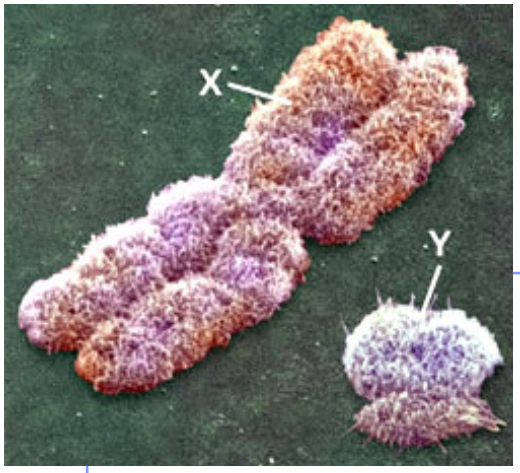
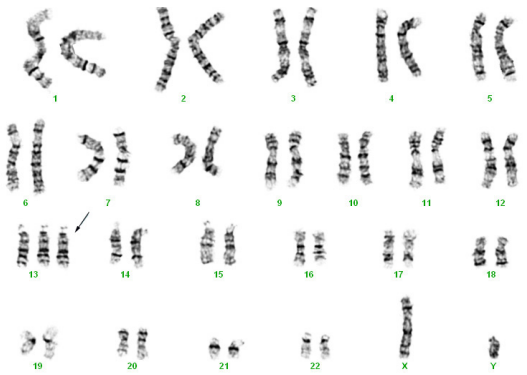
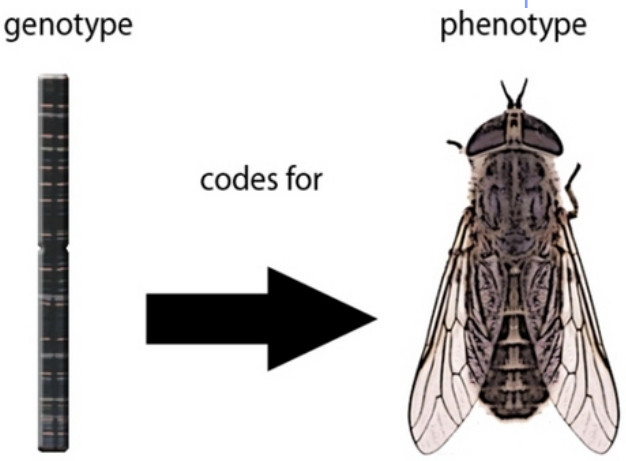




Linked genes and Sex-Linked genes



Mendel vs. Morgan's Allele Notation

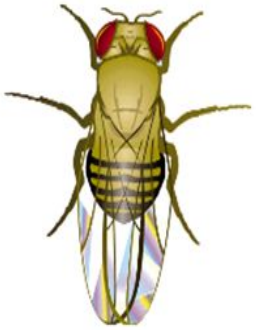
Mendel didn't know how heredity and genetics worked.

- He used upper case letters to refer to a dominant trait of a character
- He used lower case letters to refer to a recessive trait of a character

The embryologist, Thomas Hunt Morgan, began in 1907 extensive research on fruit flies and heredity.

He hypothesized that this genetic information is carried on physical DNA molecules = chromosomes

- He used letters with a + superscript to refer to the **wild-type** version of a gene *[the version most often seen in nature]*
- He used letters without the + superscript to refer to the **mutant** version, or allele, of the gene



+ means it is the wild type trait (yellowish body in this case.

bl means that this fly is carrying the mutant allele for black body

both are mutant alleles, vestigial wings

black body

vg+vg bl+bl x vg vg bl bl

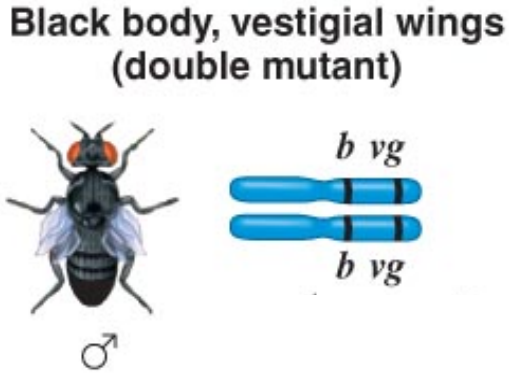
+ means it is the wild type trait (long wings)

vg means it is carrying the mutant allele for vestigial wings

or just use the old fashioned way

AaBb x aabb

Morgan discovers Linked Genes



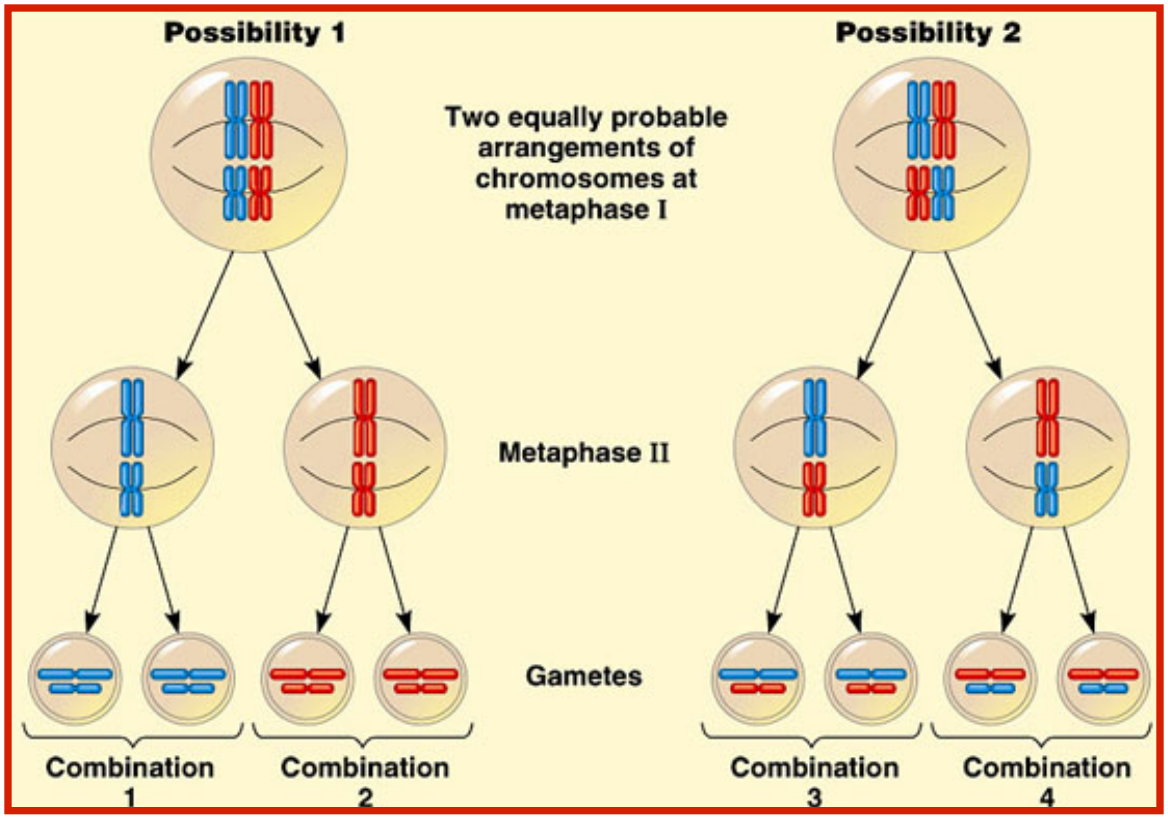
- Mendel's second law (of independent assortment) breaks down in one important way:
  - When two genes lie close together on the SAME chromosome.
- Alleles [traits] for two or more genes [characters] inherited from one parent tend to stick together when transmitted to the next generation when they are part of the same *DNA molecule instead of sorting independently into gametes*
  - Genes found on the same chromosome instead of different types of chromosomes are called Linked Genes
    - Ex: Body color and wing shape in fruit fly
      - When a parent completes meiosis to make a gamete, if two genes are close together on the *same* piece of DNA, the *same* chromosome, there is a higher chance that those two *versions* of genes, those two alleles, will be passed down to the gamete *together* instead of a different combination of alleles for these two genes being passed down.

Recall meiosis

- Remember, homologous chromosomes pair up [synapse] during Prophase I of meiosis to form tetrads.
  - According to the Law of Independent Assortment: Each tetrads lines up at the Metaphase I plate independently of the other tetrads, with one homolog of each tetrad randomly facing one pole and the other homolog facing the opposite pole.

See figure: If 2 genes are on different non-homologous chromosomes [one of the large chromosome & one on the small chromosome], how the large chromosomal tetrad lines up during Metaphase 1 is independent of how the small chromosomal tetrad lines up.

- If the the individual is heterozygous for both genes [one red allele & the other a blue allele version], then the individual COULD make the four types of gametes shown.



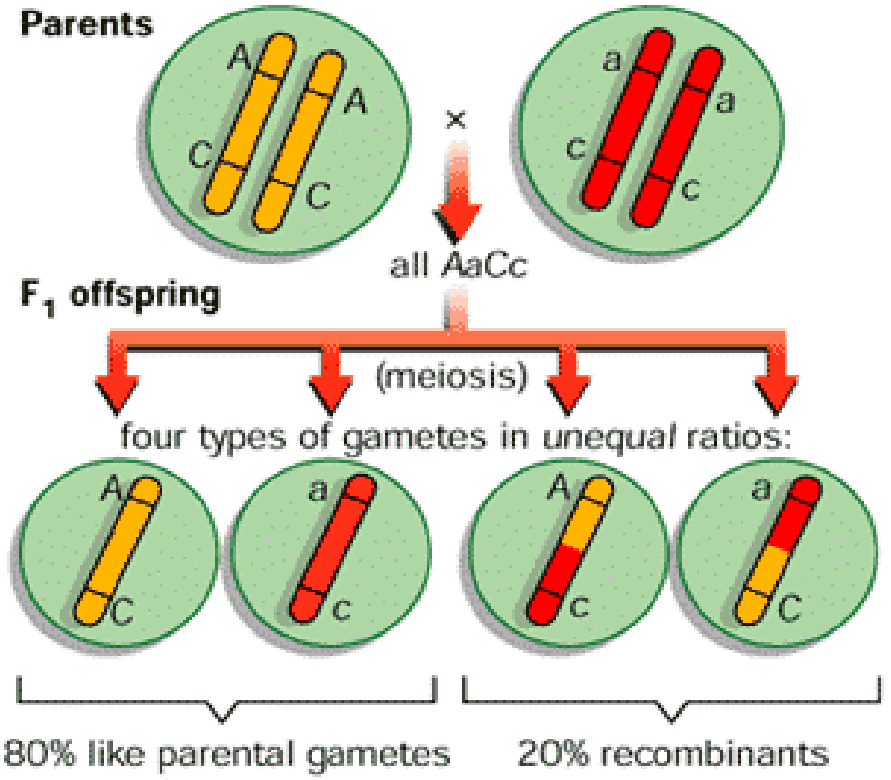
Linked Genes

- **Remember, when homologs pair up during Prophase I of meiosis to form tetrads:**
  - **Crossing over between nonsister homologous chromatids occurs**
    - **Crossing over allows for the allele combinations of all the genes on each homologous DNA molecules to be altered when alleles, version of genes, are potentially swapped with other alleles between homologs.**

In the figure: If a P generation mating occurs, AACC x aacc, all F1 offspring are genotype AaCc. But, which gametes can an AaCc parent make if the A gene and C gene are located on the SAME chromosome instead?

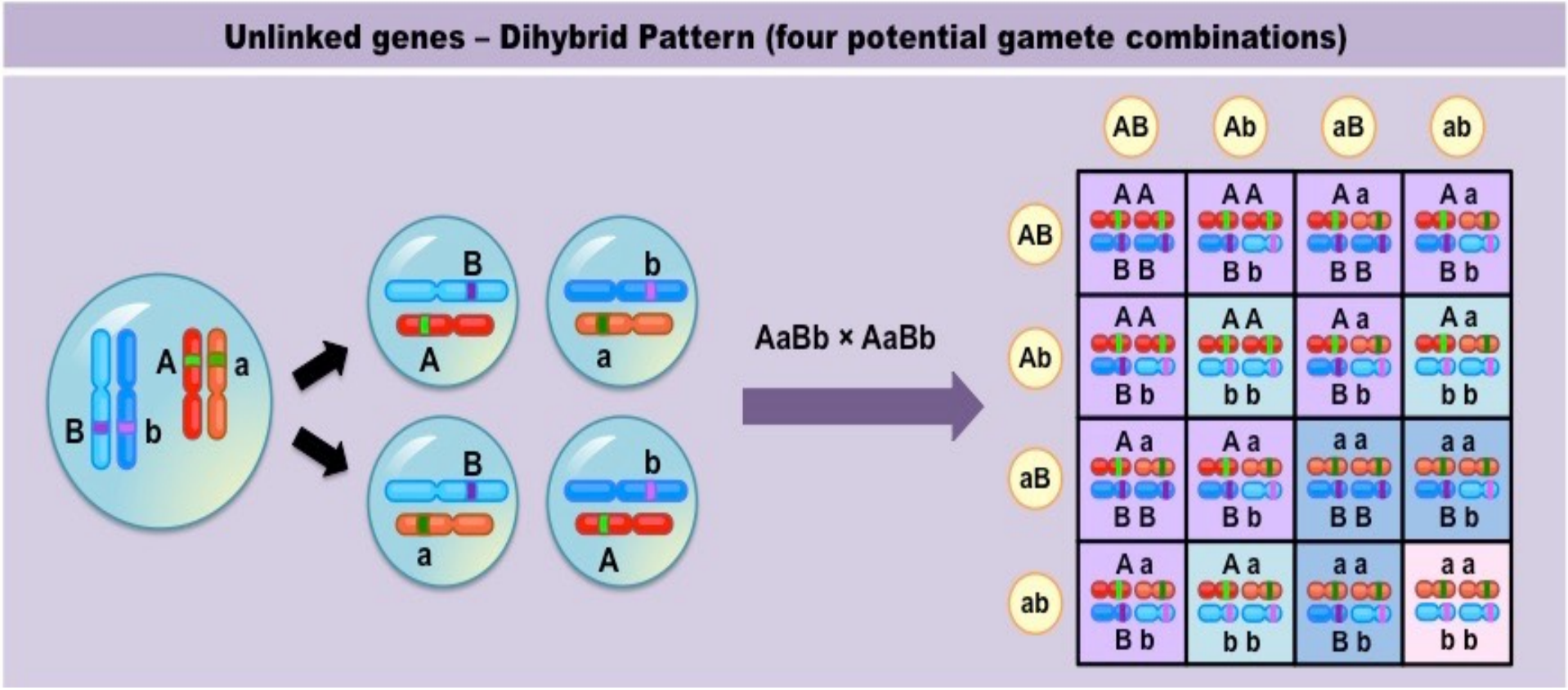
The closer two genes are on the same chromosome the LESS likely it is that crossing over will change the original versions of these two genes found on a chromosome.

Recombinant chromosomes in gametes are far less likely to occur the closer two genes are ---------->



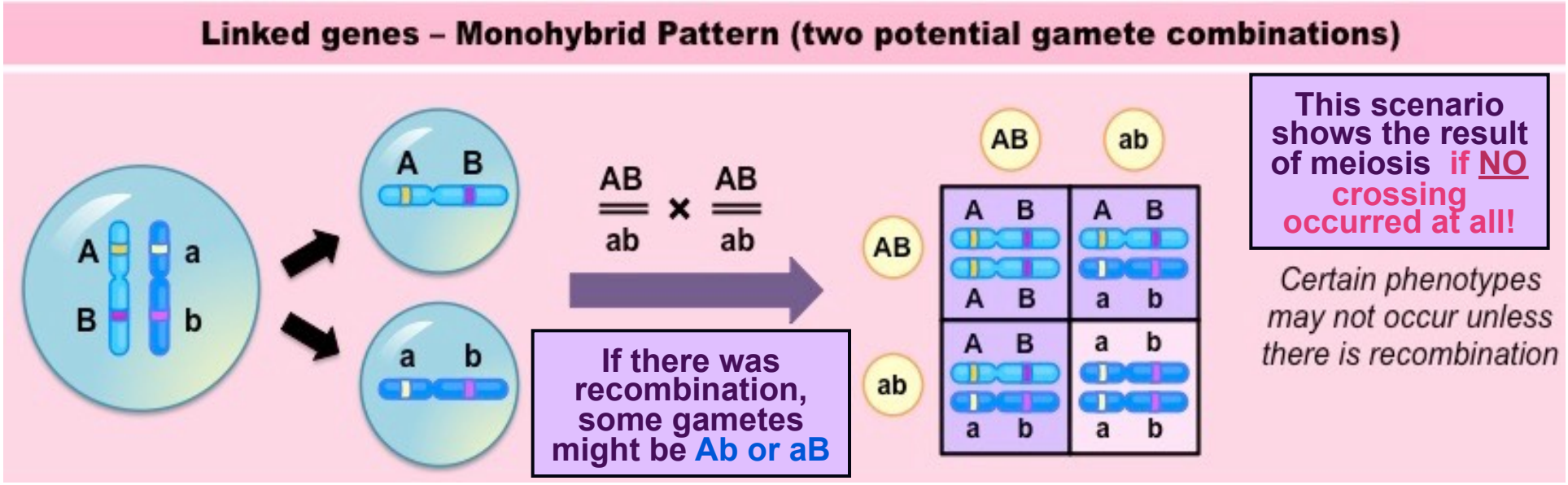
Meiosis when genes sort INDEPENDENTLY

- When two parents both with Genotype AaBb make gametes [where the genes sort INDEPENDENTLY - meaning the A gene is located on a DIFFERENT chromosome from the B gene], the following gametes are all EQUALLY possible, depending on how the tetrad carrying the "A/a" gene and the tetrad carrying the "B/b" gene line up during Metaphase I:
  - AB, Ab, aB, ab



Meiosis when genes *DO NOT* sort independently

- **When two parents both with Genotype AaBb make gametes [where the genes DO NOT sort INDEPENDENTLY - meaning the A gene is located on THE SAME chromosome as the B gene], gametes with any combination of A alleles and B alleles may not be equally likely.**
  - **If the A & B genes are located very far apart on DNA, crossing over occurs 50% or more of the time so gametes AB & Ab & aB & ab are all equally possible.**
  - **If the A & B genes are located closer together on DNA, crossing over occur less often [less than 50% of the time] between the two genes. In the picture below, given which alleles for genes A & B are on each homolog, the parent will make most often only two types of gametes: AB & ab**
    - **Only IF crossing over occurs in the DNA between the A and B genes during tetrad formation,will recombinant gametes be made: Ab & aB [not shown]**



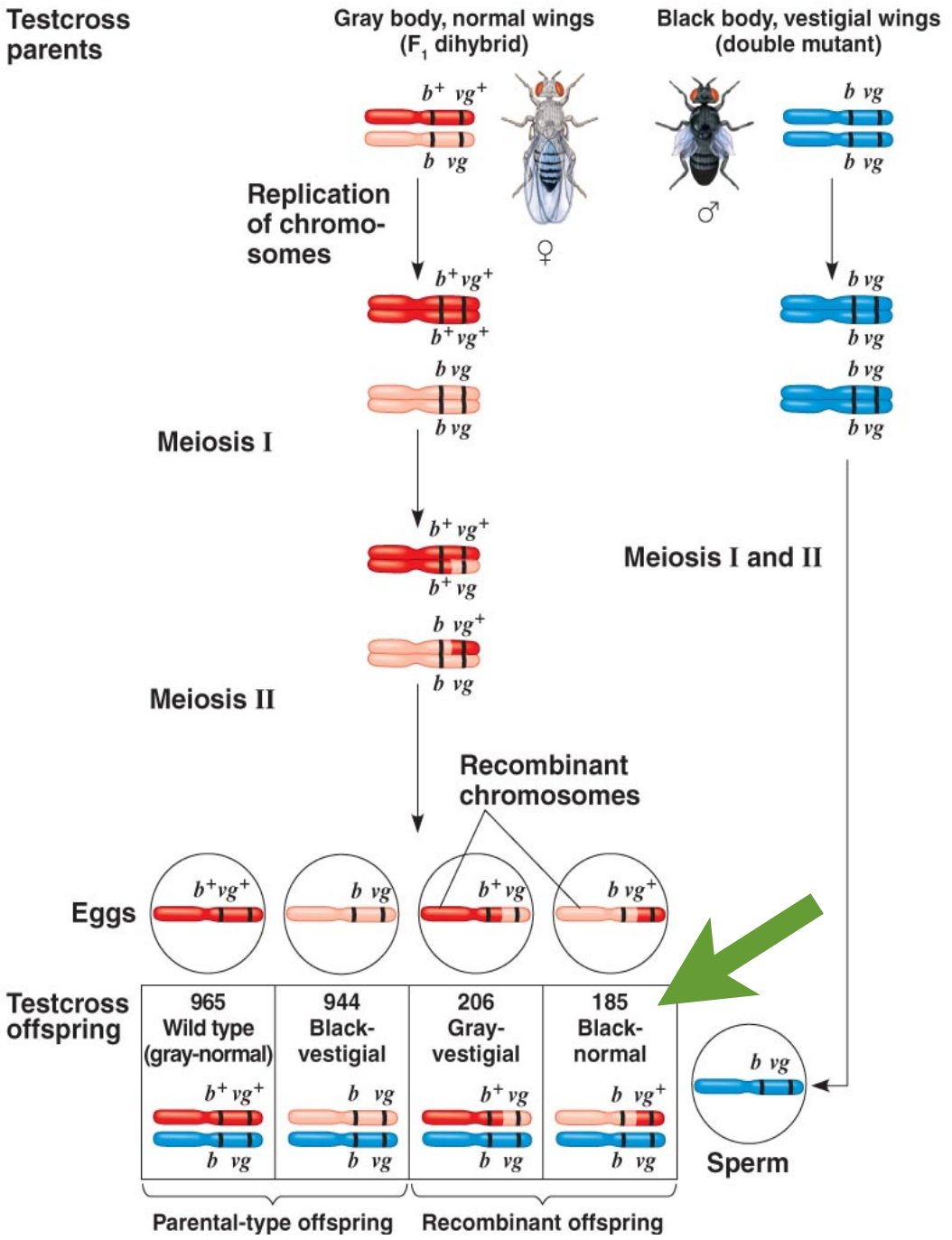
Linked Genes

- **When genes were linked, Morgan found much higher proportion of parental phenotypes than recombinant phenotypes in the offspring than would be expected if genes assorted independently** ***[than if the two genes were found on different types of chromosomes and not the same one].***

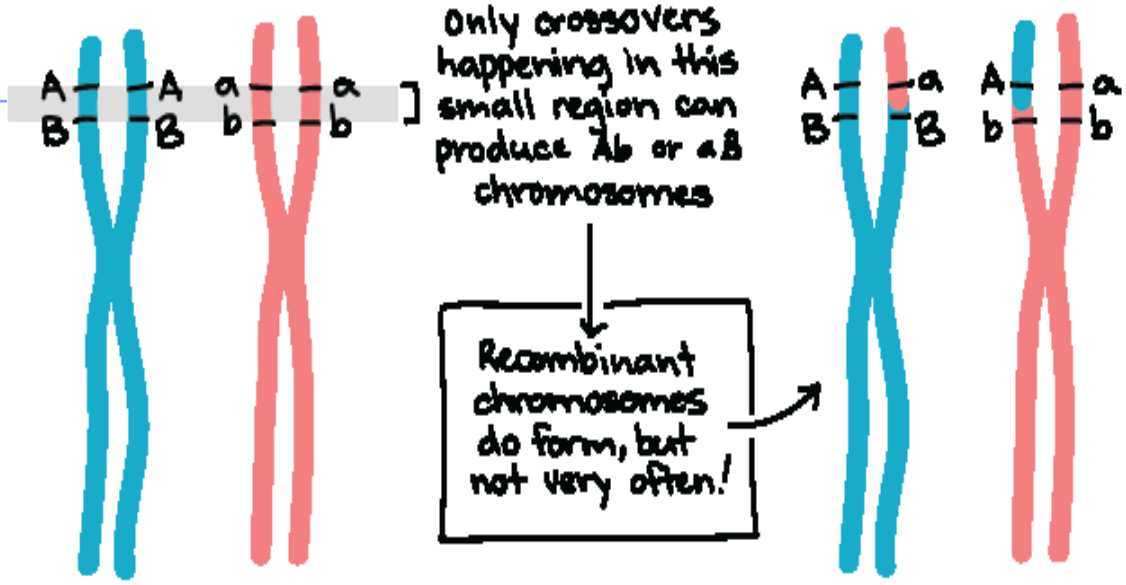
He expected phenotypes in a 1:1:1:1 ratio among offspring in this b^+bvg^+vg x bbvgvg cross ***[each offspring expected 25% of the time]***

He actually observed high #'s of parental types & low #'s of recombinant types [count the # of each fly offspring in the figure]

- ***Some recombinants did arise, however, though in lower numbers!***



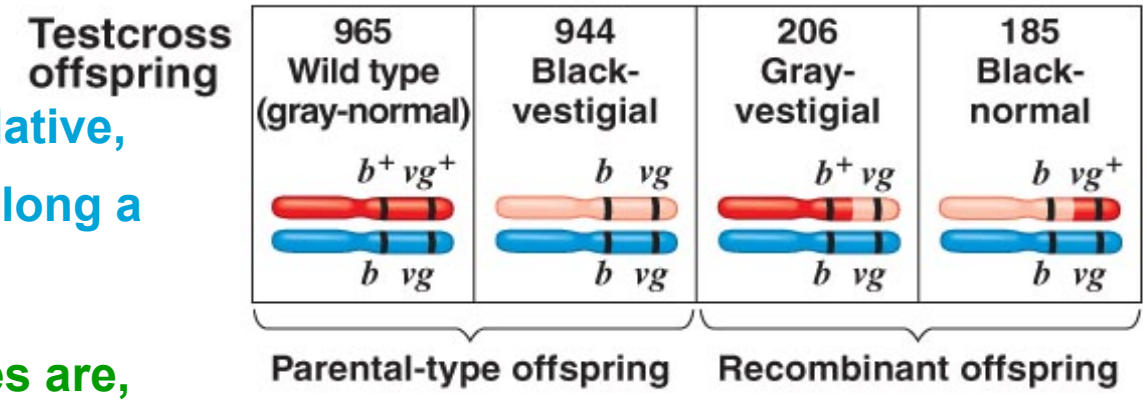
Linked Genes



By measuring the frequency of Recombinant chromosomes in the progeny, we can estimate the distance that separates the two genes and can make a linkage map:

- Map that shows the relative, linear order of genes along a chromosome

- The farther apart two genes are, the higher the probability that a crossover will occur between them



$$\text{Recombination frequency} = \frac{391 \text{ recombinants}}{2{,}300 \text{ total offspring}} \times 100 = 17\%$$

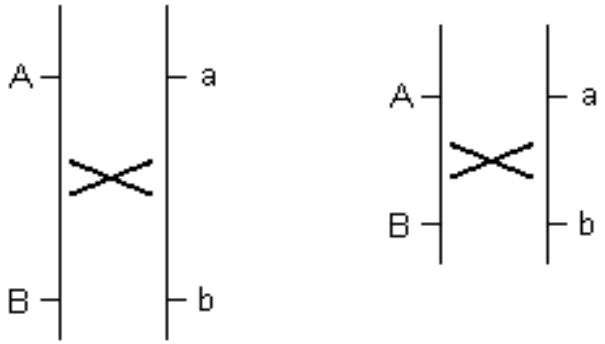
Linked Genes

- Higher recombination frequency

  = genes further apart on chromosome

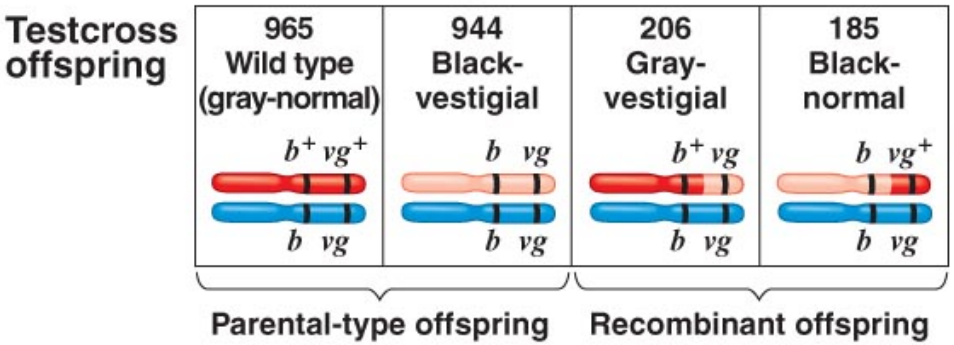
  - A value of 0 (0%) means that the two genes are so close to each other that they never recombine
  - A value of 0.5 (50%) implies that the genes might be genetically unlinked and have a 50/50 chance of recombining
    - Might still be physically linked but behave as though they are on two different types chromosomes

- Each map unit corresponds to 1% recombination and is named a centiMorgan in honors of Morgan. *[unit: cM]*

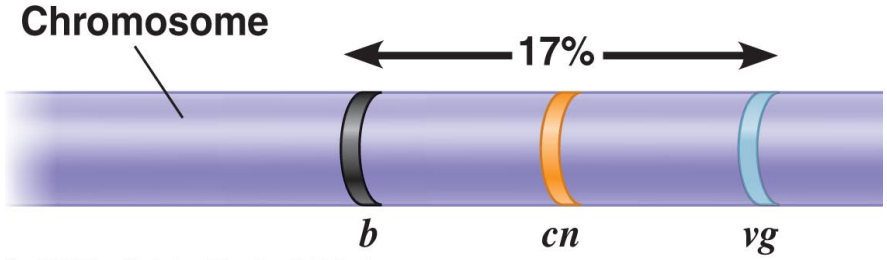


genes far apart, crossovers are relatively frequent

genes close together, crossovers are less likely to occur between them



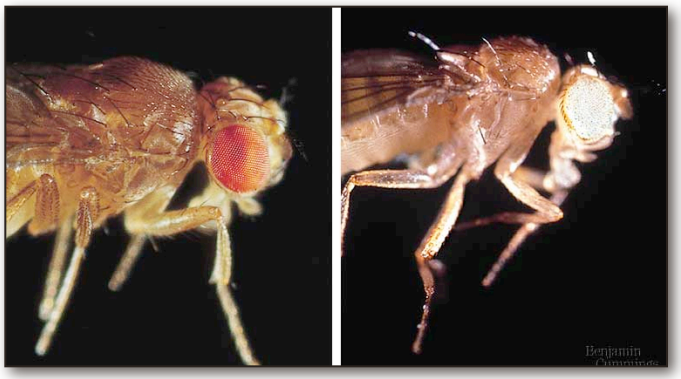
$$\text{Recombination frequency} = \frac{391 \text{ recombinants}}{2{,}300 \text{ total offspring}} \times 100 = 17\%$$



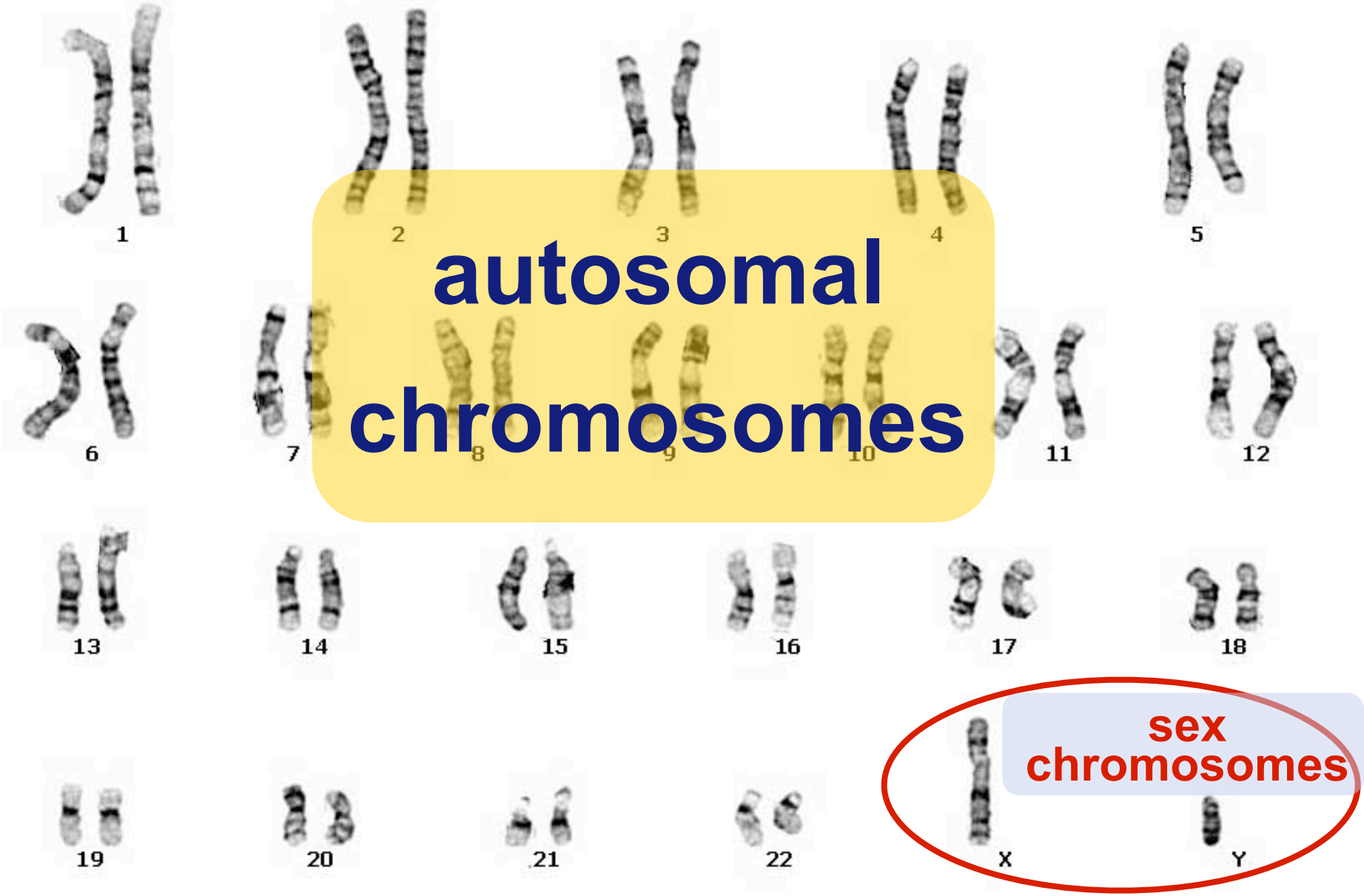
Sex-linked traits

1910 | 1933

- Refers to the genes found on sex chromosomes
  - As opposed to autosomal chromosomes
- First discovered by T.H. Morgan at Columbia U.
  - *Using Drosophila* breeding
    - Fruit flies are good genetic subjects
      - Prolific breeders
      - 2-week generation times
      - Only 4 pairs of chromosomes to track
      - XX = female, XY = male [like humans]



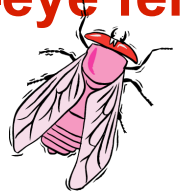
Classes of human chromosomes



Discovery of sex-linked genes (genes located on the sex chromosomes - historically the X chromosome)

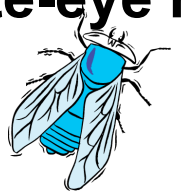
P

true-breeding red-eye female



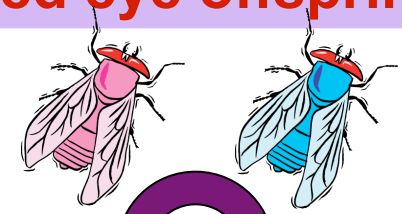
X

true-breeding white-eye male



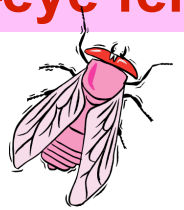
F_1 generation (hybrids)

100% red eye offspring



F_2 generation

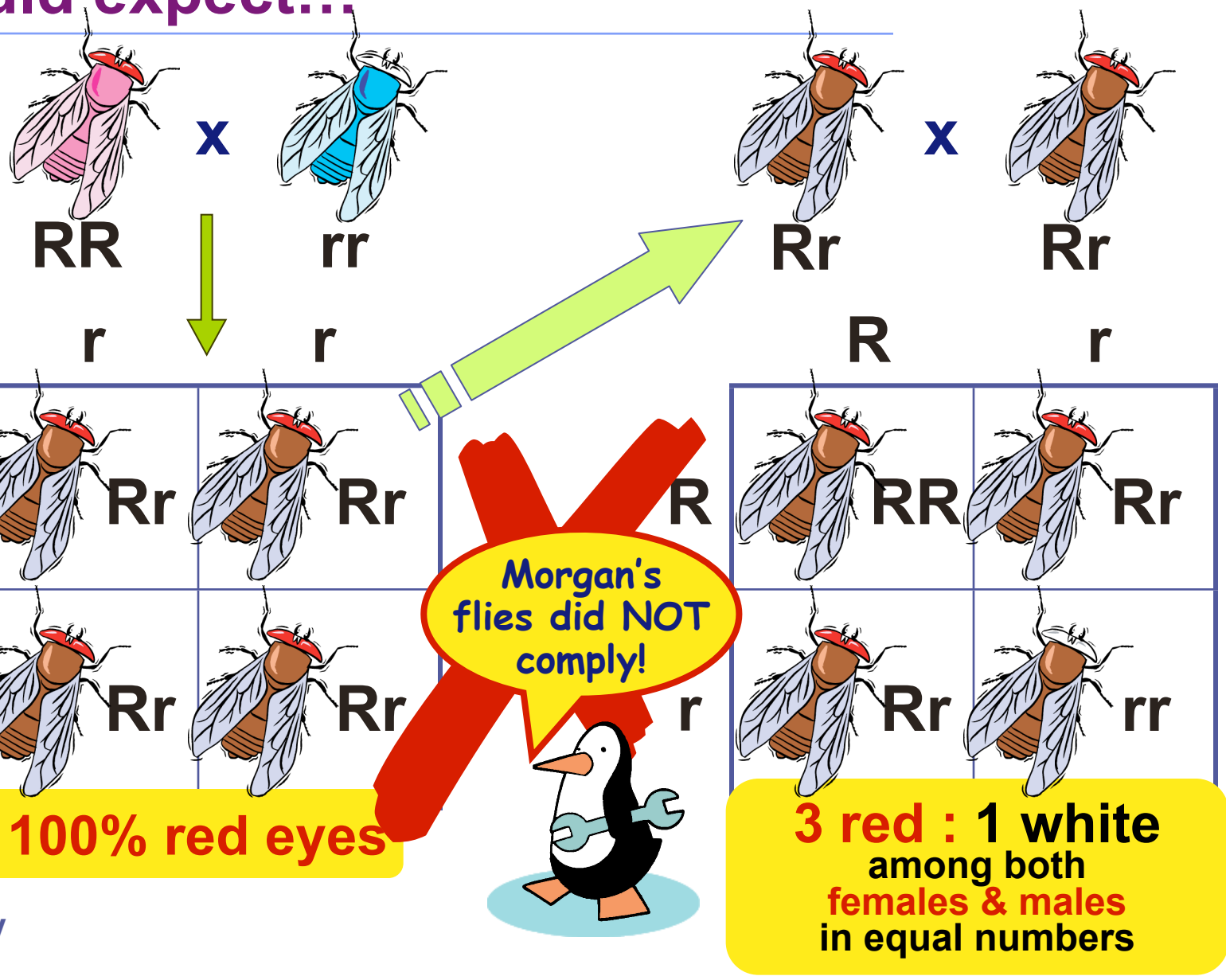
100% red-eye female



50% red-eye male
50% white eye male

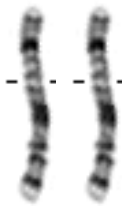
In the F_2 generation, Morgan saw the 3:1 ratio, BUT curiously, ONLY MALES inherited white eyes!

If gene was on autonomous chromosome would expect…

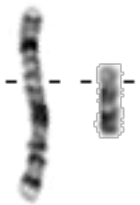


Genetics of Sex

- In humans & other mammals, there are 2 sex chromosomes: X & Y
  - 2 X chromosomes



    - develop as a female: XX
    - gene redundancy, like autosomal chromosomes
  - an X & Y chromosome

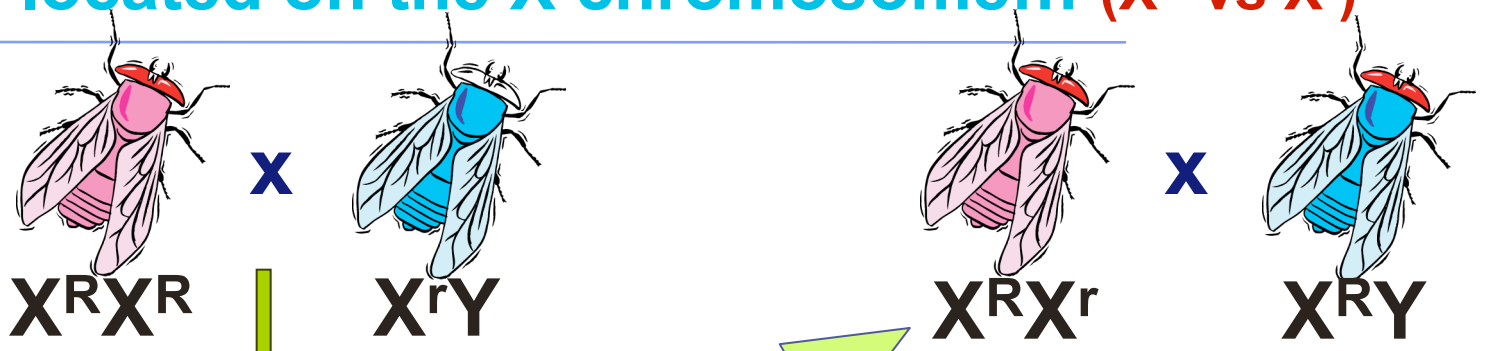


    - develop as a male: XY
    - no redundancy

	X	Y
X	XX	XY
X	XX	XY

50% female : 50% male

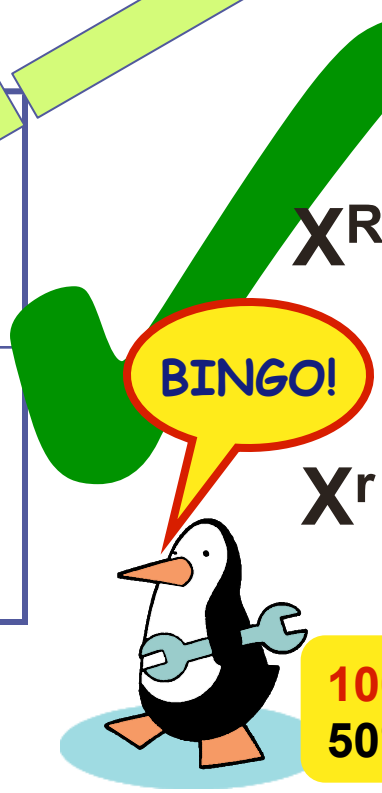
What's up with Morgan's flies? The eye color gene was located on the X chromosome!!! (X^R vs X^r)



	X^r	Y
X^R	X^RX^r	X^RY
X^R	X^RX^r	X^RY

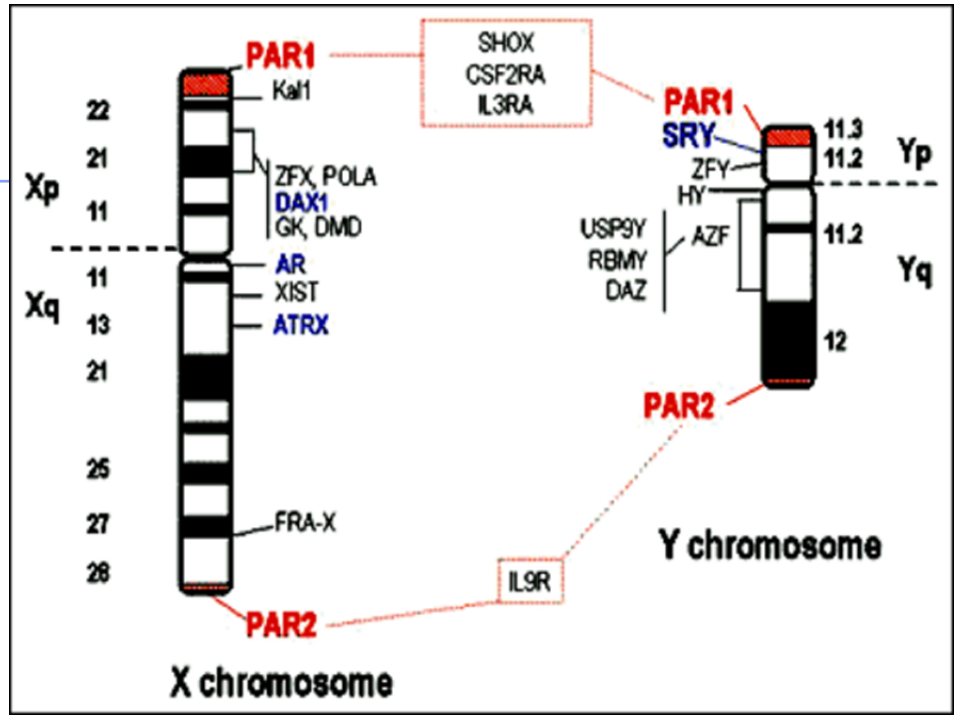
100% red eyes (male & female)

	X^R	Y
X^R	X^RX^R	X^RY
X^r	X^RX^r	X^rY



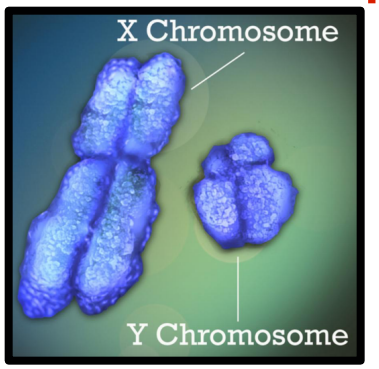
100% red females
50% red males; 50% white males

Sex chromosomes genes



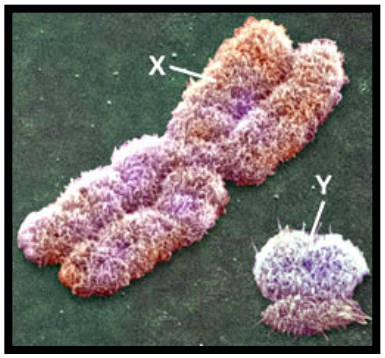
- Y chromosome
  - few genes (~78)
    - < 30 code for proteins
  - Includes the

    SRY gene:
    - sex-determining region of Y
      - master regulator for maleness
        - Protein encoded by SRY gene regulate expression of other genes in our chromosomes that determine 'maleness'
        - In absence of SRY, gonads develop into ovaries not testes
      - One gene with many phenotypic effects = pleiotropy!



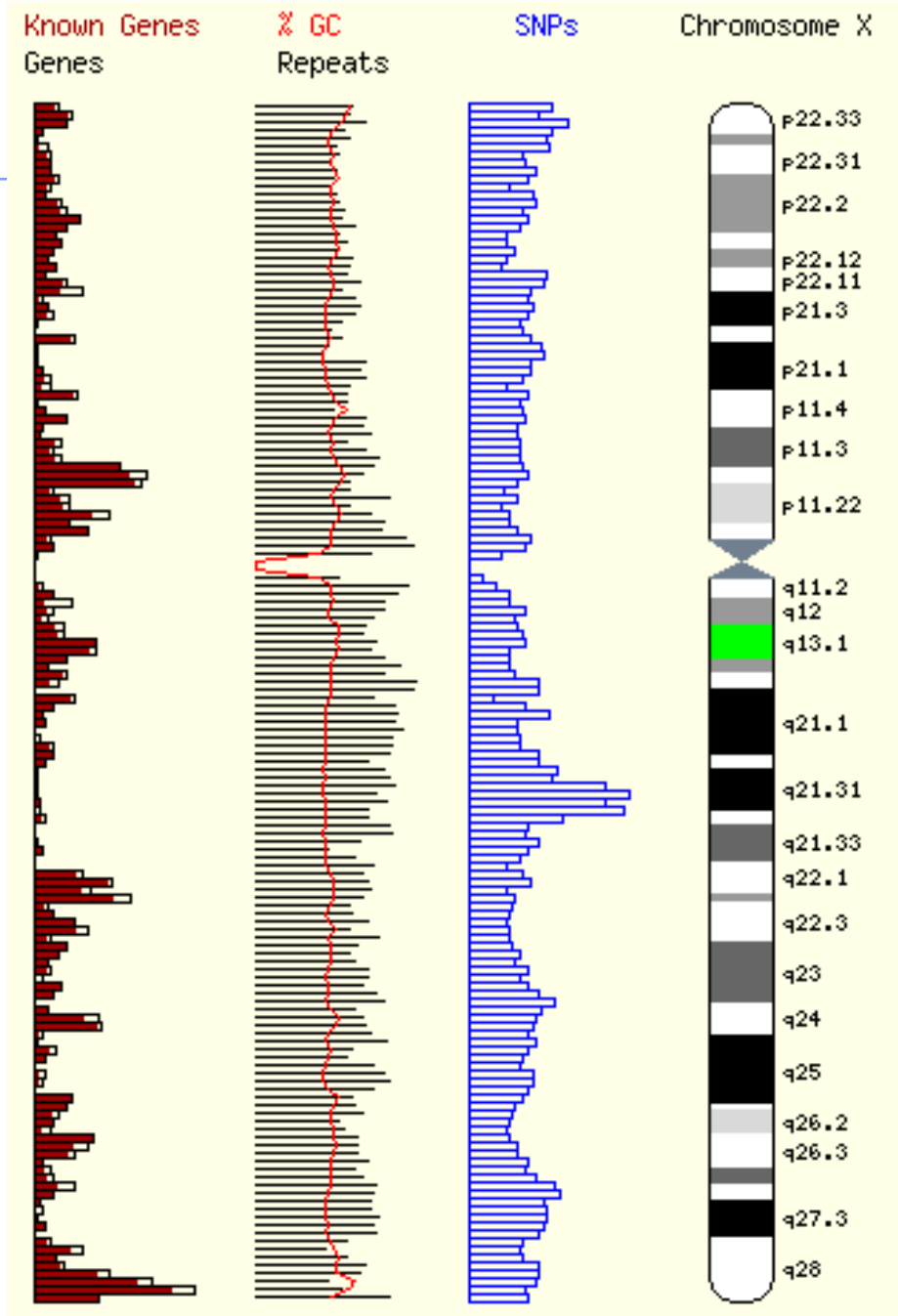
Sex chromosomes genes

- X chromosome
  - Carries other genes for traits beyond sex determination
    - Mutations in these genes can lead to disease:
      - EX: Hemophilia
      - EX: Duchenne muscular dystrophy



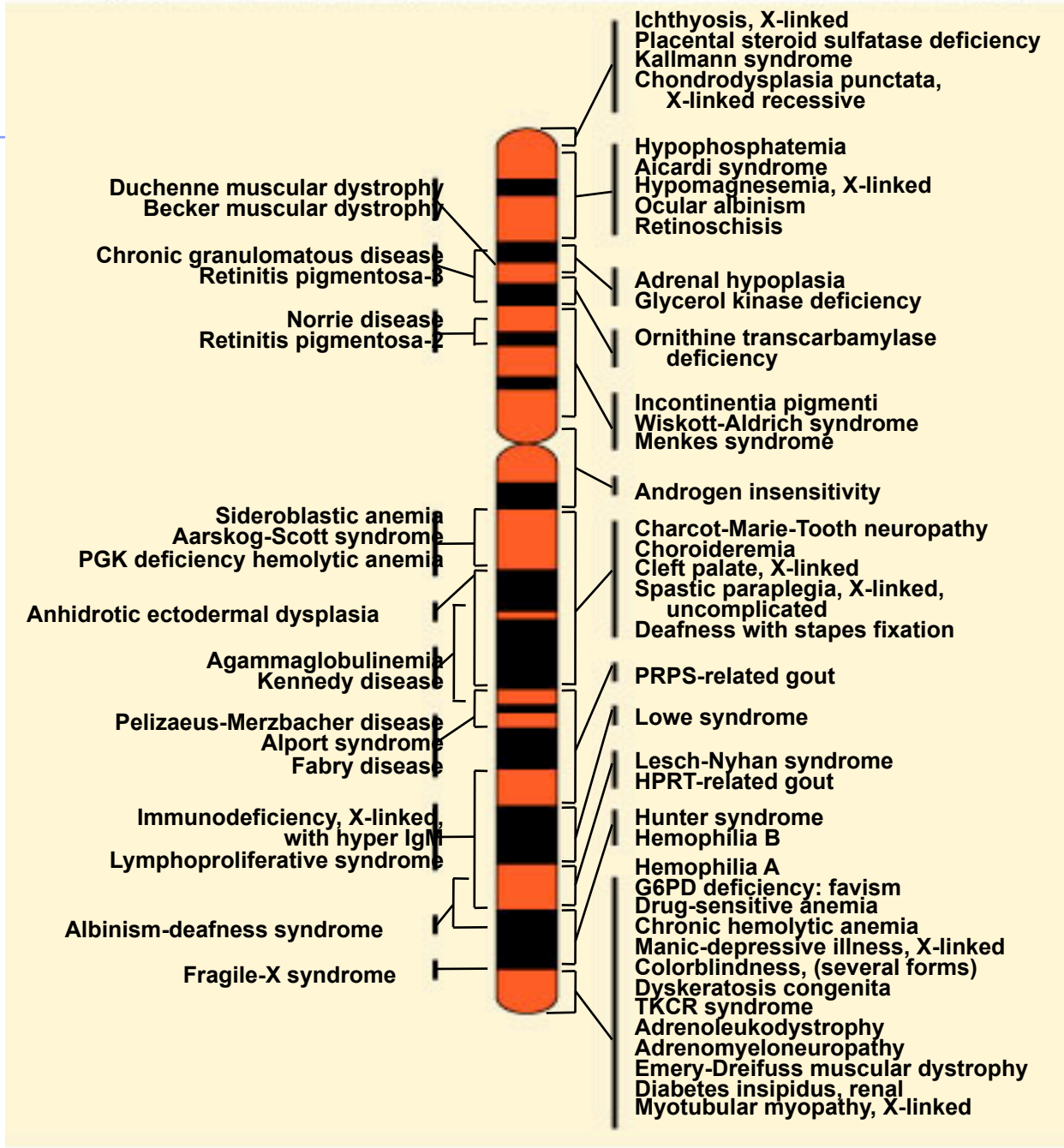
- Pass away in by early 20s.
- absence of an X-linked gene for a key muscle protein, called dystrophin.
- progressive weakening of the muscles and loss of coordination.

      - EX: Color-blindness



Human X chromosome

- **Sex-linked**
  - usually means "X-linked"
  - more than 60 diseases traced to genes on X chromosome
    - Fathers pass sex-linked alleles to all their daughters but to none of their sons
    - Mothers can pass sex-linked allele to both sons and daughters

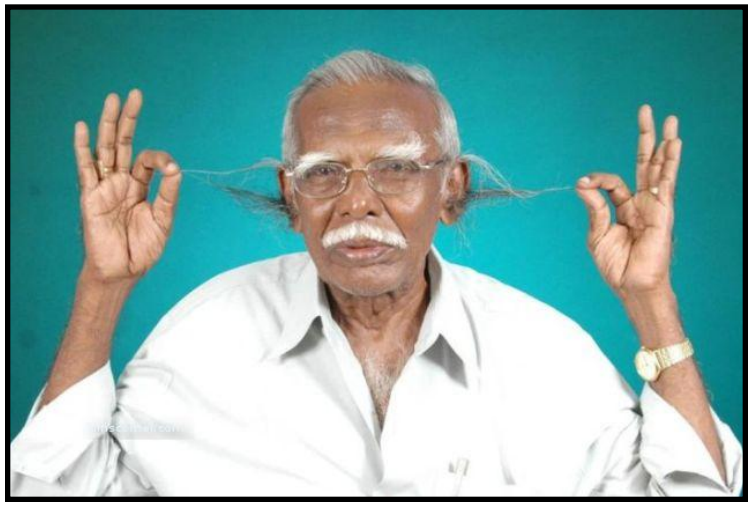


Sex-linked traits summary

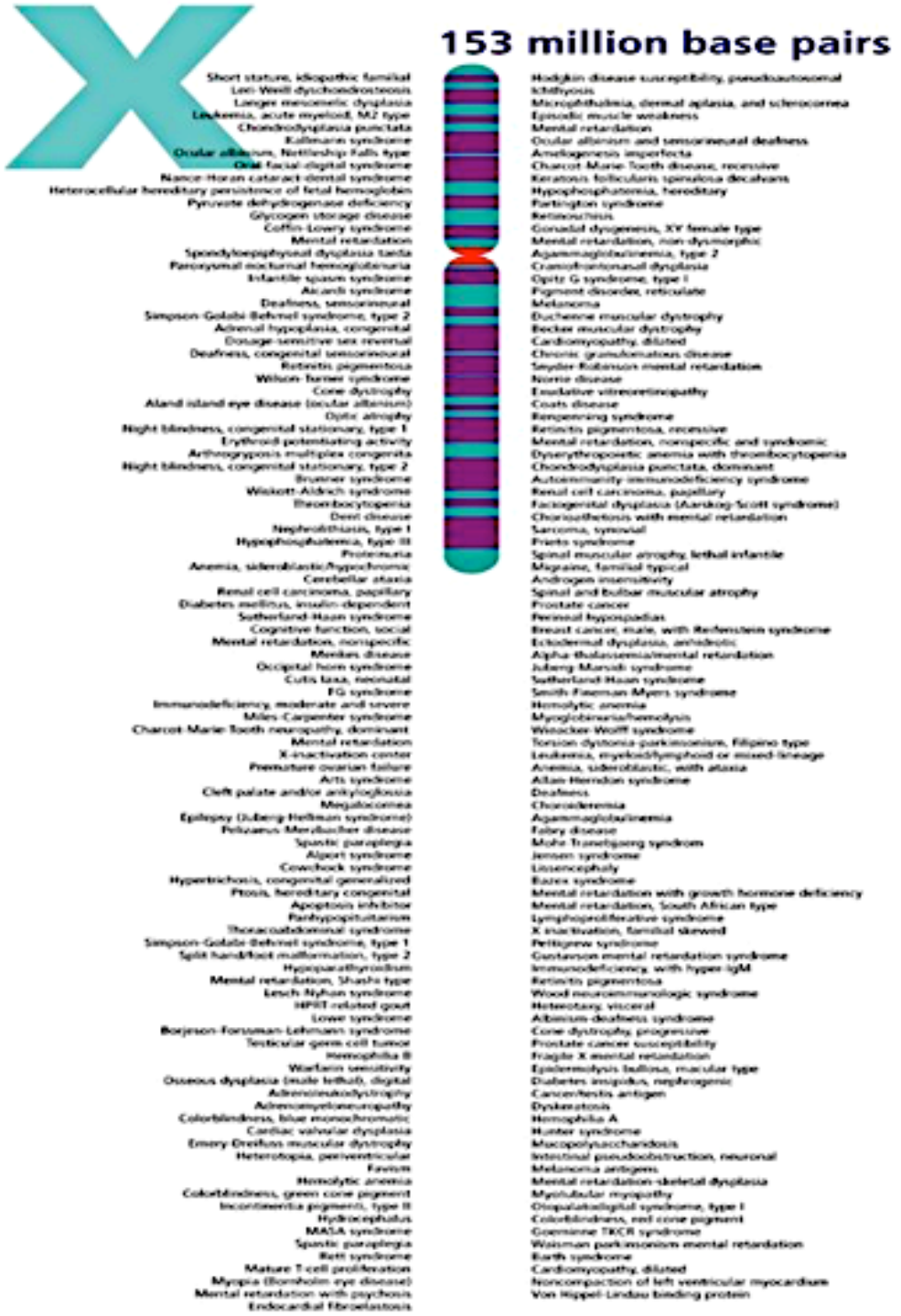
- **X-linked**
  - follow the X chromosomes
  - females get their X's from both parents
  - males get their X from their mother
    - trait is never passed from father to son directly

- **Y-linked**
  - Follow the Y chromosomes
  - very few genes / traits
  - trait is only passed from father to son
    - females cannot inherit trait on a Y

Ex: Hypertrichosis pinnae
[excessively long ear hair]



- Females can be **heterozygour or homozygous** for a gene on the X because they have two copies of the X chromosome
- Males are considered **hemizygous** for a gene on the X because they only get one copy of the X chromosome
  - *their phenotype is determined by that one copy only*



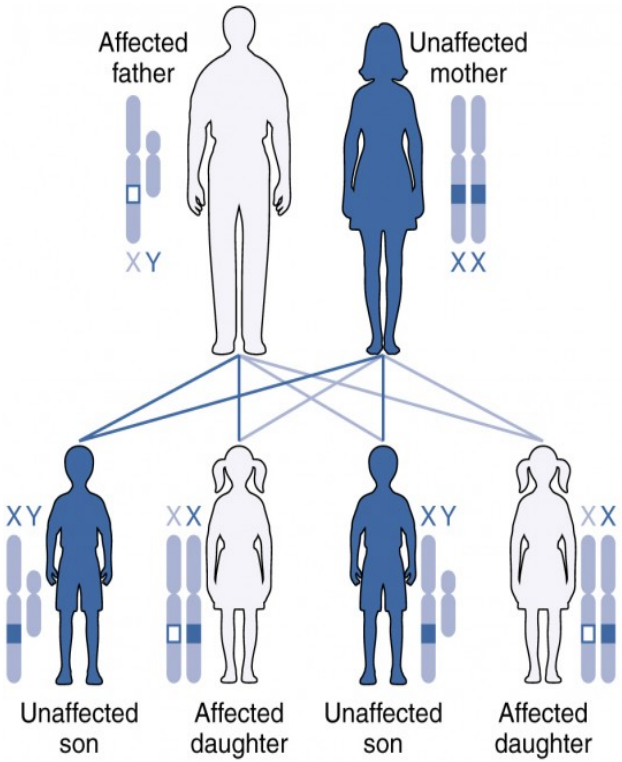
Males usually only have one copy of genes on the X chromosome, X-linked genes

e.g., X^HX^h or X^HX^H girls
X^HY or X^hY males
So males have X-linked recessive disorders more often, but females have X linked dominant disorders more often.

Sex-linked dominant disorders

- **When a gene is found on an autosome *[chromosomes #1-22]*, you do not write the allele as a superscript, *but when found on a sex chromosome*, you DO write the allele as a superscript of *X or Y*.**
  - **What are the parental genotypes here if it's a dominant disorder?**

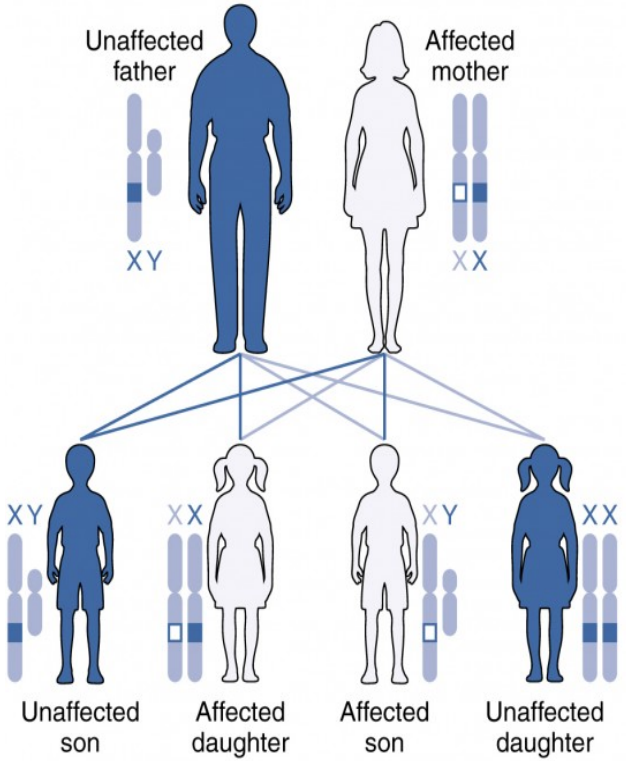
X^RY x X^rX^r



(a) X-linked dominant, affected father

Probabilities:
0% sons affected
100% daughters affected

X^rY x X^RX^r



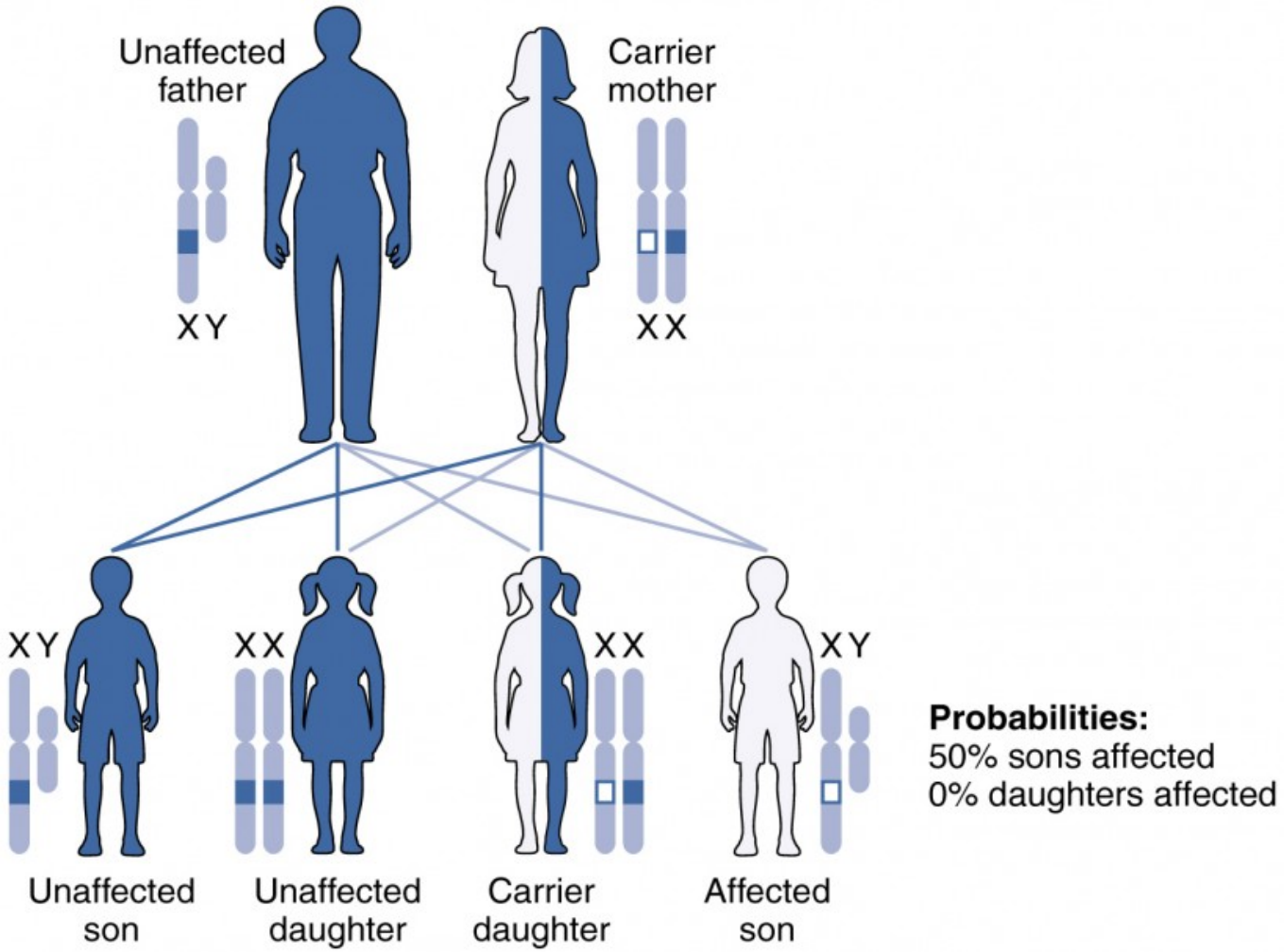
(b) X-linked dominant, affected mother

Probabilities:
50% sons affected
50% daughters affected

Sex-linked recessive disorders

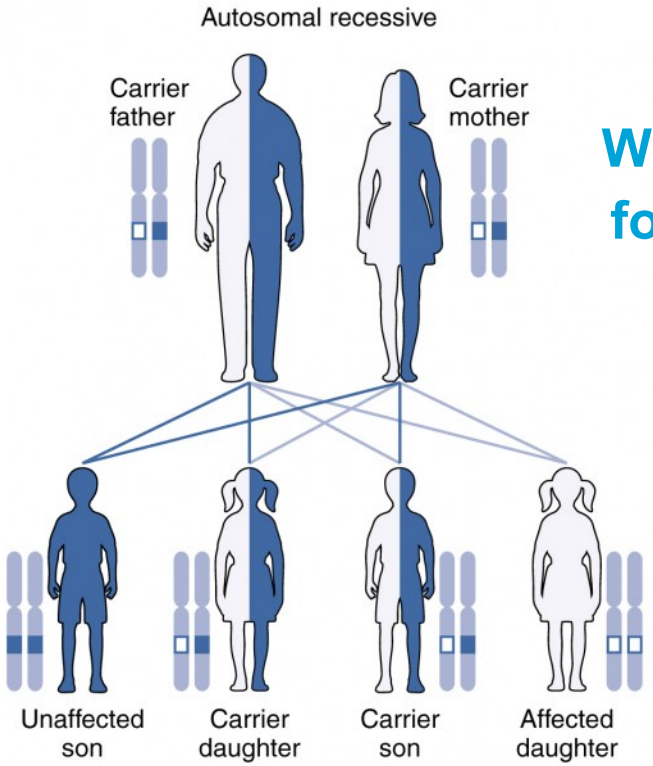
- What are the parental genotypes here if it's a recessive disorder?

$X^RY \times X^RX^r$



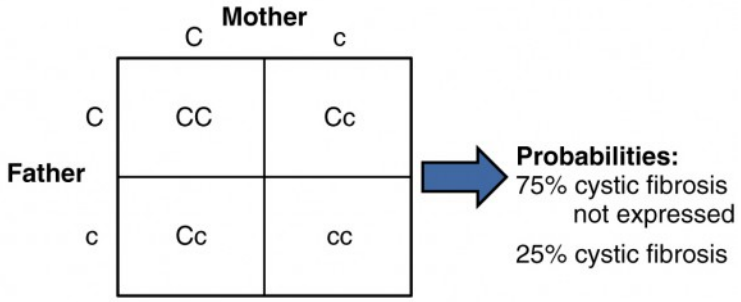
Autosomal recessive [& dominant] disorders

- **Remember, if it is an autosomal gene, both males and females inherit two copies of the gene, one from each parent.**
  - **The sex of the parent does not affect which child develops the phenotype in question**
  - **The sex of the child does not affect the phenotype the child displays. *[males and females can inherit a phenotype with equal likelihood].***
- **Because the gene is not located on the X or Y, you do not write the alleles as superscripts of a sex chromosome.**



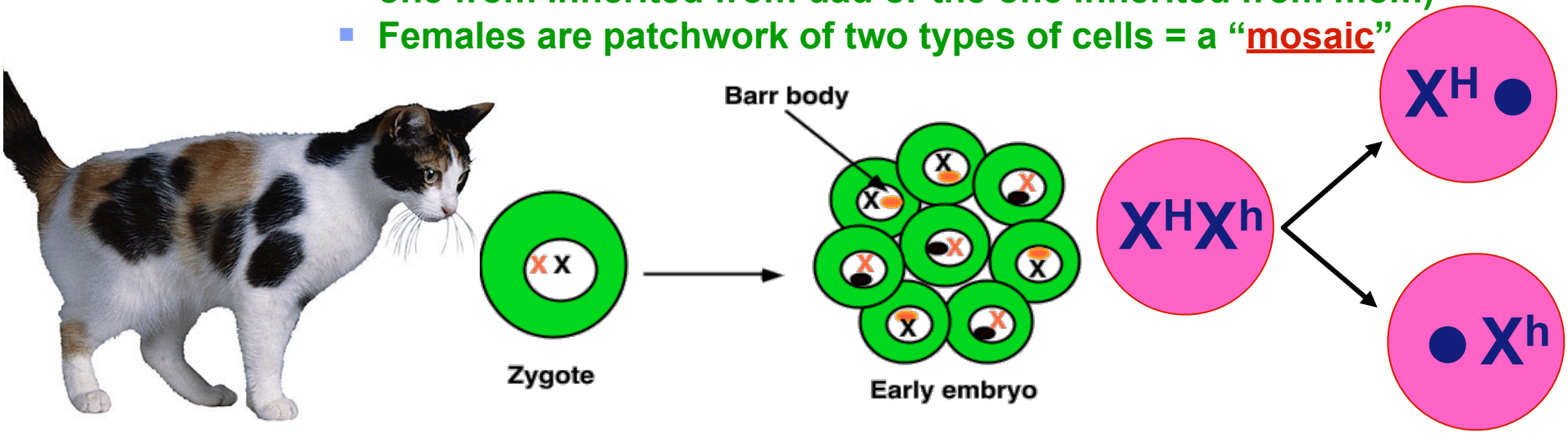
What are these parental phenotypes for an autosomal recessive gene C?

Cc x Cc



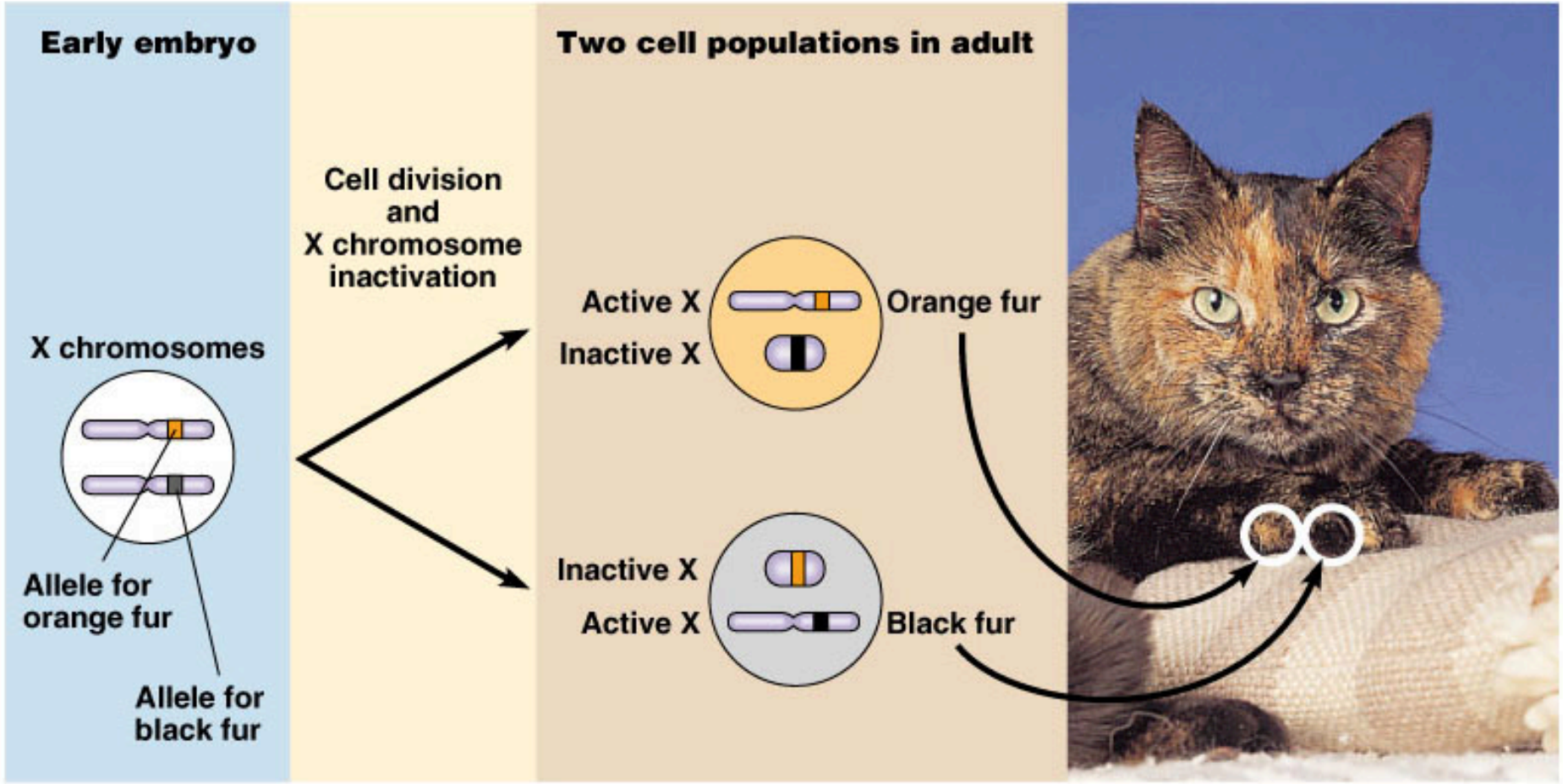
X-inactivation

- **Female mammals inherit 2 X chromosomes**
  - **one X becomes inactivated during embryonic development**
    - **one of the two X chromosomes in each cell inactivates by supercoiling. This irreversible process is known as Lyonization; Only ONE active X chromosome is left in each cell of the female embryo. Only the alleles on the active (uncoiled) X chromosome are expressed.**
  - **One of the 2 X's condenses into compact object = Barr body**
    - **Lyonization is random in each cell: there's no way to predict which of the two X chromosomes will become inactivated.**
      - **All mitotic descents of a cell will have the same X inactivated (the one from inherited from dad or the one inherited from mom)**
      - **Females are patchwork of two types of cells = a "mosaic"**



X-inactivation & tortoise shell cats

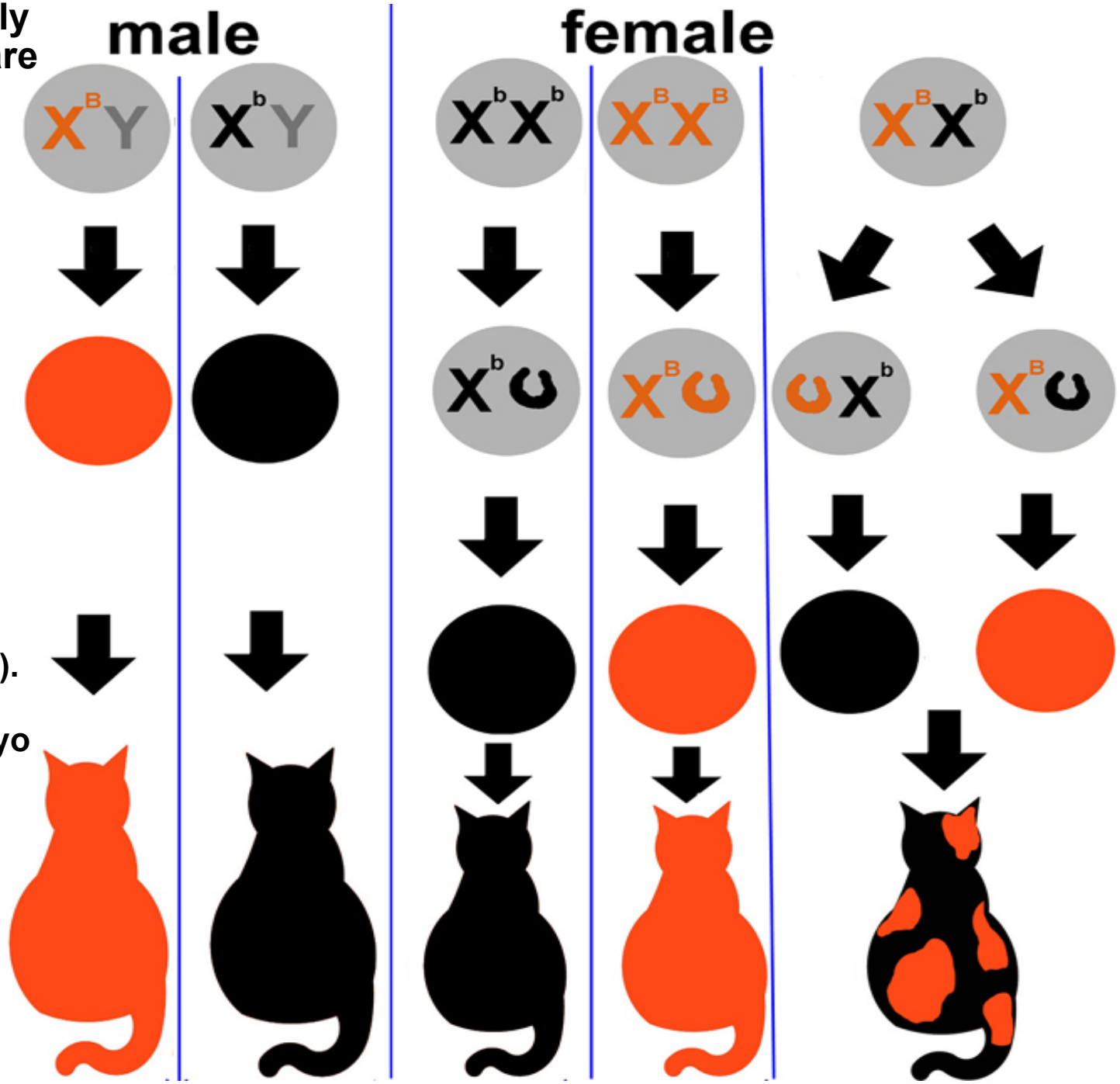
- There are 2 different cell lines making up this female cat



All males inherit only B or only b. There are no heterozygotes, because the Y does not carry the allele. Calico cats are, therefore, almost invariably female.

Can Male Cats Ever be Tortoiseshell?

In rare cases, a male cat can inherit *by mistake* two X chromosomes in addition to his Y chromosome (Klinefelter Syndrome). If this happens, each cell in the male embryo will undergo Lyonization, just as a female's would. If the two X chromosomes carry the different alleles (i.e., genotype is X^BX^bY), then the male will express calico coloration.



Exam Tips

- If a question is about one gene only (or about one character), the question may be trying to see if you can determine the inheritance pattern of that gene or of that phenotype
  - For a character (and its varying traits) determined by one gene:
    - In a heterozygote, do the different alleles behave in a completely dominant vs recessive fashion?
    - In a heterozygote, do the different alleles behave in an incomplete/ intermediate dominant fashion?
    - In a heterozygote, do the different alleles behave in a co-dominant?
    - Could the gene be located on the X or on the Y chromosome?
- If a question is about one character (with either no mention of the number of genes involved or with a mentioned of multiple genes being involved), the question may be trying to see if you can determine the inheritance mechanism of the (traits) phenotypes that can exist for that character
  - Is this character caused by one gene (and different allele combos)?
  - Is this character the result of polygenic inheritance?
  - Is this character a case of epistasis?

Exam Tips

- If a question is about multiple different characters, the question may be trying to see if you can determine the mechanism for the determination of these characters
  - Are the characters the result of one gene that exhibits pleiotropy?
  - Are the differing characters merely the result separate genes?
- If a question is about two or more genes or two or more characters, the question may be trying to see if you can identify that two or more of the genes are linked
  - Does it appear that certain combination of specific alleles for two or more genes are inherited more often together than they should be if they were assorting independently (located on different chromosomes)?
  - Do you get more parental phenotypes and fewer recombinant phenotypes in the final offspring than expected?
    - Perform all the matings from each generation (produce the Punnett Squares) as though the genes assort independently to determine the ratio and numbers of each phenotype of offspring you would expect in the generation you are to analyze.
    - Then, compare your expected ratio and number of each type of offspring to the actual observed ratio and numbers of offspring to see if the observed phenotypes and numbers match the expected in terms of parental vs recombinant phenotypes.