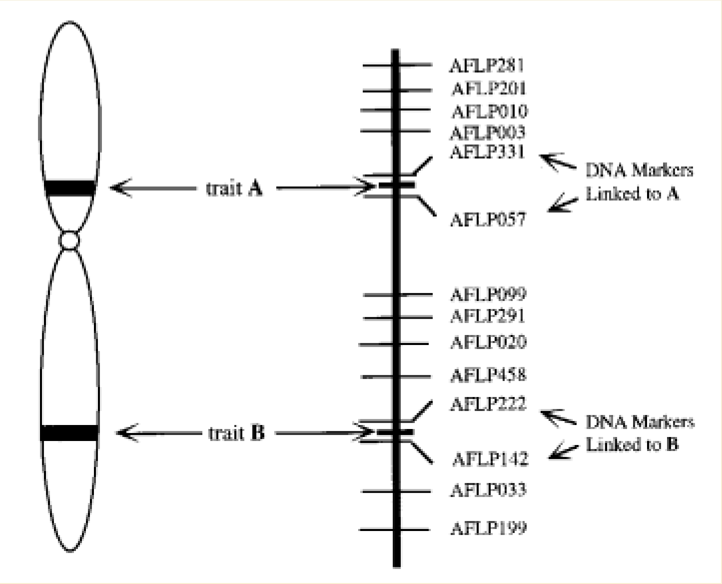
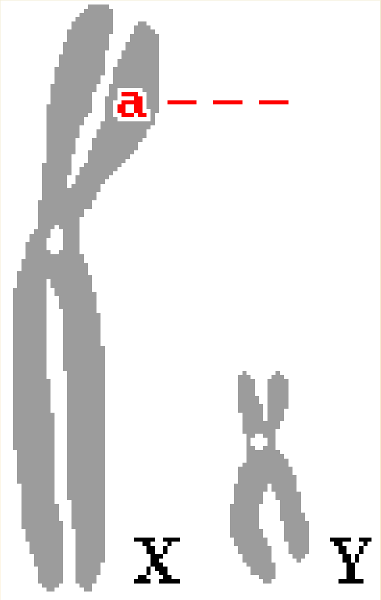
Linkage Diseqilibrium
Sex-Linkage
Sex Determination
Adaptive Significance of Sex





The Hardy-Weinberg Principle

- p = frequency for first allele in the population
- q = frequency for second allele in the population
- Calculate allele frequencies with a binomial equation:

$$p + q = 1$$

- because there are only two alleles:

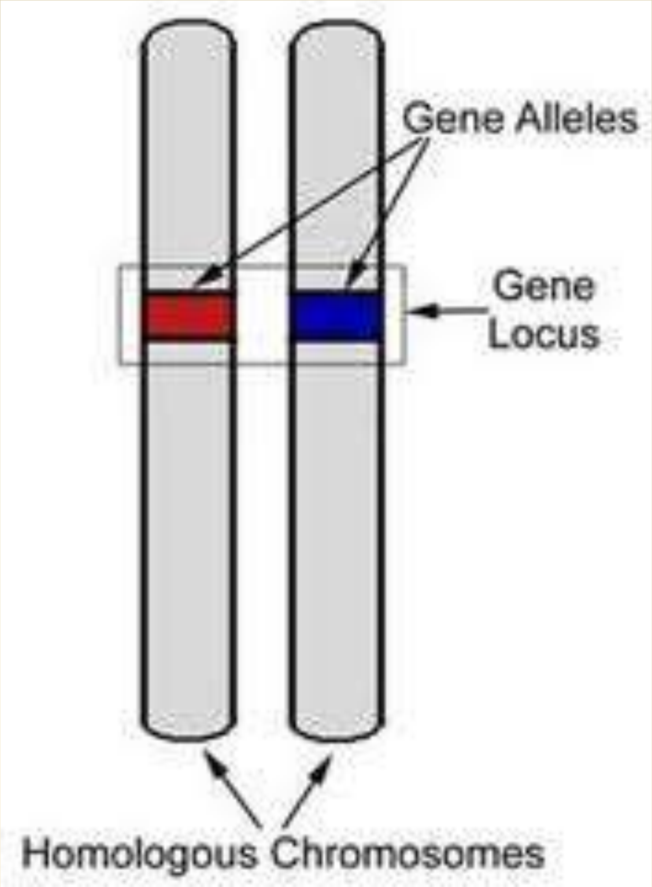
  p + q must always equal 1 (100% of the alleles)

[Note: more alleles can be handled, with three alleles: $p + q + r = 1$]

Linkage Disequilibrium

Locus - location on a chromosome where a gene occurs.

Single locus Hardy-Weinberg models are simple. However, many traits are controlled by combined influence of many genes.



Linkage Disequilibrium

Different loci do not exist in complete isolation from one another.

Some genes are so close to one another on chromosomes that the rate of recombination between them is very low.

Non-random associations of alleles across loci is referred to as linkage disequilibrium (or **gametic phase disequilibrium**).

These non-random associations persist longer for physically linked loci, but are also possible for physically separate loci.

What about two loci?

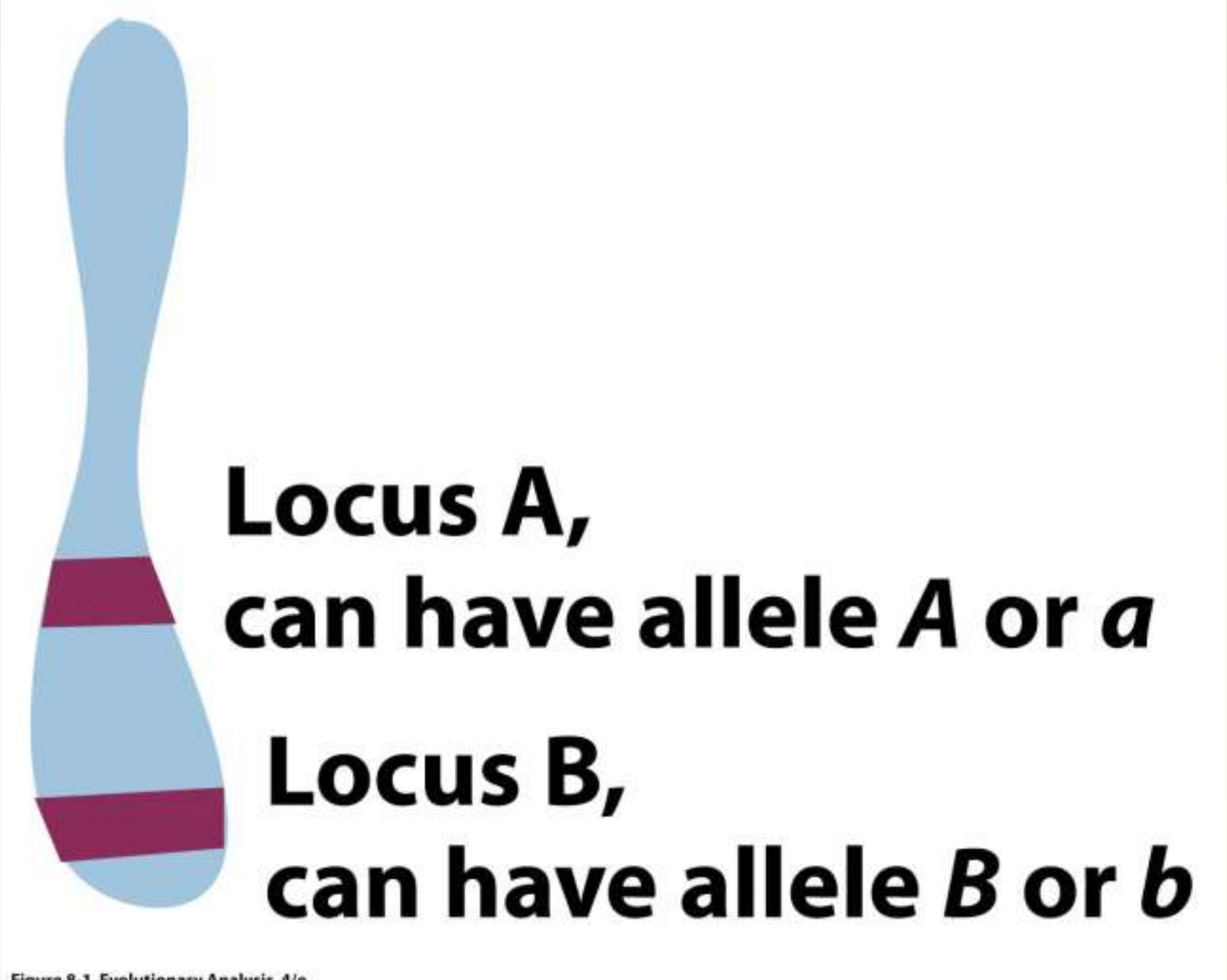


Figure 8-1 Evolutionary Analysis, 4/e

Haplotype - multilocus genotype

Contraction of ‘haploid-genotype’

- The genotype of a chromosome (gamete)

E.g. with two genes A and B with alleles A and a, and B and b

Possible haplotypes

- AB; Ab; aB, ab

Will selection at the A locus affect evolution of the B locus? (sometimes)

The setting and terminology

- Deals with the consideration of two loci simultaneously
- The loci are physically linked on the same chromosome
- Locus A with alleles “***A***”, “***a***” and locus B with alleles ”***B***” and “***b***”
- We track **not only** frequencies of alleles but also frequencies of chromosomes

More terminology

Possible chromosome genotypes for this example are:

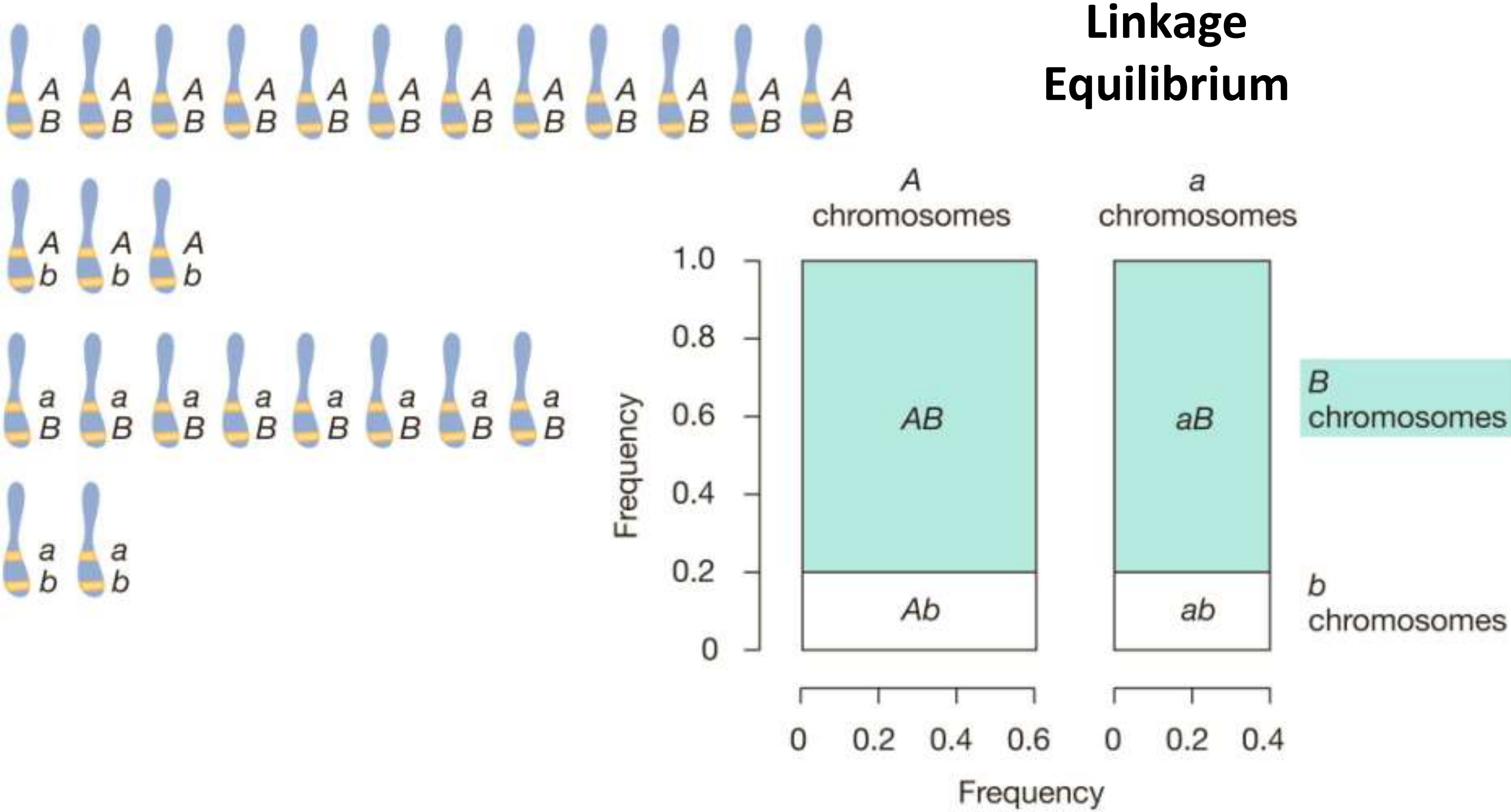
AB; ***Ab***; ***aB***; ***ab***

These multi-locus **genotypes of chromosomes** (or gametes) are called **haplotypes** (for haploid genotype)

These haplotypes may occur in either Linkage Equilibrium or Linkage Disequilibrium

Linkage Equilibrium

(a) A population in linkage equilibrium



Frequency calculations

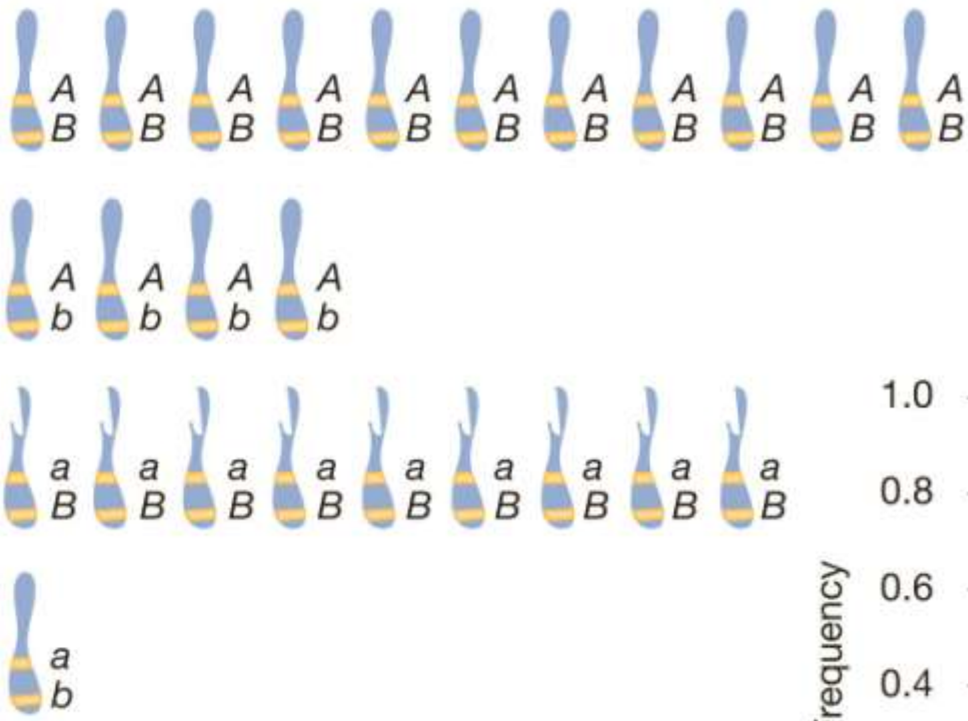
Allele *A*: 15 ÷ 25 = 0.6
a: 10 ÷ 25 = 0.4
B: 20 ÷ 25 = 0.8
b: 5 ÷ 25 = 0.2

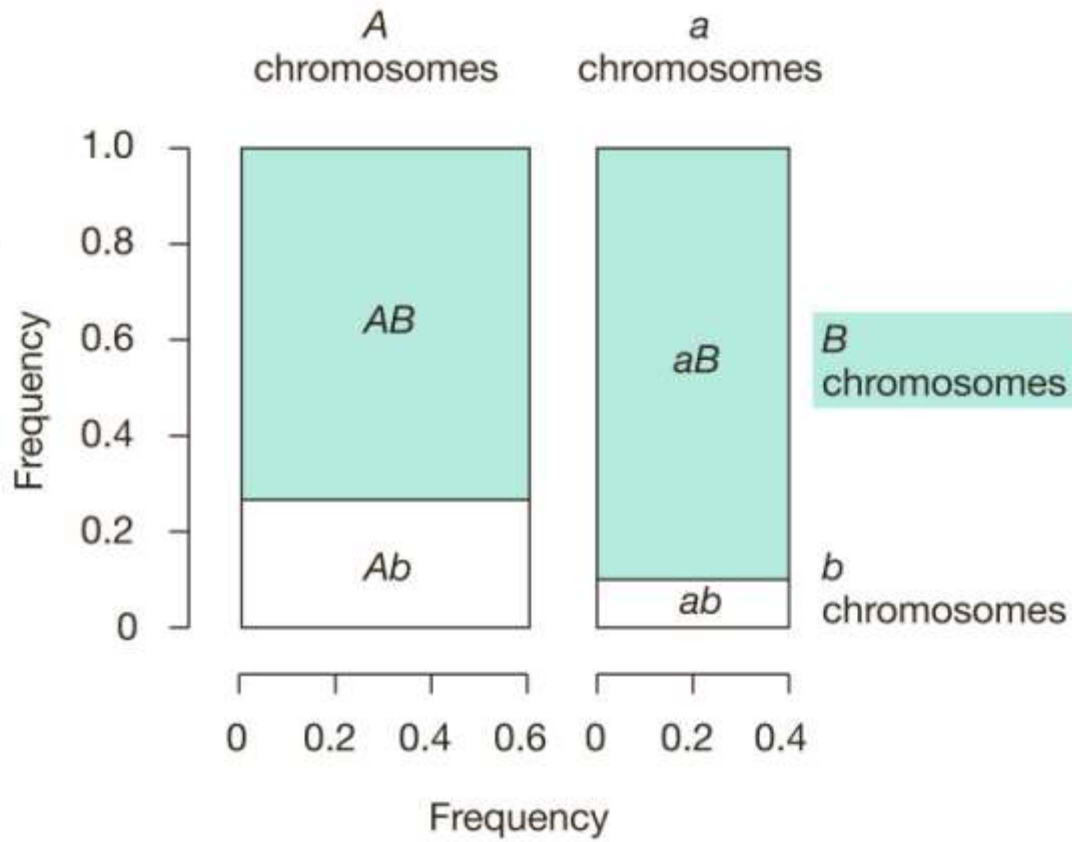
Chromosome *AB*: 12 ÷ 25 = 0.48
Ab: 3 ÷ 25 = 0.12
aB: 8 ÷ 25 = 0.32
ab: 2 ÷ 25 = 0.08

Allele *B* on *A* chromosomes: 12 ÷ 15 = 0.8
B on *a* chromosomes: 8 ÷ 10 = 0.8

Linkage Disequilibrium

(b) A population in linkage disequilibrium





Frequency calculations

Allele *A*: 15 ÷ 25 = 0.6	Chromosome *AB*: 11 ÷ 25 = 0.44	Allele *B* on *A* chromosomes: 11 ÷ 15 = 0.73
a: 10 ÷ 25 = 0.4	*Ab*: 4 ÷ 25 = 0.16	*B* on *a* chromosomes: 9 ÷ 10 = 0.9
B: 20 ÷ 25 = 0.8	*aB*: 9 ÷ 25 = 0.36	
b: 5 ÷ 25 = 0.2	*ab*: 1 ÷ 25 = 0.04	

Example recap:

In both populations
– A frequency = 0.6; a frequency = 0.4
– B frequency = 0.8; b frequency = 0.2

In the disequilibrium population
– Allele B more likely to be found with allele a than allele A

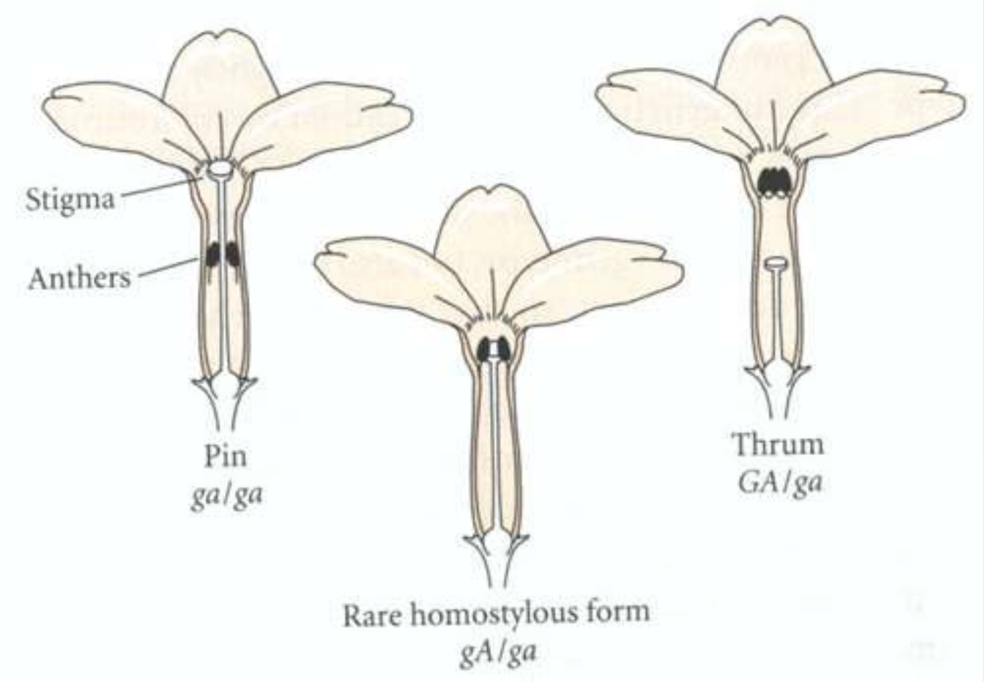
Causes of linkage disequilibrium

- **Selection** on multi-locus genotypes
- **Genetic drift**, non-random mating. Some between-locus allele combinations may increase in frequency by chance.
- Population admixture Immigration/emigration

Mutations in small populations
Inversions preventing recombination

Linkage Disequilibrium in Nature

- Physical linkage among loci is commonplace.
- Linkage disequilibrium is rare.
- Linkage disequilibrium decays at a fast enough rate that it disappears unless some mechanism maintains it.
- The primrose displays one example of linkage disequilibrium (**heterostyly**):



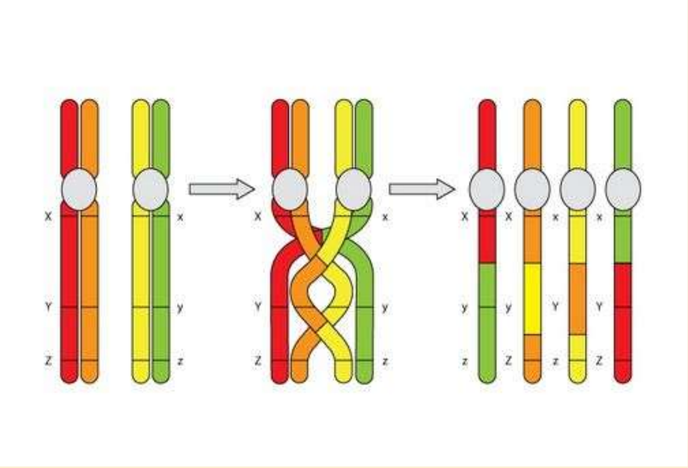
Practical reasons to measure linkage disequilibrium

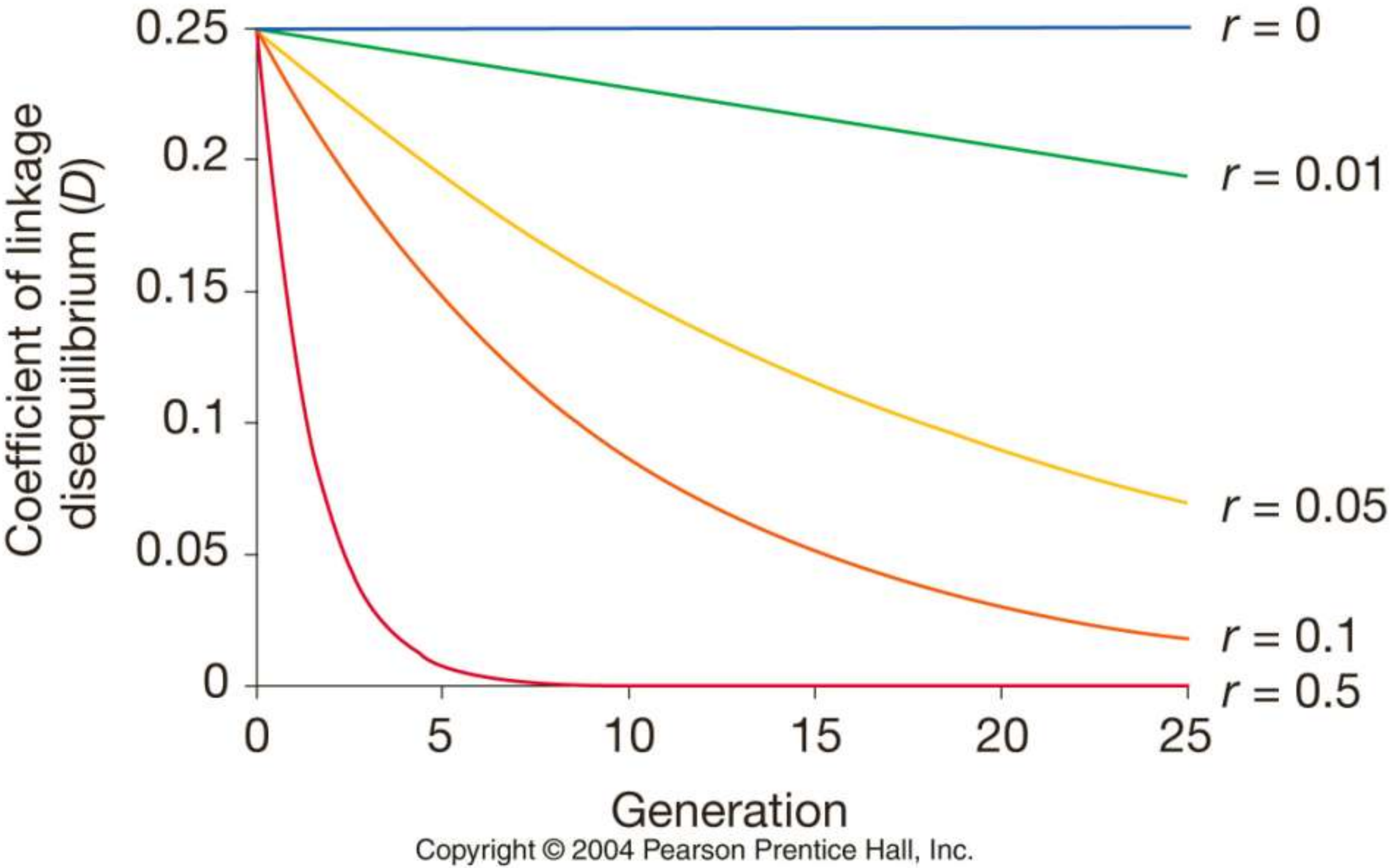
- Major uses of measures of linkage disequilibrium.
  - Can be used to reconstruct history of genes and populations
  - Can be used to identify alleles recently favored by positive selection
  - As we understand more and more about genomes, linkage disequilibrium becomes more important.

Genetic recombination

Genetic recombination tends to randomize genotypes in relation to other genotypes (i.e., it reduces linkage disequilibrium.)

Rate of decline in linkage disequilibrium is proportional to rate of recombination.





r is recombination rate, r is related to how far apart two loci are on a chromosome.

SNPs and Linkage Disequilibrium (LD)

Recent Resurgence of LD Study Motivated by SNP Markers / haplotypes (HapMap project)

High density: ~ one SNP in every 600 bp in the human genome make them easy to map.

Simple SNPs: Biallelic (occur on both alleles)

Common: ~93% are found globally (among human populations); ~7% are restricted to local populations.

SNPs / Linkage Disequilibrium

Generally speaking…

SNPs should be inherited *independently*

– Following Mendelian inheritance

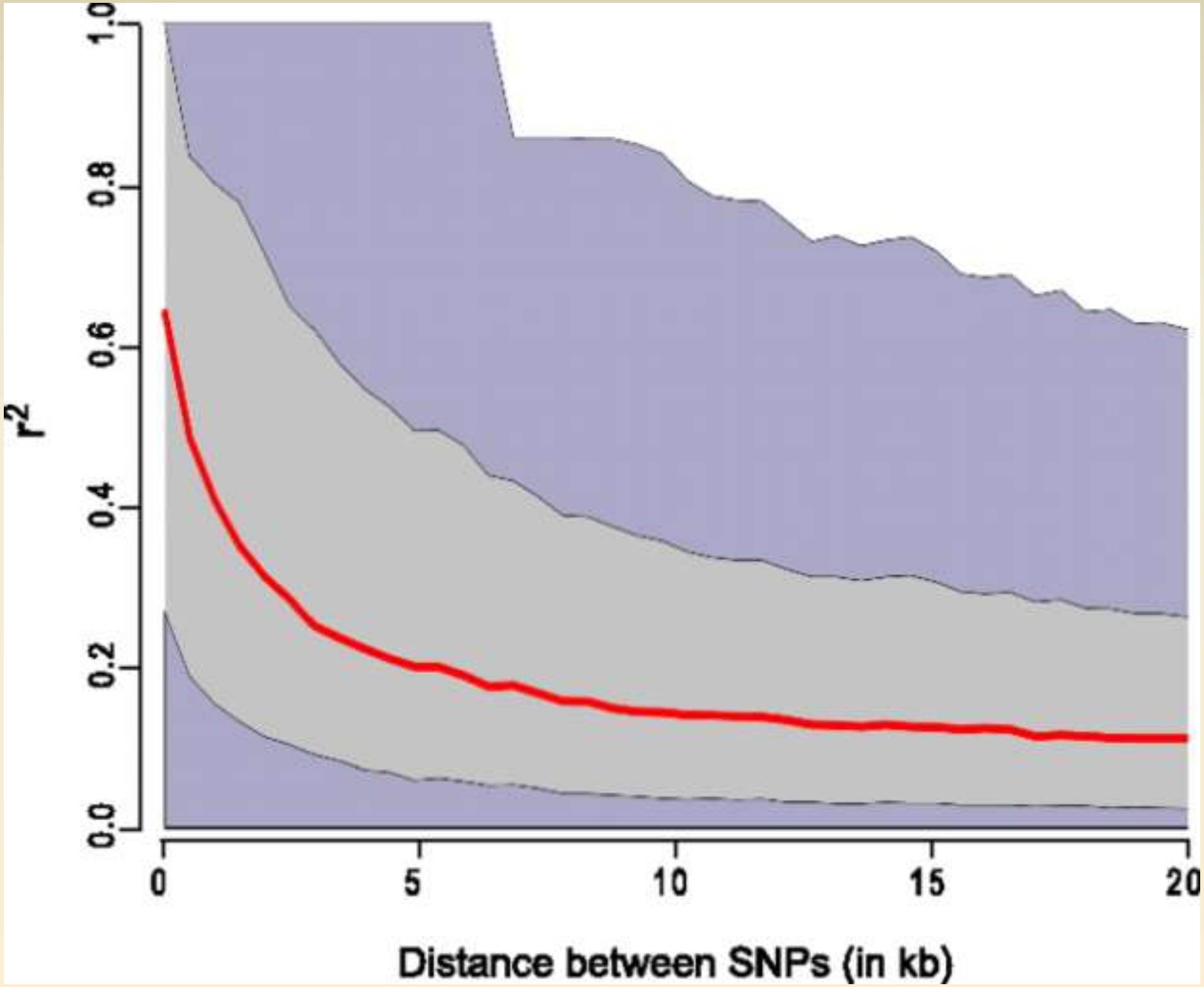
Many SNPs appear to be ***co-inherited***

– Creating 'hot spots' in the human genome

Blocks of SNPs – 'SNP haplotypes'

– We don't why or how, ***but they exist***

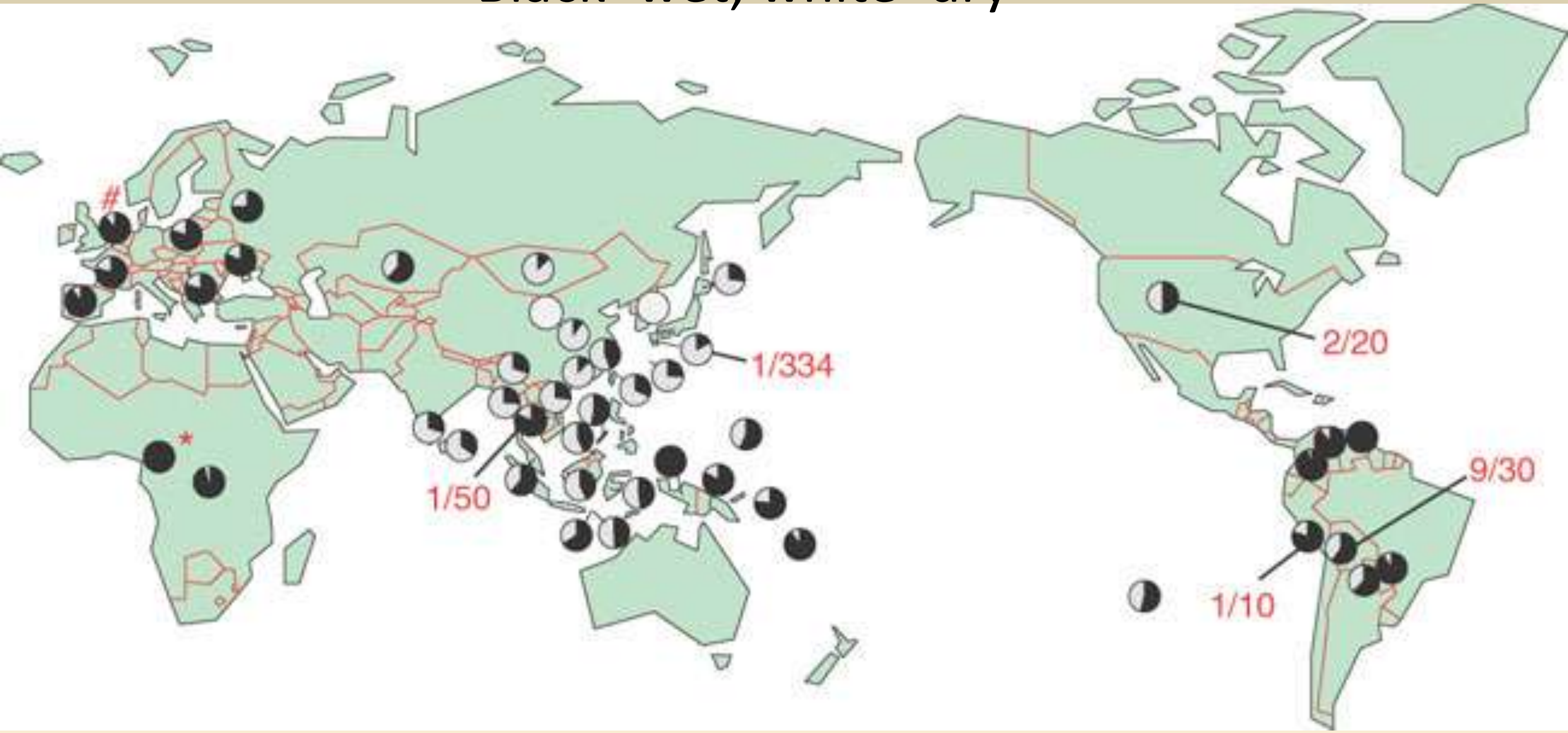
Mean LD decay (red line) as measured by pairwise r2, with the 50% and 90% ranges of values shown in light and dark gray, respectively.



Branca A et al. PNAS 2011;108:E864-E870

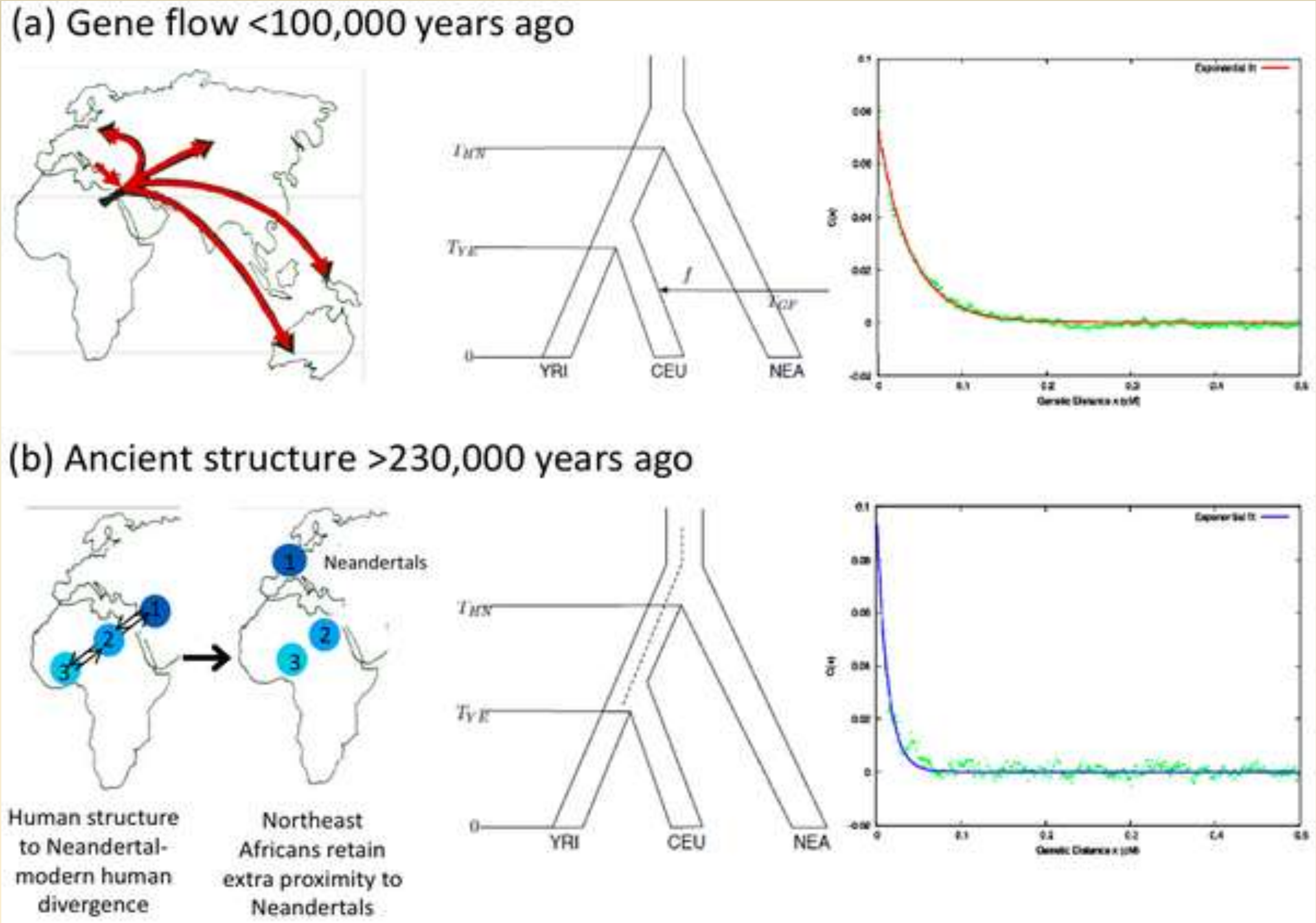
PNAS

# Earwax Types
Black=wet, white=dry



The trend is pretty clear, modal in Northeast Asia and decreasing everywhere else. Linkage disequilibrium. Recombination has not had time to break apart the correlations.

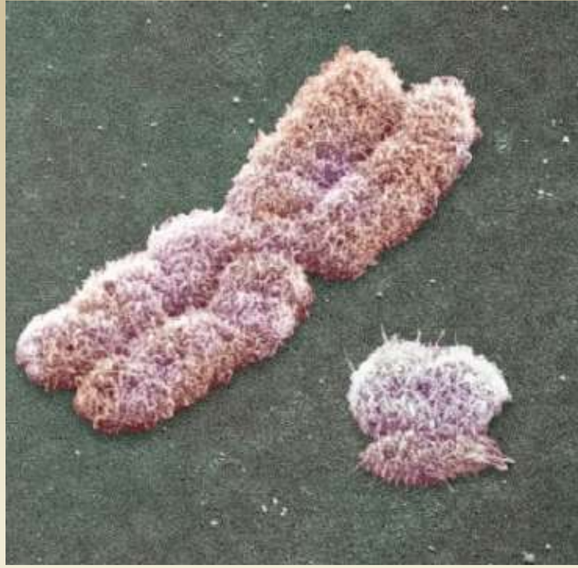
Figure 1. Linkage disequilibrium patterns expected due to recent gene flow and ancient structure.



Sankararaman S, Patterson N, Li H, Pääbo S, et al. (2012) The Date of Interbreeding between Neandertals and Modern Humans. PLoS Genet 8(10): e1002947. doi:10.1371/journal.pgen.1002947
http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1002947

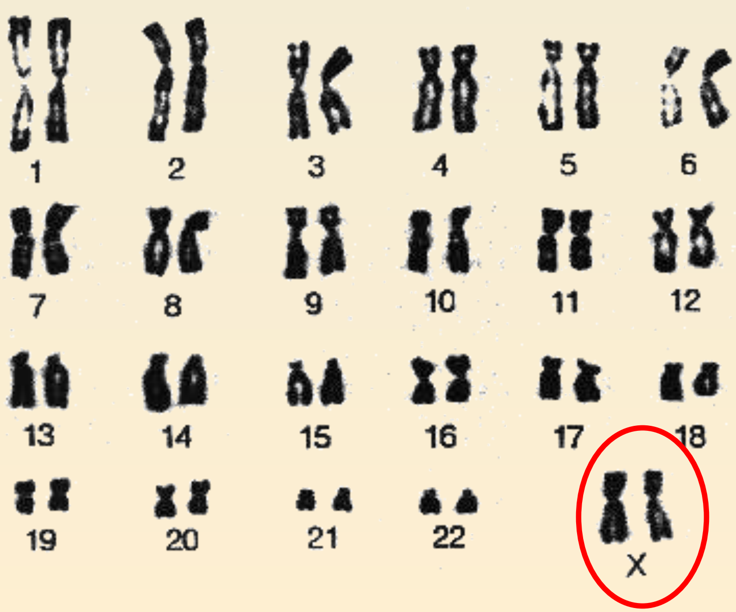
PLOS | GENETICS

Sex Linkage

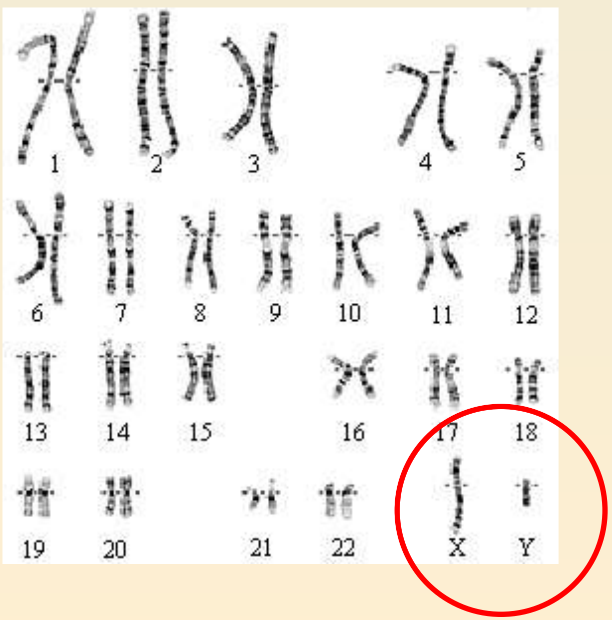


Sex Chromosomes – X, Y

Normal human female karyotype



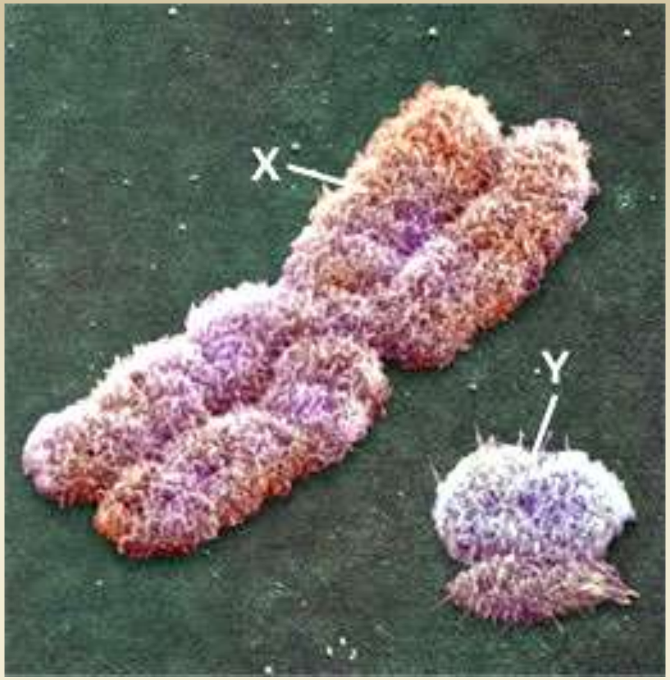
Normal human male karyotype

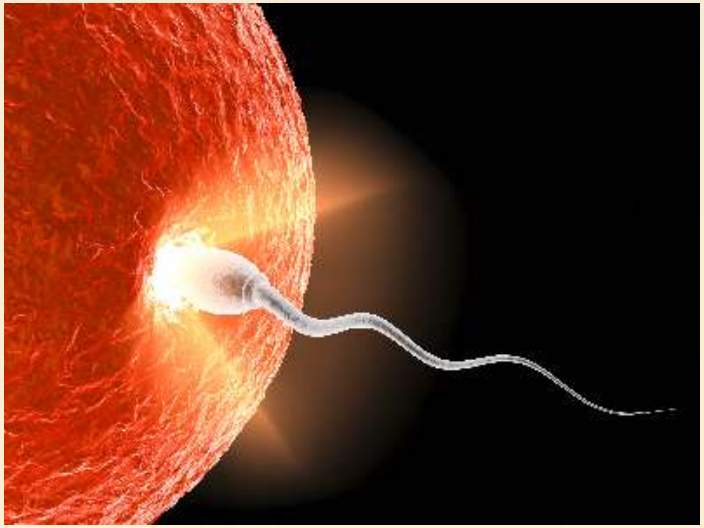


At fertilization

When an X chromosome meets a Y chromosome at fertilisation, each sex-linked gene on the X chromosome becomes expressed in the phenotype of the human male produced.

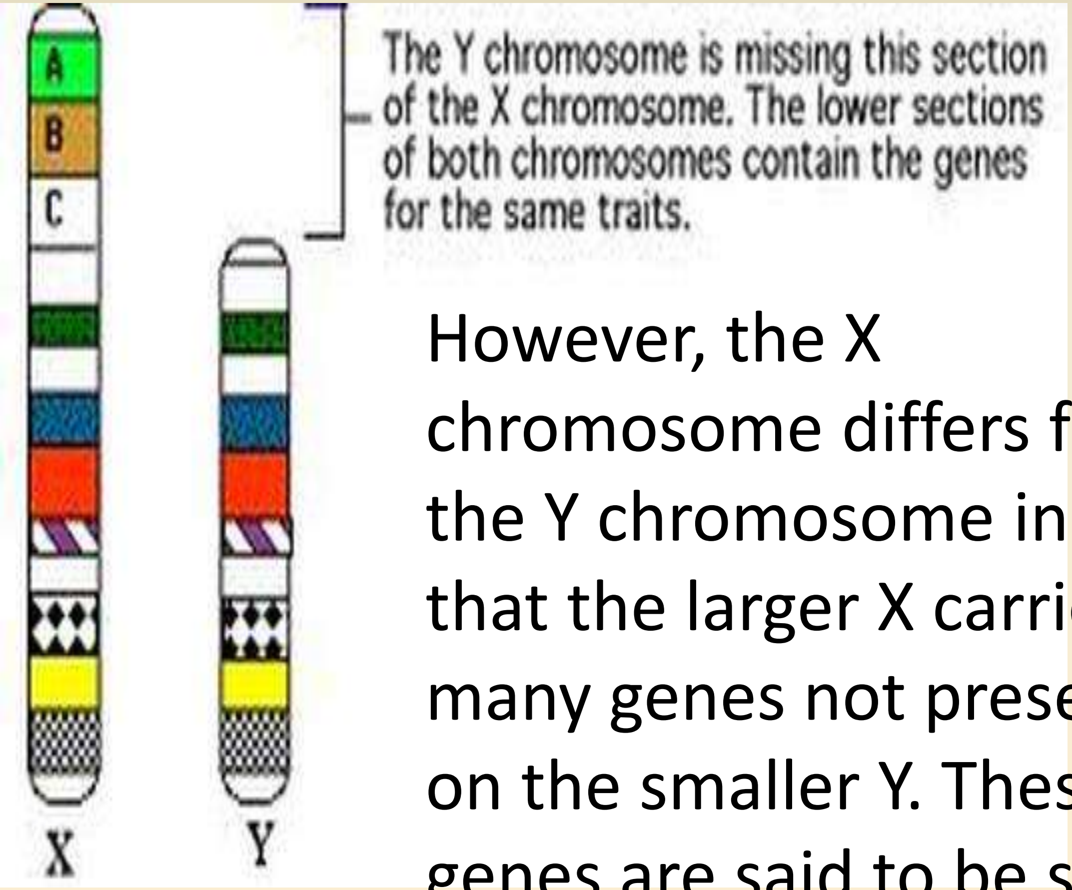
This is because his Y chromosome does not possess alleles of any of these sex-linked genes and cannot offer dominance to them.





Sex-linked genes

- The X and Y chromosomes behave as a homologous pair at meiosis.



However, the X chromosome differs from the Y chromosome in that the larger X carries many genes not present on the smaller Y. These genes are said to be sex-linked.

Human sex chromosomes

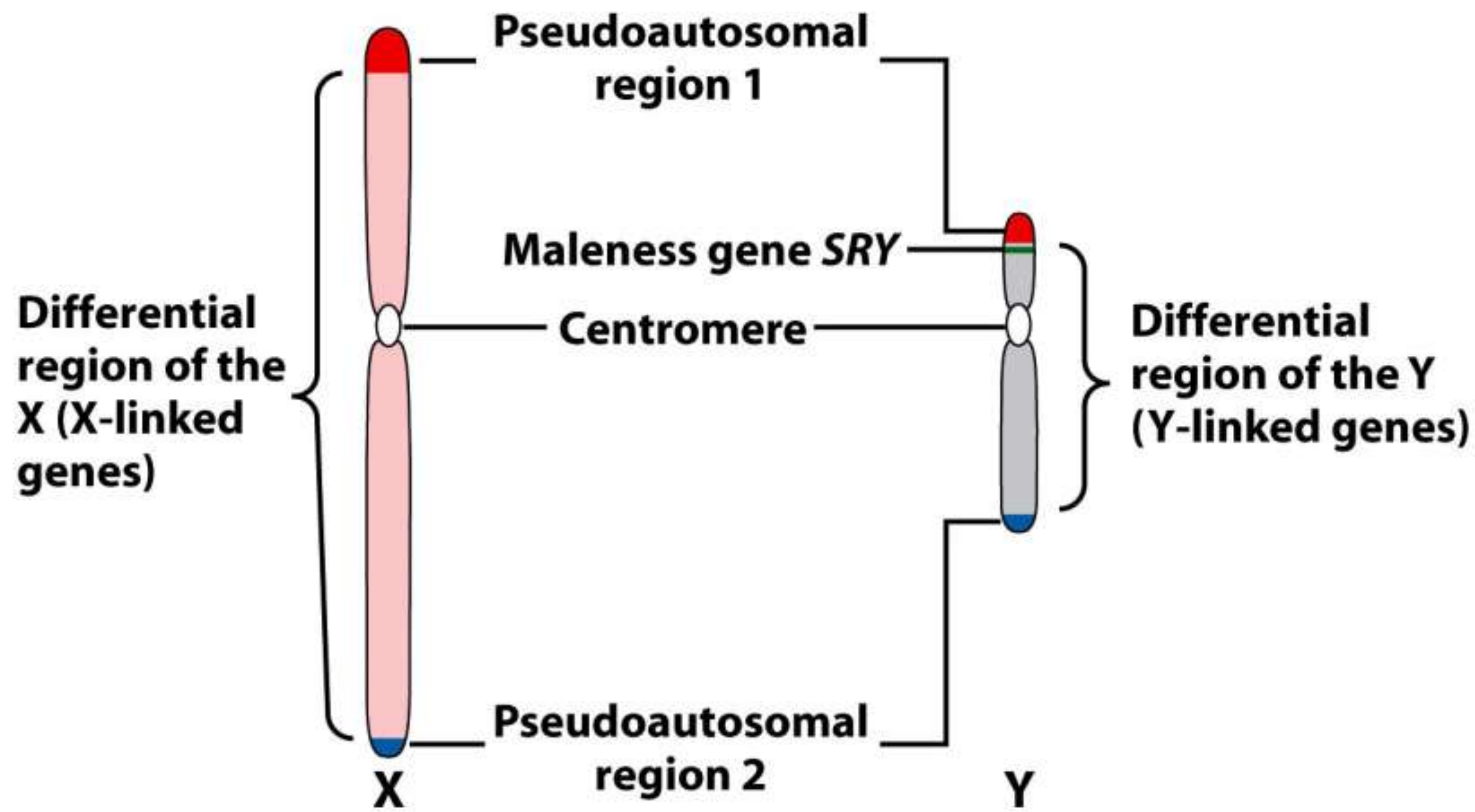
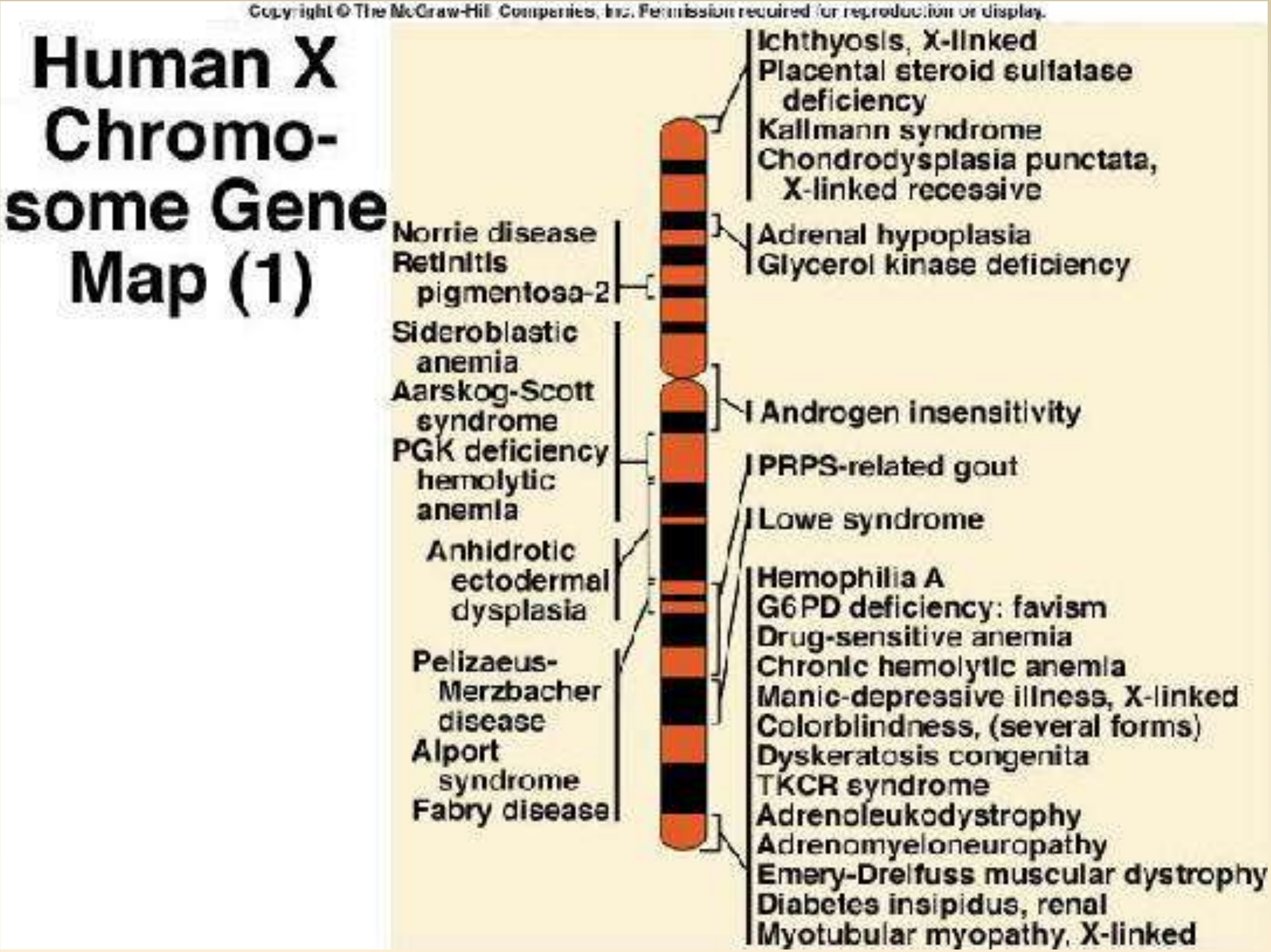
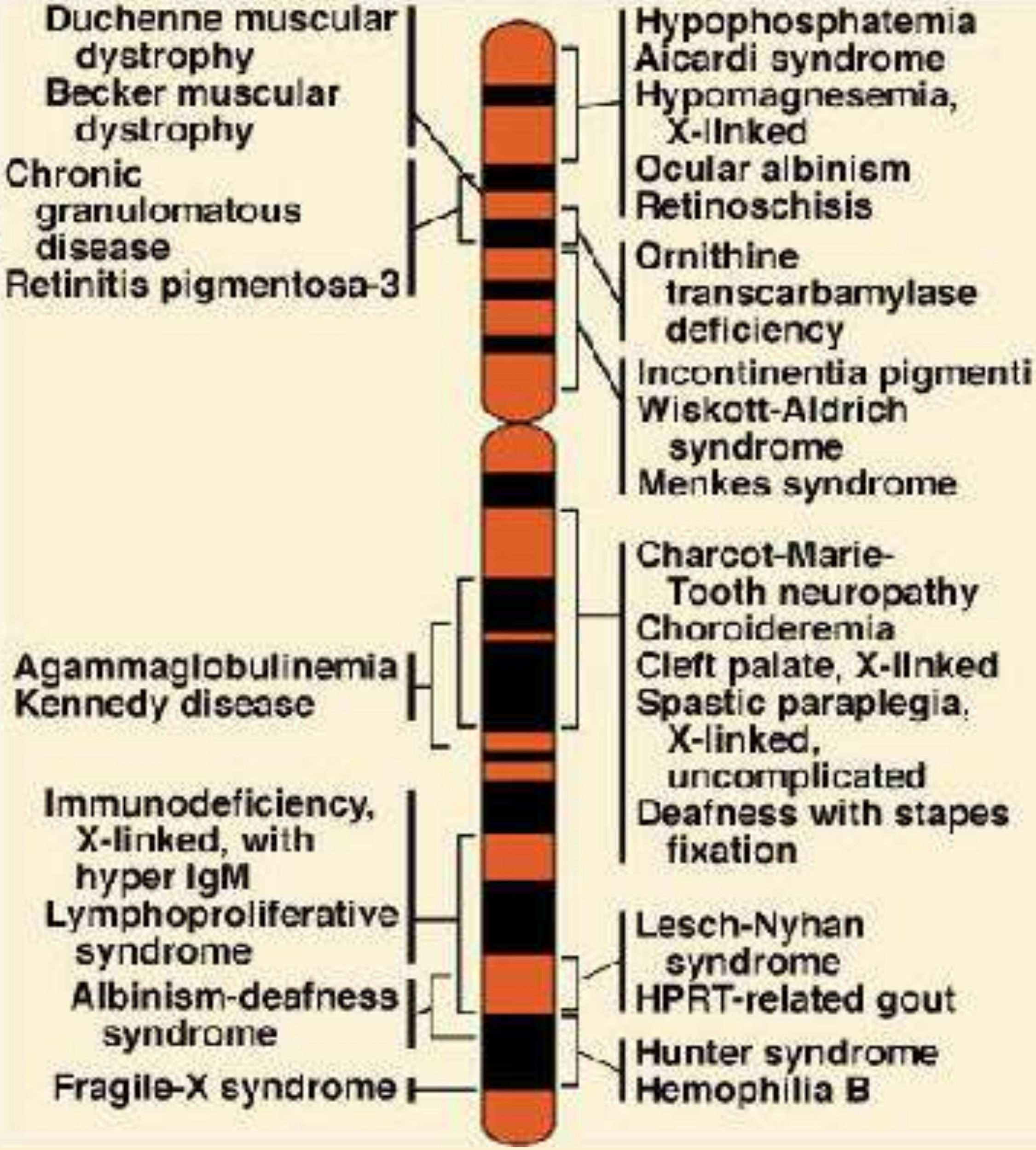


Figure 2-25
***Introduction to Genetic Analysis*, Ninth Edition**



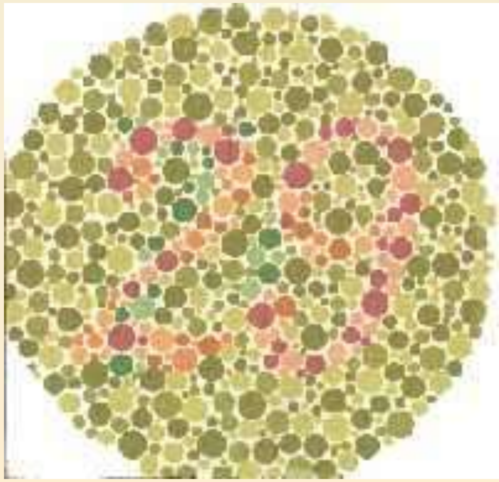
Gene map of a human X chromosome. Over 59 defects have been traced to this chromosome, which will appear more often in males if they are recessive mutations

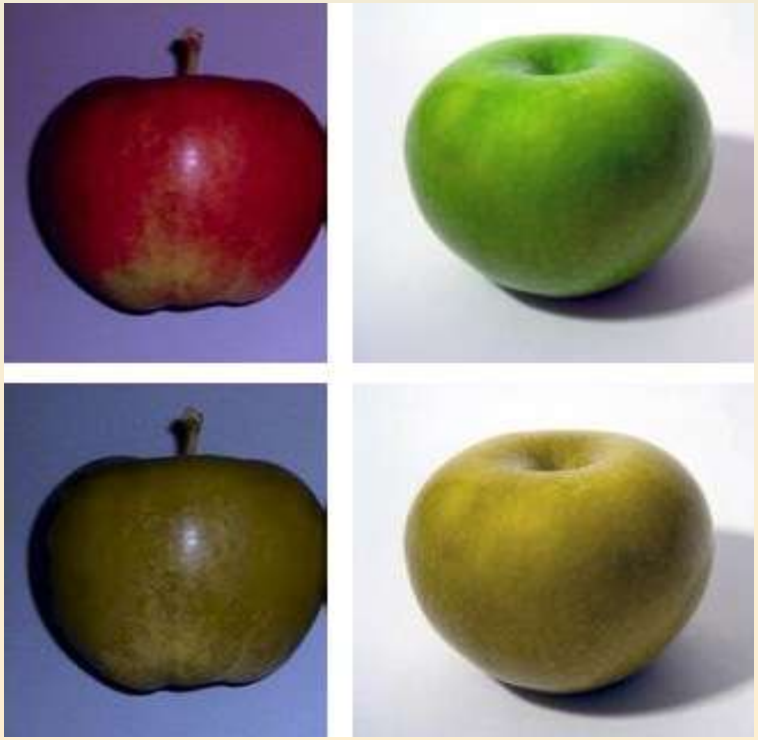
Human X Chromosome Gene Map (2)



X-linked recessive disorder - Red Green Colour Blindness

- Inability to distinguish between red and green
- A red green colour blind person does not see the number 29 below
- In humans normal vision (C) is dominant to red-green colour blindness (c)





Genetics of Colour Blindness

- Normal vision C
- Red-green colour blindness c
- These are the alleles are sex-linked because...
- Heterozygous females are carriers (Cc)

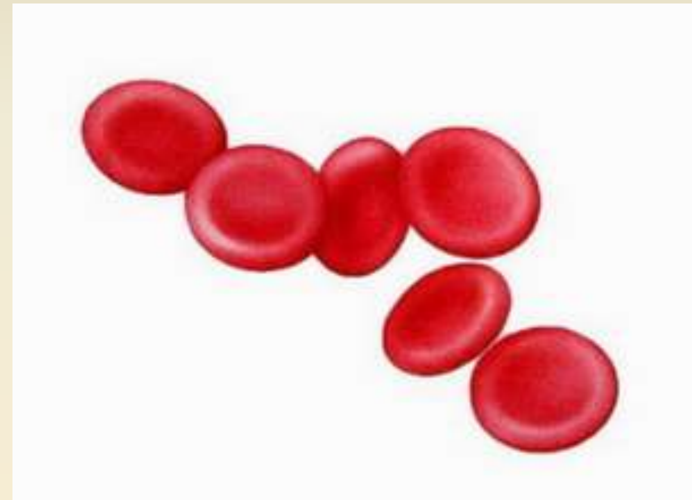
  Although they are unaffected themselves there is a 1 in 2 chance (50%) chance that they will pass the allele on to each of the offspring.

Haemophilia:
mutated form of factor VIII in platelets

- Haemophiliacs cannot make the blood clotting protein Factor VIII.
- This is a problem with blood clotting. So, if a tissue is damaged and blood vessels are broken, bleeding continues for longer than normal.
- Some bleeding is obvious such as when the skin is cut or broken. Others are less easy to spot like bleeding into or around the joints.

X-linked recessive disorder - Haemophilia

It caused by a recessive allele carried on the X (e.g. The gene is located on the non-homologous region of the x-chromosome) but not the Y chromosome.



The haemophiliac allele (X^h)is recessive to the normal allele (X^H).

Hence is sex-linked.

Haemophilia

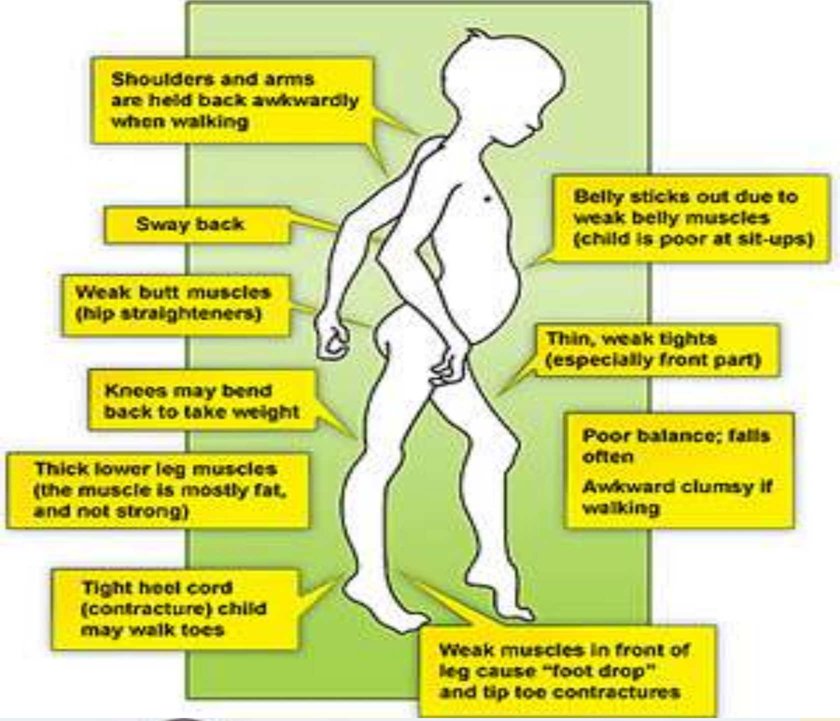
Allele Key X^H *Normal*

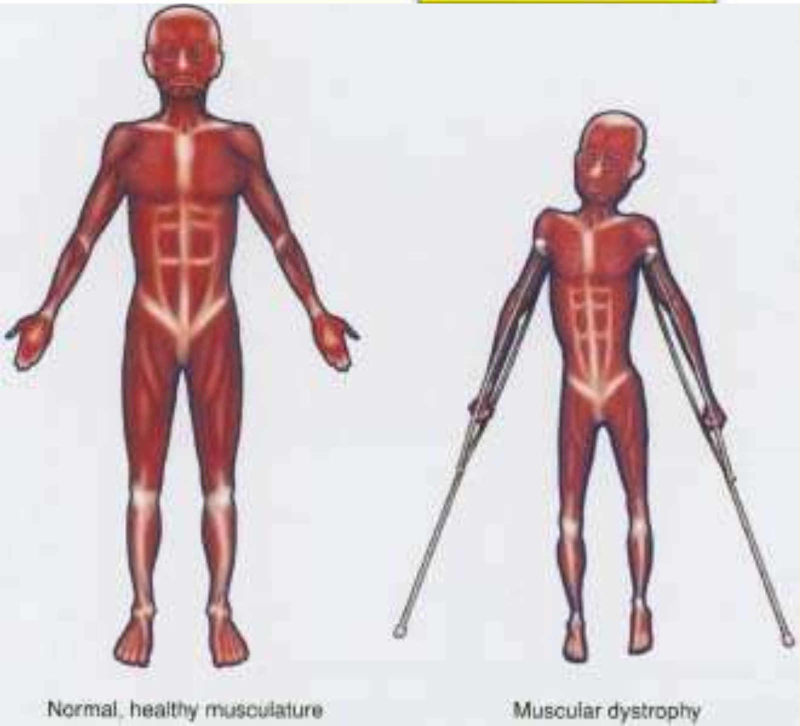
X^h *Haemophiliac*

Female Genotypes	*Male Genotypes*
$X^H X^H$	$X^H Y$
$X^H X^h$	$X^h Y$
* $X^h X^h$	

More common in males than females

- Haemophilia is more common in men than women.
- Fequency in britian is 1:5000
- Males inherit the allele from their mother and develop the disease.
- Since (until recently) the prognosis for survival was poor and haemophiliac males did not survive to pass on the allele to their daughters (its on the X-chromosome). Therefore females with haemophilia where rare.





Muscular Dystrophy

- Duchenne Muscular Dystrophy is the most common form of this disease.
- Sufferers are severely disabled from an early age.
- The normally die without passing allele onto the next generation.
- Afects 1:3000 male infants.
- Skeletal muscles loose their normal structure and fibrous tissue develops in their place.
- Caused by a recessive allele carried on the X chromosome and is sex-linked.

Sex Determination

Sex determination

Dioecious: the majority of animals exist as one of two sexes, with males producing sperm and females producing eggs.

Sexual dimorphism: in many species, the differences between sexes are not limited to the reproductive organs, but extend to other characteristics such as size, ornaments, and body shape.

Monoecious: all individuals of a species look alike and produce eggs and sperm. Common in invertebrates. Individuals with both gonads are **hermaphodites**.

Sex determination: the natural event by which an individual of a dioecious species becomes male or female. There are two main mechanisms for sex determination:

Genetic sex determination: sex is determined at fertilization by the combination of genes that the zygote receives.

Environmental sex determination: in some species, sex is determined after fertilization by environmental factors (temperature, population size, or sex of others).

Sex was the first character to be successfully interpreted in terms of the chromosomes.

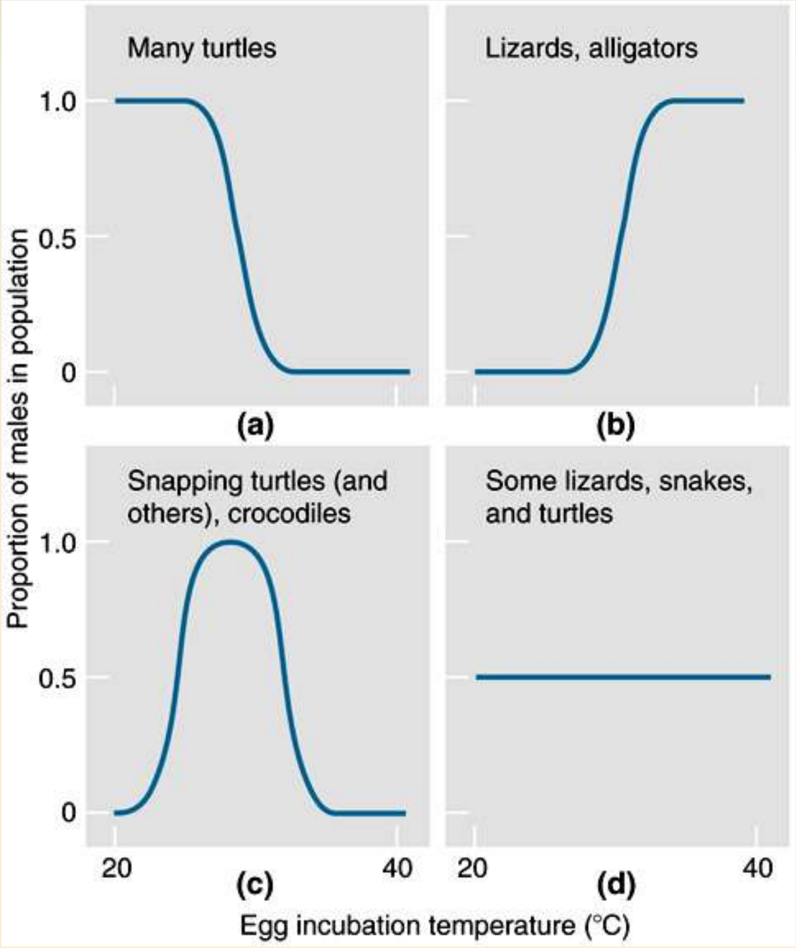
Most plants are hermaphroditic or monoecious, each able to produce both types of sexual gametes, but about **2-4% of the angiosperms are dioecious.**

Grasshoppers have 23 chromosomes in males and 24 in females.

In the majority of animals, as well as in several dioecious plants, **one pair of chromosomes can be distinguished morphologically from the rest**. This unequal pair is limited to one of the sexes.

Honeybee, males develop from unfertilized eggs (haploid)

Temperature: in many reptiles (crocodiles, turtles, and some lizards) sex is determined by incubation temperature during a brief but specific stage of embryogenesis. Small differences in ambient temperature have amazing differences on sex ratio.



Map turtles: the sex ratio drops from 1 (all male) to 0 (all female) when ambient temp increases from 28 to 30 C.

Alligators: the pattern is reversed in alligators and lizards.

Crocodiles: a third pattern exists. The males develop at intermediate temp. and females develop at the two extremes of higher of lower temp.

In many other reptiles, temperature has no effect on sex determination.

It is not clear why the temperature is important. Presumably, the different temp. favors either males or females.

Adaptive Value of Sex

Adaptive significance of sex

Many risks and costs associated with sexual reproduction.

Searching for a mate requires time and energy and exposes organisms to predators.

Mate may require investment (food, territory, defense).

Risk of sexually transmitted disease.

How is sexual reproduction maintained in the face of alternative asexual strategies? (Why sex?)

Fission
Budding
Parthenogenesis
Hermaphroditism
Haplodiploidy

Reproduction

The ability to produce new individual organisms, either **asexually** from a single parent organism, **or sexually** from two parent organisms.

Asexual reproduction

is not limited to **single-celled organ**isms - **most plants**

- **binary fission-** Bacteria

- **budding** - yeasts and Hydras

- **conjugation** - bacteria may exchange genetic information

- **parthogenesis, fragmentation** and **spore formation**

Sex is not universal

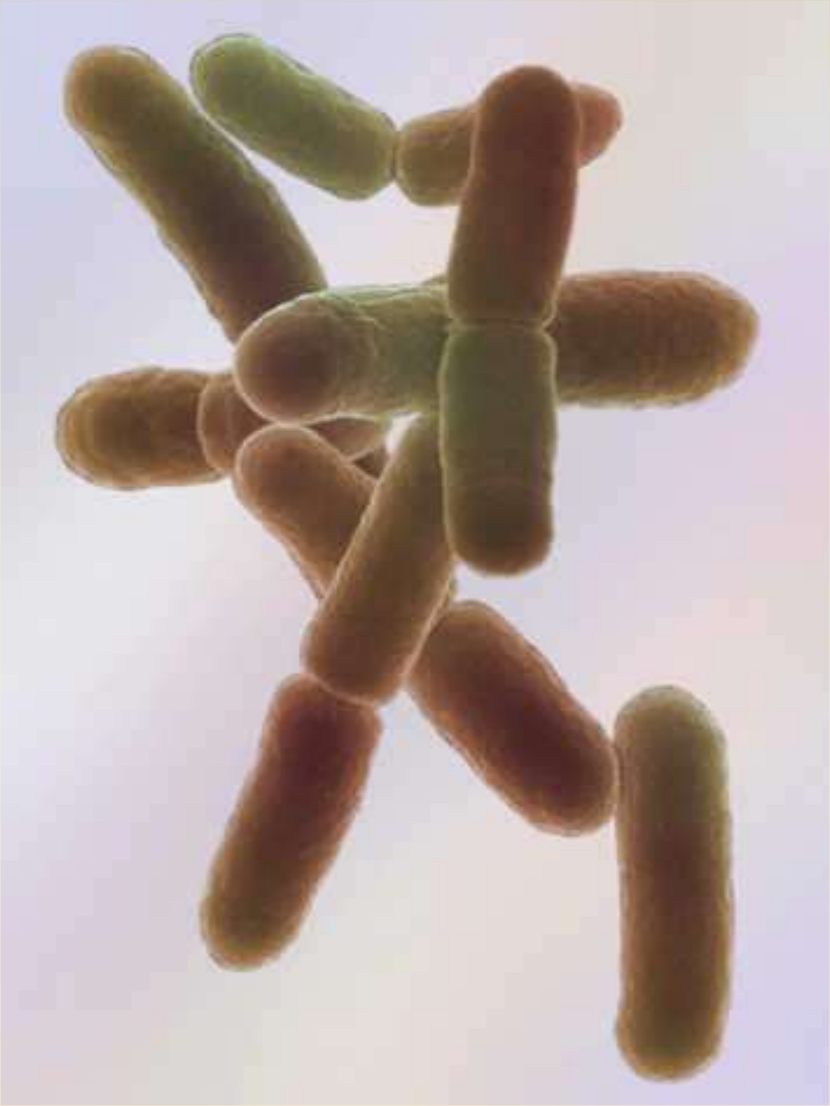
- Sex occurs in Eukaryotes, and not in Bacteria or Archaea
  - Bacteria: high mutation rate and horizontal gene transfer
  - Viruses: cost of mistakes (mutations) are not critical because the host is producing all the offspring

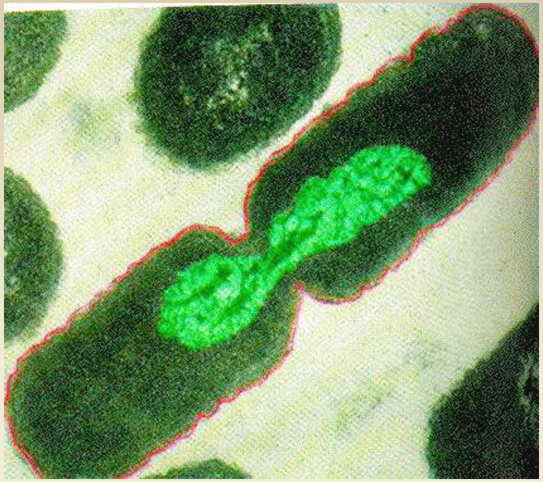
- Asexuality occurs often in plants, and in many invertebrates

- Some eukaryotes are asexual until they experience a large accumulation of deleterious mutations (mutational meltdown) or stress, then they have sex (Daphnia, ciliates, dinoflagellates)

- Some eukaryotes have more than 2 sexes (some ciliates have 32)

Bacterial Division





Conjugation

Hydra Budding

Aphis
Aphid
Green-fly

Wingless female
giving birth

baby hammerhead

Parthenogenesis

- **lower plants** (where it is called **apomixis**)
- **invertebrates** - water fleas, aphids, some bees and parasitic wasps
- **vertebrates** - some reptiles, fish, and very rarely birds and sharks

Parthenogenesis (both mitotic and sexual forms)

Organisms develop from unfertilized eggs.

Examples: some lizards, aphids, many plants

New Mexico whiptail lizard (*Cnemidophorus neomexicanus*)

Male-like behaviour in female Aspidoscelis whiptail lizard (parthenogenic sp)

Hermaphroditism (obligate or sequential)

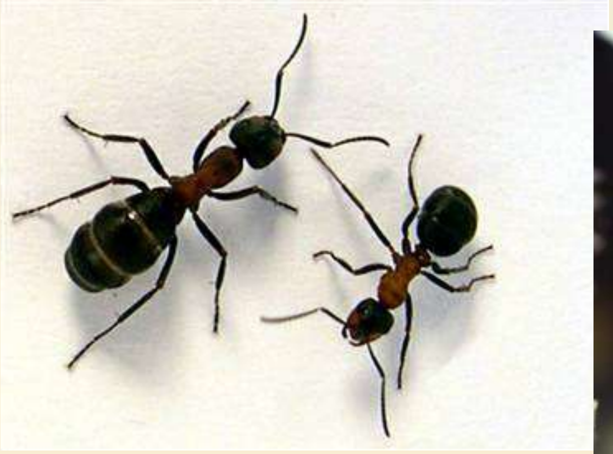
Organisms possess **both male and female** reproductive organs, or change sex at some point in their lives.

Examples: many fishes, snails, worms

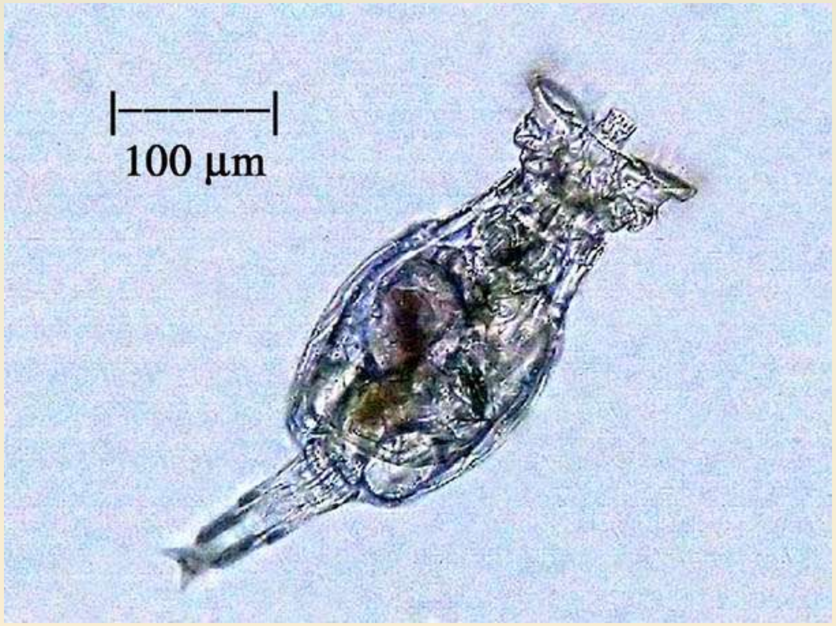
Haplodiploidy

Haploid males develop from unfertilized eggs, diploid females from fertilized eggs.

Examples: ants, bees, wasps



Bdelloid rotifers – no sex for 40 million years!

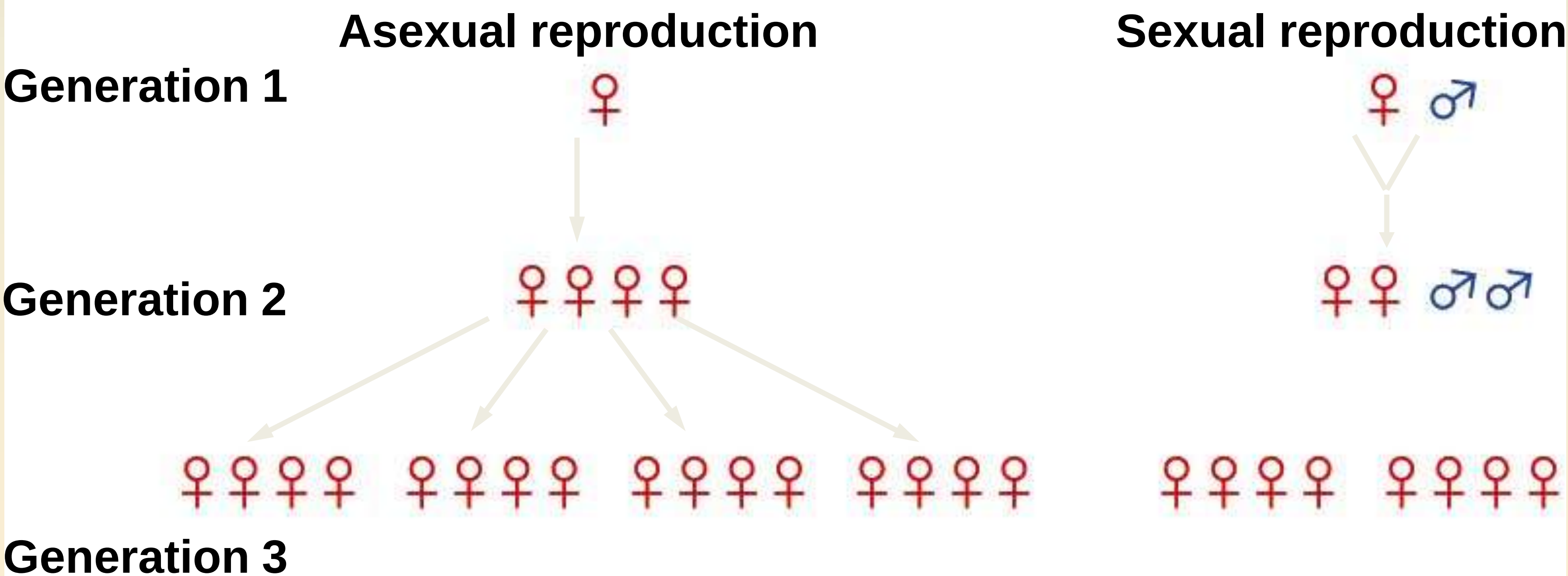


Cost of Sex

Loss of Fitness relative to clonal populations:

Reduces population growth rate by 1/2, because males cannot reproduce

Cost of Sex



Asexual populations grow twice as fast as sexual populations
Asexual reproduction would quickly replace sexual reproduction.

Asexuals will win if:

- Same number of offspring produced by sexual and asexual species, and/or
- Offspring survival not different for sexual and asexual species

The fact that **most species are sexual** suggests that one or both of these must be wrong.

Of the world's ~2 million named species less than ~2,000 are totally asexual, and they don't appear to persist very long

Asexual species are typically found at the tips of phylogenetic trees

S = sexual species

A = asexual species

What are the advantages of sexual reproduction?

- **Sexual reproduction produces offspring with genetic variation.**
- **Adaptive evolution is enhanced**

Asexual species - advantageous mutations must occur in the same lineage.

Sexual populations - advantageous mutations can be combined across lineages (through meiosis and syngamy).

Consequence of Sex:

Genetic Recombination: Mixes up combinations of alleles across loci (reduces Linkage Disequilibrium)

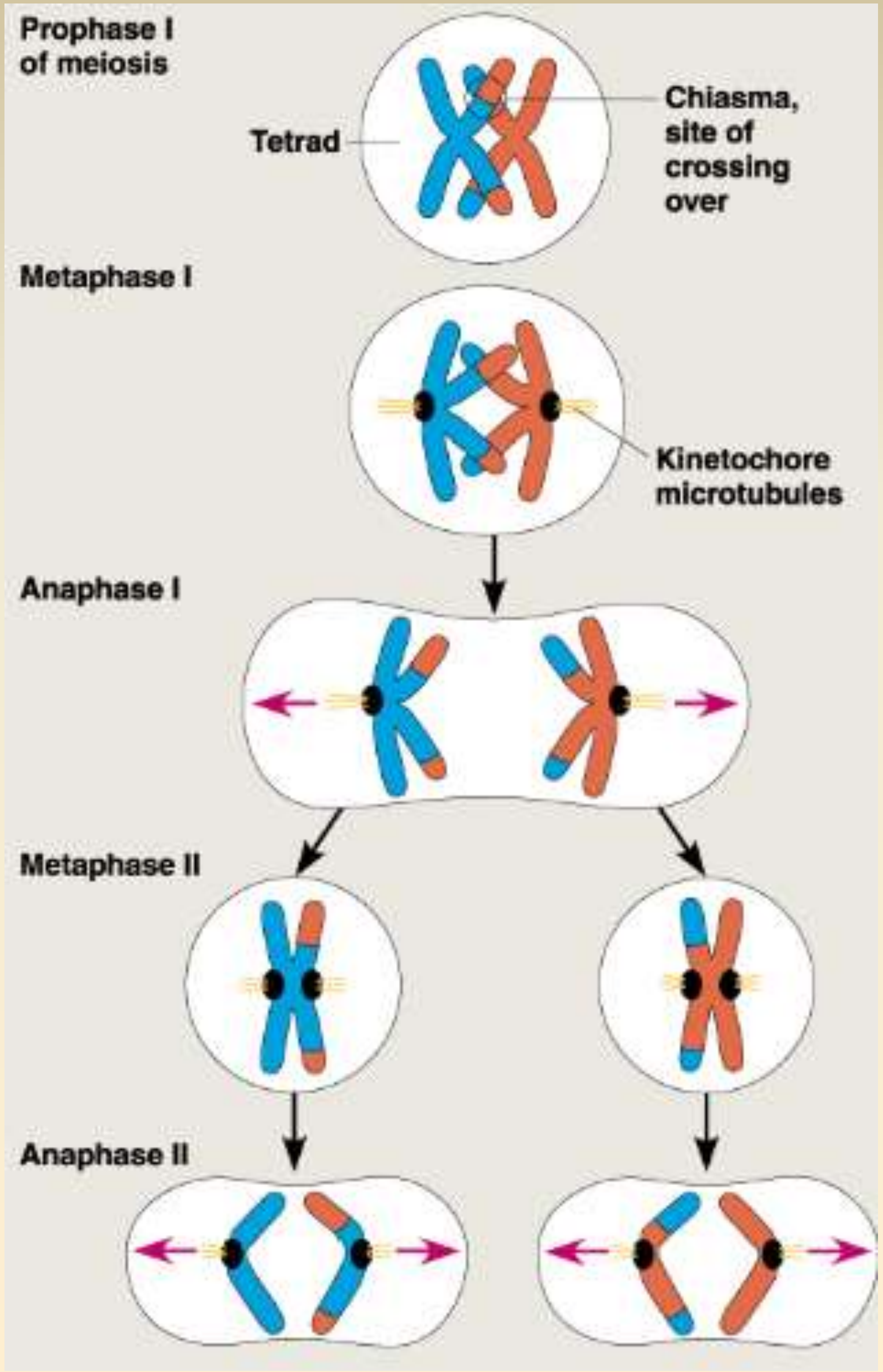
and,

Random Mating: Mixes up combination of alleles at a given locus (increases genotypic variation)

Sex Generates variation!

If there is no genetic variation, neither genetic drift nor natural selection would be able to change allele frequencies, because there would be nothing to change.

Natural Selection requires genetic variation upon which it can act



Why is genetic variation advantageous?

- **Muller's Ratchet**
  - Sex reduces genetic load
- **Red Queen Hypothesis**
  - Genetic diversity provides an advantage in escaping biological enemies
- **Tangled Bank Hypothesis**
  - Genetic variation reduces competition for resources
- **Lottery Hypothesis**
  - Sex can produce offspring with higher fitness in a temporally changing environment

Sex and drift

Sex gets rid of bad mutations

Asexual females always pass on new bad mutations

Muller's ratchet - mutations accumulate

In small pops, drift can knock out the individuals with the fewest mutations (selection may knock out individuals with most mutations)

Muller's ratchet

As highest fitness groups lost by drift, average fitness declines.

Loss of highest fitness group by drift exceeds recreation by back-mutation.

Burden called **genetic load.**

Genetic load causes asexuals to go extinct

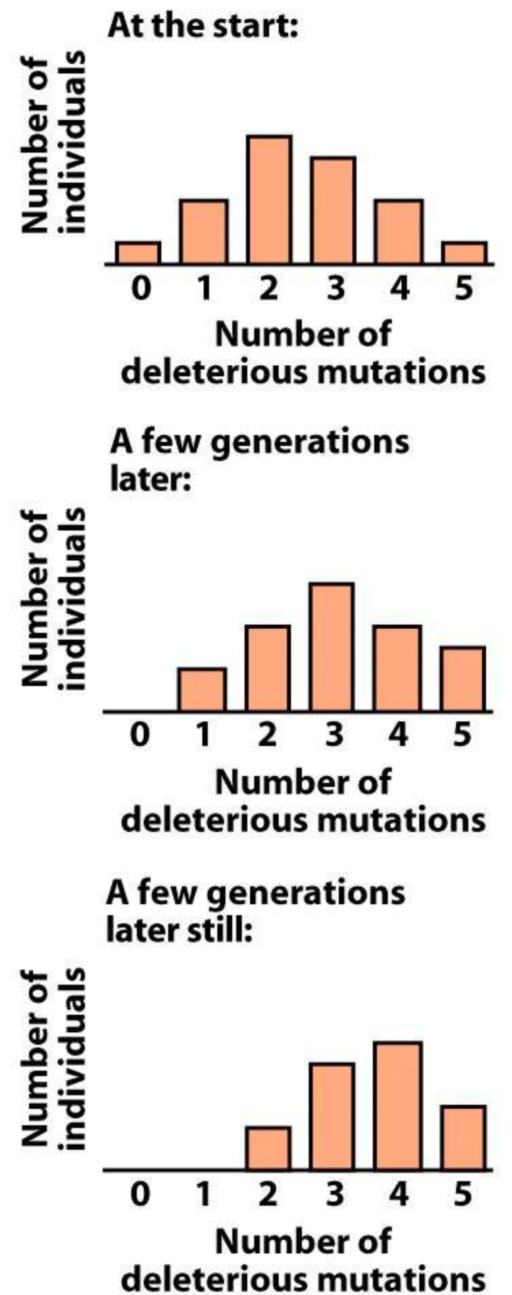


Figure 8-20 Evolutionary Analysis, 4/e

Muller’s ratchet

Asexual populations can only evolve towards ever greater loads of deleterious mutations over long term.

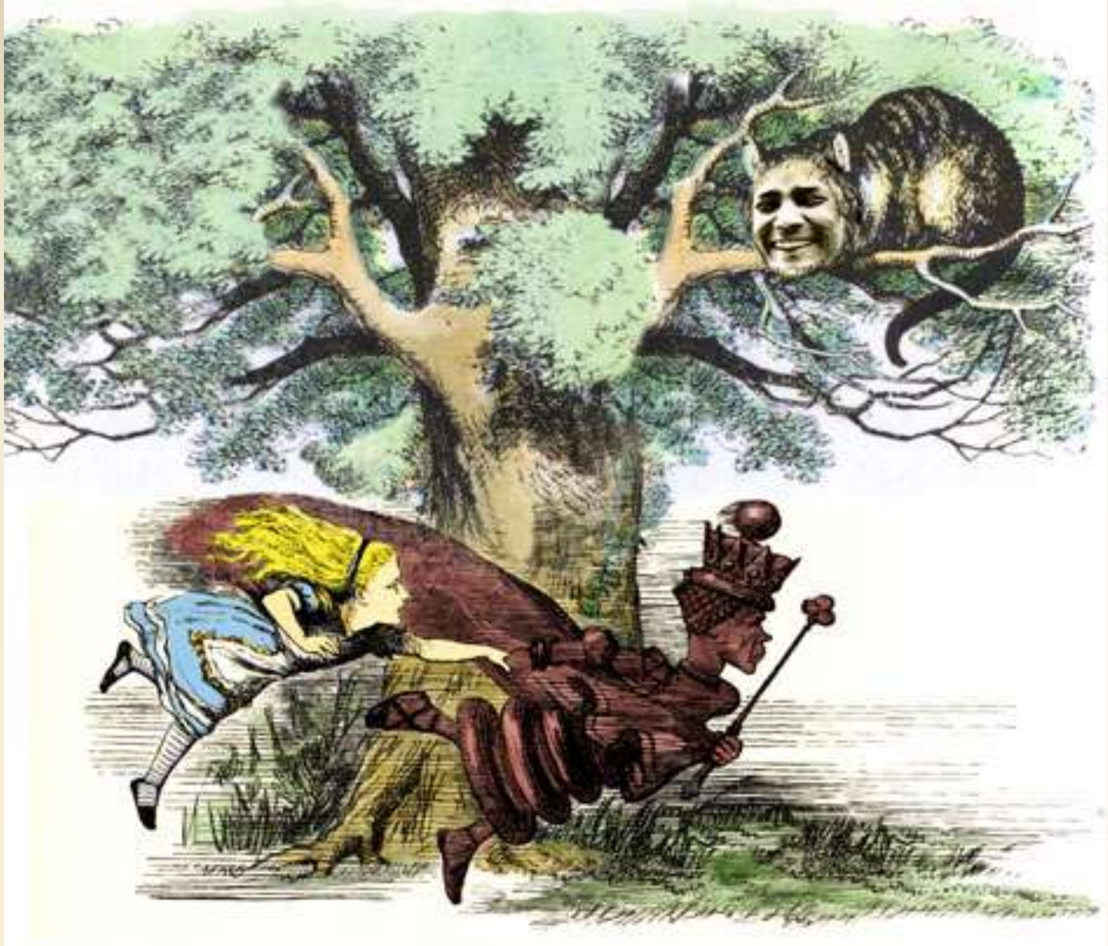
In short term asexual reproduction strongly favored

Does Muller’s ratchet occur in sexual populations?

No. Sex breaks the ratchet.

How? Sex allows recreation of zero deleterious mutation subpopulation each generation by recombination.

Through the Looking Glass – Lewis Carroll
Red Queen Hypothesis



Now, *here*, you see, it takes all the running you can do,
to keep in the same place

The Red Queen Hypothesis

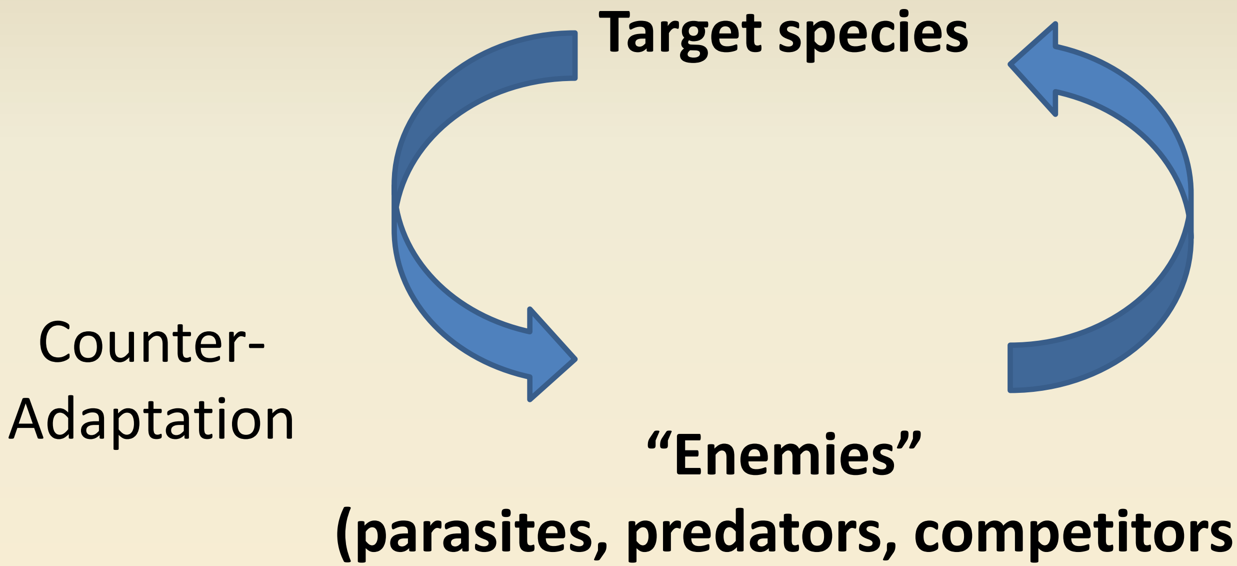
In the arms race between hosts and parasites, there is constant, strong selection for new gene combinations.

In the host-parasite arms race, parasites and pathogens are evolving fast, and hosts infected by them must also evolve fast in order to survive.

If species fail to adapt, they may go extinct

Sexual reproduction facilitates this process.

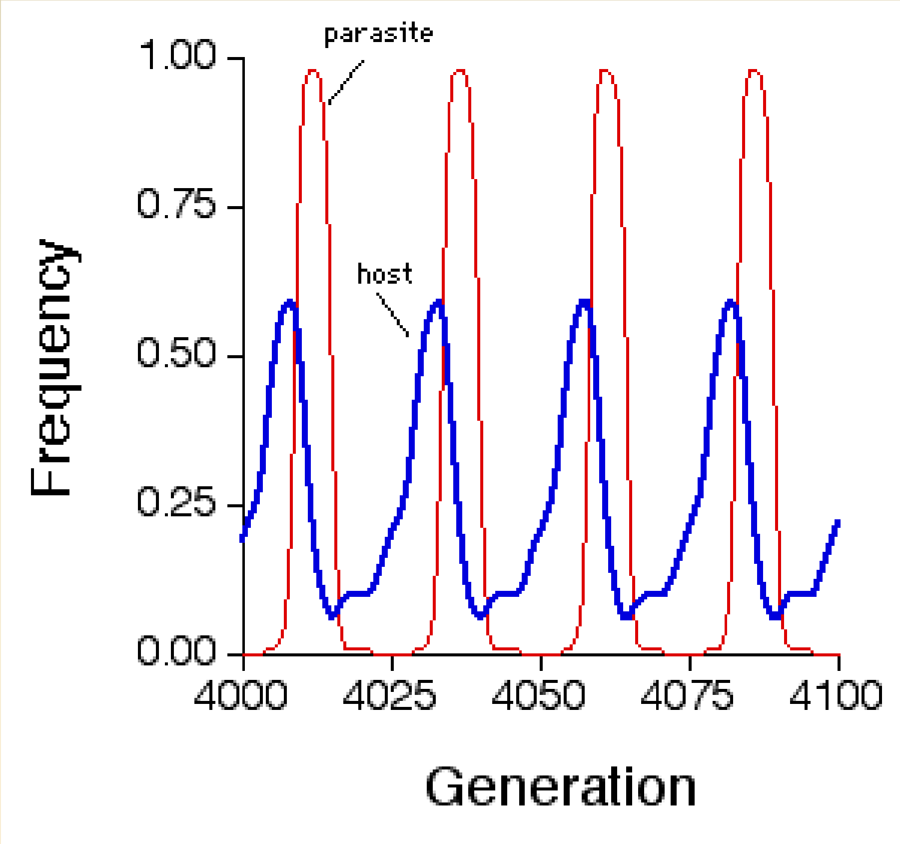
The Red Queen hypothesis is an evolutionary arms race



Sexual reproduction confers species variability and a faster generational response to selection by making offspring genetically unique.

Sexual species are able to improve their genotype in changing conditions.

Red Queen dynamics:



Results from a computer simulation for host-parasite coevolution. Note that both genotypes oscillate over time, as if they were "running" in circles.

Tangled Bank Hypothesis

In a spatially variable environment, parents that produce offspring that can use a variety of resources will be favored those that produce genetically identical offspring

A diverse set of siblings may be able to extract more food from its environment than a clone, because each sibling uses a slightly different niche

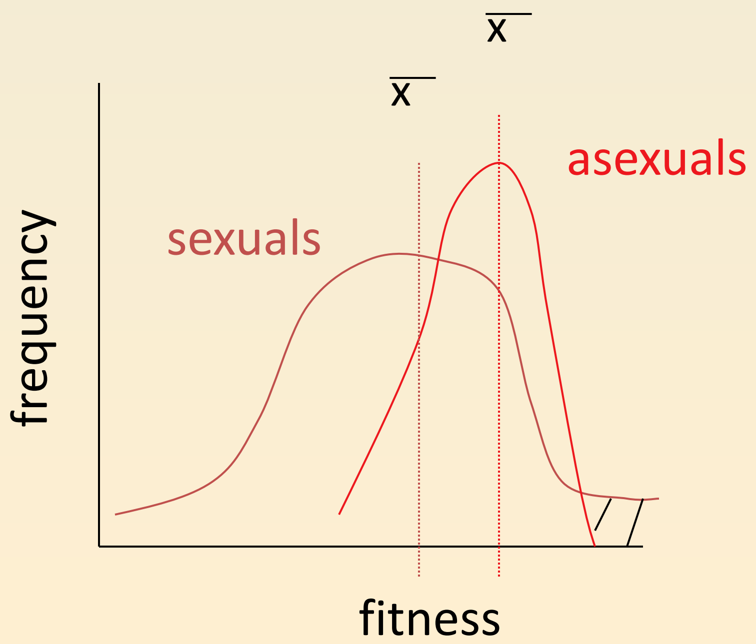
Lottery Model

Sexuals are favored when the environment changes over time

Asexuals: buy 100 lottery tickets all with the same number

Sexuals: buy 100 tickets, each with a different number

Sexual reproduction should predominate in unpredictable environments, while asexual reproduction should be found more frequently in stable environments



Within Eukaryotes

Sexual species tend to last longer

Asexual species are often good early colonizers of novel habitats because of rapid growth rate (many invasive plants are asexual)

In Eukaryotes, less than 1% are asexual

Cost of Individuality

Many clonal organisms grow and divide and are in a sense "immortal"

We are unique individuals and produce novel genetic architectures before dying (Sex = Death)

Sex: Benefits and Costs

Benefits:

- Breakdown Linkage Disequilibrium
- Increase in Genotypic Variation
- Purge deleterious mutations more easily
- Bring together favorable mutations
- Evolution of "individuality"

Costs:

- Lower Reproduction Rate (1/2)
- Have to find mates (not all individuals reproduce)
- Pass on only ½ of your genome
- Death of unique individuals in the parental generation

End