

# Roadmap

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- Natural selection:
  - Harmful recessives
  - Harmful dominants
  - Mutation/selection equilibrium
  - Relative fitness, population mean fitness
- Next time: Overdominance and underdominance in detail

## Natural selection

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- Different success of different genotypes:
  - Different survival
  - Different fecundity (number of offspring)
- A fitness advantage, on average, means more copies of your genes in the next generation
- We'll see later that survival of relatives can also influence gene propagation and therefore fitness

# Assumptions

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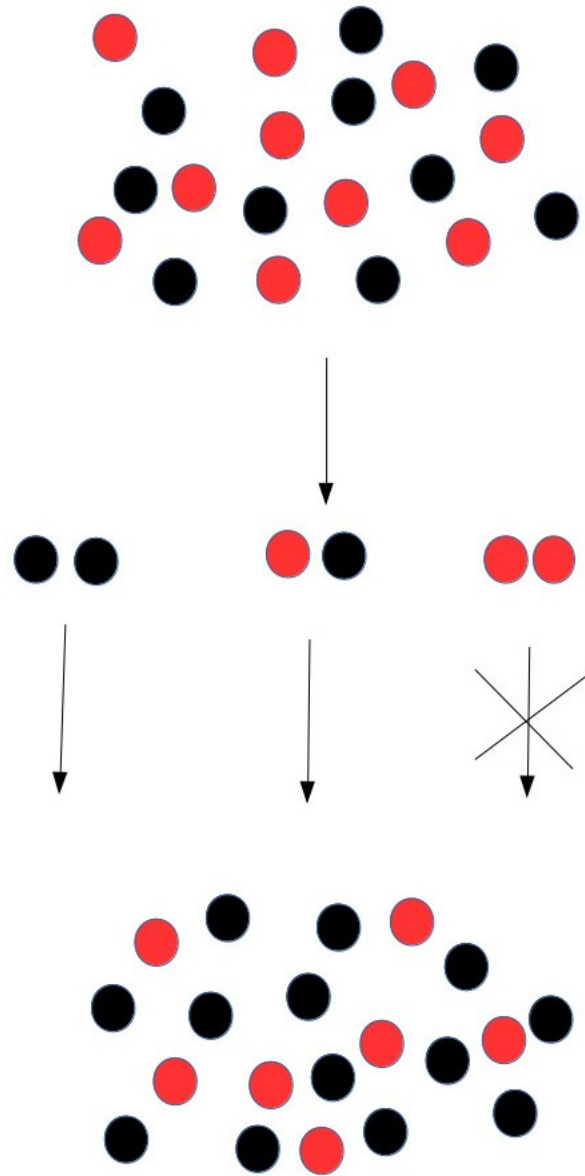
For this section, we will assume:

- A large population, so that chance fluctuations are not important
- Random mating
- No new mutations
- Constant environment

## Selection against a recessive

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- Assume red is a lethal recessive
- When a red/red individual occurs, it dies
- What is change in allele frequency in 1 generation?



## One generation of selection

We could write this as follows (black is A, red is a):

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Fitness	1.0	1.0	0.0

Starting frequencies:

$$p_A = 0.5$$

$$p_a = 0.5$$

What will happen?

## One generation of selection

First, use H-W to predict the frequency of each genotype in the newborns:

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Frequency	0.25	0.5	0.25

## One generation of selection

First, use H-W to predict the frequency of each genotype in the newborns:

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Frequency	0.25	0.5	0.25

Then, apply selection. This will reduce the total number of individuals; we MUST allow for the new total (75%).

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Frequency	0.25/0.75	0.5/0.75	0/0.75
—or—	0.333	0.667	0.0

## One generation of selection

First, use H-W to predict the frequency of each genotype in the newborns:

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Frequency	0.25	0.5	0.25

Then, apply selection. This will reduce the total number of individuals; we MUST allow for the new total (75%).

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Frequency	0.25/0.75	0.5/0.75	0/0.75
—or—	0.333	0.667	0.0

Then the new allele frequencies are straightforward:

$$p_A = 0.333 + 1/2 (0.667) = 0.667 \text{ (previous value 0.5)}$$

$$p_a = 1/2 (0.667) + 0 = 0.333 \text{ (previous value 0.5)}$$



## What will happen in the long run?

We have seen a substantial drop in  $p_a$  in one generation, from 0.5 to 0.333. Will this continue? Let's consider a case where the recessive has become rare:

$$p_A = 0.9$$

$$p_a = 0.1$$

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Frequency	0.81	0.18	0.01

## What will happen in the long run?

We apply selection:

Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Frequency	0.81/0.99	0.18/0.99	0/0.99
—or—	0.818	0.182	0.0

New allele frequencies:

$$p_A = 0.818 + 1/2 (0.182) = 0.909 \text{ (previous value 0.9)}$$

$$p_a = 1/2 (0.182) + 0 = 0.091 \text{ (previous value 0.1)}$$

The change is much less dramatic.

## **Behavior of rare, harmful recessives**

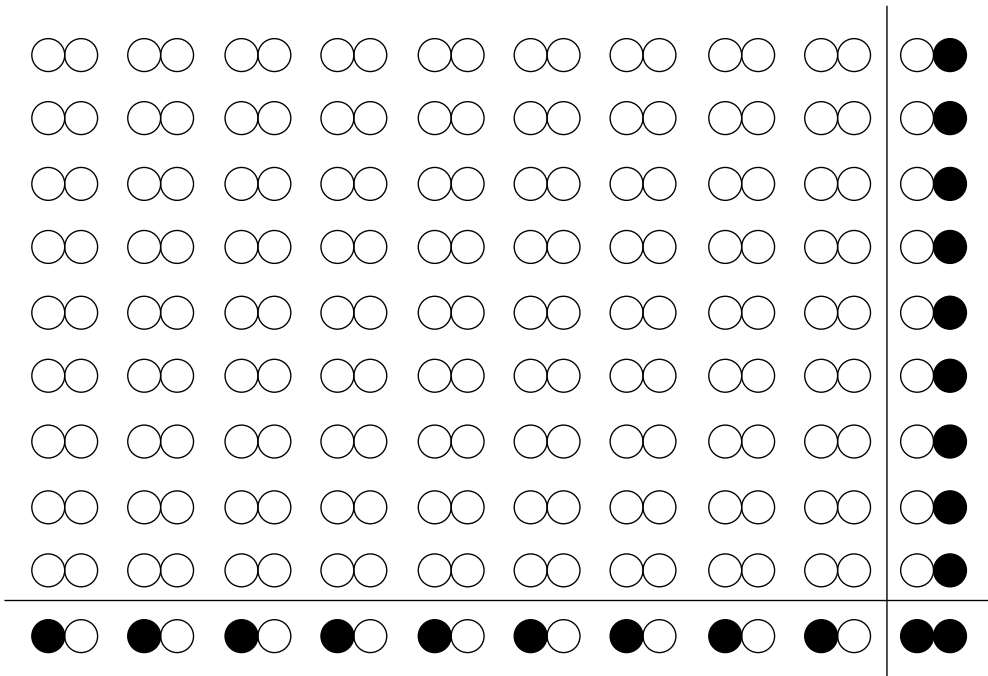
Harmful recessive alleles decrease rapidly when common, but when they are rare they “hide” in heterozygotes and selection cannot eliminate them easily.

Harmful recessives are (as a class) abundant in natural populations. The average human is estimated to have 1-3 of them.

# How rare recessives hide

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## Rare alleles occur mostly in heterozygotes



**This shows a population in Hardy–Weinberg equilibrium  
at gene frequencies of 0.9 A : 0.1 a**

**Genotype frequencies:**

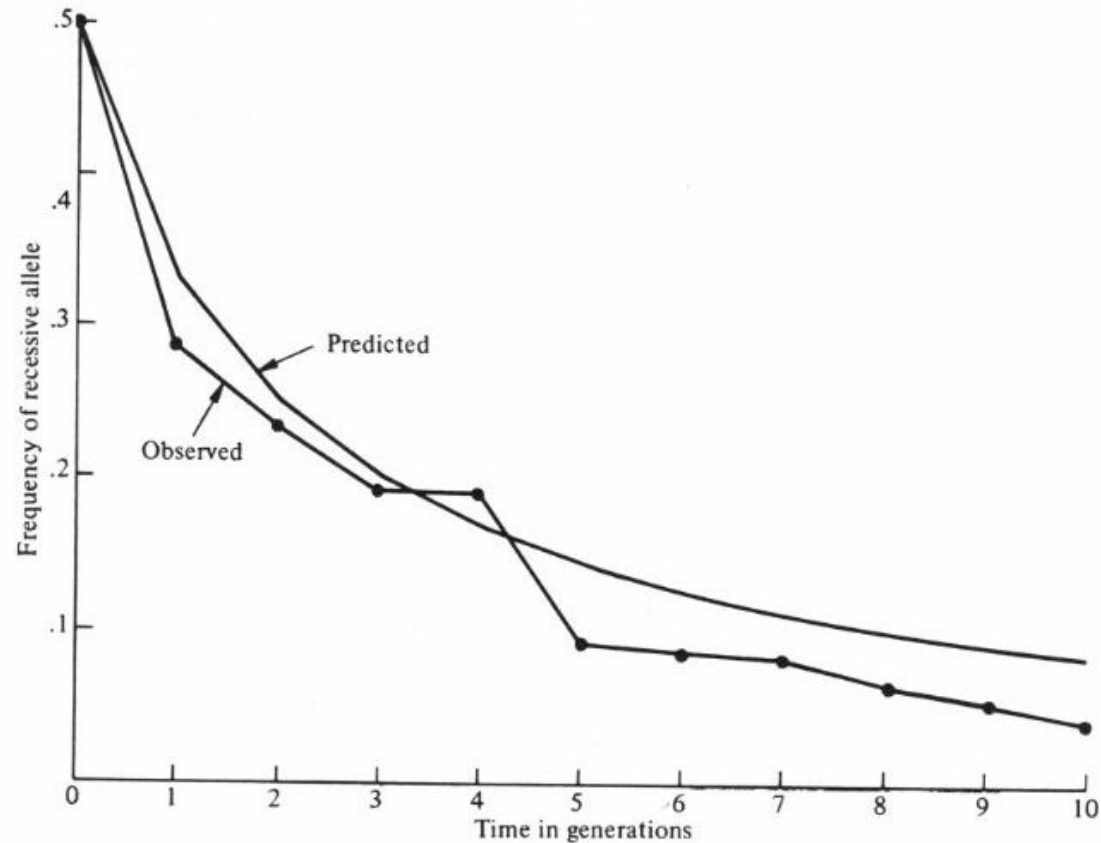
**0.81 AA : 0.18 Aa : 0.01 aa**

**Note that of the 20 copies of a,**

**18 of them, or  $18 / 20 = 0.9$  of them are in Aa genotypes**

# What will happen in the long run?

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**FIGURE 3.4.** Experiment illustrating selection against a recessive lethal gene. The frequency of the recessive allele is on the vertical axis, time in generations is on the horizontal axis. [Data from B. Wallace (1963), The elimination of an autosomal lethal from an experimental population of *Drosophila melanogaster*, *Amer. Natur.* **97**: 65–66.]

## How about milder selection? (Practice problem)

Many alleles are harmful but not universally fatal.

We can write the fitness of a genotype in relation to the fittest genotype. For example, if only 20% of red/red offspring die due to their genotype:

Genotype	AA	Aa	aa
Fitness	1.0	1.0	0.8

Starting from  $p_A=0.5$ , what will happen in one generation?

## How about milder selection?

The calculation is similar to the previous ones:

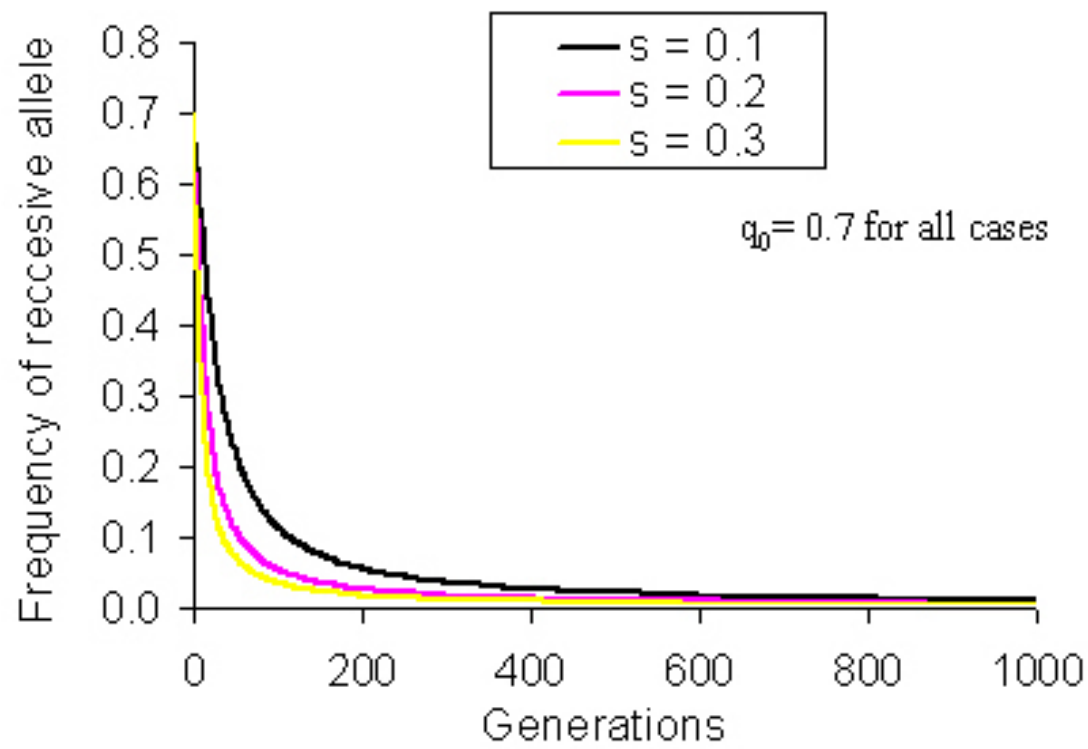
Genotype	AA	Aa	aa
Before selection	0.25	0.50	0.25
Death due to selection	0	0	0.05
After selection	0.25/0.95	0.5/0.95	0.2/0.95
After selection	0.26	0.53	0.21

New allele frequencies:

$$p_A = 0.525$$

$$p_a = 0.475$$

The frequency of red decreases more slowly with the weaker selection.





## **How about harmful dominants?**

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Suppose we killed both black/black and black/red? Black vanishes immediately.

Weaker selection will not be so dramatic. In the next slide selection against both homozygote and heterozygote will be 50%.

## How about harmful dominants?

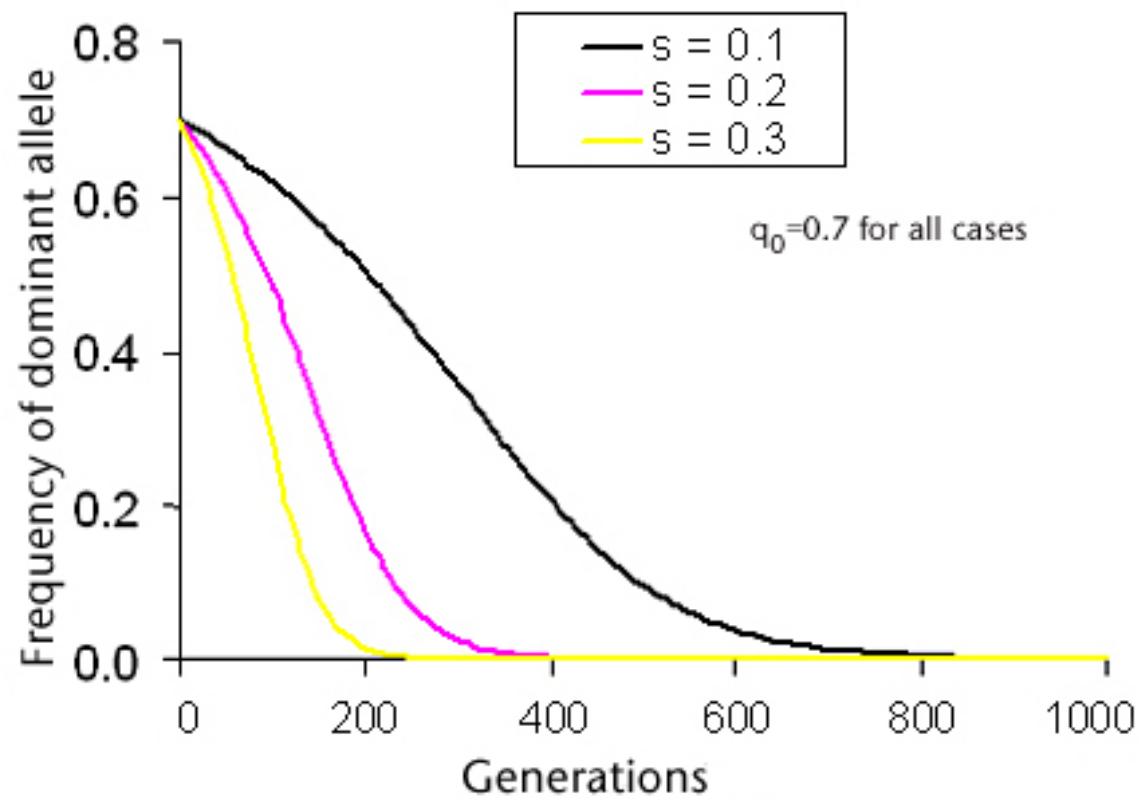
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Genotype	AA	Aa	aa
Fitness	0.5	0.5	1.0
Before selection	0.25	0.50	0.25
Death due to selection	0.125	0.25	0.0
After selection	0.125/0.625	0.25/0.625	0.25/0.625
After selection	0.2	0.4	0.4

New allele frequencies:

$$p_A = 0.4$$

$$p_a = 0.6$$



## **Harmful dominants?**

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- Strongly harmful rare dominants decrease very rapidly
- Such alleles are seldom detected in the wild
- Human examples:
  - achondroplastic dwarfism
  - retinoblastoma
  - Huntington's Disease
- All three have high mutation rates
- Huntington's also has weaker selection because its worst effects often develop after childbearing age

## Generalized selection schemes

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Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Fitness	1.0	0.8	0.3
Fitness	1.0	$1-hs$	$1-s$

- The selection coefficient  $s$  is the *decrease in fitness* of the homozygote.
- Range of  $s$ :
  - $s = 0$  means the allele is neutral
  - $s = 0.5$  means the homozygote is half as fit as normal
  - $s = 1$  means the homozygote always dies or is sterile
- Another way of thinking about  $s$  is as the strength of selection

## Generalized selection schemes

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Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Fitness	1.0	0.8	0.3
Fitness	1.0	1-hs	1-s

- The dominance coefficient  $h$  is the degree to which the heterozygote resembles the mutant homozygote
- Range of  $h$ :
  - $h = 0$  the heterozygote is like the wildtype homozygote (i.e. mutation is recessive)
  - $h = 0.5$  the heterozygote is exactly between the two homozygotes
  - $h = 1$  the heterozygote is like the mutant homozygote (i.e. mutation is dominant)

## Generalized selection schemes

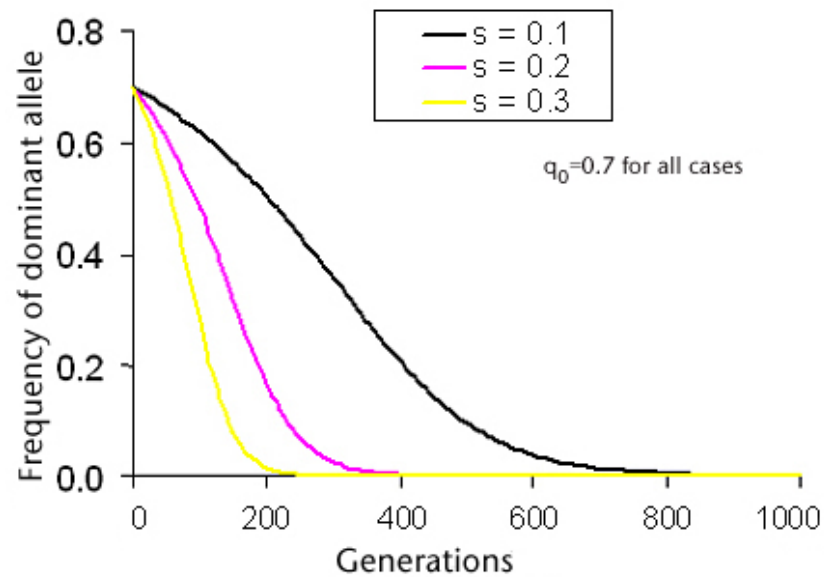
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Genotype	black/black (AA)	black/red (Aa)	red/red (aa)
Fitness	1.0	0.8	0.3
Fitness	1.0	1-hs	1-s

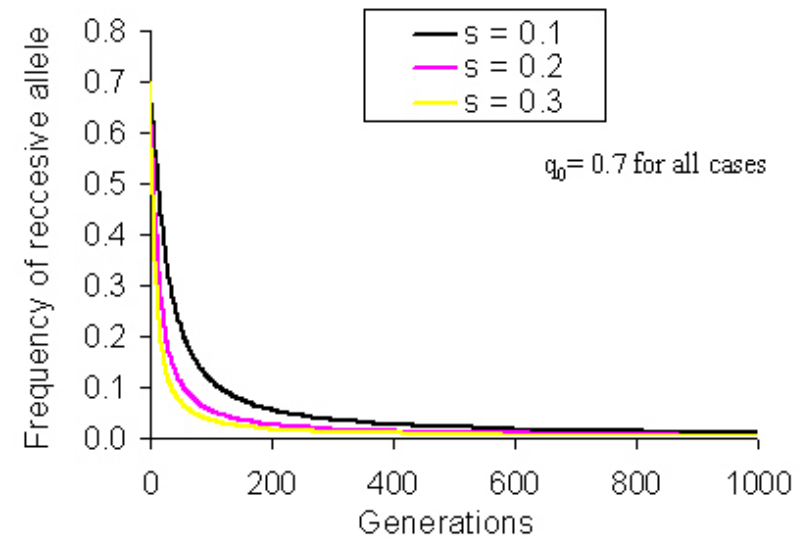
- This nomenclature is **not** generally used for overdominant or underdominant alleles
- When in doubt, just write out the three fitnesses

# Constrasting selection vs. dominant and recessive

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Harmful dominant



Harmful recessive



## **Mutation/selection balance**

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- Harmful alleles can persist in the population due to mutation
- For every allele destroyed by selection, one arises by mutation
- This is the “mutation/selection equilibrium”

## Mutation/selection balance

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- For a dominant (or a gene in a haploid organism):

$$p(\textit{mutant}) = \mu/s$$

- For a recessive:

$$p(\textit{mutant}) = \sqrt{\mu/s}$$

## Mutation/selection balance

$$p(\text{mutant}) = \sqrt{\mu/s}$$

- “In 1959, the median age of survival of children with cystic fibrosis in the US was 6 months” –Wikipedia
- Assume  $\mu = 10^{-7}$
- What is the mutation/selection equilibrium for this allele?

## Mutation/selection balance

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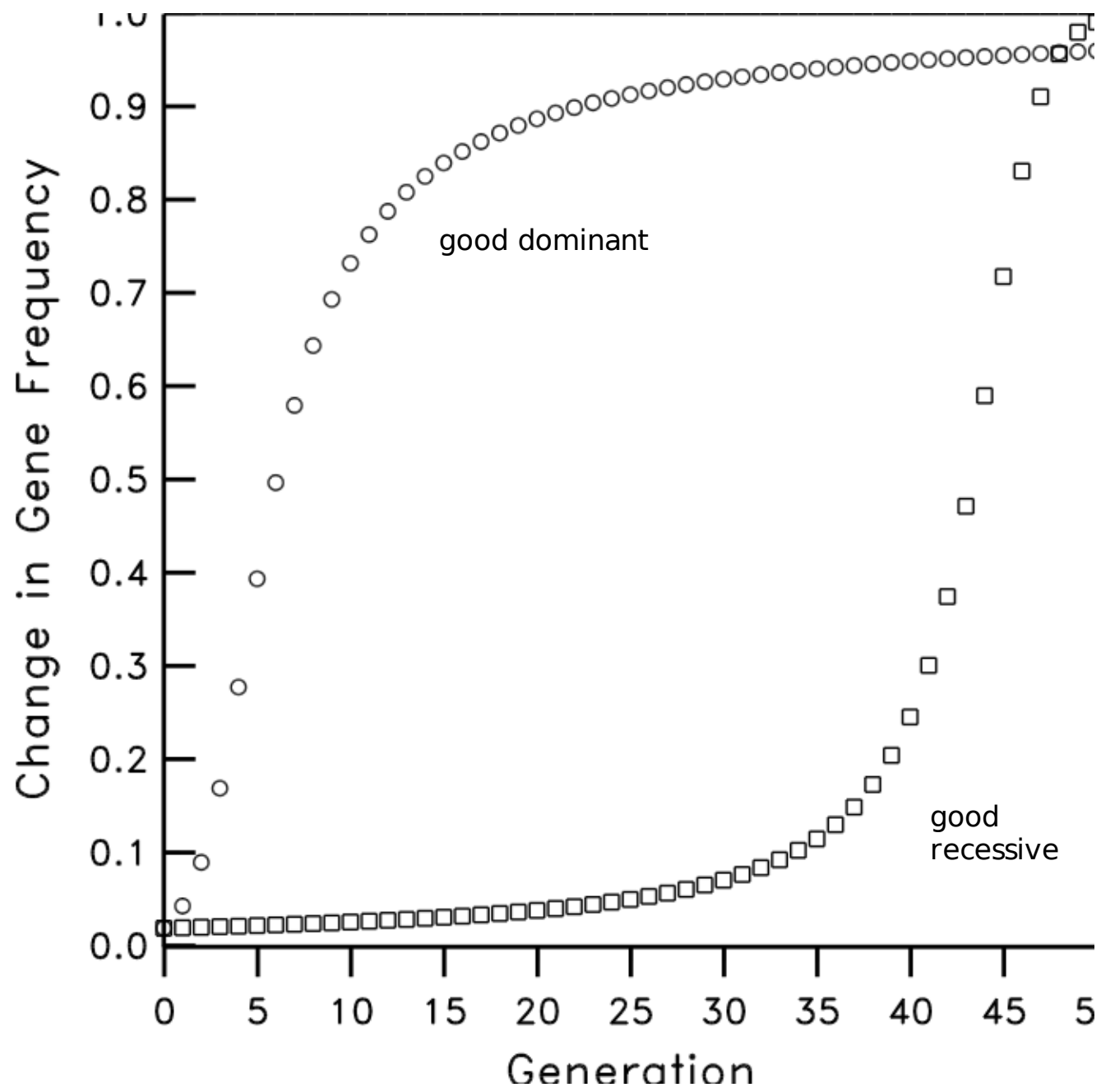
$$p(\text{mutant}) = \sqrt{\mu/s}$$

- Equilibrium suggests a frequency of 0.00032
- Real frequency in Europeans 0.04 – 100x higher
- What could be happening here?

## General observations

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- An allele that is recessive and rare hides from selection
  - If it is good, it increases slowly
  - If it is bad, it decreases slowly
- An allele that is dominant and rare is easily seen by selection
  - If it is good, it increases rapidly
  - If it is bad, it decreases rapidly
- When an allele is common, its partner is rare—it's easiest to think about what happens to the partner



## Mean fitness increases

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- We can define the mean fitness of a population as the average over its members
- Suppose that we examined this population:

Genotype	AA	Aa	aa
Frequency	0.25	0.5	0.25
Fitness (w)	1.0	1.0	0.8

$$\begin{aligned}\text{Mean fitness} \quad & w(\text{AA}) * p(\text{AA}) = 0.25 \\ & w(\text{Aa}) * p(\text{Aa}) = 0.5 \\ & w(\text{aa}) * p(\text{aa}) = 0.2 \\ & \text{Total} = 0.95\end{aligned}$$

## Mean fitness increases

After one generation of selection:

Genotype	AA	Aa	aa
Old Frequency	0.25	0.5	0.25
Fitness (w)	1.0	1.0	0.8
New Frequency	0.25/0.95	0.5/0.95	0.2/0.95
New Frequency	0.263	0.526	0.211

New allele frequencies:  $p(A) = 0.526$ ,  $p(a) = 0.474$

At the start of the next generation:

Genotype	AA	Aa	aa
New Frequency	0.278	0.499	0.225
Fitness (w)	1.0	1.0	0.8



## Mean fitness increases

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New allele frequencies:  $p(A) = 0.526$ ,  $p(a) = 0.474$

At the start of the next generation:

Genotype	AA	Aa	aa
New Frequency	0.278	0.499	0.225
Fitness ( $w$ )	1.0	1.0	0.8

Mean fitness  $w(AA) * p(AA) = 0.278$

$w(Aa) * p(Aa) = 0.499$

$w(aa) * p(aa) = 0.180$

Total = 0.957

## **Mean fitness increases**

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- In single-locus cases like these, mean fitness always increases
- With dominant, intermediate or recessive inheritance, long-term result always maximises mean fitness
- This is not necessarily true with overdominance or underdominance

## **Fisher's “Fundamental Theorem”**

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- The rate of increase of mean fitness is equal to the genetic variance in fitness
- True for single-locus cases; not always true for multiple loci
- Implications:
  - Mean fitness is non-decreasing
  - Amount of available variance limits rate of evolution

## Discussion question

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- Start with a population of  $A$  with fitness 1.0
- Suddenly add a new, better allele:

Genotype	AA	Aa	aa
Fitness	0.9	0.9	1.0
- The mean fitness seems to go down?!

## **Fitness is relative**

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- Except for lethal alleles, fitness is generally best thought of as relative
- The best genotype we are aware of is given a fitness of 1
- Individuals of that genotype may still fail to survive or reproduce!
- A newly arisen allele might be better
- If we found one, we would redefine "fitness of 1" to the new level

## How much selection is enough?

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- In the idealized situations we are examining:
  - ANY selection will cause an increase of the favored allele
  - Speed will depend on  $s$ , initial frequency, and dominance
- To observe selection in real situations:
  - Must be strong enough to overcome drift (random effects)
  - 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*

## One-minute responses

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- 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?
- Drop off on your way out