

Defects in nuclear proteins and transcription factors

A developmental defect in gene regulation can alter the shape, identity, and number of skeletal elements.

Genes discussed in the skeletal chapter encode transcription factors—not structural bone matrix proteins.

The phenotype depends on where and when the factor directs developmental programs.

A single gene can influence multiple organs, making associated findings diagnostic.

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Learning objectives

Use the affected structure and extra-skeletal clues to infer the disrupted developmental regulator.



- Distinguish dysostosis from skeletal dysplasia and explain mesenchymal patterning.
- Connect six named transcription factors with the defining clinical syndromes.
- Apply morphology, organ-system associations, and appropriate genetic testing to cases.

Developmental anomalies: Two organizing terms

Location and distribution help classify congenital skeletal abnormalities.

Dysostosis

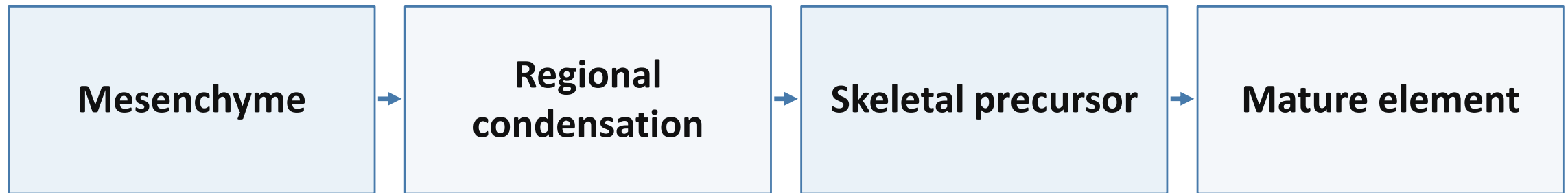
- Abnormal individual skeletal elements
- Regional or patterned malformations
- Example: Absent or abnormal digit

Skeletal dysplasia

- More widespread skeletal growth disorder
- Can affect axial and appendicular skeleton
- Example: Generalized chondrocyte dysfunction

Mesenchymal condensation is an early control point

Patterning errors arise before the mature shape of a bone is recognizable.



- Mesenchymal cells aggregate at future skeletal sites.
- Selected condensations adopt a chondrogenic or osteogenic developmental program.
- Loss of spatial control can produce missing, fused, duplicated, or malformed skeletal parts.

Two routes to a mature skeletal element

Skeletal morphogenesis depends on specification followed by tissue differentiation.

Intramembranous

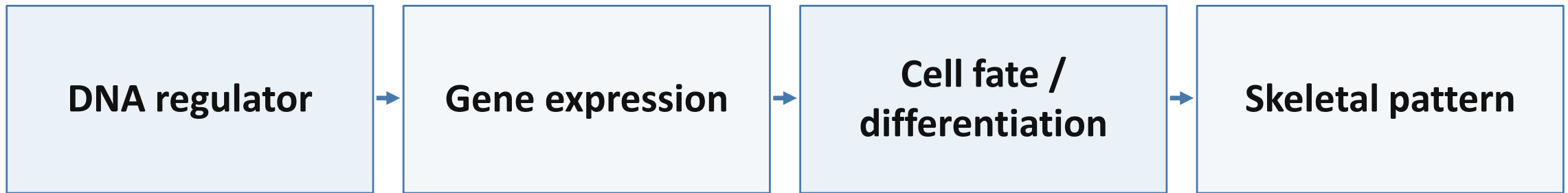
- Mesenchymal cells → osteoblasts
- Important in skull vault and clavicle
- RUNX2 is required for osteogenesis

Endochondral

- Mesenchymal cells → cartilage model
- Chondrocyte growth and maturation
- SOX9 regulates chondrogenesis

A transcription factor is not a structural scaffold

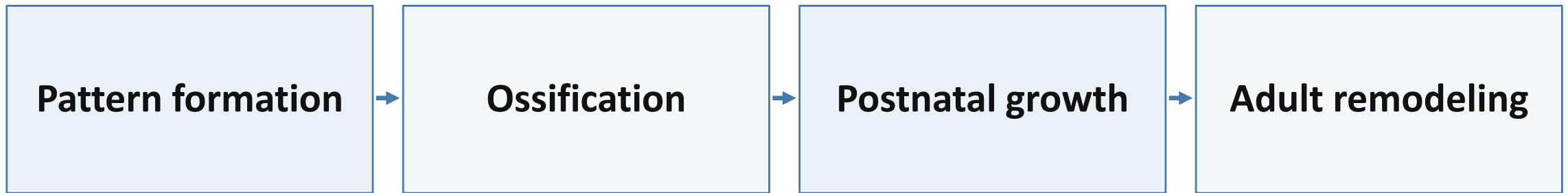
Gene-regulatory proteins act upstream of the tissue phenotype.



- A transcription factor recognizes regulatory DNA or works in a transcriptional complex.
- Its downstream targets control lineage commitment, differentiation, and tissue architecture.
- The phenotype reflects altered gene expression, not necessarily loss of a bone matrix protein.

Developmental timing explains persistent malformation

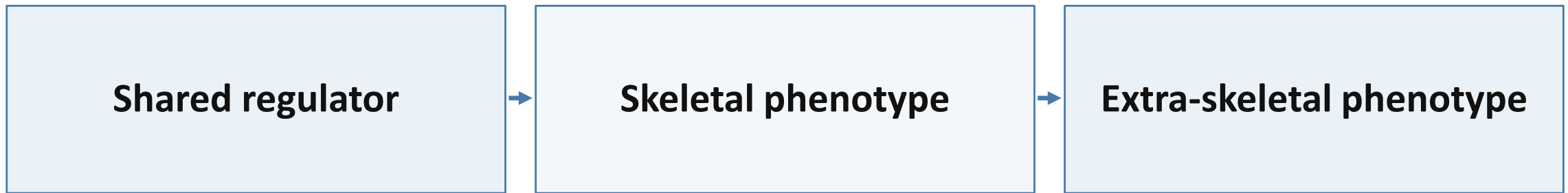
Congenital patterning errors cannot be interpreted as ordinary adult remodeling defects.



- Embryonic specification determines whether a skeletal part forms and where it lies.
- Postnatal growth changes the dimensions of an established skeletal template.
- Adult remodeling maintains tissue balance but cannot recreate absent developmental structures.

Why one regulator may affect multiple organs

Developmental transcription factors often have context-dependent roles.



- A shared gene may participate in limb, heart, kidney, eye, pigmentation, or gonadal pathways.
- Distribution of abnormalities can be more informative than any single skeletal sign.
- Syndromic evaluation must include clinically relevant non-skeletal structures.

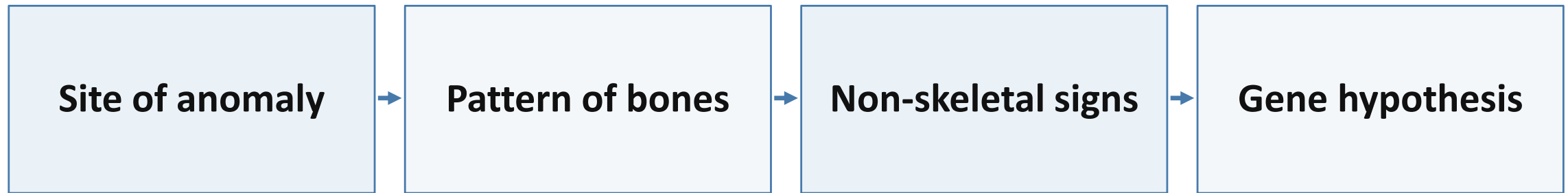
The six gene–phenotype associations

The chapter groups six clinically distinctive developmental disorders under transcription-factor defects.

Gene	Associated disorder	Hallmark phenotype
HOXD13	Brachydactyly D/E	Digits and hand/foot rays
RUNX2	Cleidocranial dysplasia	Skull, clavicles, teeth
SOX9	Campomelic dysplasia	Cartilage, long bones, sex development
TBX5	Holt–Oram syndrome	Upper limbs and heart
LMX1B	Nail–patella syndrome	Nails, patellae, kidney
PAX3	Waardenburg types I/III	Hearing, pigment, craniofacial ± limbs

Read a phenotype anatomically

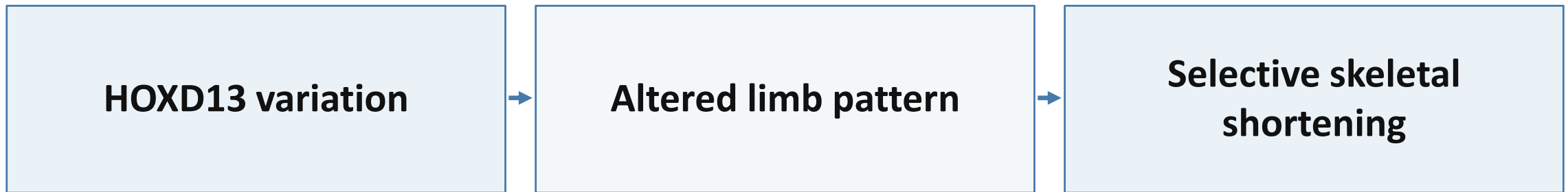
Identify the predominant affected site before assigning a syndrome.



- Distal digits → consider HOXD13-associated patterning defects.
- Cranium, clavicles, and dentition → prioritize RUNX2-related disorder.
- Long bones, forelimbs, patellae, or craniofacial features direct different gene hypotheses.

HOXD13 directs distal limb patterning

The anatomical distribution of shortening is central to this diagnosis.



- HOXD13 encodes a homeobox transcription factor involved in limb patterning.
- Specific pathogenic variants can alter formation of digits and the smaller long bones of hands and feet.
- The same gene can produce different, partially overlapping limb phenotypes.

Brachydactyly requires skeletal localization

Short digits may result from different bones being short.

Phalangeal

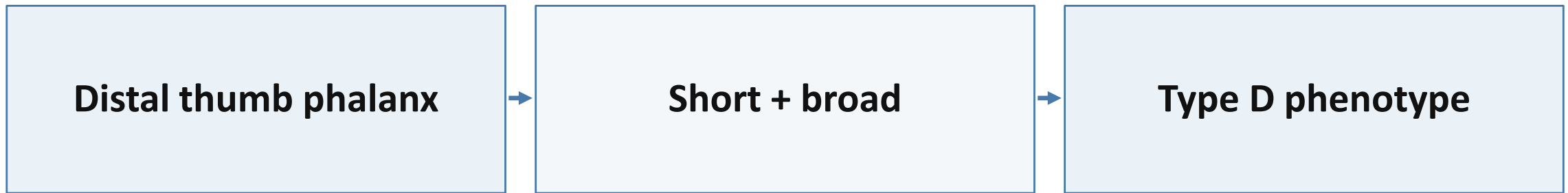
- Digit segment is short
- Type D emphasizes the thumb distal phalanx

Metacarpal / metatarsal

- Metacarpal or metatarsal is short
- Type E emphasizes short rays

Brachydactyly type D: The thumb tip

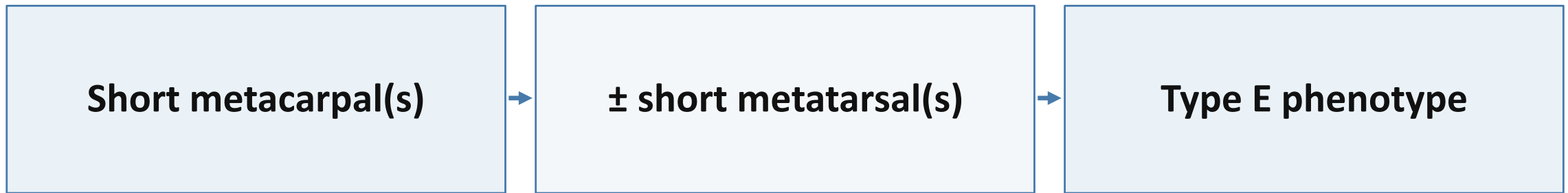
Type D is defined by a short, broad distal phalanx of the thumb.



- The nail-bearing distal thumb segment is the primary affected element.
- This clinical label describes morphology; It is not specific to one pathogenic variant.
- HOXD13-associated families may show overlapping D-like abnormalities.

Brachydactyly type E: Short metapodials

Type E is characterized by short metacarpals and/or metatarsals.



- Hand and foot rays may be unequally affected or asymmetrical.
- Distal phalanx anomalies can coexist but do not define type E.
- This precise distinction corrects ambiguity in the supplied chapter's abbreviated description.

Type D versus type E: Identify the short bone

Do not classify a short digit without examining which segment is reduced.

Type D — distal thumb phalanx



Proximal → distal phalanx

Short, broad distal phalanx

Type E — metacarpal



Metacarpal → proximal → distal

Short metacarpal or metatarsal

HOXD13 produces an allelic phenotype spectrum

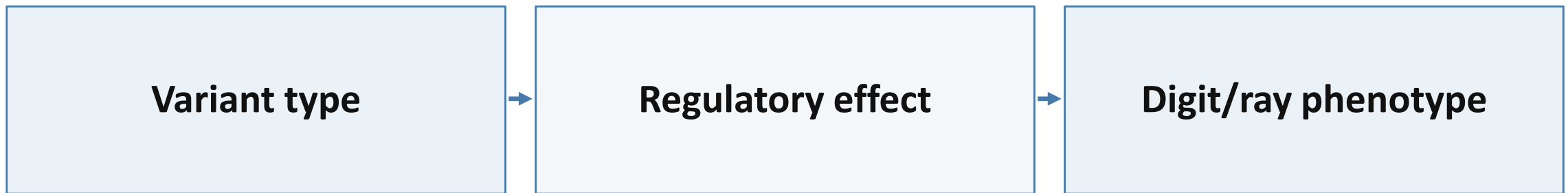
One developmental regulator can cause different skeletal patterns.



- Published variants are associated with brachydactyly and synpolydactyly.
- Phenotypic effects can vary within a family and between limbs.
- The gene association does not mean all forms of brachydactyly are HOXD13-related.

Variant mechanism is not always simple loss of function

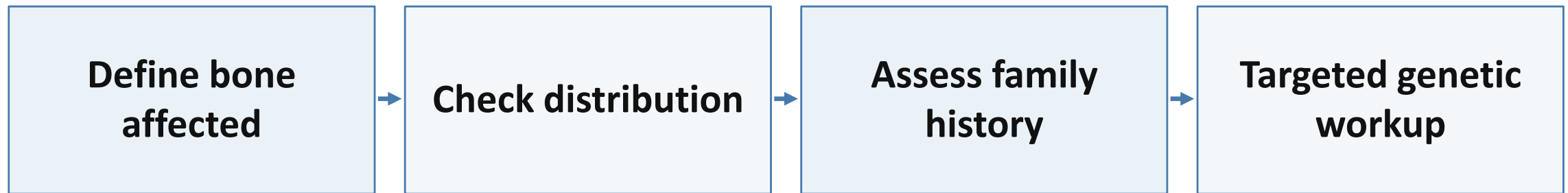
Different substitutions can change sequence-specific DNA interactions.



- HOXD13 homeodomain missense variants have shown altered DNA-binding properties in vitro.
- Polyalanine expansions and other variants have distinct genotype–phenotype associations.
- Clinical morphology cannot reliably identify a specific variant on its own.

Brachydactyly: Diagnostic reasoning

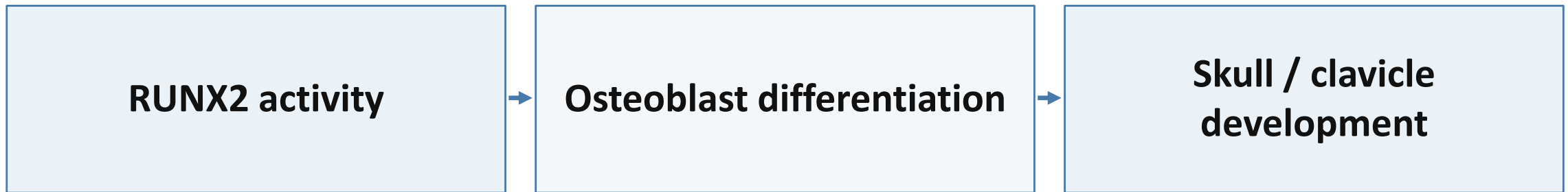
First establish whether the anomaly is isolated or part of a syndrome.



- Inspect both hands and feet, including the specific bony elements affected.
- Ask about similar familial limb findings; Expressivity may vary.
- Molecular testing is guided by the pattern rather than the label “short fingers” alone.

RUNX2 is central to osteoblast differentiation

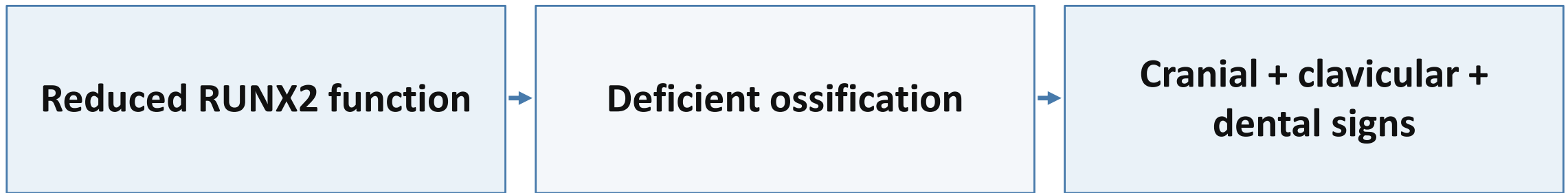
RUNX2 is needed to generate osteogenic tissue during skeletal formation.



- Its transcriptional activity participates in osteoblast differentiation and skeletal morphogenesis.
- The skull and clavicles show conspicuous consequences when RUNX2 activity is deficient.
- Dental development also depends on the associated developmental program.

RUNX2 loss of function: Cleidocranial dysplasia

The defining syndrome couples cranial, clavicular, and dental abnormalities.



- Autosomal dominant inheritance with RUNX2 loss of function.
- The classic triad is delayed cranial suture closure, abnormal clavicles, and dental anomalies.
- Expression ranges from full skeletal involvement to mild or predominantly dental disease.

Clavicular dysplasia: A distinctive structural clue

The clavicles may be hypoplastic, discontinuous, or absent.



- Clavicular abnormality is often bilateral but need not be symmetrical.
- Shoulders may be unusually mobile when clavicles are severely deficient.
- The finding has greater specificity in combination with cranial and dental signs.

Open fontanelles and cranial sutures

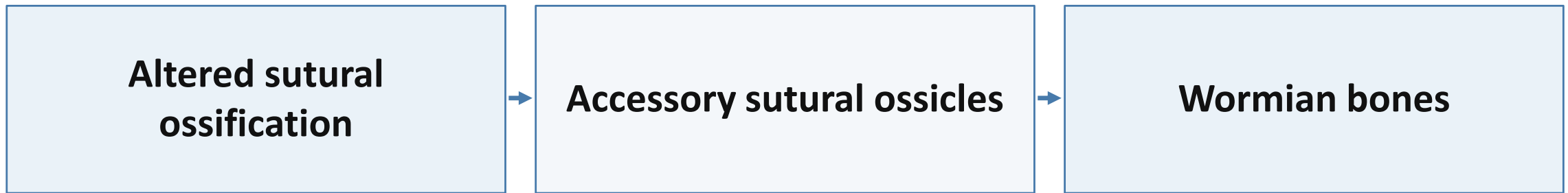
Delayed skull ossification leaves sites of membranous separation persistent.



- Fontanelles may remain patent beyond the usual period of closure.
- Cranial sutures can be conspicuously wide or remain open.
- Imaging findings should be read together with clavicular and dental abnormalities.

Wormian bones are accessory sutural bones

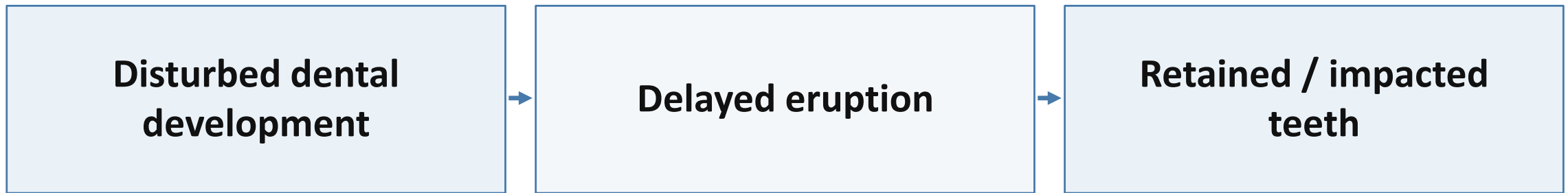
Small additional ossicles may develop within cranial sutures.



- Wormian bones are one recognized radiographic sign of cleidocranial dysplasia.
- They represent altered cranial ossification architecture.
- They are not individually diagnostic without the larger phenotype.

Delayed eruption of permanent teeth

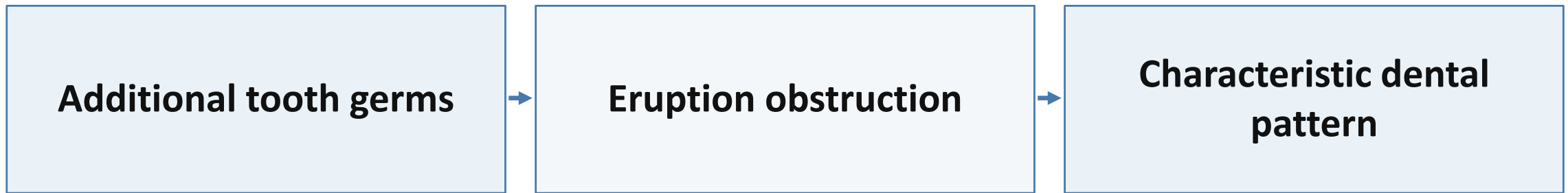
Dental delay can be a leading clinical presentation.



- Primary teeth may be retained when permanent teeth fail to erupt on schedule.
- Impacted permanent teeth and dental crowding may complicate eruption.
- The dental phenotype should prompt inspection of the clavicles and skull.

Supernumerary teeth refine the diagnosis

An excess of tooth germs is a strong supporting clue in the appropriate skeletal setting.



- Supernumerary teeth may be accompanied by impacted permanent teeth.
- Dental panoramas help identify the number and position of unerupted teeth.
- The combination with open sutures and clavicular hypoplasia strongly suggests RUNX2 dysfunction.

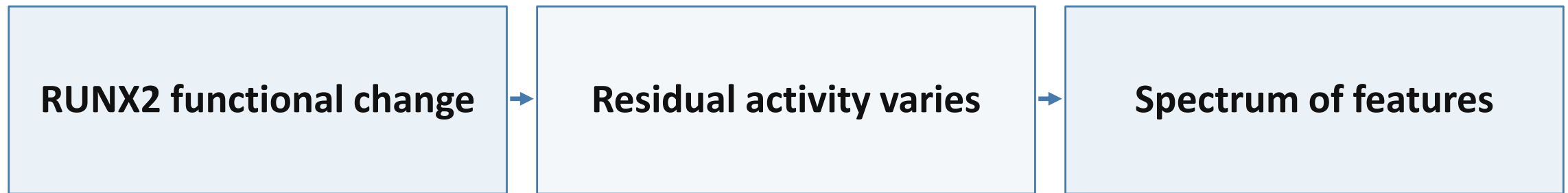
Cleidocranial dysplasia: Recognize the triad

A three-organ structural constellation is more distinctive than short stature alone.

Cranium	Clavicles	Dentition
• Open or delayed sutures • Patent fontanelles • Wormian bones may occur	• Hypoplasia / aplasia • Shoulder mobility may increase • Sometimes asymmetric	• Delayed permanent teeth • Supernumerary teeth • Impaction / malocclusion

RUNX2 genotype and phenotype are variable

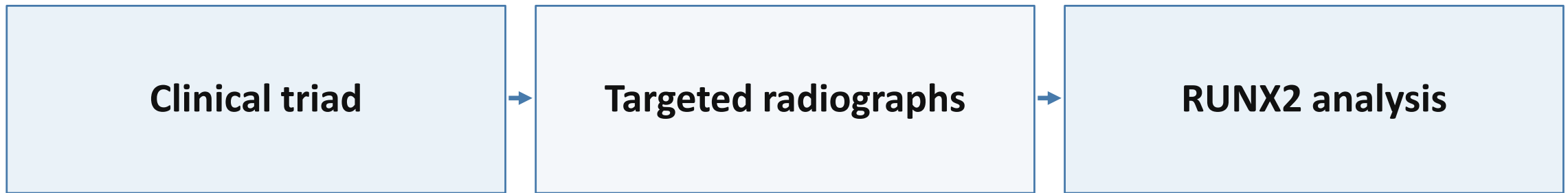
Residual transcriptional activity helps explain a phenotypic continuum.



- Classic disease is commonly associated with reduced functional RUNX2 dosage.
- Some alleles yield milder skeletal or predominantly dental manifestations.
- Genetic interpretation requires clinical correlation; The variant alone does not quantify severity.

Cleidocranial dysplasia: Diagnostic sequence

Clinical recognition is followed by imaging and molecular confirmation.



- Examine cranial sutures, shoulder girdle, stature, and eruption of teeth.
- Document the relevant skull, clavicle, and dental radiographic features.
- Interpret RUNX2 molecular results in conjunction with family history and phenotype.

Differential: Delayed cranial mineralization

Not every open fontanelle indicates a RUNX2-related disorder.

RUNX2-related CCD

- Delayed eruption; Supernumerary teeth
- Clavicular hypoplasia
- Sutural patency

Hypophosphatasia pattern

- Premature deciduous tooth loss
- Generalized mineralization defect
- Biochemical ALP is diagnostically relevant

SOX9 governs chondrocyte differentiation

SOX9-dependent gene regulation is essential to the cartilage developmental program.



- SOX9 contributes to chondrocyte differentiation and cartilage matrix gene regulation.
- Deficiency disrupts skeletal organization during early development.
- Clinical outcomes extend beyond cartilage because SOX9 has other embryonic roles.

Campomelic dysplasia: The skeletal pattern

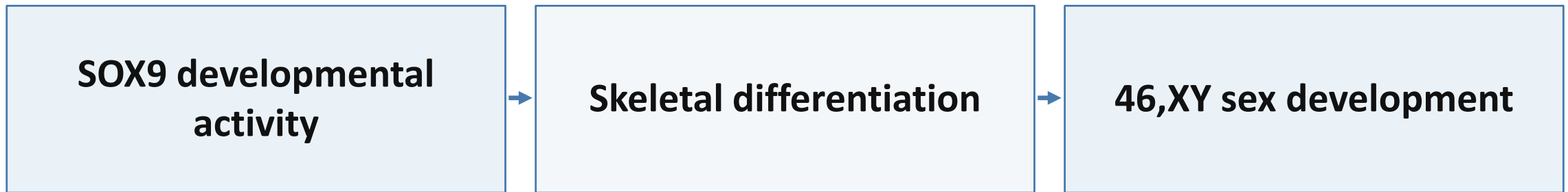
Long-bone bowing and shortening are key manifestations.



- The disorder affects long-bone development and can produce markedly bowed limbs.
- Clubfeet and other skeletal abnormalities may accompany the long-bone phenotype.
- Characteristic craniofacial and airway findings strengthen suspicion.

SOX9 also participates in testis determination

Sex-development findings reflect SOX9 function outside the skeleton.



- SOX9 acts downstream of SRY in testis developmental signaling.
- Individuals with a 46,XY karyotype may have atypical or female external genitalia.
- This association connects skeletal morphology with gonadal differentiation pathways.

Airway compromise drives early clinical risk

In campomelic dysplasia, respiratory instability is clinically consequential.



- Laryngotracheomalacia and other airway abnormalities can cause severe respiratory compromise.
- The risk differs mechanistically from a syndrome caused mainly by a very small rib cage.
- Early airway evaluation is important when the phenotype is suspected.

Campomelic dysplasia may lack obvious bowing

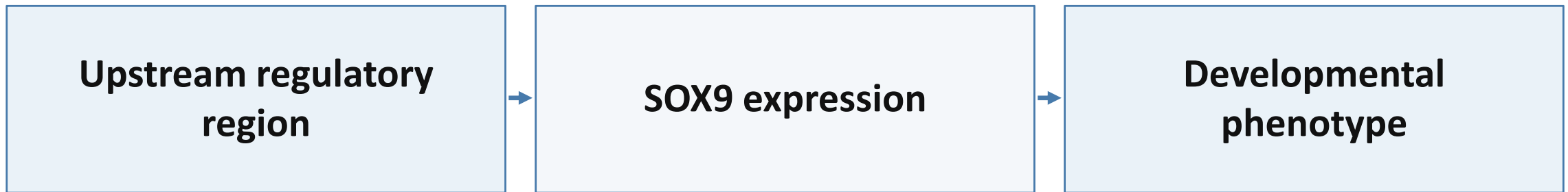
Absence of classic camptomelia does not exclude a SOX9-related disorder.



- An acampomelic presentation is recognized in the SOX9 phenotypic spectrum.
- Assessment should integrate airway, facial, skeletal, and sex-development findings.
- Clinical genetics may be required when imaging is not archetypal.

SOX9 disruption can involve noncoding regulation

A normal coding sequence is not the entire genetic explanation.



- Upstream chromosomal rearrangements can interrupt SOX9 regulatory elements.
- Such changes may alter SOX9 expression while leaving coding exons intact.
- Suspected cases may require assessment for structural/regulatory variants.

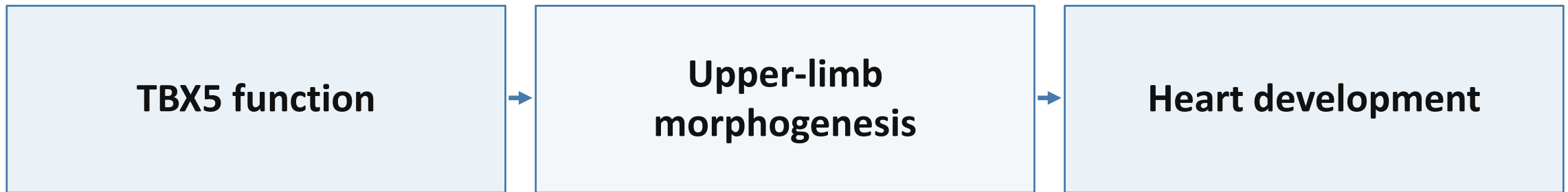
Campomelic dysplasia: Integrated recognition

Skeletal dysplasia and non-skeletal findings form one developmental syndrome.

Skeletal	Airway / facial	Sex development
• Short, bowed long bones • Clubfeet may occur • May be acampomelic	• Laryngotracheomalacia • Pierre Robin sequence • Cleft palate may occur	• 46,XY DSD is possible • Variable genital phenotype • SOX9 pathway involvement

TBX5 links upper-limb and cardiac development

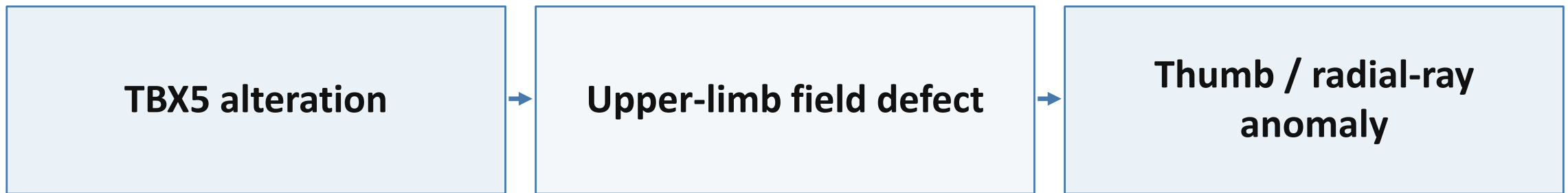
Holt–Oram syndrome is a heart–hand disorder.



- TBX5 is a T-box transcription factor involved in upper-limb patterning.
- The same developmental regulator participates in cardiac formation.
- The coexistence of upper-limb and cardiac defects is diagnostically important.

Holt–Oram: Upper-limb radial-ray abnormalities

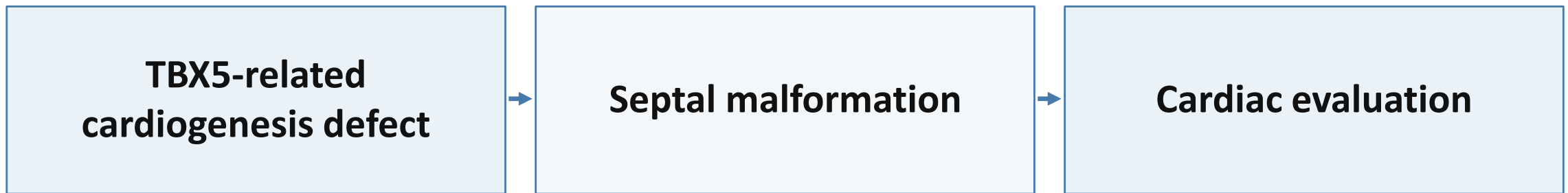
Thumb, radius, and carpal structures are major examination targets.



- An affected thumb may be hypoplastic, absent, or triphalangeal.
- Radius and carpal abnormalities can extend the limb phenotype.
- Upper-limb findings can be asymmetric; Lower-limb predominance suggests an alternative diagnosis.

Holt–Oram: Congenital cardiac defects

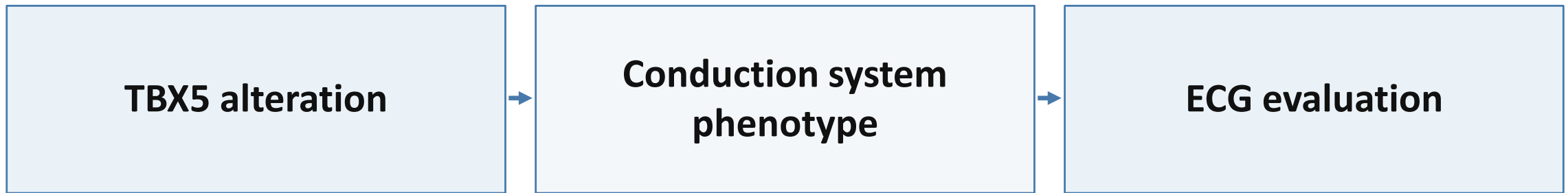
An upper-limb malformation should trigger attention to heart anatomy.



- Atrial or ventricular septal defects are characteristic cardiac associations.
- Cardiac structural abnormalities and limb anomalies may vary in severity independently.
- An echocardiographic assessment is relevant to syndrome characterization.

Conduction disease is a separate Holt–Oram clue

The cardiac phenotype extends beyond anatomical septal defects.



- Conduction abnormalities may occur with or without major structural cardiac disease.
- Electrocardiographic assessment complements echocardiographic evaluation.
- The combination of a radial-ray phenotype and conduction disease strengthens the gene hypothesis.

Holt–Oram: Systematic phenotype recognition

Do not call every upper-limb anomaly Holt–Oram syndrome.

Upper limb	Cardiac anatomy	Cardiac conduction
• Thumb / radius / carpal anomaly • Unilateral or asymmetric possible • Typically preaxial structures	• Septal defects are characteristic • Evaluate by echocardiography • Severity is variable	• Conduction disease may coexist • Evaluate by ECG • Requires independent assessment

LMX1B links limb dorsal identity to organs

Nail–patella syndrome is a recognizable multi-system developmental disorder.



- LMX1B participates in dorsal limb patterning.
- The phenotype prominently affects nails, patellae, and elbows.
- Podocyte and ocular consequences explain why a skeletal diagnosis needs renal and eye review.

Nails are an accessible diagnostic sign

Nail abnormalities can reveal a broader underlying skeletal phenotype.



- Nails may be hypoplastic, absent, ridged, or dystrophic.
- The thumbs are often more conspicuously affected than other digits.
- Examination should extend from nails to knee and elbow anatomy.

Patellar abnormalities define the syndrome

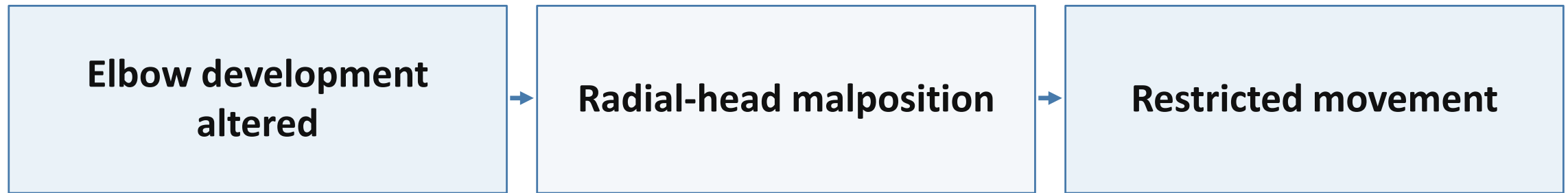
The patellae may be small, dysplastic, unstable, or absent.



- Patellar deficiency may be associated with knee pain or instability.
- Clinical examination can show restricted or abnormal knee mechanics.
- Radiographs help characterize patellar morphology in context.

Elbow and radial-head abnormalities

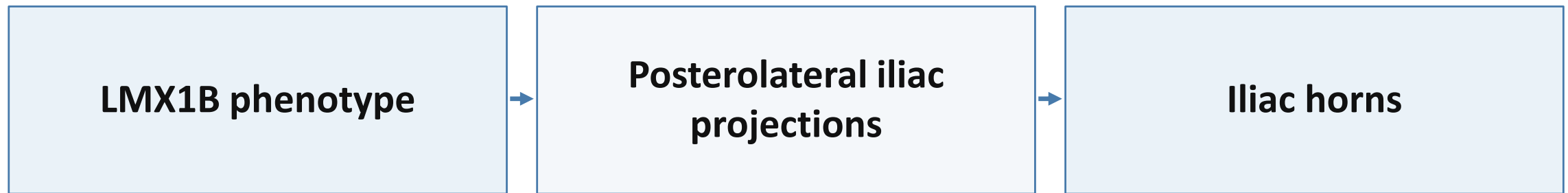
Nail–patella syndrome is not limited to the knee.



- Elbow movement may be restricted, particularly pronation and supination.
- Radial-head malposition and other elbow dysplasia may occur.
- The nail–knee–elbow combination is a strong pattern-recognition triad.

Iliac horns: A specific radiographic clue

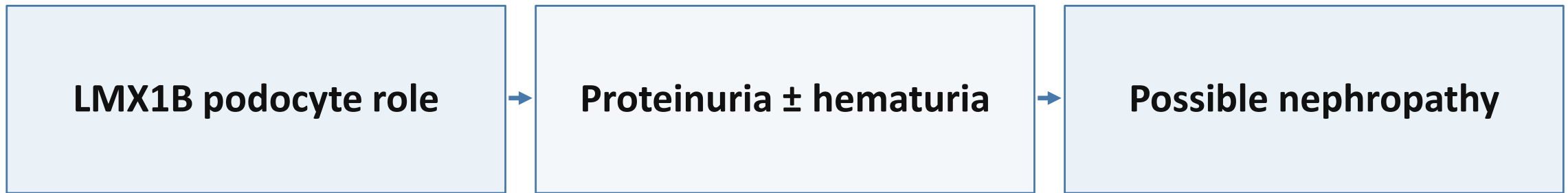
Posterolateral iliac projections can support nail–patella syndrome.



- Iliac horns are bilateral bony projections from the iliac bones.
- They are a distinctive radiographic feature when present.
- They are not required for the diagnosis and should not replace systemic evaluation.

Renal involvement can dominate long-term risk

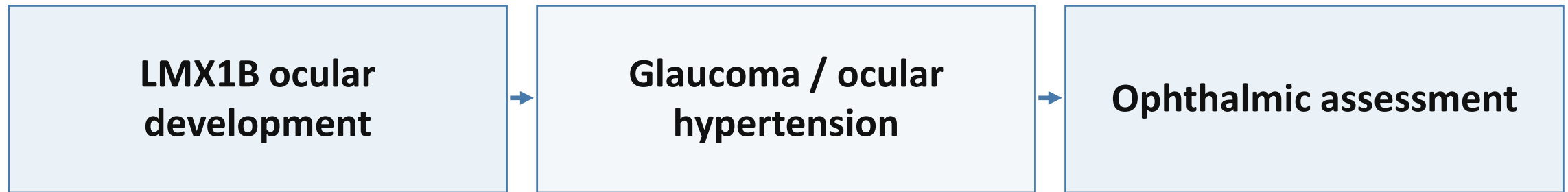
Proteinuria may be an early manifestation of LMX1B-associated nephropathy.



- Kidney involvement may present with proteinuria, sometimes with hematuria.
- Progression to chronic kidney disease is possible in some affected patients.
- The extent of nail or patellar changes does not safely exclude renal disease.

Eye findings broaden the LMX1B phenotype

Ocular surveillance is relevant even when skeletal signs lead to diagnosis.



- Primary open-angle glaucoma and ocular hypertension occur more often in nail–patella syndrome.
- The phenotype reflects LMX1B function beyond limb development.
- Eye assessment and renal evaluation address different non-skeletal risks.

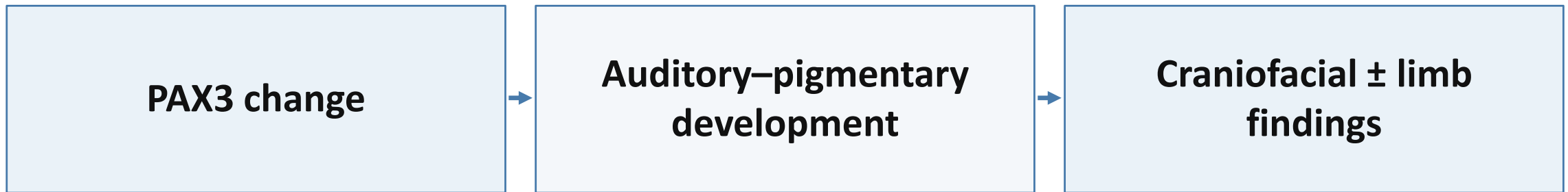
Nail–patella: Combine musculoskeletal and organ clues

The syndrome requires an integrated phenotype rather than a single radiograph.

Limb signs	Kidney	Eye
• Nail dysplasia • Patellar aplasia / hypoplasia • Elbow abnormalities; Iliac horns	• Proteinuria ± hematuria • Progressive disease is possible • Requires separate renal assessment	• Increased glaucoma risk • Possible ocular hypertension • Needs clinical ophthalmic review

PAX3 affects neural-crest-associated phenotypes

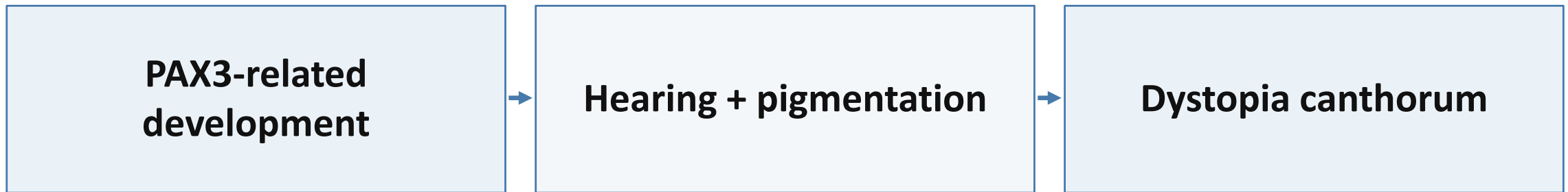
Waardenburg syndrome links auditory and pigmentary development.



- PAX3 encodes a developmental transcription factor with roles in early cell-lineage specification.
- Phenotype centers on hearing, pigmentation, and craniofacial morphology.
- The limb phenotype becomes especially important in Waardenburg type III.

Waardenburg type I: Cardinal constellation

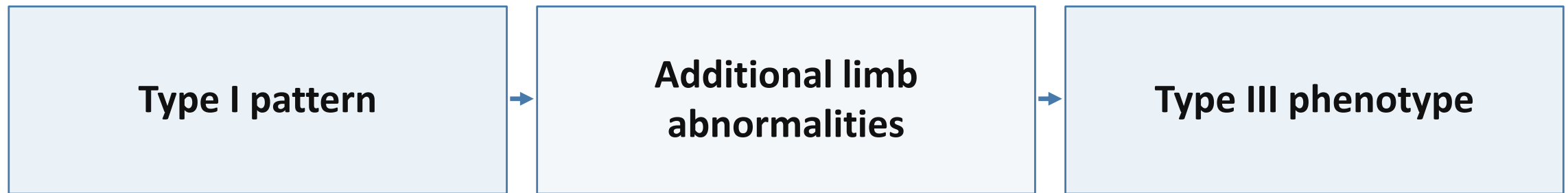
Hearing loss, pigment change, and dystopia canthorum form a key syndrome pattern.



- Congenital sensorineural hearing loss may be present.
- Pigmentary variation may affect hair, irides, and skin.
- Dystopia canthorum describes lateral displacement of the medial canthi.

Waardenburg type III adds limb involvement

Type III combines Waardenburg features with upper-limb musculoskeletal anomalies.



- Limb muscle hypoplasia, joint contractures, or hand anomalies can accompany the auditory–pigmentary signs.
- Type I and III are related PAX3-associated phenotypes.
- Limb defects should not be confused with TBX5-associated heart–hand syndrome.

Waardenburg I versus III

The presence of upper-limb abnormalities shifts the differential.

Type I

- Hearing and pigmentation phenotype
- Dystopia canthorum is typical
- No defining major limb pattern

Type III

- Overlaps type I features
- Limb muscle/joint abnormalities
- May include carpal fusion or syndactyly

From gene function to organ-specific findings

A developmental regulator leaves a recognizable anatomical signature.

Gene	Associated disorder	Hallmark phenotype
HOXD13	Brachydactyly D/E	Digits and hand/foot rays
RUNX2	Cleidocranial dysplasia	Skull, clavicles, teeth
SOX9	Campomelic dysplasia	Cartilage, long bones, sex development
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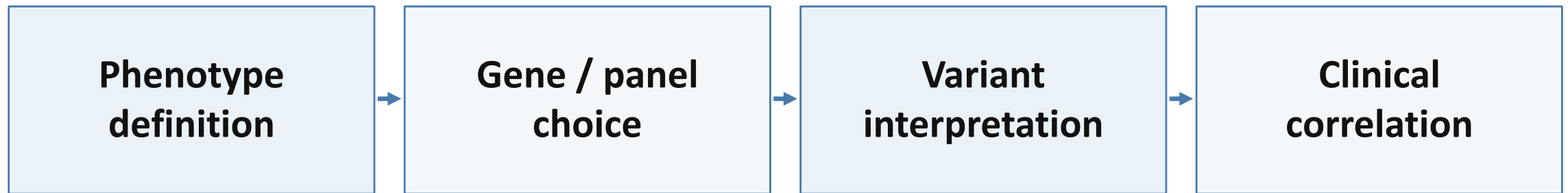
Most discriminating non-skeletal clues

Extra-skeletal findings can separate disorders with superficially similar limb defects.

Heart or airway	Kidney or eye	Hearing or dentition
• TBX5: Heart defects / conduction • SOX9: Unstable airway • Consider urgent associated risks	• LMX1B: Proteinuria / glaucoma • Assess beyond limb shape • Do not infer renal status from nails	• PAX3: Hearing / pigmentation • RUNX2: Eruption + extra teeth • Combine findings with morphology

Molecular diagnosis requires phenotype fit

Gene identification is most informative when the clinical pattern has been well defined.



- Use anatomy and associated organ abnormalities to prioritize plausible genes.
- Different variant classes may alter dosage, DNA binding, or noncoding regulation.
- A variant of uncertain significance is not itself a molecular diagnosis.

Defects in regulators versus bone matrix

Different molecular classes can produce skeletal malformation by distinct routes.

Transcription-factor defect

- Disrupted developmental pattern
- Abnormal condensation or cell fate
- Examples: RUNX2, SOX9, TBX5

Structural protein defect

- Abnormal matrix composition/assembly
- Bone/cartilage tissue fragility or growth
- Examples: Type I or II collagen

Case: Skull, clavicles, and permanent teeth

CLINICAL FINDINGS

A child has persistent cranial sutures, small clavicles, and numerous unerupted permanent teeth.

INTERPRETATION

- Best syndromic diagnosis: Cleidocranial dysplasia.
- Most likely regulator: RUNX2.
- The diagnostic reasoning depends on the combined cranial–clavicular–dental pattern.

Case: Bowed limbs and compromised airway

CLINICAL FINDINGS

A newborn has bowed long bones, Pierre Robin sequence, and airway instability.

INTERPRETATION

- Best mechanistic hypothesis: SOX9-related campomelic dysplasia.
- Assess for associated 46,XY sex-development findings when clinically relevant.
- The airway problem can reflect tracheobronchomalacia, not solely thoracic narrowing.

Case: Unusual nails, small patellae, proteinuria

CLINICAL FINDINGS

An adolescent has dystrophic nails, patellar hypoplasia, limited elbow movement, and proteinuria.

INTERPRETATION

- Best syndrome: Nail–patella syndrome (LMX1B).
- The renal finding is an important systemic manifestation, not an incidental skeletal symptom.
- Include renal and ophthalmic review in clinical evaluation.

Case: Abnormal thumb and an atrial septal defect

CLINICAL FINDINGS

A patient has a triphalangeal thumb and a congenital cardiac septal defect.

INTERPRETATION

- Consider TBX5-related Holt–Oram syndrome.
- Examine radial-ray and carpal elements; Assess ECG as well as cardiac structure.
- A similar hand anomaly without the cardiac pattern has a broader differential.

Case: Hearing loss, pigmentation, and limb contracture

CLINICAL FINDINGS

A child has congenital hearing loss, heterochromia, dystopia canthorum, and upper-limb contractures.

INTERPRETATION

- Consider PAX3-related Waardenburg syndrome type III.
- The extra limb feature distinguishes this presentation from a typical type I pattern.
- PAX3-associated craniofacial and sensory findings support the syndromic diagnosis.

Case: A short thumb tip versus short hand rays

CLINICAL FINDINGS

Two relatives have short digits; One has a broad thumb tip and the other has shortened metacarpals.

INTERPRETATION

- Thumb-tip distal phalanx shortening is type D morphology.
- Metacarpal shortening is type E morphology.
- Overlapping HOXD13-related phenotypes make precise bone-level description essential.

Consolidated gene–syndrome map

The involved transcription factor predicts an anatomical cluster rather than a single isolated sign.

Gene	Associated disorder	Hallmark phenotype
HOXD13	Brachydactyly D/E	Digits and hand/foot rays
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PAX3	Waardenburg types I/III	Hearing, pigment, craniofacial ± limbs

Final synthesis: Six distinct patterning signatures

Integrate site of skeletal malformation with sentinel organ findings.



- HOXD13: Digits and rays; RUNX2: Skull–clavicle–teeth; SOX9: Cartilage, airway, sex development.
- TBX5: Upper limb–heart; LMX1B: Nail–patella–kidney; PAX3: Pigment–hearing–craniofacial ± limb.
- The biological lesson is altered embryonic gene regulation, not simply abnormal bone mineralization.

Source and interpretation notes

Textbook core and independently checked condition-specific detail were kept distinguishable.

- Primary: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Ch 26, pp 1066–1068; Table 26.1.
- Supplement: GeneReviews entries for RUNX2, SOX9, TBX5, LMX1B and PAX3; Johnson et al. for HOXD13.
- Brachydactyly E is defined by short metacarpals/metatarsals in the supplemental genetics literature.