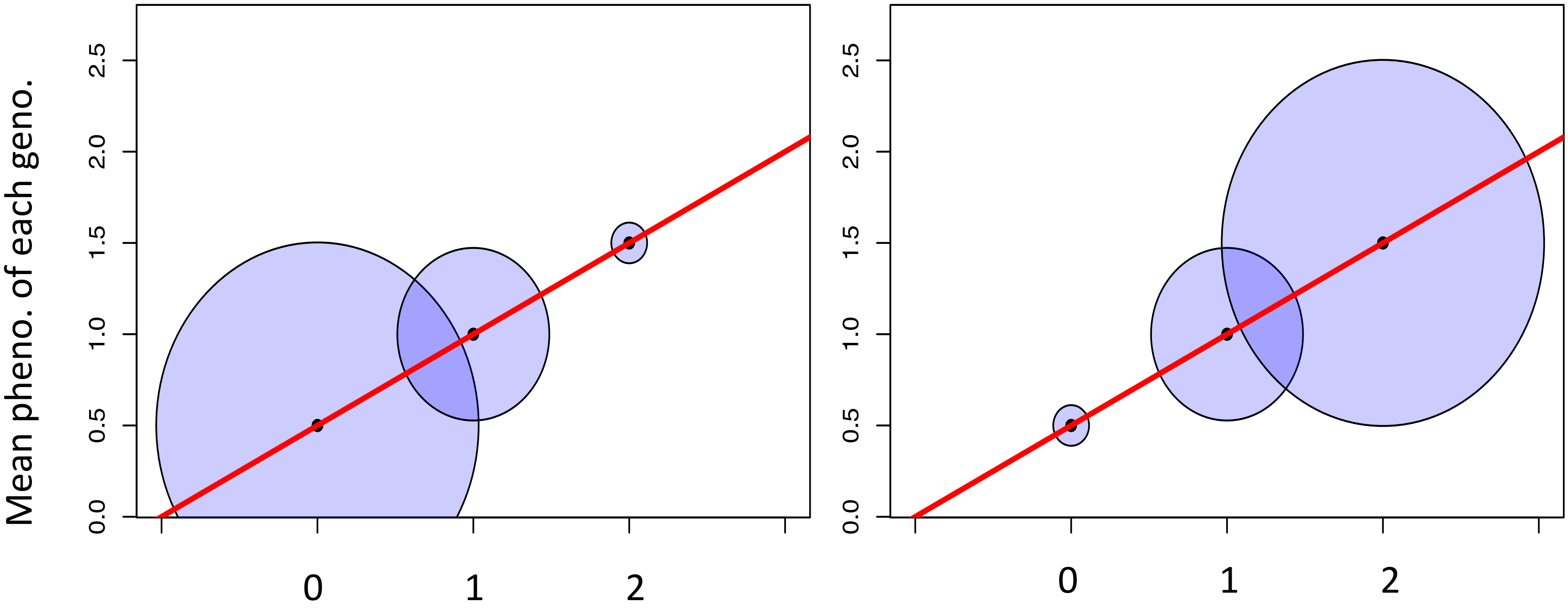
“Natural selection of phenotypes cannot in itself produce cumulative change, because phenotypes are extremely temporary manifestations. They are the result of interactions between genotype and environment that produces what we recognize as an individual. Such an individual consists of genotypic information and information recorded since conception. Socrates consisted of the genes his parents gave him, the experiences they and his environment later provided, and the growth a development mediated by numerous meals. For all I know, he may have been very successful in the evolutionary sense of leaving numerous offspring. His phenotype, nevertheless, was utterly destroyed by the hemlock and has never since been duplicated. If the hemlock had not killed him, something else soon would have. So however natural selection may have been acting on Greek phenotypes in the forth century B.C., it did not of itself produce any cumulative effect.

The same argument holds also for genotypes. With Socrates’ death, not only did his phenotype disappear, but also his genotype.[…] The loss of Socrates’ genotype is not assuaged by any consideration of how prolifically he may have reproduced. Socrates’ genes may be with us yet, but not his genotype, because meiosis and recombination destroy genotypes as surely as death.”

GC Williams

Additive effect of alleles

The additive effect on an allele is the effect of an allele averaged over the genetic backgrounds it can occur in. What is gain in phenotype for extra copy of allele A.



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Additive effect of A allele = $\alpha_A = p\,X_2 + q\,X_1$

Additive effect of a allele = $\alpha_a = p\,X_1 + q\,X_0$

The contribution of locus to the additive variance is = $2pq\,(\alpha_A - \alpha_a)^2$

However, unless the allele is truly additive in its effect there is unexplained variance

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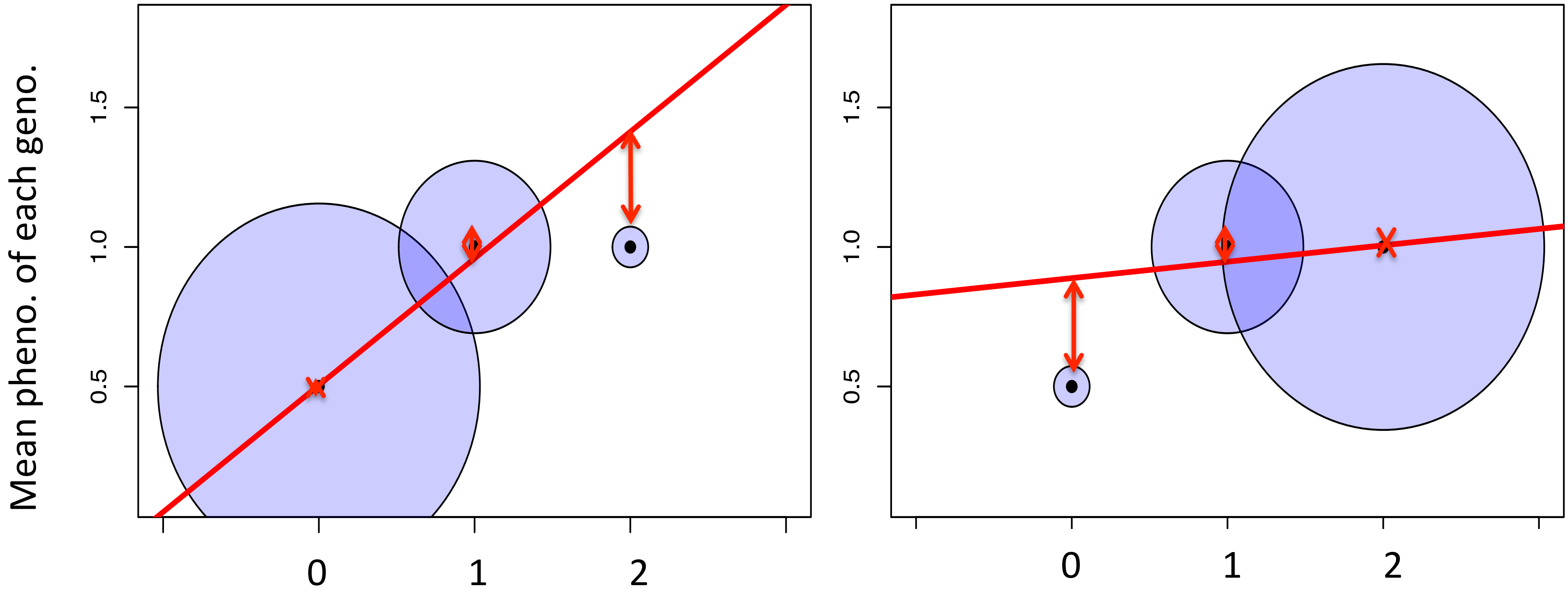

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Components of total phenotypic variance, V_P

$$V_P = V_E + \underbrace{V_A + V_D + V_I}_{V_G}$$

- **V_A** = variance among individuals due to the additive effects of alleles that vary among them
- **V_D** = variance among individuals due to non-additive allele interactions (e.g. dominance)
- **V_E** = variance due to individuals experiencing different environments
- **V_I** = variance due to epistatic interactions between loci.

$$h^2 = \frac{V_A}{V_A + V_D + V_I + V_E}$$

Narrow sense
Heritability

Haploid model of selection

Consider alleles A_1 and A_2 at frequency p_t and $q_t = 1 - p_t$ at time t, and assume that the population size N is so large that we can ignore genetic drift.

Diploid model of selection

Consider alleles A_1 and A_2 at frequency p_t and $q_t = 1 – p_t$ at time t, and assume that the population size N is so large that we can ignore genetic drift.

Genotype	A_1A_1	A_1A_2	A_2A_2
Absolute fitness	W_{11}	W_{12}	W_{22}

Change in allele frequencies due to viability selection

$$p_{t+1} = f_{11} + \frac{1}{2} f_{12} = \frac{w_{11} p_t + w_{12} q_t}{\overline{w}} p_t$$

$$\Delta p_t = p_{t+1} - p = \frac{w_{11} p_t + w_{12} q_t}{\overline{w}} p_t - p_t$$

$$\overline{w}_1 = w_{11} p_t + w_{12} q_t$$

$$\overline{w}_2 = w_{12} p_t + w_{22} q_t$$

Marginal fitnesses of A_i: weighted mean fitness across genotypes carrying A_i

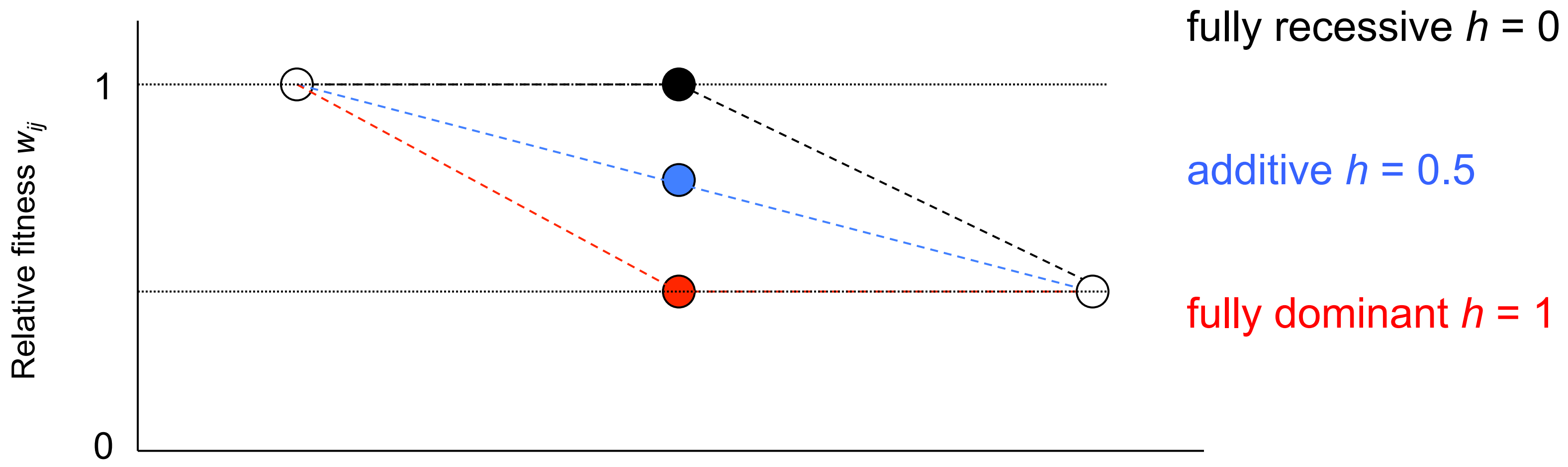
$$\Delta p_t = \frac{\overline{w}_1 - \overline{w}_2}{\overline{w}} p_t q_t, \qquad \Delta q_t = -\Delta p_t$$

Frequency of A_1 is expected to increase if the marginal fitness of A_1 is higher than A_2, regardless of how small the difference

$$\Delta p_t = \tfrac{1}{2} p_t q_t \frac{d\overline{w}}{dp_t}$$

Alternative formulation by Haldane (1924). Frequency of A_1 increases if mean fitness is an increasing function of frequency of A_1.

Directional selection



	A_1A_1	A_1A_2	A_2A_2
w_{ij}	1	$1 - hs$	$1 - s$

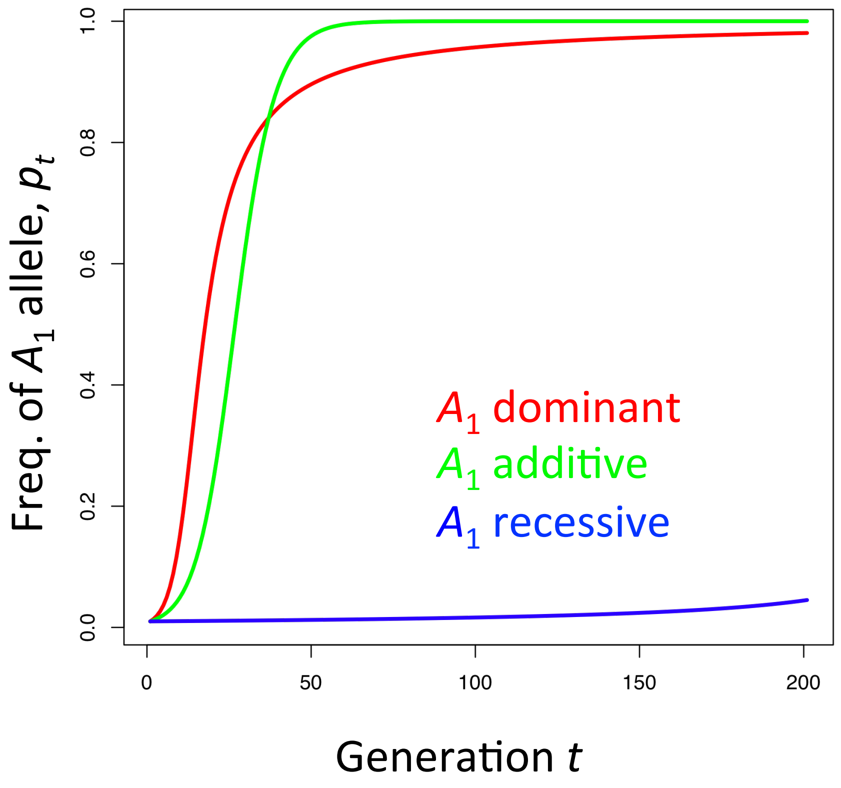
$$\overline{w}_1 = w_{11}p_t + w_{12}q_t = p_t + (1-hs)q_t$$

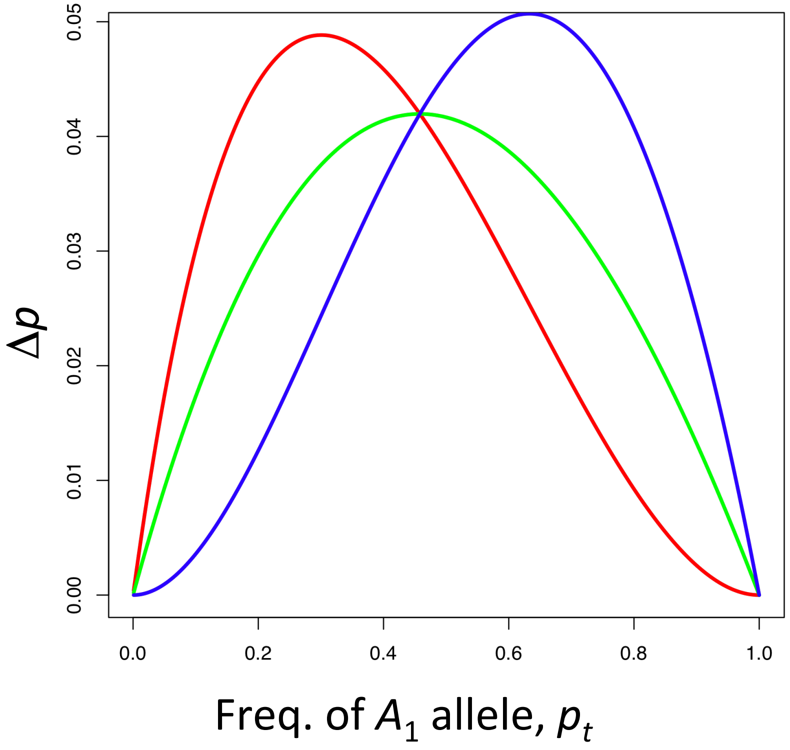
$$\overline{w}_2 = w_{12}p_t + w_{22}q_t = (1-hs)p_t + (1-s)q_t$$

$$\Delta p_t = \frac{\overline{w}_1 - \overline{w}_2}{\overline{w}} p_t q_t = \frac{p_t hs + q_t s(1-h)}{\overline{w}} p_t \underset{s<<1}{\overset{h=1/2}{\approx}} \frac{1}{2} s p_t q_t$$

$$\bar{w}_1 = w_{11}p_t + w_{12}q_t = p_t + (1-hs)q_t$$
$$\bar{w}_2 = w_{12}p_t + w_{22}q_t = (1-hs)p_t + (1-s)q_t$$

$$\Delta q_t = \frac{\bar{w}_2 - \bar{w}_1}{\bar{w}} p_t q_t = \frac{-p_t hs - q_t s(1-h)}{\bar{w}} q_t$$



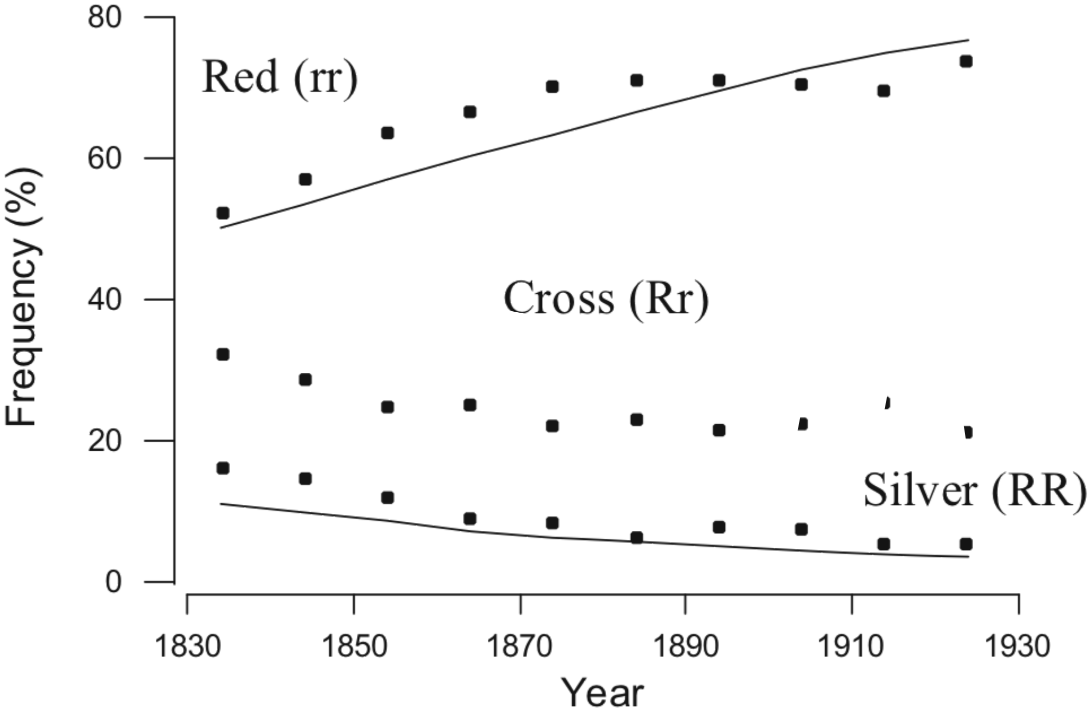


A new advantageous additive allele takes on average ½ ln(2N)/s generations to reach (near) fixation, where N is the population size.

Beneficial dominant alleles are quick to spread but slow to fix.

Red Morph:
Homozygotes rr and heterozygotes rR

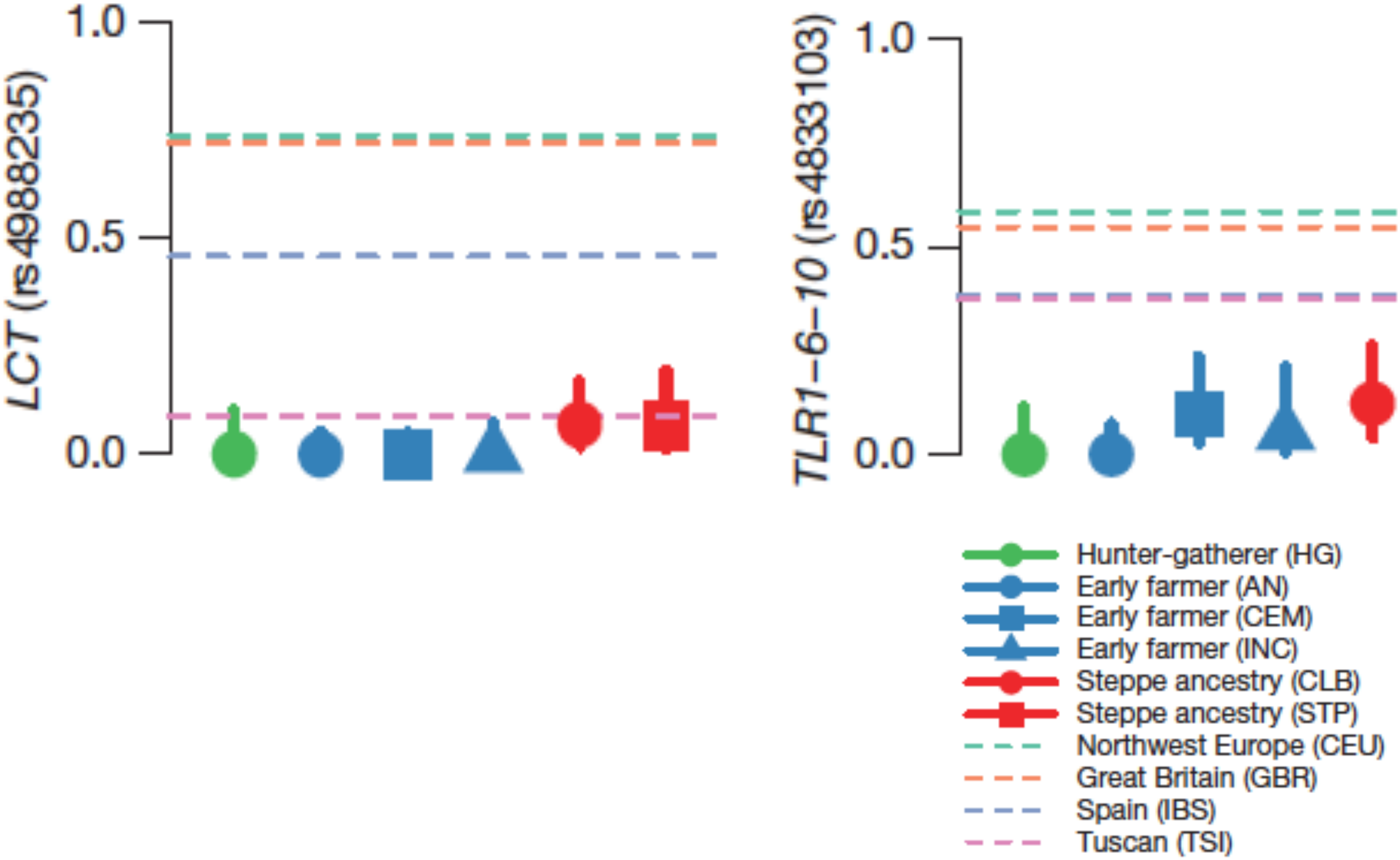
Silver fox morph :RR homozygote



Silver fox pelts were particularly valuable to hunters

Genome-wide patterns of selection in 230 ancient Eurasians

Iain Mathieson[1], Iosif Lazaridis[1,2], Nadin Rohland[1,2], Swapan Mallick[1,2,3], Nick Patterson[2], Songül Alpaslan Roodenberg[4], Eadaoin Harney[1,3], Kristin Stewardson[1,3], Daniel Fernandes[5], Mario Novak[5,6], Kendra Sirak[5,7], Cristina Gamba[5,8]†, Eppie R. Jones[8], Bastien Llamas[9], Stanislav Dryomov[10,11], Joseph Pickrell[1]†, Juan Luís Arsuaga[12,13], José María Bermúdez de Castro[14], Eudald Carbonell[15,16], Fokke Gerritsen[17], Aleksandr Khokhlov[18], Pavel Kuznetsov[18], Marina Lozano[15,16], Harald Meller[19], Oleg Mochalov[18], Vyacheslav Moiseyev[20], Manuel A. Rojo Guerra[21], Jacob Roodenber
Josep Maria Vergès[15,16], Johannes Krause[23,24], Alan Cooper[9], Kurt W. Alt[19,25,26], Dorcas Brown[27], David Anthony[27], Carles Lalueza-Fox[28], Wolfgang Haak[9,23]*, Ron Pinhasi[5]* & David Reich[1,2,3]*



Why is there so much polymorphism?

- The paradox of variation in population genetics:

Selection quickly fixes alleles that are beneficial so why is there so much genetic polymorphism within natural populations?

Three broad explanations:

- Selection sometimes acts to maintain variation, balancing selection
- Mutation-selection balance
- Mutation-drift balance (Neutral theory).

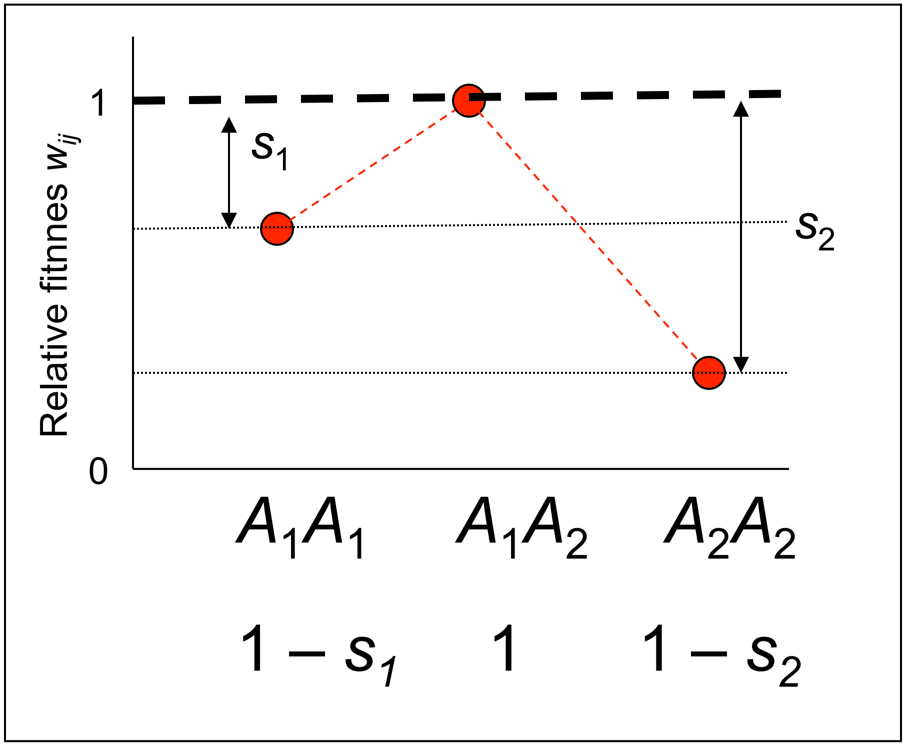
Selection can act to maintain polymorphism within a population

- Selection can maintain balanced polymorphisms in the population

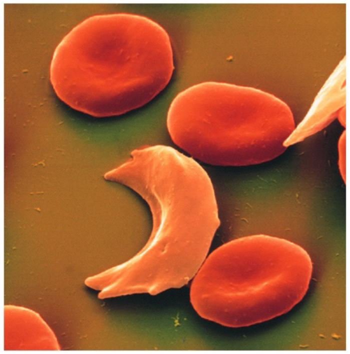
- Balancing selection can result when:
- The heterozygotes for an allele are fitter than either homozygote (termed heterozygote advantage or overdominance)

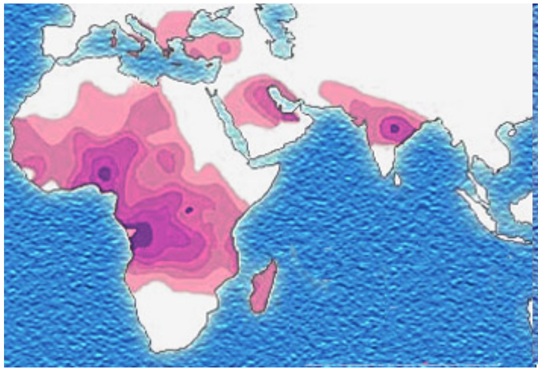
Overdominance

(Heterozygote superiority)

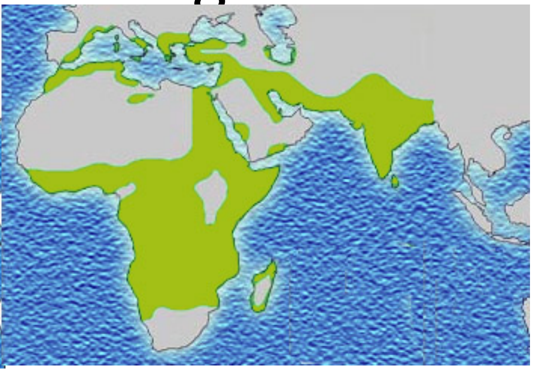


Selective maintenance of genetic variation





Sickle allele dist



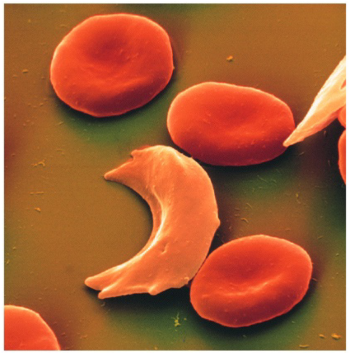
Malaria dist

Data on sickle genotype frequencies in infants and adults in Tanzania (Allison 1956)

Genotype	AA	AS	SS	Freq S allele
Freq infant	0.66	0.31	0.03	0.186
Freq adult	0.61	0.38	0.007	0.198
Fitness	0.93	1.23	0.24	
Rel fitness	0.76	1	0.18	

Heterozygote has highest fitness = *heterozygote advantage* = overdominance
Anemia and malaria are opposing selective factors

See also Haldane 1949



Selective maintenance of genetic variation

Genotype	AA	AS	SS
Rel fitness	0.76	1	0.18

Freq S allele= 0.4

Freq infant	0.36	0.48	0.16	
Rel fit xFreq.	0.76x0.36	1 x0.48	0.18x0.16	
	=0.274	=0.48	=0.028	$\bar{w}$=Sum=0.782
Freq adult	0.35	0.61	0.037	

New S frequency = f_{SS}+ ($f_{AS}/2$) = 0.34

Freq. S allele = 0.1

Freq infant	0.81	0.18	0.01	
Freq. x Rel fit	0.76x0.81	1 x0.18	0.01x0.18	
	=0.616	=0.18	=0.0018	$\bar{w}$=Sum=0.797
Freq adult	0.772	0.225	0.0023	

New S frequency = f_{SS}+ ($f_{AS}/2$) = 0.115

Overdominance (heterozygote advantage)

A_1A_1	A_1A_2	A_2A_2
$1 - s_1$	1	$1 - s_2$

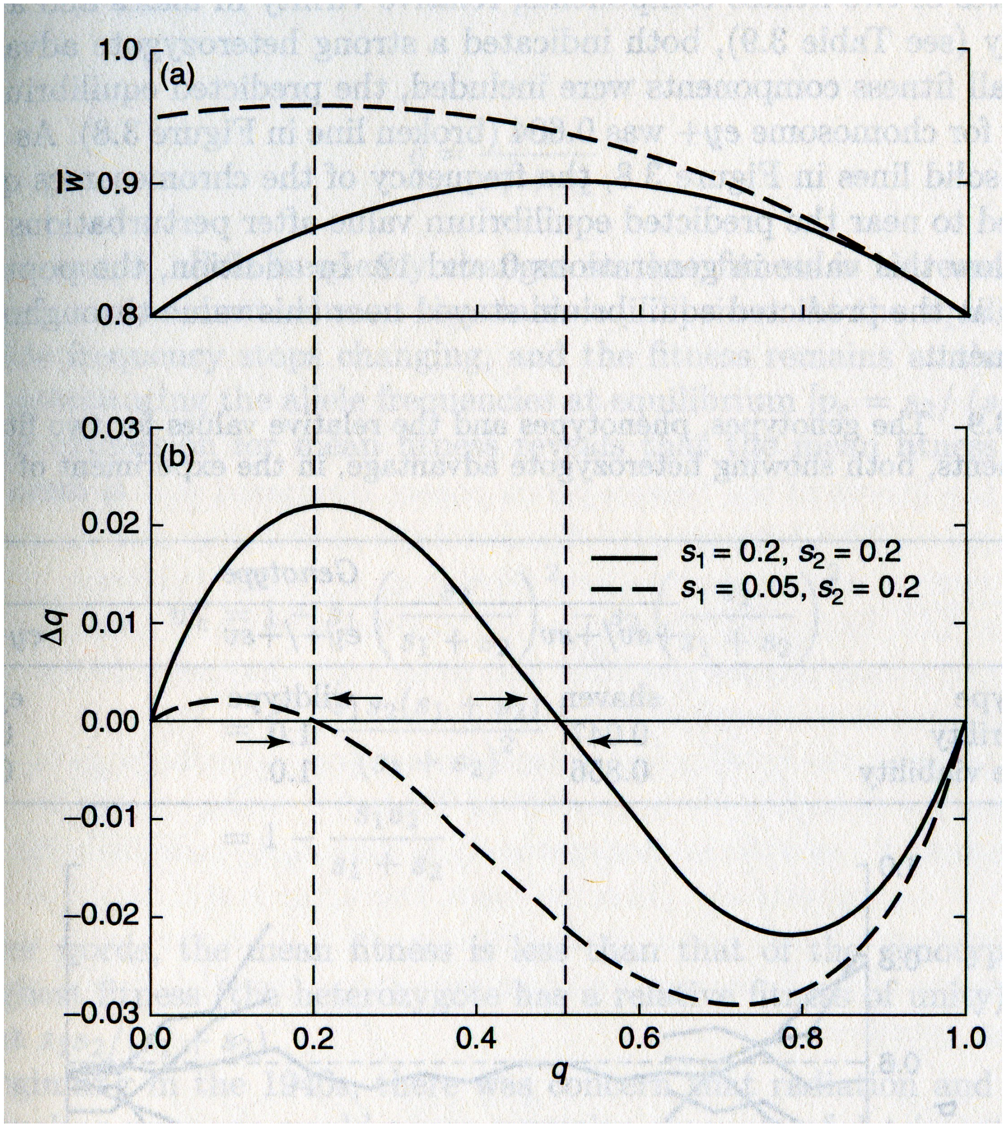
$$s_1 > 0,\ s_2 > 0$$

$$\overline{w_1} = (pw_{11} + qw_{12})$$
$$\overline{w_2} = (pw_{12} + qw_{22})$$

$$\Delta p = \frac{pq(\overline{w_1} - \overline{w_2})}{\overline{w}}$$

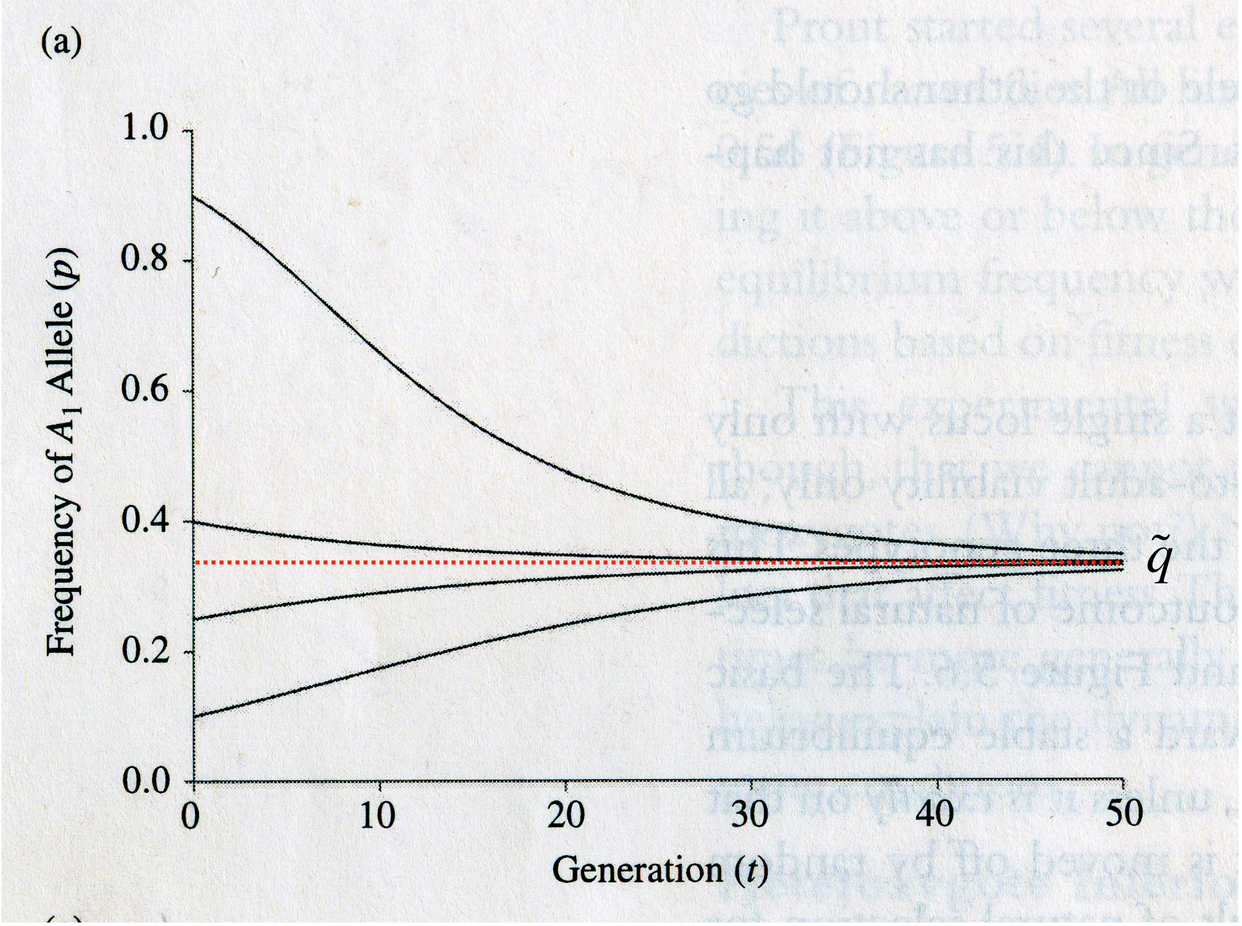
At equilibrium $\Delta p = 0$
Two boring eq. $p = 0$, $q = 0$
Polymorphic eq.
$pw_{11} + qw_{12} = pw_{12} + qw_{22}$

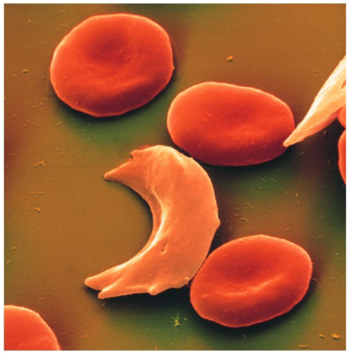
Over-dominance results in a *balanced polymorphism*



At equilibrium $\Delta p = 0$
i.e. $pw_{11} + qw_{12} = pw_{12} + qw_{22}$

At equilibrium, freq of $A_1 = p_{\text{eq}} = s_2/(s_1 + s_2)$
freq of $A_2 = q_{\text{eq}} = s_1/(s_1 + s_2)$





Heterozygote advantage (Over dominance)

	A_1A_1	A_1A_2	A_2A_2
	$1-s_1$	1	$1-s_2$
Rel fitness	0.76	1	0.18

$s_1=1-0.76=0.24$

$s_2=1-0.18=0.82$

At equilibrium $\Delta p = 0$

$$\Delta p = \frac{pq(\overline{w}_1 - \overline{w}_2)}{\overline{w}}$$

At equilibrium, freq $A_1 = p_{eq} = s_2/(s_1+s_2)$

freq $A_2 = q_{eq} = s_1/(s_1+s_2)$

$$q_{eq} = \frac{0.24}{0.24+0.82} = 0.226$$

Additive effect of alleles

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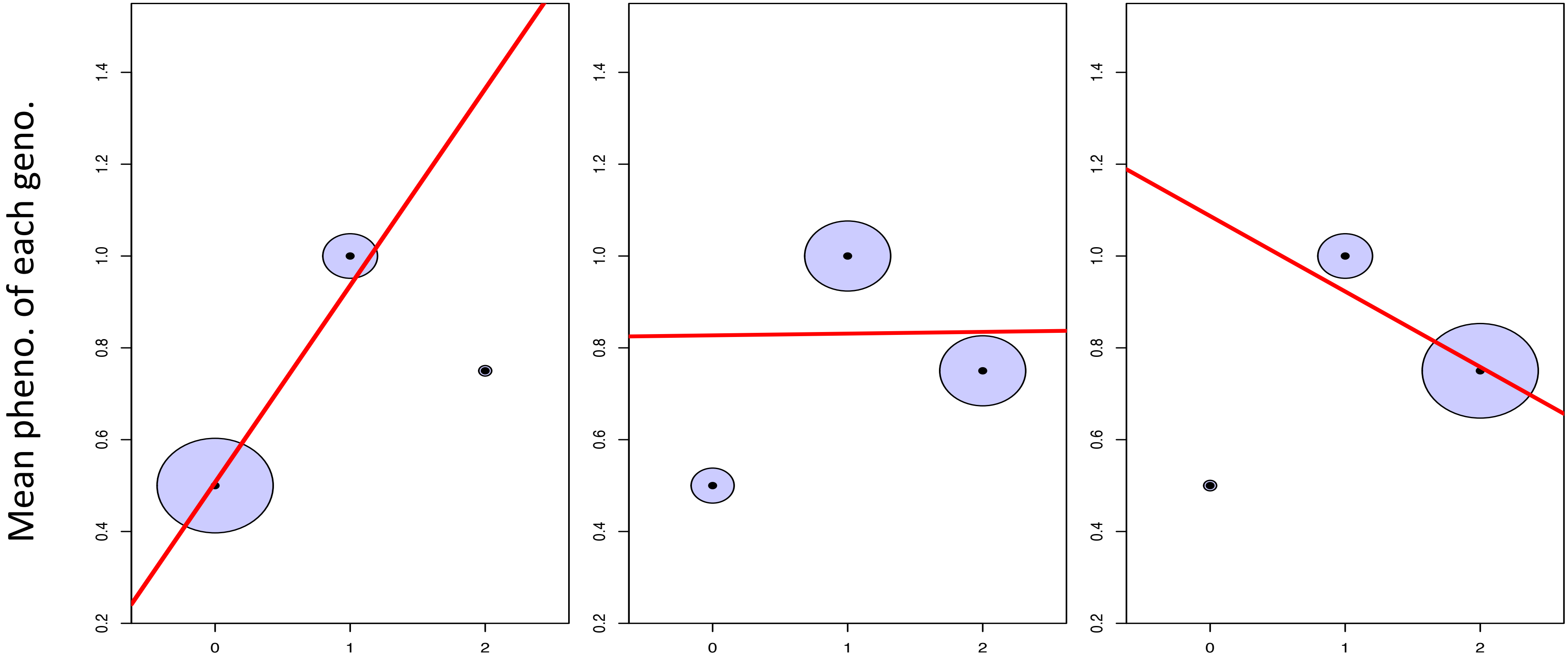

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The contribution of locus to the additive variance is = $2pq (\alpha_A - \alpha_a)^2$

However, unless the allele is truly additive in its effect there is unexplained variance

Balancing Selection

Modes of selection maintaining variation are collectively referred to as *balancing selection*

Heterozygote advantage is just one form of balancing selection

A broad class of balancing selection is *negative frequency dependent selection*

- Fitness negatively correlated with frequency
- Occurs in many systems due to interactions between individuals or species
- e.g. prey/predator or pathogen/host dynamics