

# Rett Genetics: 220 today's goals

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- Understand the genetics of RTT
- Understand what is meant by mutation
- Understand the basis of the complex relationship between mutation and symptoms.



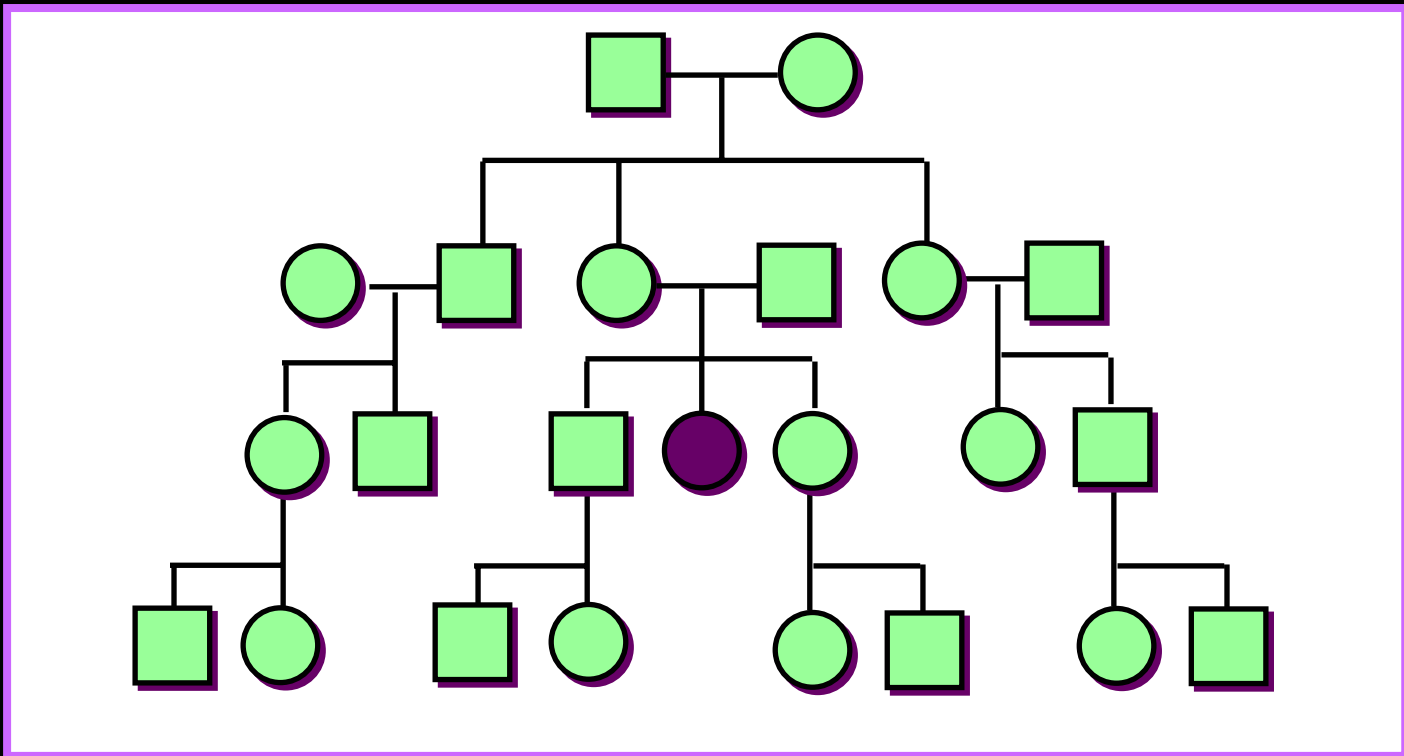
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302-651-6804

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**Most cases of Rett syndrome  
are GENETIC  
but  
NOT usually inherited**



# Rett syndrome is usually **sporadic** in families



>99% of cases have no  
history



# Chromosomes

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Humans: 46 chromosomes

23 pairs

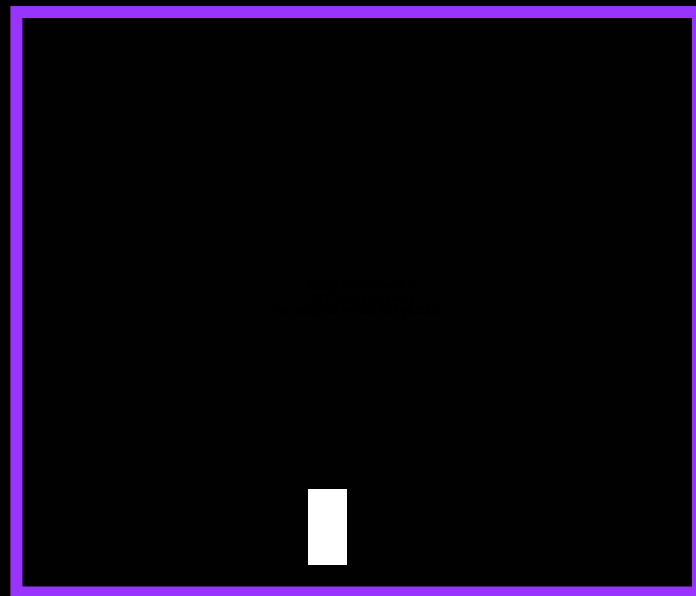
22 pairs of autosomes

1 pair sex chromosomes

X and Y chromosome

XX: female

XY: male



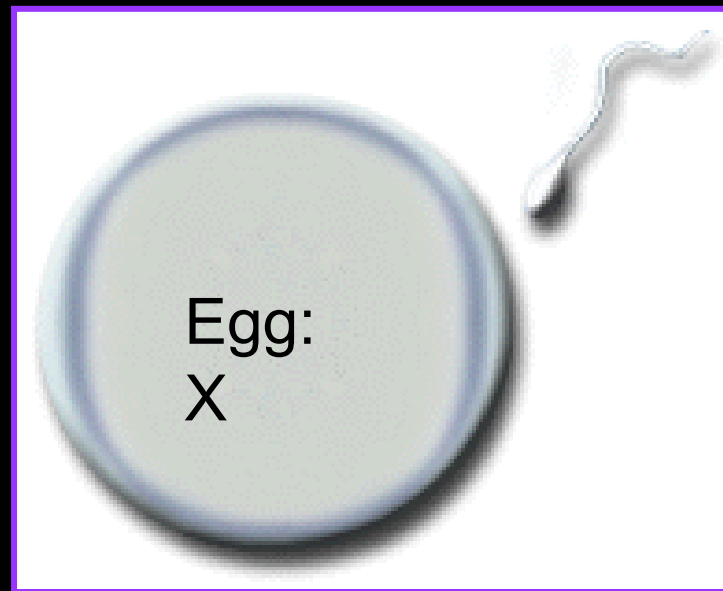
One copy of each pair from each parent

Each carries thousands of genes



# The sex chromosomes determine gender

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Sperm:  
X or Y

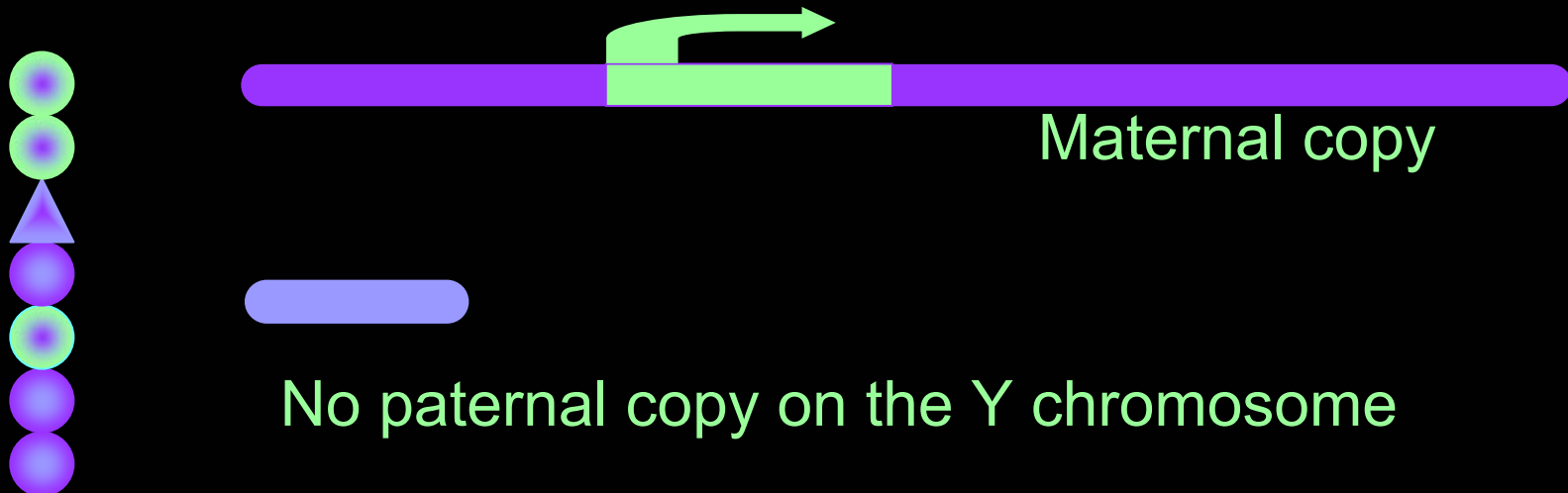
Egg:  
X



# X linked or Sex linked inheritance

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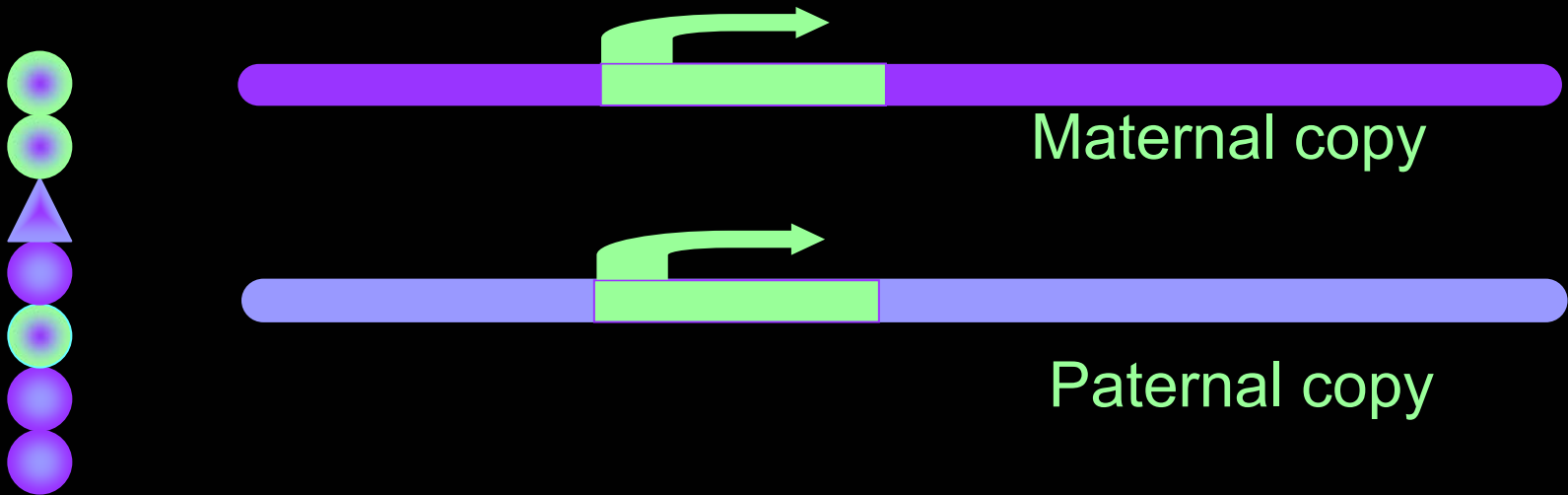
Males (XY) have only one copy of genes on the X chromosome



# X linked or Sex linked inheritance

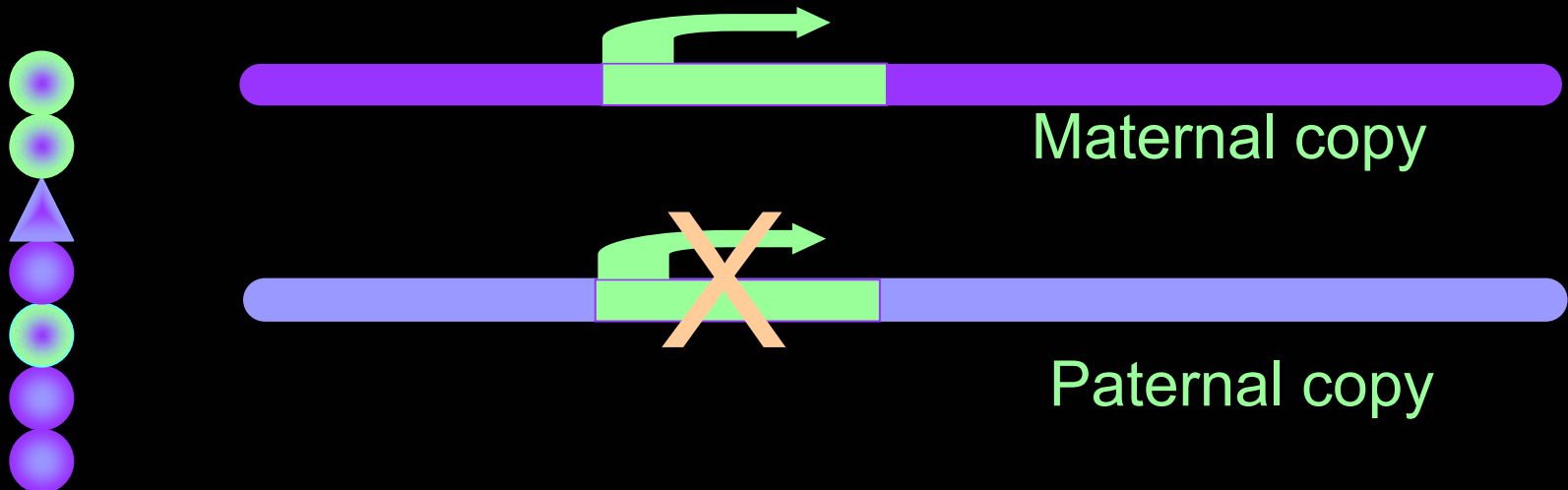
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Females have two copies of genes on the X chromosome



# X linked or Sex linked inheritance

But ..... we use only one copy per cell for most of them- the process of turning off one copy of the X chromosome in each cell is called **X-inactivation**

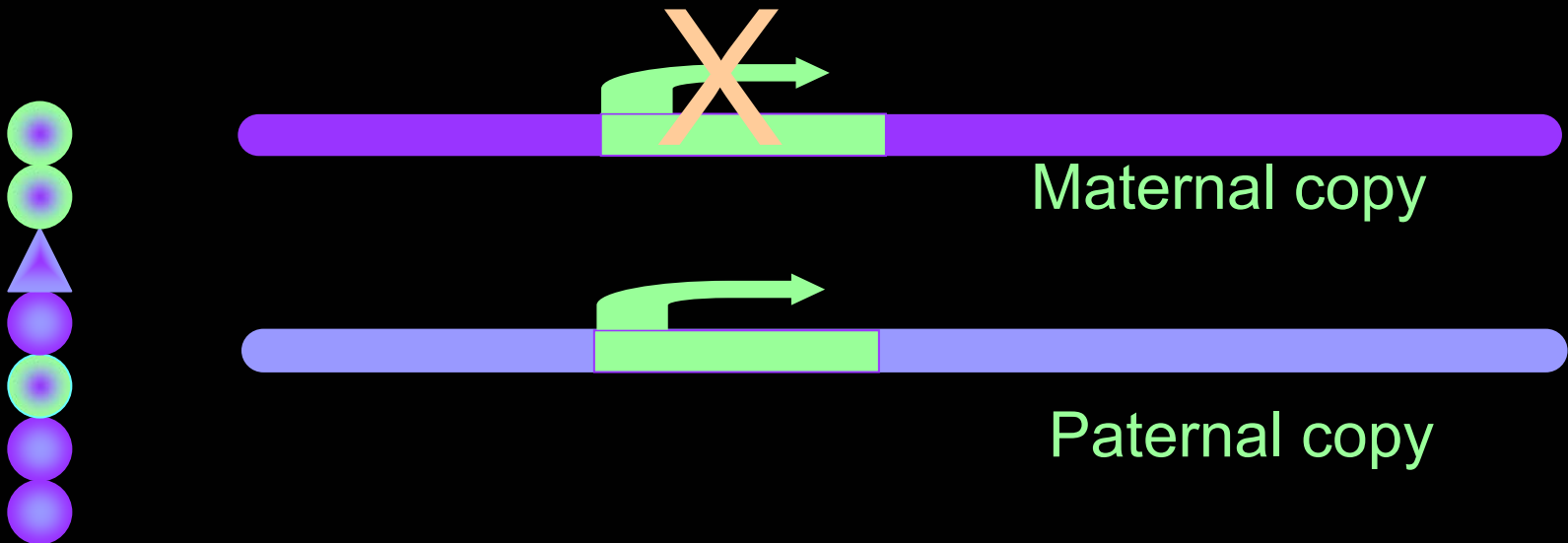




# X linked or Sex linked inheritance

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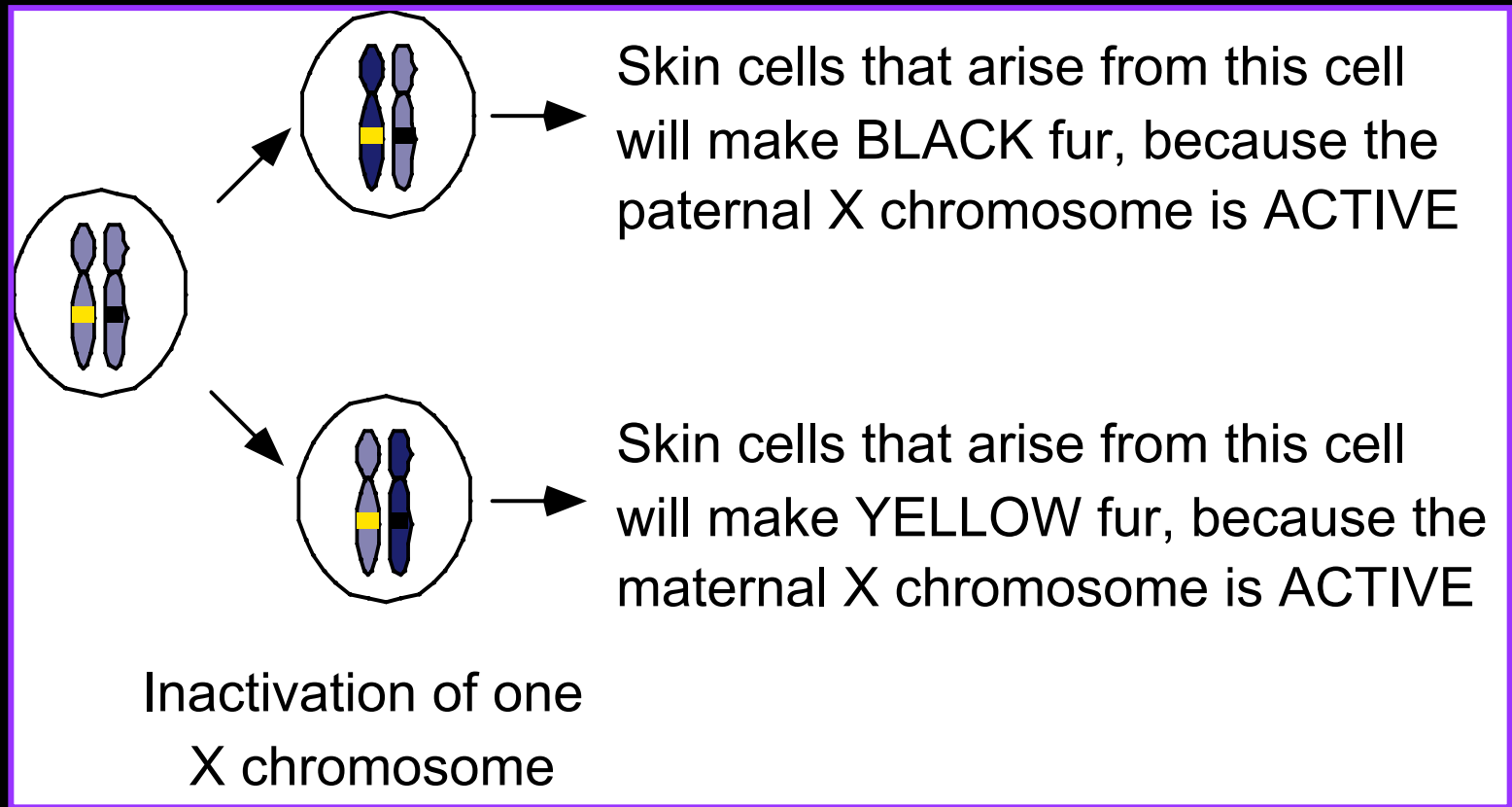
- Generally random (equally likely for mat vs. pat X)
- Happens very early in development (before 2 weeks after conception)
- Maintained in subsequent generations of cells



# X-chromosome inactivation

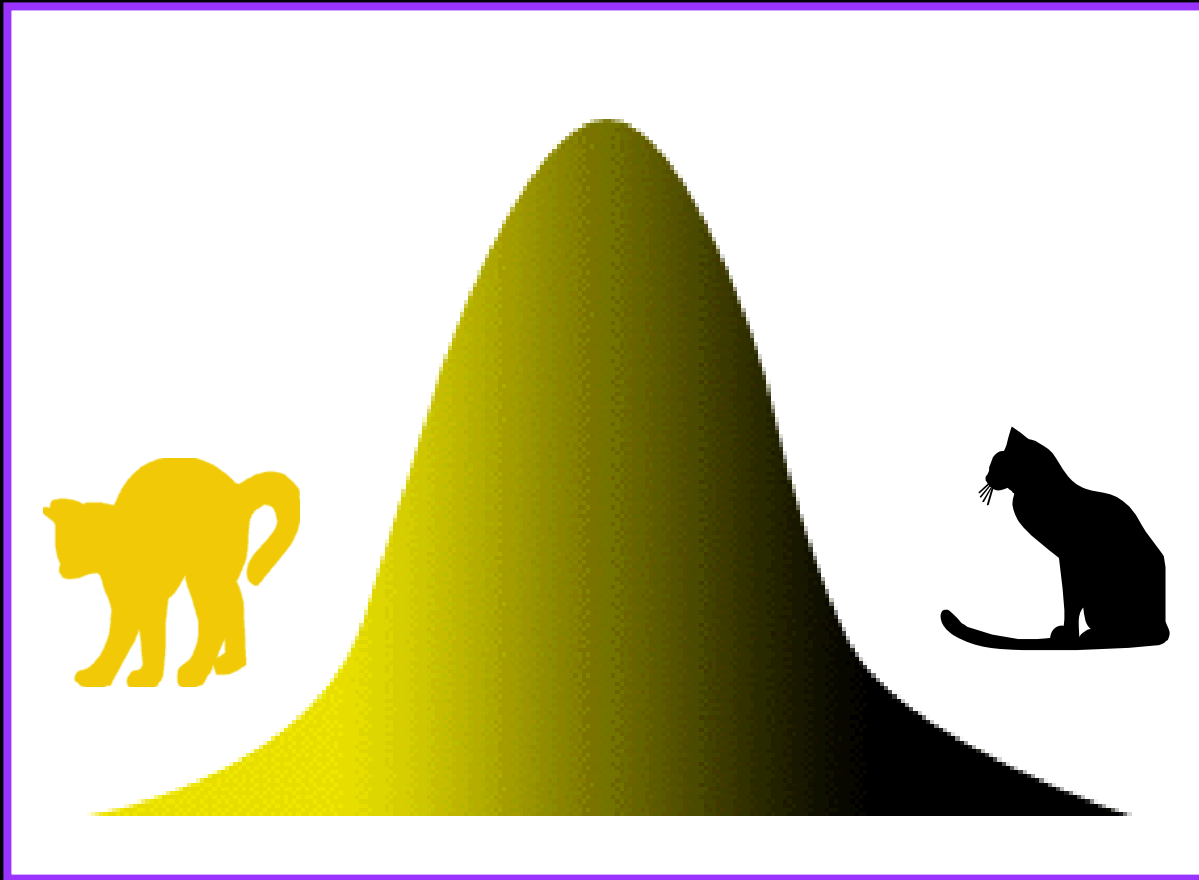


# X-Chromosome Inactivation: lessons learned from calico cats



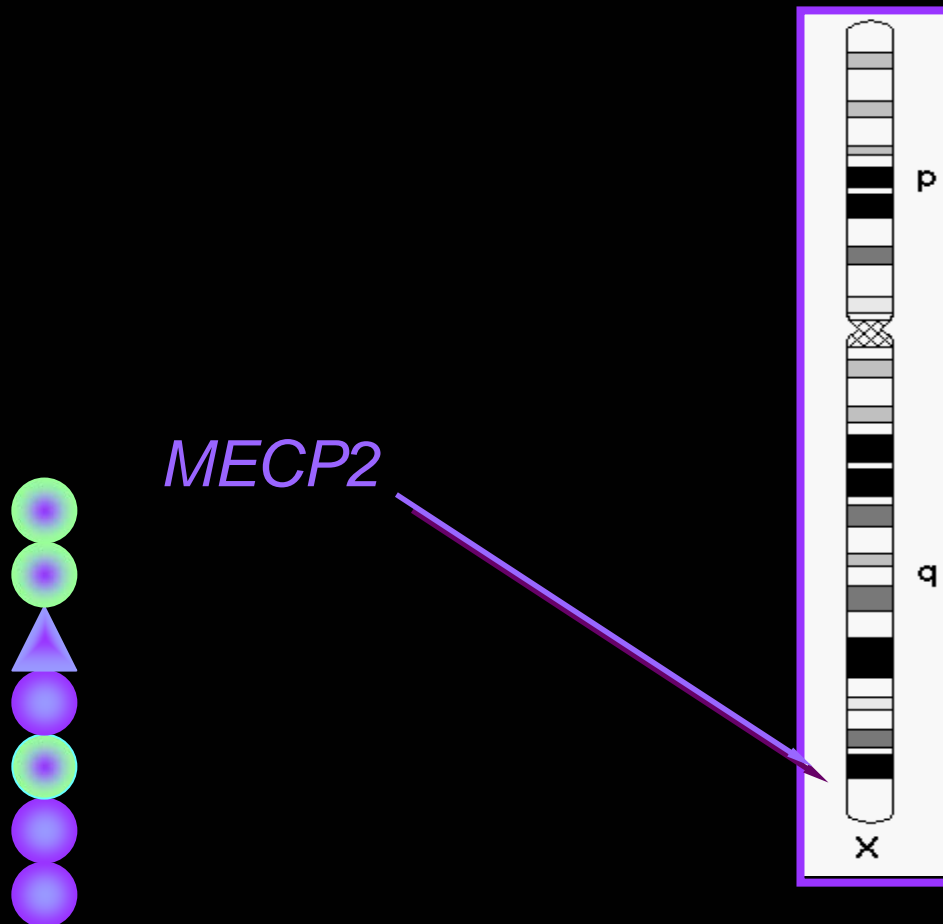
# X-chromosome inactivation

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# Rett syndrome is caused by mutations in *MECP2*

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*MECP2*

Amir et al, 1999

# Genes are like recipes

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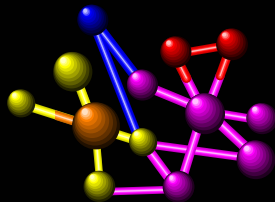
Gene

+

RNA

=

Functional Protein



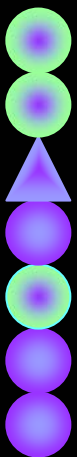
Ingredient list

+

Instructions

=

Food



# What is a mutation?

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- A **gene**: segment of DNA that encodes information on how to build a protein. The code used is only four nucleotides or bases (ACGT)
- A **mutation** is like a **typographical error** that occurred during the copying of the gene
- It causes the protein made from the gene to form *incorrectly*
- Annotated at DNA or protein level



# MECP2 gene organization

Large gene (~85-90,000 base pairs)

The coding sequence for the protein is ~1500 nucleotides, which are split into four segments or exons





# Piña Colada

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- In a blender, combine:
  - 4 oz cream of coconut
  - 4 oz pineapple juice
  - 3 oz light rum
  - 2 cups of ice



- Blend well and serve, garnish with a cherry. Serves 2.



# Missense: Piña Colada



- In a blender, combine:
  - 4 oz cream of coconut
  - 4 oz pineapple juice
  - 8 oz light rum
  - 2 cups of ice

*Missense mutation: a substitution that does alter the product*

- Blend well and serve, garnish with a cherry. Serves 2.

- Common missense mutations: R106C, R133C, T158M, R306C



# Nonsense: Piña Colada

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- In a blender, combine:

- 4 oz cream of coconut
- 4 oz pineapple juice
- 8 oz light. rum
- 2 cups of ice

*Nonsense mutation:  
a change in the gene  
that causes an  
incomplete protein to  
be formed*

- Blend well and serve, garnish with a cherry.  
Serves 2.

- Common nonsense mutations: R168x, R255X,  
R270X, R294X



# Frameshift: Piña Colada



- In a blender, combine:

- 4 oz cream of coconut

- 4 oz pineapple juice

- 8 oz light rum

- 2 cu~~z~~p so fic

- eBlen dwel lan dserv e, garnis hwit h

- Common frameshifts: 806delG, 3' deletions

*Frameshift mutation:  
insertion or deletion  
that changes the  
reading frame and  
affects the final  
product*



# Piña Colada



- In a blender, combine:

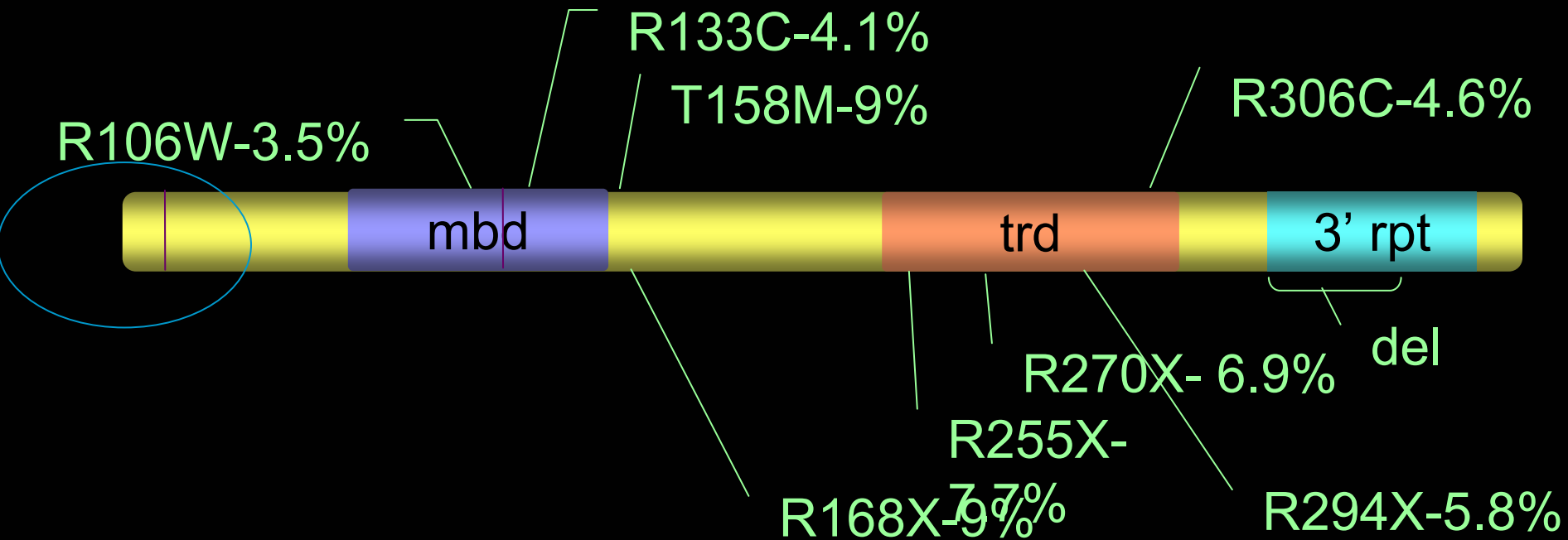
- 4 oz creme of coconut
- 4 oz pineapple juice
- 3 oz light rum
- 2 cups of ice

*Polymorphism: a benign change in the gene that does not alter the protein product*

- Blend well and serve, garnish with a cherry. Serves 2.



# Common mutations



- C-> T changes in DNA sequence
  - Nonsense and missense mutations
- Frameshifts (C-terminal deletions)

# Mutation studies

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- *MECP2* mutations
  - ~95% sporadic cases of classical Rett syndrome
  - Decreased in atypical cases (3/4)
  - <1/10 Rett-like boys
  - Phenotype database - InterRett

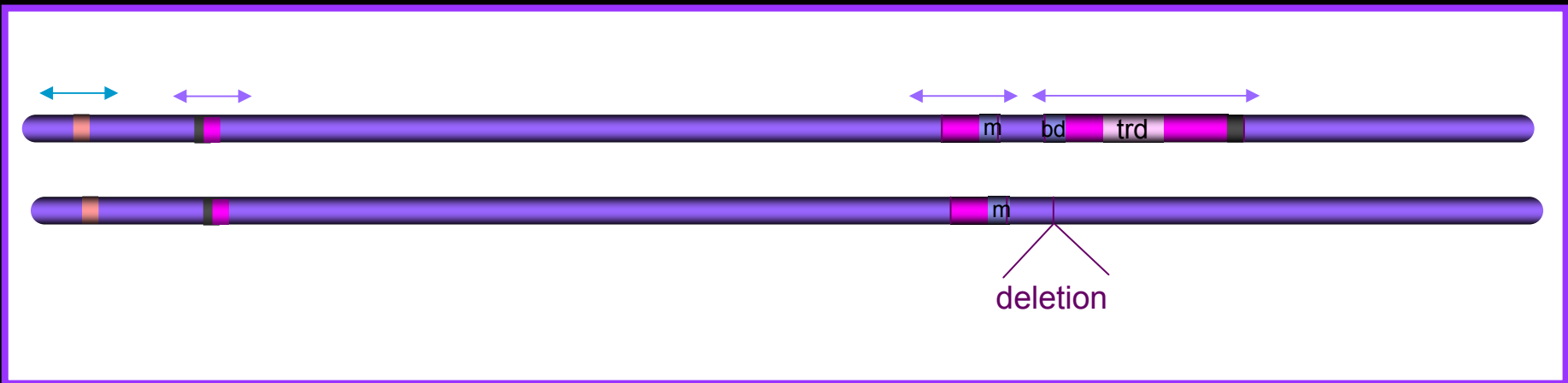


# How do they test for mutations?

Most labs focus on the coding region

Examine each base of the DNA sequence.

If a big piece is missing, it could be missed by this approach.





# Interpreting your daughters' mutation results

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- Gene mutation
    - Change in the DNA
    - Insertions and deletions
  - Protein effect
    - Change in the protein product
- 316C-T, 473C-T, 502C-T, 763C-T, 808C-T, 880C-T, 806DelG, various deletions
  - R133C, T158M, R168X, R255X, R270X, R294, G269fs



# “Negative” mutation results.

- For patients without identified mutation in *MECP2*
  - Could be duplication or deletion of the gene depending on how the mutation screening was done
- What should you do?
  - Examine the mutation analysis report
  - When was it done?
    - The earliest studies did not screen for all the types of mutations that are screened now.
  - What approach did they use?
    - Just sequencing?
    - Did they do MLPA or Southern blot to look for deletions or duplications?
  - Did they screen the whole gene?
  - Talk to your geneticist!

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Rett syndrome  $\neq$  MECP2 mutation

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MECP2 mutation  $\neq$  Rett syndrome



5% of girls with Rett syndrome will have no detectable mutation

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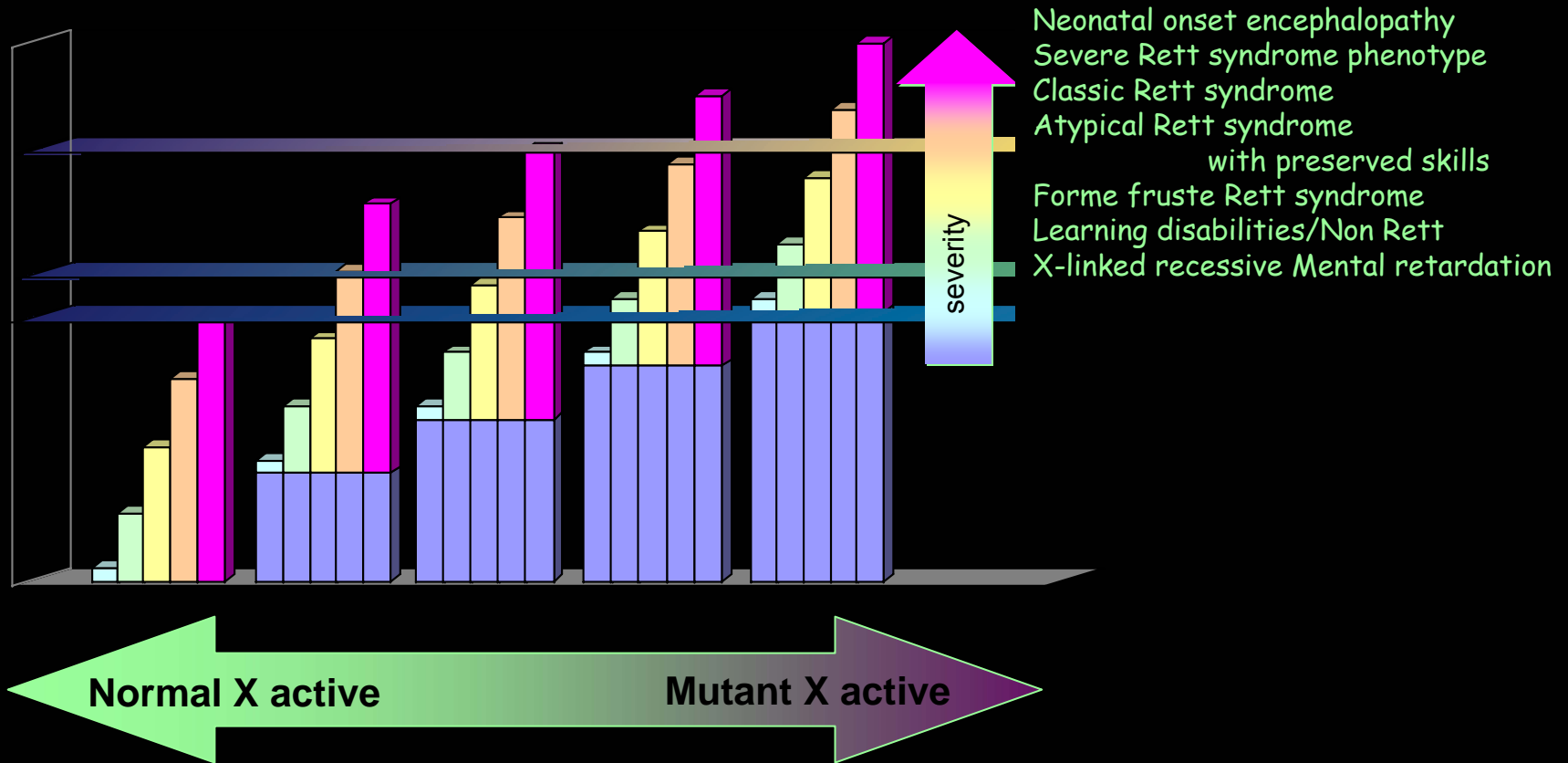
Why are the symptoms so different in girls who carry the same mutation in the gene ?



# Every female is different



# Mutation and XCI influence outcome



# Symptoms resulting from *MECP2* Mutations

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## Girls

Rett Syndrome

Classical

Atypical

Normal Females

Skewed X inactivation

Mild learning disabilities

Autism

Angelman syndrome

## Boys

Severe, newborn onset

Rett syndrome

- Klinefelter (XXY)
- Mosaicism
- ‘Mild’ Mutations

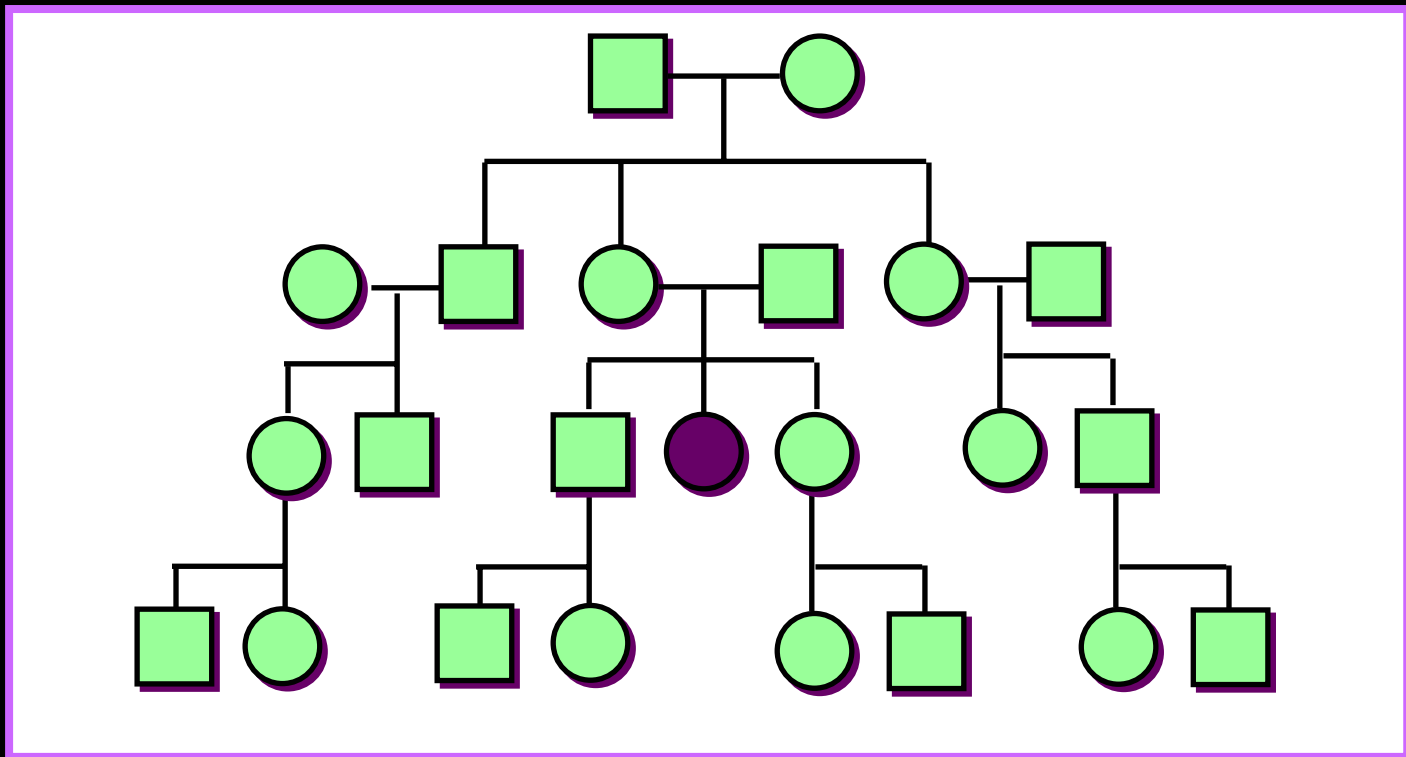
Familial mental retardation  
(X-linked recessive)

w/ neurologic symptoms

w/ psychiatric symptoms



# Why is Rett syndrome sporadic?



>99% of cases have no  
history





# *De novo* mutations

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- Mutation occurs during formation of egg or sperm
- Not carried by either parent in the rest of their cells
- May be only in one germ cell or a small group of them.
- More common in sperm



# Recurrence Risk Counseling-Rett syndrome

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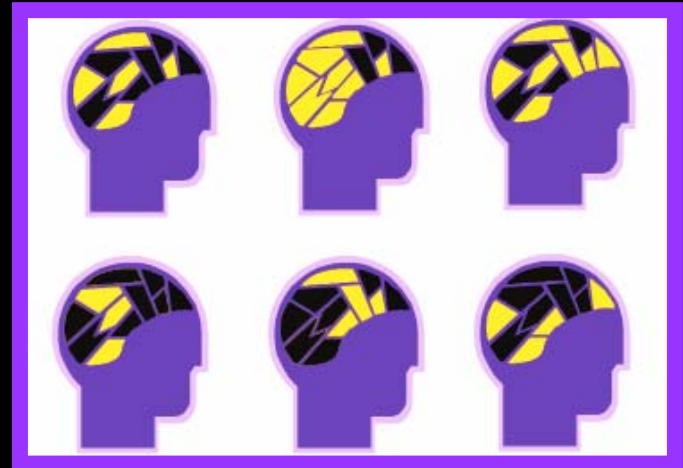
- Risk of second affected child <1%
  - Germline mosaicism (either parent)
  - Carrier mothers with skewed X-inactivation
- Recommendations:
  - Mutation analysis for mothers if they are planning more pregnancies
  - Prenatal Diagnosis (amniocentesis or CVS)
    - Can only be done if mutation is known
    - Screen Male or Female pregnancies



# Should we do X-inactivation studies

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- Not usually useful clinically as predictor of symptoms unless the child is an “outlier” clinically.
- Blood may not reflect regional changes in brain.

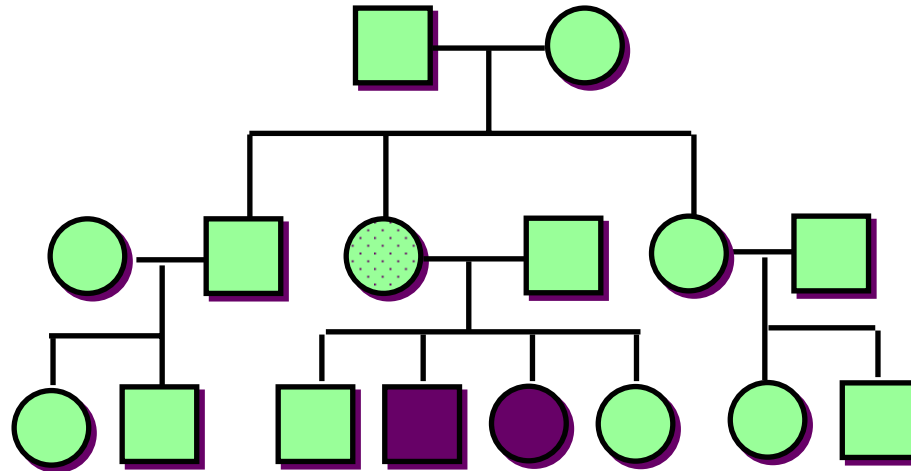


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So, how can there be  
recurrences in some  
families??



# Skewing of X inactivation in Mothers

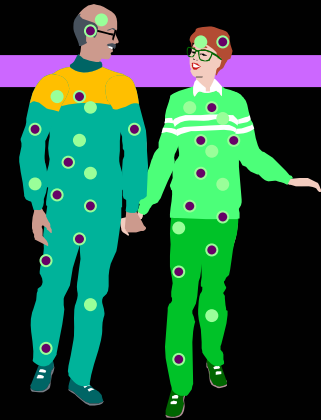
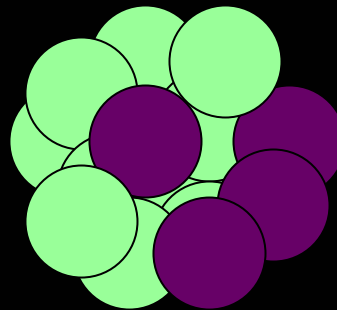
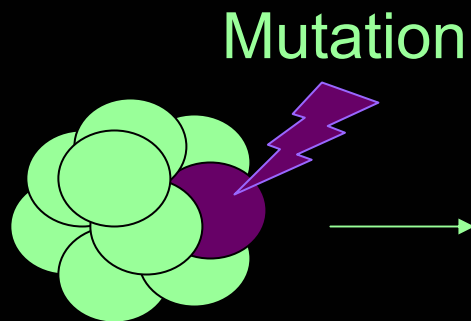


Mothers may carry a mutation silently by having “skewed” X-chromosome inactivation

Recurrence risk rises to 50% from <1% so it is important to know.

Take home message: Mothers who are planning to have more kids should be screened for a mutation in the gene.

# Mosaicism



Somatic mosaicism



Germline mosaicism



# Recurrence risk counseling

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- Normal brothers don't need to be screened
- Normal sisters can carry a mutation silently (rare, but can happen)
- Can screen normal sisters of affected child when they are of reproductive age



# Thanks!!

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- IRSF
- Rett families
- Naghmeh Dorrani
- Alan Percy
- John Christadoulou
  - Rettbase
- Paige & Kathryn

