

Prader–Willi Syndrome and Angelman Syndrome

Genomic imprinting, parent-of-origin effects, clinical phenotypes and
molecular diagnosis

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain how genomic imprinting creates parent-specific allelic expression.
- Compare the clinical signatures of Prader–Willi and Angelman syndromes.
- Trace deletion, uniparental disomy and imprinting defects to lost gene function.
- Interpret the complementary roles of methylation, deletion and SNP-based assays.

One chromosomal region produces two distinct disorders because parental origin changes gene activity.

A shared locus does not imply a shared phenotype

Prader–Willi syndrome

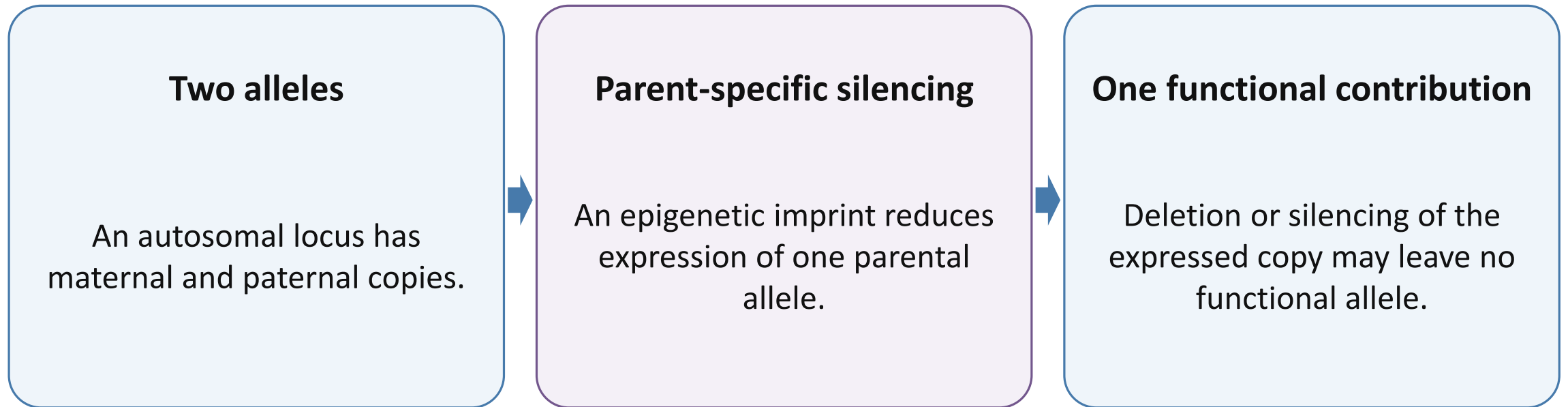
- Loss of paternal-expression functions in 15q11.2–q13.
- Characteristic hypotonia, hyperphagia and obesity.
- Hypogonadism, short stature and intellectual disability.

Angelman syndrome

- Loss of maternal UBE3A function in relevant neurons.
- Microcephaly, ataxic gait and seizures.
- Intellectual disability and inappropriate laughter.

The identity of the affected parent determines which genes lack active alleles.

Why genomic imprinting changes inheritance



The functional genotype depends on allele activity, not just copy number.

Imprinting is an epigenetic mechanism

- The DNA sequence need not be changed to silence an allele.
- Maternal and paternal versions of an autosomal locus can be functionally unequal.
- Selective transcriptional repression establishes the parent-of-origin effect.

Imprinting is a property of gene expression, not simply chromosome inheritance.

Maternal imprinting: The maternal allele is silent

**Maternal allele
SILENCED**

- The term specifies which parental allele is inactivated.
- For maternally imprinted loci, paternal expression remains available.
- The PWS-associated gene region is maternally imprinted.

Maternal imprint $\neq$ maternal expression.

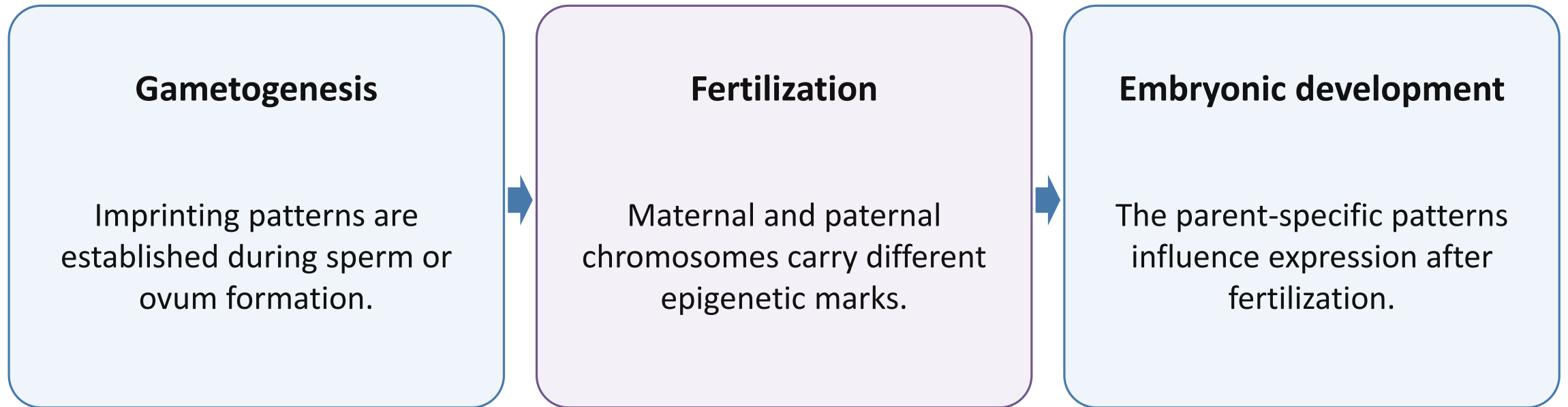
Paternal imprinting: The paternal allele is silent

**Paternal allele
SILENCED**

- A paternally imprinted gene is expressed predominantly from its maternal copy.
- In relevant neurons, UBE3A shows this expression pattern.
- Loss of the maternal contribution can therefore be pathogenic.

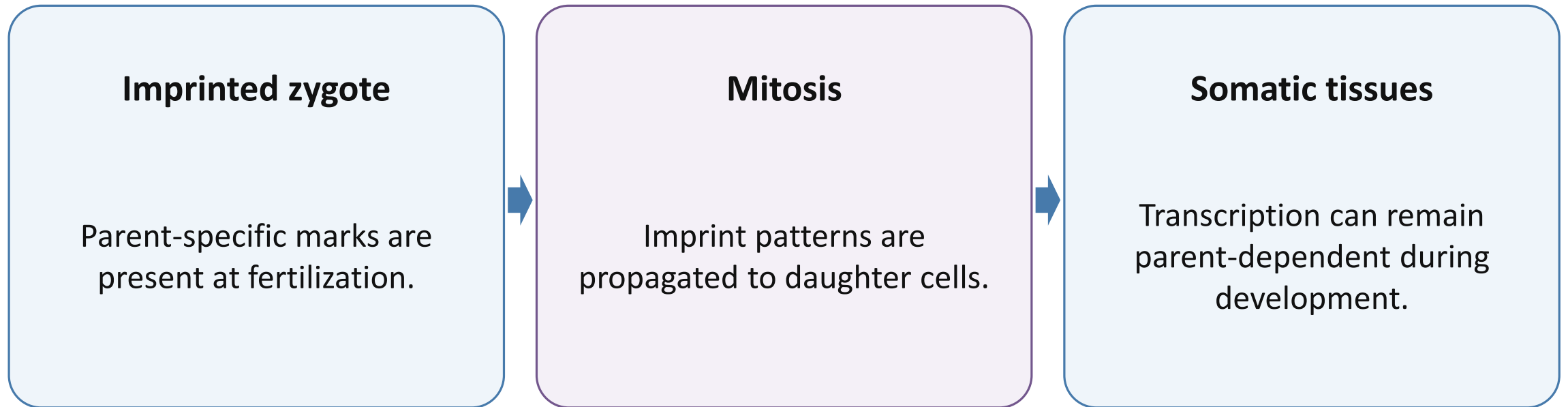
Paternal imprint $\neq$ paternal expression.

Imprints are established before fertilization



These inherited epigenetic differences can persist in somatic cells.

Imprinting is maintained through cell division



Parent-of-origin expression is a stable developmental property.

CpG methylation provides an imprint mark

DNA methylation at CpG sites

- Imprinting to differential CpG methylation.
- Distinct methylation states can be detected with molecular assays.
- A methylation difference can reveal parent-specific regulation without a DNA deletion.

An epigenetic test can identify a functional abnormality that a copy-number test misses.

Imprinting-control regions coordinate nearby genes

Imprinted genes

Affected genes may be clustered rather than isolated.



Cis-acting control

Common regulatory elements govern expression across the cluster.



Regional consequence

A defect can alter several parentally expressed genes.

Regional control helps explain why PWS is not necessarily attributable to one protein-coding gene.

Chromosome 15q11.2–q13: Two regulatory programs

15q11.2–q13

- The source describes the PWS-associated gene set and UBE3A within this interval.
- Their parent-specific expression directions differ.
- The illustrated locus is schematic—not a physical gene-order or scale map.

The same deletion interval can remove different functional contributions.

Normal parent-specific expression in neurons

Origin of chromosome 15	PWS-associated gene region	UBE3A in neurons
Paternal chromosome 15	ACTIVE	SILENCED
Maternal chromosome 15	SILENCED	ACTIVE

Paternal activity supplies the PWS gene region; Maternal activity supplies neuronal UBE3A.

Original schematic; PWS region and UBE3A are conceptual functional units, not physical gene-scale features.

Normal PWS-region expression favors the paternal copy

- PWS-associated genes are maternally imprinted.
- The maternal allele is ordinarily silent for this gene set.
- The paternal chromosome supplies the functional expression.
- Loss of that paternal contribution produces the PWS molecular state.

PWS: Loss of paternally expressed functions.

Normal neuronal UBE3A expression favors the maternal copy

- UBE3A is paternally imprinted in specific brain regions.
- The maternal allele is the main active copy in those neurons.
- A deleted maternal copy cannot be fully replaced by the silent paternal allele.

Angelman syndrome: Loss of functional neuronal UBE3A.

UBE3A imprinting is tissue-dependent

Relevant brain regions

- Paternal UBE3A is imprinted.
- Maternal UBE3A provides essential expression.
- Loss impairs neuronal synapse formation and plasticity.

Most other tissues

- Expression from both UBE3A alleles.
- The paternal allele is not uniformly silenced across the body.
- A single whole-body expression rule is misleading.

The relevant phenotype reflects tissue-specific imprinting, not universal gene silence.

The normal expression matrix

Functional locus	Paternal chromosome	Maternal chromosome
PWS-associated genes	Expressed / active	Imprinted / silent
UBE3A in relevant neurons	Imprinted / silent	Expressed / active
UBE3A in most other tissues	Expressed	Expressed

Identify which parental copy normally supplies the functional product.

Loss of a paternal versus maternal contribution

Paternal 15q loss

- Eliminates normally active PWS-region functions.
- Maternal PWS gene region remains imprinted.
- Result: Prader–Willi syndrome.

Maternal 15q loss

- Eliminates the normally active neuronal UBE3A copy.
- Paternal neuronal UBE3A remains imprinted.
- Result: Angelman syndrome.

Parent of origin—not merely cytoband—is decisive.

Prader–Willi syndrome: Clinical signature

- Intellectual disability and hypotonia.
- Short stature and small hands and feet.
- Profound hyperphagia with obesity.
- Hypogonadism.

The source describes a combined neurodevelopmental, growth and endocrine phenotype.

Hypotonia in Prader–Willi syndrome

Hypotonia

- A major clinical component of the syndrome.
- Occurs alongside neurodevelopmental impairment.
- The feature is not by itself sufficient to assign a molecular diagnosis.

A distinctive constellation is more informative than one isolated clinical finding.

Hyperphagia and obesity in Prader–Willi syndrome

**Profound
hyperphagia**

- Excessive food-seeking and intake are prominent phenotype.
- Obesity is a characteristic associated manifestation.
- These findings help distinguish PWS from the Angelman phenotype.

The appetite phenotype is a clinically prominent discriminator.

Growth and distal extremity findings in PWS

Short stature
Small hands and feet

- Both features are included' core PWS description.
- They complement the metabolic and developmental findings.
- No single external morphologic measurement is required to understand the imprinting mechanism.

The diagnosis is not reducible to a single dysmorphic feature.

Hypogonadism adds an endocrine dimension to PWS

Hypogonadism

- One of the characteristic PWS manifestations.
- Occurs within a multisystem imprinting disorder.
- The genetic defect affects a region rather than an isolated endocrine organ.

Clinical effects extend beyond cognition and behavior.

Paternal deletion: The PWS-expression region is lost

Origin of chromosome 15	PWS-associated gene region	UBE3A in neurons
Paternal chromosome 15	DELETED	SILENCED
Maternal chromosome 15	SILENCED	ACTIVE

An intact but maternally imprinted PWS region cannot replace the lost paternal function.

Original schematic; Inactive and deleted are different molecular states.

Prader–Willi syndrome from paternal deletion

Paternal deletion

A 15q11.2–q13 interval is lost from the paternal chromosome.



Maternal imprint

The corresponding maternal PWS-associated genes are normally silent.



Loss of expression

No normally active paternal gene contribution remains.

A structural chromosomal lesion produces a parent-specific functional deficiency.

Why an intact maternal allele does not rescue PWS

- The DNA of the maternal PWS region may be present.
- Presence of an allele does not guarantee transcriptional activity.
- The maternally imprinted state makes that allele functionally unavailable.
- Thus, the effect resembles loss of the active copy.

Molecular copy number and functional gene dosage are different concepts.

Maternal uniparental disomy causes PWS

Origin of chromosome 15	PWS-associated gene region	UBE3A in neurons
Paternal chromosome 15	— no paternal copy —	— no paternal copy —
Maternal chromosome 15	SILENCED (both maternal copies)	ACTIVE (both maternal copies)

Two maternal chromosome 15 copies leave no paternal-expression PWS gene set.

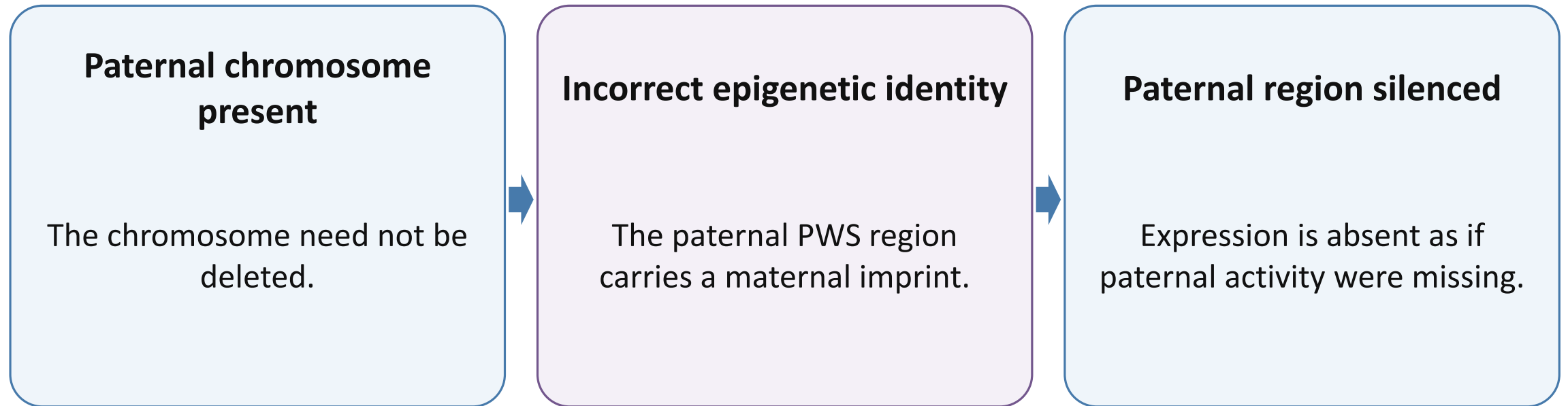
For this UPD schematic, the maternal-row functional state applies to both inherited chromosome copies.

Uniparental disomy changes chromosome origin

- Uniparental disomy (UPD) means both copies of a chromosome pair come from one parent.
- Maternal UPD of chromosome 15 can result in PWS.
- Cytogenetic copy number may remain diploid despite complete loss of paternal origin.

UPD is an inheritance-origin abnormality, not necessarily a deletion.

PWS from an imprinting defect



Imprint errors can phenocopy deletion or maternal UPD.

PWS is a multigene-expression disorder

- Robbins does not attribute the entire syndrome to a single gene.
- A series of paternally expressed genes in 15q11.2–q13 is implicated.
- Several implicated transcripts include small nucleolar RNAs.
- The exact contribution of each component is not fully defined in the source.

Avoid inventing a single-gene mechanism for this regional imprinting disorder.

Small nucleolar RNAs are noncoding effectors

Small nucleolar RNAs (snoRNAs)

- They are noncoding RNAs, not translated into protein.
- The source associates them with post-transcriptional modification of ribosomal RNA and other small nuclear RNAs.
- Loss of these functions is believed to contribute to the PWS phenotype.

RNA function—not merely protein loss—belongs in the disease model.

The exact snoRNA pathogenesis remains uncertain

- The source assigns a contributing role to small nucleolar RNA dysfunction.
- It explicitly states that precise pathogenic mechanisms remain unclear.
- Any detailed, linear pathway from one snoRNA to obesity or hypogonadism would exceed this source.

Distinguish established parent-of-origin causality from unresolved downstream biology.

Three distinct lesions converge on PWS

Paternal deletion

Normally expressed paternal genes are removed.



Maternal UPD

Only maternally imprinted copies are inherited.



Paternal imprinting defect

Present paternal genes receive the wrong silent state.

All three eliminate the expected paternal PWS-region expression.

Angelman syndrome: Clinical signature

- Intellectual disability and microcephaly.
- Ataxic gait and seizures.
- Inappropriate laughter.
- A neuronal UBE3A-expression defect underlies the phenotype.

Angelman has a dominant neurologic phenotype rather than the classic PWS appetite phenotype.

Ataxic gait is a major Angelman clue

Ataxic gait

- Gait ataxia among the characteristic manifestations.
- It accompanies intellectual disability and seizures.
- The sign is part of a broader neuronal disorder, not an isolated motor condition.

A motor-coordination abnormality is clinically discriminating.

Seizures contribute to Angelman phenotype

Seizures

- A cardinal manifestation in the source description.
- Occurs with microcephaly and impaired neurodevelopment.
- The condition is linked to loss of UBE3A-related neuronal function.

Clinical neurology and genomic imprinting intersect directly.

Microcephaly signals neurodevelopmental involvement

Microcephaly

- Robbins explicitly identifies microcephaly in Angelman syndrome.
- It occurs alongside the characteristic ataxic and seizure phenotype.
- The source does not require a particular head-circumference cutoff here.

Use the source-defined clinical pattern without inventing diagnostic thresholds.

Inappropriate laughter: Recognizable but not diagnostic

Inappropriate laughter

- A distinctive behavioral manifestation noted.
- Should be interpreted together with developmental and neurologic findings.
- The molecular diagnosis depends on parental gene expression, not this symptom alone.

Behavioral phenotype complements but cannot replace molecular characterization.

Maternal deletion removes active neuronal UBE3A

Origin of chromosome 15	PWS-associated gene region	UBE3A in neurons
Paternal chromosome 15	ACTIVE	SILENCED
Maternal chromosome 15	DELETED	DELETED

Paternally silenced neuronal UBE3A cannot replace the missing maternal UBE3A.

Original schematic; Deletion may also remove neighboring loci, while the illustrated Angelman mechanism centers on UBE3A.

Angelman syndrome from maternal deletion

Maternal deletion

A 15q11.2–q13 interval containing UBE3A is lost.



Paternal imprint

The paternal UBE3A copy is silenced in relevant neurons.



Functional absence

Those neurons lack maternal UBE3A activity.

A deletion of the opposite parental origin has a different outcome.

Paternal UBE3A cannot fully compensate in neurons

- The paternal gene is present in many Angelman mechanisms.
- Its imprinting silences expression in specific brain regions.
- Therefore, a maternal deletion can remove the only normally active neuronal allele.

The functional deficit is tissue dependent.

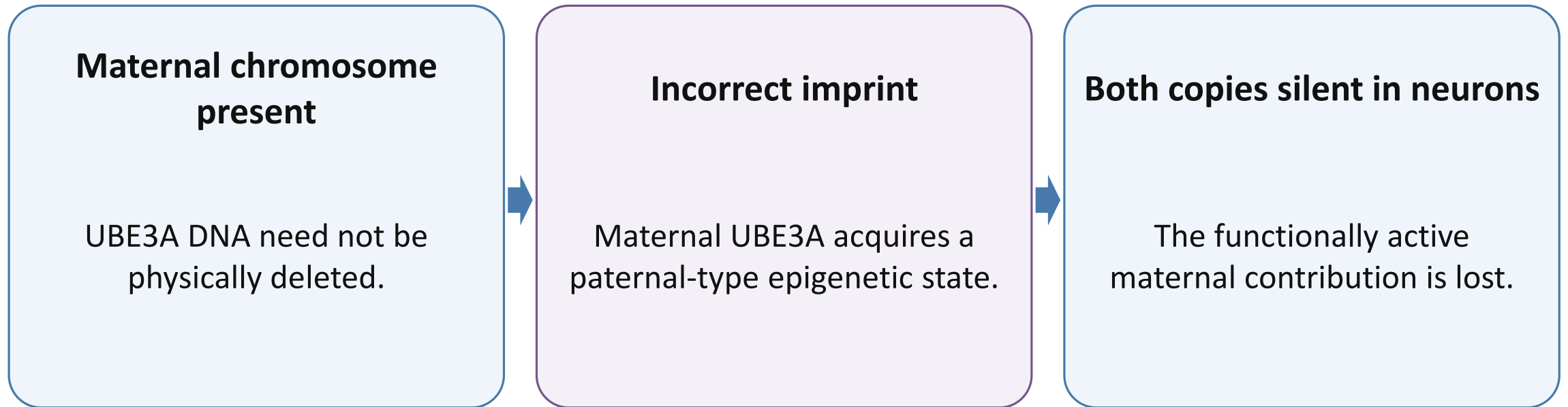
Paternal uniparental disomy can cause Angelman

Origin of chromosome 15	PWS-associated gene region	UBE3A in neurons
Paternal chromosome 15	ACTIVE (both paternal copies)	SILENCED (both paternal copies)
Maternal chromosome 15	— no maternal copy —	— no maternal copy —

Two paternal copies do not provide a maternally active neuronal UBE3A allele.

For this UPD schematic, the paternal-row state applies to both inherited chromosome copies.

Angelman from a maternal imprinting defect



An epigenetic state error can mimic a maternal deletion.

Three lesion classes converge on Angelman

Maternal deletion

Active maternal neuronal
UBE3A is removed.



Paternal UPD

No maternally derived UBE3A
allele is inherited.



Maternal imprinting defect

The maternal UBE3A allele is
inappropriately silenced.

Each mechanism disrupts functional maternal UBE3A expression in neurons.

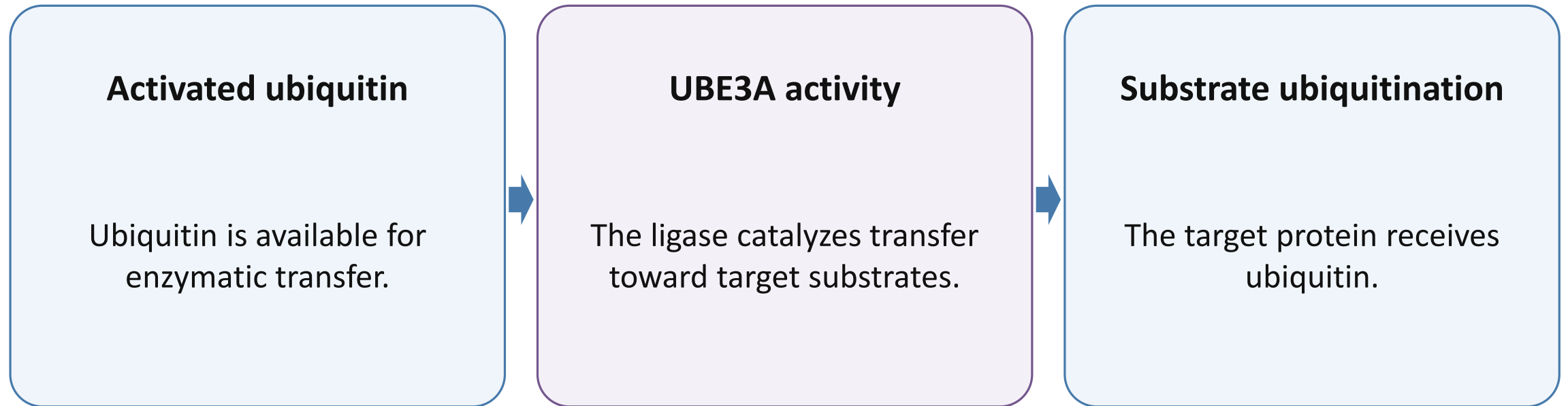
UBE3A encodes a ubiquitin ligase

UBE3A **Ubiquitin ligase**

- UBE3A codes for an enzyme participating in target-protein ubiquitination.
- It catalyzes the transfer of activated ubiquitin to protein substrates.
- The source links UBE3A deficiency to synapse formation and plasticity.

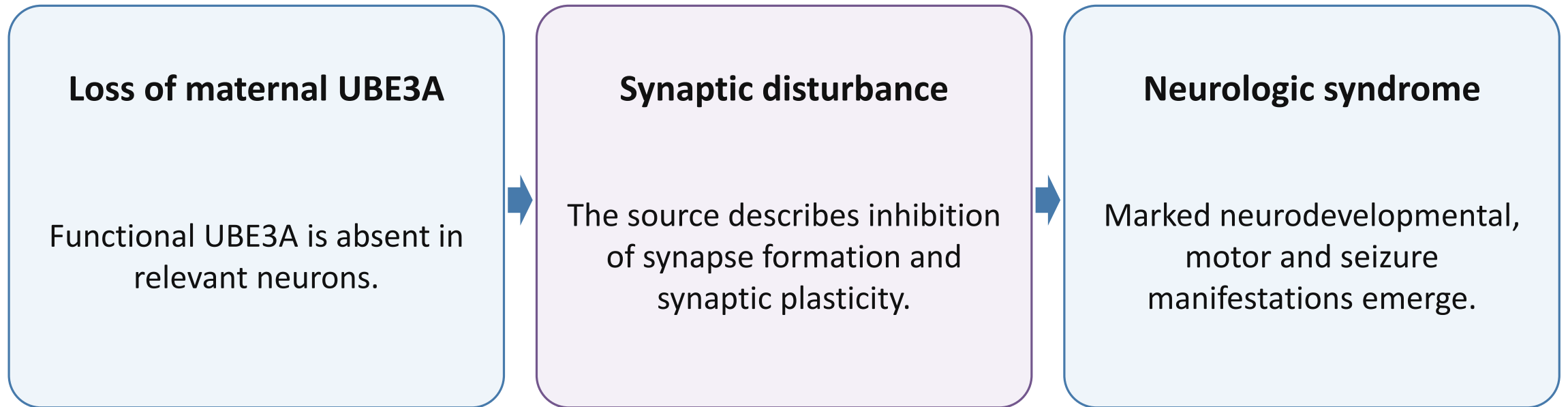
Angelman is linked to a defined protein-coding gene and neuronal function.

Ubiquitin transfer: A conceptual UBE3A function



This is an enzymatic role, not a full substrate-specific signaling pathway.

UBE3A loss affects neuronal connectivity



Do not infer unprovided substrates or quantitative effects from this model.

UBE3A expression is not identical in every tissue

Context	Paternal UBE3A	Maternal UBE3A
Specific brain regions	Imprinted / inactive	Active
Most other tissues	Expressed	Expressed
Maternal deletion, relevant neurons	Imprinted / inactive	Absent

Tissue-specific imprinting explains the predominance of neurologic consequences.

Clinical comparison at the bedside

Phenotype	Prader–Willi	Angelman
Neurodevelopment	Intellectual disability	Intellectual disability
Motor / tone	Hypotonia	Ataxic gait
Growth / head	Short stature; small hands and feet	Microcephaly
Behavior / feeding	Hyperphagia; obesity	Inappropriate laughter
Additional hallmark	Hypogonadism	Seizures

The phenotypes overlap in cognition but differ in their defining associated features.

Molecular comparison: What is missing?

Question	Prader–Willi	Angelman
Locus	15q11.2–q13	15q11.2–q13
Required active origin	Paternal	Maternal (neuronal UBE3A)
Pathogenic deletion origin	Paternal	Maternal
Pathogenic UPD origin	Two maternal copies	Two paternal copies
Imprinting defect	Paternal gets maternal-type imprint	Maternal gets paternal-type imprint

Always state the parent of origin when describing a 15q lesion.

Deletion of the same interval: Reciprocal outcomes

Paternal deletion

- Removes paternal PWS-associated expression.
- Maternal PWS region is silent.
- Leads to the PWS phenotype.

Maternal deletion

- Removes maternal neuronal UBE3A expression.
- Paternal neuronal UBE3A is silent.
- Leads to the Angelman phenotype.

Deletion location alone does not determine the syndrome.

Uniparental disomy: Opposite parental directions

Two maternal copies

- Diploid chromosome number may appear normal.
- Missing paternal-origin PWS functions.
- Molecular consequence: PWS.

Two paternal copies

- Diploid chromosome number may appear normal.
- Missing maternal-origin neuronal UBE3A.
- Molecular consequence: Angelman.

UPD requires determining chromosome origin, not only chromosome count.

Imprinting defects: The wrong epigenetic label

Prader–Willi

- Paternal chromosome acquires a maternal-type imprint.
- PWS-region expression is suppressed.
- No deletion is required.

Angelman

- Maternal chromosome acquires a paternal-type imprint.
- Neuronal UBE3A expression is suppressed.
- No deletion is required.

The physical allele can be intact yet functionally unavailable.

Structural normality does not exclude imprinting disease

**Two chromosomes
≠ two active copies**

- Deletion is a DNA copy-number abnormality.
- UPD is a parent-of-origin abnormality that can preserve copy number.
- An imprint defect alters epigenetic expression without necessarily deleting DNA.

Three mutation classes can converge on the same expression phenotype.

Robbins' approximate mechanism frequencies require context

- For PWS, the text specifically reports paternal deletions in about 65–70% of cases.
- The figure gives illustrative categories: Deletion ~70%; UPD ~20–25%; Imprinting defect ~1–4%.
- Do not interpret these summary figures as identical subtype frequencies for both syndromes.

Percentages here reproduce the textbook presentation and are not updated syndrome-specific estimates.

What different assay classes actually measure

Assay class	Primary biological signal	Key question
Methylation assay	CpG methylation state	Is the expected parent-specific imprint present?
FISH deletion assessment	Presence of chromosomal DNA interval	Is a segment physically deleted?
SNP-array analysis	Genotype and copy-number pattern	Is there copy loss or informative loss of heterozygosity?

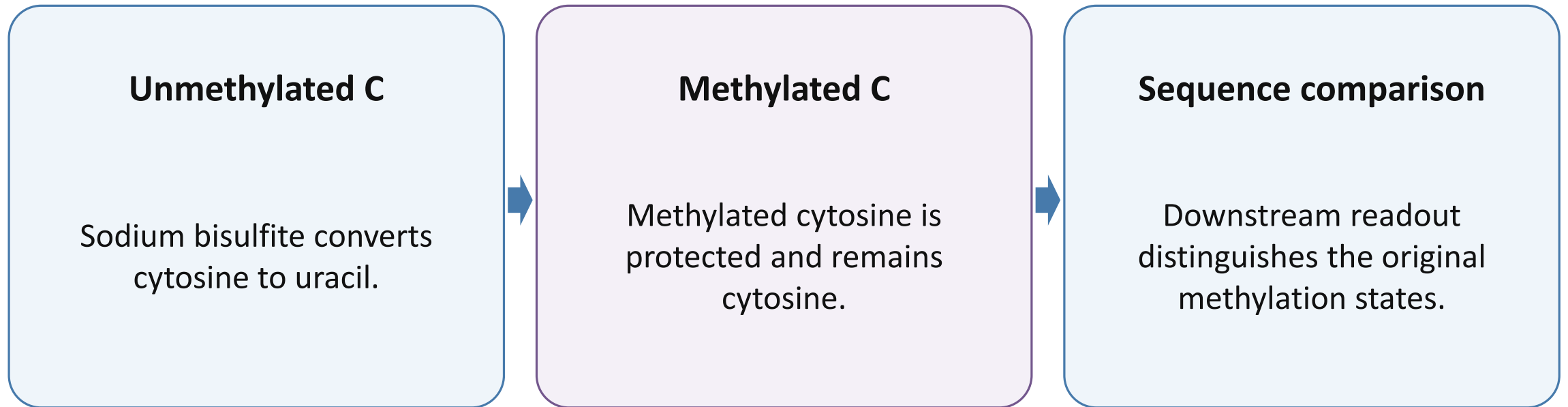
One assay signal should not be treated as equivalent to another.

Methylation analysis is central to both disorders

- Methylation status of marker genes as a molecular diagnostic basis.
- Parent-specific methylation can reveal an abnormal imprinting pattern.
- It complements structural deletion assays.
- A methylation result describes epigenetic state; It may not itself assign the causal mutation class.

Imprinting disorders require more than a conventional chromosome count.

Bisulfite treatment exposes CpG methylation



Bisulfite-based methods translate an epigenetic difference into a sequence-readable difference.

Other methylation-detection principles

- Proteins that selectively bind methylated DNA can enrich methylated fragments.
- Methylation-sensitive restriction enzymes discriminate DNA by cleavage behavior.
- Direct-read technologies can detect modified bases using polymerase or nanopore signals.

Multiple assay technologies target the same molecular property: DNA methylation.

FISH reveals deletion, not the entire imprinting mechanism

FISH

- Fluorescence in situ hybridization can detect chromosome 15 interval deletions.
- It does not directly measure parent-specific DNA methylation.
- A patient with UPD or a pure imprinting defect may lack the deletion sought by FISH.

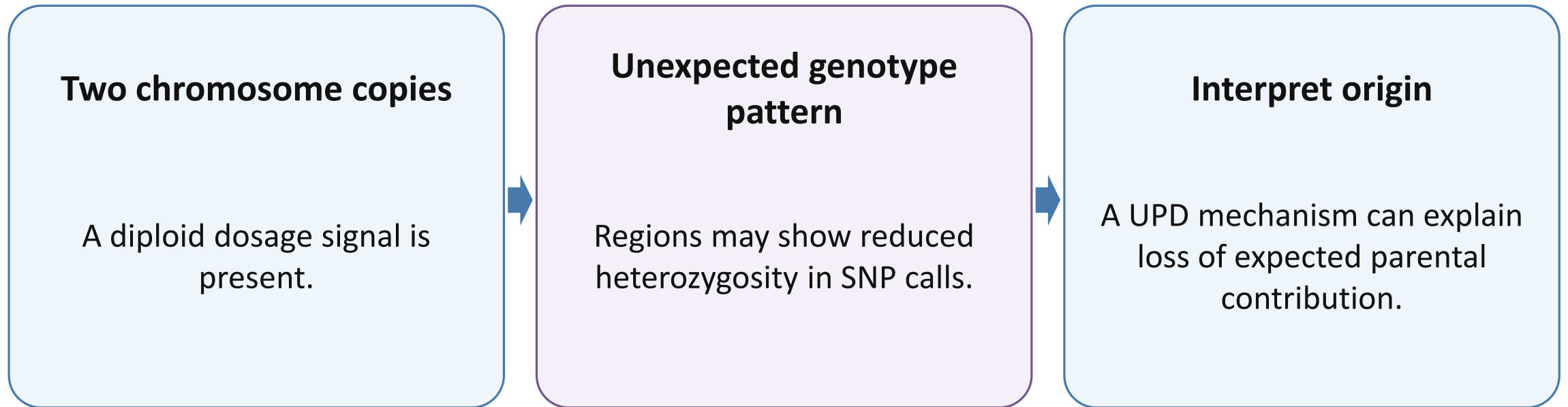
A negative deletion assay cannot exclude an imprinting disorder.

SNP arrays can expose copy-neutral inheritance clues

- SNP arrays combine copy-number information with genotype calls.
- Decreased heterozygosity in regions affected by certain UPD states.
- Diploid copy number and unusual genotype patterns can coexist.
- Parental-origin interpretation requires suitable informative evidence.

Copy-neutral genetic alterations can be invisible to tests limited to dosage.

An illustrative copy-neutral UPD pattern



This is a conceptual interpretation—not a fabricated patient SNP plot.

Combining assays: Complementary inferences

Observation	What it supports	What remains unresolved
Deletion detected	Structural loss in 15q region	Parental origin / functional pattern
Abnormal methylation	An imprinting-pattern abnormality	Deletion versus UPD versus imprint defect
Diploid copy number	No detected deletion at assay resolution	UPD / imprint abnormality may remain
SNP loss of heterozygosity	Possible copy-neutral inheritance abnormality	Parent of origin / full molecular classification

These are interpretation principles, not a laboratory testing guideline.

Diagnostic reasoning: Normal chromosome count

A child has a characteristic imprinting-disorder phenotype. Routine chromosome counting identifies two copies of chromosome 15.

Clinical / laboratory clues

- Chromosome copy number is not equivalent to parental origin.
- Imprinting defects do not necessarily alter DNA dosage.

Is a chromosome-15 imprinting disorder excluded?

Interpretation: Normal dosage may conceal UPD

No

- Two copies can both be maternally or paternally inherited.
- An imprint defect can silence an otherwise present allele.
- Parent-specific methylation and additional molecular tests address the functional question.

A normal chromosome count does not exclude PWS or Angelman syndrome.

Case application: Prader–Willi phenotype

A child with developmental impairment has hypotonia, short stature, striking hyperphagia, obesity and hypogonadism.

Clinical / laboratory clues

- Clinical pattern strongly resembles the PWS phenotype.
- A paternal deletion, maternal UPD or paternal imprint error can converge on this pattern.

Which parental-expression program is missing?

PWS case: Name the lost functional origin

Paternal PWS-region expression

- The maternal PWS-associated region is normally imprinted.
- Deleting the paternal interval removes its functional contribution.
- Maternal UPD and paternal imprint defects also remove effective paternal expression.

The correct molecular abstraction is absence of paternally expressed PWS-region genes.

Case application: Angelman phenotype

A child has intellectual disability, microcephaly, ataxic gait, seizures and recurrent inappropriate laughter.

Clinical / laboratory clues

- The combined features fit the Angelman phenotype.
- Neuronal UBE3A is normally expressed from the maternal allele.

Which gene and parental origin explain the pattern?

Angelman case: Identify the affected functional gene

**Maternal
UBE3A in neurons**

- Loss of maternal UBE3A removes the active neuronal allele.
- The paternally inherited neuronal UBE3A allele is imprinted.
- The lost ligase activity is linked to altered synapse formation and plasticity.

The affected parental copy is the maternal UBE3A allele.

Mechanism check: Predict the syndrome

Genomic finding	Expected syndrome	Mechanistic reason
Paternal 15q11.2–q13 deletion	Prader–Willi	Loss of active PWS-region genes
Maternal 15q11.2–q13 deletion	Angelman	Loss of active neuronal UBE3A
Two maternal chromosome 15 copies	Prader–Willi	No paternal-origin PWS activity
Two paternal chromosome 15 copies	Angelman	No maternal-origin neuronal UBE3A

The parent-of-origin rule correctly predicts these four textbook mechanisms.

Final synthesis: The causal rule

- Imprinted alleles are present but normally silent in relevant cells.
- PWS is linked to missing paternal-expression functions in 15q11.2–q13.
- Angelman is linked to missing maternal UBE3A function in neurons.
- Deletion, UPD and imprinting errors can produce the same functional deficit.
- Methylation, copy-number and SNP information answer complementary questions.

Always ask: Which parental allele is normally active, and what made it unavailable?

Primary source and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 5, sections on Genomic Imprinting and Prader–Willi Syndrome and Angelman Syndrome.
- Molecular diagnostic explanations also draw on adjacent sections on SNP arrays and epigenetic alterations.
- All diagrams are original editable conceptual schematics; textbook figure 5.31 was not reproduced.