FSHD genetics and genetic counselling

FSHD 360 Conference
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Disclosures

No competing interests to report

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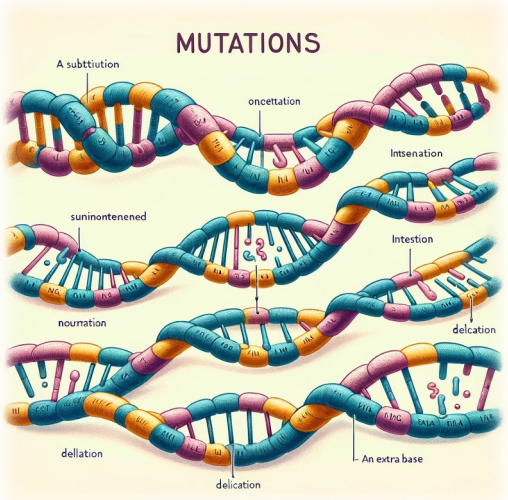
Overview

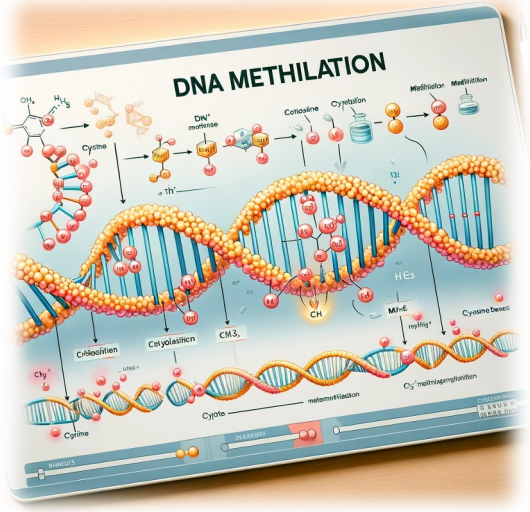
- Basic concepts in genetics
- Genetics of FSHD
- Genetic implications

Basic concepts in genetics

Genetic mutations



DNA methylation



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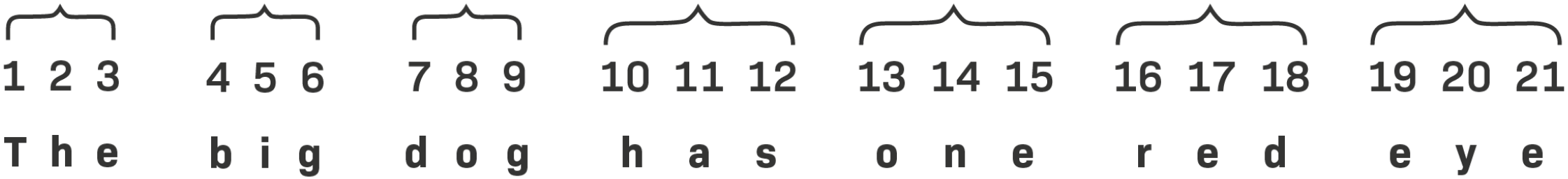
Genetic mutations: three letter codes

Sentence example:



- Single base change
- Insertion/deletion (inframe vs frameshift)
- Stopgain

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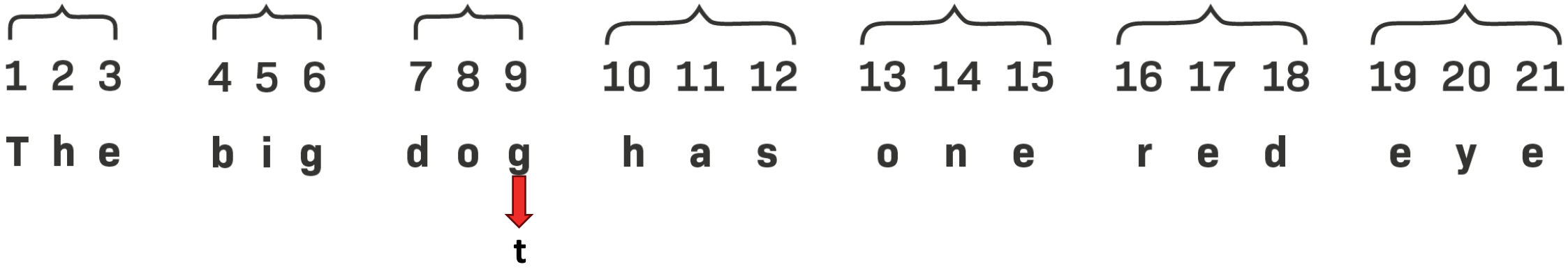
Genetic mutations: three letter codes

Sentence example:



- **Single base change**: The big dot has one red eye
- Insertion/deletion (inframe vs frameshift)
- Stopgain

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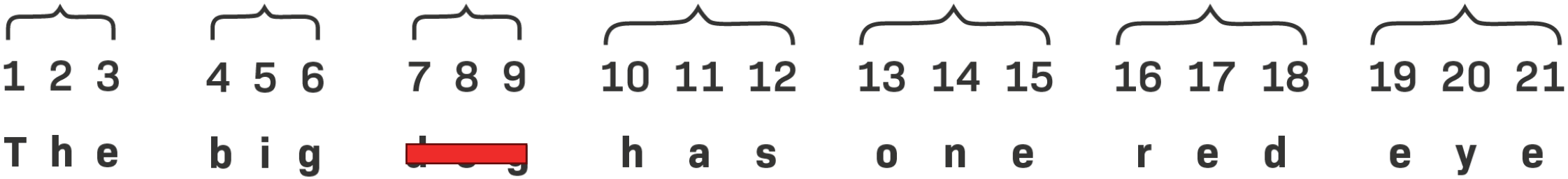
Genetic mutations: three letter codes

Sentence example:



- Single base change
- **Insertion/deletion** (inframe vs frameshift)
  - The big ___ has one red eye
- Stopgain

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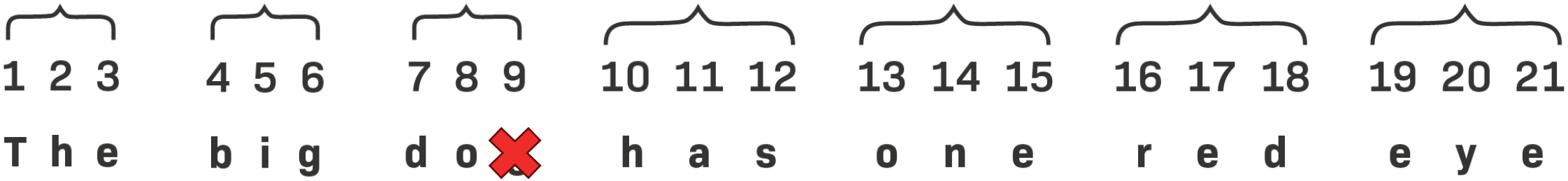
Genetic mutations: three letter codes

Sentence example:



- Single base change
- **Insertion/deletion** (inframe vs frameshift)
  - The big doh aso ner ede ye
- Stopgain

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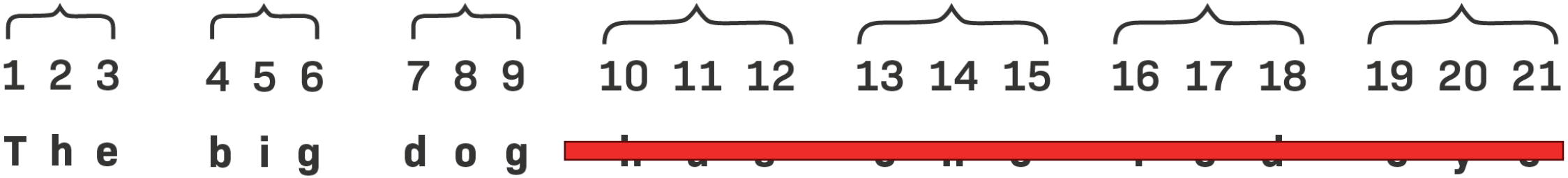
Genetic mutations: three letter codes

Sentence example:



- Single base change
- Insertion/deletion (inframe vs frameshift)
- **Stopgain**: The big dog

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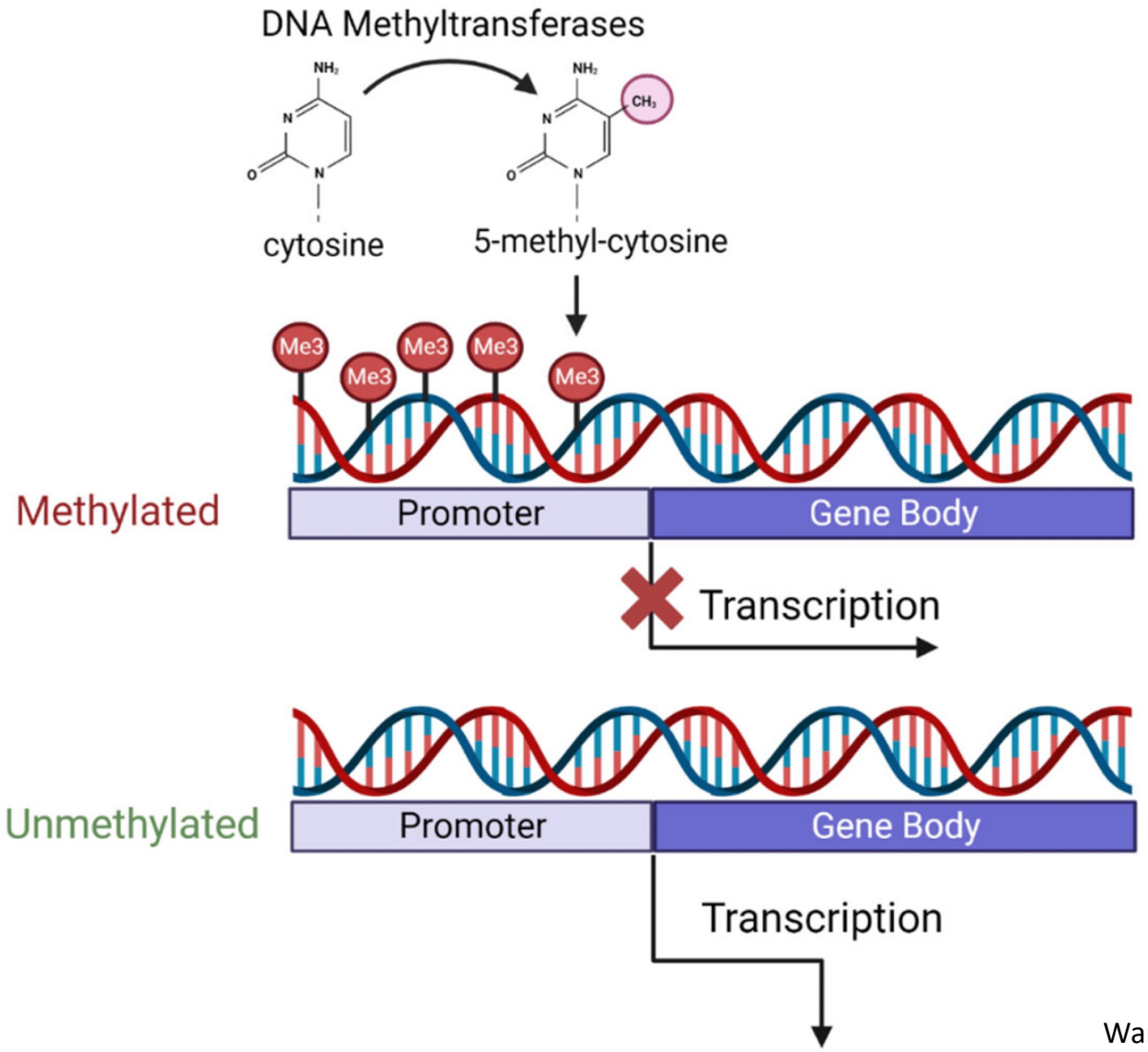
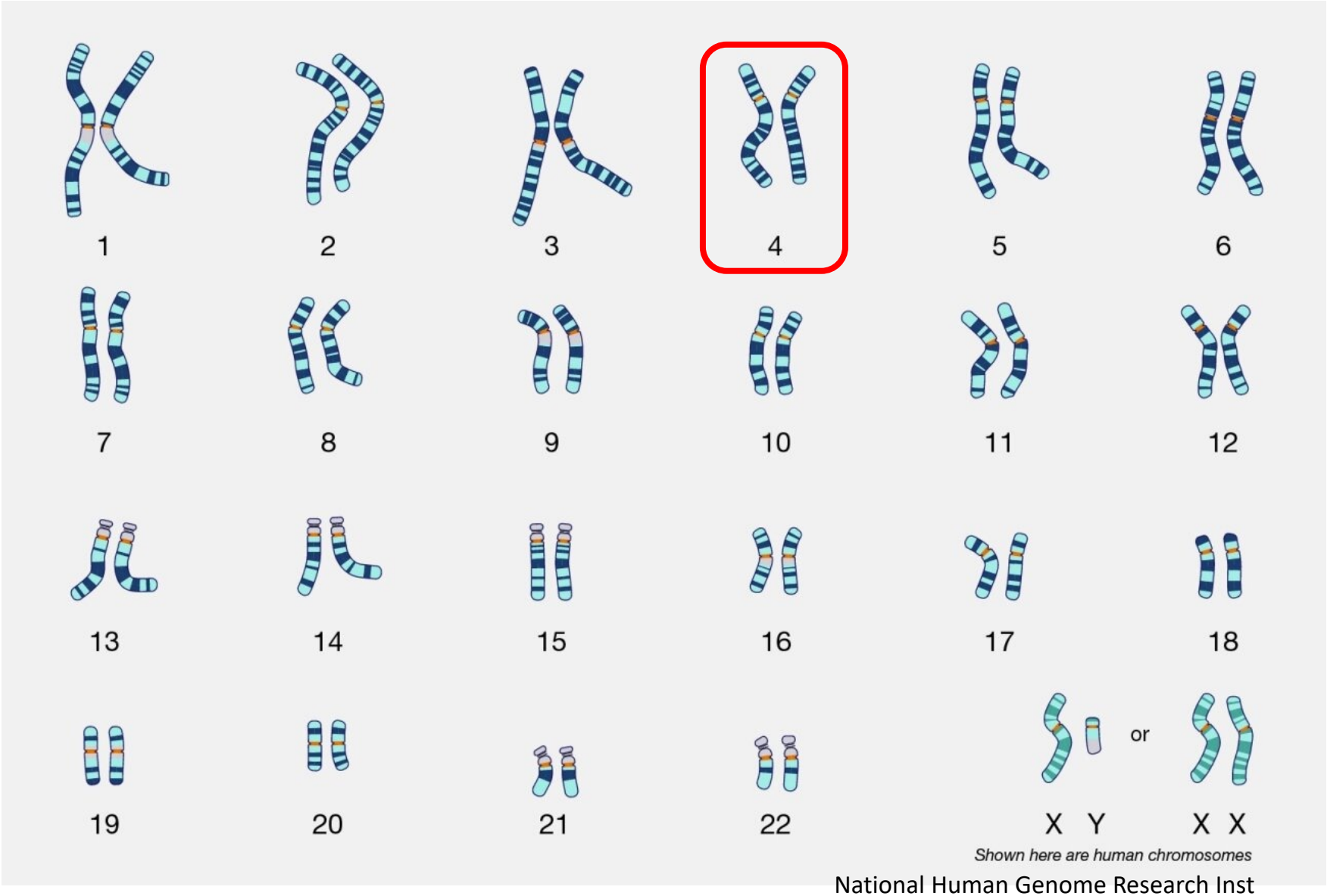
DNA methylation



Wang *Biomedicines* 2023

Human chromosomes



National Human Genome Research Inst

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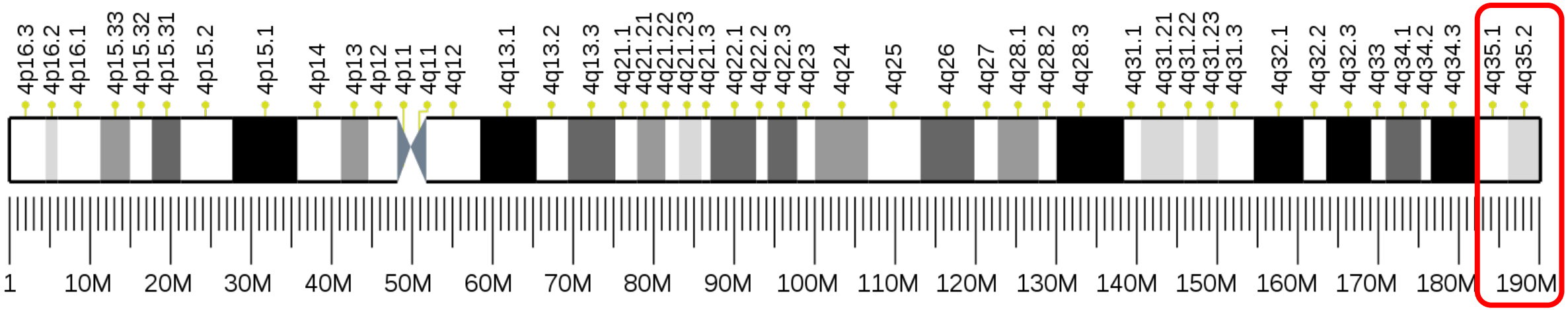
Chromosome 4



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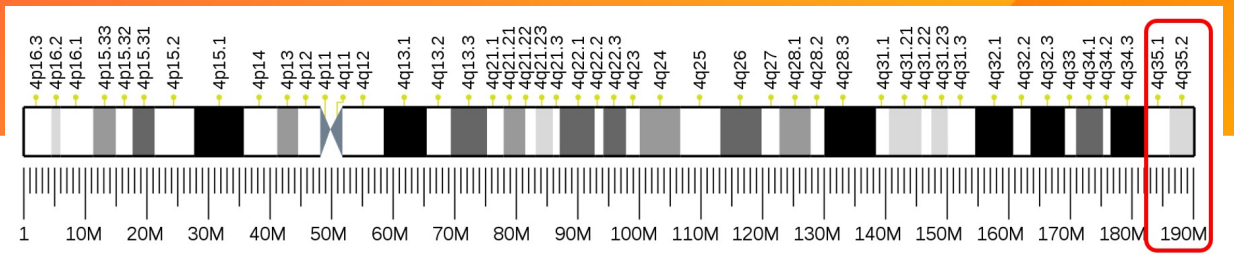
Chromosome 4q35



- *DUX4* is a gene normally only expressed in embryogenesis
- Heavily suppressed by methylation
- When expressed, is toxic to muscle

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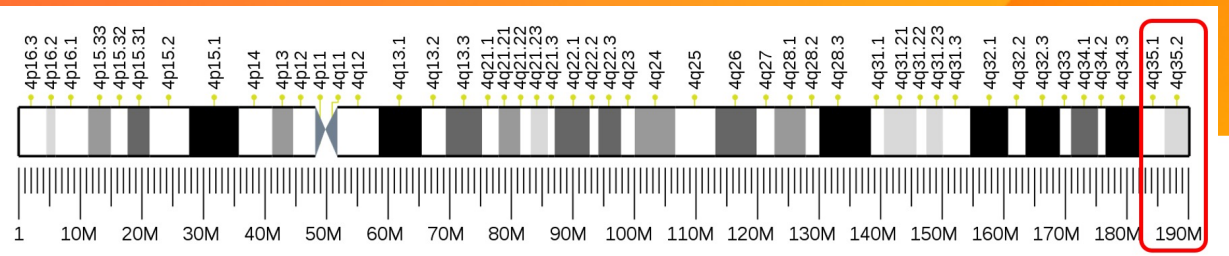
Chromosome 4q35



- If the D4Z4 region is deleted, there is less methylation of *DUX4* promoter and increased DUX4
- FSHD1: The most common cause of FSHD (95%)

FSHD1
Contraction of microsatellite region

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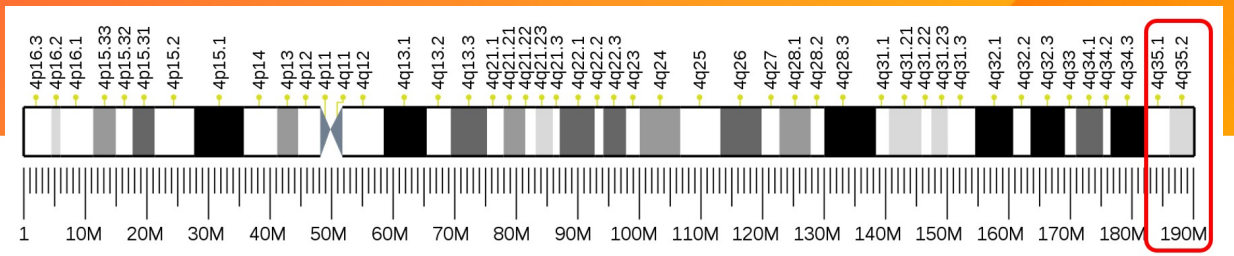
Chromosome 4q35



- Mutations that affect methylation of the D4Z4 region also cause FSHD, even without D4Z4 contraction

FSHD2
Failed de-repression
SMCHD1 mutation

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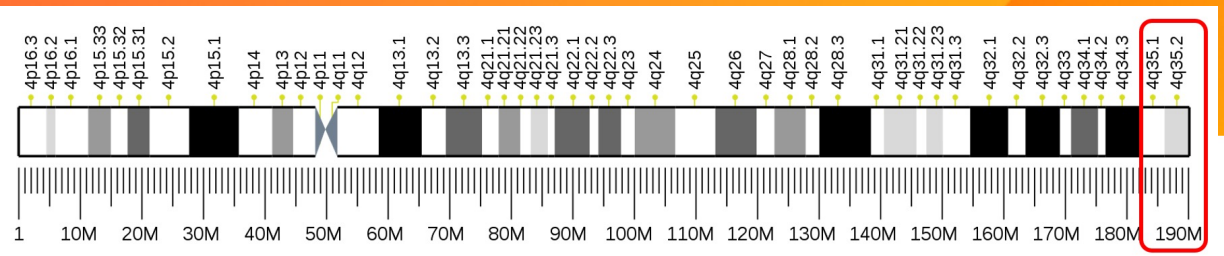
Chromosome 4q35



FSHD2
Failed de-repression
SMCHD1 mutation

CpG islands

D4Z4 microsatellite region

DUX4 / PAS

FSHD1
Contraction of microsatellite region

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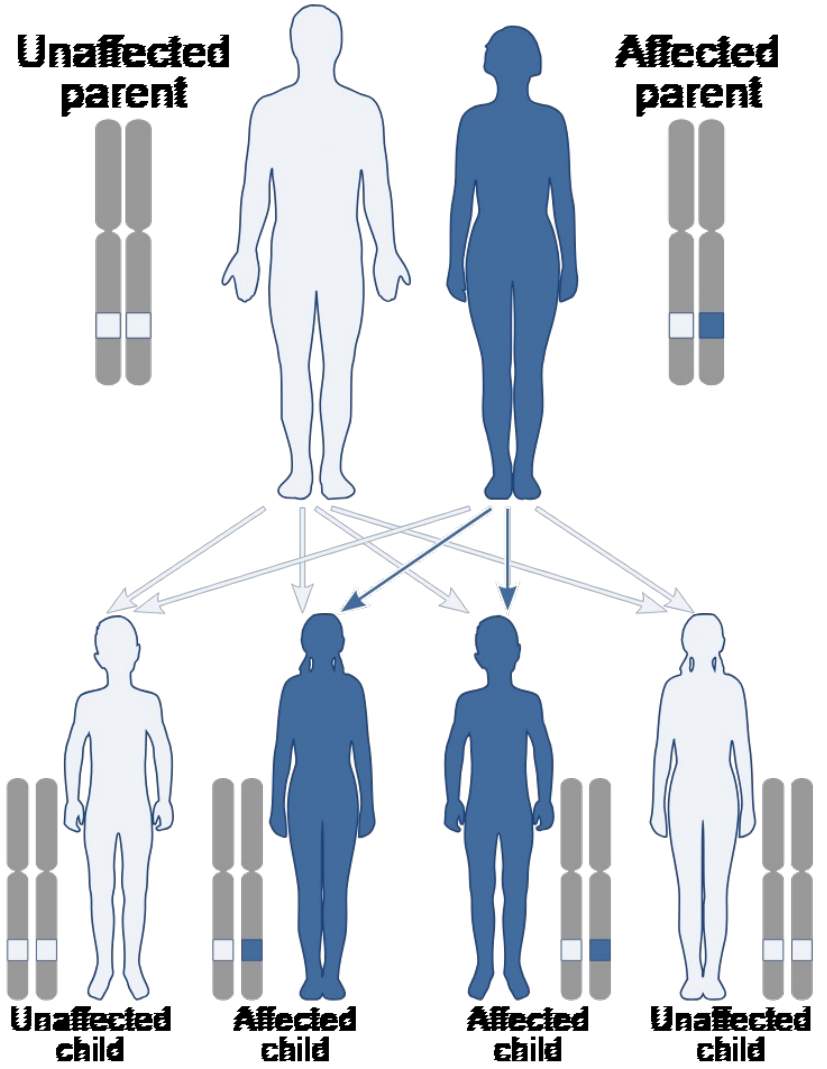
Implications of a genetic diagnosis

- Autosomal dominant inheritance
- Penetrance and onset age
- *De novo* cases

Autosomal dominant inheritance

- Only one mutant copy required
- 50/50 chance to pass on to each child



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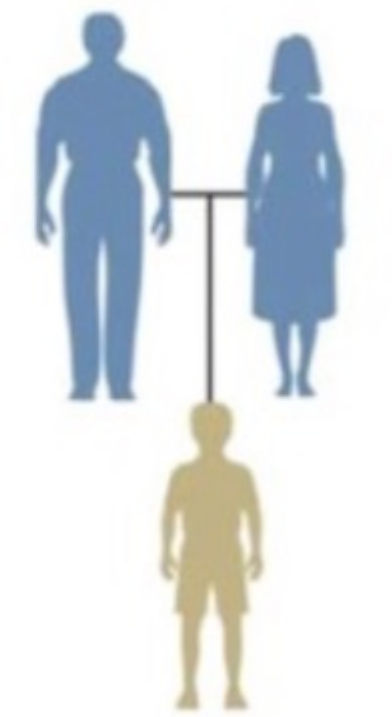
Penetrance and onset age

- Penetrance: likelihood of developing disease from a mutation
- Variable onset and severity
  - Usually onset age 15-30y
  - Approx 20% eventually require wheelchair
- Sex differences:
  - Penetrance 95% by age 30y in males (>females)
  - Males higher clinical severity scores (?)
  - Females more likely to progress to wheelchair (?)

De novo cases

- Mutation/contraction occurs spontaneously on permissive haplotype
- No family history will be present
- Up to 30% of FSHD cases



Wikipedia commons

FSHD diagnostic testing

- Genetic testing: D4Z4 microsatellite contraction to <11 repeats (or in <5% of cases, demethylation of D4Z4 without contraction)

- Decision to test is straightforward in symptomatic cases
- Difficult decision in presymptomatic cases

Diagnostic result

- Medical attention for symptoms
- Key questions
  - Disclosure: whether to disclose, when, to whom
  - Family planning
  - Financial planning
- Genetic counselling
  - Prior and after testing, but “never too late”

Testing for presymptomatic cases

To test…

- Family planning
- Screening in affected children (when?)
- Financial/life planning
- Reproductive technologies
- Psychological harms ("responsibility" vs "survivor guilt")

…or not to test

- Not treatable (yet)
- May not affect family decisions
- Insurance implications
- Access
- Psychological harms (uncertainty)

Testing for presymptomatic cases

- There is no “right” answer
- The answer is highly personal, individual, circumstantial
- Doctors and genetic counsellors as resources
  - Prior and after testing
- Virtual resources for genetic counselling (regional variation)

What to expect at genetic counselling

- On own or with other family
  - Can be a safe space for disclosure
- Review of family history
- Education
- Thought experiments
- Discussions of views and values
- No rush

Thank you