

Single-Gene Disorders

Disorders of Epigenetic Machinery

Chromatin regulation, Mendelian disease and Rett syndrome

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Learning objectives

- Explain how chromatin state controls access to DNA without changing its sequence.
- Distinguish epigenetic writers, erasers, readers, and chromatin-remodeling factors.
- Connect MECP2 dysfunction to Rett syndrome and its clinical trajectory.
- Interpret the inheritance and phenotypic heterogeneity of this disease group.

An additional mechanism of Mendelian disease

Conventional examples

- Structural proteins alter tissue integrity.
- Transport proteins alter molecular movement.
- Enzymes interrupt metabolic pathways.

Epigenetic machinery

- The primary lesion affects regulation of gene activity.
- Multiple downstream genes can become misregulated.
- Effects depend on cellular lineage and development.

The genetic lesion is in a single gene; Downstream expression effects may be broad.

DNA sequence and epigenetic state are distinct

Inherited variant

Changes the sequence of
a gene encoding a
regulator



Defective regulator

Alters chromatin marking
or accessibility



**Gene-expression
disturbance**

Impairs cell and tissue
function

A sequence variant can cause disease by altering control of other genes.

Why cells with similar DNA have different functions

Shared genome

- Most differentiated somatic cells carry essentially the same DNA sequence.
- The sequence alone does not specify a single cell phenotype.

Lineage-specific expression

- Different genes are transcriptionally available in different cells.
- Chromatin organization helps maintain cell identity.

Epigenetic organization contributes to cell type–specific transcription.

What is an epigenetic state?

- A chemical state associated with DNA or DNA-bound proteins.
- Influences DNA packaging and transcriptional availability.
- May be modified without altering the underlying base sequence.
- Its functional effect depends on genomic location and context.

Chromatin accessibility is a functional spectrum

Euchromatin

- Relatively dispersed chromatin.
- DNA is generally more accessible to transcription factors.
- Often associated with actively transcribed genes.

Heterochromatin

- More compact chromatin.
- Access to regulatory DNA is restricted.
- Often associated with transcriptional inactivity.

“Open” and “closed” summarize relative access, not an absolute binary.

Chromatin architecture shapes transcription

Histone-bound DNA

Nucleosomes package
the DNA



Accessible regulatory site

Transcriptional
machinery can engage

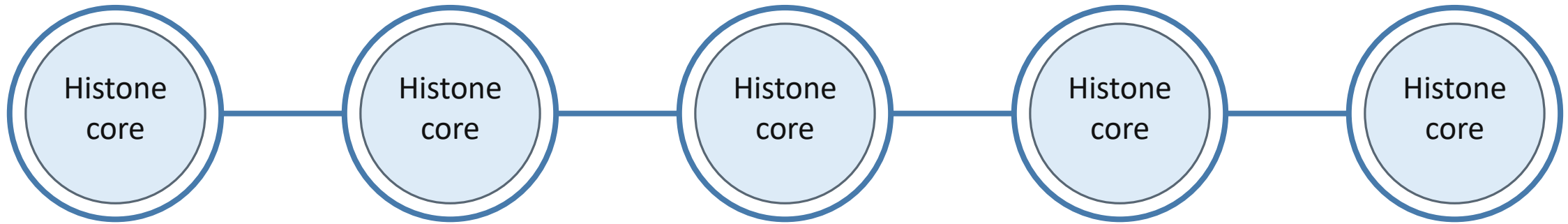


Gene expression

RNA synthesis becomes
possible

Nucleosome placement and marks influence whether regulatory sequences can be used.

A nucleosome is the basic repeating unit



DNA wrapping around histone cores, connected by linker DNA

- DNA wraps around a core histone octamer.
- Successive nucleosomes are connected by linker DNA.
- The repeating DNA–histone structure forms chromatin.

The histone octamer has a defined composition

H2A

Two copies

H2B

Two copies

H3

Two copies

H4

Two copies

The nucleosome core contains eight histone proteins: Two of each type.

Linker DNA and histone H1 support packing

- DNA links neighboring nucleosome core particles.
- Histone H1 associates with linker DNA and supports higher-order organization.
- Higher-order packaging changes access to transcriptional control sites.

Position matters: A promoter can be exposed or obscured

Accessible promoter

- Regulatory DNA is less occluded by nucleosomes.
- Transcription factors can more readily bind.

Occluded promoter

- Nucleosome position restricts physical access.
- Initiation of transcription is less favored.

The schematic describes chromatin accessibility; It is not a quantitative assay.

Chromatin remodelers reposition nucleosomes

Nucleosome placement

A promoter or enhancer
is covered



Remodeling complex

Repositions nucleosomes
on DNA

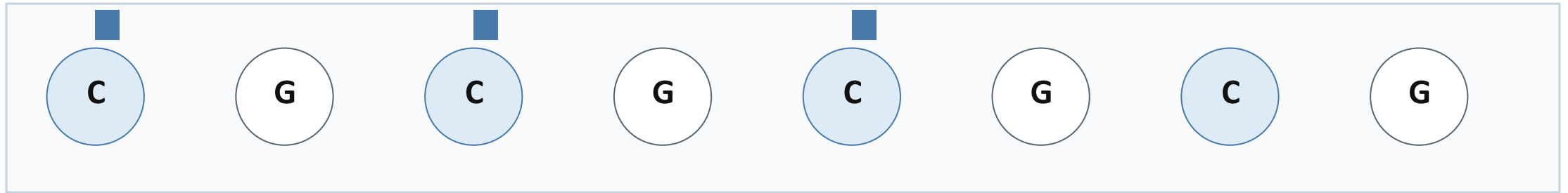


Changed accessibility

Regulatory factors gain or
lose access

A remodeler changes positioning; It is not synonymous with adding a chemical mark.

DNA methylation marks cytosine at CpG sites



Methyl marks on selected cytosines (schematic)

- The major DNA mark discussed by Robbins is 5-methylcytosine.
- Methylation occurs at the C5 position of cytosine.
- CpG denotes cytosine followed by guanine along a DNA strand.

DNA methylation can repress regulatory regions

CpG methylation

Mark at a gene
regulatory region



Methylated-DNA readers

Proteins recognize the
modified CpG



Silencing machinery

Chromatin becomes less
transcriptionally
permissive

High methylation in gene regulatory elements typically associates with silencing.

The position of an epigenetic mark changes its meaning

- Regulatory-region DNA methylation commonly correlates with gene silencing.
- Histone methylation can activate or repress depending on the modified residue.
- It is inaccurate to label all “methylation” simply as activating or silencing.

Histone modifications constitute a regulatory code

- Histone proteins undergo covalent posttranslational modifications.
- Acetylation, methylation, and phosphorylation are discussed.
- Combinations of modifications influence chromatin structure and transcription.

Histone acetylation generally favors open chromatin

Histone lysine acetylation

Acetyl groups are added

**Less compact
configuration**

Transcription-factor
access is favored

**Higher transcriptional
potential**

Permissive chromatin
state

This is a tendency, not proof that every acetylated locus is transcriptionally active.

Histone acetyltransferases are epigenetic writers

Histone substrate

Lysine residues are
available



HAT activity

Transfers an acetyl group



Acetylated chromatin

Frequently more
permissive to
transcription

A writer installs a mark; The consequence depends on the marked site.

Histone deacetylases remove acetyl marks

Acetylated histone

Acetyl marks are present



HDAC activity

Removes acetyl groups



Chromatin compaction

Transcription is often less favored

Deacetylation is one mechanism by which silencing complexes act.

Histone methylation is residue dependent

Activating context

- Methylation of certain histone residues is associated with active transcription.
- The target residue must be specified to infer function.

Repressive context

- Methylation at other residues is associated with condensed chromatin.
- “Histone methylation” alone does not predict direction.

Avoid treating histone methylation as equivalent to CpG methylation.

Histone phosphorylation is context dependent

- Specific histone serines can be phosphorylated.
- The effect depends on the modified site and biological context.
- Phosphorylation may accompany either accessible or condensed chromatin.

Three classes of mark-handling proteins

Writers

Install chemical marks on DNA or histones.

Erasers

Remove previously installed chemical marks.

Readers

Recognize marks and recruit effectors.

Chromatin remodelers form a related functional category that changes nucleosome positioning.

Writers alter the information carried by chromatin

Writer gene mutation

Mark installation may be
perturbed



Altered mark landscape

Regulatory regions may
be misconfigured



Expression consequences

Cell programs may be
disrupted

Effects vary by gene, affected mark, and tissue.

Erasers make chromatin states reversible

Existing histone mark

Chromatin carries a
modification



Eraser removes mark

Mark balance can change

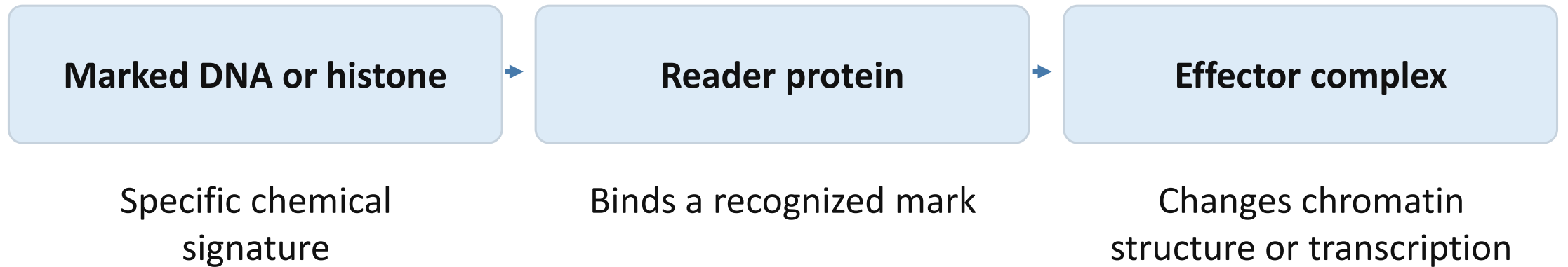


Regulatory state shifts

Transcriptional access
may change

A loss of eraser function may disrupt normal chromatin transitions.

Readers translate chemical marks into regulatory actions



MeCP2 illustrates a reader of methylated CpG DNA.

Remodelers regulate placement rather than mark chemistry

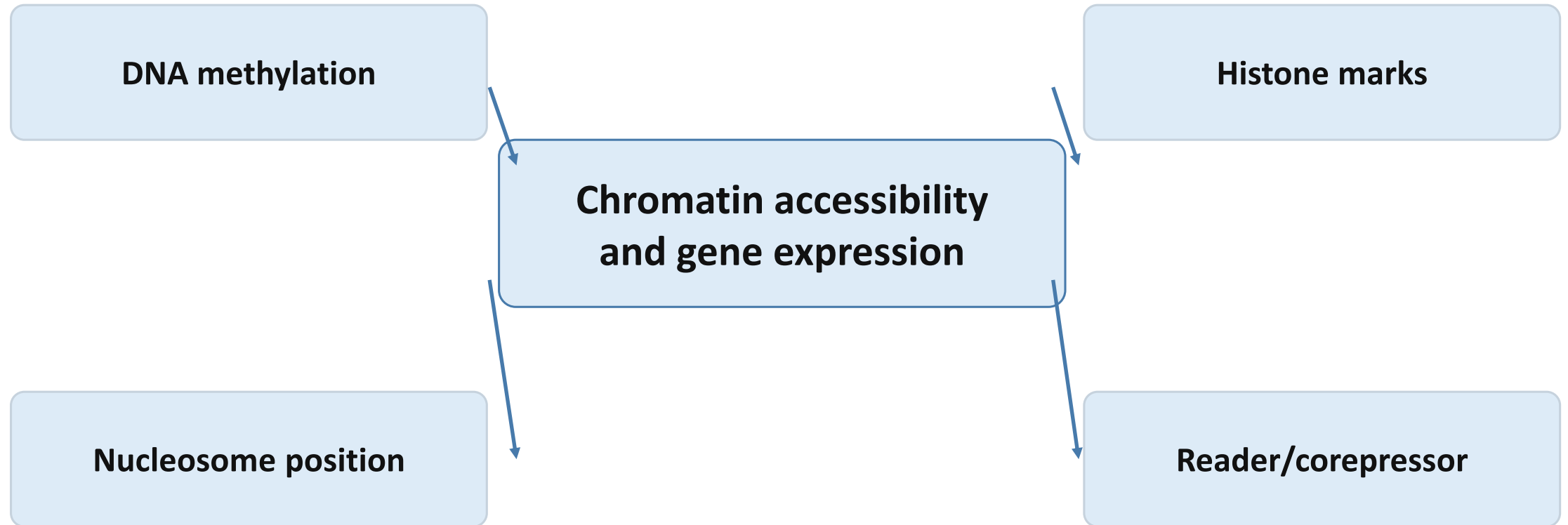
Chemical-mark machinery

- Writer: Adds a modification.
- Eraser: Removes a modification.
- Reader: Interprets a modification.

Chromatin remodeling

- Changes nucleosome position on DNA.
- Alters exposure of promoters and enhancers.
- May work together with mark-dependent complexes.

Epigenetic control is an integrated system



Integrated control: Marks, readers, and remodelers are complementary mechanisms.

Why a single mutation may affect many genes

One regulator is defective

Its normal targets are not correctly controlled



Multiple regulatory loci

Gene-expression patterns may be altered



Developmental phenotypes

Different organs and neural circuits may be affected

The reach of the mechanism explains clinical breadth; It does not imply every target is affected identically.

Mendelian epigenetic disorders are heterogeneous

- Different causal genes affect writers, erasers, readers, or remodelers.
- Clinical manifestations vary across affected genes.
- Many syndromes involve neurologic dysfunction and intellectual disability.
- A shared regulatory mechanism does not imply a single clinical phenotype.

Most reported syndromes follow a dominant pattern

- Many epigenetic-machinery disorders as autosomal dominant.
- Rett syndrome is an important X-linked exception.
- Inheritance depends on the gene and specific pathogenic variant.

Why neurodevelopment is frequently involved

Developing nervous system

Needs timed, lineage-specific gene programs



Chromatin regulators

Coordinate access to many loci



Regulatory disturbance

Can affect neural development and function

A mechanistic interpretation consistent with the neurologic predominance.

Examples in the Mendelian epigenetic group

Syndrome named in Robbins	Teaching point
Kabuki syndrome	Example of a Mendelian disorder involving epigenetic regulation
Wilson–Turner syndrome	Included among genetically heterogeneous epigenetic disorders
Weaver syndrome	Part of the listed spectrum
Rubinstein–Taybi syndrome	Illustrates syndromic neurodevelopmental involvement
Smith–Magenis syndrome	Another syndrome in the textbook grouping

Phenotypic variation does not invalidate a common mechanism

Shared pathway level

- Abnormal regulation of chromatin and gene expression.
- Mutations can involve mark addition, removal, recognition, or remodeling.

Different clinical outcomes

- Affected proteins act at different loci and developmental stages.
- Features can vary across organ systems and age.

The disease group is mechanistically related, not phenotypically uniform.

Do not equate an epigenetic disorder with a DNA methylation defect

Broad disease class

- Histone writers and erasers.
- Histone or DNA-mark readers.
- Chromatin-positioning machinery.

Specific molecular lesion

- Rett syndrome primarily involves the reader MeCP2.
- The responsible gene is MECP2.
- The defect is not simply “too much methylation.”

Rett syndrome is the textbook prototype

- Rett syndrome illustrates a single-gene defect of epigenetic reading.
- An X-linked MECP2-related condition.
- Classically recognized after initially unremarkable early development.
- Its characteristic phenotype evolves through developmental stagnation and regression.

MECP2 encodes a methyl-CpG-binding protein

MECP2 gene

X-linked gene



MeCP2 protein

Recognizes methylated
CpG DNA



Chromatin regulation

Recruits transcription-
silencing factors

Gene symbol MECP2; Protein name MeCP2.

MeCP2 binds a chemical signal on DNA

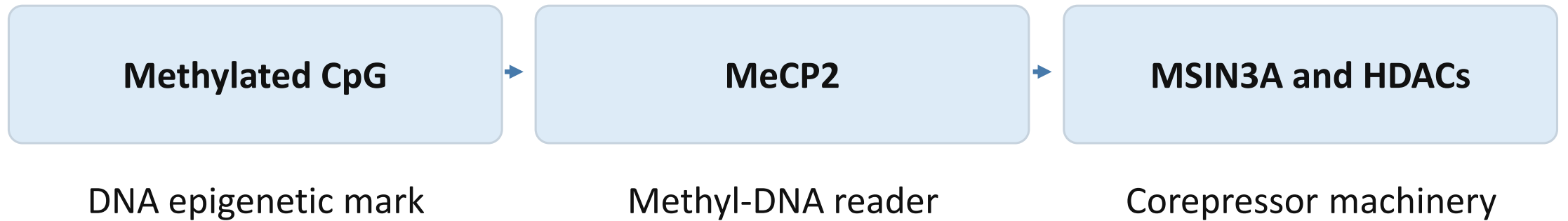
DNA containing methylated CpG



**MeCP2
DNA reader**

Specific recognition of a DNA methylation mark permits recruitment of downstream factors.

MeCP2 connects methylated DNA to corepressors



This depicts the repressive mechanism illustrated Fig. 5.18.

MSIN3A and HDACs cooperate in transcriptional repression

MeCP2 recruitment

Reader binds methylated
CpG



MSIN3A scaffold

Corepressor components
assemble



HDAC activity

Histone acetyl marks are
removed

Deacetylation helps establish less permissive chromatin.

Normal MeCP2 supports controlled silencing

Methylated CpG

MeCP2 can recognize the mark



Silencing factors

MSIN3A and HDAC activity are recruited



Heterochromatin tendency

Transcription is repressed at affected loci

Simplified textbook mechanism; Transcriptional effects are locus specific.

Loss of MeCP2 disrupts interpretation of methylated DNA

Functional MeCP2

- Recognizes methylated CpG DNA.
- Helps recruit chromatin-silencing machinery.
- Contributes to normal regulatory control.

MeCP2 loss of function

- The mark cannot be interpreted normally by MeCP2.
- Recruitment of effectors is perturbed.
- Gene regulation becomes abnormal.

Do not infer that all genomic sites become uniformly derepressed.

Rett syndrome reflects a defect in reading, not DNA sequence copying

What is altered?

- The protein responsible for reading a DNA mark is deficient.
- The underlying methylated CpG remains a conceptually distinct feature.

What follows?

- Altered coordination between DNA marks and chromatin complexes.
- Abnormal regulation of gene-expression programs.

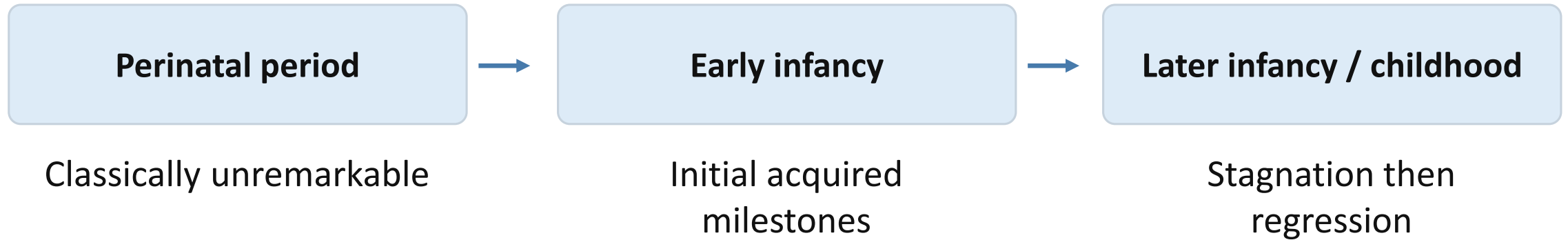
Rett syndrome has an X-linked molecular basis

- MECP2 is located on the X chromosome.
- The classic presentation mainly in girls.
- MeCP2-related disease is also recognized in hemizygous males.
- Sex-linked genotype and phenotype should not be conflated.

Reported frequency is a context, not a screening test

- Rett syndrome affects approximately 1 in 10,000 female births.
- That estimate does not establish the probability for an individual patient.
- The clinical phenotype and molecular basis must be assessed together.

The early developmental history is diagnostically informative



The sequence describes the classic presentation, not every possible MECP2 phenotype.

Neurodevelopmental stagnation precedes loss of skills

Development

Early gains in function



Stagnation

Acquisition of new skills
slows or stops



Regression

Previously acquired
abilities are lost

Stagnation and regression are different clinical observations.

Loss of purposeful hand use is a core clinical clue

Previously acquired ability

- Purposeful manual activity develops in early childhood.
- Hand use contributes to everyday learned tasks.

Classic Rett evolution

- Purposeful hand movement is lost.
- Stereotyped wringing and clasping may appear.

Hand stereotypies have specific descriptive value

- Repetitive hand wringing and clasping.
- The movements accompany loss of purposeful manual function.
- Both observations should be described rather than reduced to “abnormal movements.”

Speech regression indicates broader neurodevelopmental loss

- Children may lose speech abilities that were previously acquired.
- Language loss occurs alongside motor and behavioral changes.
- The combination signals a regressive developmental process.

Motor dysfunction progresses beyond hand movements

- Loss of acquired motor skills is part of the classic presentation.
- Abnormal gait and ataxia may develop.
- Clinical evaluation must consider changing motor function over time.

Breathing abnormalities and seizures expand the phenotype

Respiratory manifestations

- Breathing problems may occur.
- The finding broadens the disorder beyond motor and language domains.

Neurologic manifestations

- Seizures may develop.
- The syndrome encompasses progressive neurologic dysfunction.

Microcephaly and developmental dysfunction may coexist

- Microcephaly is included in the classic syndrome description.
- It accompanies progressive neurologic dysfunction rather than defining the entire syndrome.
- The evolution of milestones remains central to recognizing the phenotype.

Rett syndrome in males has a wider recognized spectrum

Historical assumption

- MeCP2 mutations were once regarded as incompatible with life in hemizygous males.

Textbook update

- Affected males are now recognized.
- Phenotypes range from severe congenital encephalopathy to intellectual disability.

An affected male should not be excluded on sex alone.

Clinical recognition requires a trajectory, not a single symptom

Early developmental history

Determine previously acquired milestones

Change in function

Identify stagnation or regression

Associated findings

Examine hand, gait, breathing and seizures

Mechanistic suspicion is strengthened by the combination and evolution of signs.

Teaching case: Identify the unifying syndrome

Clinical vignette

A young girl initially acquires developmental milestones. Subsequently, language and purposeful hand use regress, repetitive hand-wringing develops, and walking becomes abnormal.

What syndrome and affected epigenetic reader best explain this pattern?

Case explanation: Trace the molecular lesion

MECP2 pathogenic variant

Functional MeCP2
becomes deficient



Methyl-CpG recognition

Recruitment of silencing
partners is disturbed



Neural gene regulation

Developmental and
functional programs are
affected

Clinical findings do not permit prediction of specific altered target genes from this textbook account.

Epigenetic disease versus an enzyme-storage disease

Enzyme defect

- A metabolic reaction is interrupted.
- Upstream substrates may accumulate.
- Pathologic storage or substrate toxicity may result.

Epigenetic regulator defect

- A regulatory protein is impaired.
- Chromatin state or mark interpretation is disturbed.
- Multiple transcriptional programs may be affected.

Both can be single-gene disorders, but their proximal mechanisms differ.

Mendelian epigenetic disease versus complex disease

Mendelian epigenetic syndrome

- A pathogenic variant in one regulator can be causative.
- Inheritance is gene-dependent; Many are dominant.

Complex multigenic disorder

- Multiple inherited variants interact with other factors.
- No single-gene lesion necessarily explains the phenotype.

Mechanistic grouping and inheritance grouping answer different questions.

Three interpretation errors to avoid

Chemistry ≠ outcome

Not every methyl group represses transcription.

One gene ≠ one target

A regulator can influence many gene-expression programs.

X-linked ≠ girls only

MECP2-associated disease occurs in males as well.

Second case: Which functional class is deficient?

Clinical vignette

Methylation remains a recognizable DNA modification, but a mutant protein can no longer bind methylated CpG and recruit chromatin-silencing factors.

Is the primary lesion in a writer, eraser, reader, or nucleosome remodeler?

Diagnostic synthesis: From phenotype to mechanism

Clinical pattern

Developmental
regression and
characteristic findings



Gene-level inference

Consider MECP2
involvement



Molecular mechanism

Defective methyl-CpG
reading and repression

Teaching linkage, not a replacement for a clinical diagnostic protocol.

Key mechanistic conclusions

- Epigenetic marks help establish transcriptionally permissive or repressive chromatin.
- Writers, erasers, readers, and remodelers operate at different regulatory steps.
- Mendelian disruption of one regulator can have broad developmental effects.
- MeCP2 loss illustrates defective interpretation of methylated DNA in Rett syndrome.

Key clinical conclusions

- Many Mendelian epigenetic disorders feature neurologic dysfunction.
- The classic Rett pattern combines early developmental gains, stagnation, and regression.
- Loss of purposeful hand use, stereotypies, speech and gait abnormalities are discriminating clues.
- MECP2-associated disease is recognized in both females and males.

References

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 5, “Genes and Human Diseases,” including “Disorders of Epigenetic Machinery.”
- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 1, “Histone Organization.”
- Textbook conceptual mechanism: Fig. 5.18 (Rett syndrome / MeCP2); original figure not reproduced.