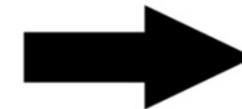


# Linked genes and Sex-Linked genes

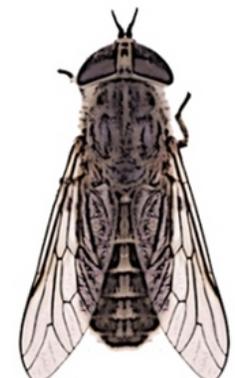
genotype



codes for



phenotype



# Mendel vs. Morgan's Allele Notation



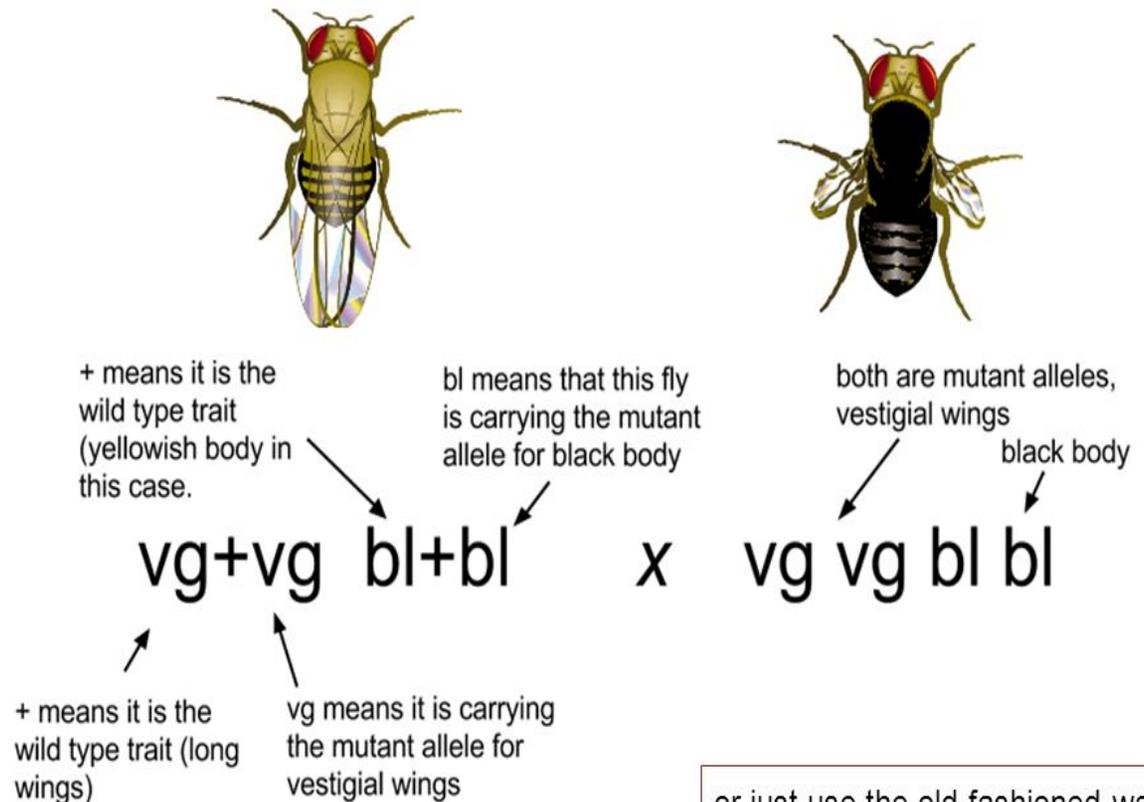
Mendel didn't know how heredity and genetics worked.

- ◆ 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



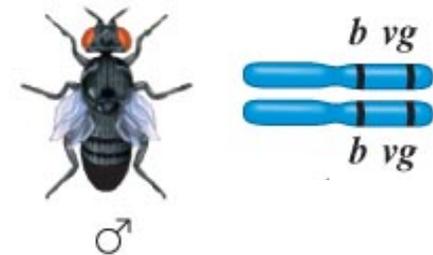
or just use the old fashioned way

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.

Black body, vestigial wings  
(double mutant)

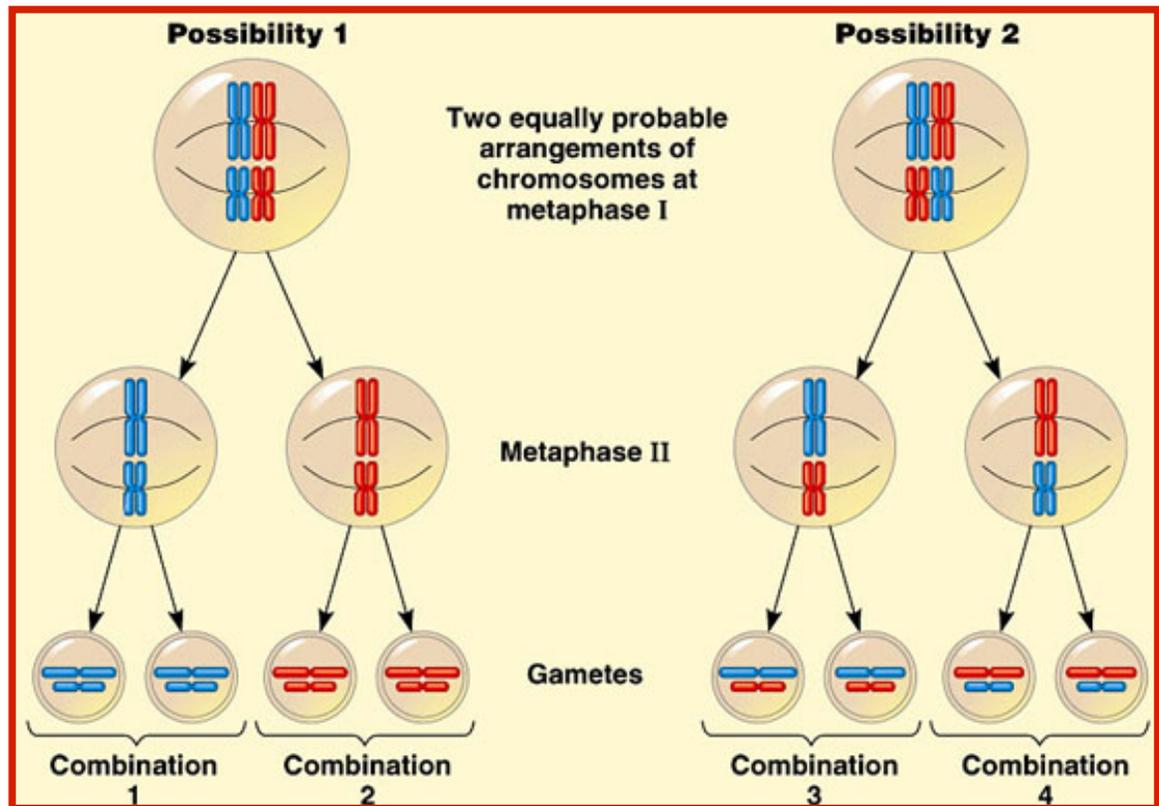


# Recall meiosis

- 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.



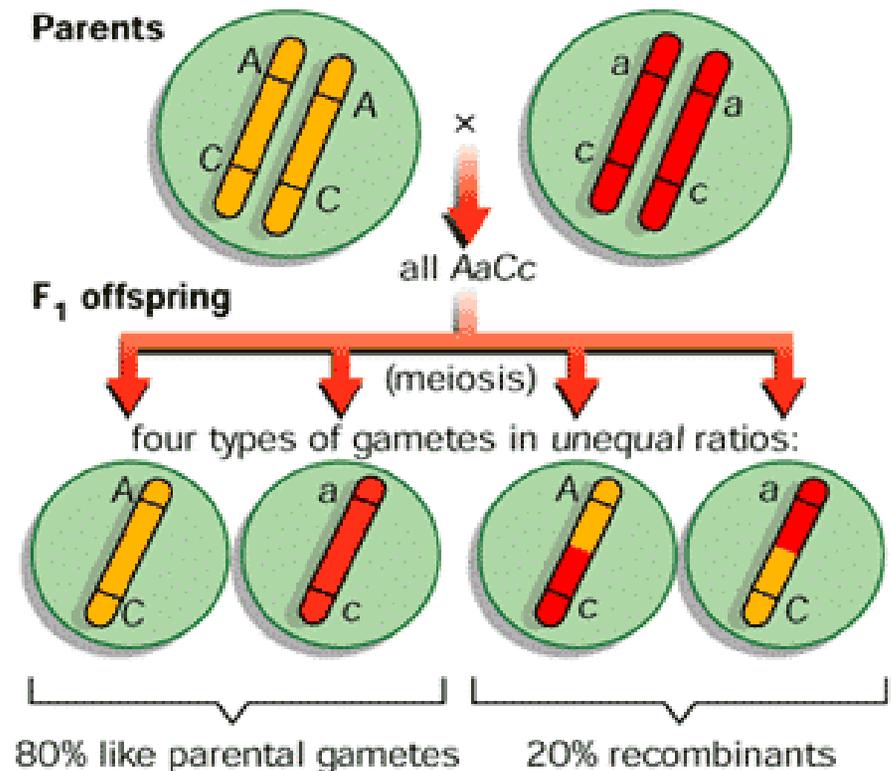
# Linked Genes

- 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 F<sub>1</sub> 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.*

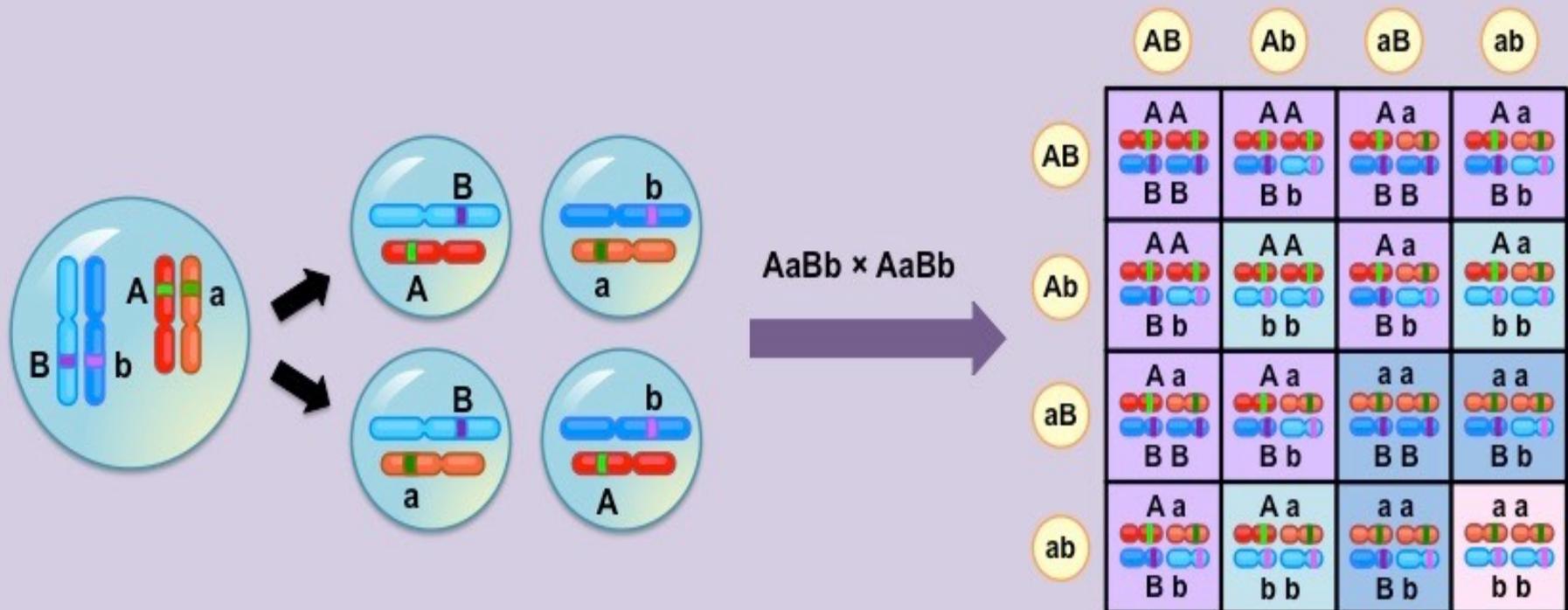
Recombinant chromosomes in gametes are far less likely to occur the closer two genes are ----->



# 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**

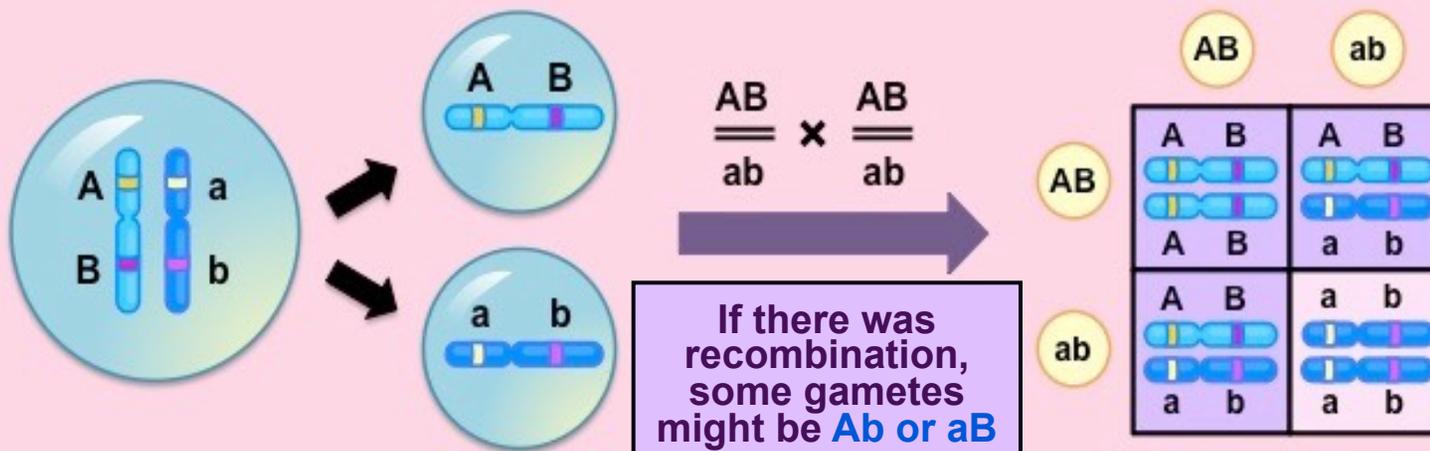
## Unlinked genes – Dihybrid Pattern (four potential gamete combinations)



# 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 – Monohybrid Pattern (two potential gamete combinations)



If there was recombination, some gametes might be **Ab** or **aB**

This scenario shows the result of meiosis if **NO** crossing over occurred at all!

*Certain phenotypes may not occur unless there is recombination*

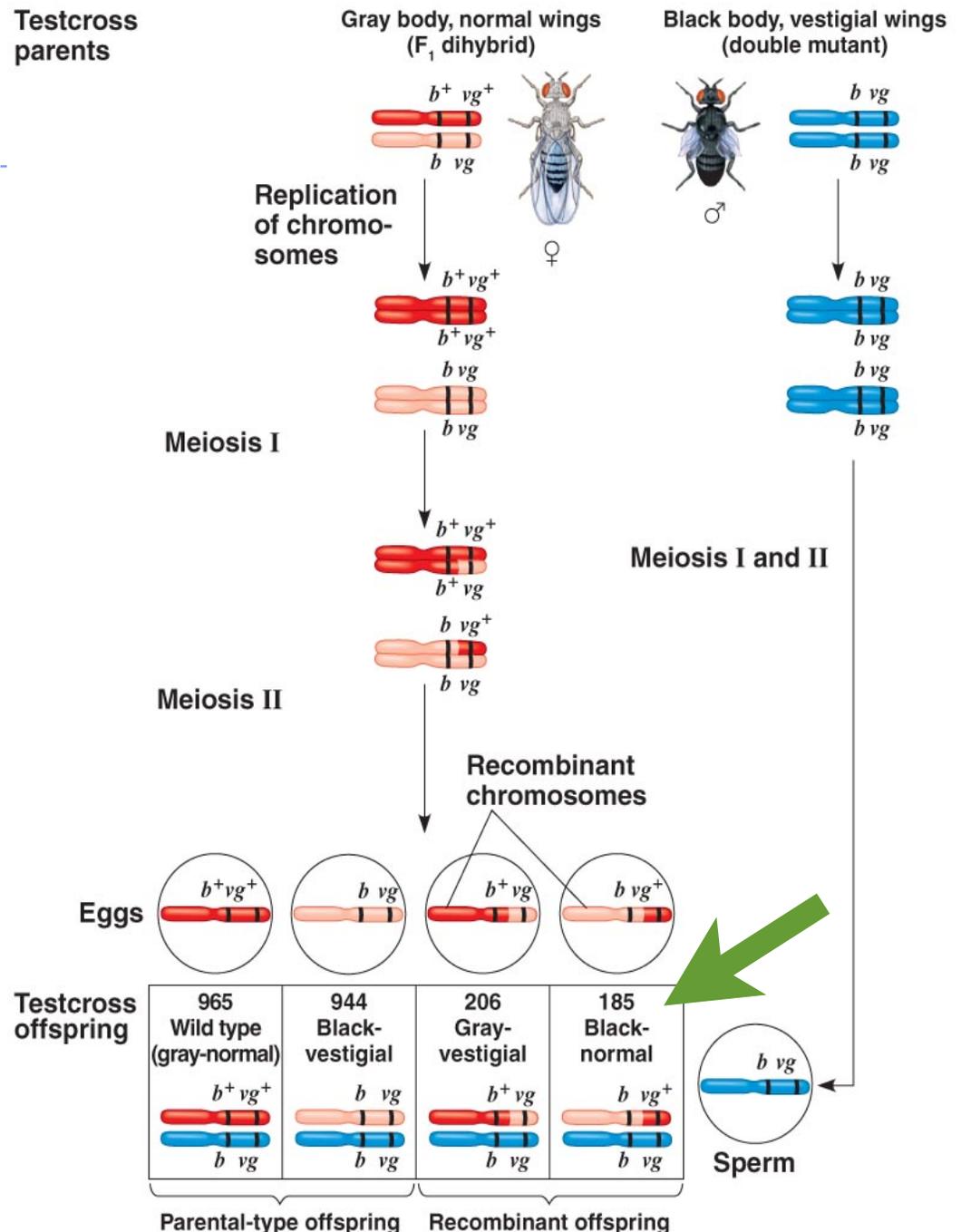
# Linked Genes

- 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  $b^+bvg^+vg \times bbvgvg$  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!

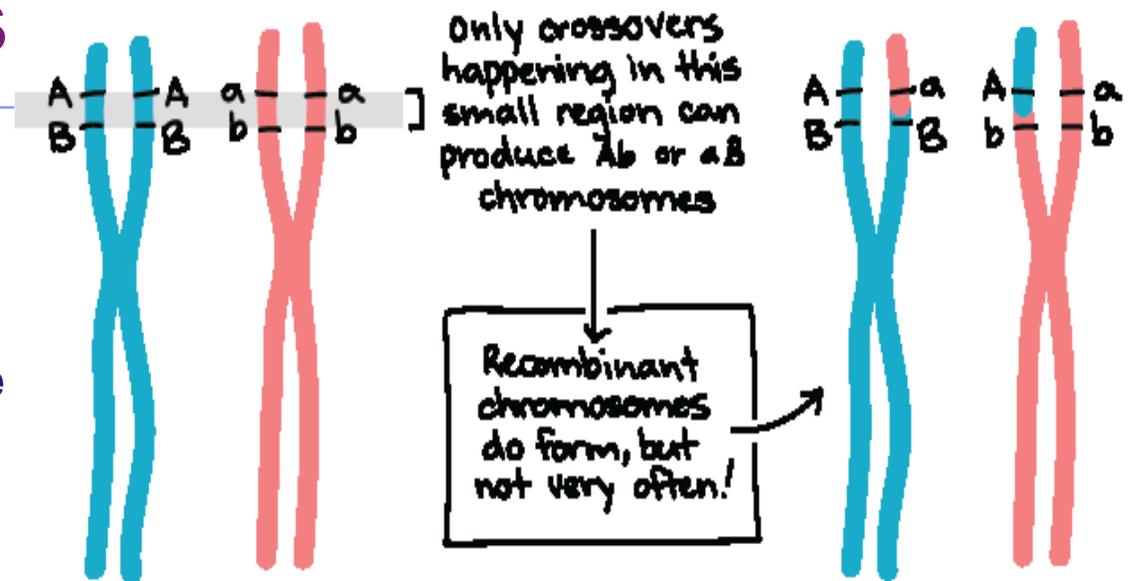


# Linked Genes

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



Testcross offspring

965 Wild type (gray-normal)	944 Black- vestigial	206 Gray- vestigial	185 Black- normal
$b^+ vg^+$	$b vg$	$b^+ vg$	$b vg^+$
$b vg$	$b vg$	$b vg$	$b vg$
Parental-type offspring		Recombinant offspring	

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

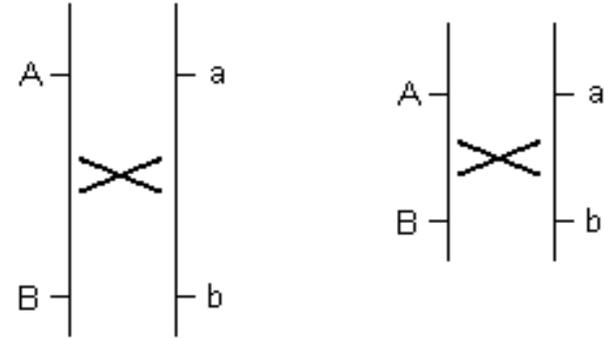
# Linked Genes

- ◆ 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]

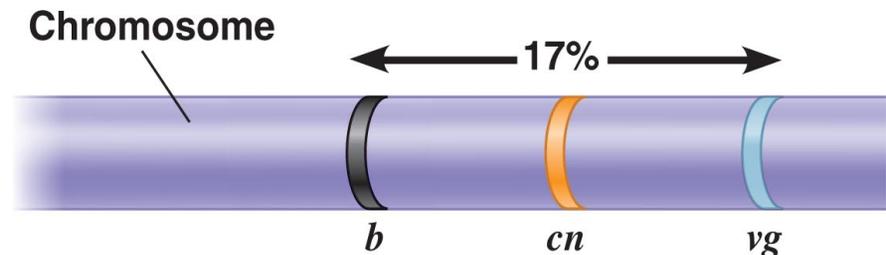


genes far apart, crossovers are relatively frequent

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

Testcross offspring	965 Wild type (gray-normal)	944 Black-vestigial	206 Gray-vestigial	185 Black-normal
	$b^+ vg^+$	$b vg$	$b^+ vg$	$b vg^+$
	$b vg$	$b vg$	$b vg$	$b vg$
	Parental-type offspring		Recombinant offspring	

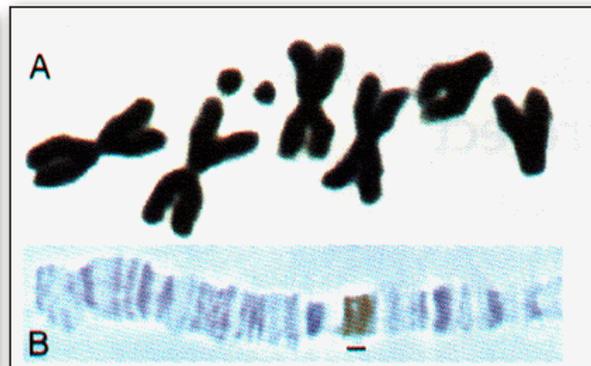
$$\text{Recombination frequency} = \frac{391 \text{ recombinants}}{2,300 \text{ total offspring}} \times 100 = 17\%$$



1910 | 1933

# Sex-linked traits

- 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]



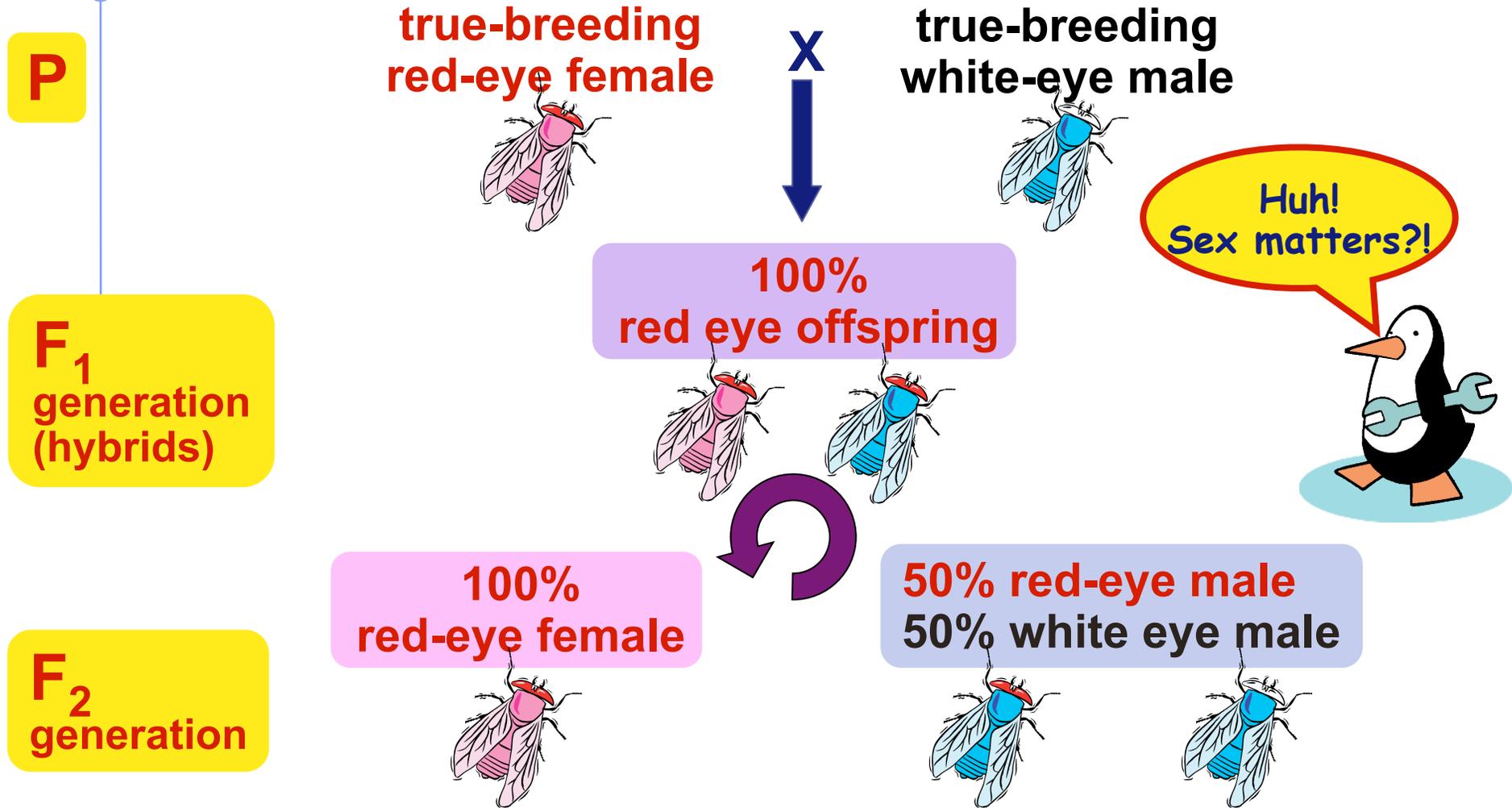
# Classes of human chromosomes



**autosomal  
chromosomes**

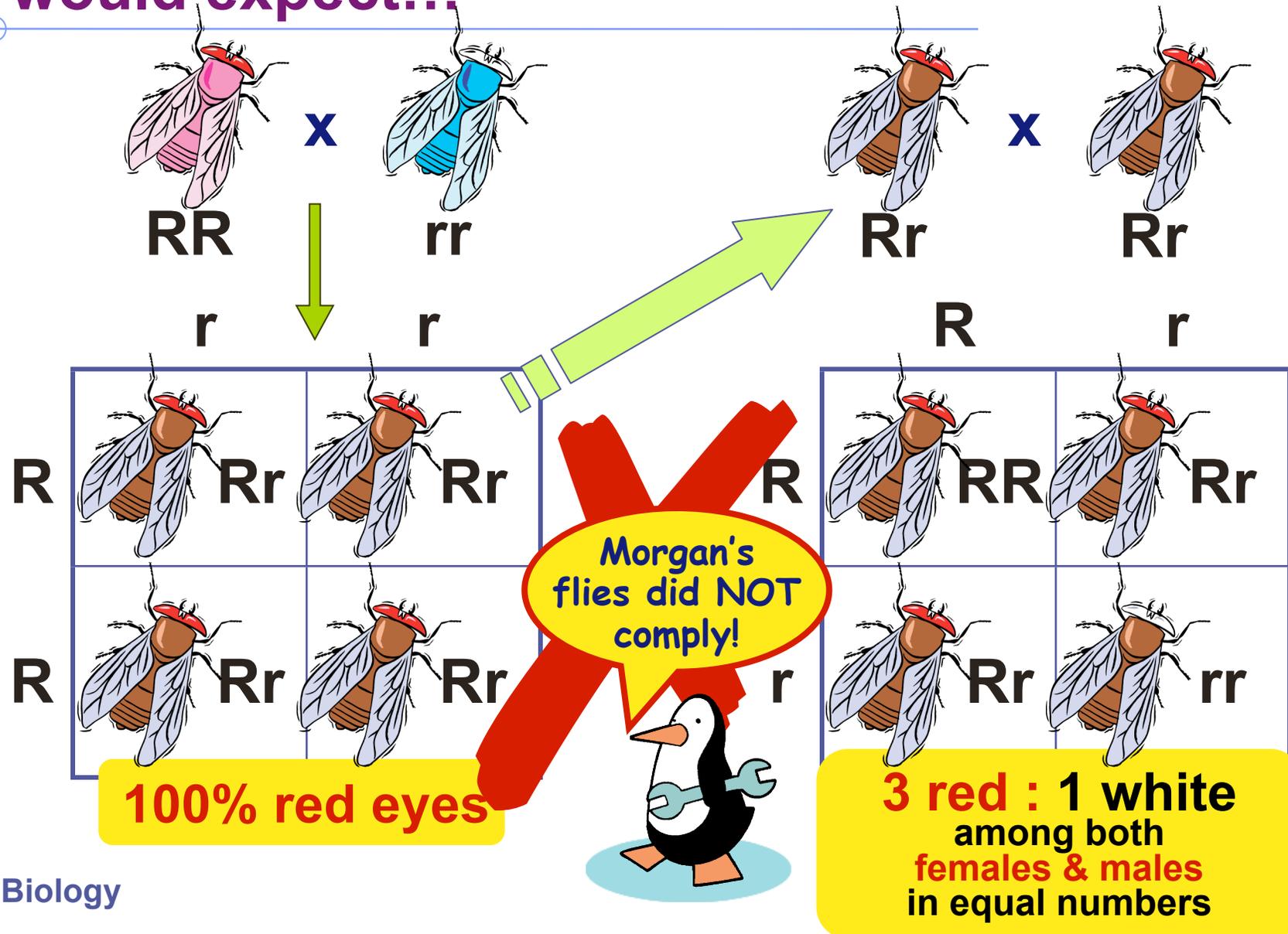


# Discovery of sex-linked genes (genes located on the sex chromosomes - historically the X chromosome)



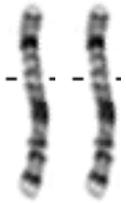
In the F<sub>2</sub> generation, Morgan saw the 3:1 ratio, BUT curiously, ONLY MALES inherited white eyes!

# If gene was on autonomous chromosome would expect...



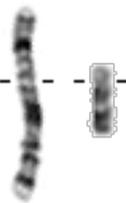
# Genetics of Sex

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



- ◆ **2 X chromosomes**

- develop as a female: **XX**
- gene redundancy, like autosomal chromosomes



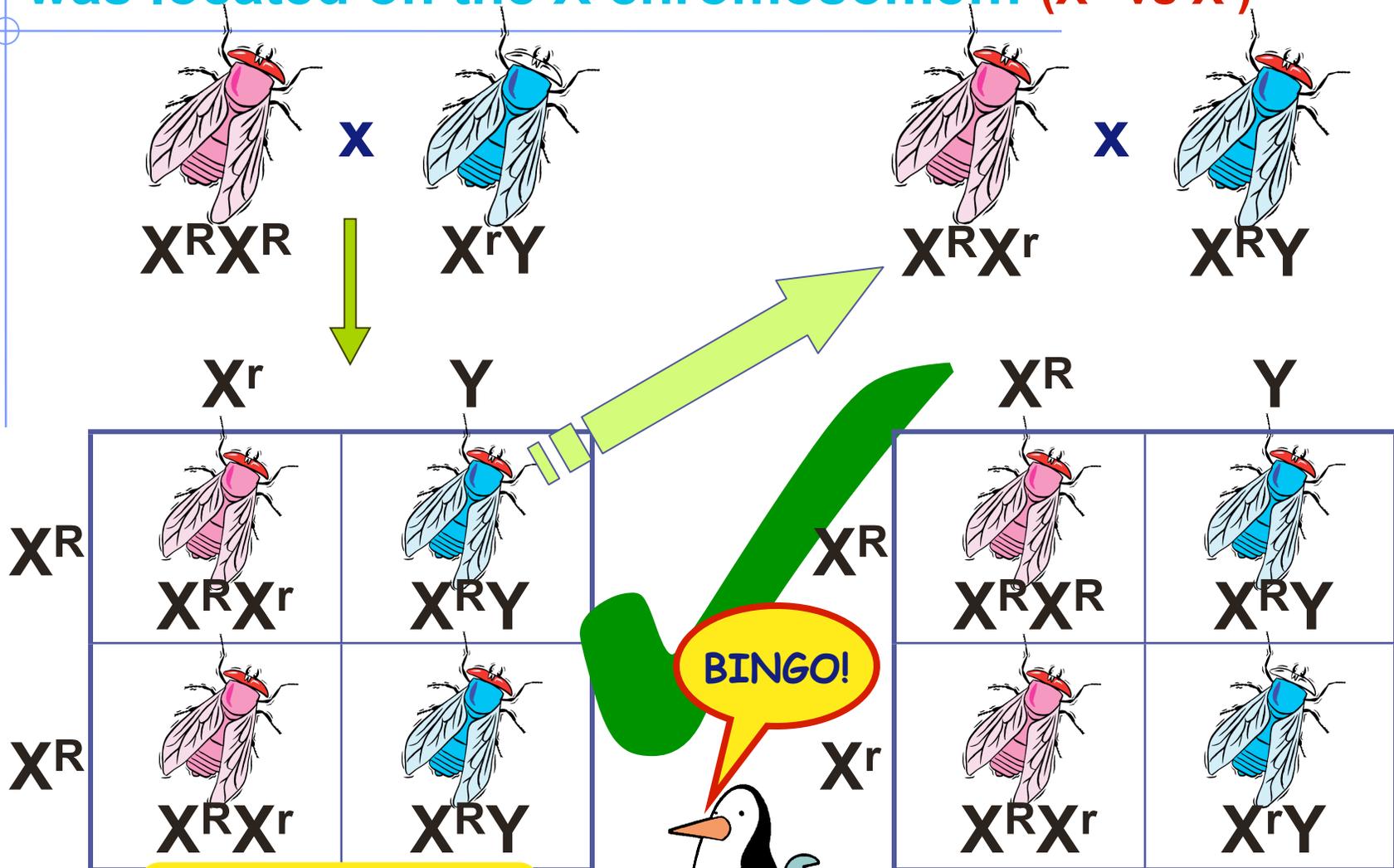
- ◆ **an X & Y chromosome**

- 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 $X^r$ )



**BINGO!**

**100% red eyes (male & female)**

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

# Sex chromosomes genes

## ■ Y chromosome

- ◆ few genes (~78)
  - < 30 code for proteins

## ◆ Includes the

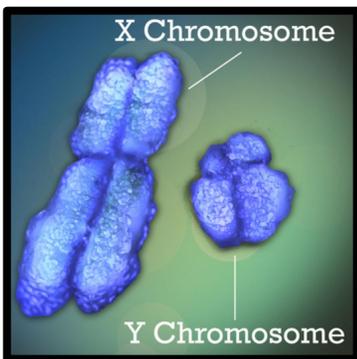
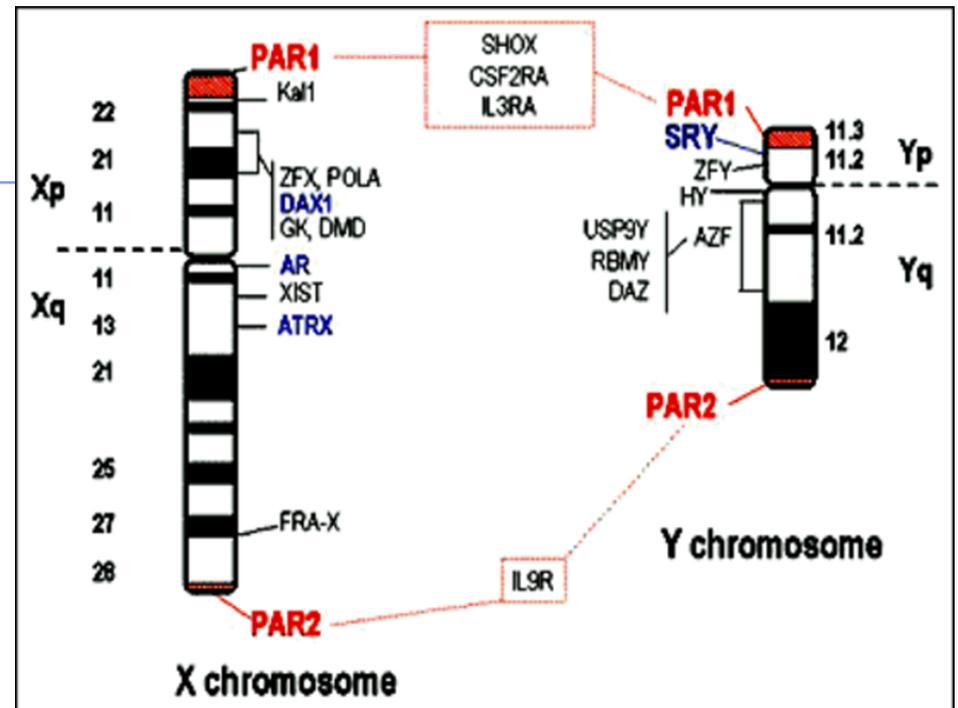
### SRY gene:

- 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

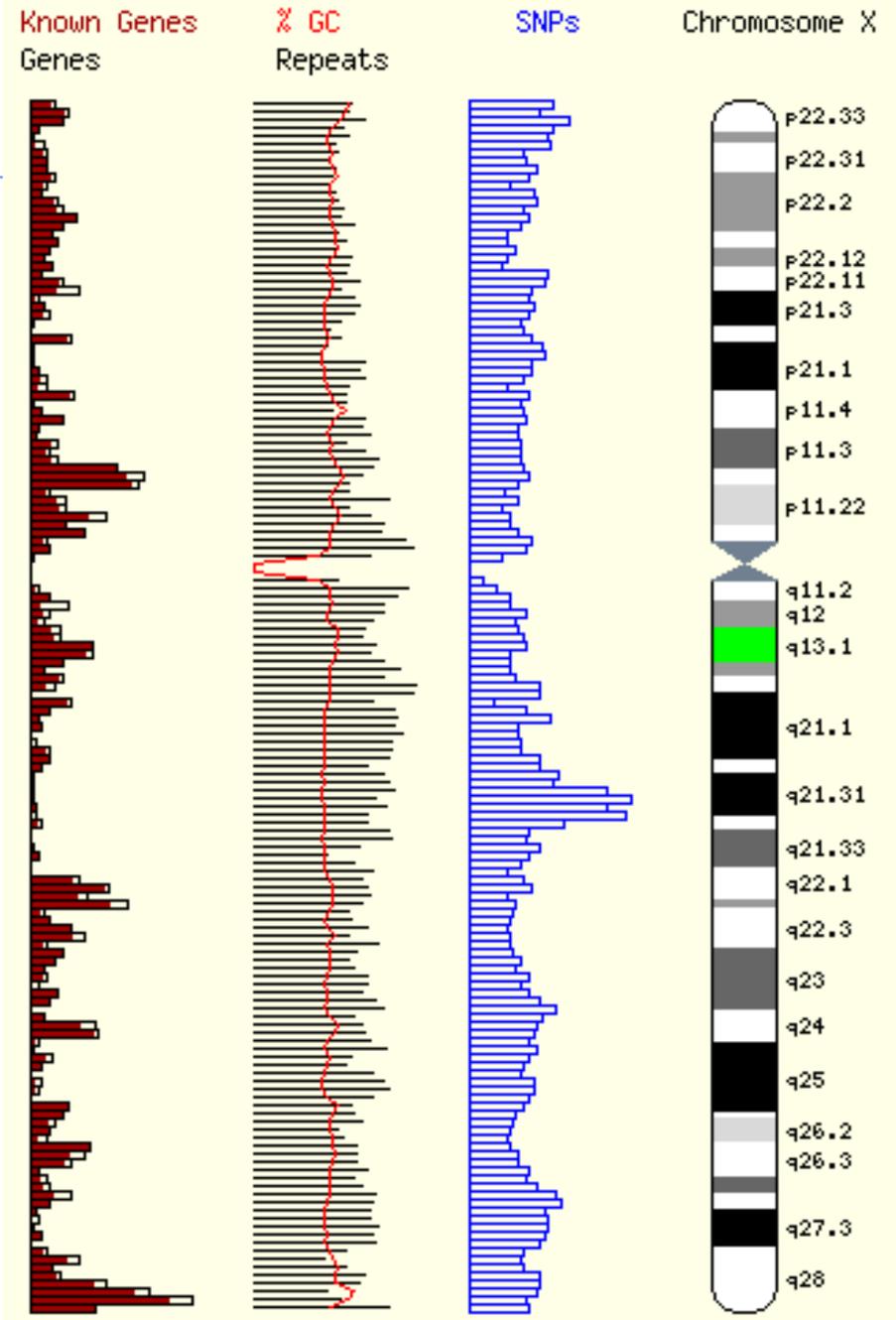
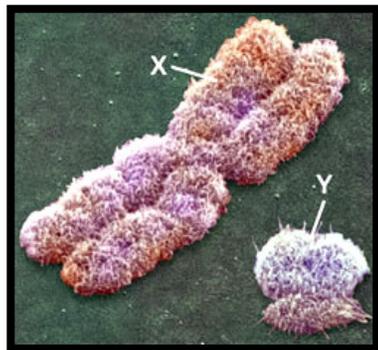
dystrophy

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





# Sex-linked traits summary

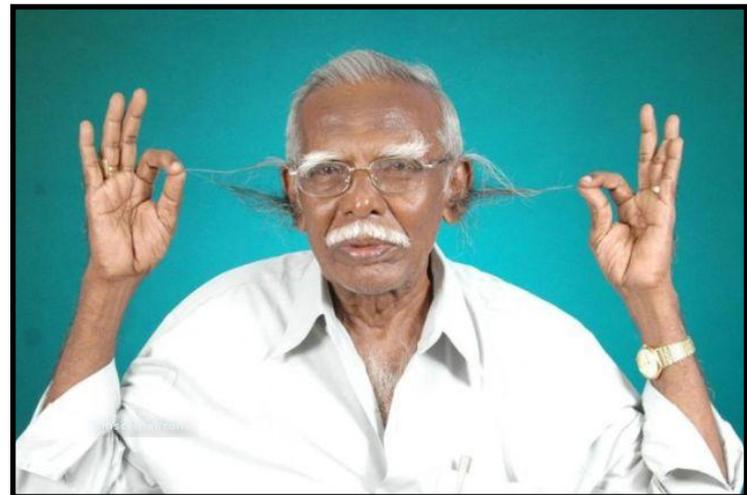
## ■ X-linked

- ◆ 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 heterozygous 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*



153 million base pairs



- Short stature, idiopathic familial
- Levi-Wail dyschondrosteosis
- Langer mesomelic dysplasia
- Leukemia, acute myeloid, M2 type
- Chondrodysplasia punctata
- Kallmann syndrome
- Ocular albinism, Nettleship-Falls type
- Oral-facial-digital syndrome
- Nance-Horan cataract-oral syndrome
- Heterocellular hereditary persistence of fetal hemoglobin
- Pyruvate dehydrogenase deficiency
- Glycogen storage disease
- Coffin-Lowry syndrome
- Mental retardation
- Spondyloepiphyseal dysplasia tarda
- Paroxysmal nocturnal hemoglobinuria
- Infantile spasms syndrome
- Aicardi syndrome
- Deafness, sensorineural
- Simpson-Golabi Behmel syndrome, type 2
- Adrenal hypoplasia, congenital
- dosage-sensitive sex reversal
- Deafness, congenital sensorineural
- Retinitis pigmentosa
- Wilson disease
- Cone dystrophy
- Aland island eye disease (ocular albinism)
- Optic atrophy
- Night blindness, congenital stationary, type 1
- Erythroid potentiating activity
- Arthropogonias multiplex congenita
- Night blindness, congenital stationary, type 2
- Brunner syndrome
- Wiskott-Aldrich syndrome
- Thrombocytopenia
- Deaf disease
- Nephroblastosis, type 1
- Hypophosphatemia, type III
- Proximal
- Anemia, sideroblastic/hypochromic
- Cerebellar ataxia
- Renal cell carcinoma, papillary
- Diabetes mellitus, insulin-dependent
- Sutherland-Haas syndrome
- Cognitive function, local
- Mental retardation, nonspecific
- Meckel disease
- Occipital horn syndrome
- Cutis laxa, neonatal
- FG syndrome
- Immunodeficiency, moderate and severe
- Milan-Carpenter syndrome
- Charcot-Marie-Tooth neuropathy, dominant
- Mental retardation
- X-inactivation center
- Premature ovarian failure
- Arts syndrome
- Cleft palate and/or arylglucosidase
- Megalocornea
- Epilepsy (Juberg-Hellman syndrome)
- Poliomyelitis, Merzbacher disease
- Spastic paraplegia
- Alport syndrome
- Cowchock syndrome
- Hypertichosis, congenital generalized
- Pituitary hereditary congenital
- Apoptosis inhibitor
- Parhyopoptarism
- Thoracoabdominal syndrome
- Simpson-Golabi Behmel syndrome, type 1
- Split hand/foot malformation, type 2
- Hypoparathyroidism
- Mental retardation, Shasho type
- Emch-Mylhan syndrome
- HPRT-related gout
- Lower syndrome
- Bojeron-Forsman-Lehmann syndrome
- Testicular germ cell tumor
- metaphilia B
- Wolfein sensitivity
- Osteous dysplasia (osteofibrous, digital)
- Adrenomedullarydystrophy
- Adrenomedullarydystrophy
- Colorblindness, blue monochromatic
- Cardiac valvular dysplasia
- Emery-Dreifuss muscular dystrophy
- Heterotopia, periventricular
- Ferret
- Hemolytic anemia
- Colorblindness, green cone pigment
- Incontinentia pigmenti, type II
- Hydrocephalus
- MASA syndrome
- Spastic paraplegia
- Reit syndrome
- Mature T cell proliferation
- Myopia (Blomholm eye disease)
- Mental retardation with psychosis
- Endocardial fibroelastosis

- Hodgkin disease susceptibility, pseudoautosomal
- Ichthyosis
- Microphthalmia, dermal aplasia, and sclerocornea
- Episodic muscle weakness
- Mental retardation
- Ocular albinism and sensorineural deafness
- Amelogenesis imperfecta
- Charcot-Marie-Tooth disease, recessive
- Keratin 10/follicular keratins decalves
- Hypophosphatemia, hereditary
- Peritrigon syndrome
- Retinoblastoma
- Gonadal dysgenesis, XY female type
- Mental retardation, non-dysmorphic
- Agammaglobulinemia, type 2
- Craniofrontonasal dysplasia
- Optic G syndrome, type I
- Fagnot disorder, reticulate
- Melanoma
- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Cardiomyopathy, dilated
- Chronic granulomatous disease
- Snyder-Robinson mental retardation
- Normo disease
- Exudative vitreoretinopathy
- Coats disease
- Rosenberg syndrome
- Retinitis pigmentosa, recessive
- Mental retardation, nonspecific and syndromic
- Dyserythropoietic anemia with thrombocytopenia
- Chondrodysplasia punctata, dominant
- Autism spectrum disorder
- Renal cell carcinoma, papillary
- Facioscapular dysplasia (Aarskog-Scott syndrome)
- Chorioretinitis with mental retardation
- Sarcoma, synovial
- Fried's syndrome
- Spinal muscular atrophy, lethal infantile
- Migraine, familial typical
- Androgen insensitivity
- Spinal and bulbar muscular atrophy
- Prostate cancer
- Penoscrotal hypospadias
- Breast cancer, male, with Reberstein syndrome
- Echocardial dysplasia, arched
- Alpha-thalassaemia/mental retardation
- Juberg-Marsh syndrome
- Sutherland-Haas syndrome
- Smith-Faesman Myers syndrome
- Hemolytic anemia
- Myoglobinuria/hemolysis
- Winkler-Wortl syndrome
- Torsion dystonia-parkinsonism, Filipino type
- Leukemia, myeloid/lymphoid or mixed lineage
- Anemia, sideroblastic, with ataxia
- Alan-Hemidin syndrome
- Deafness
- Chromolemia
- Agammaglobulinemia
- Foley disease
- Mohr-Trantergaard syndrome
- Jensen syndrome
- Lissencephaly
- Baxex syndrome
- Mental retardation with growth hormone deficiency
- Mental retardation, South African type
- Lymphoproliferative syndrome
- X inactivation, familial skewed
- Pettigrew syndrome
- Gusterson mental retardation syndrome
- Immunodeficiency, with hyper IgM
- Retinitis pigmentosa
- Wood neuroendocrinologic syndrome
- Heterotaxy, visceral
- Albinism-deafness syndrome
- Cone dystrophy, progressive
- Prostate cancer susceptibility
- Fragile X mental retardation
- Epileptiformy bulbous, muscular type
- Diabetes insipidus, nephrogenic
- Carcinoma antigen
- Dyskeratosis
- Hemophilia A
- Hunter syndrome
- Mucopolysaccharidosis
- Intestinal pseudoobstruction, neuronal
- Melanoma antigen
- Mental retardation-skeletal dysplasia
- Myotubular myopathy
- Ornithinolytic syndrome, type I
- Colorblindness, red cone pigment
- Goemanne TRCR syndrome
- Waisman parkinsonism mental retardation
- Bath syndrome
- Cardiomyopathy, dilated
- Noncompaction of left ventricular myocardium
- Von Hippel-Lindau binding protein

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

e.g.,  $X^H X^h$  or  $X^H X^H$  girls  
 $X^H Y$  or  $X^h Y$  males

So males have X-linked recessive disorders more often, but females have X linked dominant disorders more often.



50 million base pairs

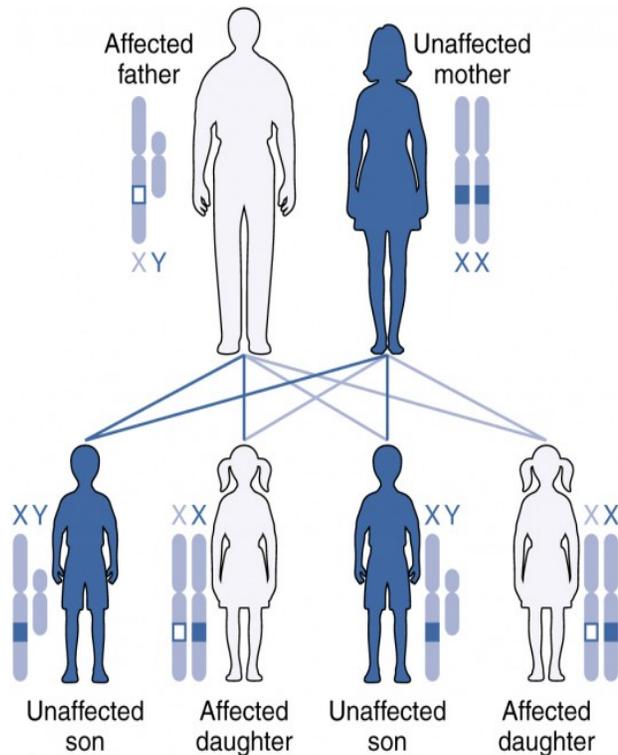


- Short stature homeo box, Y-linked
- Short stature
- Leri-well dyschondrosteosis
- Langer mesomelic dysplasia
- Interleukin-3 receptor, Y chromosomal
- Sex-determining region Y (testis-determining)
- Gonadal dysgenesis, XY type
- Protocadherin 11, Y-linked
- Azoospermia factors
- Male infertility due to spermatogenic failure
- Growth control, Y-chromosome influenced
- Chromodomain proteins
- Retinitis pigmentosa, Y-linked

# 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?

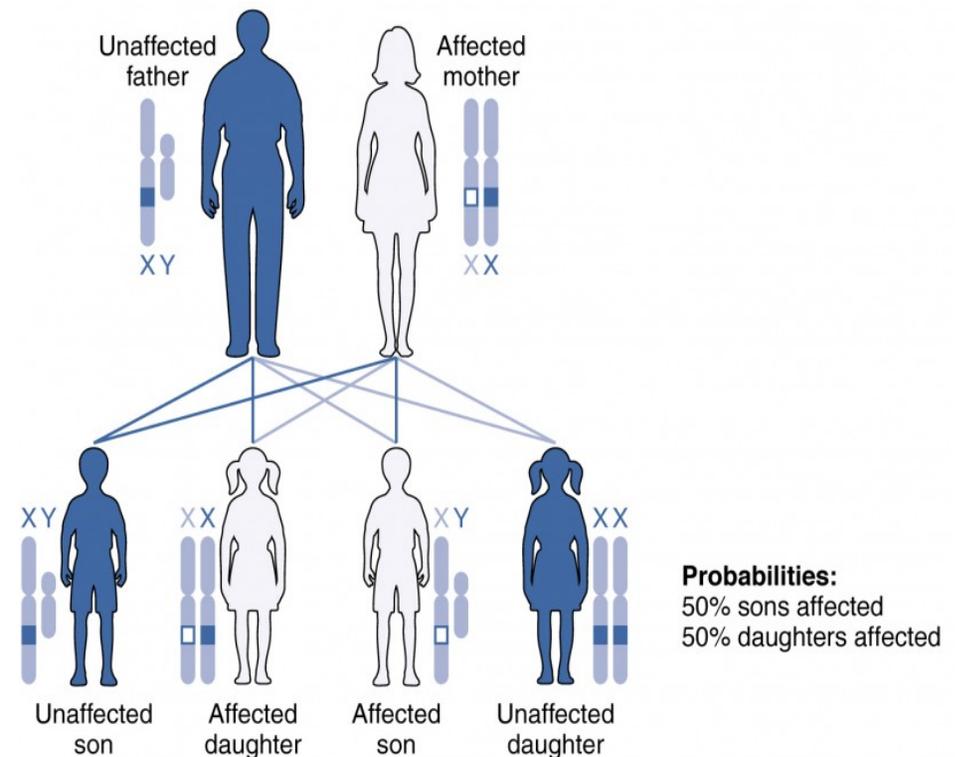
$X^R Y \times X^r X^r$



(a) X-linked dominant, affected father

$X^r Y \times X^R X^r$

**Probabilities:**  
0% sons affected  
100% daughters affected

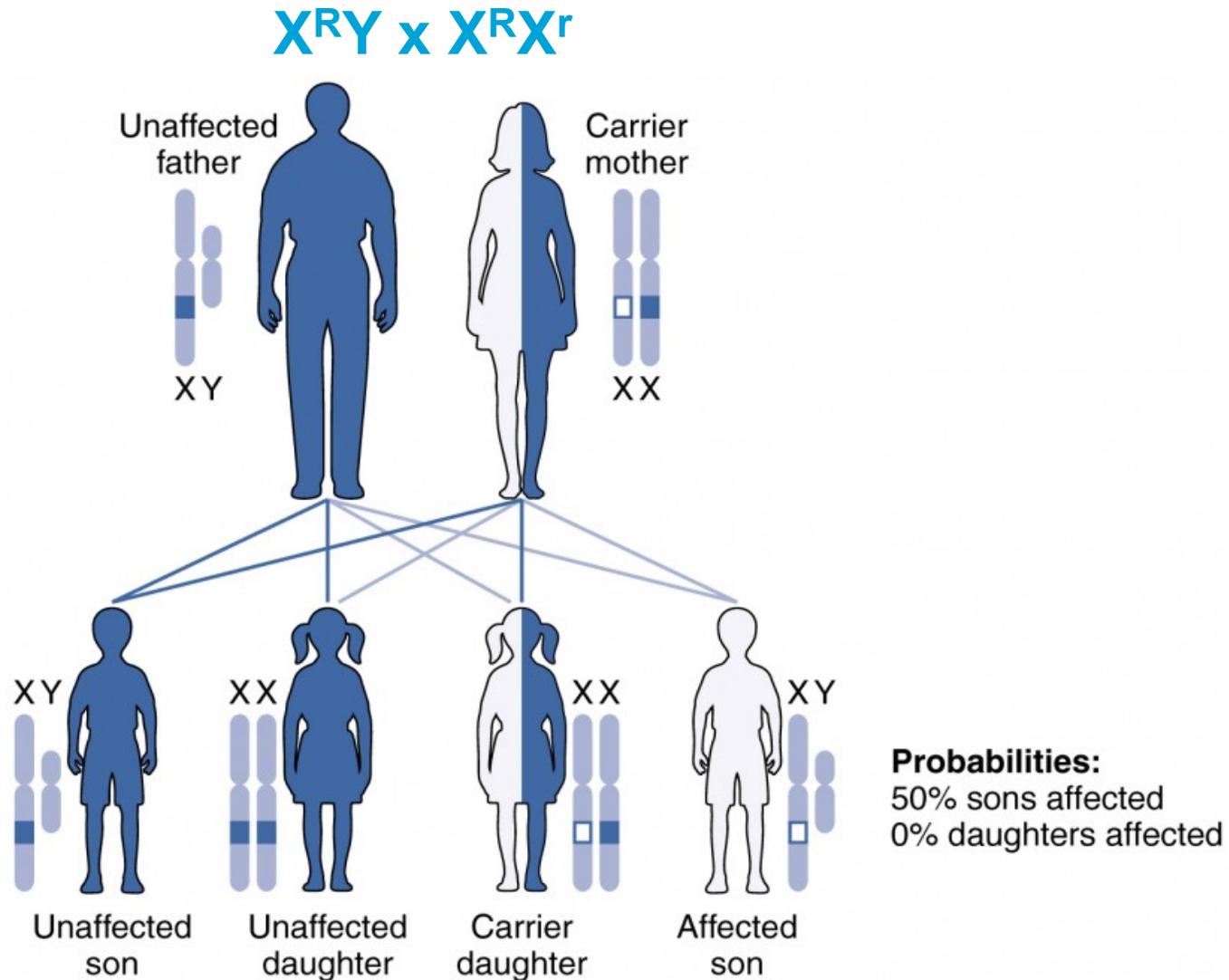


**Probabilities:**  
50% sons affected  
50% daughters affected

(b) X-linked dominant, affected mother

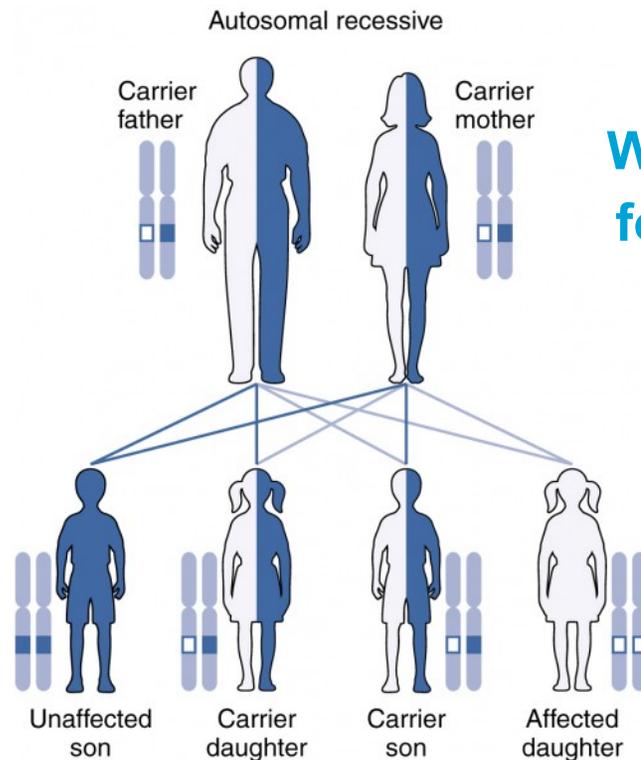
# Sex-linked recessive disorders

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



# 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?

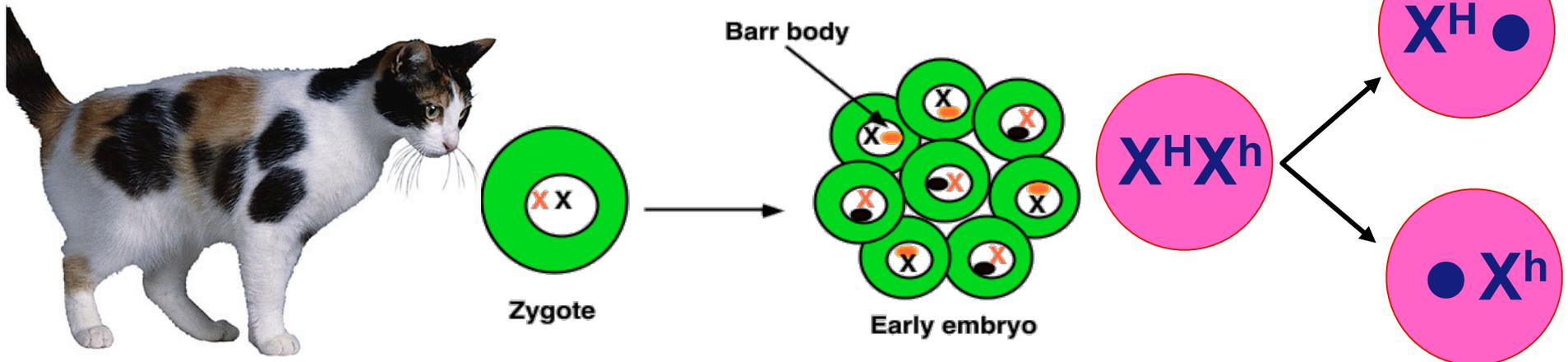
$Cc \times Cc$

		Mother	
		C	c
Father	C	CC	Cc
	c	Cc	cc

Probabilities:  
75% cystic fibrosis not expressed  
25% cystic fibrosis

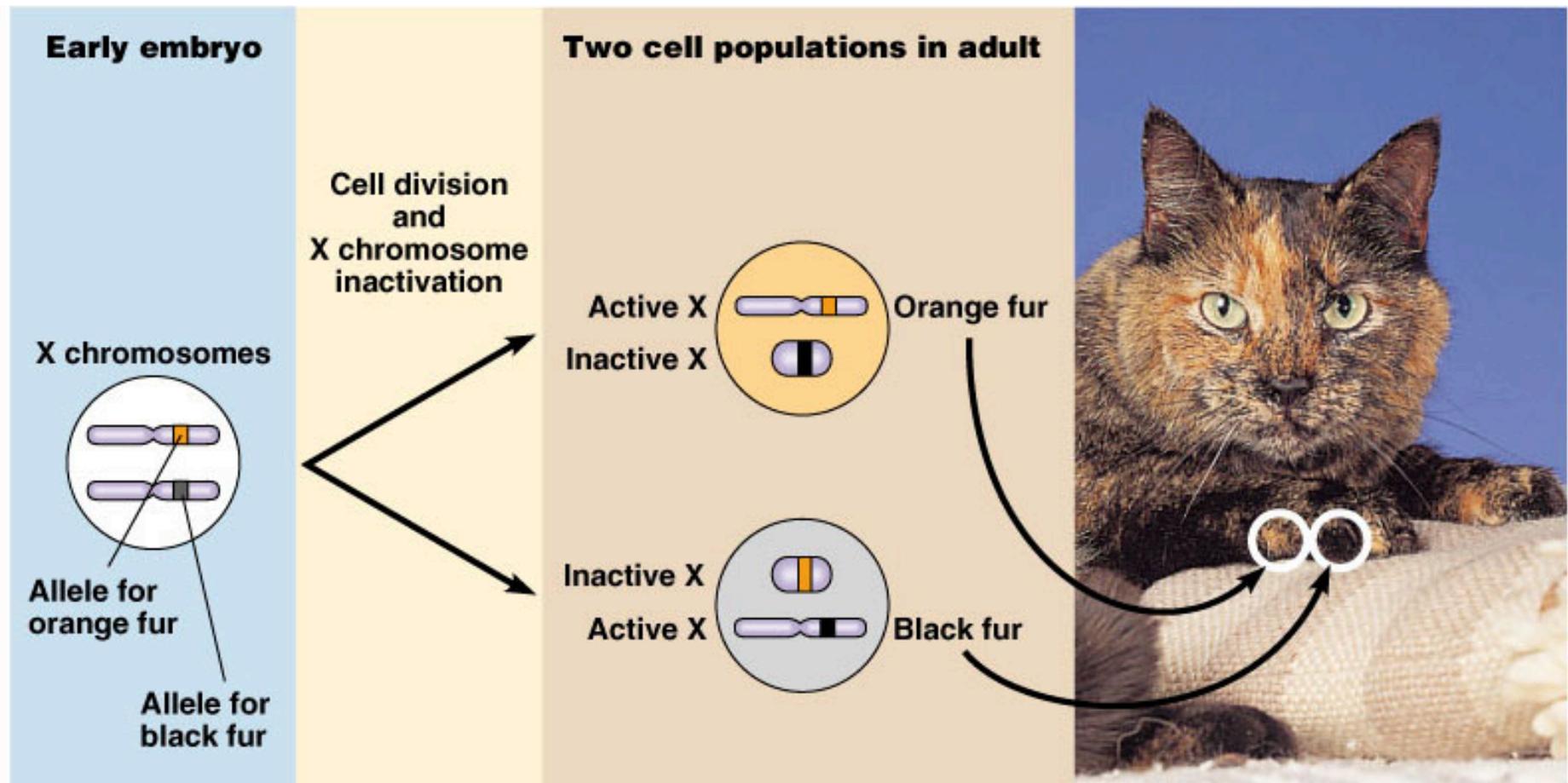
# X-inactivation

- 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

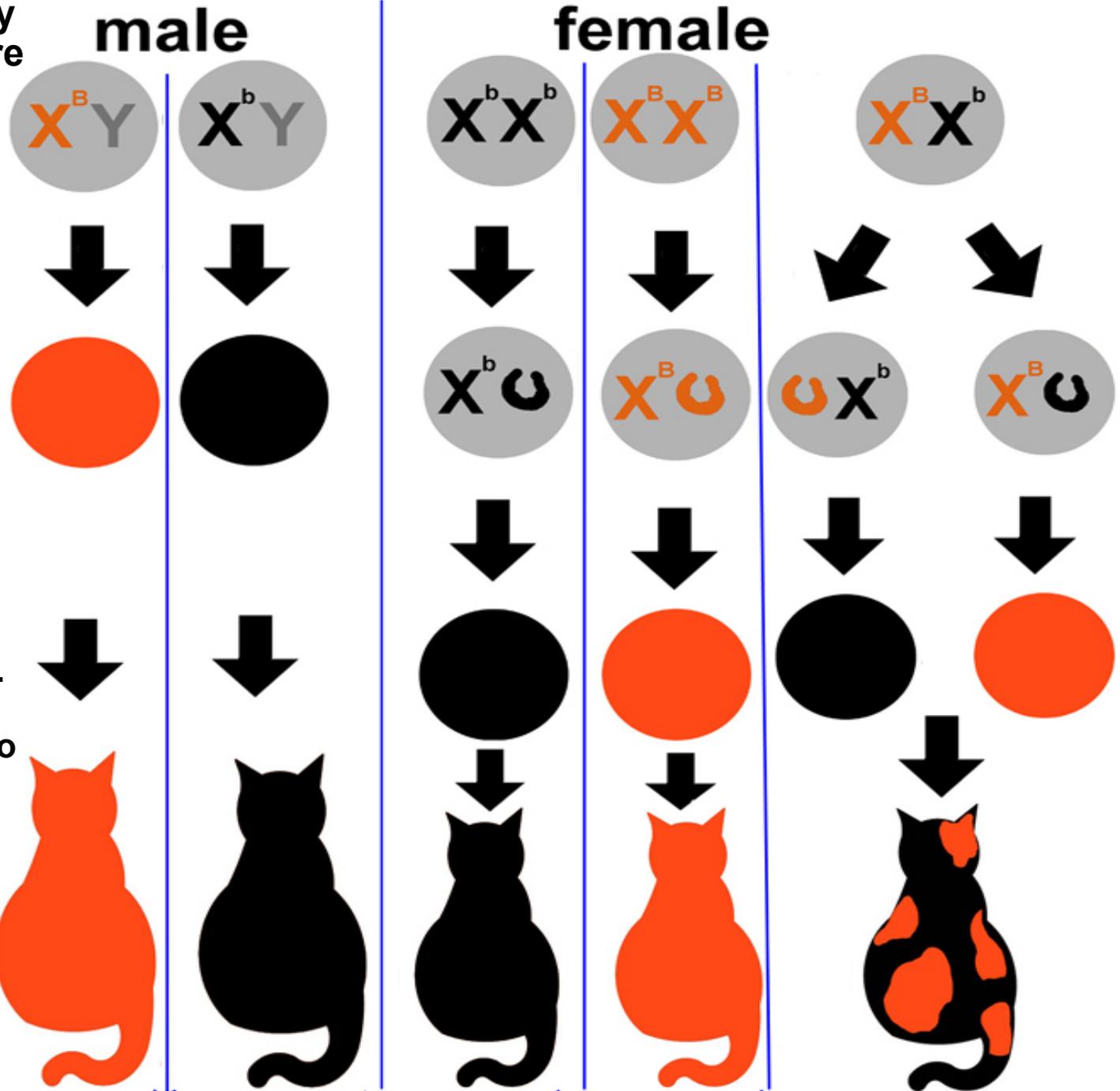


All males inherit only B or only b. There are **no** heterozygotes, because the Y does not carry the allele.

**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  $X^B X^b Y$ ), 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.