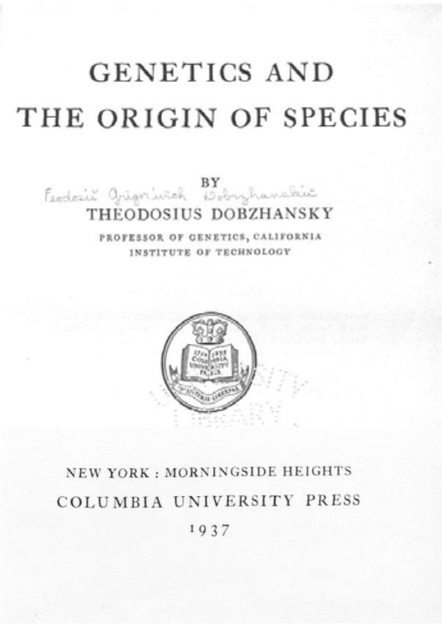
Why is population genetics important?

Dobzhansky (1964)

Nothing in biology makes sense except in the light of evolution.



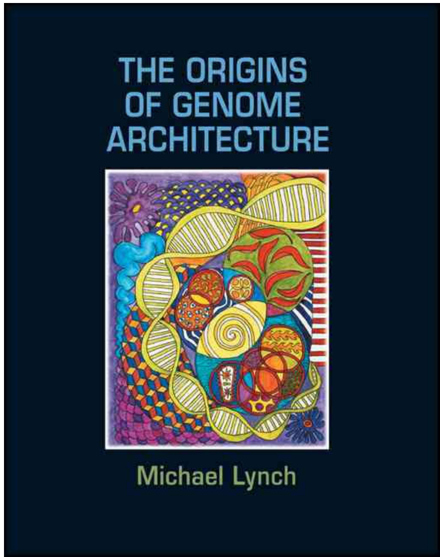
GENETICS AND
THE ORIGIN OF SPECIES

BY
THEODOSIUS DOBZHANSKY
PROFESSOR OF GENETICS, CALIFORNIA INSTITUTE OF TECHNOLOGY

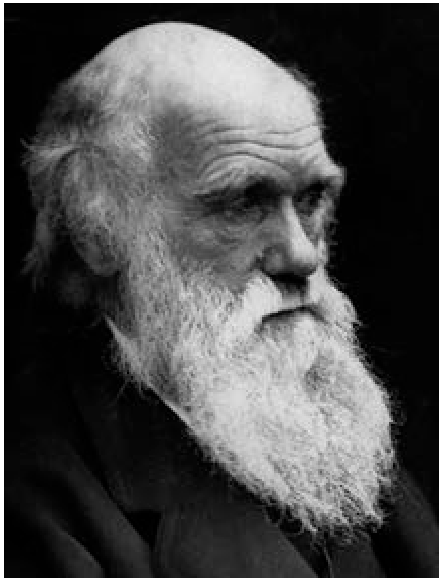
NEW YORK : MORNINGSIDE HEIGHTS
COLUMBIA UNIVERSITY PRESS
1937

Lynch (2007)

Nothing in evolution makes sense except in light of population genetics.



History of population genetics



Darwin Born 1809

Origin of Species 1859

After Darwin

Mendel1866

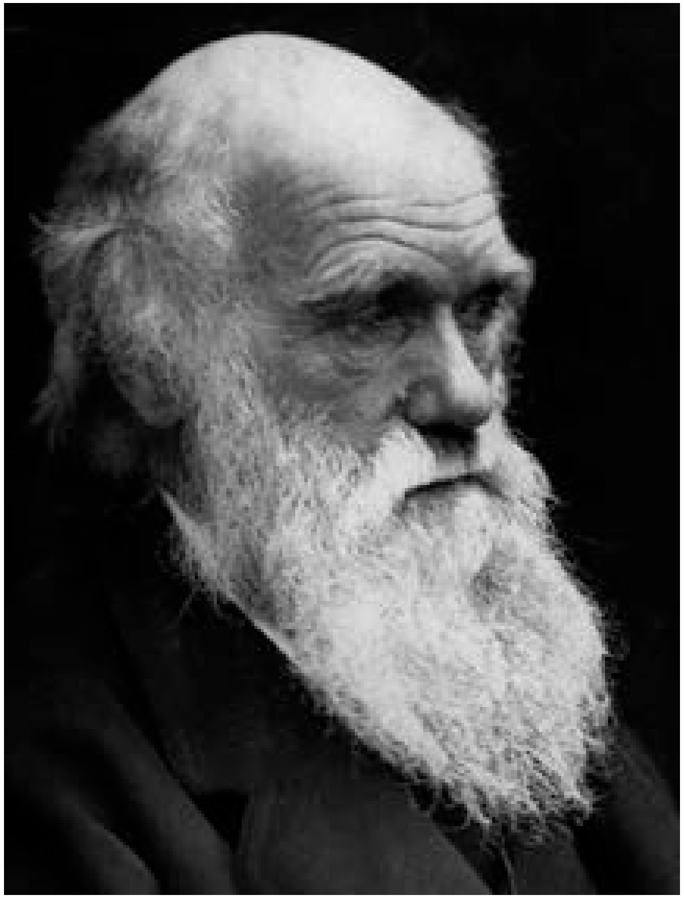
Rediscovery of Mendel’s work 1900

Battle among Mendelians and Biometricians

The evolutionary synthesis

1000 genomes project

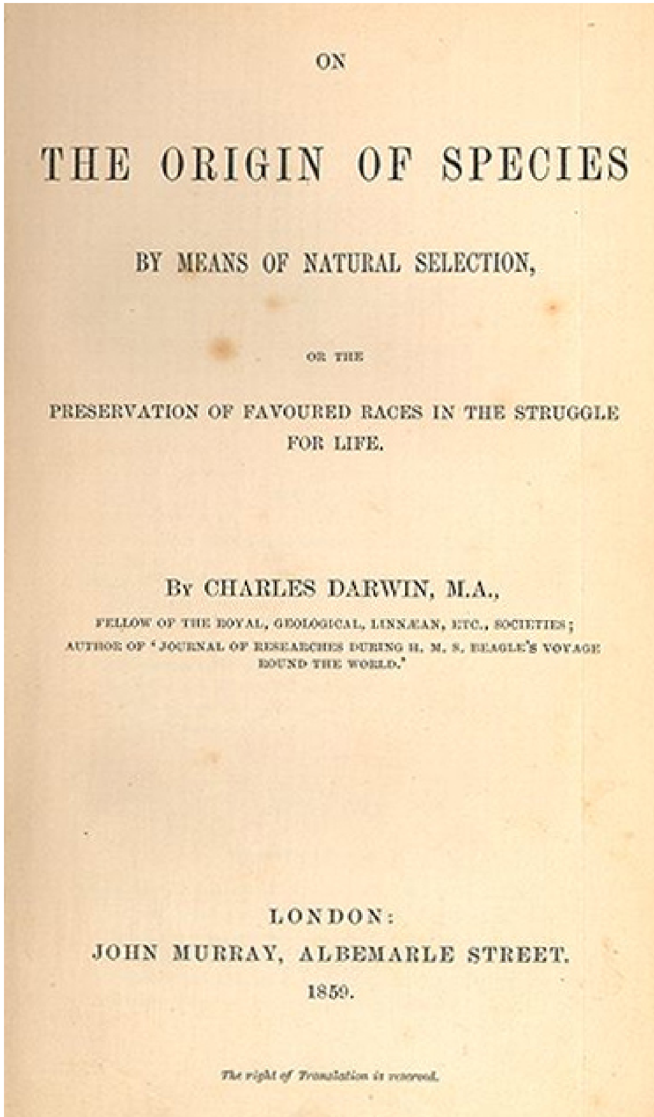
Darwin



Charles Robert Darwin
(1809–1882)

Studies medicine
Interest in natural history
Does never get a degree
nor a permanent job…
Don’t do that, unless you
marry a rich woman…

Darwin


ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

BY CHARLES DARWIN, M.A.,

FELLOW OF THE ROYAL, GEOLOGICAL, LINNÆAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

The right of Translation is reserved.

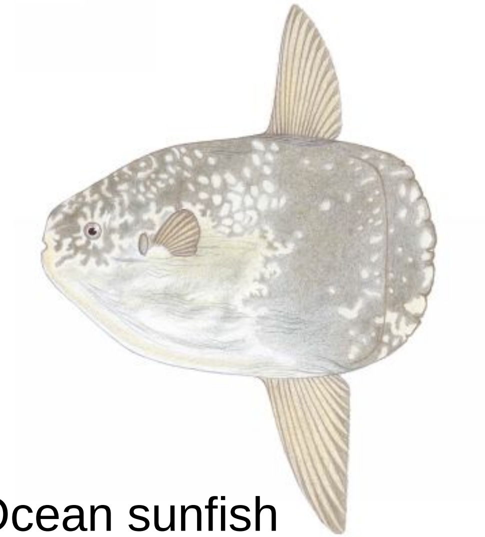
1859

Two conclusions
1) Common descent
2) Natural selection

But:

Very little about speciation
Nothing about the origin of life

Natural selection



Ocean sunfish
Females can produce as many as 300 million eggs at a time

Tendency for geometric growth

Variation

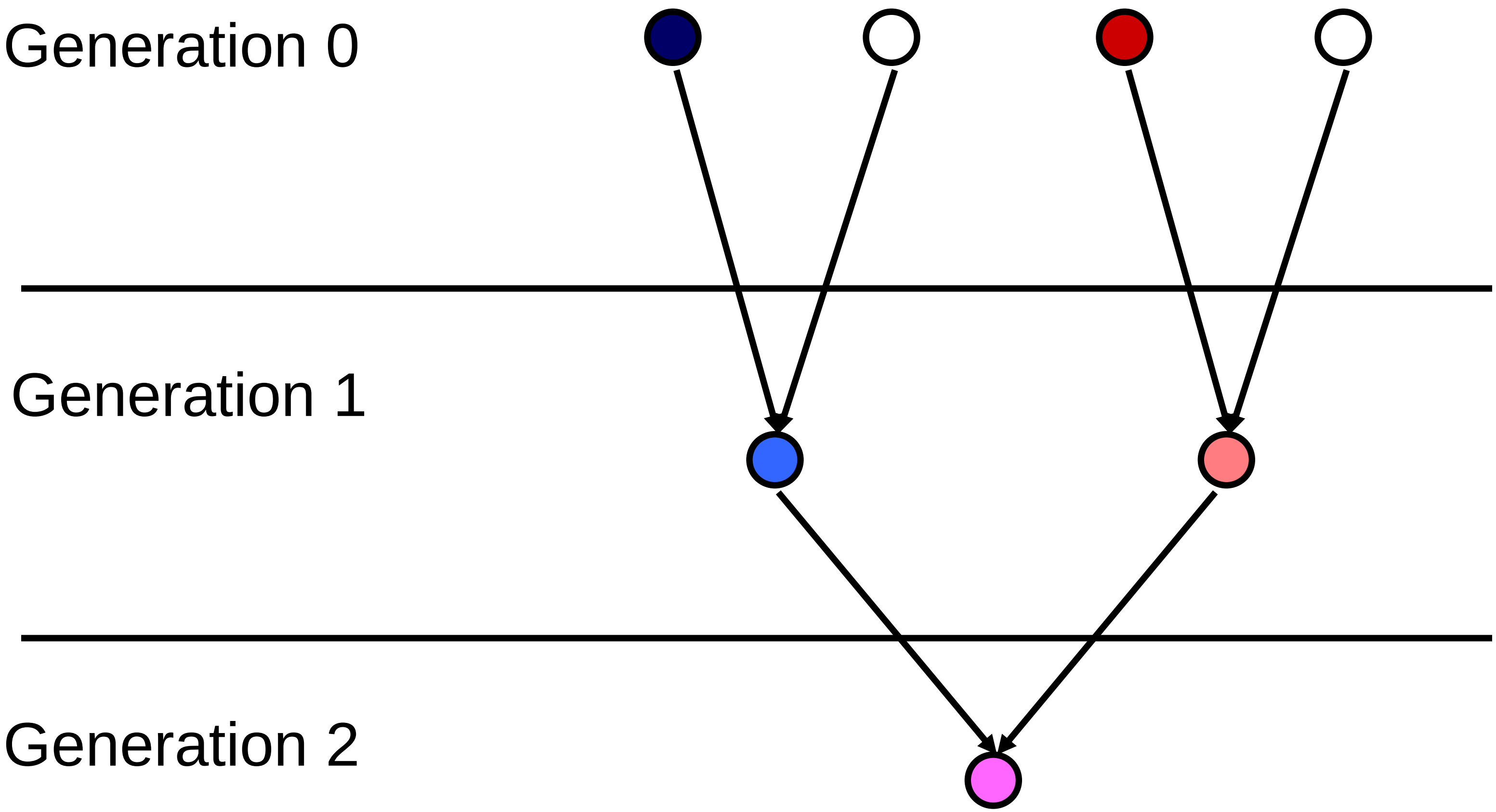
(“variation” or “sports”)

Most important: survival and reproduction

Inheritance

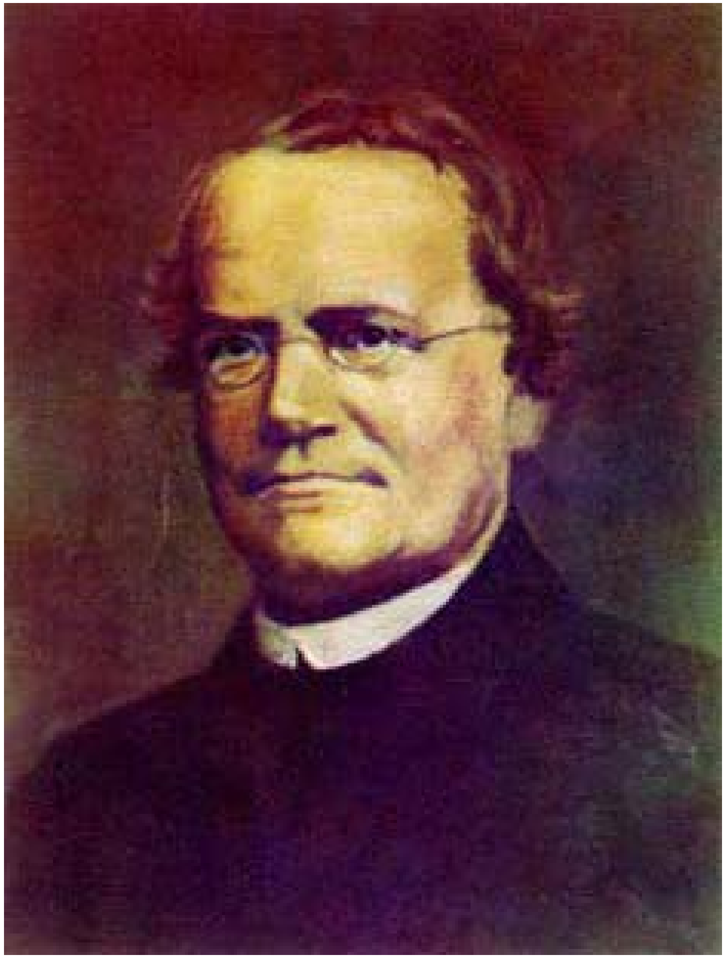
A small problem for Darwin

Blending inheritance

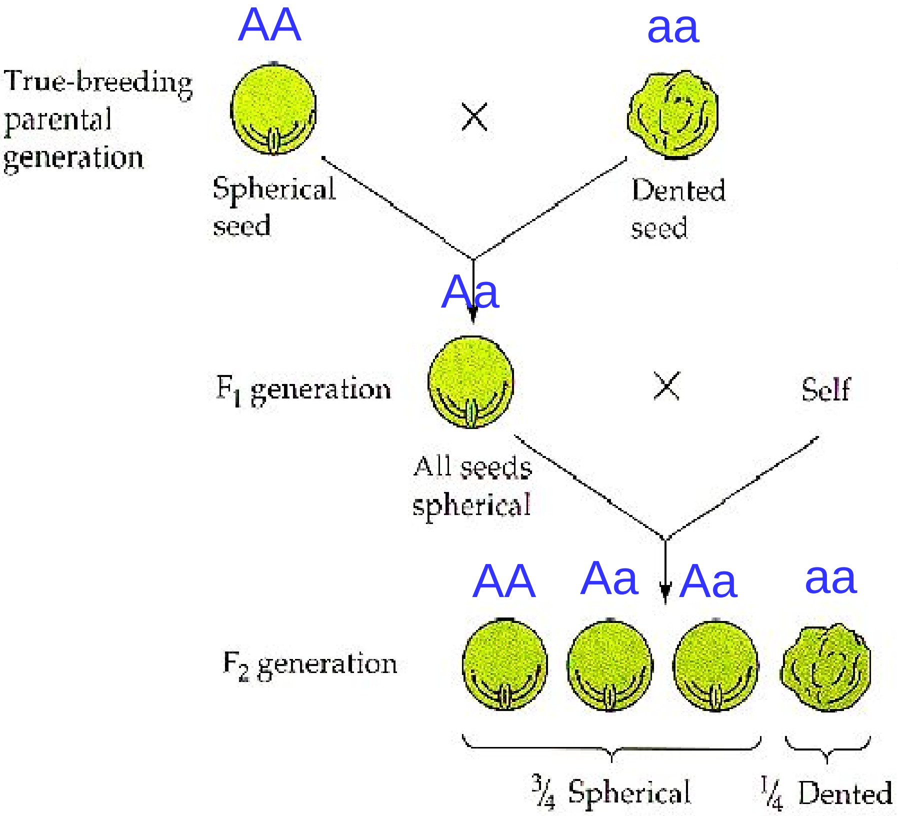


Mendel

Introduces his laws in 1866



Gregor Mendel
1822-1884



The work remains unknown in his time.

Mendel's laws are rediscovered in 1900

Hugo De Vries

Carl Correns

Erich von Tschermak

Mendel’s laws are rediscovered in 1900

de Fries (1900)

If one calls D the grains of pollen or the ovules having a dominant character and R those which have the recessive character, one can represent the number and the nature of the hybrids by the following representative formula in which the numbers of D and R are equal:

$$(D+R)(D+R) = \boxed{D^2 + 2DR + R^2}$$

This repeats the statement that there will be 25 per 100 of D, 50 per 100 of DR and 25 per 100 of R.

Note how close this is to the Hardy-Weinberg principle!

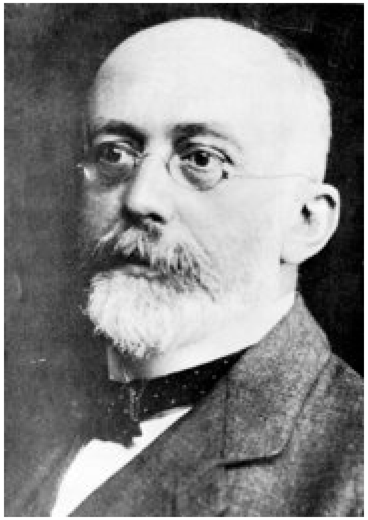
The Hardy-Weinberg principle

Derived independently in 1908 by

Hardy (British mathematician)

Weinberg (German physician)

Consider an autosomal locus with two alleles

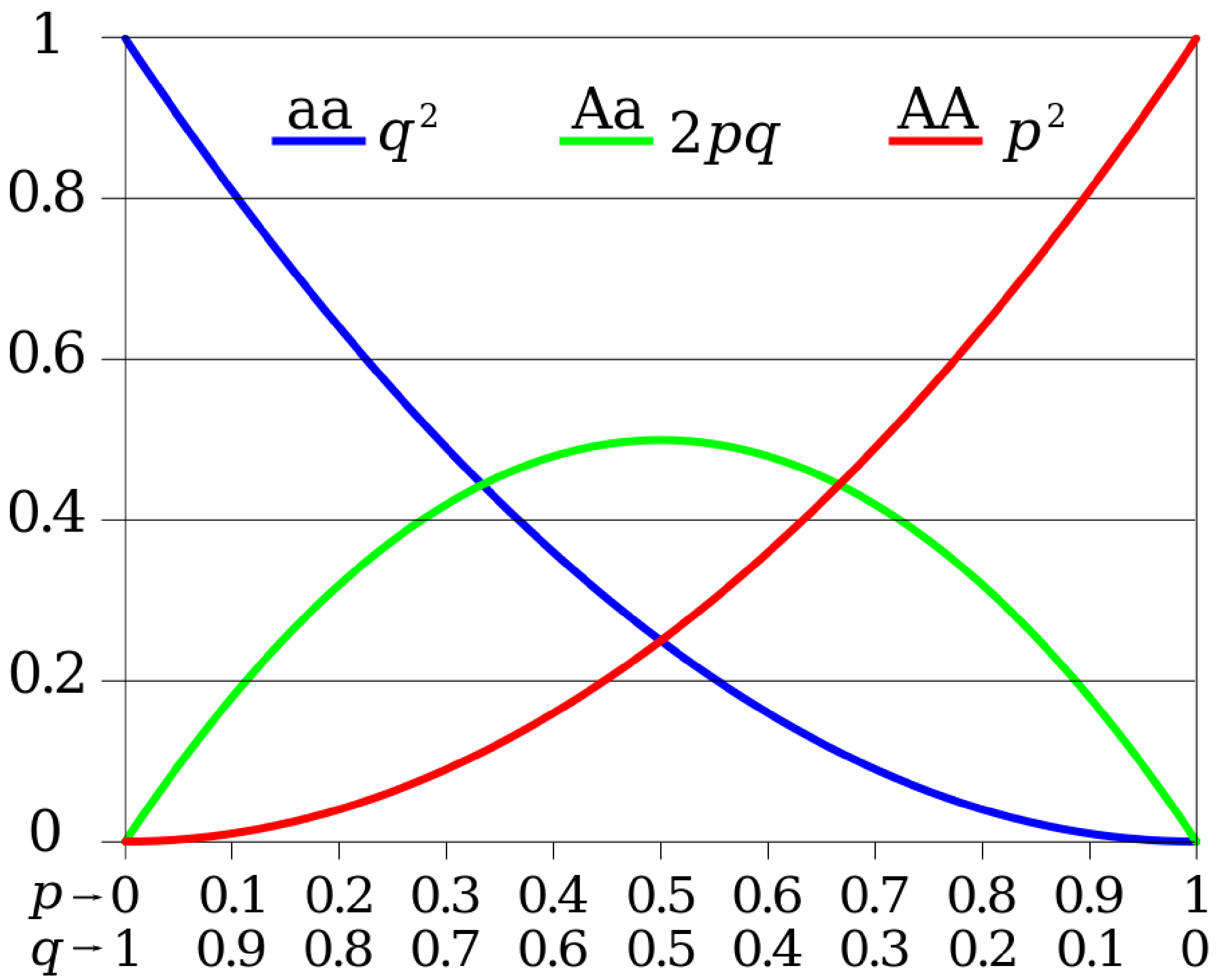


A has frequency p

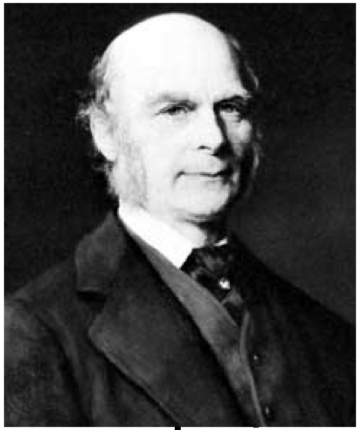
a has frequency q

$$p + q = 1$$

The Hardy-Weinberg principle



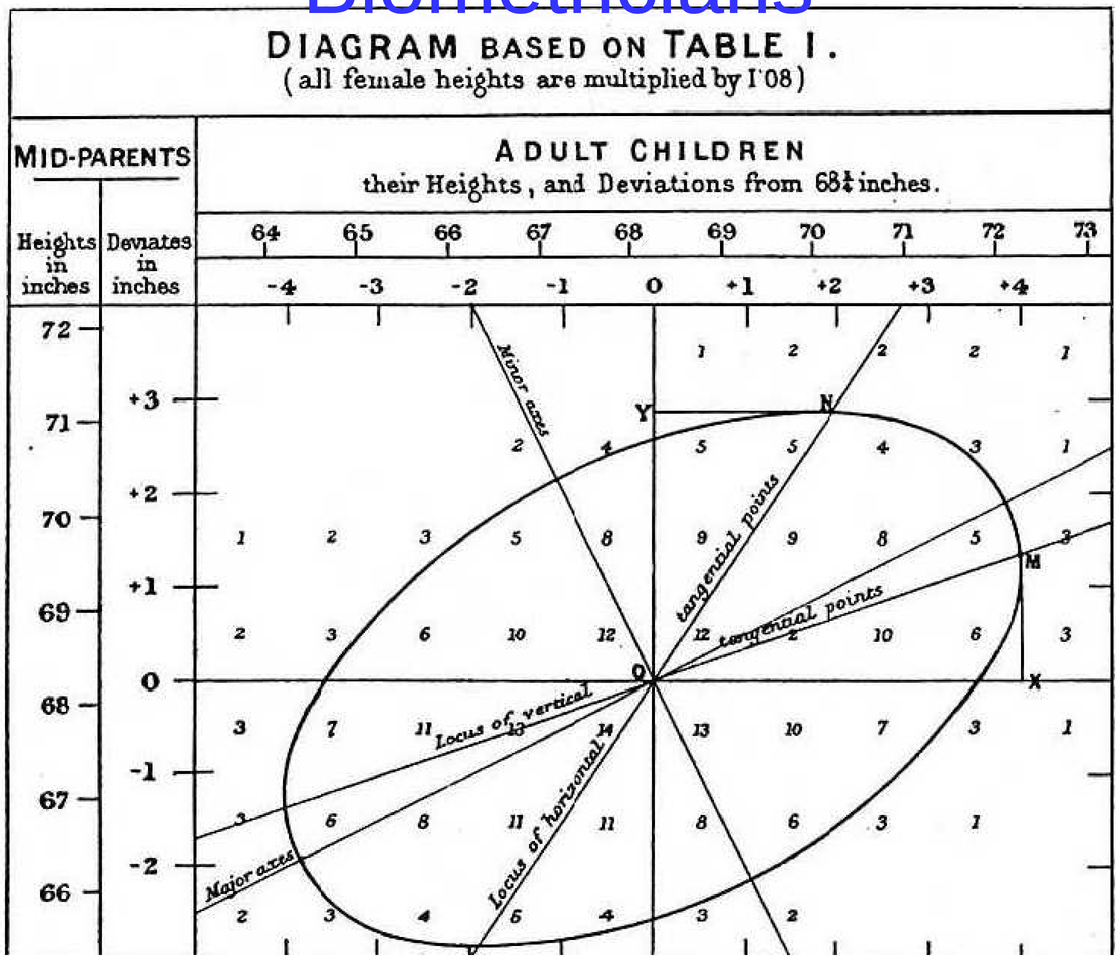
Battle between Mendelians and Biometricians



Biometricians

- Francis Galton (1822–1911)
  - Darwin's half-cousin
  - *Hereditary Genius* (1869),
  - Introduces regression and correlation analysis
- Karl Pearson (1857–1936)
  - Establishes mathematical statistics
  - Studies effect of natural selection
  - on quantitative characters

Battle between Mendelians and Biometricians



Galton studies quantitative characters, like height in humans

Battle between Mendelians and Biometricians

Lasts until 1918

Biometricians focus on ***small*** changes over many generations (like Darwin)

Mendelians consider genes with ***large*** effects on phenotype. Evolution proceeds in large jumps.

Fisher (1918)

The Correlation between Relatives on the Supposition of Mendelian Inheritance. By **R. A. Fisher,** B.A.

Shows that characters with continuous distribution are inherited through variation in Mendelian genes with small effects.

Integrates Darwin's theory with Mendelian genetics.

(and introduces the term "variance")

Ronald A. Fisher

1890–1962

English statistician, population geneticist and evolutionary biologist

Known for/introduces

Maximum likelihood

Analysis of variance

Fundamental theorem of natural selection

Fisher’s principle (1:1 sex ratio)

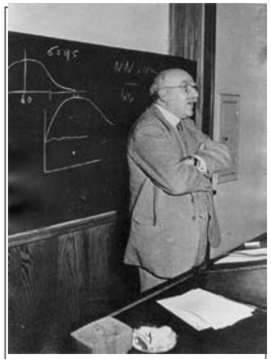
Founders of population genetics

Fisher (1890–1962)

1930: *The Genetical Theory of Natural Selection*

Sewall Wright (1889–1988)

1931 *Evolution in Mendelian Populations*



Haldane (1892–1964)

1932 *The Causes of Evolution*

Founders of population genetics

Around 1930, R was not available to make nice figures

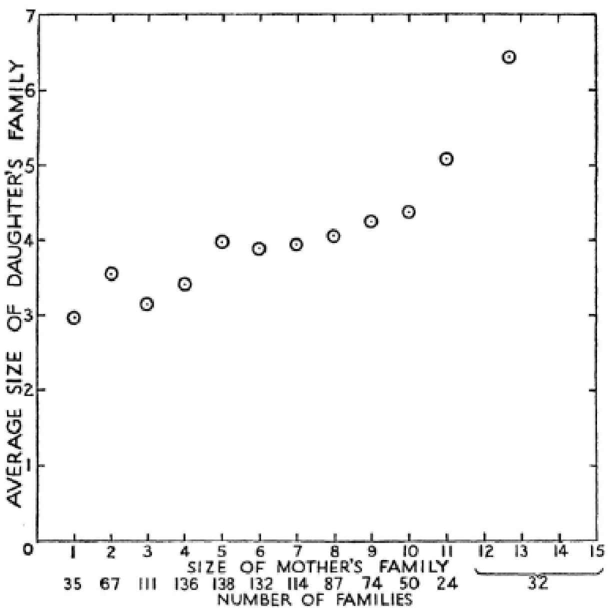


FIG. 10. Average number of children born to peeresses, according to the size of the families of their mother.

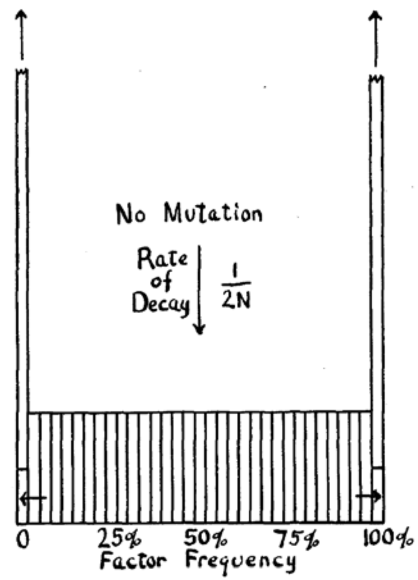


FIGURE 3.—Distribution of gene frequencies in an isolated population in which fixation and ss of genes each is proceeding at the rate 1/4N in the absence of appreciable selection or muta- n. $y = L_0 e^{-T/2N}$.

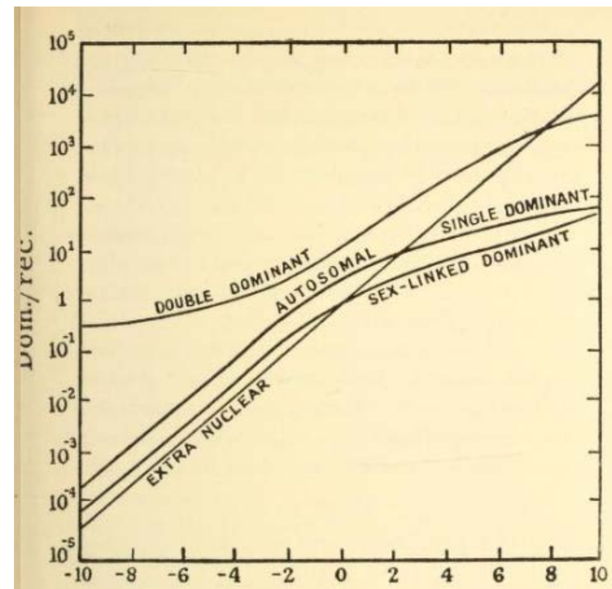


FIG. 8.—Theoretical results of selection on the composition of a population when dominants are favoured. Abscissa,

Fisher Wright Haldane

Some differences in opinion

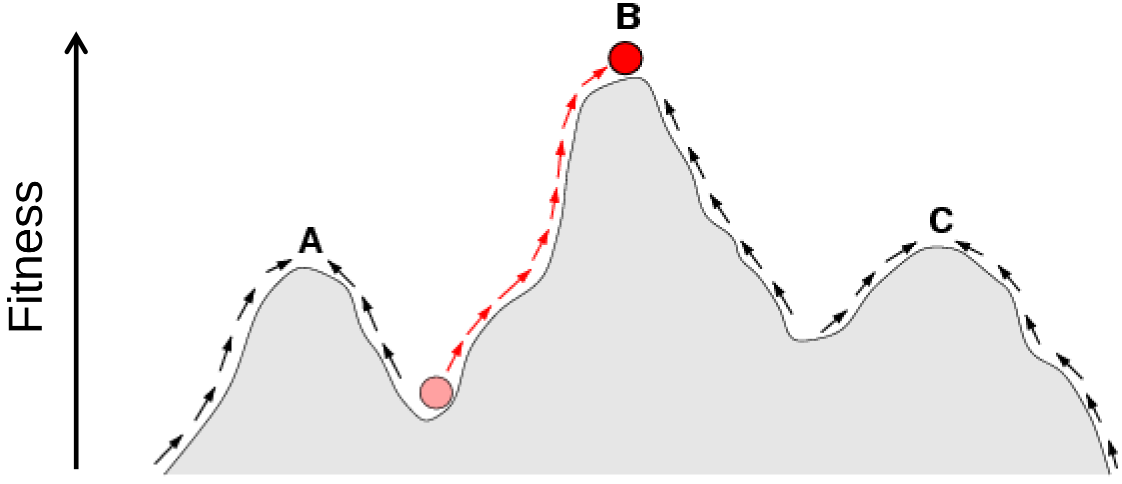
Fisher

Focus on natural selection in large populations.

1930: Fundamental theorem of natural selection

Sewall Wright

Introduces "Shifting balance theory"



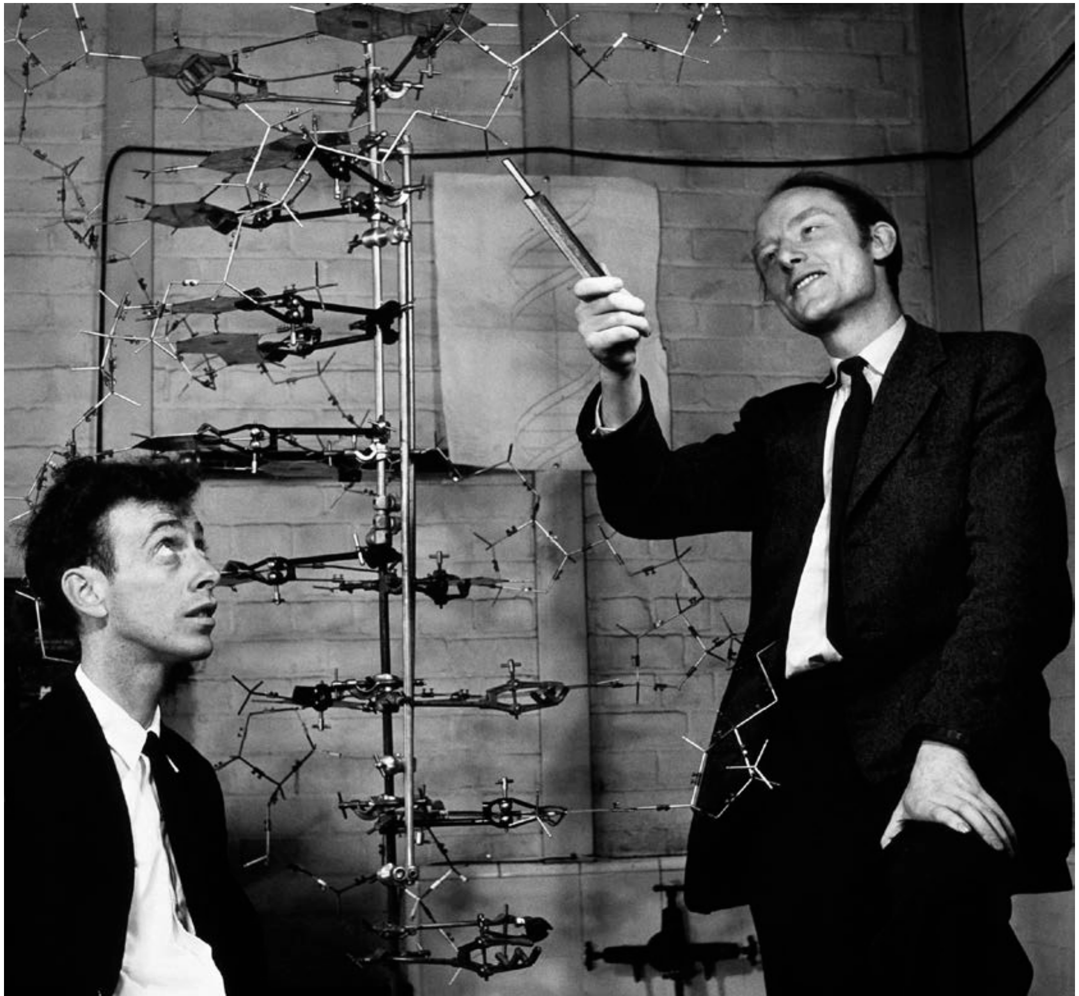
The evolutionary synthesis (1930–1940s)

Integates

- Theory
  - Fisher (1890-1962)
  - Haldane (1892-1964)
  - Wright (1889-1988)
- Genetics
  - Dobzhansky (1900-1975)
- Systematics
  - Mayr (1904-2005)
  - Stebbins (1906-2000)
- Paleontology
  - Simpson (1902-1984)

Evolutionary milestones

1953 DNA-structure, Watson & Crick



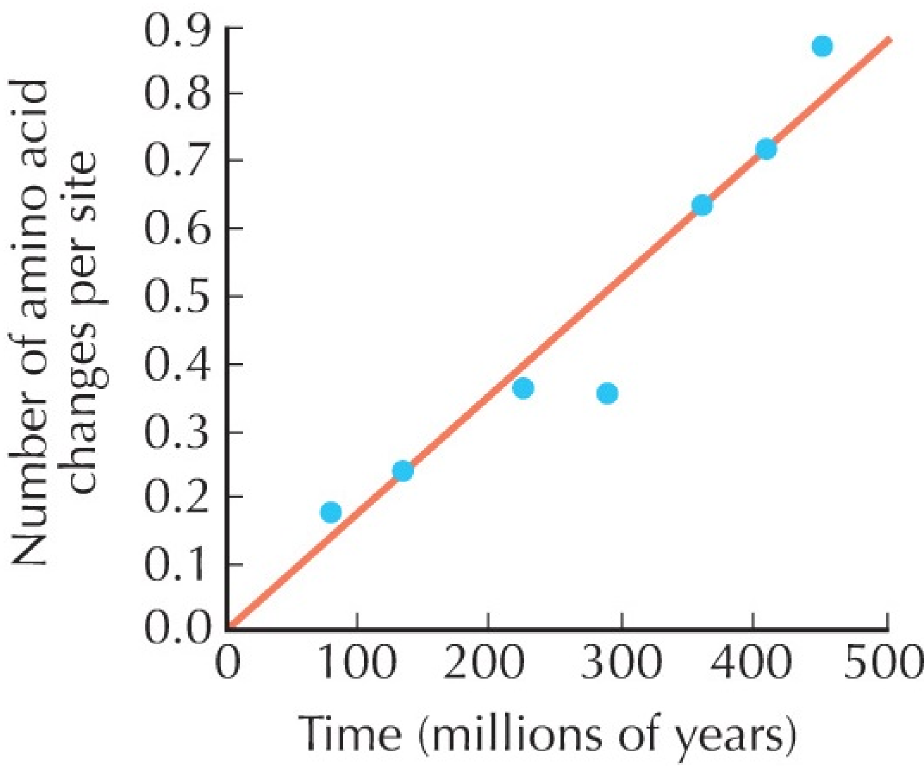
Evolutionary milestones

1962 Comparison of protein sequences in different species, molecular clock, Zuckerkandl & Pauling

α-hemoglobine in vertebrates

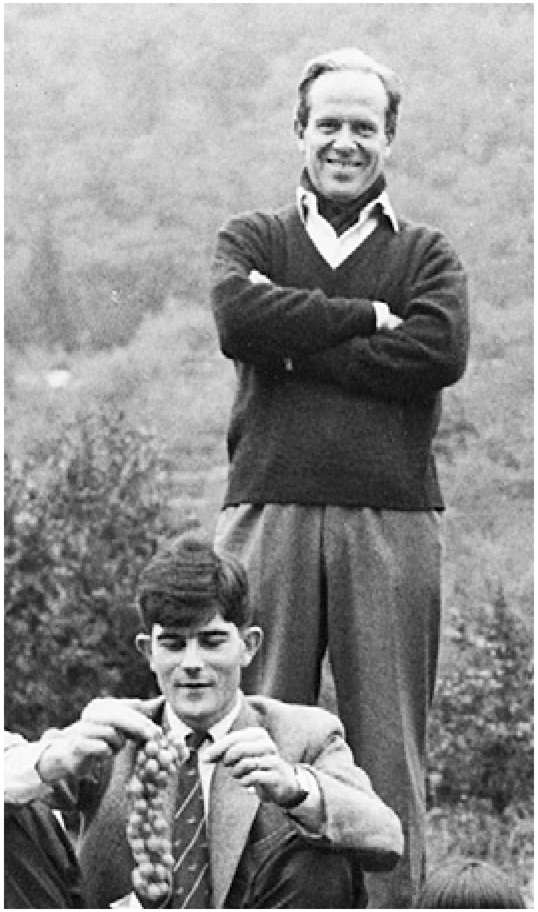
Calibrated from fossils

The clock ticks at a constant rate



Evolutionary milestones

1963/1964 Cavalli-Sforza & Edwards introduce maximum likelihood in phylogenetics



Luca Cavalli-Sforza
(Born 1922)

Founders of numerical phylogenetics

Anthony Edwards
(Born 1935)

Evolutionary milestones

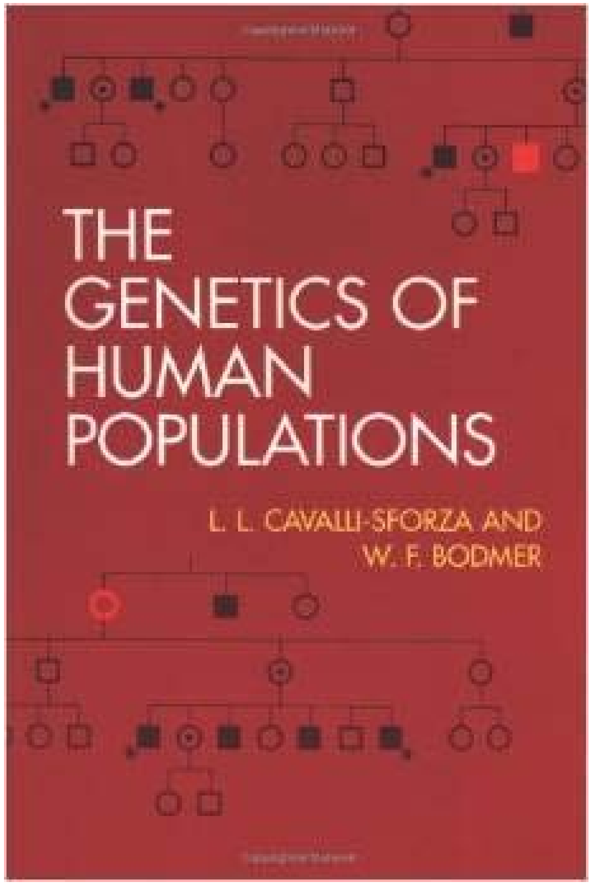
1971 Cavalli-Sforza & Bodmer

(1922 –) (1936 –)

The Genetics of Human Populations

Classical presentations of human population genetics before the genomics era

Walter Bodmer
(Born in Frankfurt)
Worked with Fisher in Cambridge
Currently leading the project
People of the British Isles
(4.500 samples typed for 600.000 SNPs)



Evolutionary milestones

Before the molecular era (< 1966):

- How variable is the genome?
- How can it be explained?
- What's your opininion about the variability?

Classical theory

- Very little variation
- Mutation-selection balance

Balance theory

- A lot of variation
- Overdominant selection

Evolutionary milestones

$A_1\ B_1\ C_1\ D_1\ E_{\boxed{2}}\ F_1\ G_1\ H_1\ I_1\ J_1\ K_1\ L_1\ M_1\ N_1\ O_1$

Classical theory

$A_1\ B_1\ C_1\ D_1\ E_1\ F_1\ G_1\ H_1\ I_1\ J_1\ K_1\ L_1\ M_1\ N_1\ O_1$

$A_1\ B_2\ C_5\ D_4\ E_2\ F_5\ G_2\ H_1\ I_2\ J_7\ K_3\ L_4\ M_5\ N_2\ O_6$

Balance theory

$A_3\ B_2\ C_3\ D_1\ E_6\ F_5\ G_1\ H_1\ I_5\ J_6\ K_1\ L_5\ M_2\ N_1\ O_7$

Please note: the genome is depicted as a string of genes

Evolutionary milestones

H.J. Muller
1890-1967
Noble prize
1946

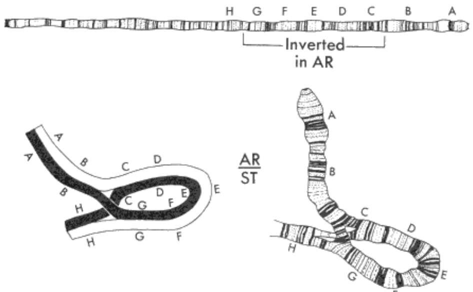
Background

Classical theory

Muller studies radiation-induced mutations in *Drosophila*

Balance theory

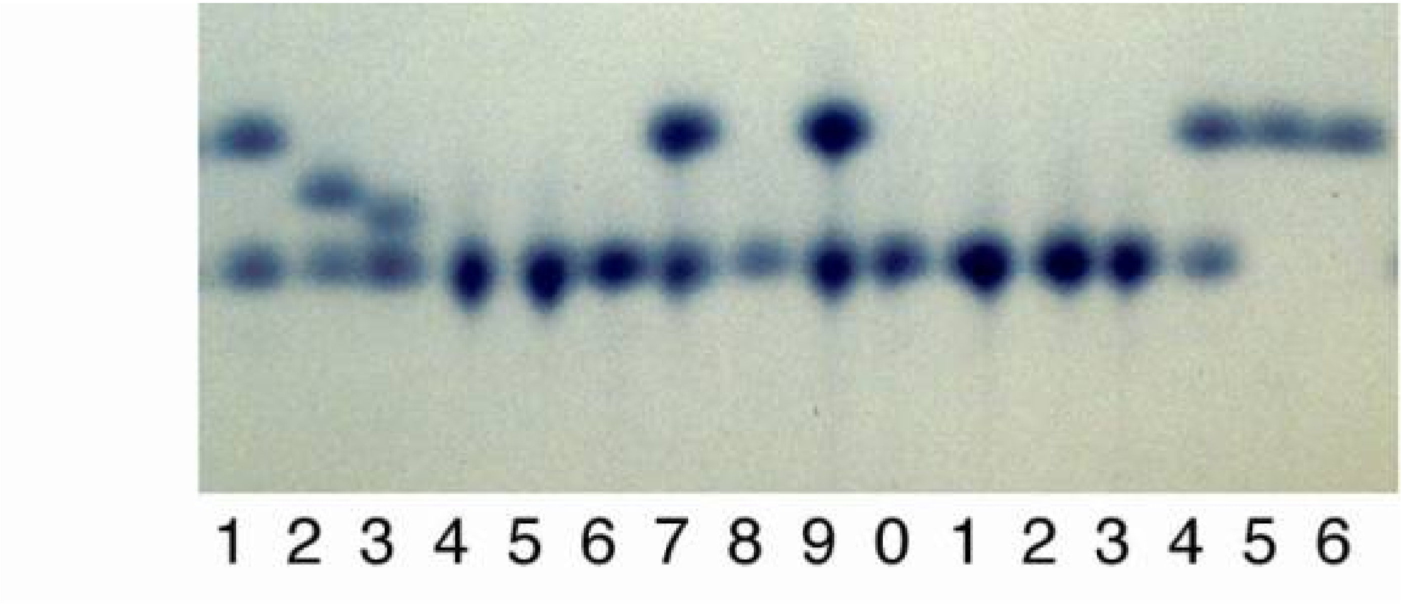
Dobzhansky studies chrosomal inversions in *Drosophila*



T. Dobzhansky
1900-1975

Evolutionary milestones

1966 enzyme electrophoresis



Lewontin & Hubby and Harris find substantial variation based on enzyme electrophoresis

Evolutionary milestones

$A_1\ B_1\ C_1\ D_1\ E_2\ F_1\ G_1\ H_1\ I_1\ J_1\ K_1\ L_1\ M_1\ N_1\ O_1$

Classical theory

$A_1\ B_1\ C_1\ D_1\ E_1\ F_1\ G_1\ H_1\ I_1\ J_1\ K_1\ L_1\ M_1\ N_1\ O_1$

Selectionists view:
Heterozygotes have a higher fitness than homozygotes

Neutral theory (Neoclassical theory)
No difference in fitness
Balance between genetic drift and neutral mutation

$A_1\ B_2\ C_5\ D_4\ E_2\ F_5\ G_2\ H_1\ I_2\ J_7\ K_3\ L_4\ M_5\ N_2\ O_6$

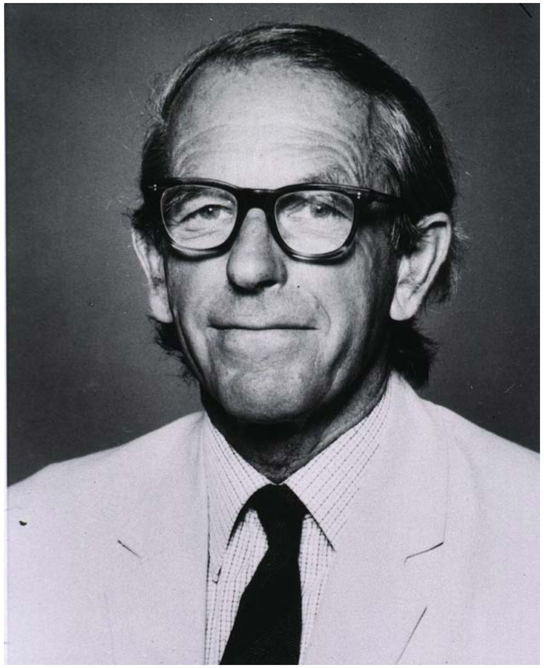
Balance theory

$A_3\ B_2\ C_3\ D_1\ E_6\ F_5\ G_1\ H_1\ I_5\ J_6\ K_1\ L_5\ M_2\ N_1\ O_7$

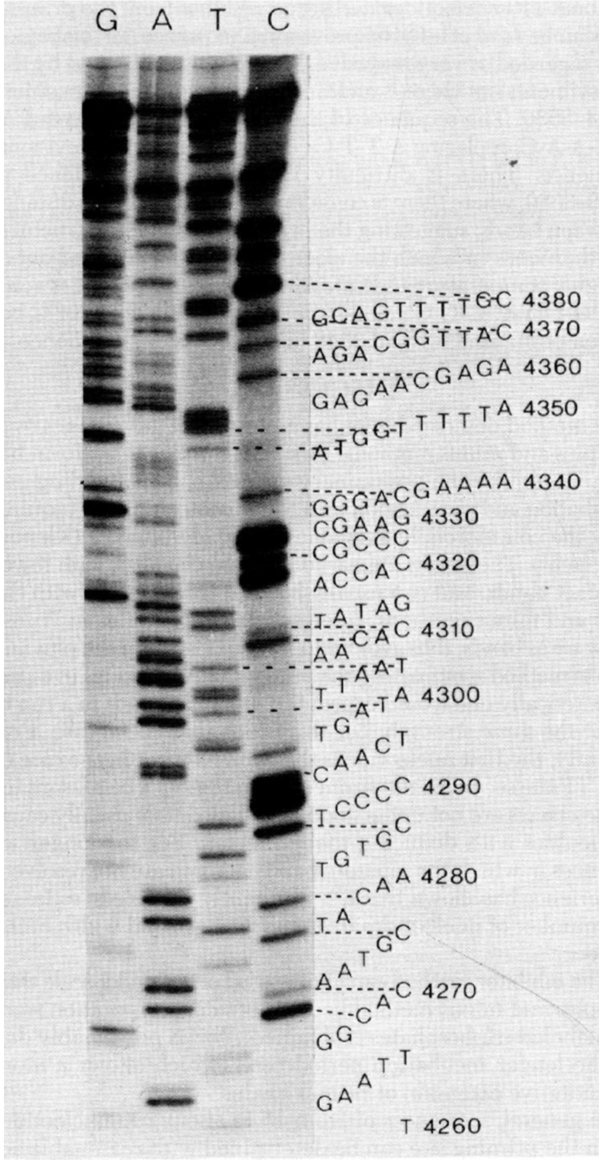
Evolutionary milestones

1977 DNA sequencing

Sanger et al. 1977. PNAS 74: 5463-5467



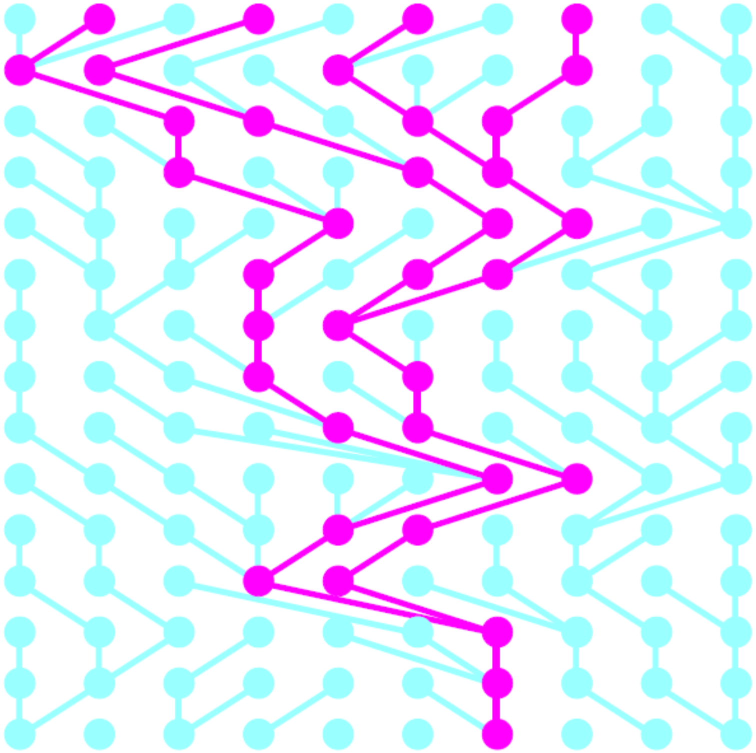
Frederick Sanger
1918-2013
Nobel prize in chemistry
1958 & 1980



Evolutionary milestones

1982 Kingman's coalescence

(born 1939, still publishing)



Evolutionary milestones

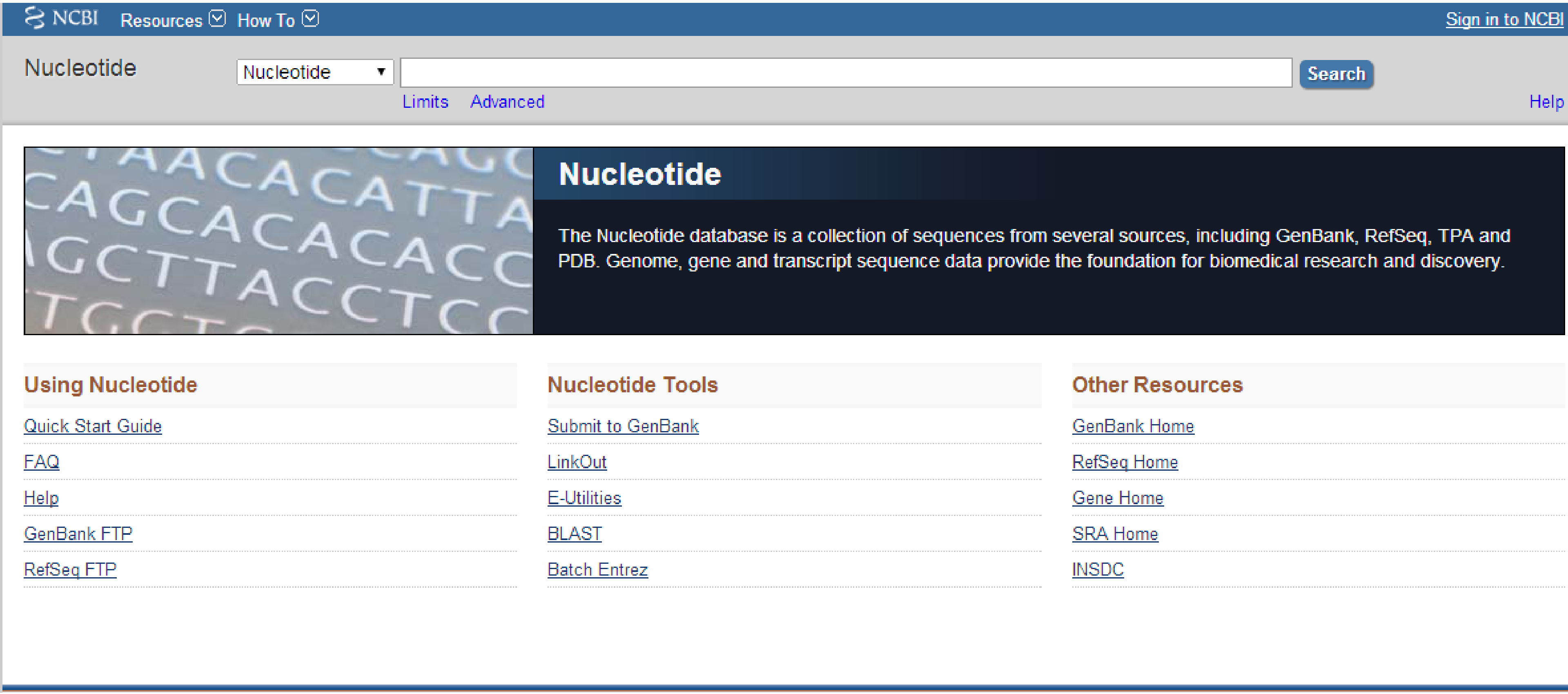
1983 PCR (Polymerase chain reaction)

Kary Mullis (1944 –) Nobel prize 1993

Baby Blue (1986)

Evolutionary milestones

1988 Genbank sequence database



Evolutionary milestones

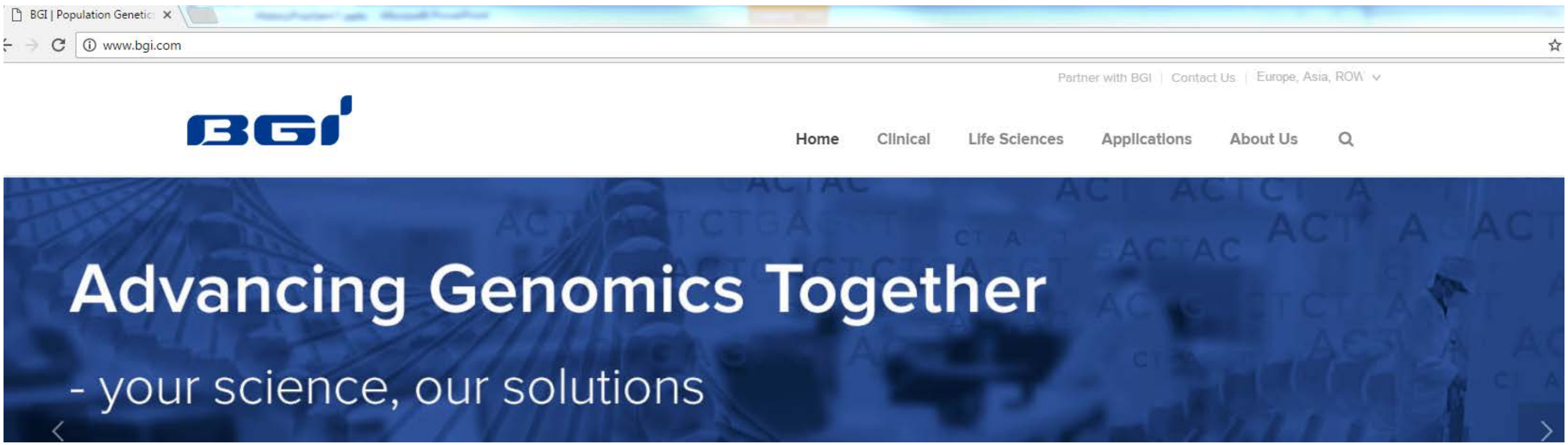
2001 Human genome

Evolutionary milestones

2010 The 1000 Genomes Project Consortium
A map of human genome variation
from population-scale sequencing

Today

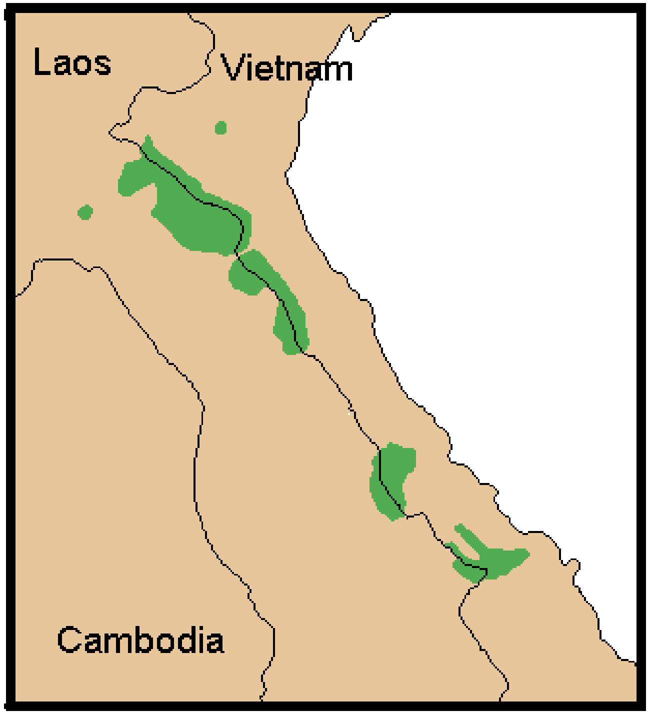
BGI: Beijing Genomics Institute; Founded 1999 now 5,000 employees



Rasmus Heller

Population genomics of the saola

Probably less than ?? surviving in the wild



<u>Data:</u>

Sequencing of 30 individuals

Ida Moltke

Anders Albrechtsen

Data:

Genome sequencing of 800
SNP-chip (10^6 SNPs) of 4000
Imputation of haplotypes

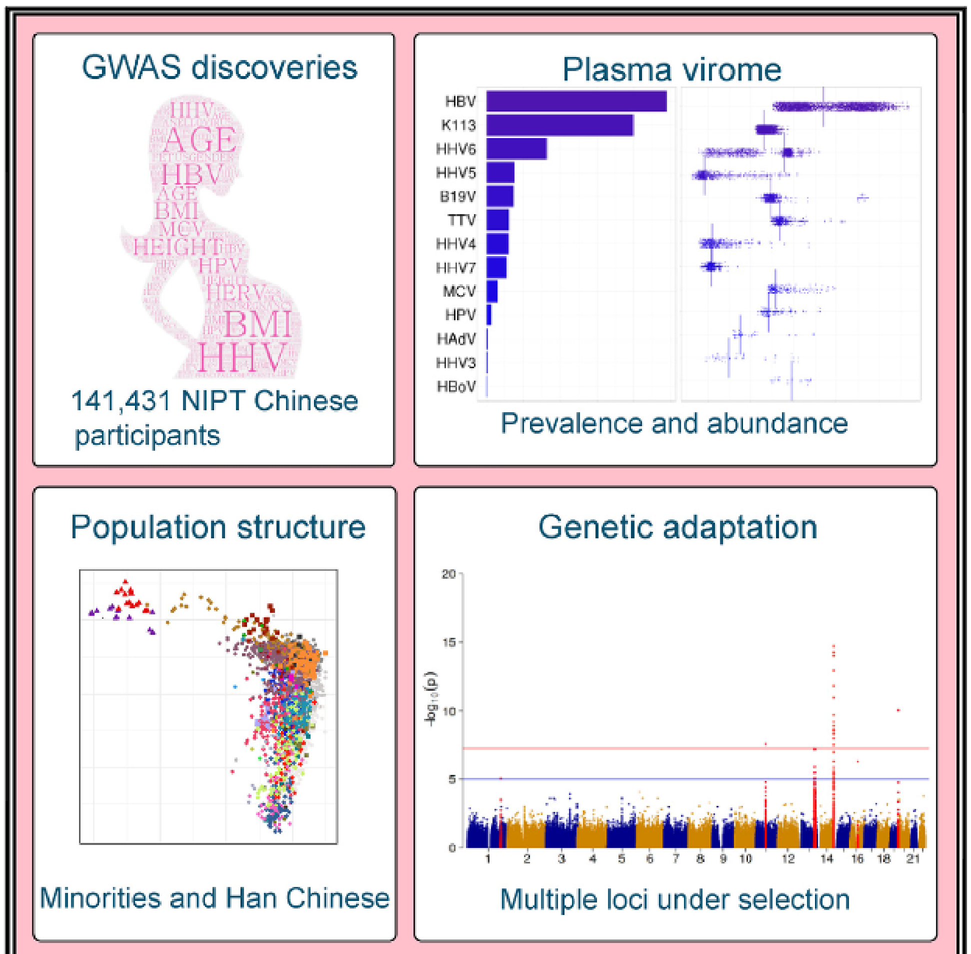
Genome wide association studies in the Greenlandic Inuit

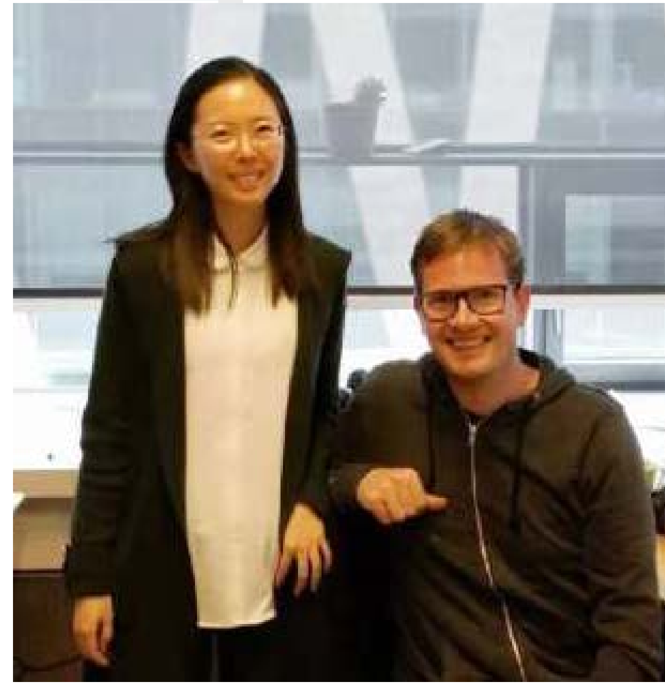
Life in the Arctic is extreme: cold temperatures and fat-rich diet

Article

Genomic Analyses from Non-invasive Prenatal Testing Reveal Genetic Associations, Patterns of Viral Infections, and Chinese Population History

Liu et al 2018. Cell





Siyang Liu Anders Albrechtsen

Low coverage (0.1 x) genome sequencing to test for trisomy 13, 18, and 21

N = 141,431


Thank you