

Outline

- Selection on:
 - Overdominant traits
 - Underdominant traits
 - Sex-linked traits

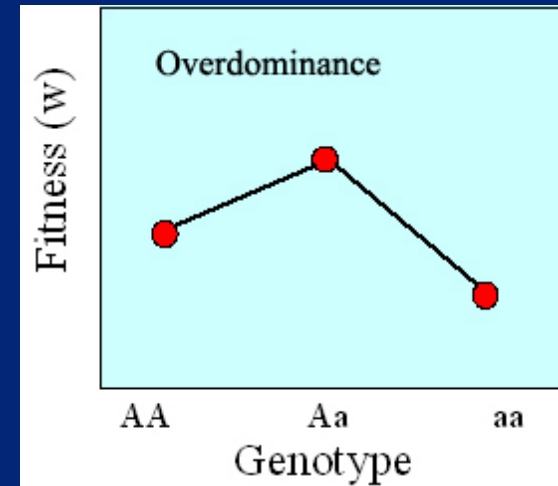
How much selection is enough?

- In the idealized situations we are examining:
 - ANY selection will cause an increase of the favored allele
 - Speed of response will depend on strength of selection and dominance structure
- In real situations:
 - Effective selection must be strong enough to overcome drift (random effects)
 - Effective selection must be strong enough to have an impact in reasonable time scale
- Selection will dominate evolution if it's stronger than drift
- This depends critically on population size

Overdominance (heterozygote advantage)

Overdominance = heterozygote most fit

- Sickle-cell trait (in presence of malaria)
- Large size of many cultivated crop plants



Overdominance

Surprising things happen when the heterozygote is most fit.

This example uses $p_A = p_a = 0.5$.

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Fitness	0.8	1.0	0.8
Before selection	0.25	0.5	0.25
Death due to selection	0.05	0.0	0.05
After selection	0.2/0.9	0.5/0.9	0.2/0.9
After selection	0.22	0.56	0.22

New allele frequencies:

$$p_A = 0.5$$

$$p_a = 0.5$$

Overdominance

- Strong selection is acting, but the allele frequencies did not change. The population is at an equilibrium state.
- If the initial frequencies were not 50/50, the population would move towards 50/50 and then stick there.
- The ratio 50/50 is because the homozygotes are equally bad. If they were unequally bad, a different ratio would be obtained.

Overdominance Practice Problem

The classic sickle cell case may have selection approximately like this (in the presence of malaria):

Genotype	AA	AS	SS
Fitness	0.8	1.0	0.0

If we start with $p_A=0.6$, what are the genotype frequencies in adults (after selection) next generation? What are the new allele frequencies?

Overdominance

The classic sickle cell case may have selection approximately like this (in the presence of malaria). Starting with $p_A=0.6$:

Genotype	AA	AS	SS
Fitness	0.8	1.0	0.0
Before selection	0.36	0.48	0.16
Death due to selection	0.07	0.0	0.16
After selection	0.29/0.77	0.48/0.77	0.0/0.77
After selection	0.38	0.62	0.00

$p_A=0.69$, so it's increasing.

How can we predict the stable equilibrium?

Overdominance

If we write the fitnesses like this:

Genotype	AA	AS	SS
Fitness	1-s	1.0	1-t

then the equilibrium frequency of A is this:

$$t/(s+t)$$

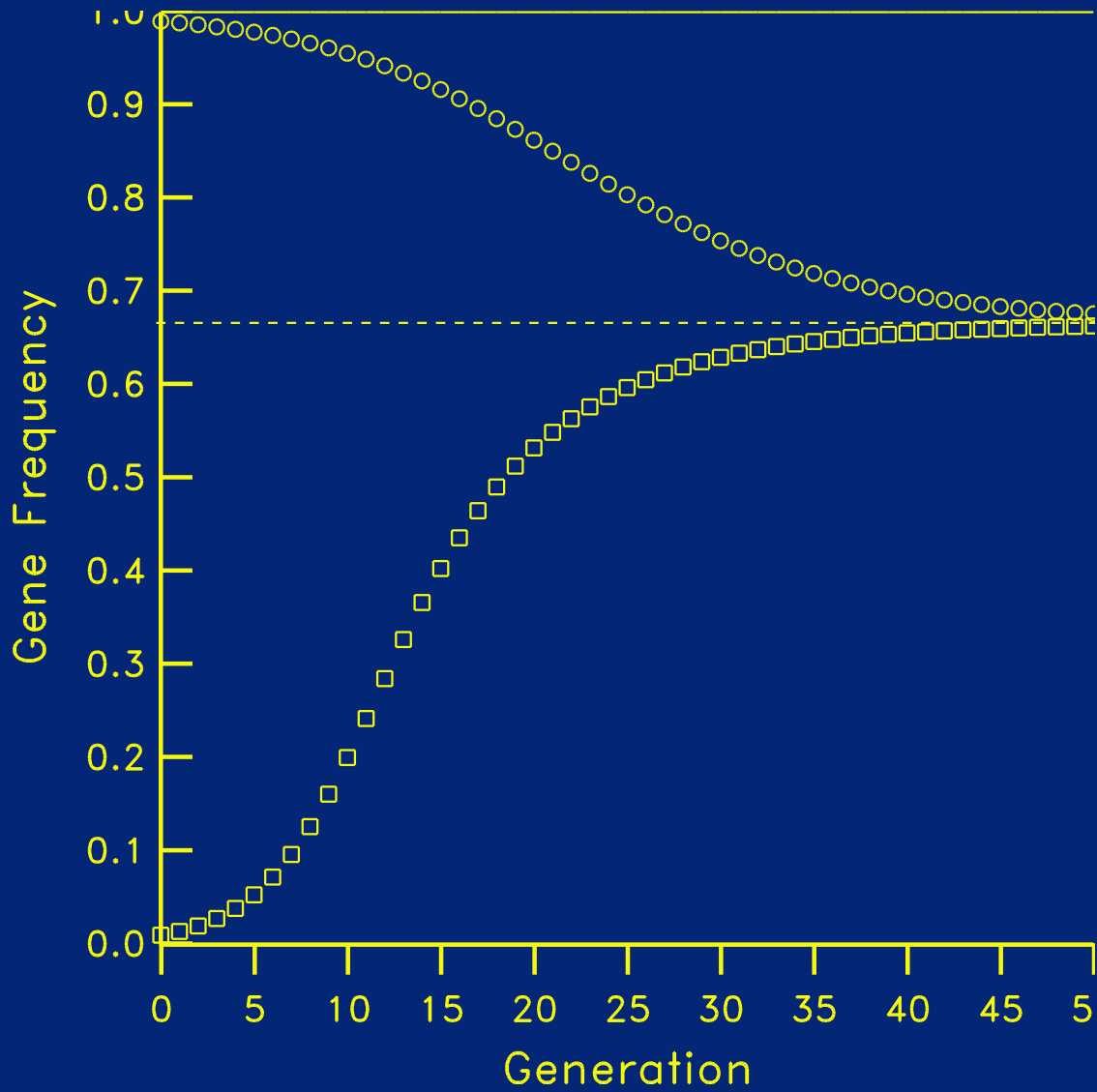
So in our example where $s=0.2$ and $t=1.0$, p_A at equilibrium is:

$$1.0 / (0.2 + 1.0) = 0.8333$$

Overdominance

- Overdominant systems have a stable equilibrium:
 - If undisturbed, they will stay there
 - If moved away, they will return
- Population maximizes its overall fitness **given the laws of Mendelian segregation.**
- An all-heterozygote population would be more fit, but is prevented by random mating and segregation
- A population with HbA and HbS pays two costs:
 - A/A people die of malaria
 - S/S people die of sickle cell anemia

Overdominance



Hard versus soft selection

- Soft selection:
 - Overall population size does not change
 - Requires excess reproductive capacity
- Hard selection:
 - Population size decreases until bad genotypes are gone
 - Selection is strong enough to overcome excess reproduction
- (Our calculations so far assume soft selection)

Genetic load

- Every overdominant locus has a cost (bad homozygotes)
- How many can a species stand?
- Depends on:
 - How bad the homozygotes are
 - How much excess reproductive capacity the species has
- Relatively few overdominant loci have been detected in wild populations

Overdominance versus drift effects—discussion question

- We cross purebred domestic plants or animals
- The crosses are larger, healthier, or more productive than their parents
- Two hypotheses:
 - Overdominance
 - Each purebred has bad recessives which are masked in the hybrid
- How could we decide between these hypotheses?

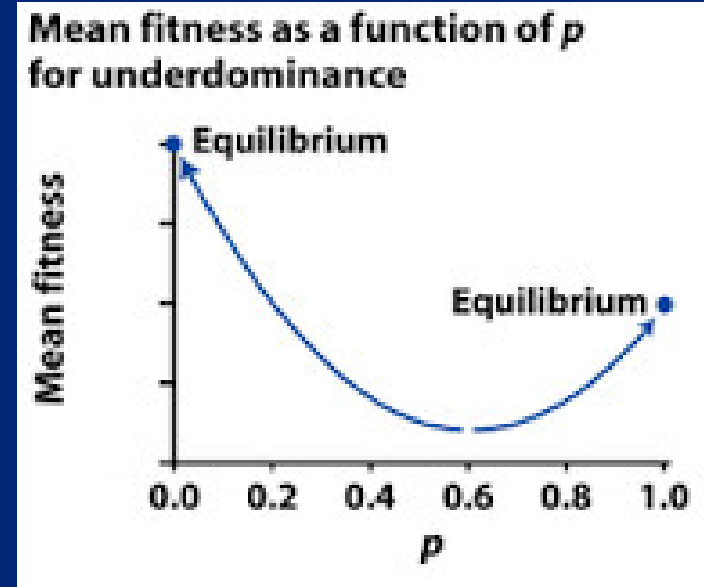
Overdominance versus drift effects

- Repeatedly backcross to one of the parent strains, selecting for the best offspring
- If the hybrid vigor is due to overdominance it will never “breed true”
- If the hybrid vigor is due to good dominants covering up bad recessives, we can improve our parent strain by crossing them in
- Eventually we will get a purebred strain that is better than before

Underdominance (heterozygote disadvantage)

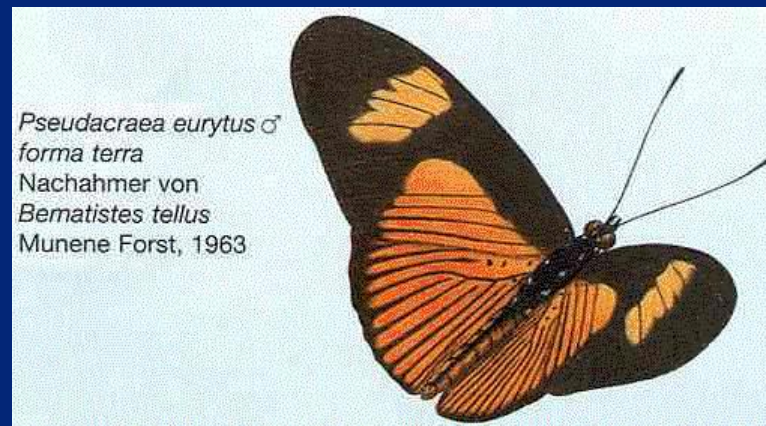
Underdominance = heterozygote least fit

- Diabetes risk is worst in HLA-DR 3/4 heterozygote
- Mimic butterflies (see next slide)



Underdominance

In the African butterfly *Pseudacraea eurytus* the orange and blue homozygotes each resemble a local toxic species, but the heterozygote resembles nothing in particular and is attractive to predators.



Underdominance

What happens to an underdominant locus, like the mimic butterflies?

$$p_A = p_a = 0.5$$

Genotype	orange/orange (AA)	orange/blue (Aa)	blue/blue (aa)
Fitness	1.0	0.8	1.0
Before selection	0.25	0.5	0.25
Selection deaths	0	0.1	0
After selection	0.25/0.9	0.4/0.9	0.25/0.9
After selection	0.28	0.44	0.28

New allele frequencies:

$$p_A = 0.5$$

$$p_a = 0.5$$

Underdominance

The heterozygote is bad, but with equal badness and equal frequencies, the population balances at an equilibrium. However, this equilibrium is **unstable**. If the gene frequencies are not at the equilibrium, they will move away until either A or a is fixed.

Underdominance

Again, we can predict the equilibrium by writing the fitnesses as follows:

Genotype	orange/orange (AA)	orange/blue (Aa)	blue/blue (aa)
Fitness	1-s	1	1-t

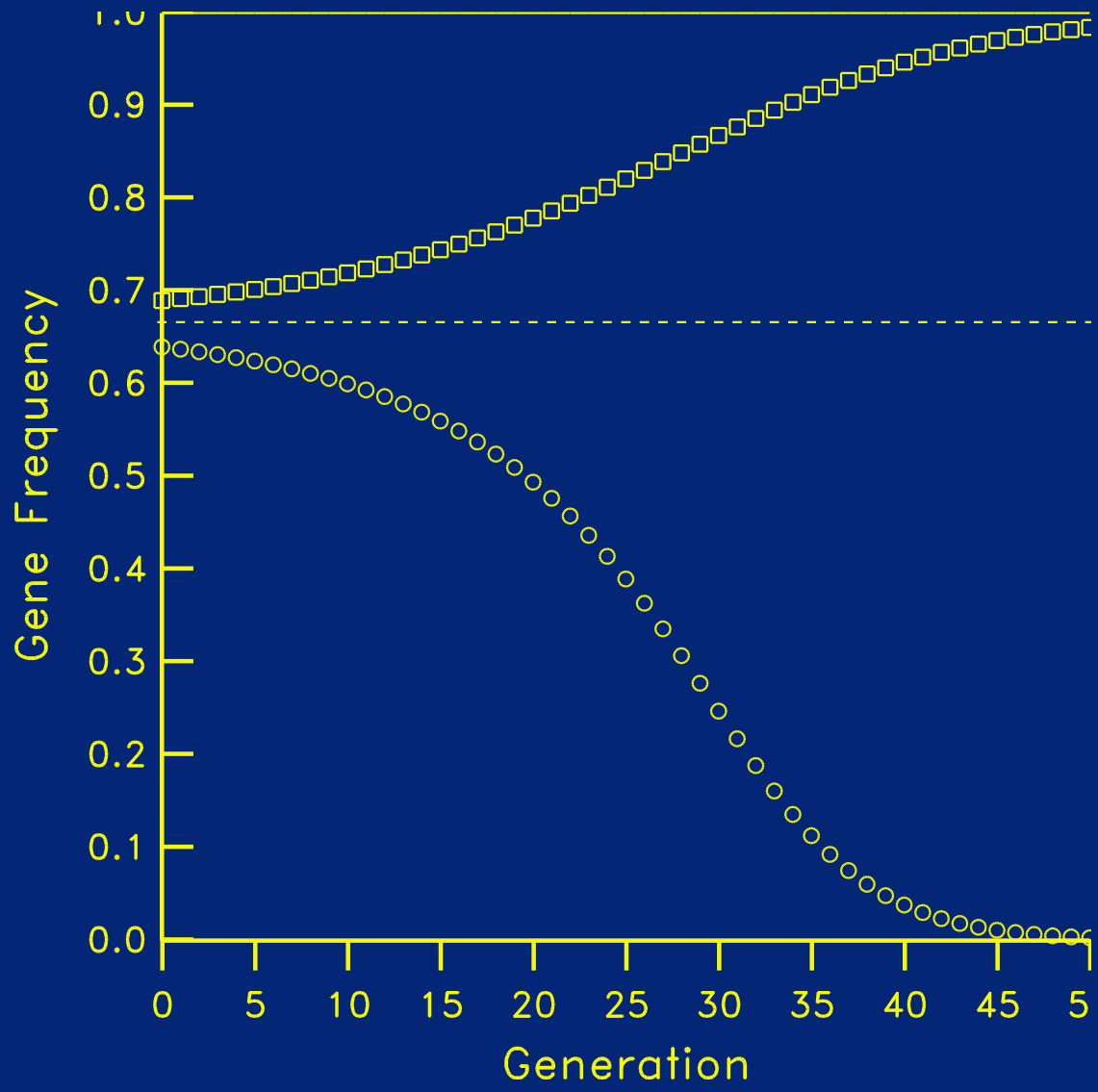
but now both s and t are negative. The unstable equilibrium is

$$p_A = t/(s+t)$$

If p_A is above the equilibrium, A will fix. If p_A is below the equilibrium, a will fix. If it is exactly at the equilibrium, chance will eventually push it one way or the other.

Underdominant loci are usually observed only in crosses between separate varieties or species. Within one population, they are rapidly fixed for one allele or the other.

Underdominance



Underdominance practice problem

What about this situation?

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Fitness	$1-s$	1	$1-t$
Fitness	1.5	1.0	1.2

What is the equilibrium?

If we start at $p_A=0.2$, what will happen?

Underdominance

What about this situation?

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Fitness	$1-s$	1	$1-t$
Fitness	1.5	1.0	1.2

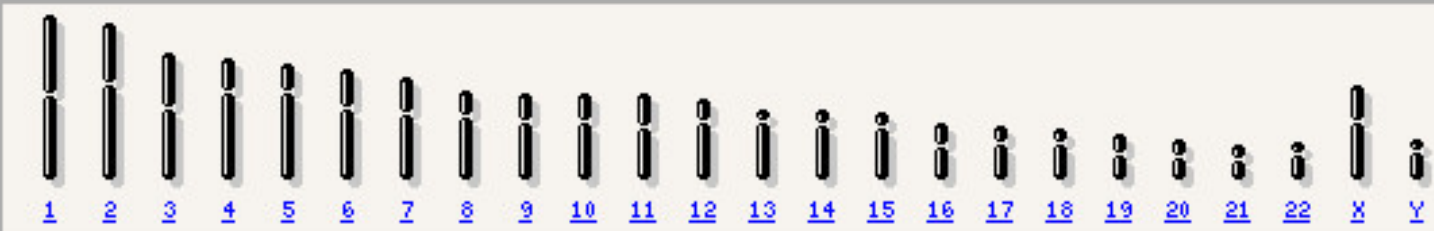
The equilibrium is $p_A=0.28$. So if the starting position is below this, the a allele will win and become fixed **even though this does not maximize population fitness**. The population rolls to a small fitness peak, even though a larger one is possible.

Underdominance

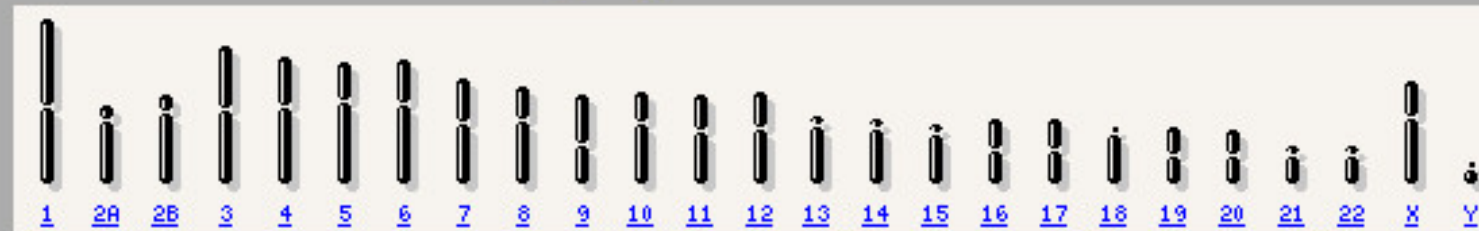
- Population which is fixed for a resists introduction of A
- Innovations which are bad in heterozygotes are hard to establish
- How can they *ever* get established?
 - Genetic drift in a small population
 - Founder effect
 - Bottleneck
 - Inbreeding or self-fertilization (makes homozygotes)

Big changes in genome structure are underdominant

Homo sapiens chromosomes



Pan troglodytes chromosomes



After National Center for
Biotechnology Information
(www.ncbi.nlm.nih.gov)

MetaPrimate.com

An underdominance mystery

- Insulin-dependent (juvenile) diabetes is a life-threatening disease
- Prior to insulin treatment most affected individuals died before they could reproduce
- High-risk HLA genotype is DR3/DR4 heterozygote
- In Europeans, $p(\text{DR3})$ around 0.12 and $p(\text{DR4})$ around 0.15
- In a system with only DR3 and DR4, what would you expect in the long term?

An underdominance mystery

- DR3 and DR4 are both old alleles
- The problems in the heterozygote could drive one of them extinct
- (We don't know which one without knowing fitness of homozygotes)
- This hasn't happened: why?

An underdominance mystery

Some possibilities:

- DR3/DR4 could be a generally good genotype despite diabetes risk
- Diabetes risk could reflect a linked gene that hasn't been there long
- Presence of many other alleles may interfere with selection on 3 and 4
- Modern environment may be different from the past
- Genetic drift

Human fitnesses are hard to measure, so this question is still unsolved

Sex linked traits

- Traits on the Y are easy to analyze
- They are haploid, so dominance and recessiveness don't matter
- Traits on the X behave more strangely

Sex linked traits

Suppose that among X chromosomes, $p(X^H) = 0.8$ and $p(X^h) = 0.2$ in both sexes.

Genotype	$X^H X^H$	$X^H X^h$	$X^h X^h$	$X^H Y$	$X^h Y$
Fitness	1.0	1.0	0.1	1.0	0.1
Pre-Selection Frequencies	0.32	0.16	0.02	0.40	0.10

We can see immediately that a rare recessive sex-linked disease shows up mostly in males.

Sex linked traits

Genotype	$X^H X^H$	$X^H X^h$	$X^h X^h$	$X^H Y$	$X^h Y$
Fitness	1.0	1.0	0.0	1.0	0.0
Pre-Selection Frequencies	0.32	0.16	0.02	0.40	0.10
Post-Selection Frequencies	0.36	0.19	0.0	0.45	0.0

The new allele frequencies are:

Females: $p(X^H) = 0.91$, $p(X^h) = 0.09$

Males: $p(X^H) = 1.0$, $p(X^h) = 0.0$

This is an example of a situation where Hardy-Weinberg will not hold next generation, because you don't have random mating. Males must mate with females, and their allele frequencies differ.

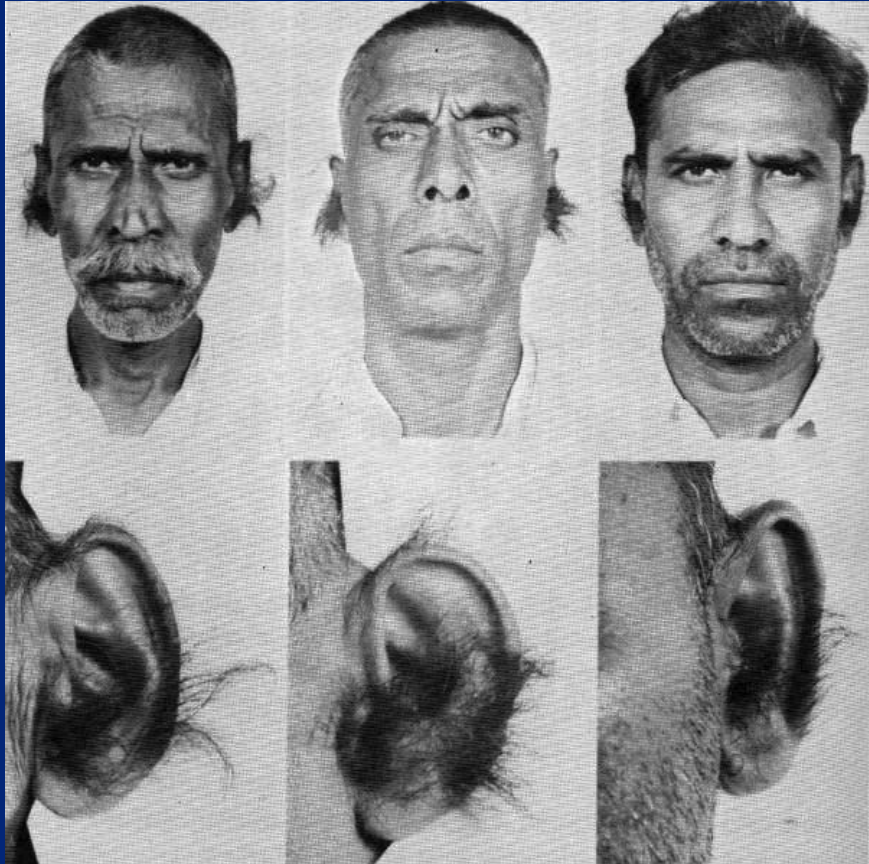
Sex linked traits

- This trait will decrease faster than an autosomal recessive because it is exposed to selection when in males
- Sex-linked traits don't go to Hardy-Weinberg in one generation like autosomal traits do, even if there is no selection.
- Without selection, they go to Hardy-Weinberg slowly over many generations
- With selection, they may never get there

Sex linked traits

- A point to bear in mind:
 - Most sex-specific traits are not sex-linked
 - They are sex-modified or sex-limited (their phenotype is controlled by sex) but the genes are actually on the autosomes
 - Most sex-linked traits (on the sex chromosomes) are unrelated to sex
 - Examples: hemophilia, color vision
 - The Y chromosome contains a few “switch” genes which control sex in humans
 - Almost all of the genes controlled by these switches are autosomal
- Why?

The only Y-linked non-sex gene I know of



Sex linked traits

- Why aren't sex-related traits sex-linked?
- Putting female traits on the X would run into the problem that males have an X too
- Why aren't male traits on the Y?
 - If sex-related traits evolved from other traits, they would tend to start off on the autosomes
 - The Y is haploid and mostly non-recombining, which can cause its genes to deteriorate
 - Having one master switch rather than many independent sex-related trait genes may be less fragile

One-minute responses

- Tear off a half-sheet of paper
- Write one line about the lecture:
 - Was anything unclear?
 - Did anything work particularly well?
 - What could be better?
- Leave at the back on your way out