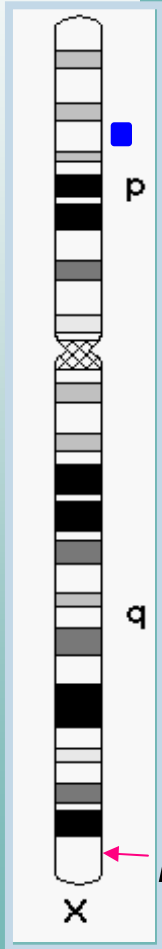


Rett Genetics 635: Goals

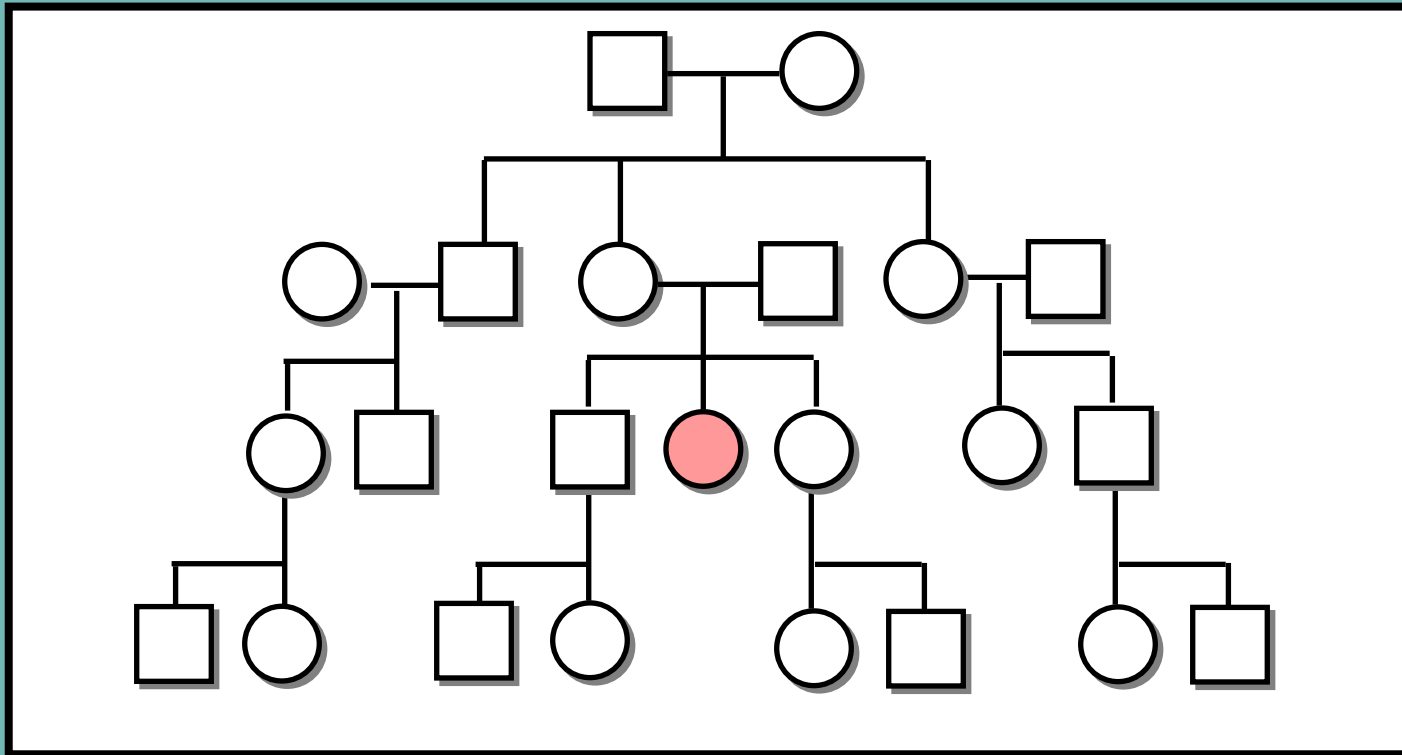


- Understand the genetics of RTT
- Understand what is meant by mutation
- Understand the basis of the complex relationship between mutation and symptoms.

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

Rett syndrome usually occurs **sporadically** in a family



>99% of cases have no family history

Chromosomes

Humans: 46 chromosomes

23 pairs

22 pairs of autosomes

1 pair sex chromosomes

X and Y chromosome

XX: female

XY: male

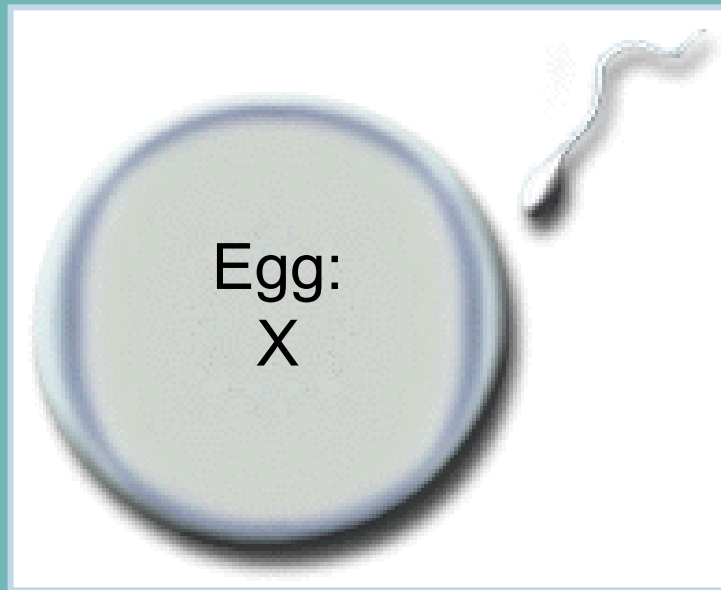
One copy of each pair from each parent

Each carries thousands of genes

QuickTime™ and a
TIFF decompressor
are needed to see this picture.



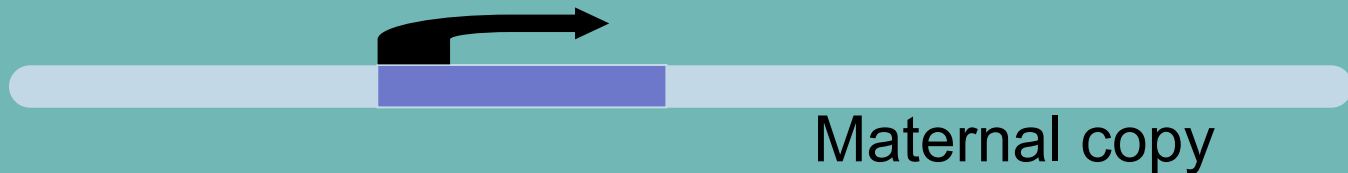
The sex chromosomes determine gender



Sperm:
X or Y

X linked or Sex linked inheritance

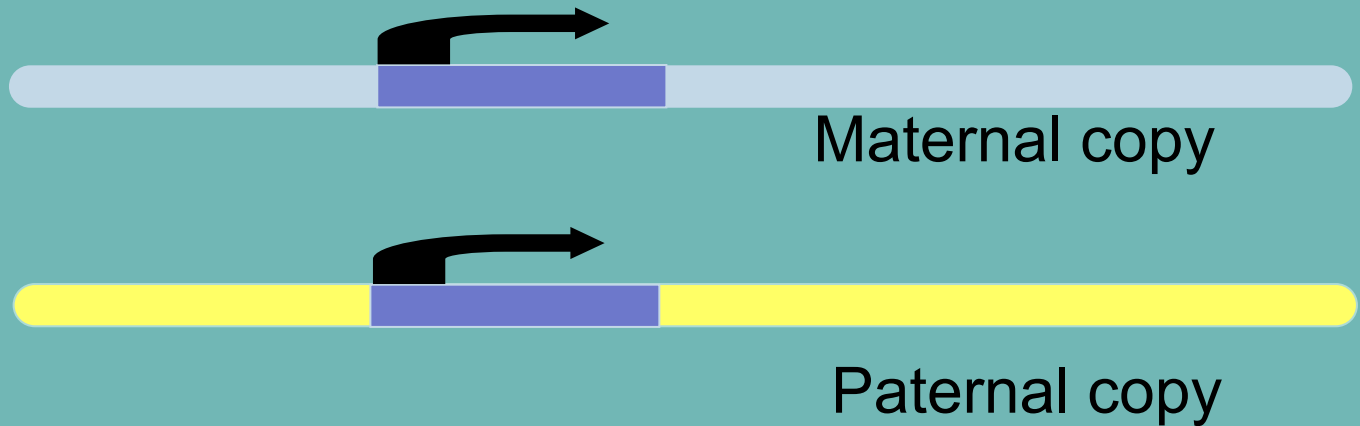
Males (XY) have only one copy of genes on the X chromosome



No paternal copy on the Y chromosome

X linked inheritance

Females have two copies of genes on the X chromosome



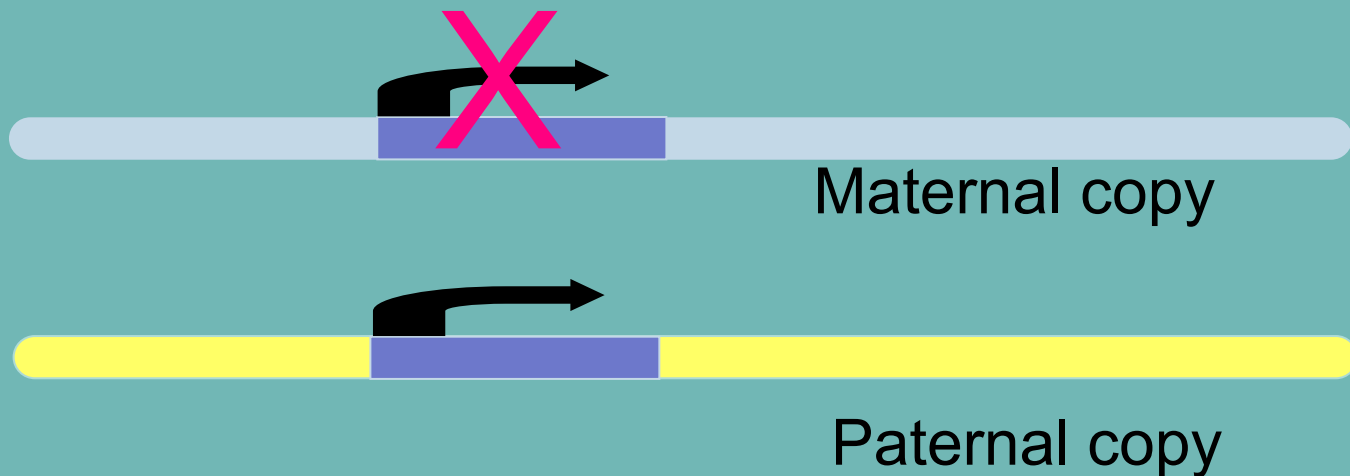
X inactivation

In each cell, one of the X chromosomes is silenced: **X-inactivation**

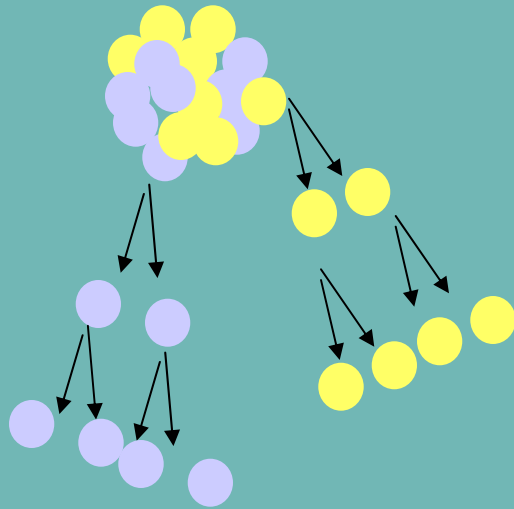


X-inactivation

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



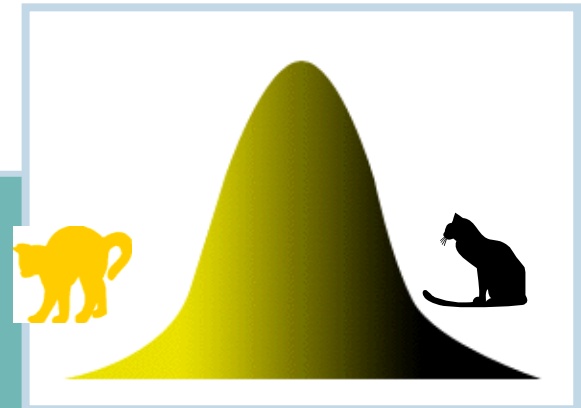
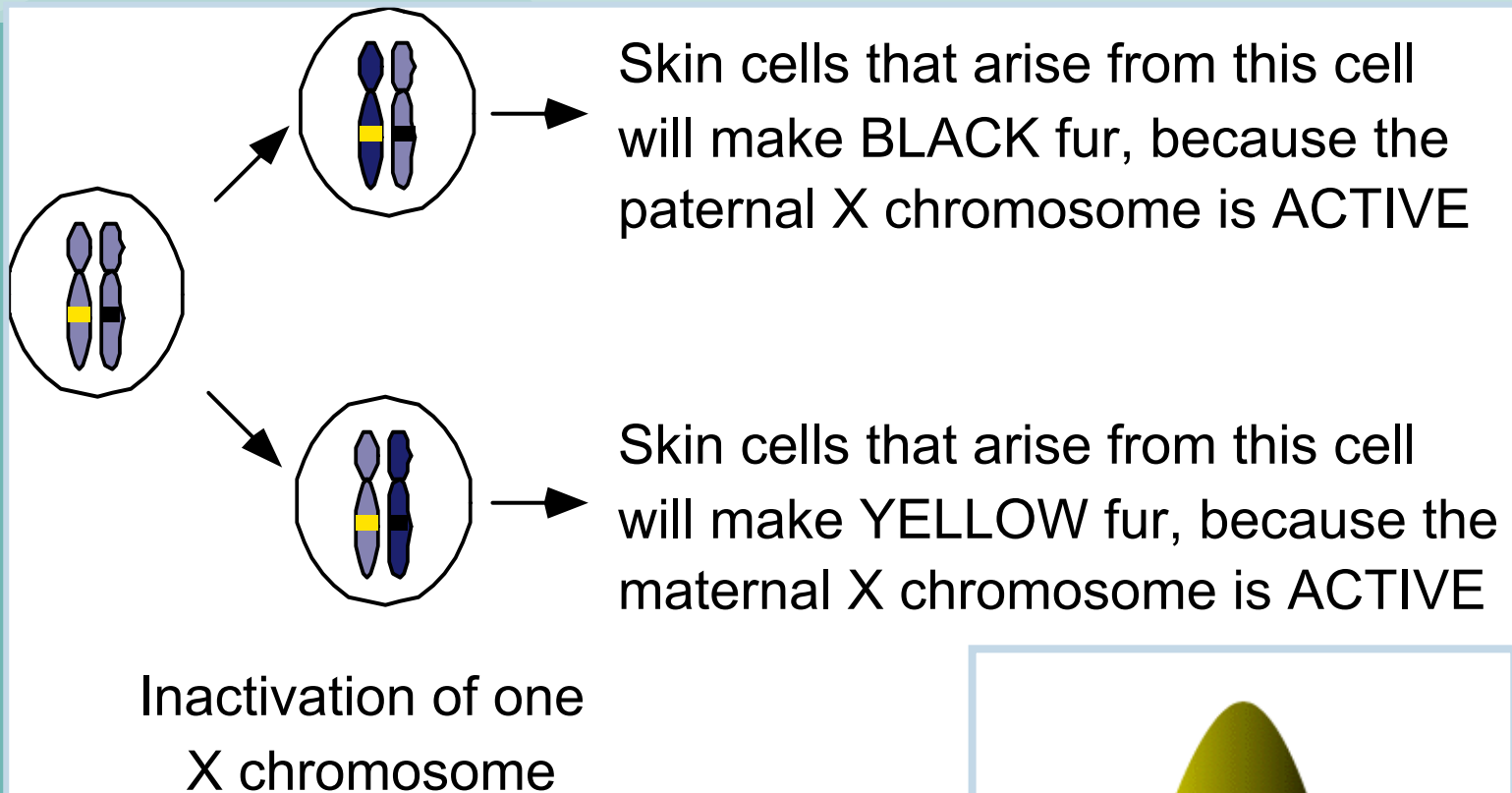
X-inactivation



- As tissues form, they may end up with more cells from one population or the other or may be randomly mixed up.



X-Chromosome Inactivation: lessons learned from calico cats



Genes are like recipes

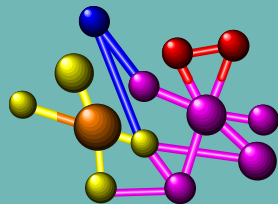
Gene

+

RNA

=

Functional Protein



Ingredient list

+

Instructions

=

Food



What is a mutation?

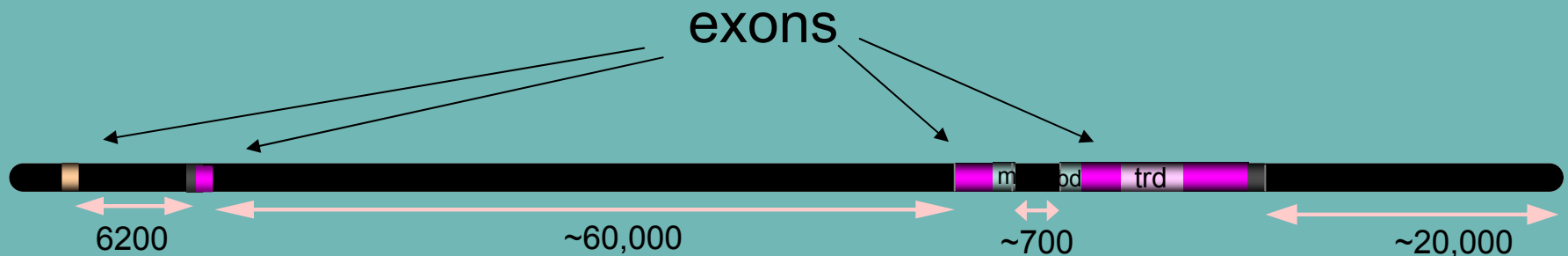
- A **gene**: segment of DNA that encodes information on how to build a protein. The code used is only four nucleotides or bases (ACGT)
- A **mutation** is like a typographical error that occurred during the copying of the gene
- It causes the protein made from the gene to form *incorrectly*
- Annotated at DNA or protein level
 - 473C-T versus T158M

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 (called exons).

Mutation screening is done on the exon sequences.



Piña Colada

- 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
 - Blend well and serve, garnish with a cherry. Serves 2.
- Missense mutation: a substitution that does alter the product*
- Common missense mutations: R106C, R133C, T158M, R306C

Nonsense:Piña Colada



- 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*

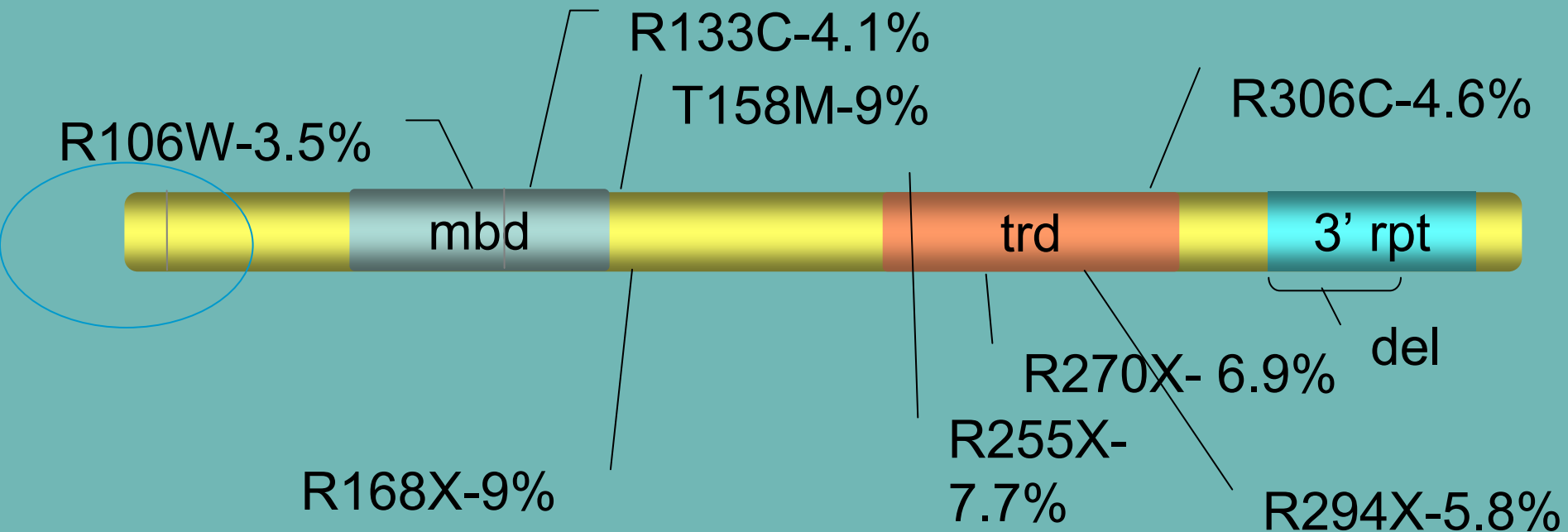
Piña Colada



- In a blender, combine:
 - 4 oz creme of coconut
 - 4 oz pineapple juice
 - 3 oz light rum
 - 2 cups of ice
- Blend well and serve, garnish with a cherry. Serves 2.

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

Common mutations



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

Mutation testing

DNA sequencing: look letter by letter at the coding sequence for errors. Will identify most mutations but can miss big deletions.

MLPA: will detect both point mutations and deletions or duplications.

Southern blot: Detects large rearrangements.



Interpreting your daughters' mutation results

- Gene mutation
 - Change in the DNA
 - Insertions and deletions
- Protein effect
 - Change in the protein product
- Often there is a note of a polymorphism identified in sequence based strategies.
- 316C-T, 473C-T, 502C-T, 763C-T, 808C-T, 880C-T, 806DelG, various deletions
- R133C, T158M, R168X, R255X, R270X, R294X, G269fs

They don't know if it's really a mutation?

- Important to check the parents and potentially other family members.
- Rules of thumb:
 - If the change is new to the child, it is likely to be the cause of her symptoms.
 - If her father carries it and is normal, it is unlikely to be a problem.
 - If mom carries it, it is helpful to test male first degree relatives to see if they have it (e.g. child's brother, mom's father or brother).

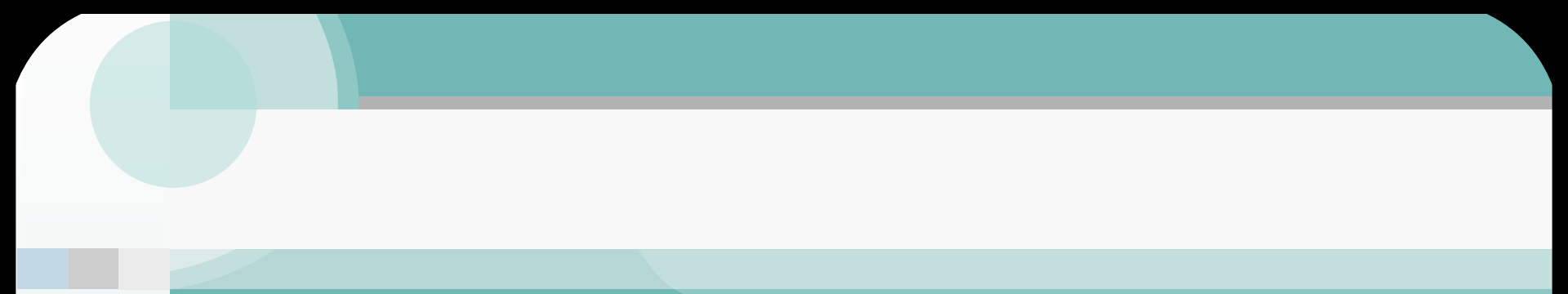
“Negative” mutation results.

- For patients without identified mutation in *MECP2*
 - Could be duplication or deletion of the gene depending on how the mutation screening was done
 - Could be another gene.
- What should you do?
 - Talk to your geneticist!
 - 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 (including exon 1)?

Rett syndrome \neq *MECP2* mutation

MECP2 mutation \neq Rett syndrome

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



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

Symptoms resulting from *MECP2* Mutations

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

Every female is different

- Some mutations appear to retain partial function of the protein better than others.
- Combined with the relative “dose” of expression of the mutant gene because of X chromosome inactivation patterns in brain (which are going to vary individually from child to child).



Why is Rett syndrome sporadic?

- 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

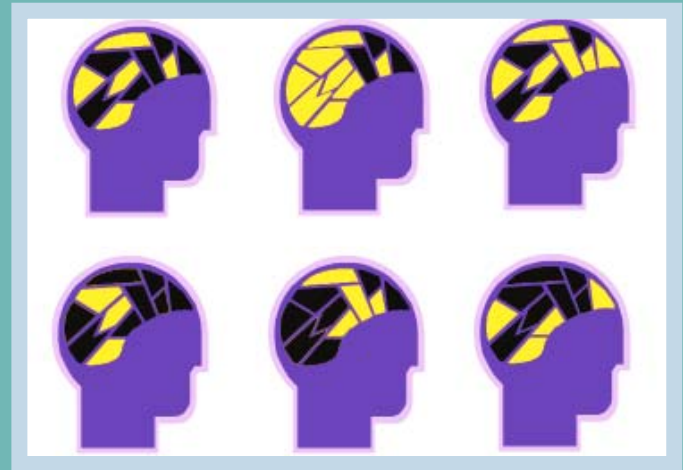


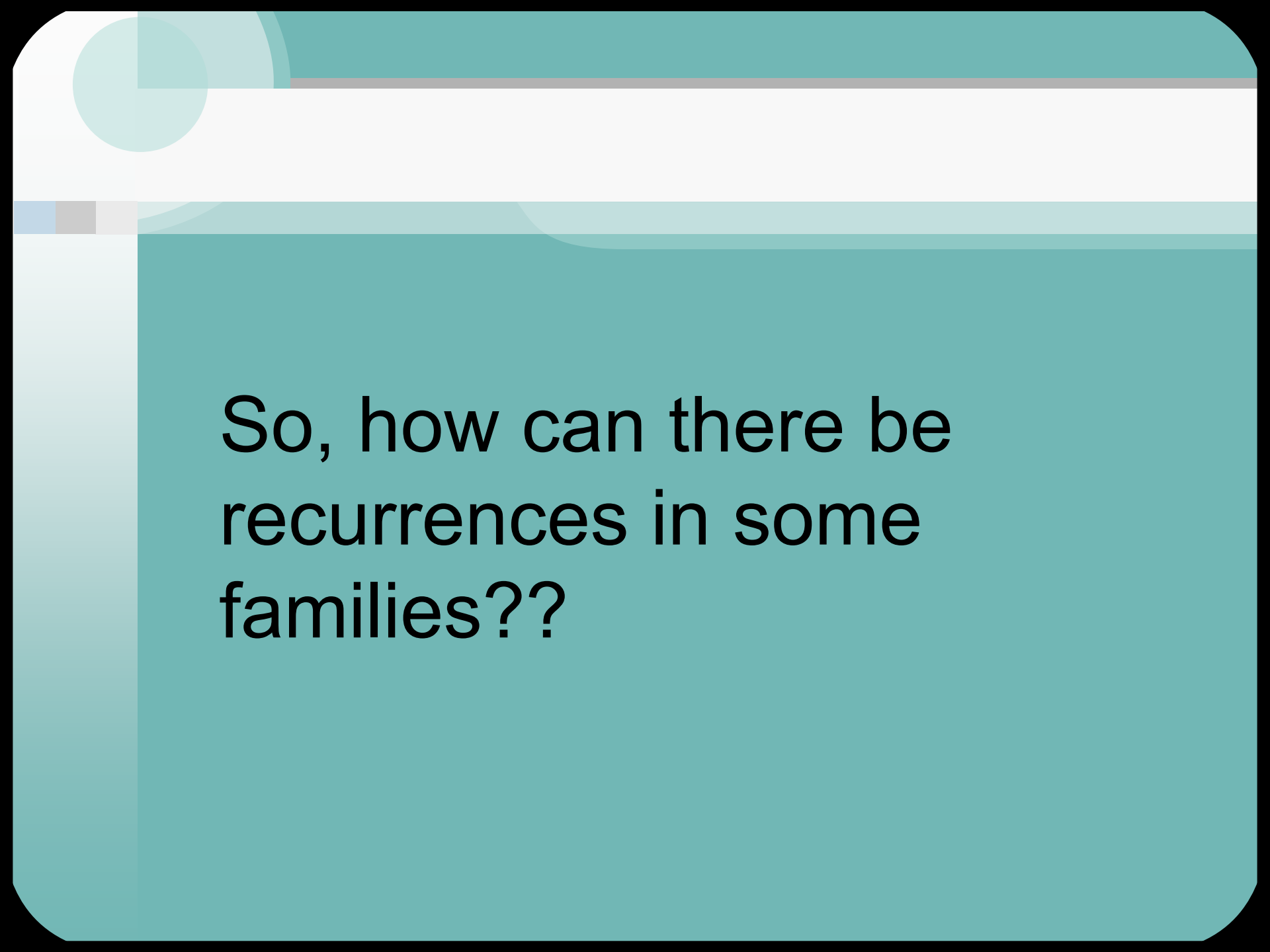
Recurrence Risk Counseling

- 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?

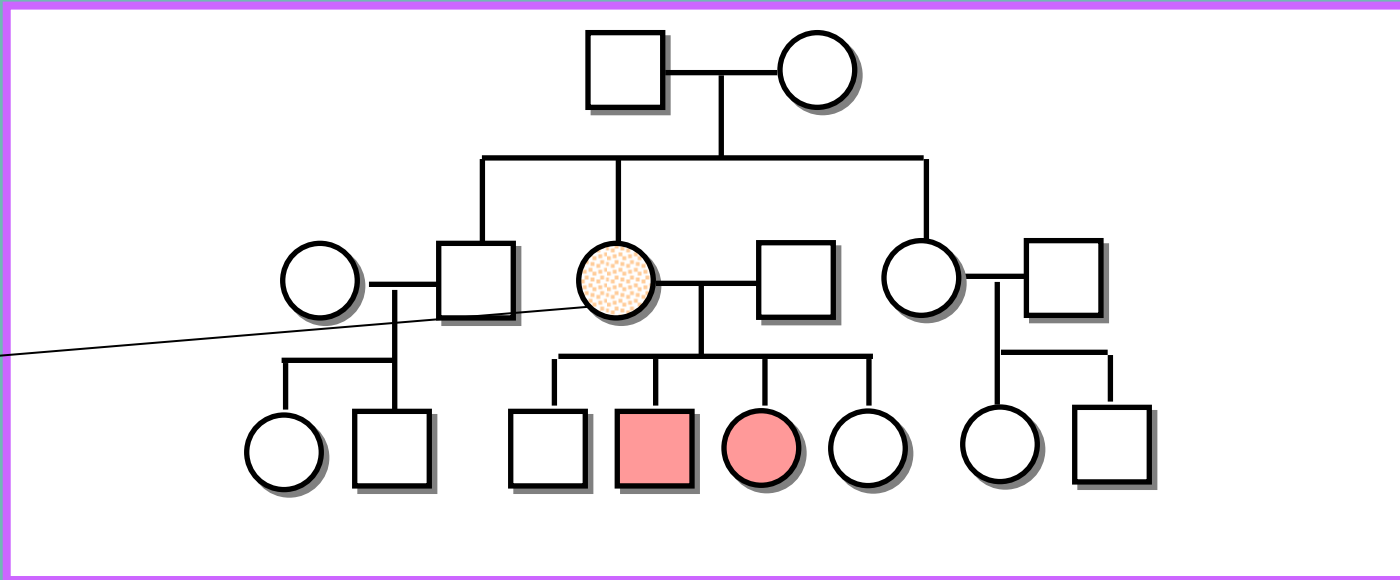
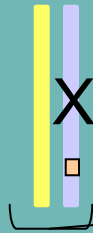
- Not usually useful clinically as predictor of symptoms unless the child is an “outlier” clinically.
- Blood may not reflect regional changes in brain.





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

Family recurrences: skewed X inactivation

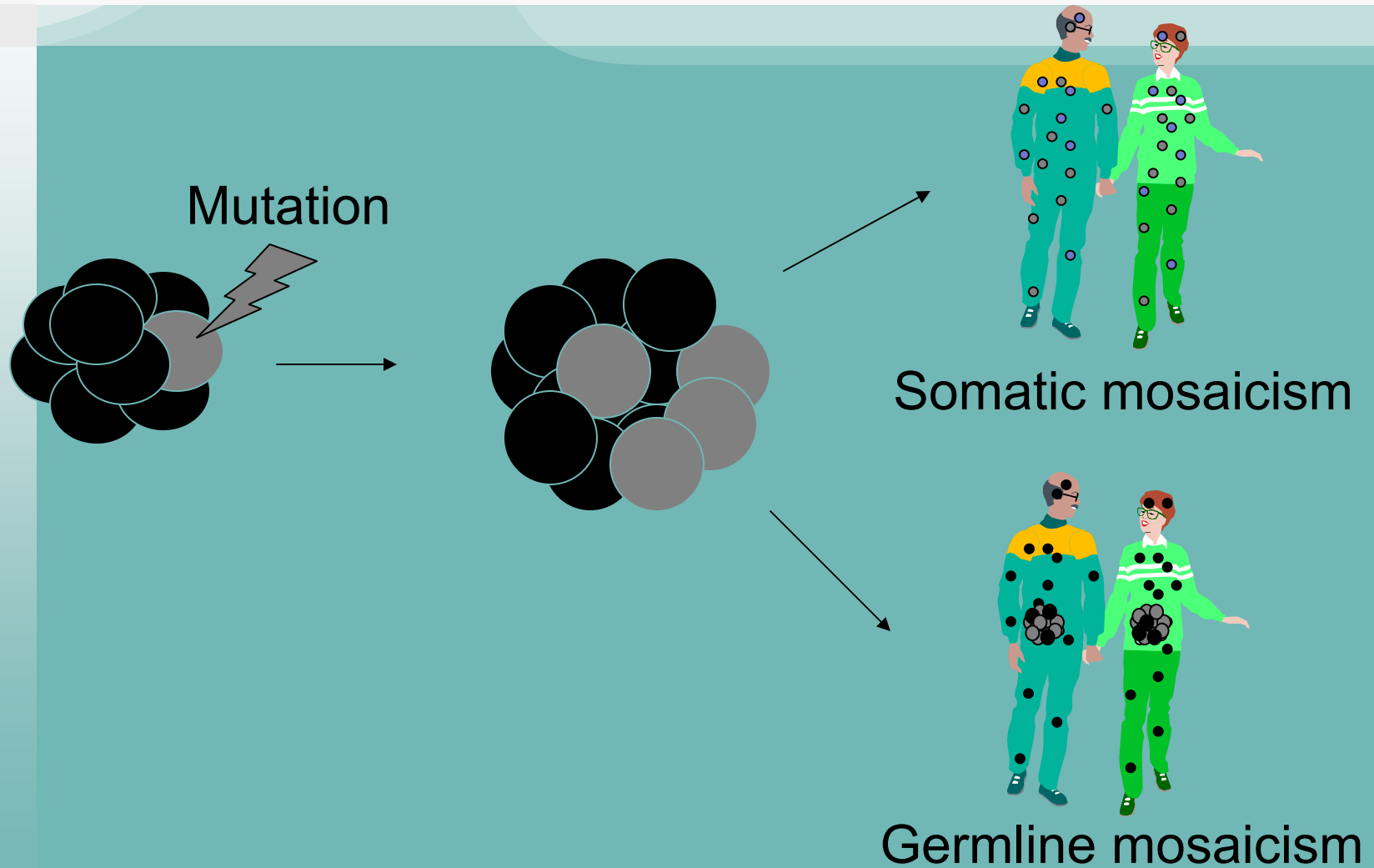


Mother has skewed X-inactivation (if not, she would have Rett syndrome)

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



Screening family members

- Normal brothers: no need
- Normal sisters could carry a mutation silently (rare, but can happen). BUT **normal sisters** of affected child should not be screened until they are of reproductive age and can decide on their own.

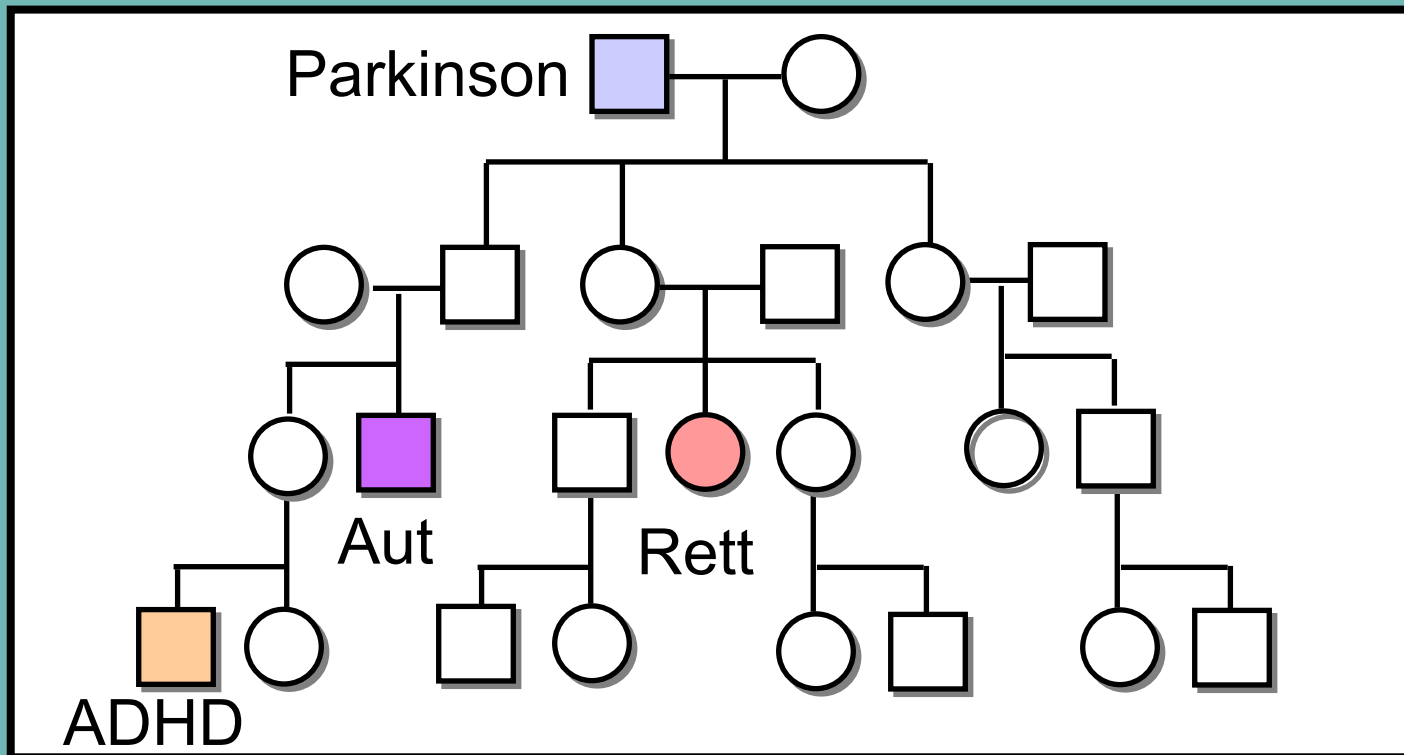
Other *MECP2* related disorders

- X-linked recessive mental retardation (occurs primarily in boys and passed down through families).
- *MECP2 duplication syndrome*: affects boys who are unable to shut down the extra copy of the gene. Detected by microarray testing or MLPA. Important to screen other family members.

Rett syndrome: Other genes

- CDKL5: Also on the X chromosome and causes an early onset form of Rett syndrome, often with severe seizures.
- FOXP1: On chromosome 14, only a few cases reported so far. Rett-like based on published descriptions.

If Rett syndrome is almost always sporadic, what about other disorders in the family (like depression, Parkinson disease, bipolar, autism)?



Individual counseling is suggested but as a general rule, this is likely coincident occurrence of relatively common disorders within a family. If the child with Rett syndrome has an MECP2 mutation and her parents, do not have one, then it is not likely to be an inherited risk causing the various symptoms.

Thanks!!

- IRSF
- Rett families
- Gary and MaryJoyce Griffin
- Paige Nues
- Jennifer Endres



Mutation and XCI influence outcome

