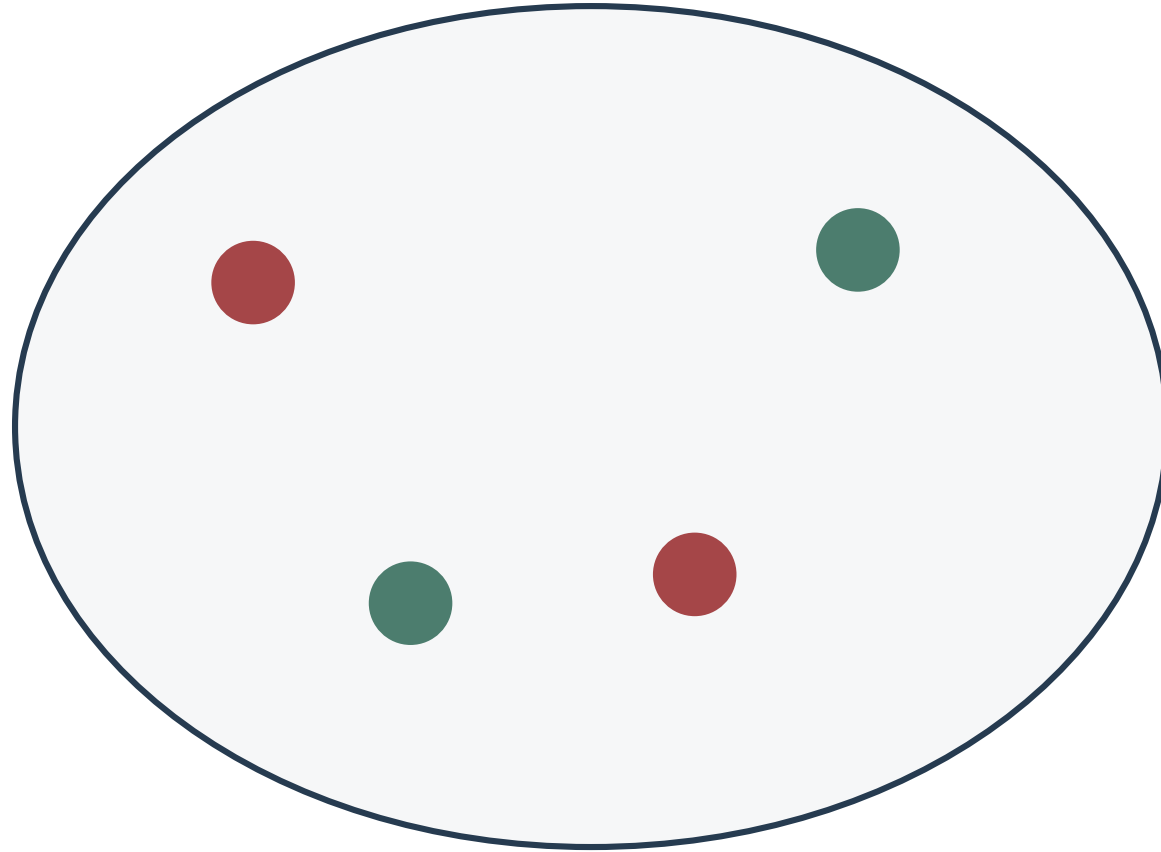


Schematic interphase nucleus

1 red + 2 green

22q11.2 loss

Interphase FISH: Normal comparator



Schematic interphase nucleus

2 red + 2 green

No deletion

FISH findings figure

Structure	Intact homologue	Deleted homologue
22q11.2 target probe	Target signal present	Target signal absent
Chromosome-22 control	Control signal present	Control signal present
Interpretation	Target region retained	Target region deleted

Editable reconstruction of the signal logic Fig. 5.23; Not copied microscopy.

Historic phenotype labels and FISH yield

Older clinical diagnosis	Deletion detected by FISH	Interpretive caution
DiGeorge syndrome	≈90%	Not every clinical case
Velocardiofacial syndrome	≈80%	Overlapping phenotype
Isolated conotruncal defects	≈30%	No other features required

Approximate textbook values; Avoid extrapolating to all present-day referrals.

Why ordinary banding can miss a small deletion

Conventional banding

Sees chromosome-scale band patterns

Needs large structural changes

A small loss may be unresolved

Targeted FISH

Interrogates selected DNA sequences

Can detect smaller structural changes

Depends on probe choice and tested locus

Robbins explains improved FISH resolution; This is not an exhaustive test comparison.

A positive FISH result has a precise meaning

- Loss of a 22q11.2 target signal supports deletion of the probed locus.
- Retention of the chromosome-22 control distinguishes regional loss from total loss in the illustrated pattern.
- The FISH signal pattern does not by itself predict symptom severity.

Case discussion: Immune and endocrine phenotype

A newborn has a congenital outflow tract cardiac malformation, reduced thymic tissue, and low serum calcium.

Interpretation task

- Which two underdeveloped organs explain the immune and endocrine findings?
- Which contiguous chromosome locus should be considered?

Case interpretation: A DiGeorge-pattern presentation

1. Thymic hypoplasia corresponds to reduced T-cell immunity.

2. Parathyroid hypoplasia corresponds to hypocalcemia.

3. The combined phenotype suggests a 22q11.2 deletion syndrome.

Hypothesis first; Demonstration of the deletion is needed for genetic confirmation.

Case discussion: Palate, face and heart

A child has cleft palate, retrognathia, an identified congenital cardiovascular anomaly and learning difficulties.

Interpretation task

- Which historic phenotype label best matches the presentation?
- Why is that label not a distinct chromosomal diagnosis?

Case interpretation: Velocardiofacial-pattern findings

1. Cleft palate and facial dysmorphism fit the classic phenotype.

2. Congenital cardiac and learning difficulties strengthen suspicion.

3. The historic label overlaps the same 22q11.2 deletion spectrum.

A molecular test addresses the chromosomal hypothesis.

Case discussion: Count the FISH signals

An interphase nucleus has one 22q11.2 target signal but two chromosome-22 control signals.

Interpretation task

- Does this pattern indicate deletion of the probed region?
- Why does the control probe matter?

Case interpretation: Target deletion with preserved control

1. Only one locus-specific signal is identified.
2. Two control signals support retention of the corresponding chromosome regions.
3. The signal arrangement matches deletion of one 22q11.2 locus.

Interpret only the tested locus; The drawing is schematic.

Case discussion: Psychiatric presentations

A patient with a known 22q11.2 deletion develops psychiatric symptoms in adulthood.

Interpretation task

- Which association makes psychiatric assessment relevant?
- Can TBX1 alone be assigned responsibility for this clinical dimension?

Case interpretation: Association without overattribution

1. Increased psychotic-illness vulnerability.

2. It estimates schizophrenia develops in approximately 25% of affected adults.

3. The source does not identify the responsible behavioral genes.

Reported risk does not make disease inevitable in an individual.

Deletion versus trisomy: A useful cytogenetic contrast

22q11.2 deletion syndrome

Loss of a defined part of chromosome 22

Regional reduction of gene copies

Variable developmental phenotype

Trisomy 21 (parent context)

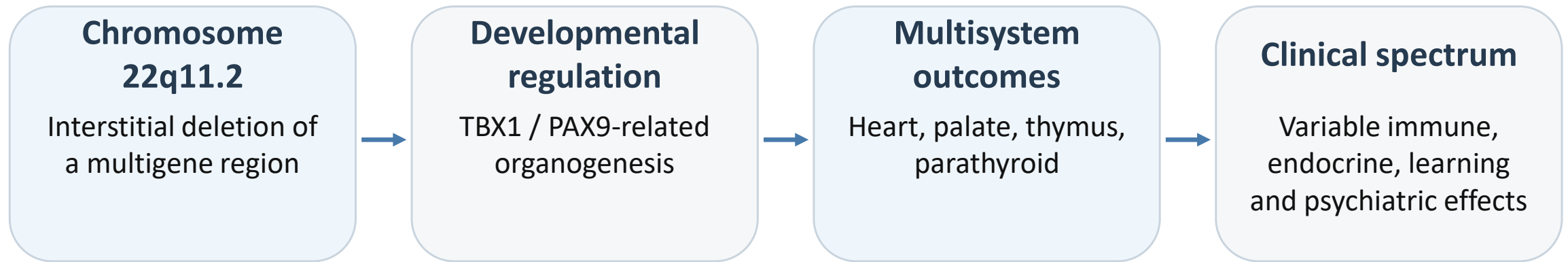
Extra complete chromosome 21 in usual form

Extra gene copies across that autosome

Different syndromic mechanism

This is a mechanism comparison, not a differential diagnosis based on clinical appearance.

Integrated mechanistic synthesis



Schematic synthesis with uncertainty: Many genotype-to-phenotype mechanisms remain unresolved.

Textbook source and interpretive boundaries

Core reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026). Chapter 5: Genes and Human Diseases. Chromosome 22q11.2 Deletion Syndrome, pp. 147–149.

Interpretive boundaries

Quantitative estimates and FISH-centered diagnostic wording follow the supplied textbook. No independent current-guideline verification or licensed histologic imagery was incorporated.