Outline

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

One minute responses

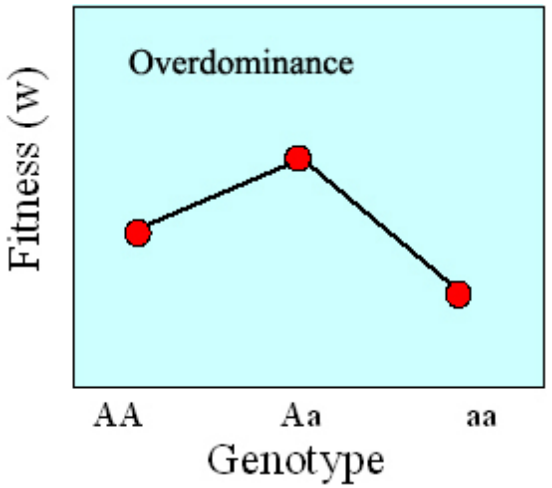
- Don't let the one-minute option stop you from asking questions during lecture!

- Q: If $h = 0.5$ is that incomplete dominance or co-dominance?
  - Yes, must be one or the other
  - Any h between 0 and 1 is incomplete dominance or co-dominance, not just 0.5
  - h has to be measured; it's hard to predict

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 pA = pa = 0.5.

Genotype	AA	Aa	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:

pA = 0.5
pa = 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 pA=0.6, what are the genotype frequencies in adults (after selection) next generation? What are the new allele frequencies?

Overdominance

The classic Starting with pA=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

pA=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)

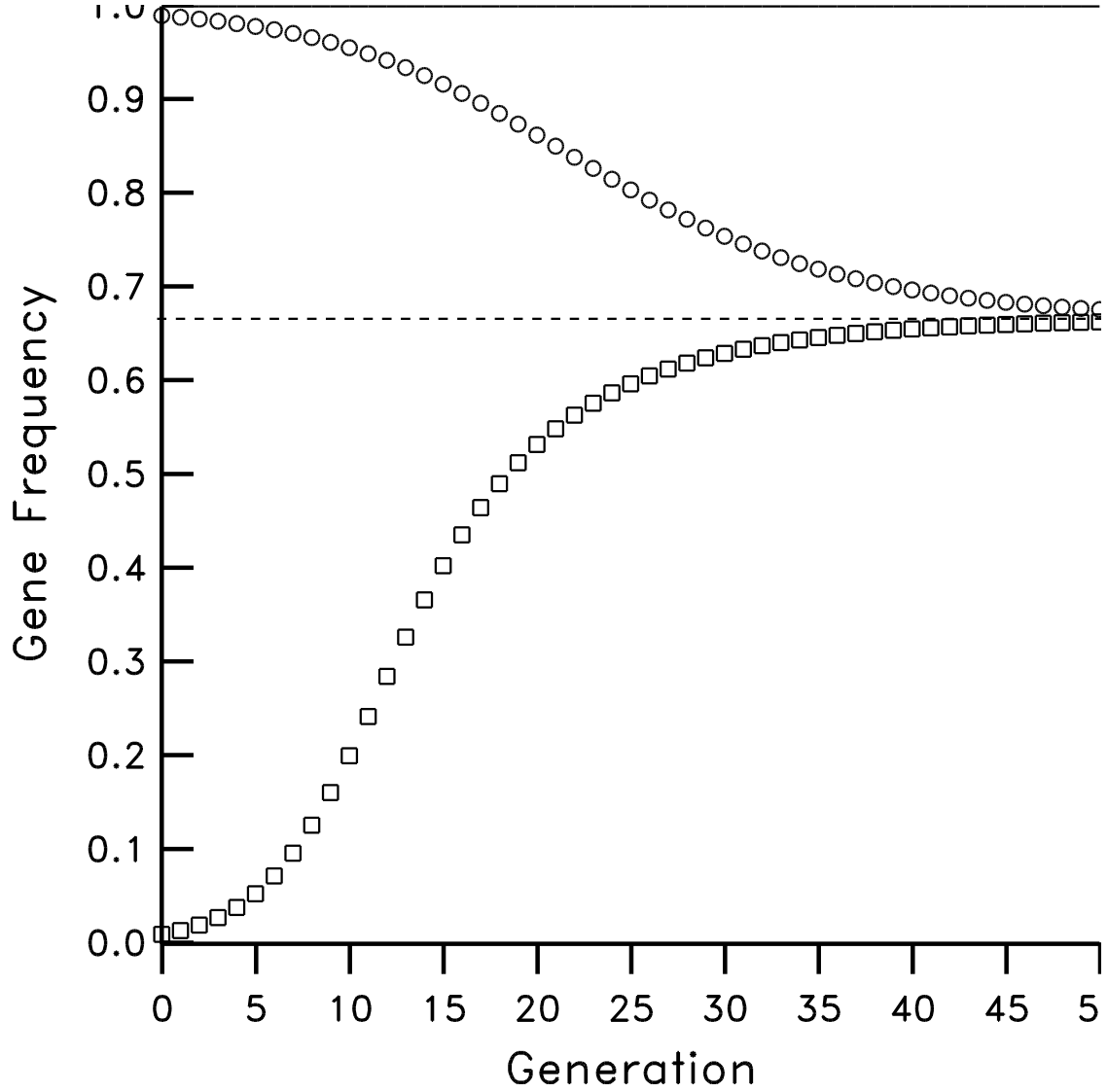
So in our example where s=0.2 and t=1.0, pA at equilibrium is:

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

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



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

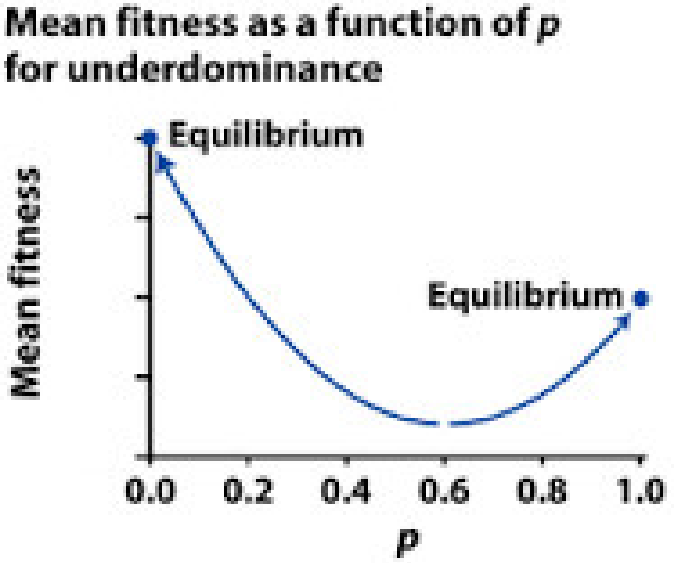
- Repeatedly backcross to one of the parent strains, selecting for the best offspring
- Overdominance
  - Good phenotype never "breeds true" (it's a heterozygote)
- Bad recessives
  - With enough patience, good phenotype will breed true

Underdominance (heterozygote disadvantage)

Underdominance = heterozygote least fit

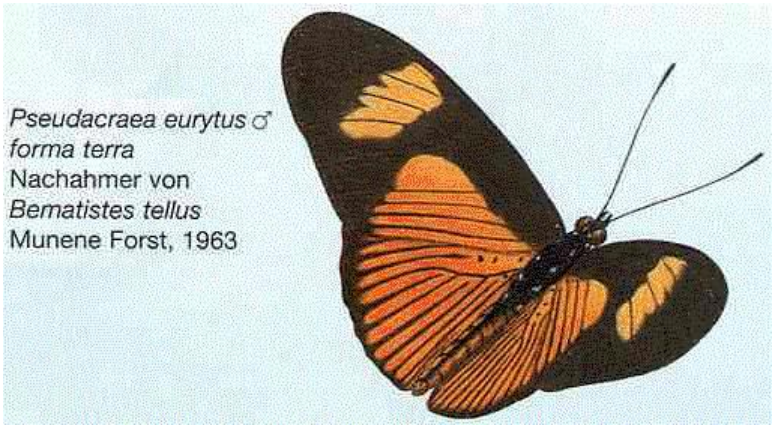
- Diabetes risk is worst in HLA-DR 3/4 heterozygote

- 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

pA = pa = 0.5

Genotype	AA	Aa	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:

pA = 0.5
pa = 0.5

Underdominance

- An equilibrium exists where there is no pressure to go up or down
- 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:

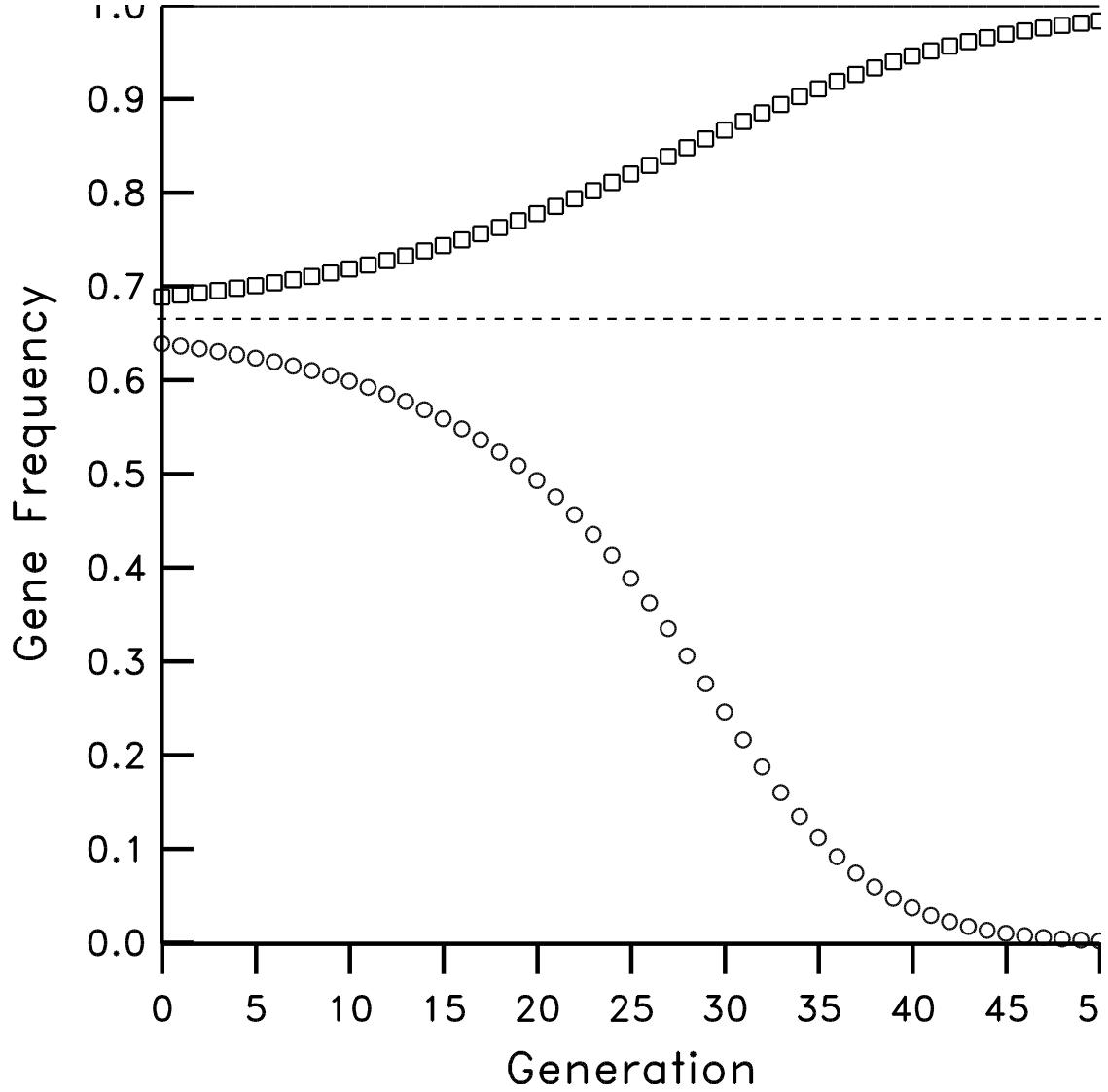
Genotype	AA	Aa	aa
Fitness	1-s	1	1-t

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

pA = t/(s+t)

- pA above the equilibrium – A will fix
- pA below the equilbrium – a will fix
- What happens if we're right at the equilibrium?

Underdominance



Underdominance practice problem

What about this situation?

Genotype	AA	Aa	aa
Fitness	1-s	1	1-t
Fitness	1.5	1.0	1.2

What is the equilibrium?

If we start at pA=0.2, what will happen?

Underdominance

What about this situation?

Genotype	AA	Aa	aa
Fitness	1-s	1	1-t
Fitness	1.5	1.0	1.2

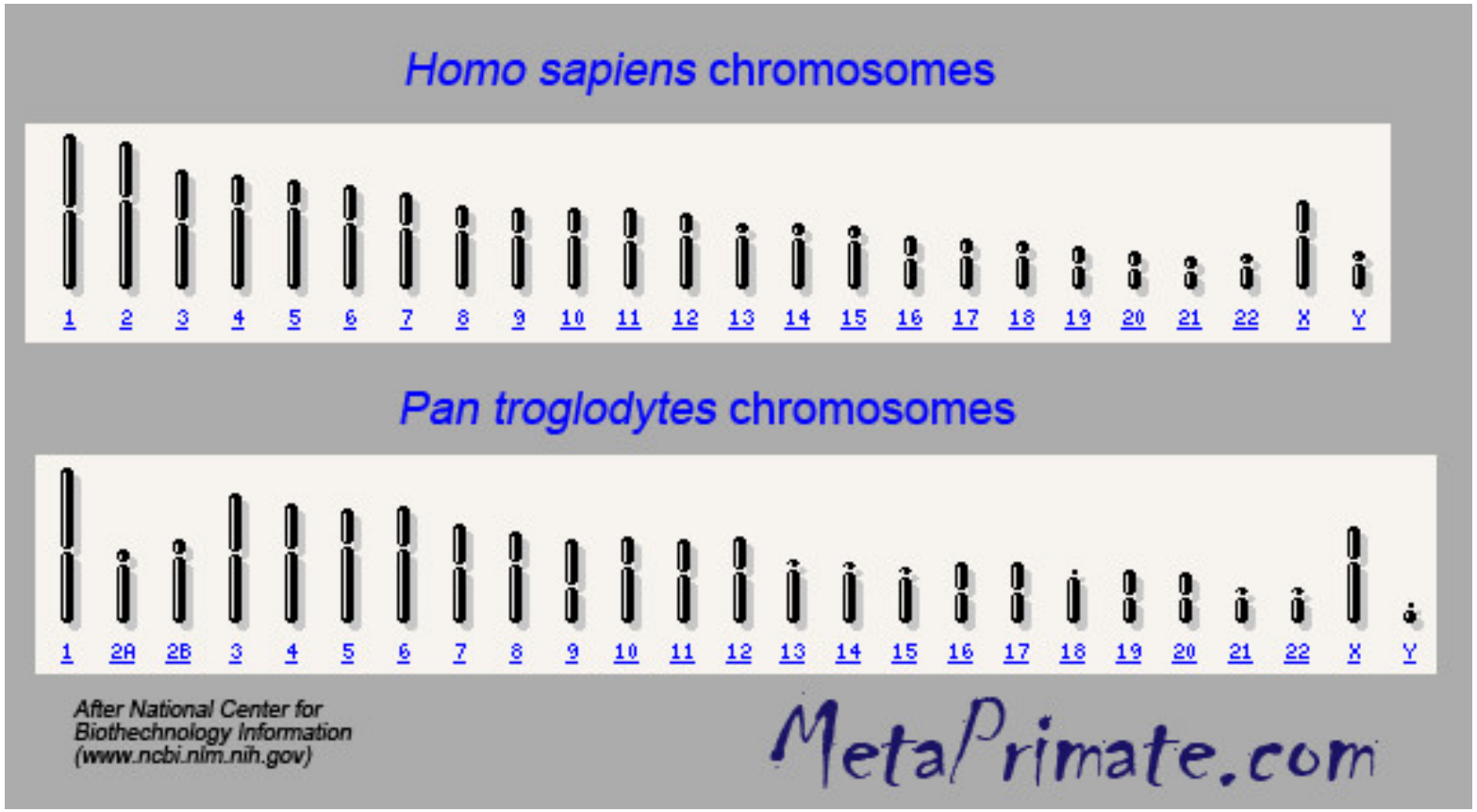
Start at pA=0.2

- Equilibrium $pA = 0.28$
- If we start below that, a will fix **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



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(DR3) around 0.12 and p(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^HX^H	X^HX^h	X^hX^h	X^HY	X^hY
Fitness	1.0	1.0	0.1	1.0	0.1
HW	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
HW	0.32	0.16	0.02	0.40	0.10
Post-Selection	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: $p(X^H) = 1.0$, $p(X^h) = 0.0$

Sex linked traits are weird

- Even if selection stops, system won't go straight to HW:
  - Mating is non-random with respect to sex
  - Males and females have different allele frequencies

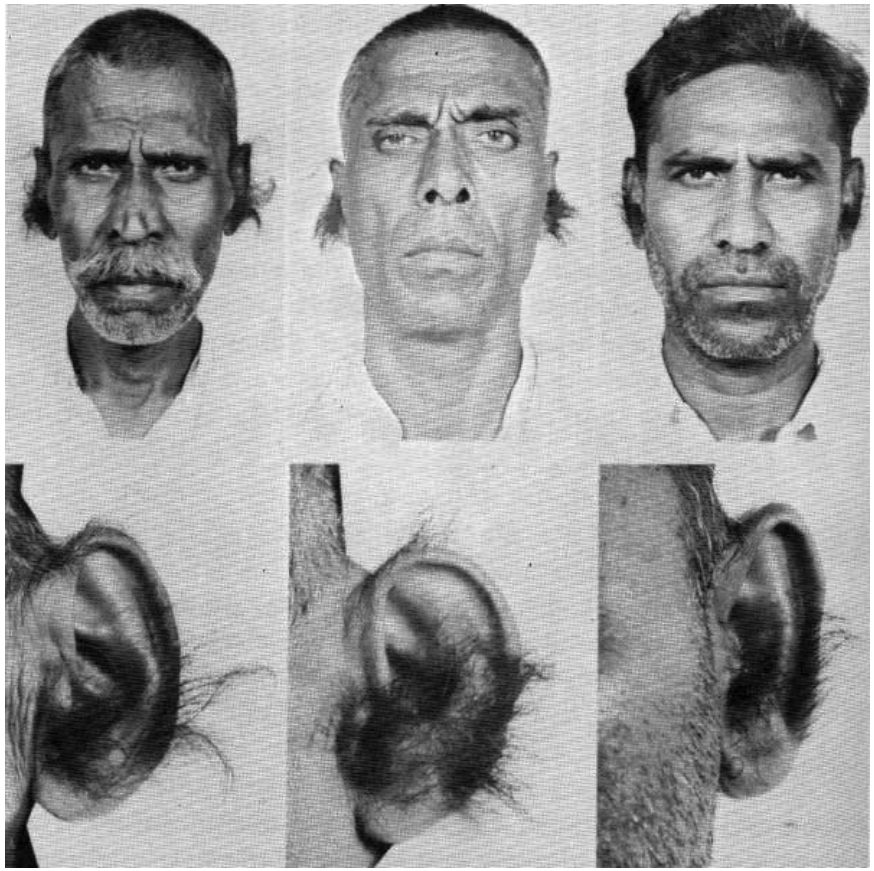
Sex linked traits

- X-linked recessive decreases faster than an autosomal recessive
- Exposed to selection when in males
- Sex-linked traits don't go to Hardy-Weinberg in one generation 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 (on X or Y)
  - Most sex-linked traits (on X) 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?
- Both males and females have X
- Why aren't male traits on the Y?
  - If sex-related traits evolved from other traits, they would 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