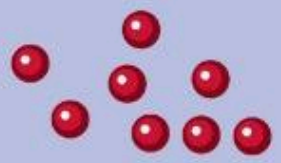
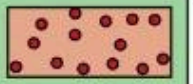
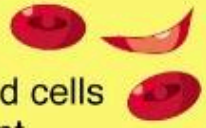
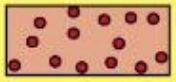
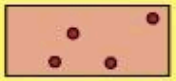
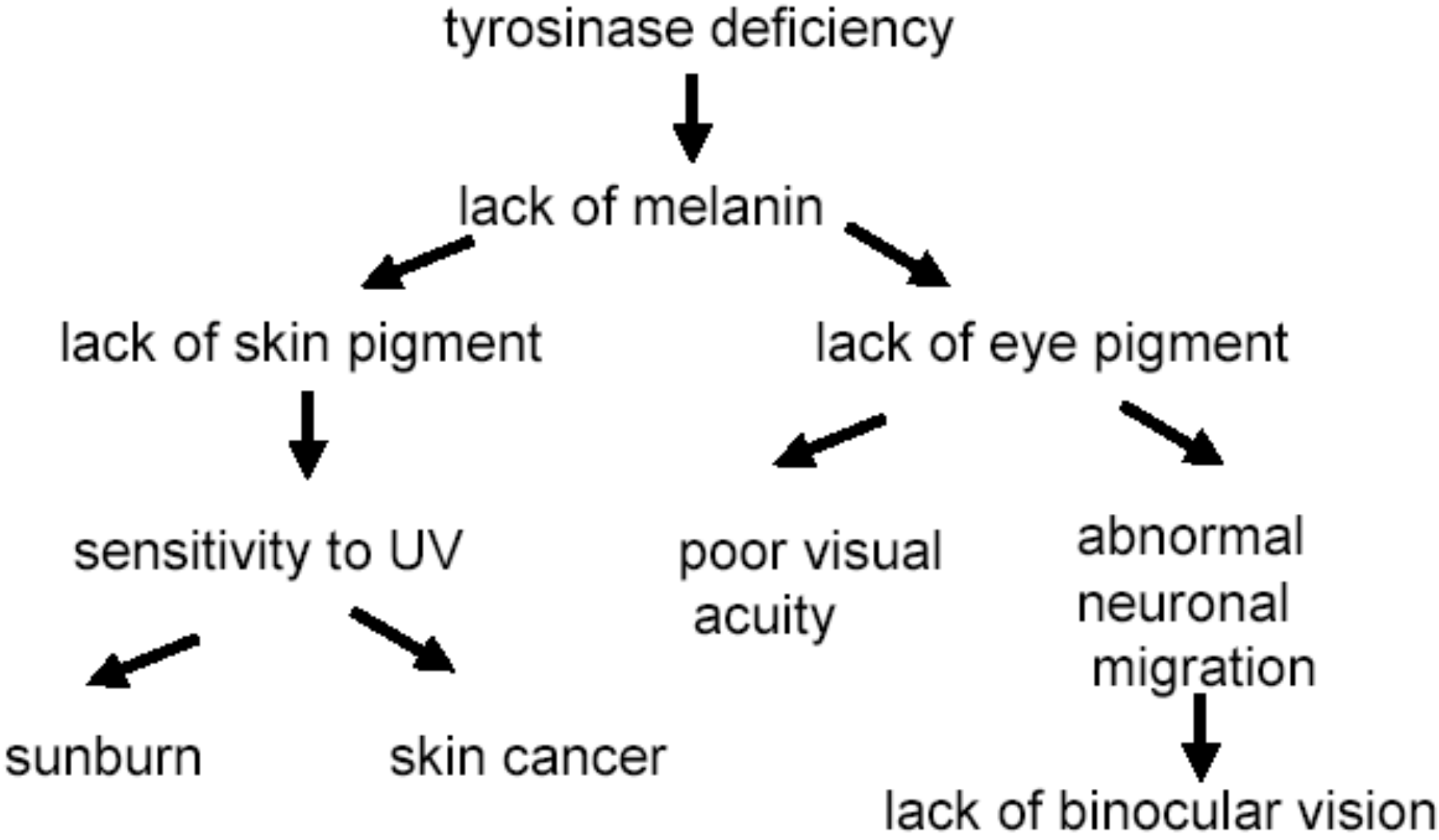
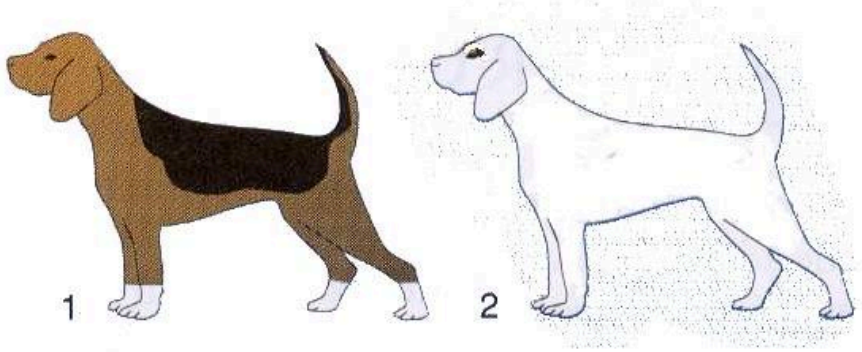
Pleiotropic mutations have effects on several different characters. In this case the dominance relationships depend on the phenotype examined.

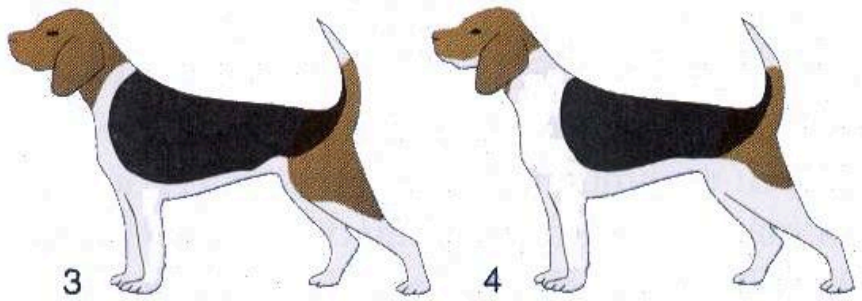
Phenotypes at Different Levels of Analysis	Normal *AA*	Carrier *AS*	Diseased *SS*	Dominance Relations at Each Level of Analysis
β–Globin polypeptide production				*A* and *S* are codominant
Red blood cell shape at sea level	 Normal	 Normal	 Sickled cells present	*A* is dominant *S* is recessive
Red blood cell concentration at sea level	 Normal cells	 Normal	 Lower	
Red blood cell shape at high altitudes	 Normal	 Sickled cells present	 Severe sickling	*A* and *S* show incomplete dominance
Red blood cell concentration at high altitudes	 Normal	 Lower	 Very low, anemia	
Susceptibility to malaria	 Normal susceptibility	 Resistant	 Resistant	*S* is dominant *A* is recessive

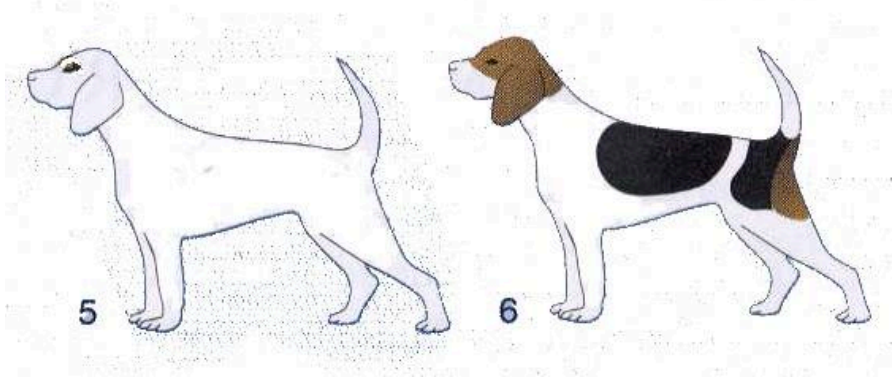
PLEIOTROPY


tyrosinase deficiency
lack of melanin
lack of skin pigment
lack of eye pigment
sensitivity to UV
poor visual acuity
abnormal neuronal migration
sunburn
skin cancer
lack of binocular vision

Penetrance





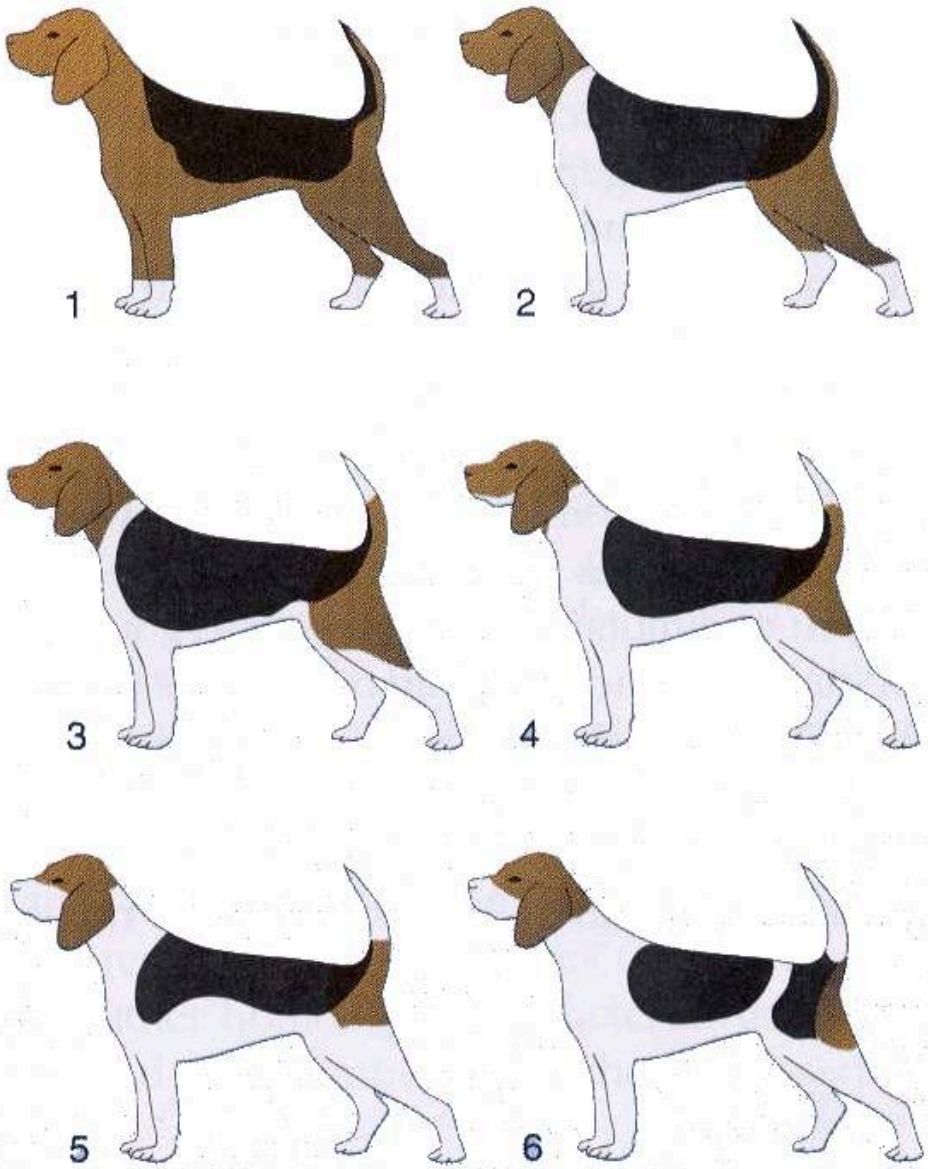


all the same genotype

…the frequency at which individuals with a given genotype manifest a specific phenotype.

- **4 of 6 dogs, or 66% of the population shows the phenotype, at some level,**
- **penetrance is usually referred to as a percentage.**

Expressivity



all the same genotype

…the degree or range within which a phenotype of a specific genotype is expressed

range of phenotypes

Phenotype strength may depend on the presence or absence of specific alleles at other genetic loci.

Himalayan rabbits carry a temperature-sensitive form of tyrosinase
Required for melanin synthesis

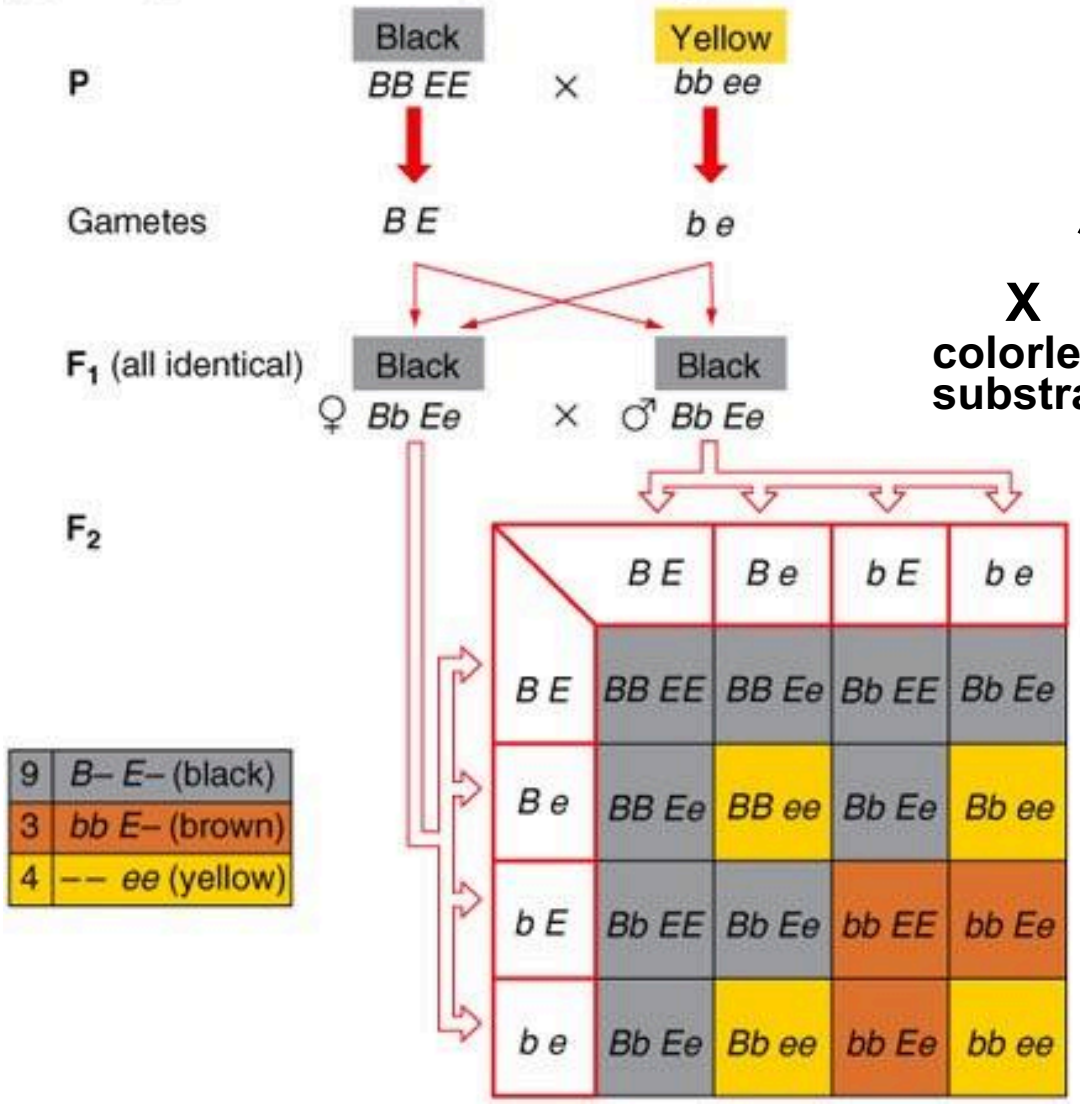
…Or phenotype may depend on the environment

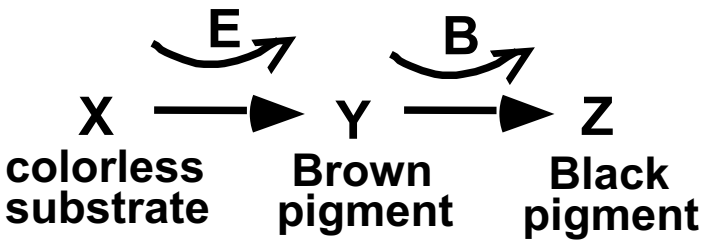
Epistasis and puppies

In epistasis the genotype at one locus masks the ability to determine the genotype at a second locus. Epistasis relationships are often found in biochemical pathways.

Recessive epistasis

Disruption of an early step in the pathway blocks the ability to determine the genotype with respect to genes involved in later steps





= 9: 3: 4

ee epistatic to bb

The functions of E and B

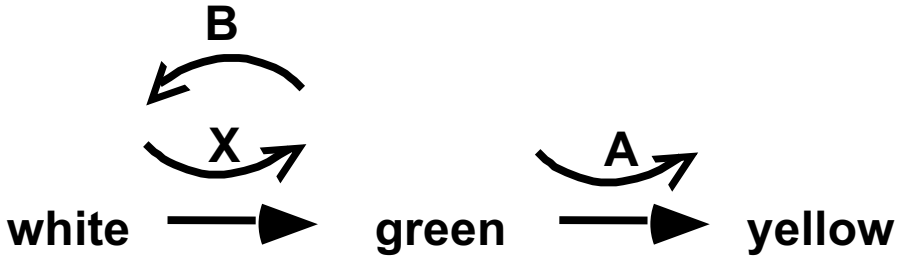
- E encodes melanocortin receptor 1 -- promotes production of eumelanin leaving dogs black or chocolate brown; null allele (e) means mc1r is not functional and dogs only produce phaeomelanin (yellow)
- B regulates distribution of melanin in hair shaft. B promotes dense packing of melanin (black) and b promotes less dense packing (chocolate brown).

Dominant epistasis produces ratios of 12:3:1 or 13:3

12:3:1---A dominant allele in one gene, B, masks the contribution of a second gene, A, (blocks color formation) regardless of the A allele. Thus in bb individuals the A- and aa genotypes can express themselves, resulting in a total of three different phenotypes.

Dominant epistasis: one possible mechanism

= 12 (white): 3(yellow): 1(green)

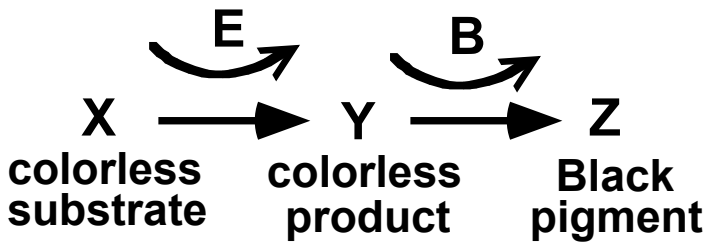


B acts to inhibit the processing of a white precursor into a green product.

In the absence of the B gene product the A product processes the green precursor into a yellow product.

Complementary gene action

Dominant alleles from two different genes must be present to produce a particular phenotype.



= 9: 7

	BE	Be	bE	be
BE	BBEE (Black)	BBEe (Black)	BbEE (Black)	BbEe (Black)
Be	BBeE (Black)	BBee (Golden)	BbeE (Black)	Bbee (Golden)
bE	bBEE (Black)	bBEe (Black)	bbEE (Golden)	bbEe (Golden)
be	bBeE (Black)	bBee (Golden)	bbeE (Golden)	bbee (Golden)

Notice that if we had a way to distinguish colorless product X from colorless product Y this would be an example of recessive epistasis.


How many genes contribute to a process
(flower color)

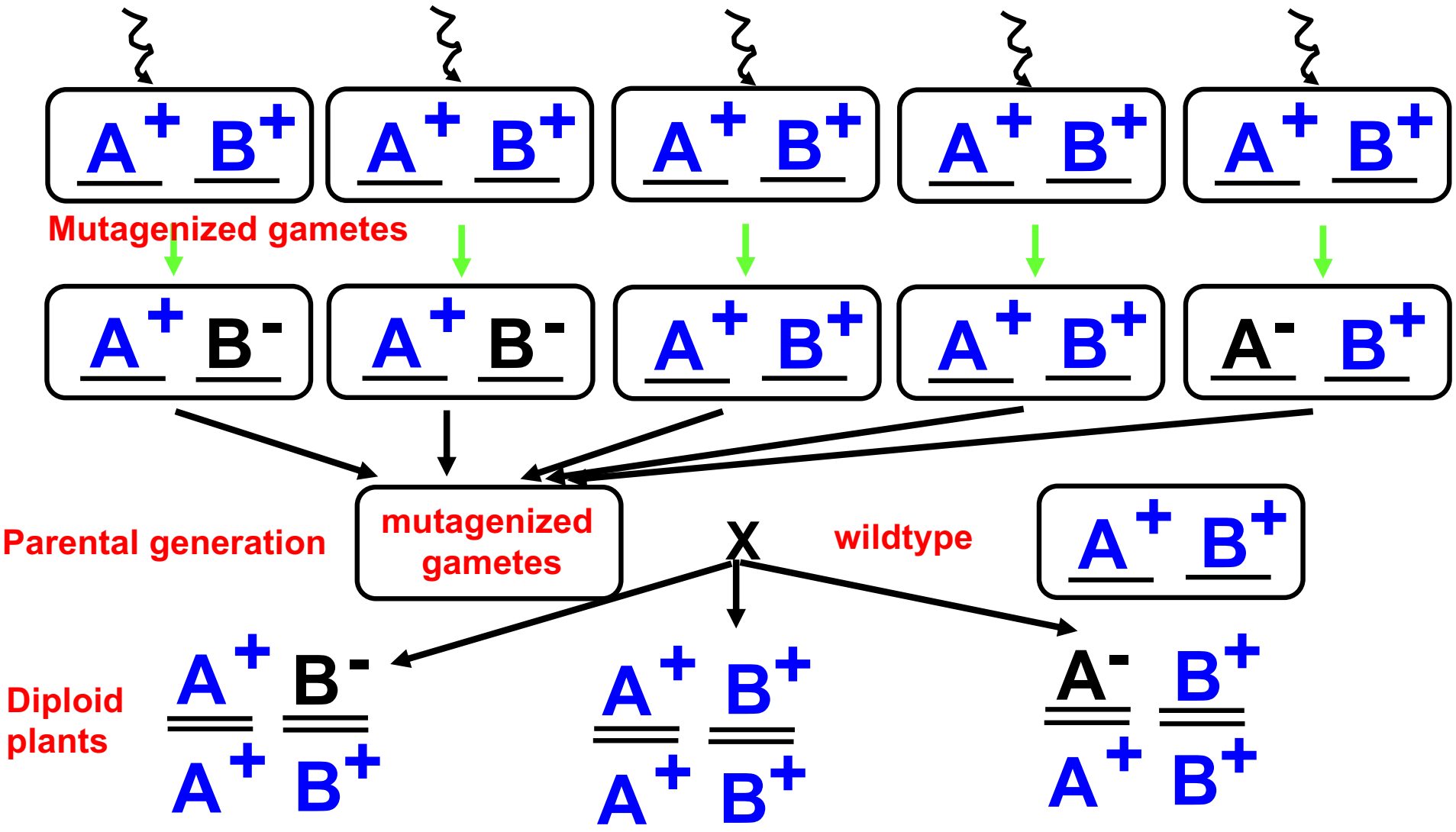
(c) A biochemical model for purple pigment production

Colorless precursor 1 → (Allele *A*: Pigment change initiated) → Colorless precursor 2 → (Allele *B*: Pigment change completed) → Purple pigment

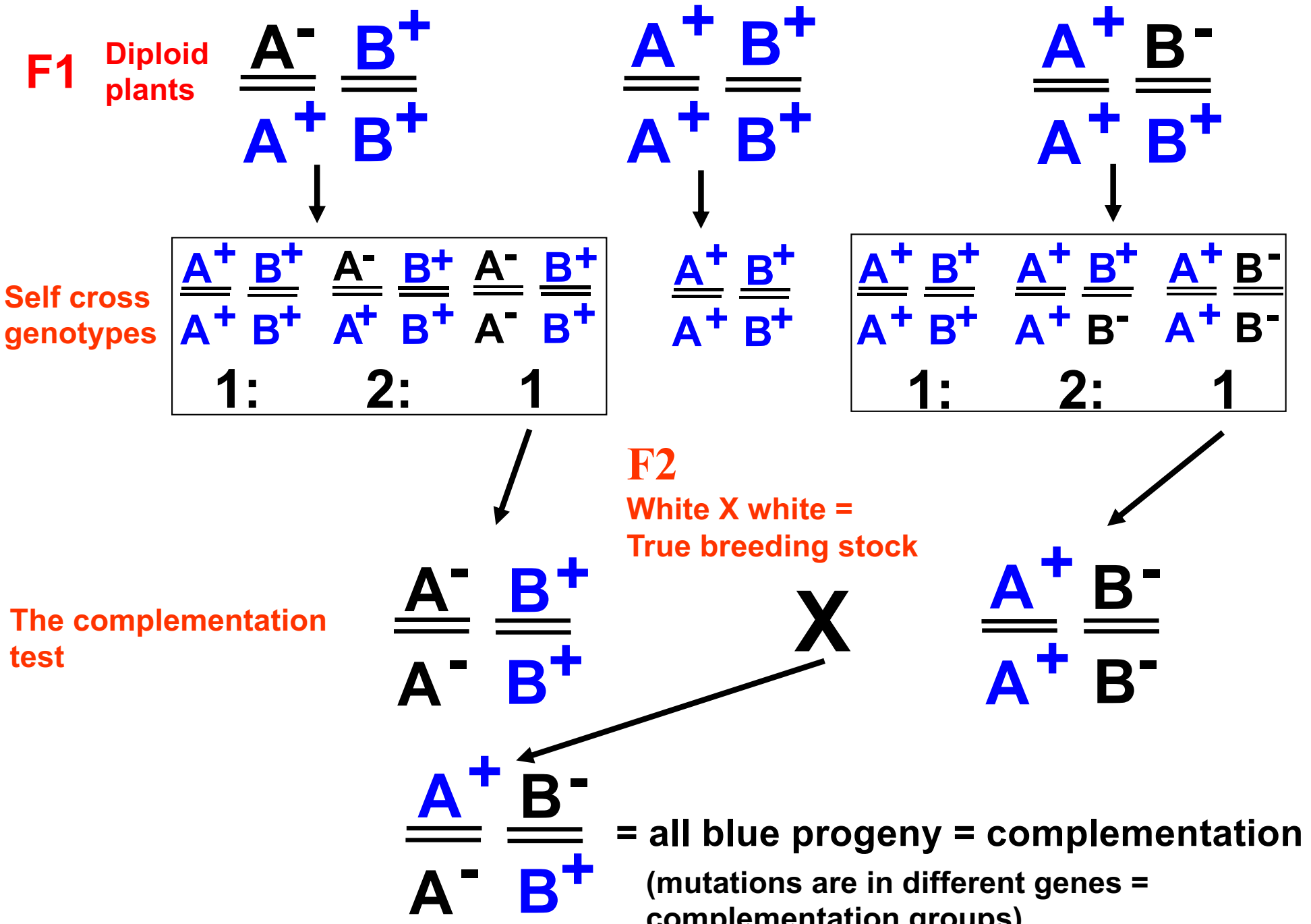
Complementation testing 1

How many genes are required to generate a particular phenotype such as flower color ?

1. Carry out a genetic screen for mutations that lack flower color.
2. Carry out complementation testing to determine which mutations effect the same gene.

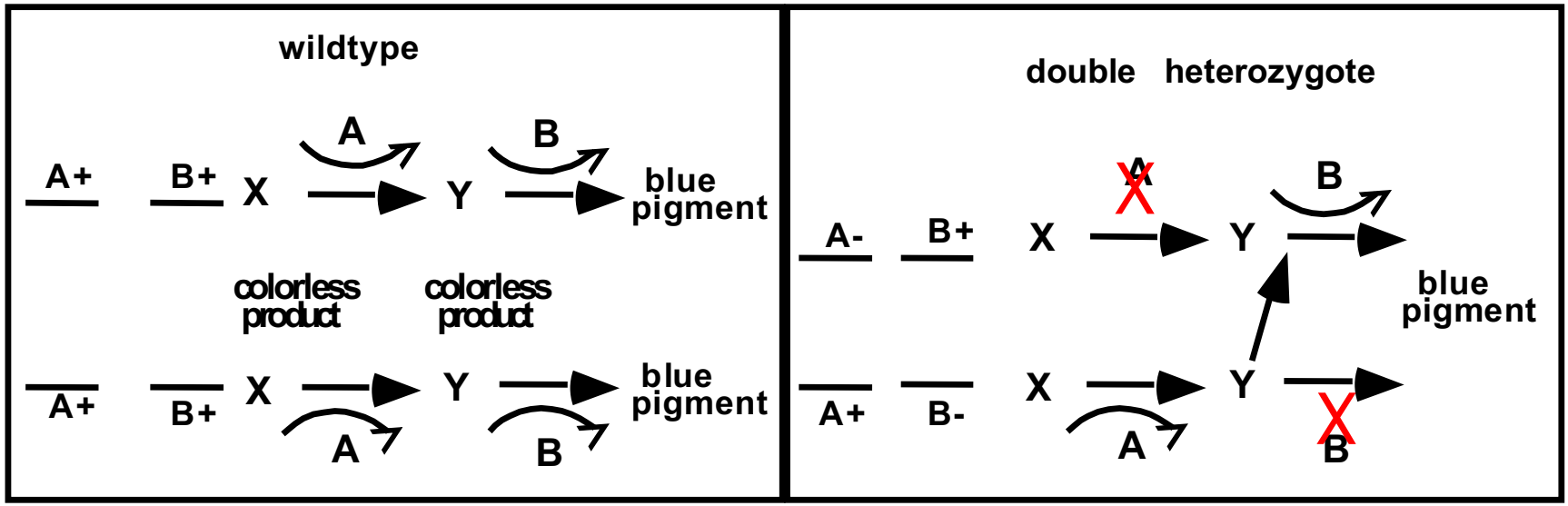


Complementation testing 2

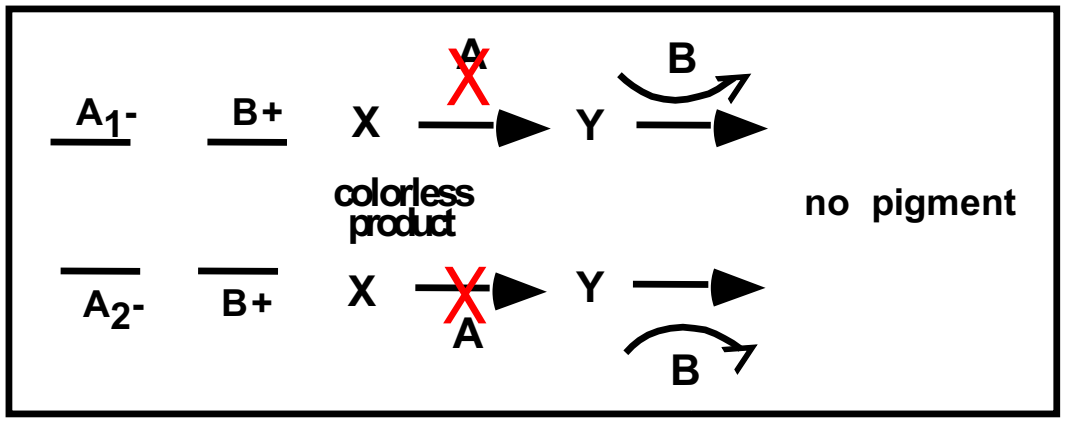


Complementation testing 3

$\frac{A-}{A-}$ $\frac{B+}{B+}$ X $\frac{A+}{A+}$ $\frac{B-}{B-}$ = all blue progeny = complementation



$\frac{A_1-}{A_1-}$ $\frac{B+}{B+}$ X $\frac{A_2-}{A_2-}$ $\frac{B+}{B+}$ = all white progeny = noncomplementation



How many different genes are required for a particular trait?
Genetic screens and complementation testing.

Phenotype

Genotype

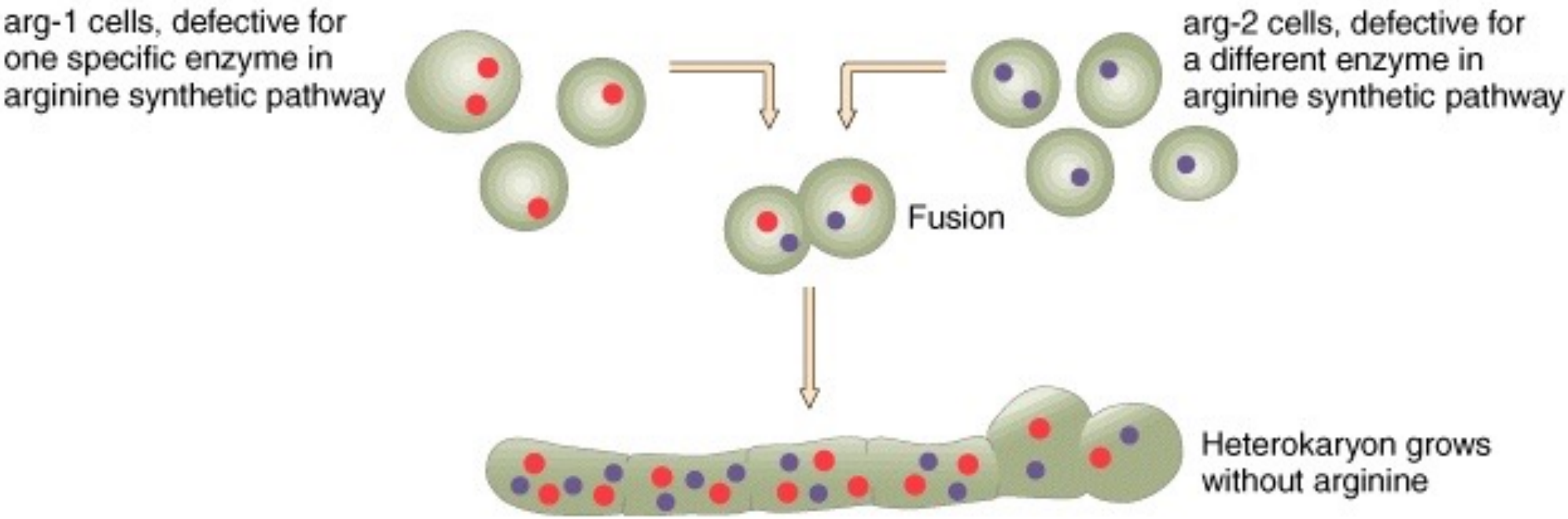
Molecular mechanism

Matings between different white-flowered lines produce purple progeny

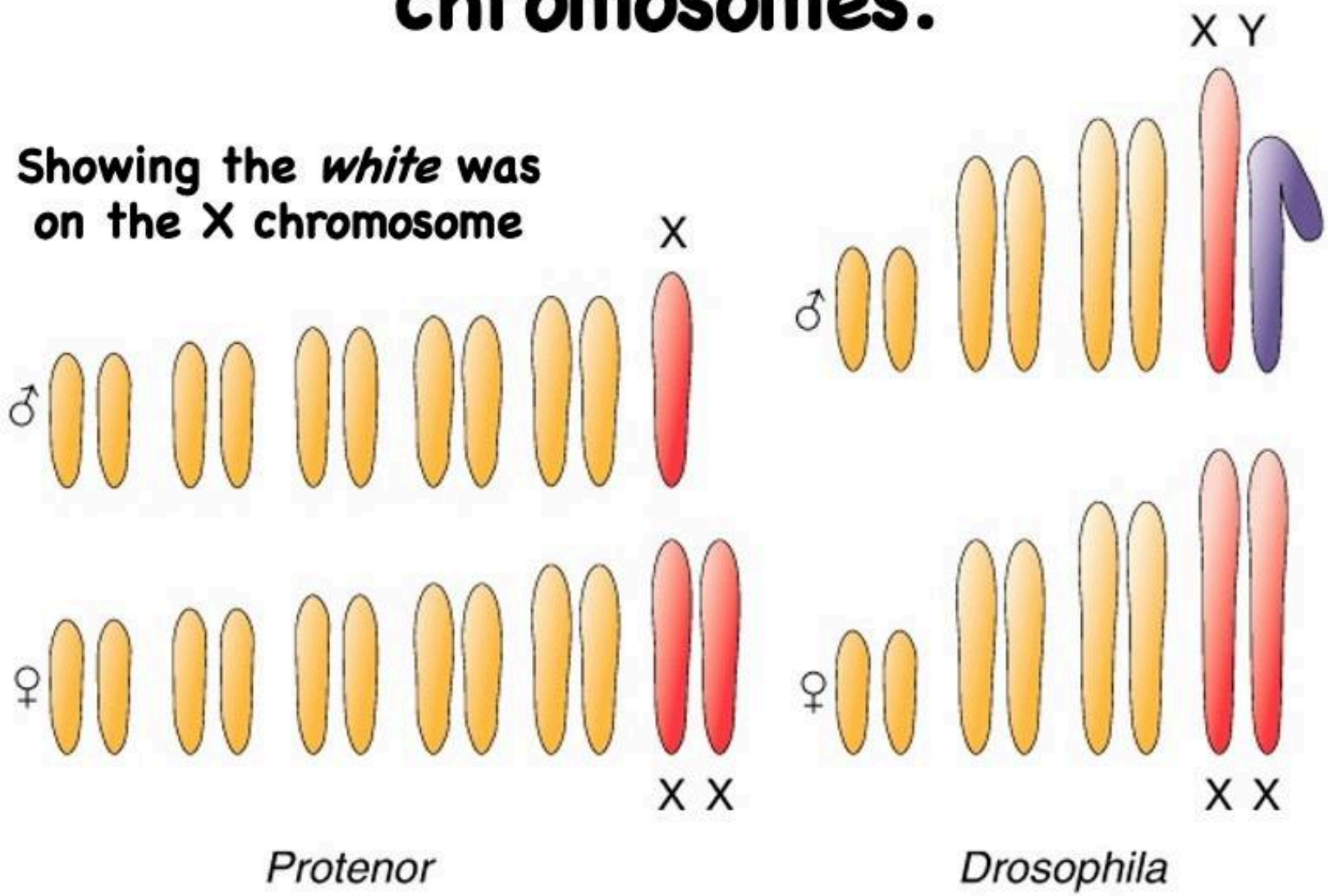
Mutations at different genes

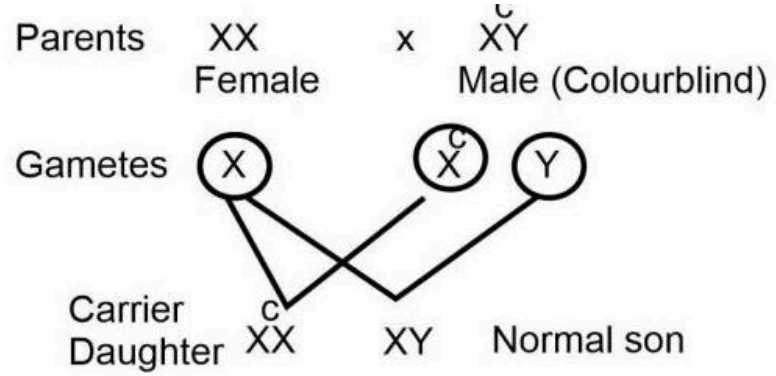
Affected genes encode different proteins that are required for the same biochemical pathway

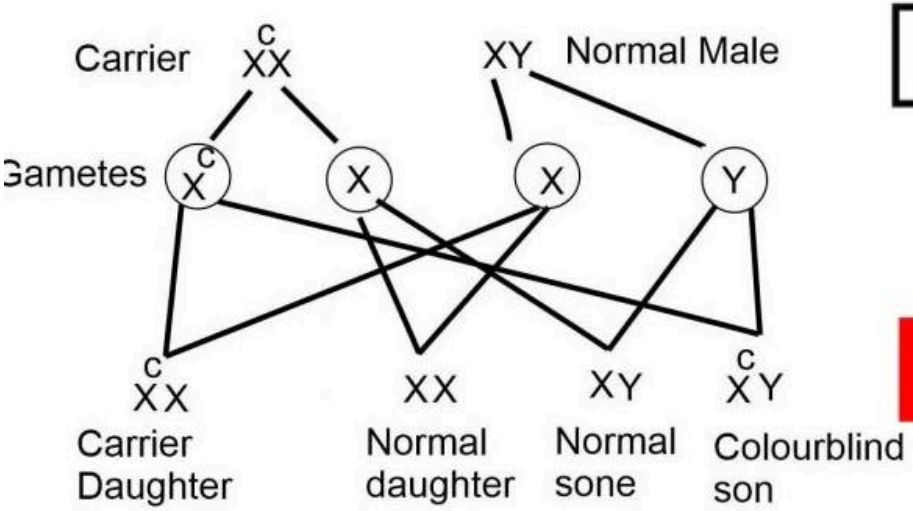
Complementation can occur during cell fusion.



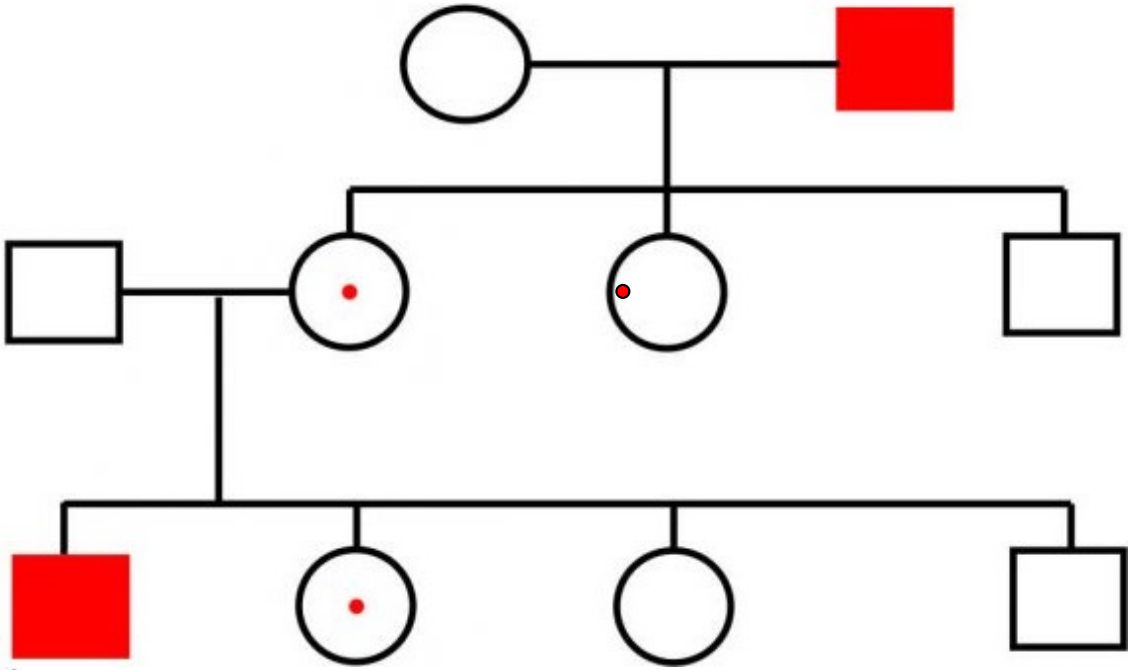
Organisms often have a pair of heteromorphic (look different) chromosomes.







Color blindness. X-linked recessive



In Drosophila (an insect) is not just the number of X chromosomes, but instead the ratio of X chromosomes to the number of autosomal sets (A) that determines sex in the fly. X:A+0.5 in the male. X:A = 1 in the female

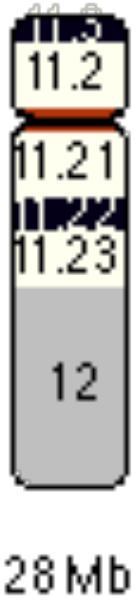
XY AA	male
XX AA	female
XO AA	male (sterile)
XXX AAA	female
XYY AAA	male
XXY AAA	intersex

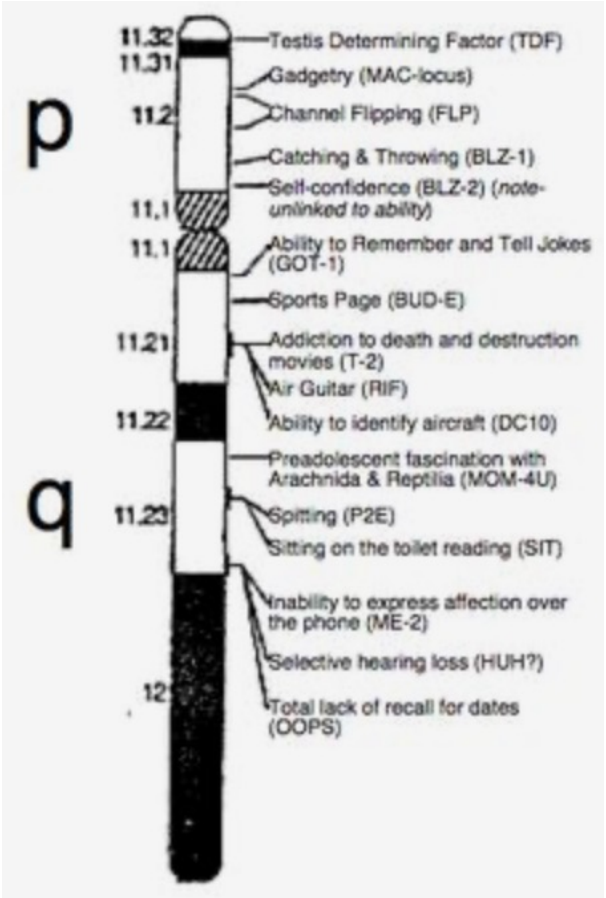
The mammalian Y chromosome contains very few genes

SRY

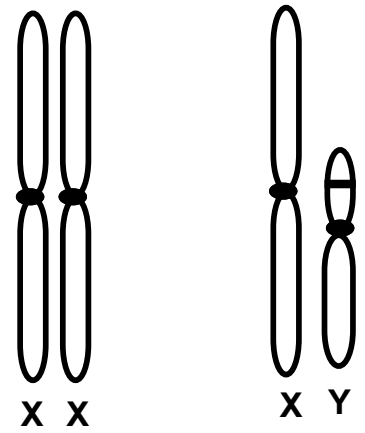
+ Genes needed for sperm development

The Y chromosome is necessary and sufficient for male development!





Sex determination in mammals
The Y chromosome and the SRY locus



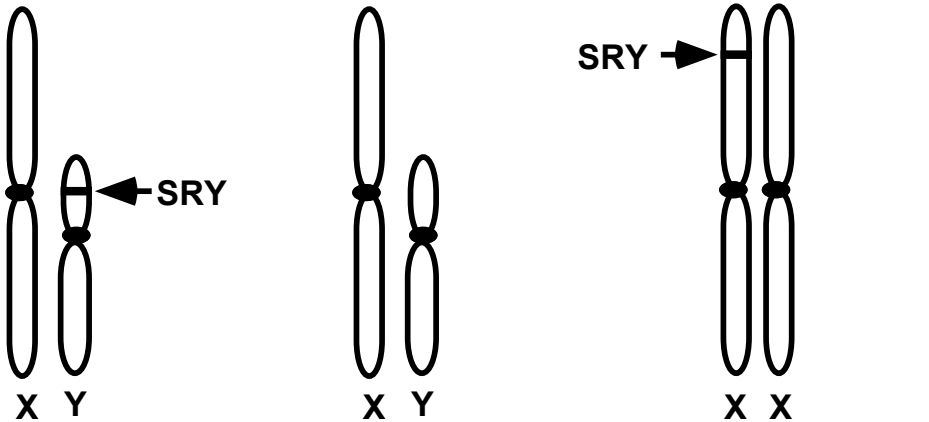
XX	female	
XY	male	
XXX	female	(normal)
XXY	male	(Kleinfelter's syndrome)
XO	female	(Turner's syndrome)

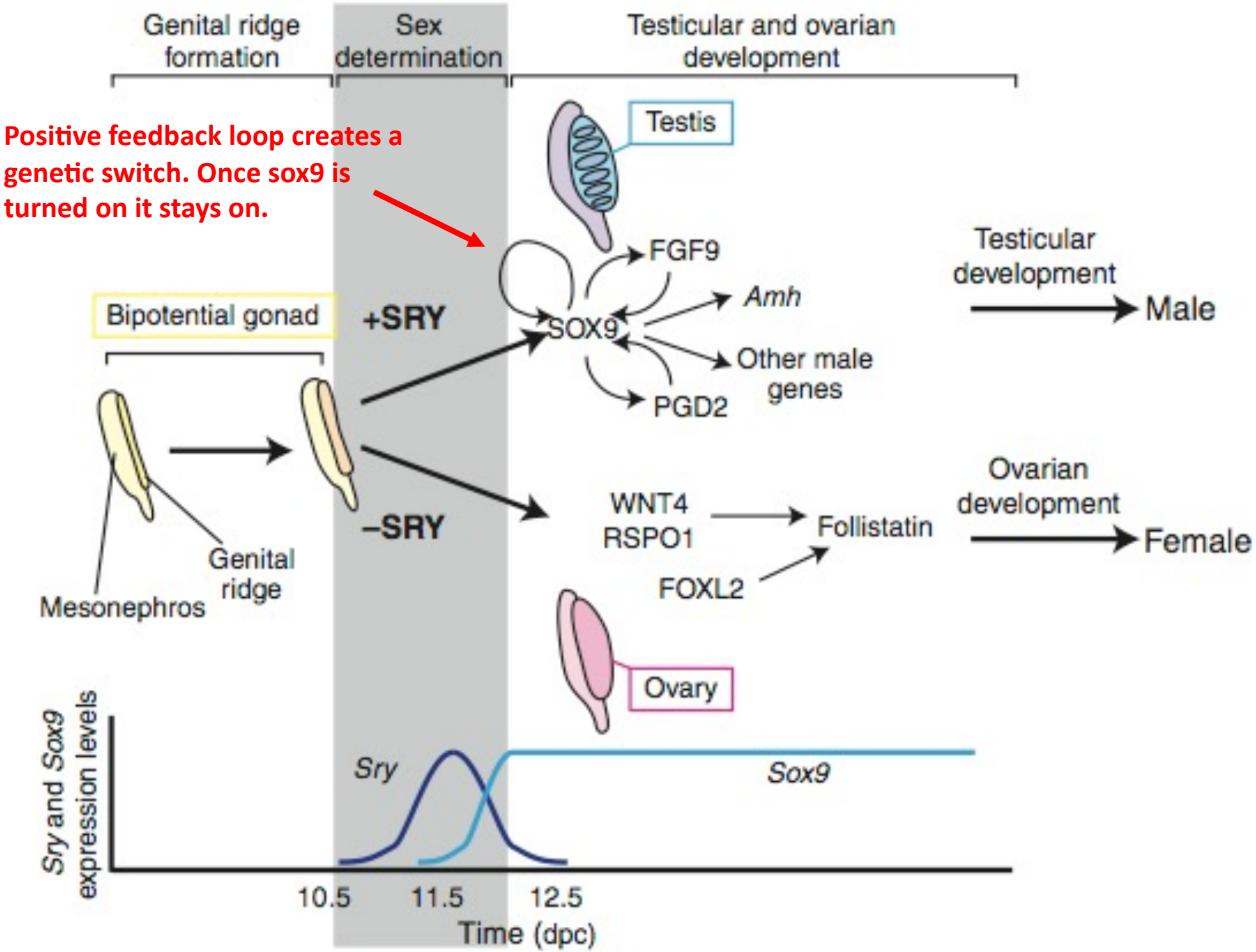
The SRY locus, present on the Y chromosome, determines sex in mammals.

1. XX individuals that show sex reversal (they are phenotypically male) have a small fragment of the Y chromosome moved to the X chromosome.

2. XY individuals that lack the SRY region of the Y chromosome are phenotypically female.

3. Generation of mice that are XX, but that have the SRY gene introduced onto their X chromosome are phenotypically male.




Genital ridge formation
Sex determination
Testicular and ovarian development
Positive feedback loop creates a genetic switch. Once sox9 is turned on it stays on.
Testis
FGF9
Testicular development
Male
Amh
Bipotential gonad
+SRY
SOX9
Other male genes
PGD2
Mesonephros
Genital ridge
–SRY
WNT4
RSPO1
Follistatin
Ovarian development
Female
FOXL2
Ovary
Sry and Sox9 expression levels
Sry
Sox9
10.5
11.5
12.5
Time (dpc)

More than 1% of us have mutations that result in altered biological sex outcome

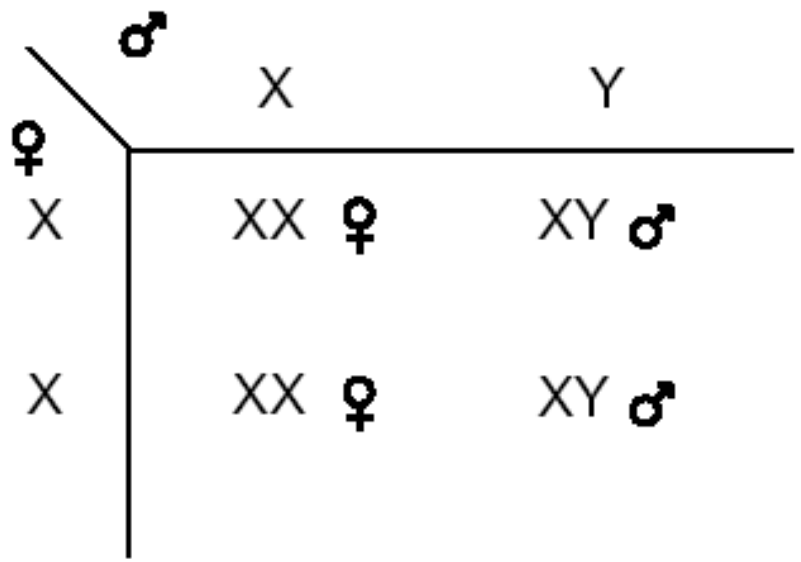
Biological outcome is different than gender

Gender refers to the socially constructed roles, behavioures, expressions and identities of girls, women, boys, men, and gender diverse people.

Fig. 1. Overview of sex determination in mice. Chronological flow of early mouse sex differentiation; the grey area indicates the period of sex determination. During mouse embryogenesis, bi-potential gonads (yellow) arise from the genital ridges by 10.5 dpc. In somatic cells of XY genital ridges, *Sry* expression (shown in dark blue beneath the schematic) starts at 10.5 dpc, reaches a peak at 11.5 dpc and then wanes by 12.5 dpc. A few hours later, *Sox9* expression (shown in light blue beneath the schematic) is upregulated to induce differentiation of Sertoli cells. *Sox9* expressi peaks at 11.5-12.5 dpc, continues to be expressed postnatally and is supported by several positive-feedback loops (including FGF9, prostaglandin D2 and SOX9 itself), and SOX9 subsequently activates many male-specific genes, including *Amh*. At 12.5 dpc, testis cords have formed, and morphological differences between testis (blue) and ovary (pink) are evident. In the absence of SRY, genes such as *Wnt4, Rspo1* and *Foxl2* are expressed in a female-specific manner and induce ovarian development, as characterized by the expression of follistatin and many other ovary-specific genes. Abbreviations: *Amh*, anti-Müllerian hormone; dpc, days post coitum; FGF9, fibroblast growth factor 9; FOXL2, forkhead box L2; PGD2, prostaglandin D2; RSPO1, R-spondin 1; SOX9, SRY box containing gene 9; SRY, sex-determining region on the chromosome Y; WNT4, wingless-type MMTV integration site family, member 4.

Many routes to sex determination

1) XX – XY

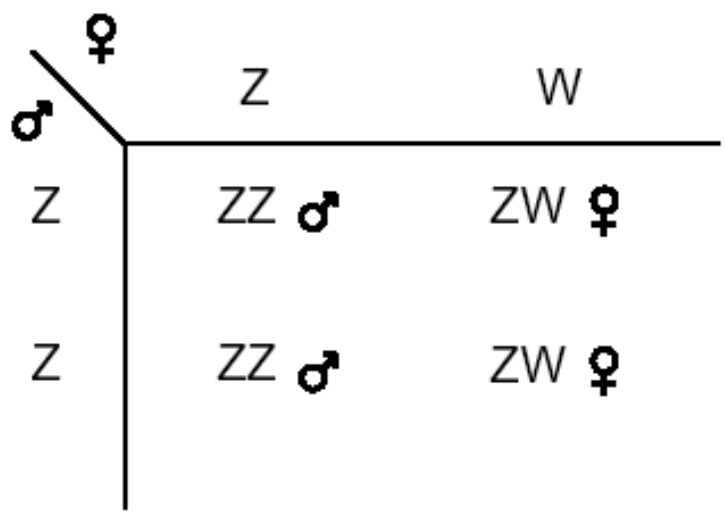


many dioecious angiosperms

many animal species

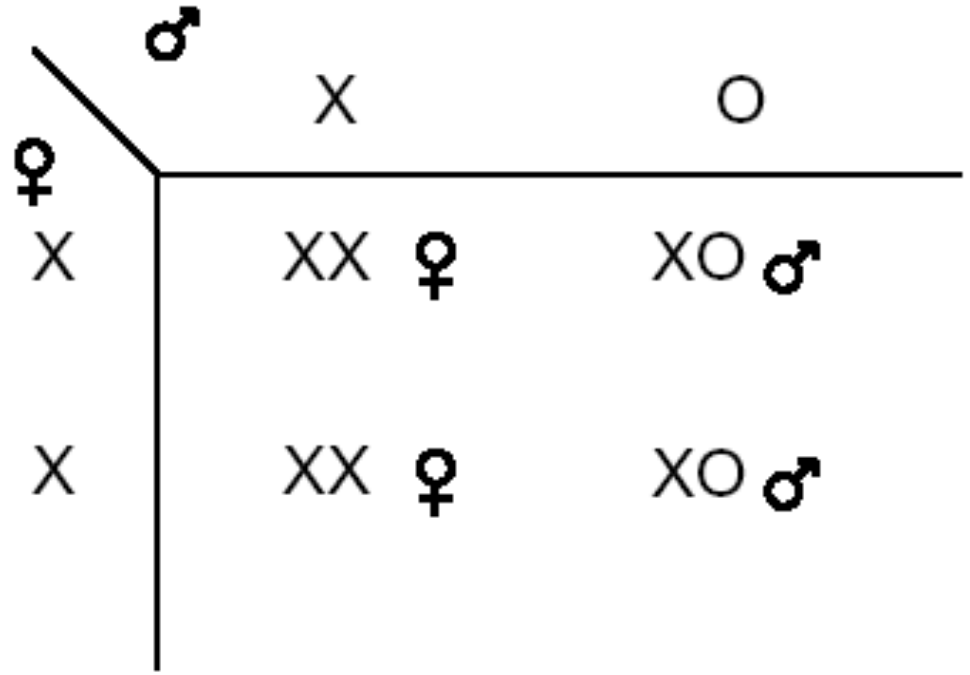
most vertbrates

2) ZW – ZZ



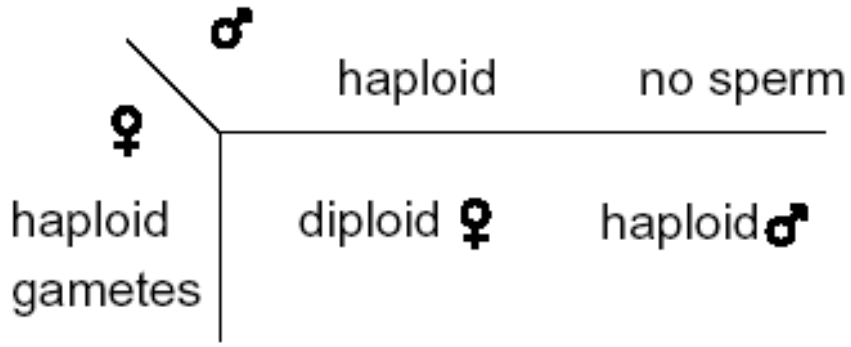
some flatworms
" crustaceans
" insects especially lepidopterans
diptera (some)
" some fish, amphibians, lizards
" most birds

3) XX – XO



many insects

5) Arrhenotoky (haplo−diploid sex determination)

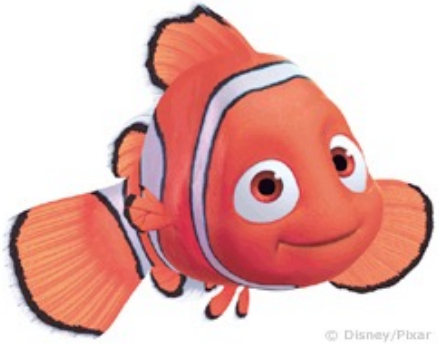


hymenoptera (ants, bees, wasps)
thysanoptera (thrips)
mites and ticks
rotifers

Yet more sex−determination systems

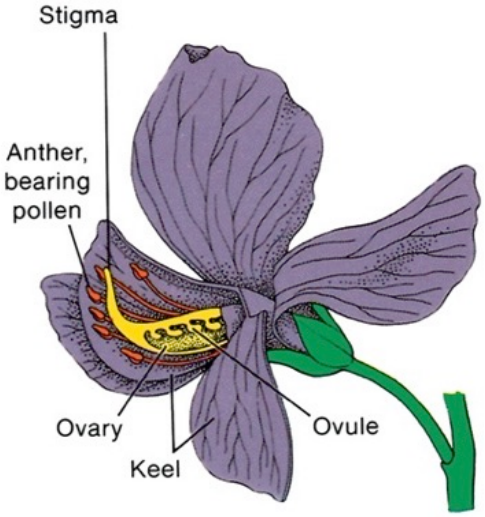
7) Sequential hermaphroditism
(start life as one sex, usually male, and switch later)

oysters, shrimp, some fish

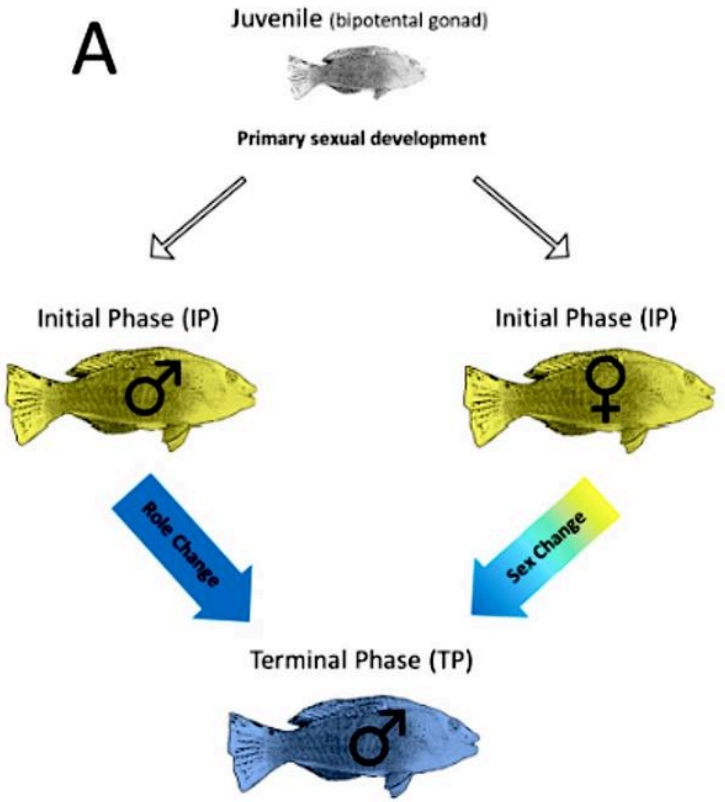


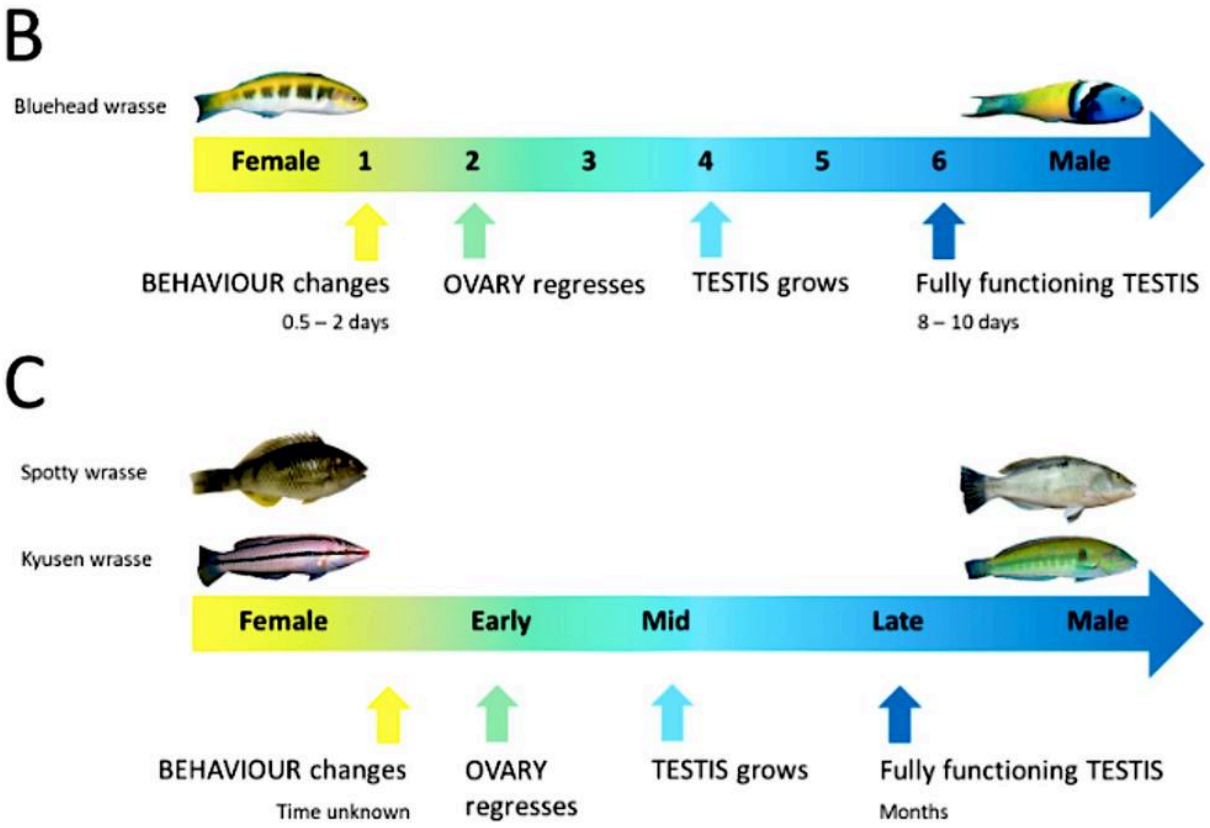
8) Self−sterility systems

In some angiosperm plants, multiple alleles which allow pollen to succeed only if it does not contain any allele at that locus which is found in the female parent (gametophytic self−incompatibility) or the male does not contain any allele at that locus found in the female (sporophytic self−incompatibility)

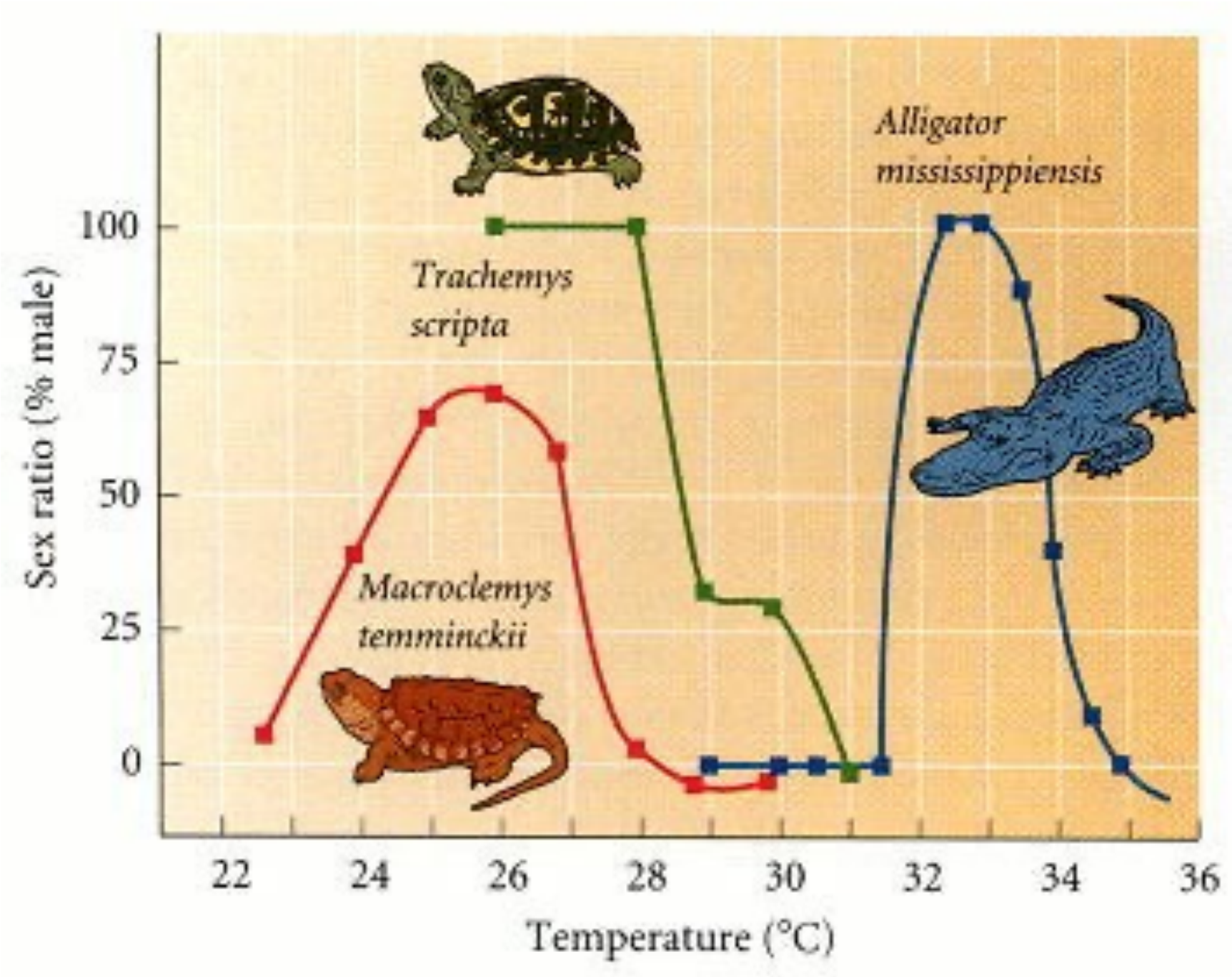


Bluehead wrasse sequential sex transformation





Temperature-dependent sex determination



Some organisms have many mating types. You must mate with Someone who has a different type than you

These fairy inkcap mushrooms (*Coprinellus disseminatus*), photographed in London, have 143 mating types. Each is able to reproduce with members of any of the other 142 types.

—

Stu's Images

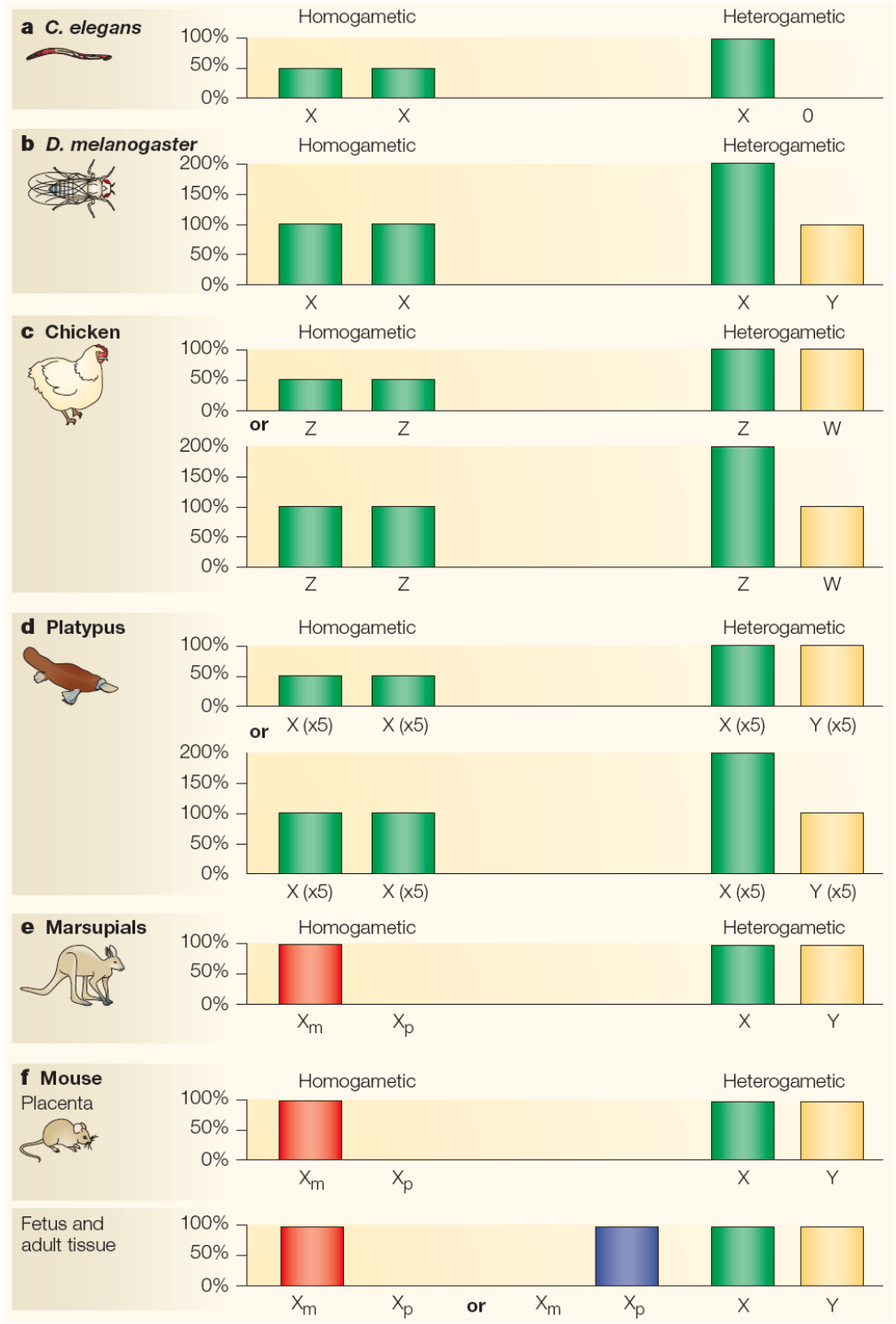
Mammals triploid for an autosomal chromosome usually die, but XXY, XYY, XXX, XXXX and XXXXX survive.

Why?

Dosage compensation

Dosage Compensation

- **X chromosomes in females provide twice the genes, as in males,**
  - **Drosophila: female genes are expressed at 50% of the male levels,**
  - **Mammals: one X chromosome in females is silenced.**


a C. elegans
Homogametic
Heterogametic
100%
50%
0%
X
X
X
0
b D. melanogaster
Homogametic
Heterogametic
200%
150%
100%
50%
0%
X
X
X
Y
c Chicken
Homogametic
Heterogametic
100%
50%
0%
or
Z
Z
Z
W
200%
150%
100%
50%
0%
Z
Z
Z
W
d Platypus
Homogametic
Heterogametic
100%
50%
0%
or
X (x5)
X (x5)
X (x5)
Y (x5)
200%
150%
100%
50%
0%
X (x5)
X (x5)
X (x5)
Y (x5)
e Marsupials
Homogametic
Heterogametic
100%
50%
0%
Xm
Xp
X
Y
f Mouse
Placenta
Homogametic
Heterogametic
100%
50%
0%
Xm
Xp
X
Y
Fetus and adult tissue
100%
50%
0%
Xm
Xp
or
Xm
Xp
X
Y

In *Drosophila* dosage compensation occurs through hyperactivation of the male X chromosome

sex	genotype	dose	pigment
Female	w^a / Df (w)	1x	1x
Female	w^a / w^a	2x	2x
Female	w^a / w^a /Dp (w^a)	3x	3x
Male	w^a / -	1x	2x
Male	w^a / - / Dp (w^a)	2x	4x

Visualizing dosage compensation in flies using w^a alleles of w

Mammalian X-inactivation: Early studies

- 1953. Two X-linked genes in the mouse, tabby and mottled, showed variegation in heterozygous females.

- 1959. X0 mouse females are shown to be viable and fertile.

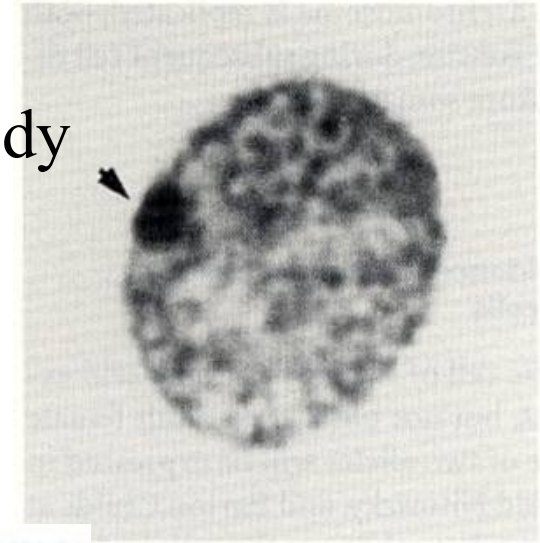
- 1961. Mary Lyon proposes that dosage compensation in mammals was achieved by transcriptional silencing of one X chromosome in female cells (Gene action in the X-chromosome of the mouse *Nature* 190: 372-373).

- Beutler et al. Two types of red blood cells in human females heterozygous for G6PDH.

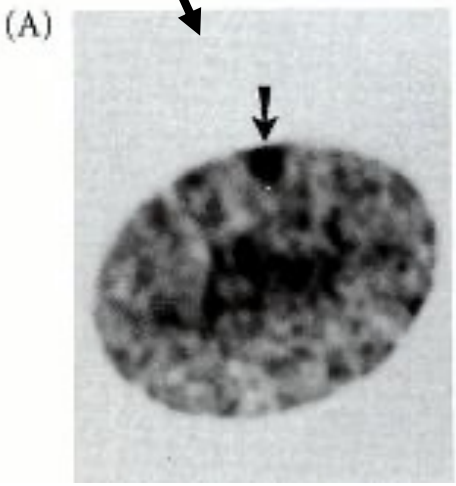
Canadian Cat Scientists Sees it First

Murray Barr noted that the nuclei of female but not male cats contained a darkly stained element. This is now known as a Barr body.

Barr Body

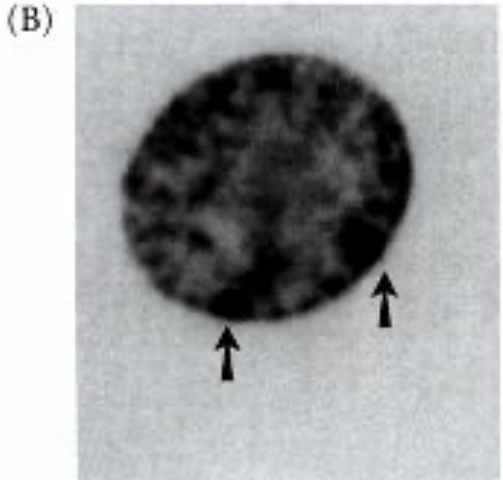


The number of Barr bodies varies with the number of X chromosomes



XX

One Barr body

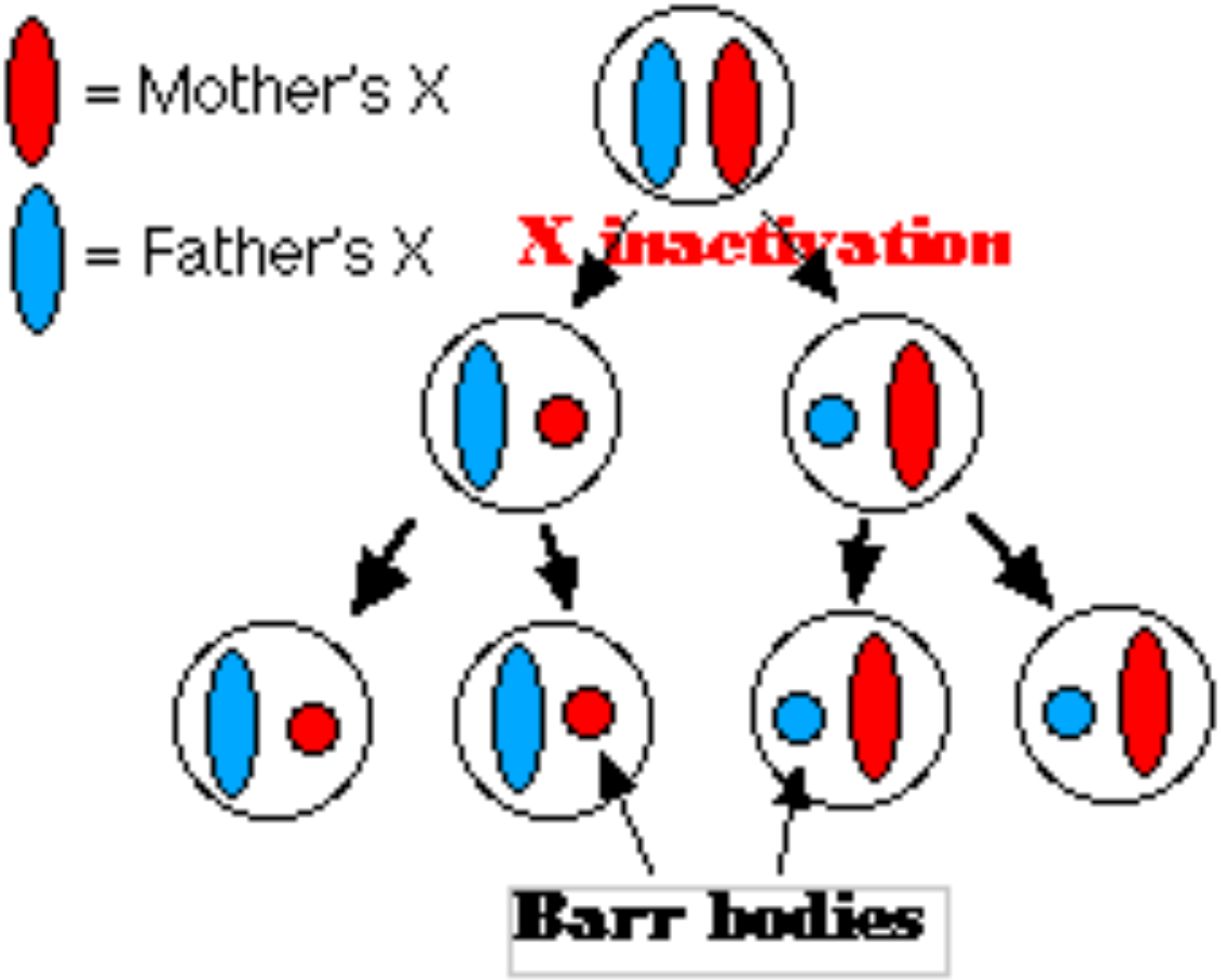


XXX

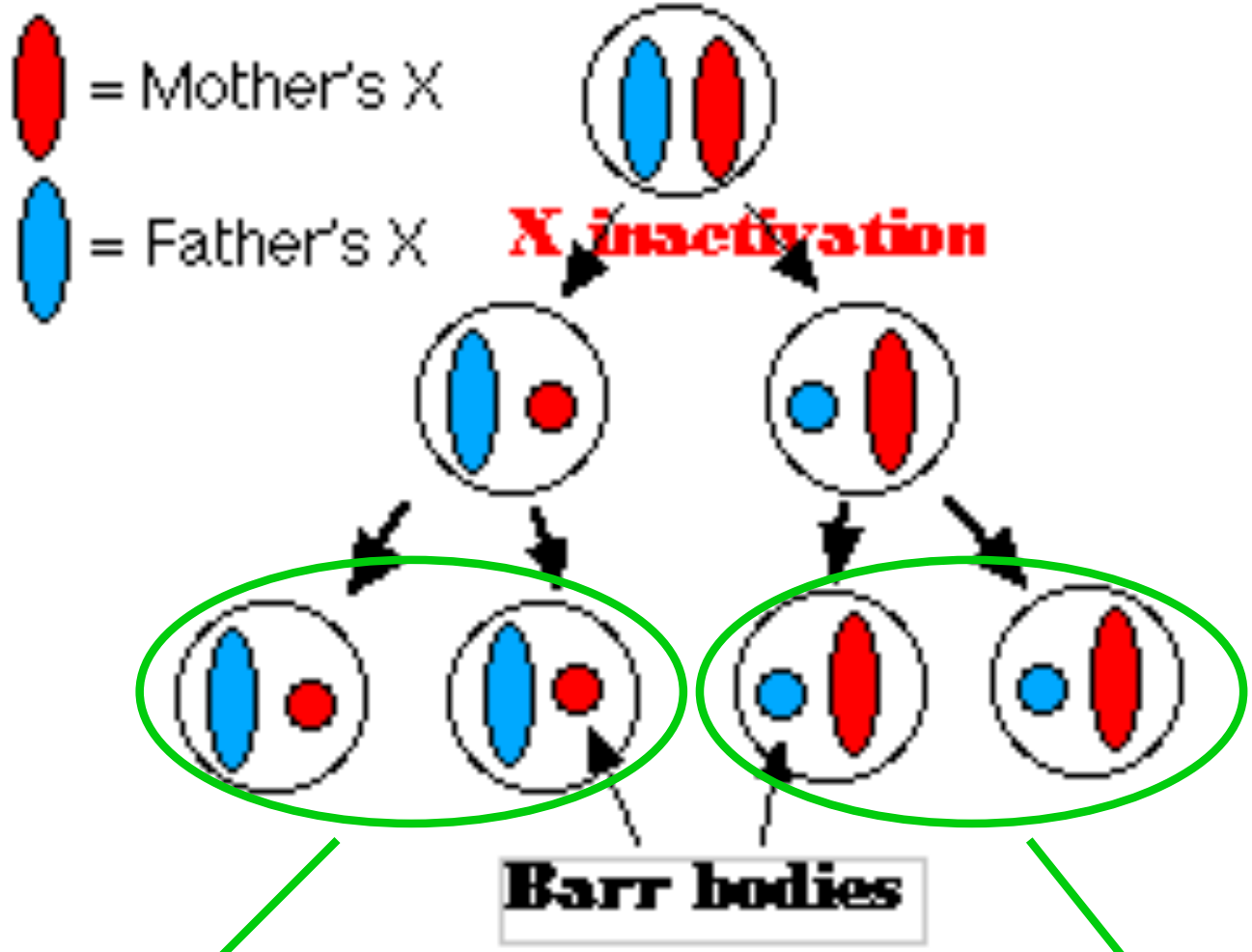
Two Barr bodies

Karyotype	# Barr bodies
XY	0
XO	0
XX	1
XXX	2
XXXX	3
XXXXX	4

In mammalian females, early in embryonic development <u>each cell</u> inactivates one X chromosome



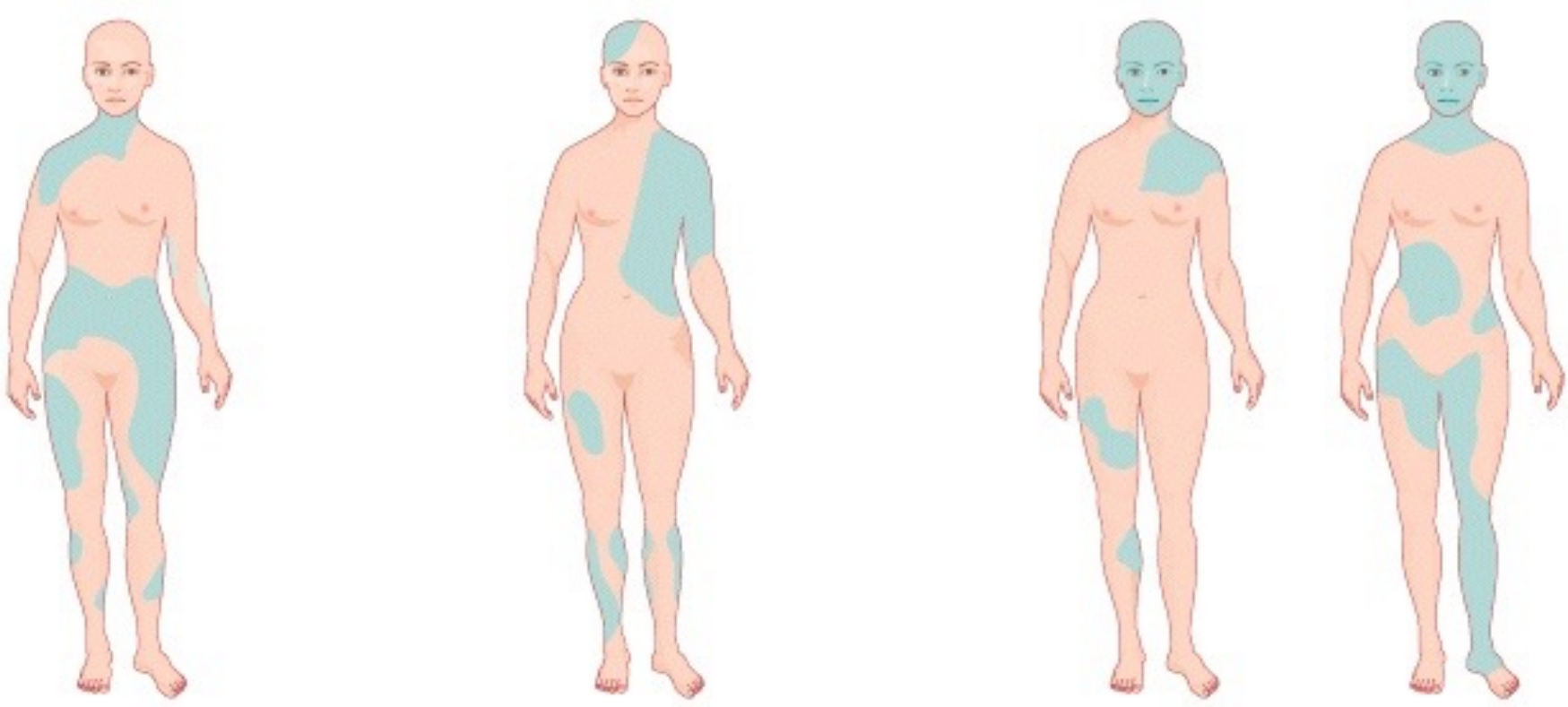
All mammalian females are mosaic!!!



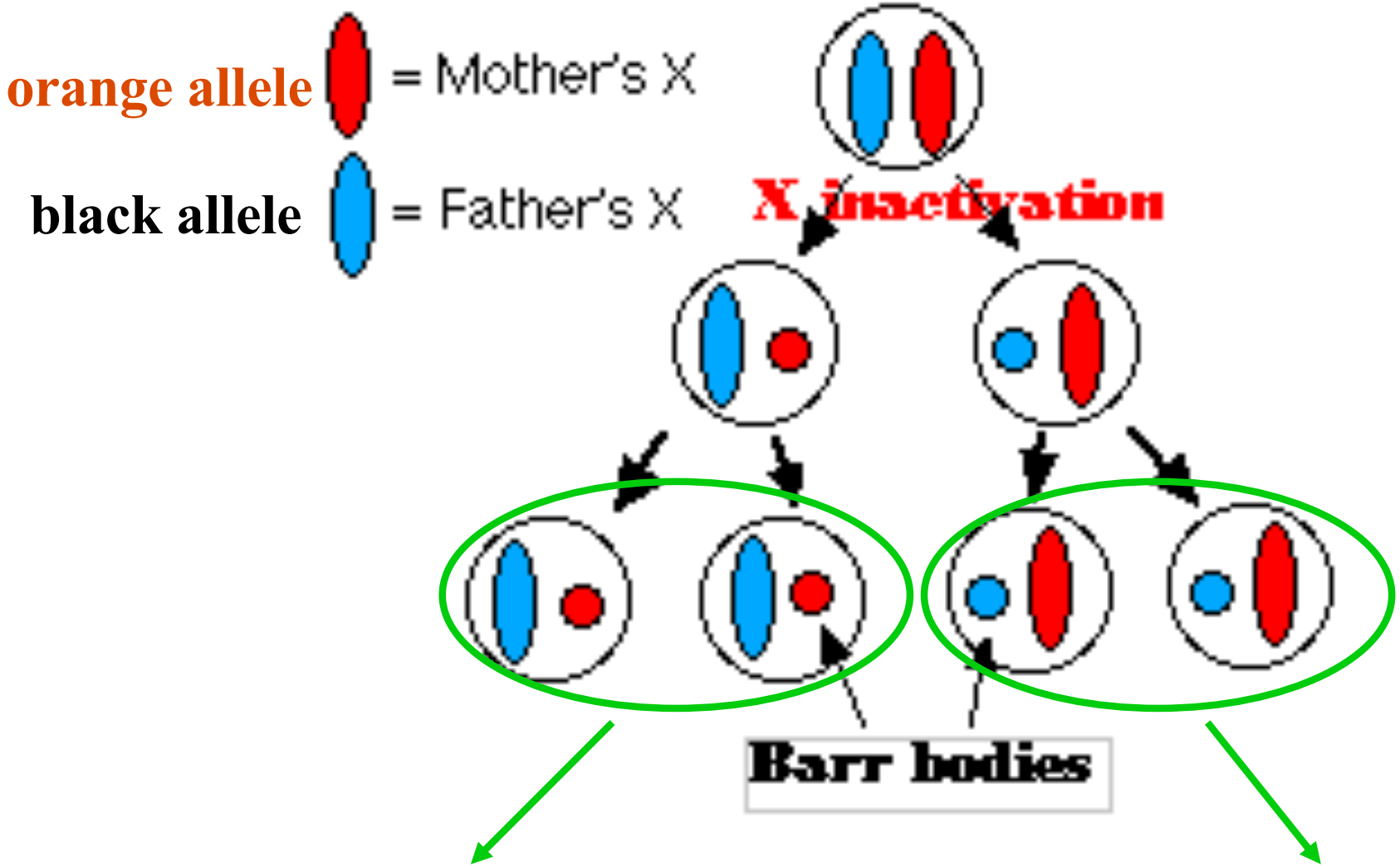
These cells express only paternal X chromosome genes.

These cells express only maternal X chromosome genes.

Certain X-linked inherited traits result in mosaicism in females.
e.g., anhidrotic ectodermal dysplasia



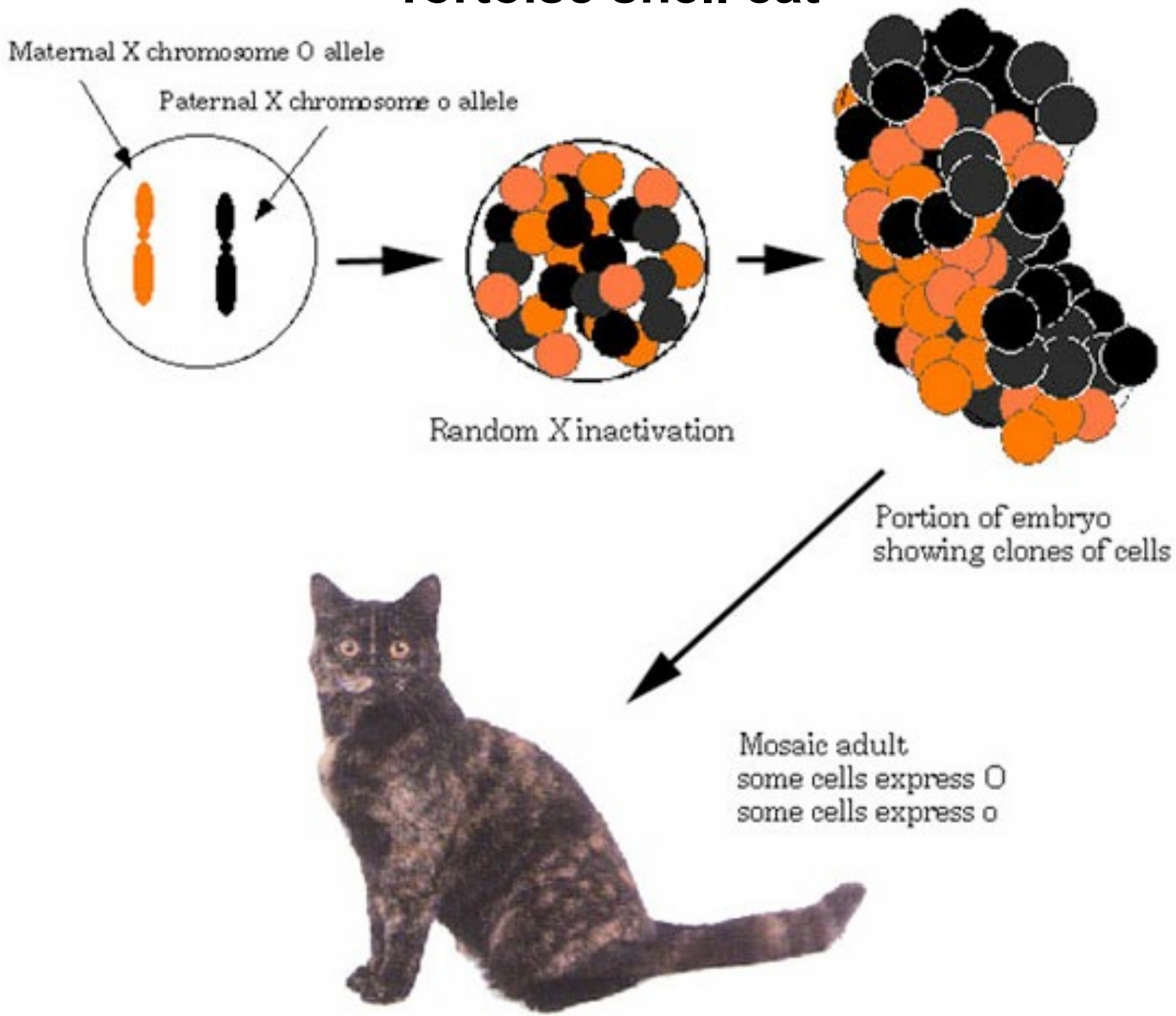
Coat color in Calico and tortoise shell cats



These cells express only paternal black allele.

These cells express only maternal orange allele.

Tortoise shell cat

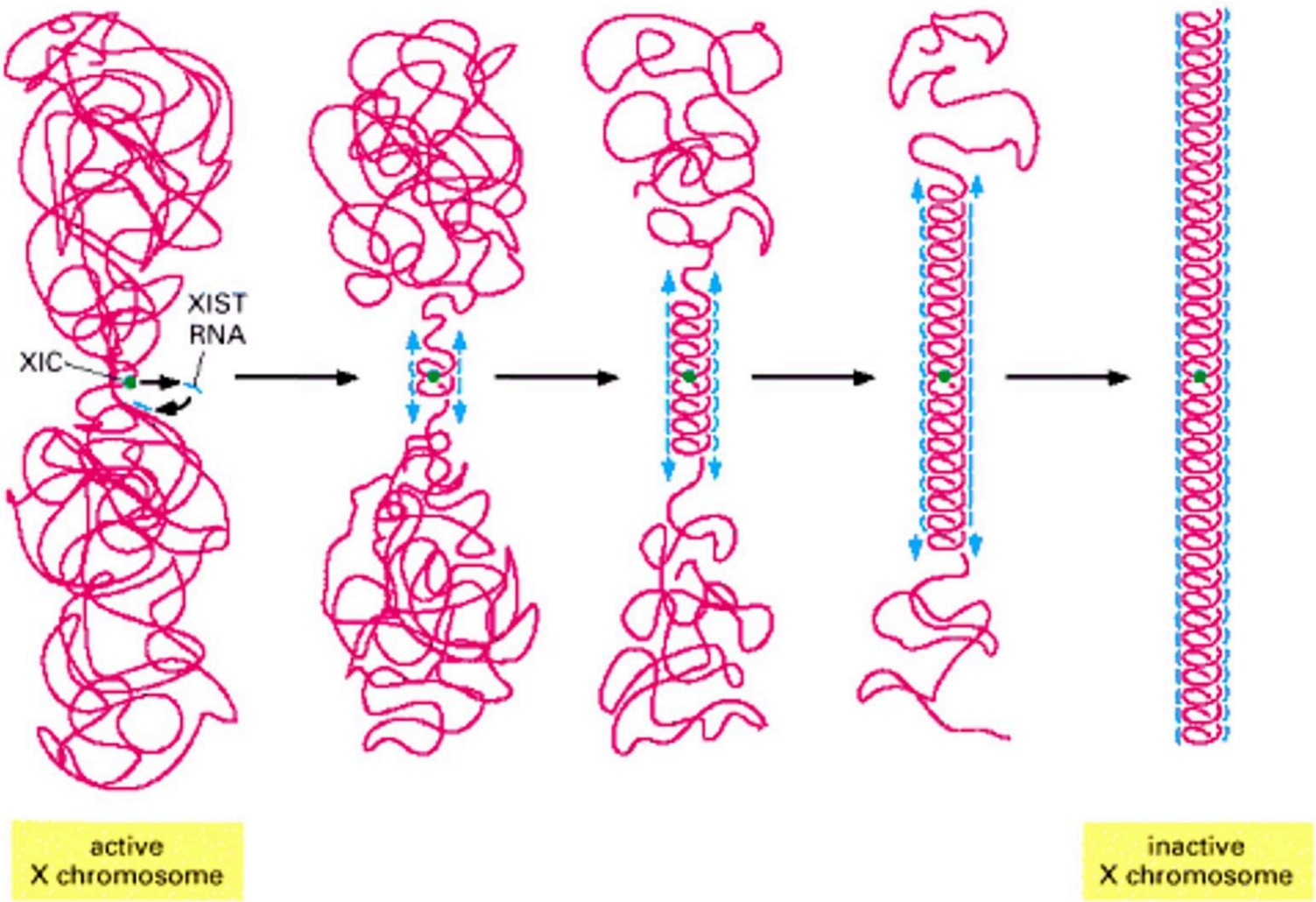


XIST

(X-*inactive specific transcript)*

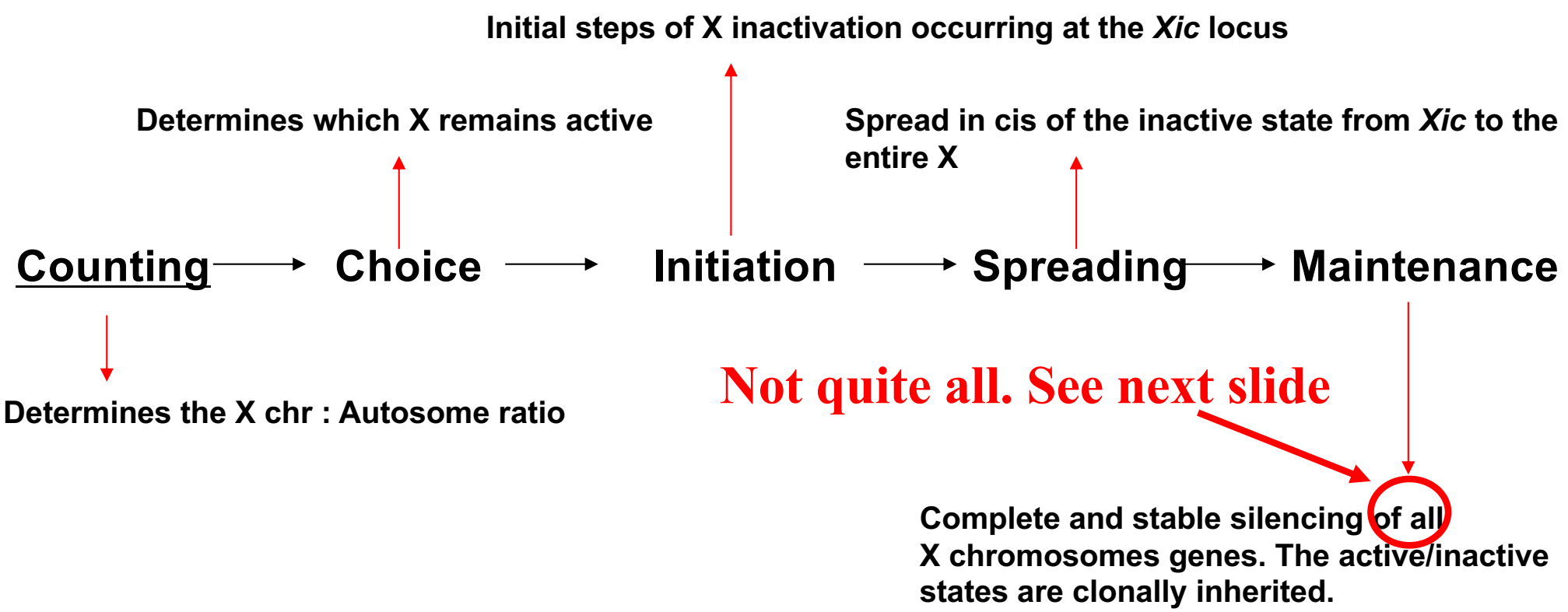
- **Identified in 1991**
- **17 kb spliced, non-coding RNA**
- **Stable expression only from inactive X**
- **”Paints” inactive X chromosome**
- **Required to initiate silencing**

MAMMALIAN X-CHROMOSOME INACTIVATION



X-chromosome inactivation begins with the synthesis of XIST (X-inactivation specific transcript) RNA from the XIC (X-inactivation center) locus. The association of XIST RNA with the X chromosome is correlated with the condensation of the chromosome.

After Alberts et al. - Molecular Biology of the Cell 2002


Initial steps of X inactivation occurring at the *Xic* locus
Determines which X remains active
Spread in cis of the inactive state from *Xic* to the entire X
Counting
Choice
Initiation
Spreading
Maintenance
Determines the X chr : Autosome ratio
Not quite all. See next slide
Complete and stable silencing of all X chromosomes genes. The active/inactive states are clonally inherited.

Does X inactivation affect all X chromosome genes?

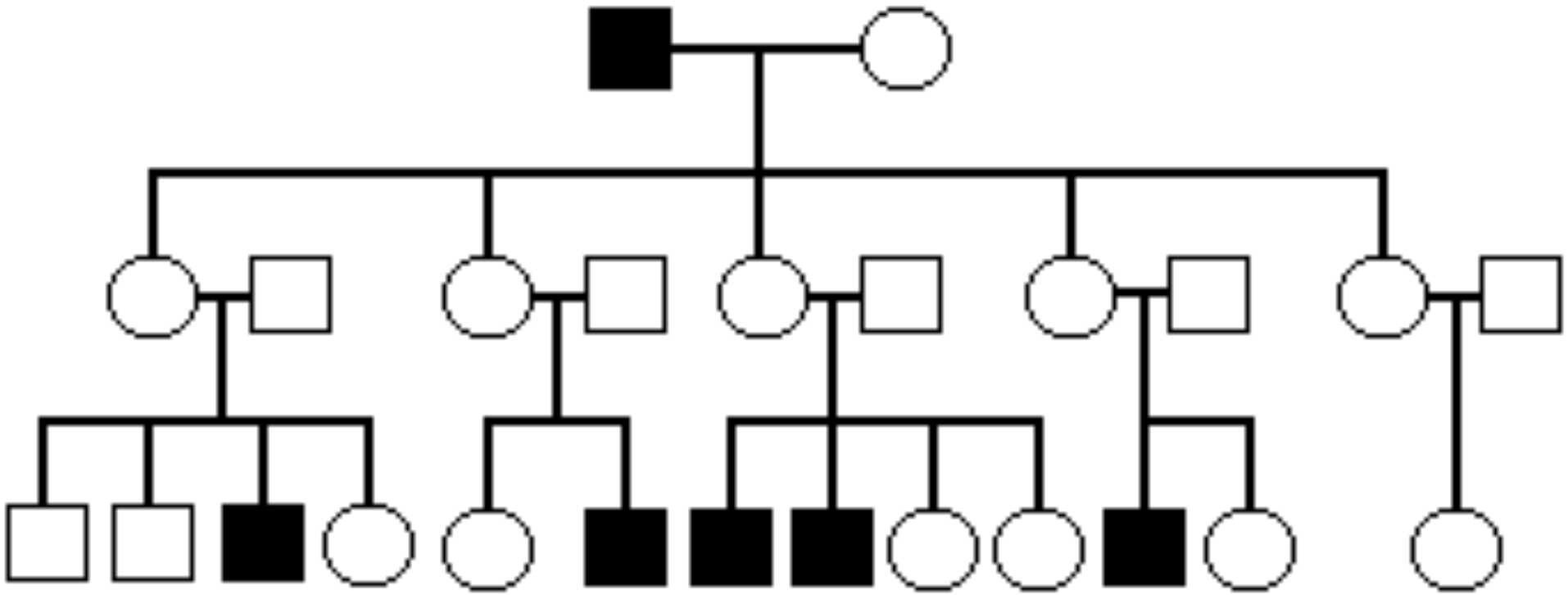
No!!!!

47, XXX	
48, XXXX	
47, XXY	**Kleinfelter syndrome males**
45, X0	**Turner syndrome females**

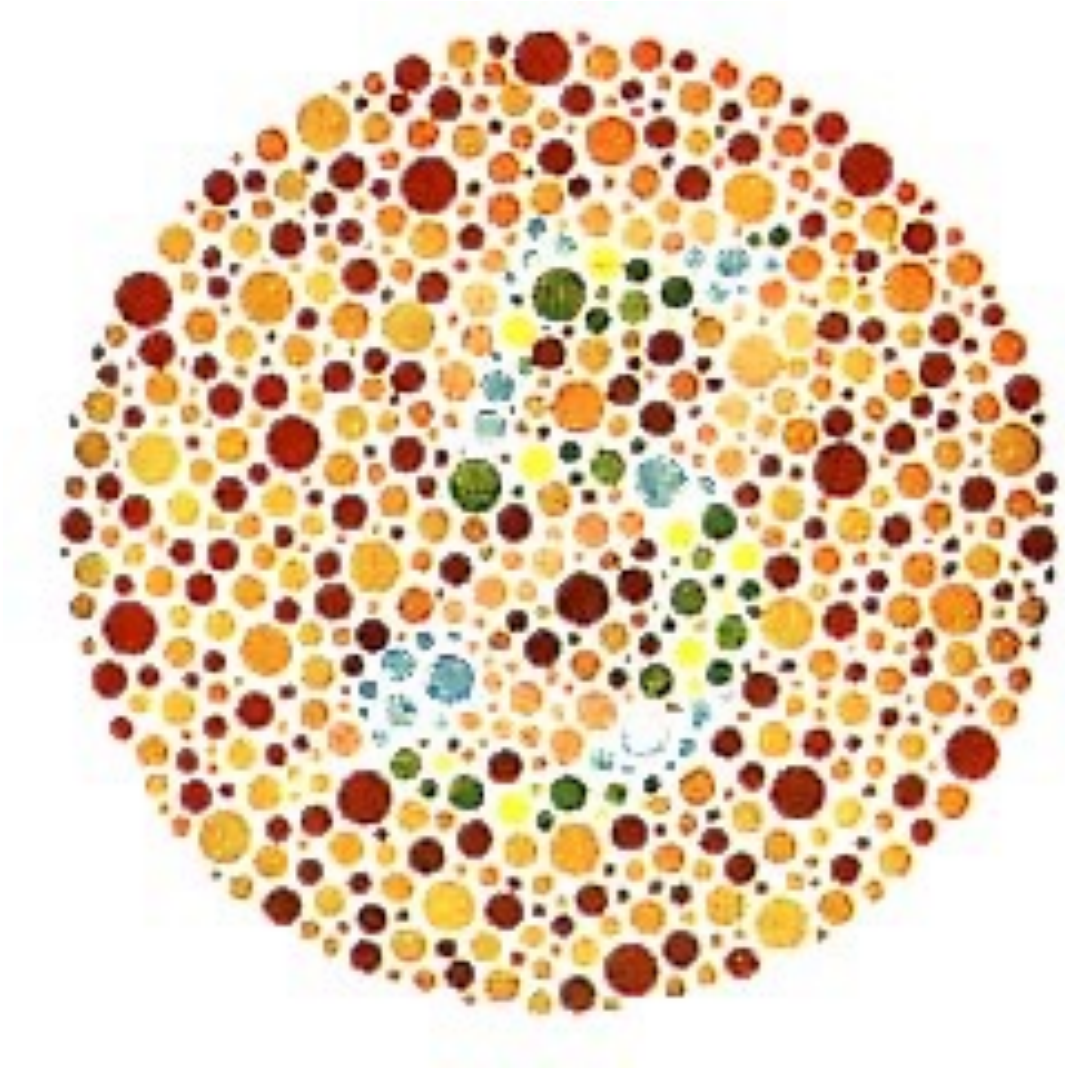
Kleinfelter: Some genes in the X chromosome escape X inactivation

Turner: Some genes on the X need to be expressed in two copies

Pedigree of recessive X-linked trait



What do you see?

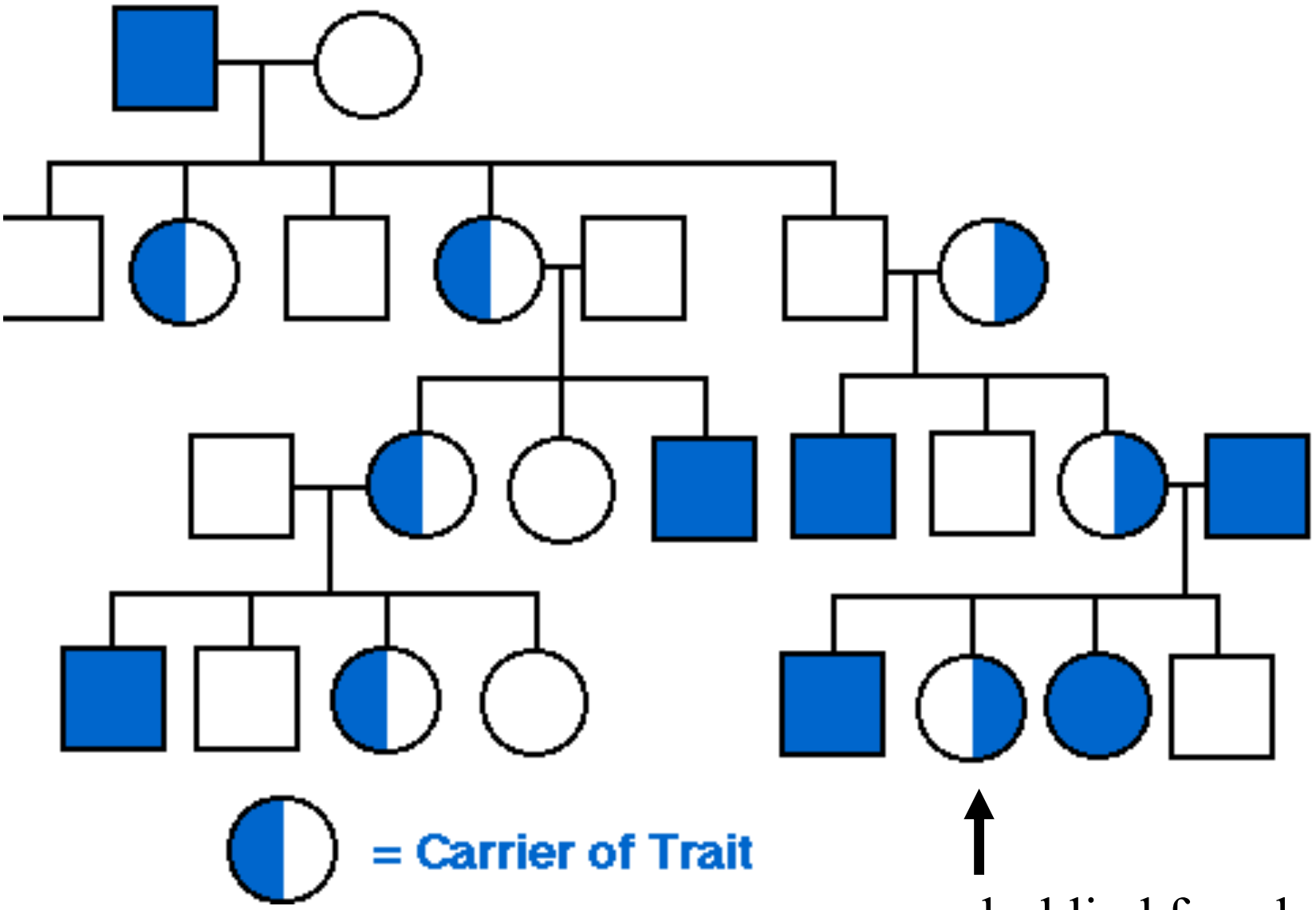


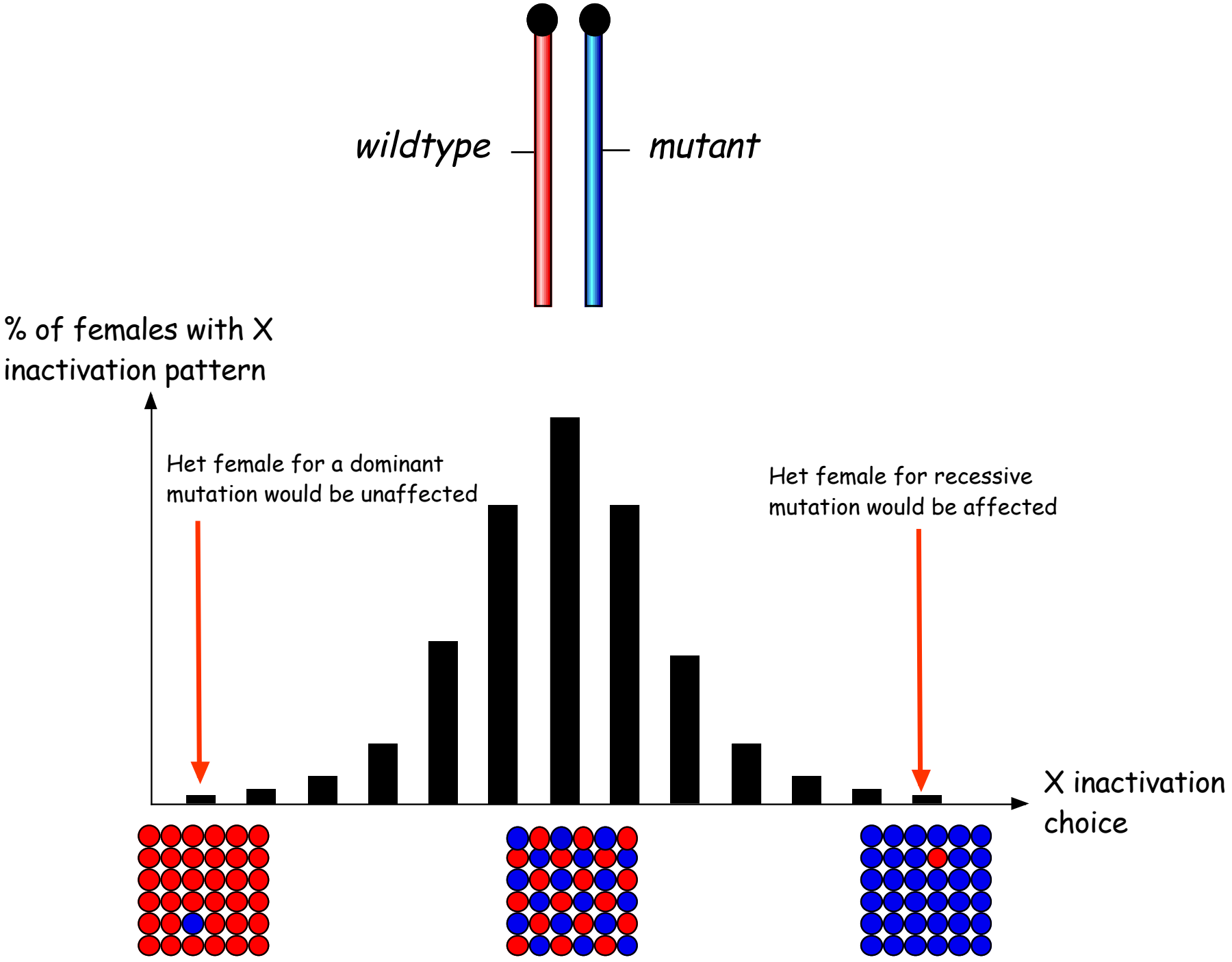
2
colorblind

5
normal vision

9
negative ctrl

Inheritance of Red-Green Color Blindness: an X-linked Recessive Trait

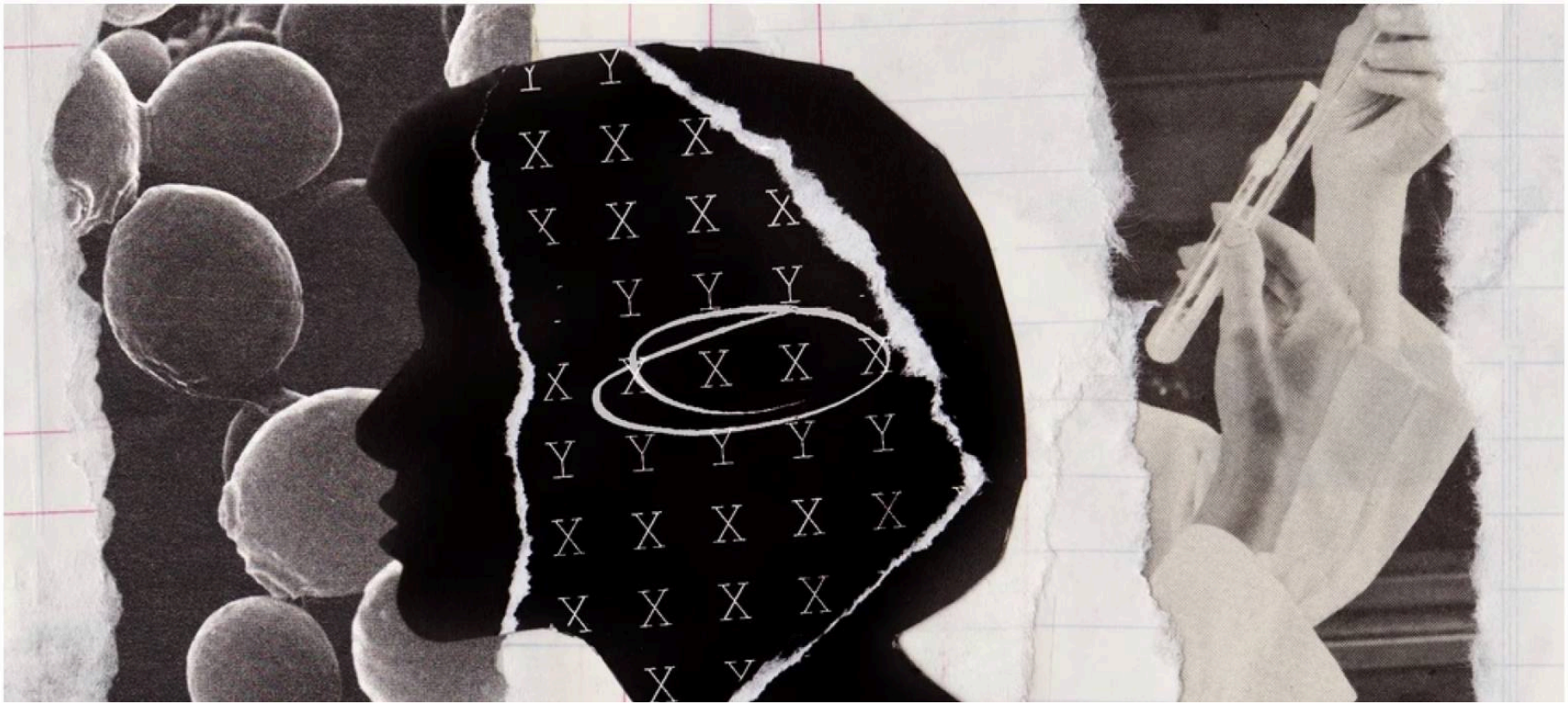



wildtype
mutant
% of females with X inactivation pattern
Het female for a dominant mutation would be unaffected
Het female for recessive mutation would be affected
X inactivation choice

Doctors Said These Women's Mutated Genes Wouldn't Harm Them

But they were always at risk of developing diseases with potentially severe effects.

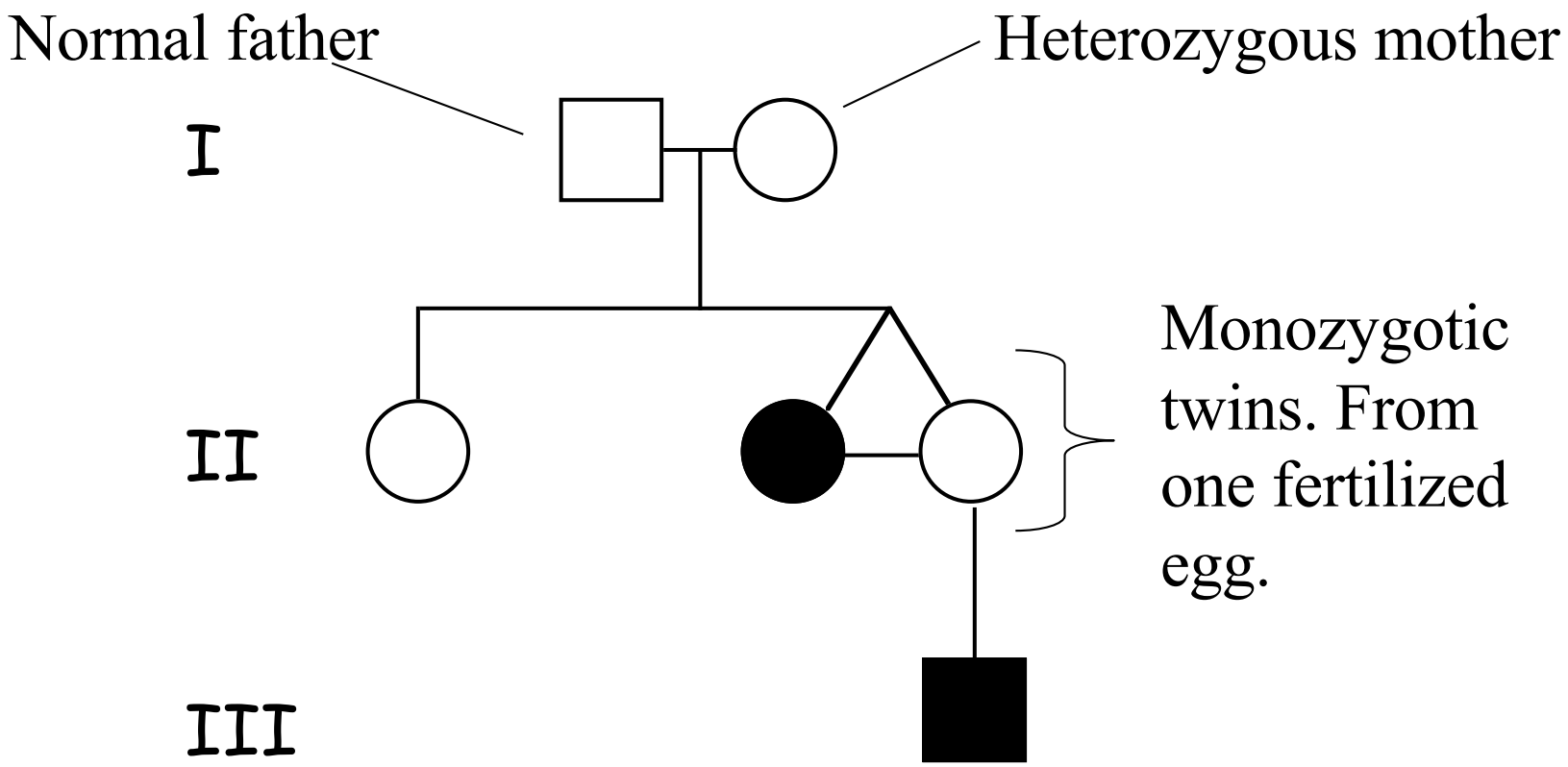
By Roxanne Khamsi



Skewed X inactivation and discordant monozygotic twins

X-linked recessive disease

Fabry disease (α-galactosidase A)
OMIM 301500



Hypophosphatemia
Is an X-linked Dominant Trait