Limitations of Genome Analysis Methods

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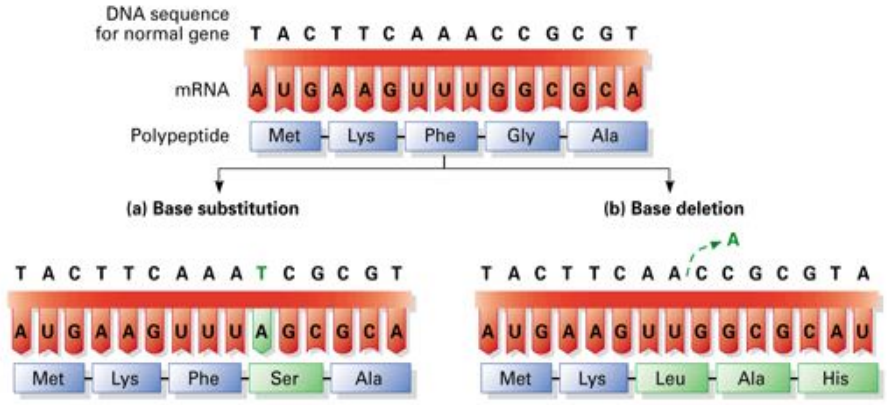
Difficult sequence variations

- Insertions and deletions
- Copy number variations
- Long and short repeat sequences
- Structural chromosomal rearrangements
- GC rich regions
- Intronic variants outside of the splice-site
- Epigenetic effects
- Mosaicism
- Regions with high sequence identity to other regions of the genome (e.g. paralogous genes and pseudogenes).

Insertions and deletions

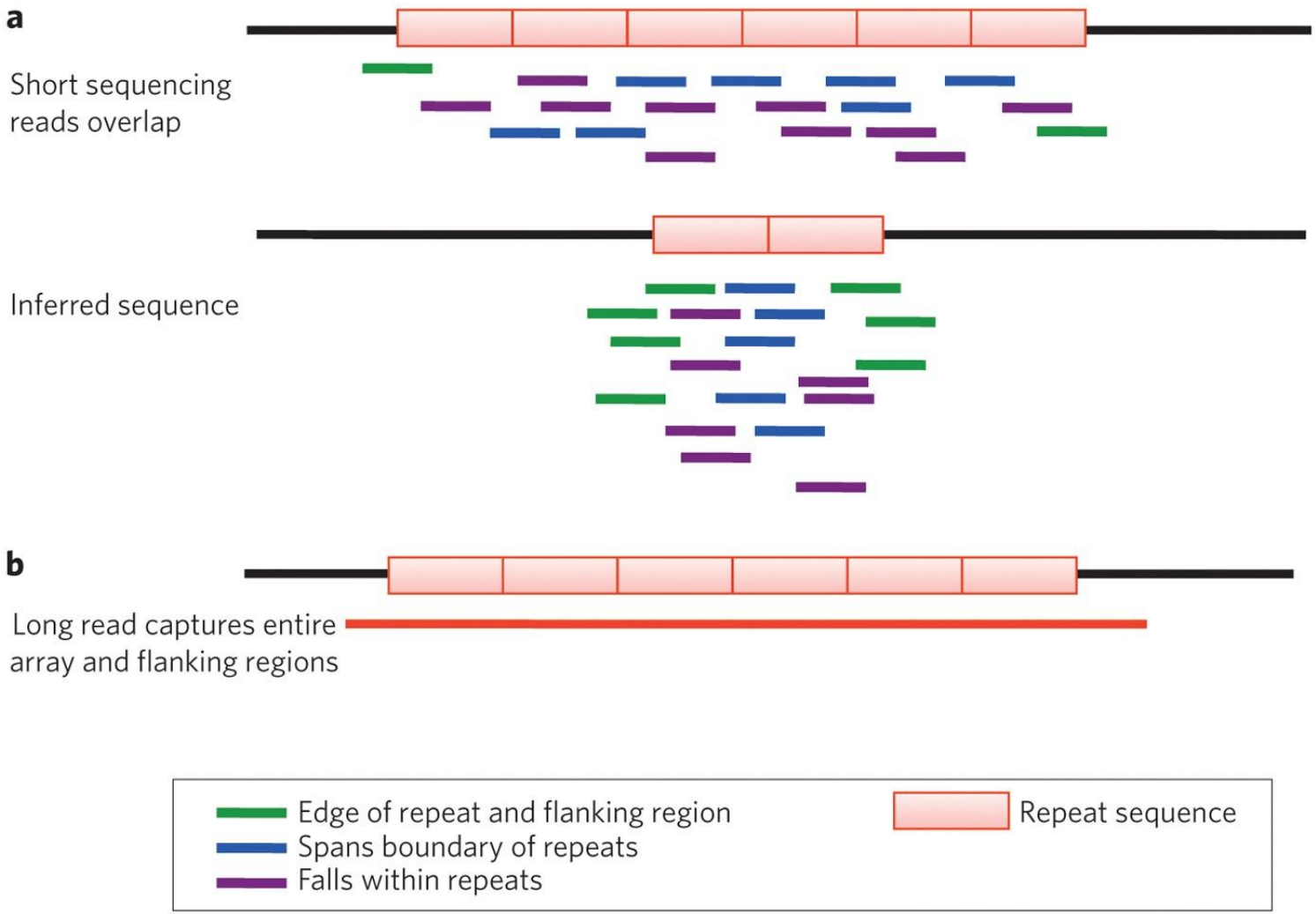
- NGS – big data
  - NGS relies on bioinformatic algorithms for automated variant calling
- Shortcomings of variant callers
  - Failure to detect somatic and germline complex indels
- Examples
  - Pindel-C introduced to detect the complex indels missed by GATK and VarScan
  - Amplicon Indel Hunter and ScanIndel for indels that lead to >5 bp net change in length
  - INDELseek for complex somatic and germline complex indels



https://bodell.mtchs.org/

Chun Hang Au et al (doi: 10.1186/s12864-016-3449-9)

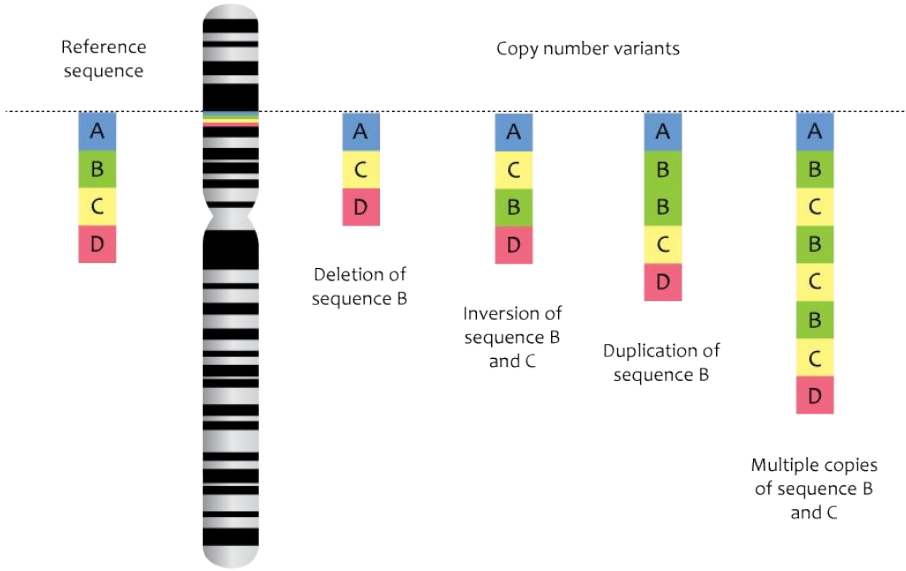
Long and short repeat sequences



Kellogg 2015 (https://www.nature.com/articles/nplants2015169)

Copy number variations (CNV)

- Whole Exome Sequencing (WES)
  - Covers only region of the genome containing the gene
  - Does not target 100% of the genes in the human genome
    - ~10% of exons may not be covered
    - Important CNVs may not be covered



Structural chromosomal rearrangements

- Detection of complex structural variation remains challenging
  - Variations with long reads

Chromosomal duplication

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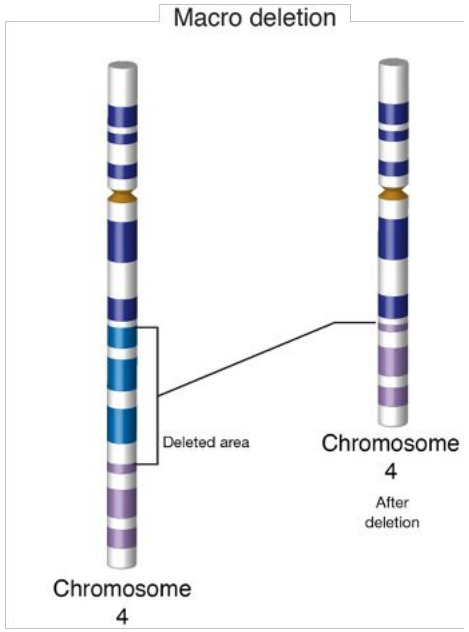

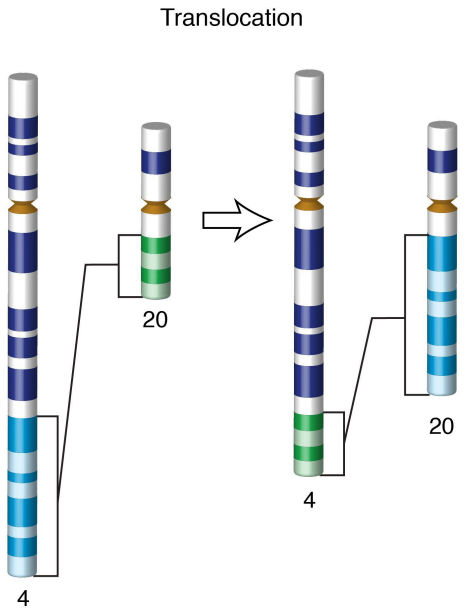

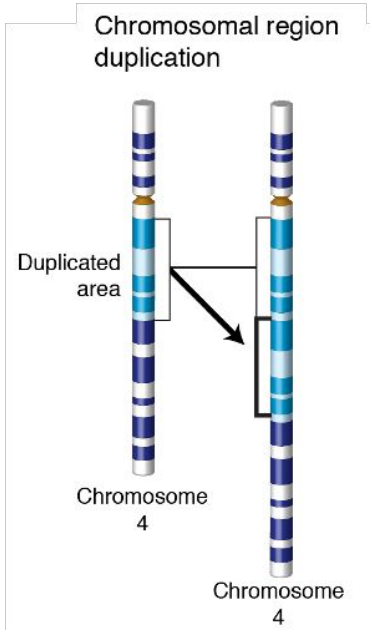

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ORIGINAL ARTICLE

Explanatory models for the cause of Fragile X Syndrome in rural Cameroon

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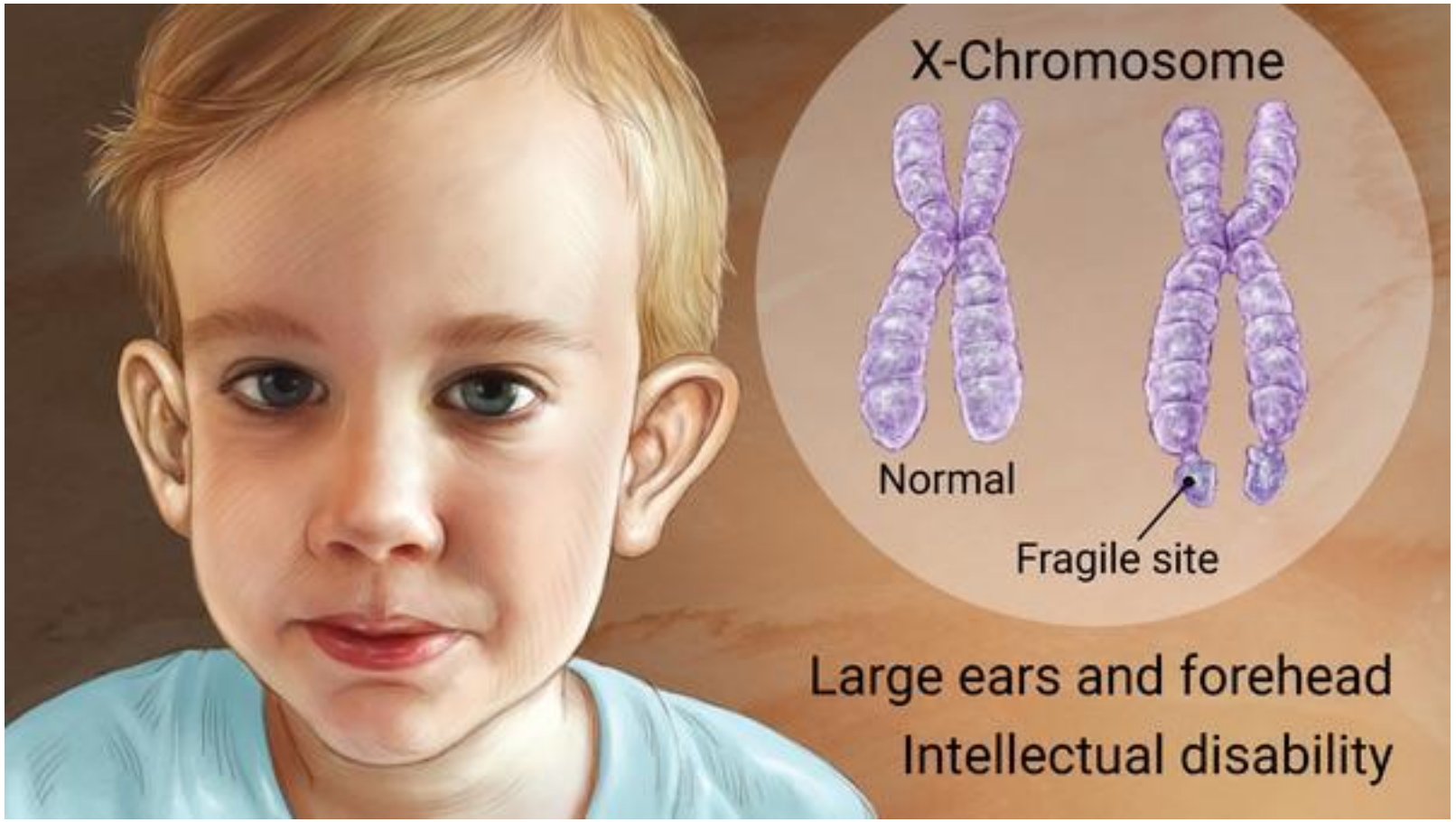
Abstract

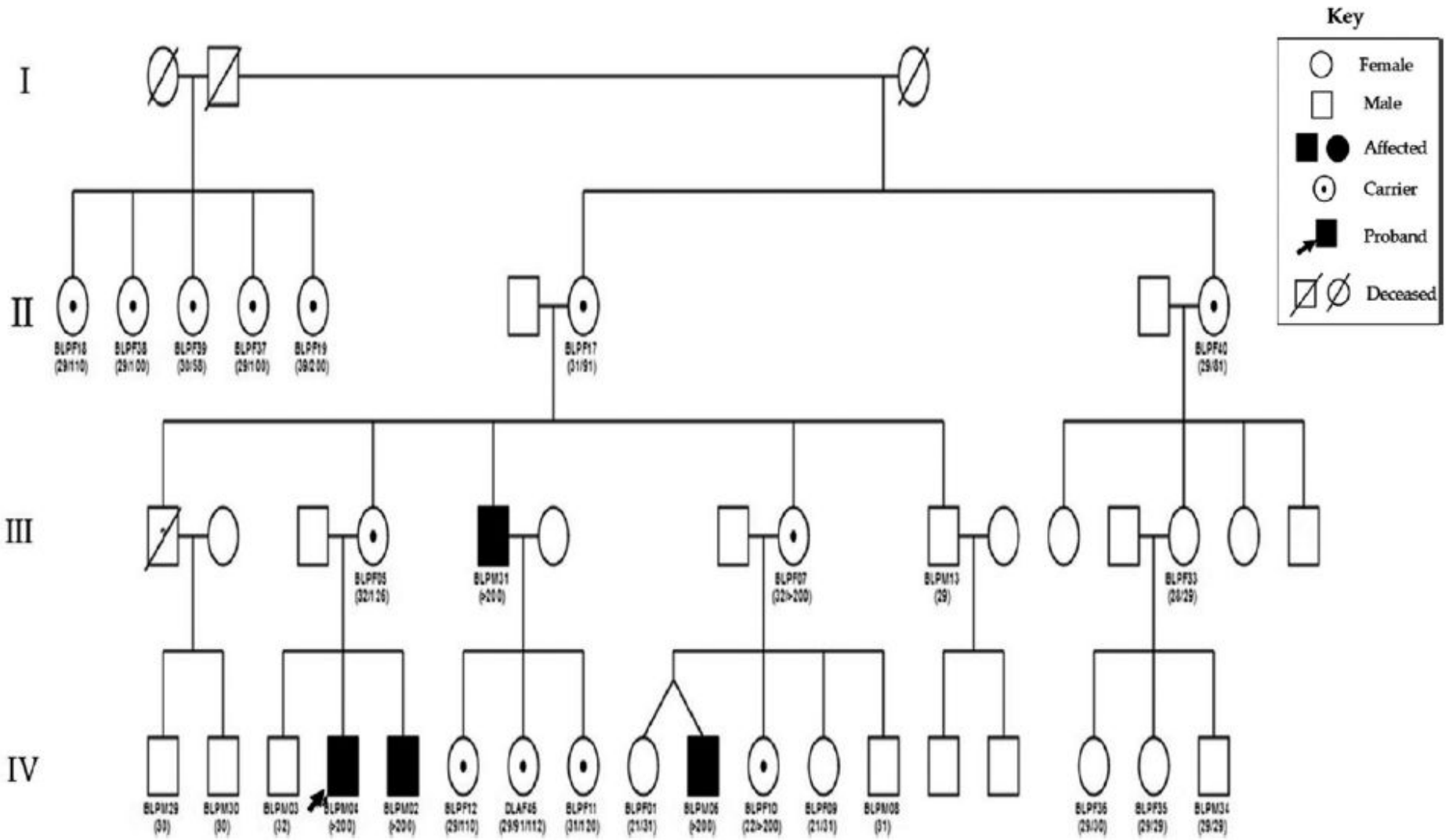
Among the myriad causes of intellectual disability (ID), Fragile X Syndrome (FXS) is the leading genetic cause. Yet, little is known of how people affected by this condition make sense of it. The present study aimed to investigate the explanatory models for the causes of FXS in an extended family mainly affected by this condi-

Fragile X syndrome (FXS)

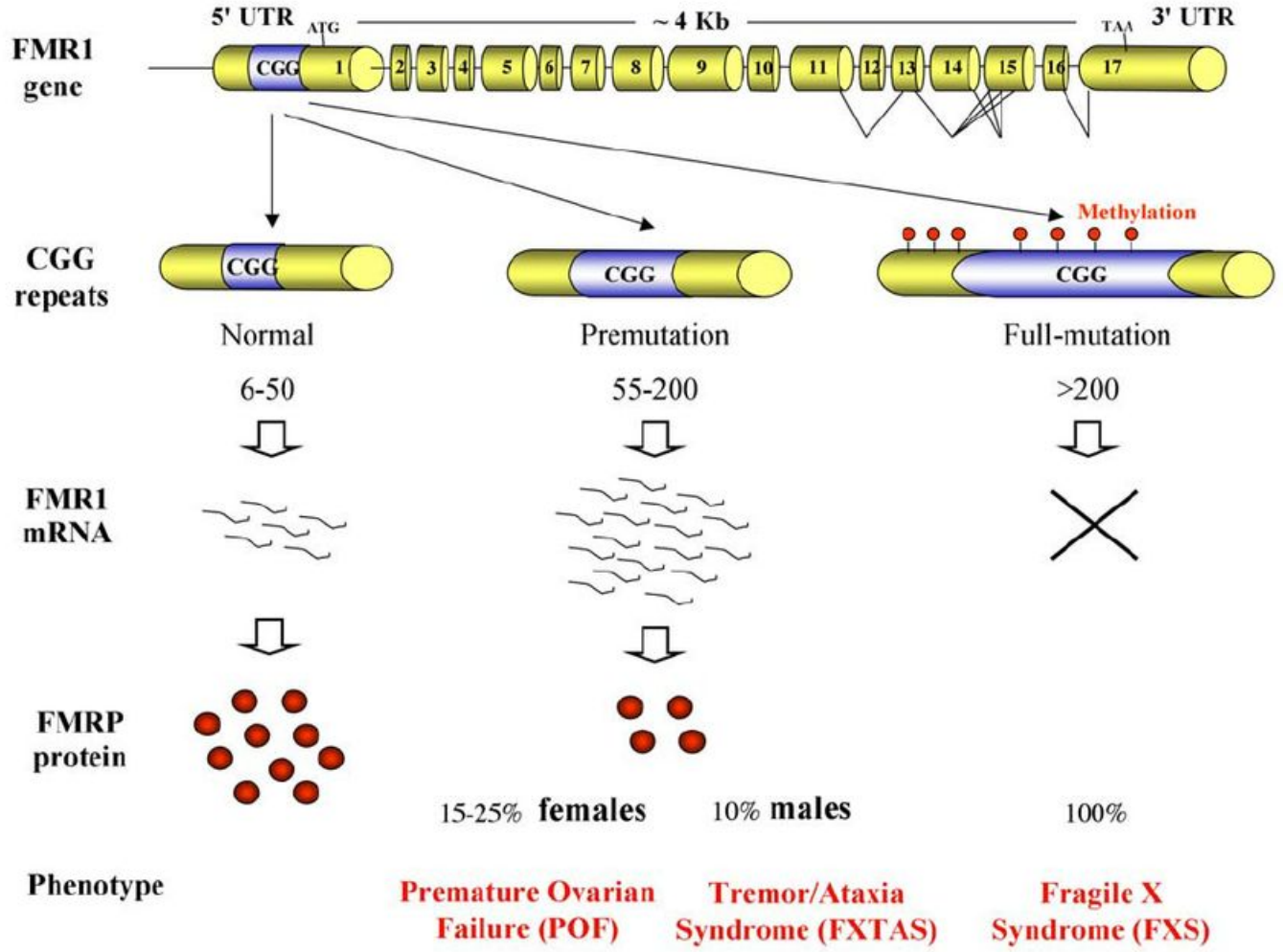


- Mild to severe intellectual disability
- Delays in talking
- Anxiety
- Hyperactive behavior
- Seizures

Dominant X-linked mode of inheritance



Molecular mechanism of FXS



Francesca Zalfa and Claudia Bagni, 2004

NGS limitations of *FMR1* screening

- Cytosine-Guanine-Guanine (CGG) repeat sequence
  - Difficulty in WES capture of the region

- Method used the Cameroonian case
  - AmplideX FMR1 PCR kit and capillary electrophoresis
  - Fragment analysis


MERRY
CHRISTMAS