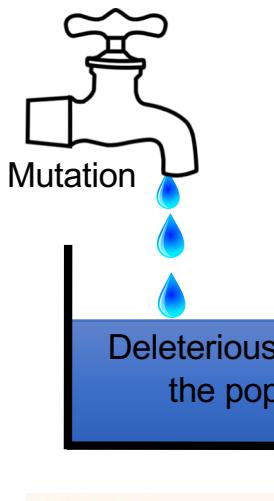
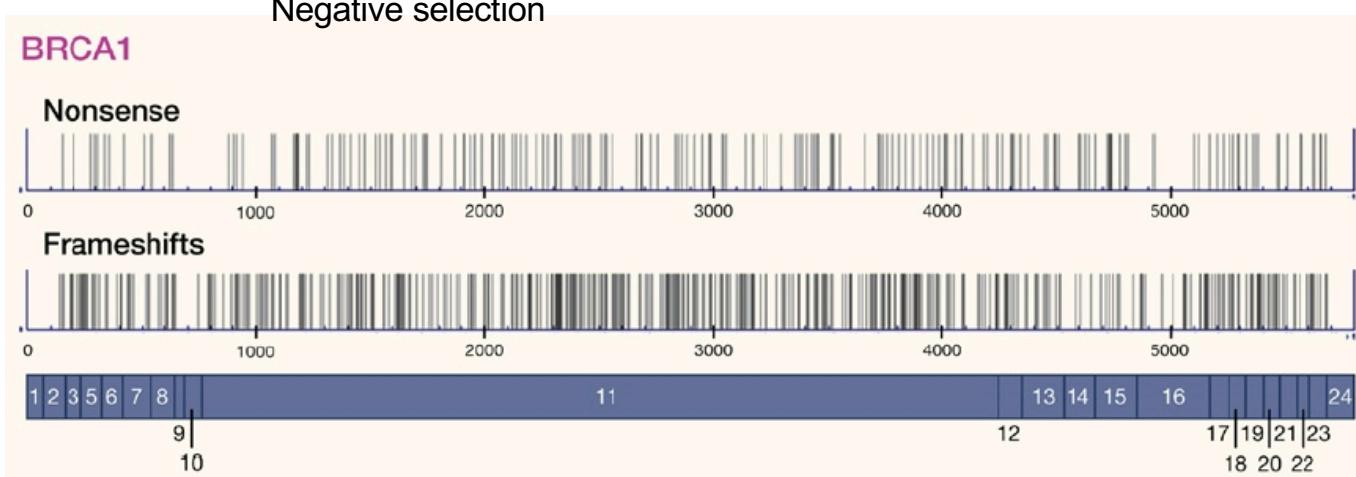


Mutation–selection balance



The gene *BRCA1* is one out of about a dozen genes known to harbour loss-of-function mutations leading to breast cancer



At *BRCA1*, more than 1000 different alleles increase susceptibility to breast and ovarian cancers. The figure shows positions of frameshift and nonsense mutations along the gene, which is in blue, with exons indicated by numbers. Modified from McClellan & King (2010) *Cell*.

Mutation-Selection Balance (MSB)

Change due to mutation: $\Delta q_{\text{mut}} = -\Delta p_{\text{mut}} = p\mu$

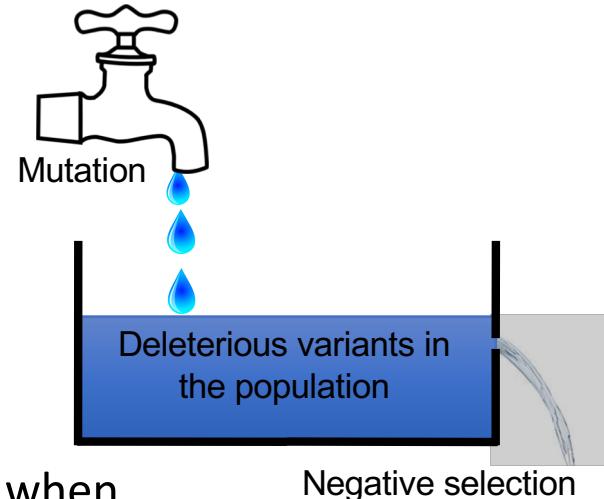
Change due to selection: $\Delta q_{\text{sel}} = -(sh) pq$

These two rates of change are at equilibrium when

$$\Delta q_{\text{mut}} + \Delta q_{\text{sel}} = 0$$

$$p\mu - (sh)pq = 0$$

$$q_{\text{eq}} = \mu/(sh)$$



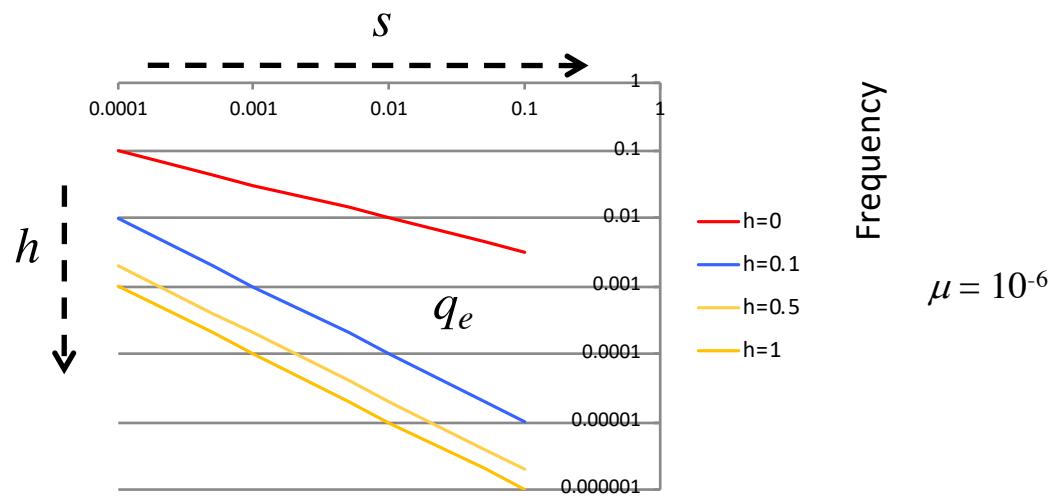
We can do a similar calculation for totally recessive mutations ($h=0$), and obtain

$$q_{\text{eq}} = \sqrt{(\mu/s)}$$

Haldane (1937)

Mutation–selection balance

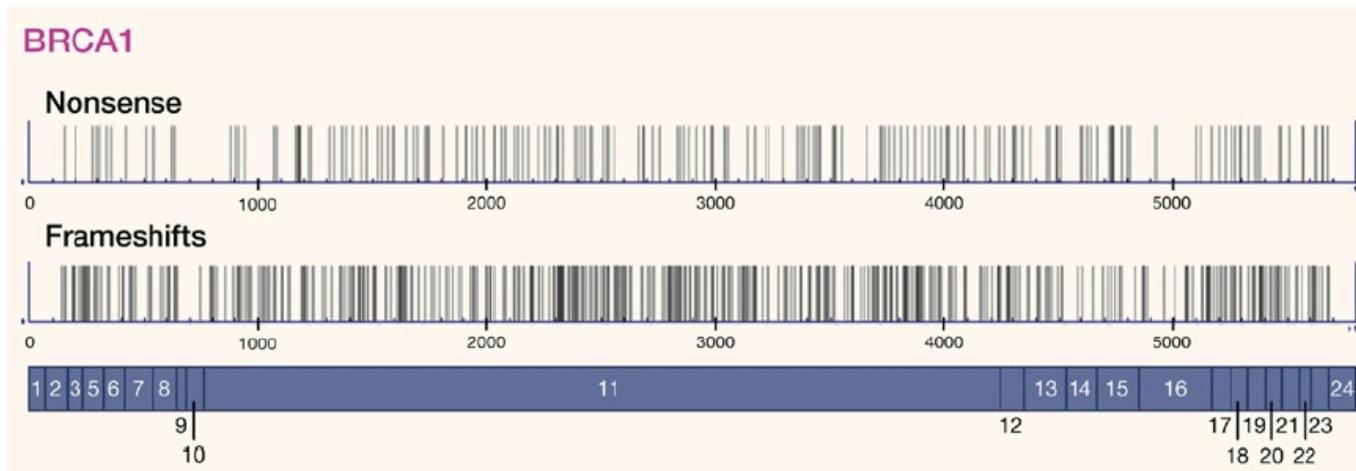
$$q_e \approx \frac{\mu}{hs} \quad \text{if} \quad h > 0 \quad q_e \approx \sqrt{\frac{\mu}{s}} \quad \text{if} \quad h = 0$$



The more dominant a deleterious mutation is, the rarer it will be at mutation–selection balance.

Per-locus mutation rates are low and selection is effective

Mutation-selection balance



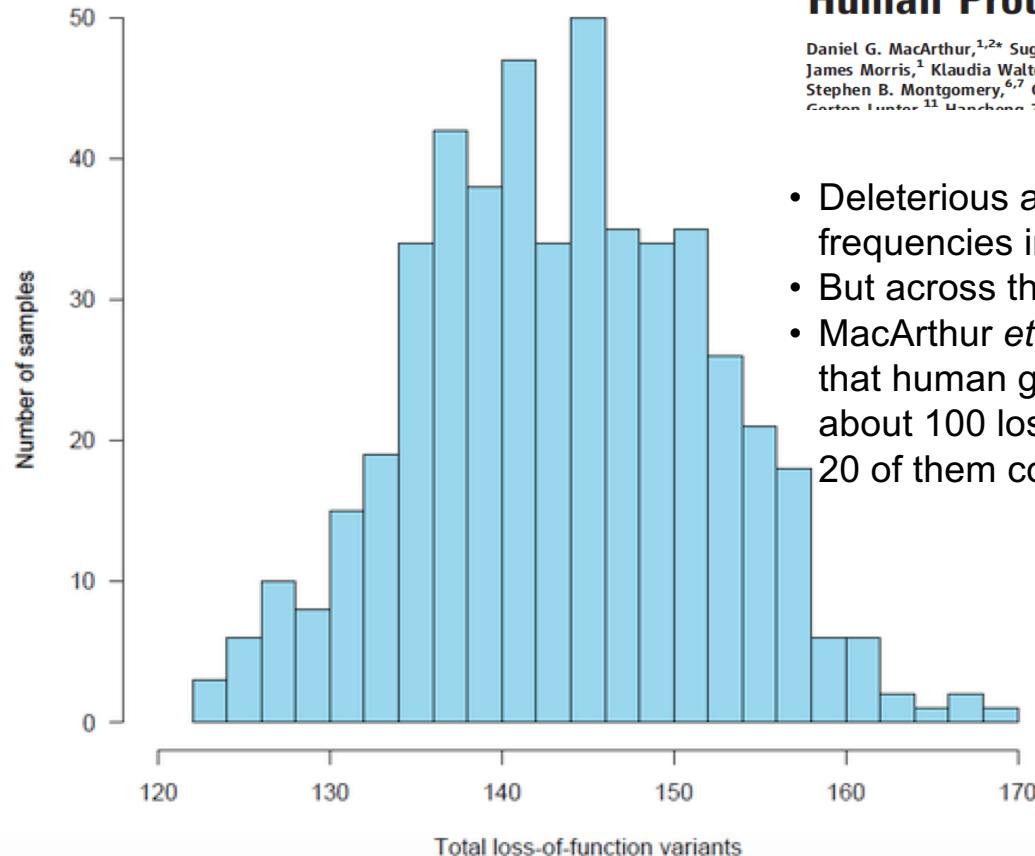
At *BRCA1*, more than 1000 different alleles increase susceptibility to breast and ovarian cancers. The figure shows positions of frameshift and nonsense mutations along the gene, which is in blue, with exons indicated by numbers. Modified from McClellan & King (2010) *Cell*.

The frequency of frameshift and nonsense mutations at *BRCA1* is about 1/1000. The *BRCA1* gene has about 2500 coding bases, and the per-base pair mutation rate in humans is about 2×10^{-8} per generation. How strong is selection against an average loss-of-function mutation?

$$\mu = 2500 * 2 \times 10^{-8}$$

$$q = 1/1000$$

Implications



A Systematic Survey of Loss-of-Function Variants in Human Protein-Coding Genes

Daniel G. MacArthur,^{1,2*} Suganthi Balasubramanian,^{3,4} Adam Frankish,¹ Ni Huang,¹ James Morris,¹ Klaudia Walter,¹ Luke Jostins,¹ Lukas Habegger,^{3,4} Joseph K. Pickrell,⁵ Stephen B. Montgomery,^{6,7} Cornelis A. Albers,^{1,8} Zhengdong D. Zhang,⁹ Donald F. Conrad,¹⁰ Gerton Lunter,¹¹ Hanhong Zhou,¹² Orcim Akhund,¹ Mark A. DePristo,¹³ Eric Bankhead,¹³

- Deleterious alleles maintained at low frequencies in the population
- But across the genome ...
- MacArthur *et al.* (2012 *Nature*) estimated that human genomes typically carry about 100 loss-of-function alleles (about 20 of them completely inactivated)

- Thus, mutation–selection balance may be an important source of fitness variation in nature

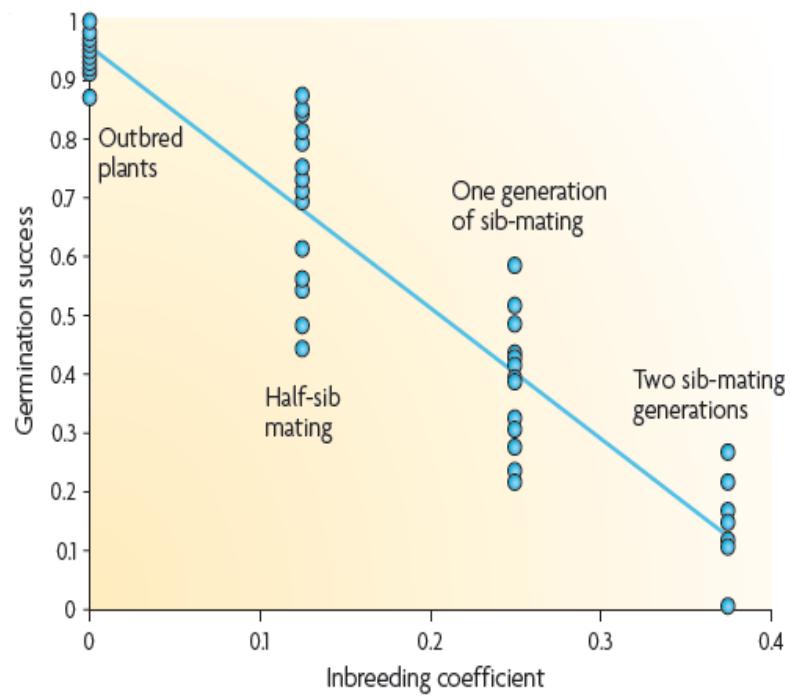
Whole-genome sequence variation, population structure and demographic history of the Dutch population

The Genome of the Netherlands Consortium*

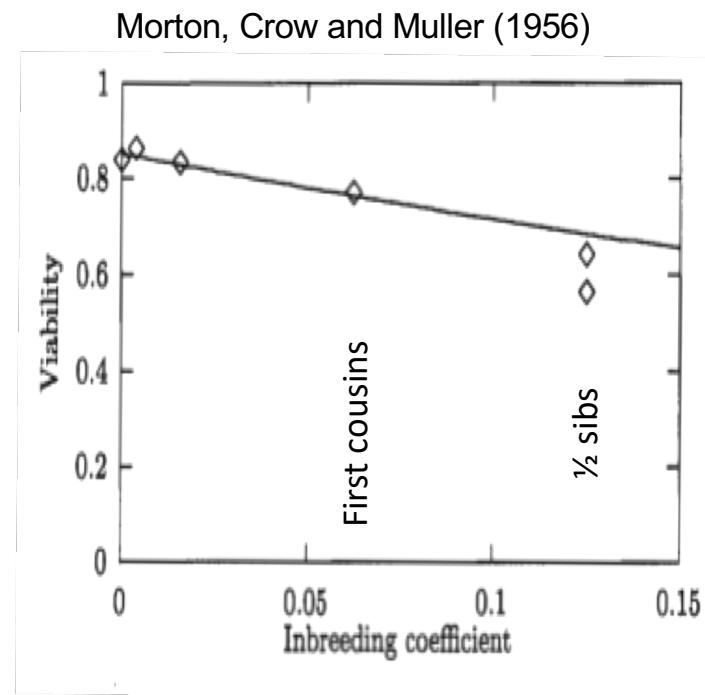
Inbreeding depression: Reduced fitness of inbred individuals (from normally outbred populations)

One of the first systematic surveys of inbreeding depression was conducted by Darwin (57 plant species)

All else being equal mutations that are more recessive should segregate at high frequencies under mutation selection balance



Silene latifolia (white campion)
from Charlesworth and Willis Nat Gen. '09

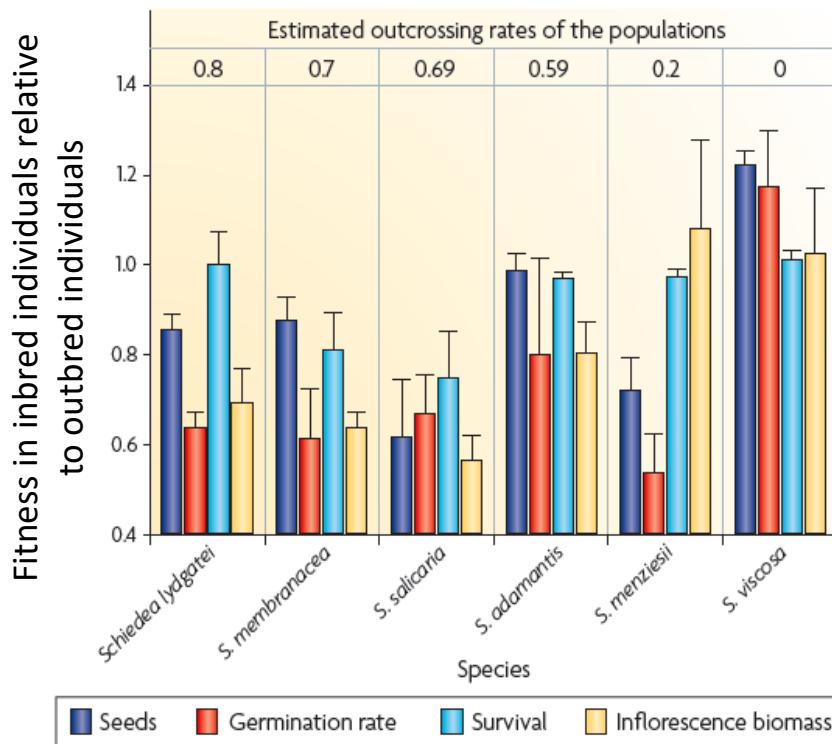


Purging of inbreeding load in partially selfing populations

Given an inbreeding coefficient of f , the equilibrium frequency is

$$q_e \approx \frac{\mu}{(h(1-f) + f)s}$$

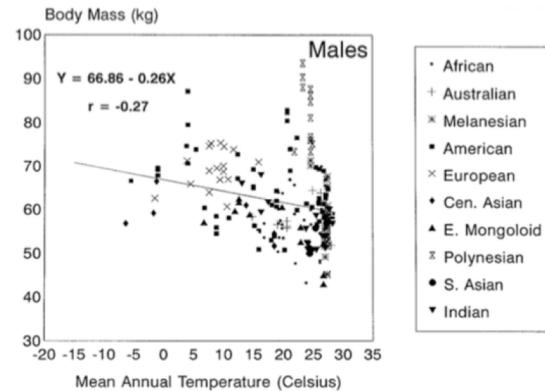
Data from various *Schiedea* species with different extent of inbreeding. From Charlesworth & Willis (2009) *Nat Rev Gen* (redrawn from Weller et al. 2005 *J Evol Bio*)



Spatially varying selection
and
migration-selection balance

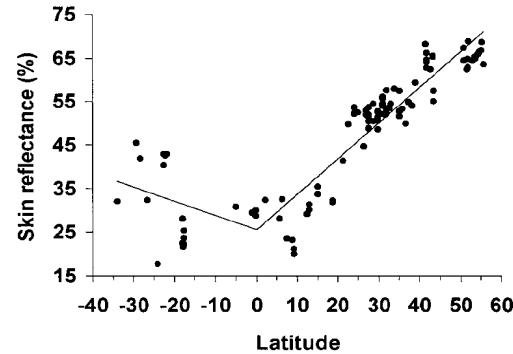
Clinal variation: local adaptation on broad scales

Human body mass and mean annual temperature



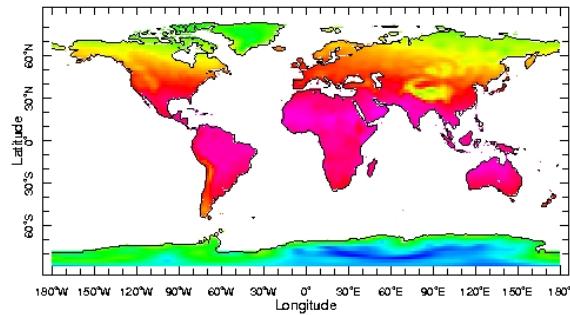
Katzmarzyk & Leonard (1998) *Am J Phys Anthropol*
previous study: Roberts (1953)

Skin reflectance and latitude

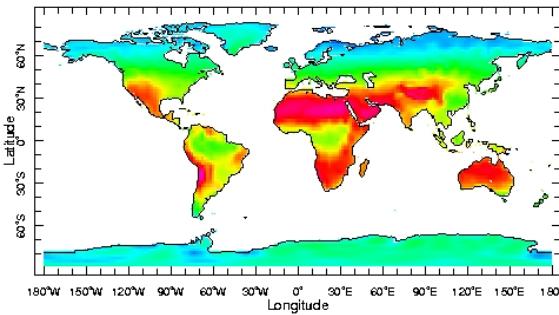


Relethford (1997) *Am J Phys Anthropol*

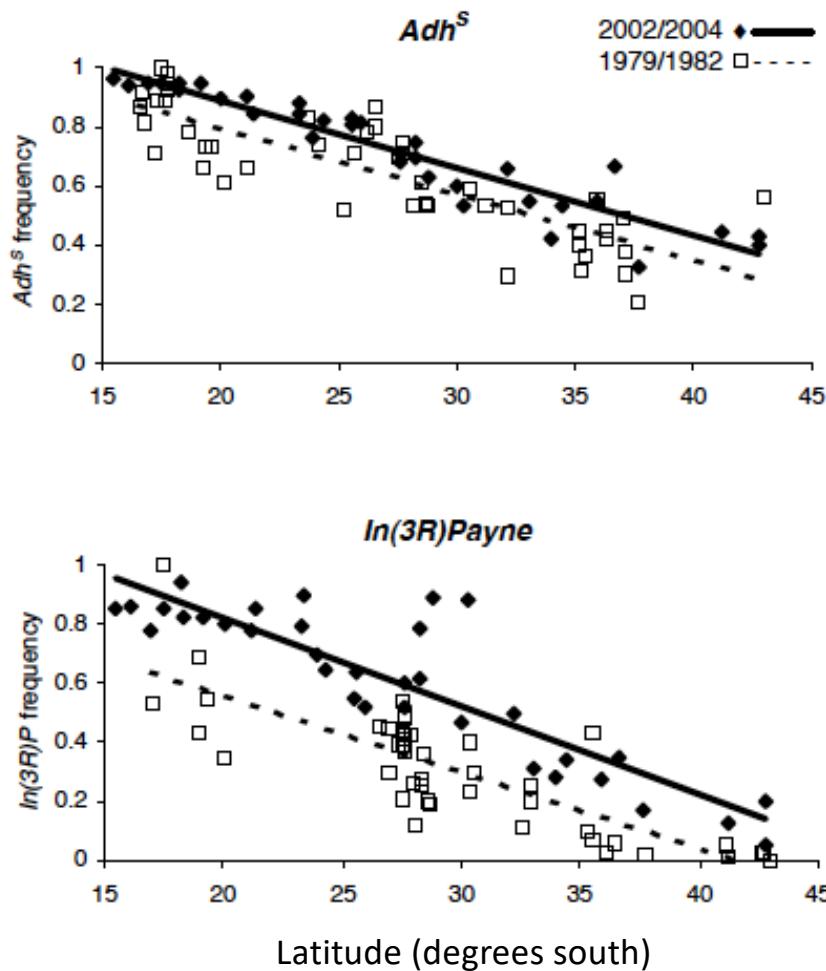
Mean temperature



Short-wave radiation



Clines in inversion frequencies in *Drosophila*



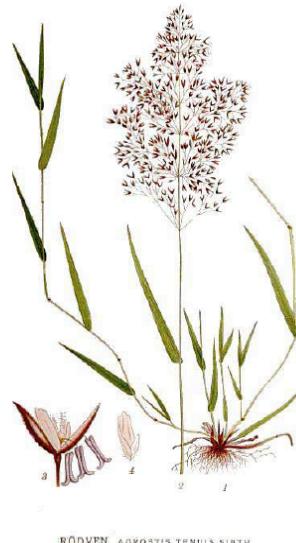
A Rapid Shift in a Classic Cline Pattern in *Drosophila* Reflecting Climate Change

P. A. Umina,¹ A. R. Weeks,² M. R. Kearney,²
S. W. McKechnie,¹ A. A. Hoffmann^{2*}

Geographical clines in genetic polymorphisms are widely used as evidence of climatic selection and are expected to shift with climate change. We show that the classic latitudinal cline in the alcohol dehydrogenase polymorphism of *Drosophila melanogaster* has shifted over 20 years in eastern coastal Australia. Southern high-latitude populations now have the genetic constitution of more northerly populations, equivalent to a shift of 4° in latitude. A similar shift was detected for a genetically independent inversion polymorphism, whereas two other linked polymorphisms exhibiting weaker clinal patterns have remained relatively stable. These genetic changes are likely to reflect increasingly warmer and drier conditions and may serve as sensitive biomarkers for climate change.

Local adaptation can occur on very short geographic scales

- Mine tailing piles contain high concentrations of zinc, copper, lead, &/or arsenic that are toxic to intolerant plant genotypes.
- Old tailings in Great Britain are sparsely populated with two grass species:
 - *Agrostis tenuis*
 - *Anthoxanthum odoratum*.



RÖDVEN, AGROSTIS TENUIS SPP.

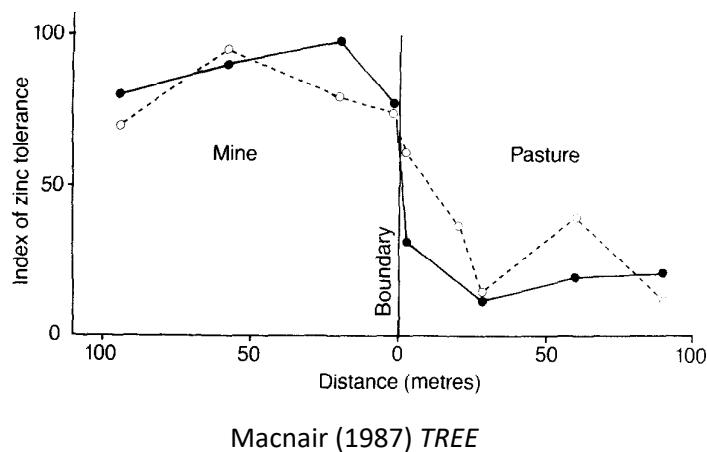
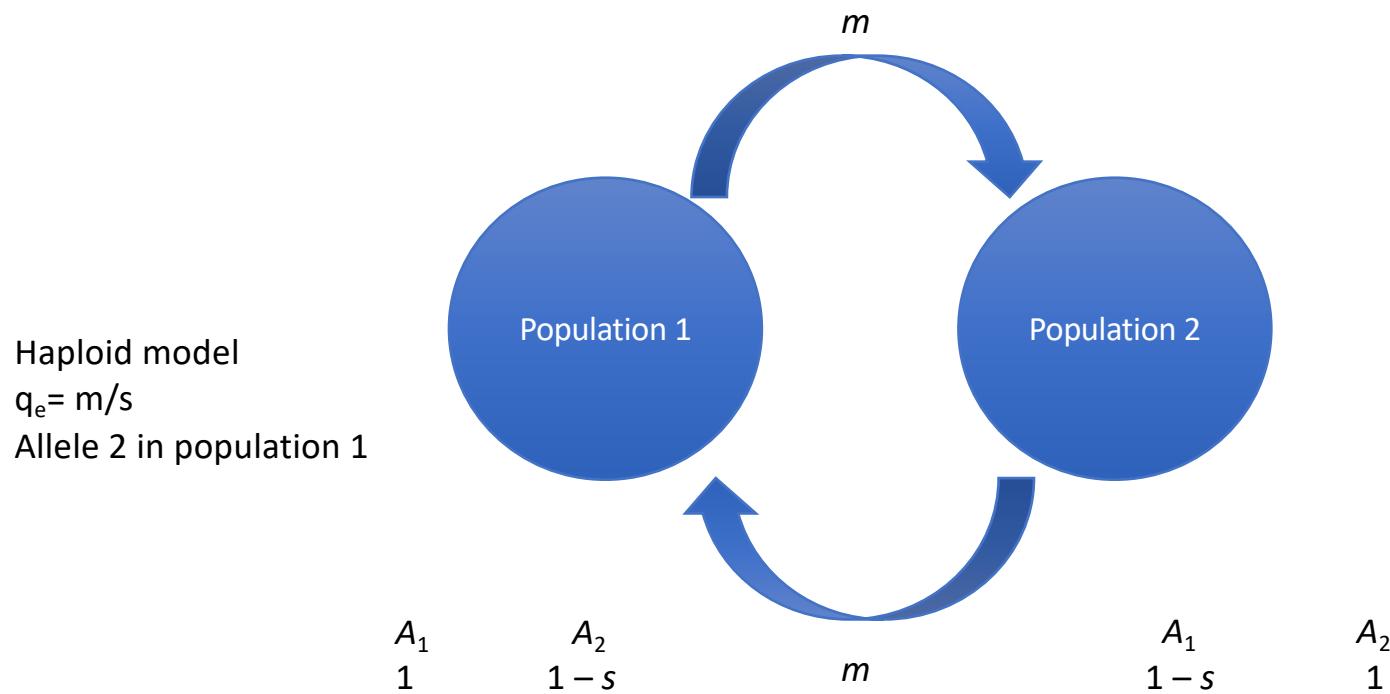


Fig. 2. The zinc tolerance of populations of *Anthoxanthum odoratum* (closed circles) and *Agrostis capillaris* (open circles) at the mine boundary at Trelogan, North Wales. All *A. capillaris* values have been multiplied by three. Redrawn after Ref. 10.

Modelling migration–selection balance

A simple haploid model



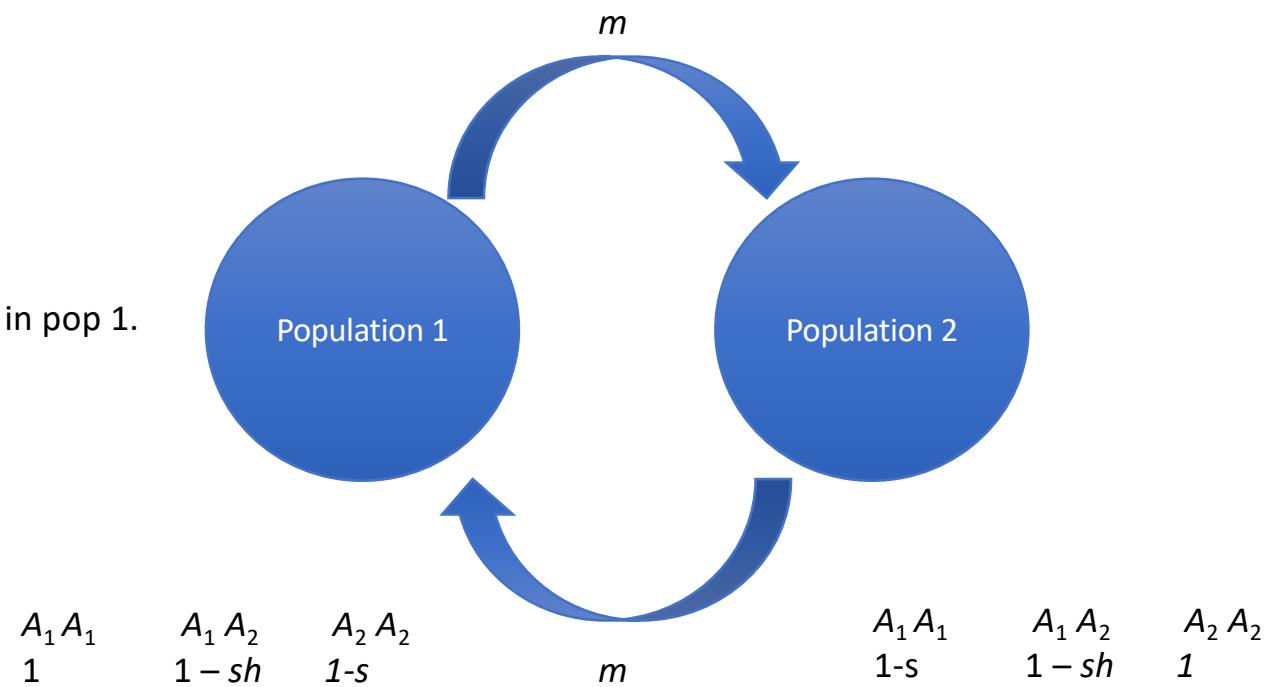
Modelling migration–selection balance

A simple diploid model

Diploid model

$$q_e = m/(sh)$$

Frequency of allele 2 in pop 1.



Example: Colour polymorphism in rock pocket mice (*Chaetodipus intermedius*) on and off black volcanic lava flows in southern Arizona (Hoekstra *et al.* 2004, *Evolution*)

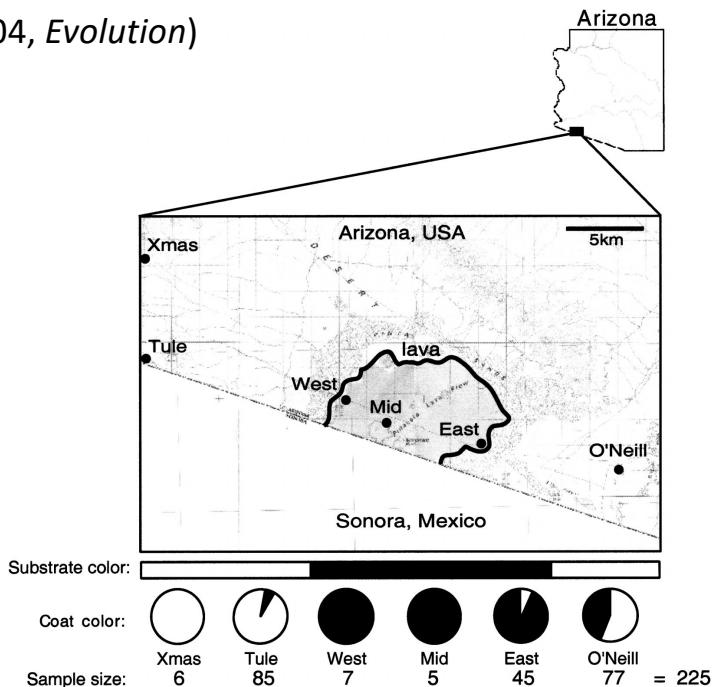
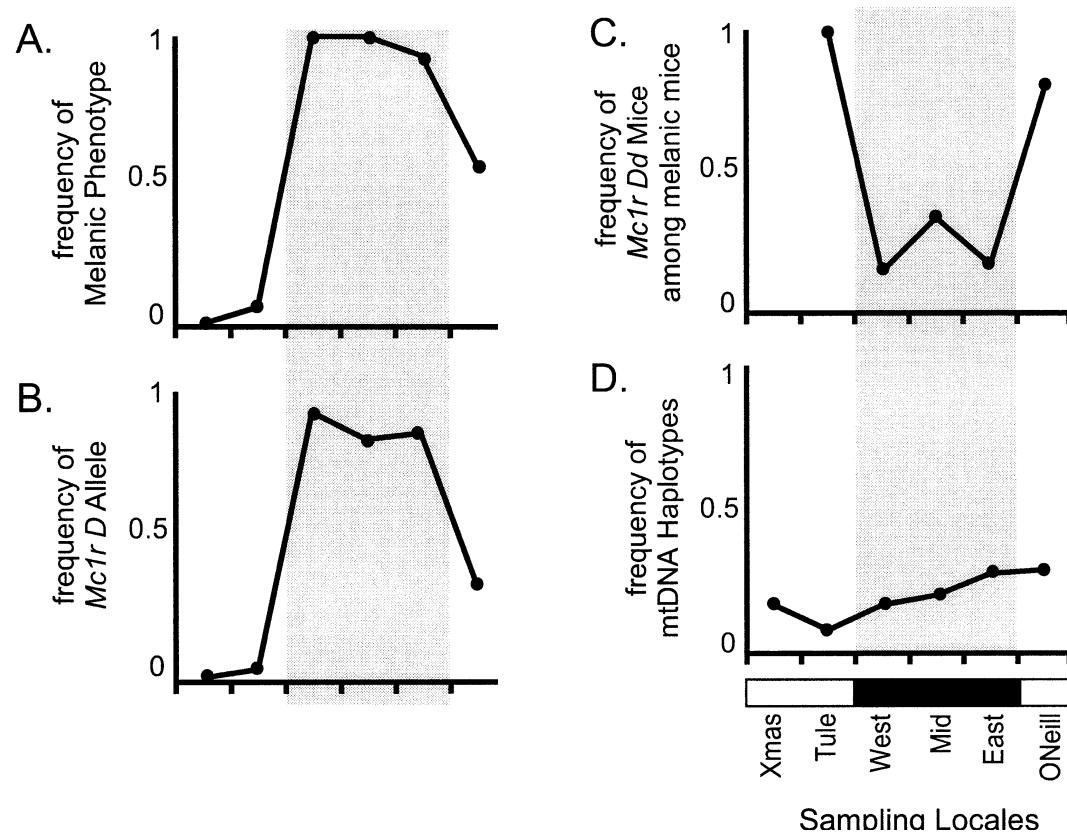


FIG. 1. Collecting sites, substrate color, and coat color frequencies on and neighboring the Pinacate lava flow in south central Arizona. Six sites were sampled: three on dark volcanic rock and three on light-colored substrate. The lava flow is surrounded by approximately 1 km of the Pinta Sands. Substrate color is indicated schematically below. Pie diagrams refer to the frequencies of light and melanic mice at each collecting site. Sample sizes are given.

Here, dark colour is due to a change at the melanocortin-1 receptor (*Mc1r*) gene, and the agent of selection is most likely predation. The dark mutation is dominant.

Hoekstra et al. (2004) *Evolution*



Tule Mountains $q_e = 0.029$