Introduction to population genetics

Population genetics

- Studies genetic variation in population a processes that affect it
- Understand evolution through mechanisms that change allel frequencies.

Hardy-Weinberg law

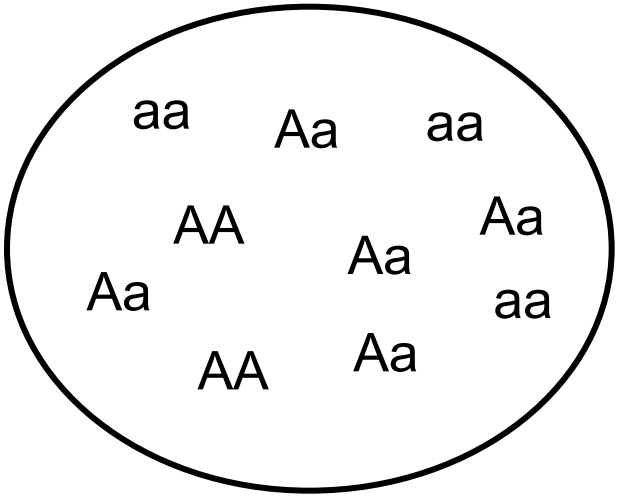
Godfrey Hardy

$$p^2 + 2pq + q^2 = 1$$

Wilhelm Weinberg

p …… frequency of alele A
q …… frequency of alele a

p^2 …… frequency of genotype AA
q^2 …… frequency of genotype aa
2pq …… frequency of genotype Aa



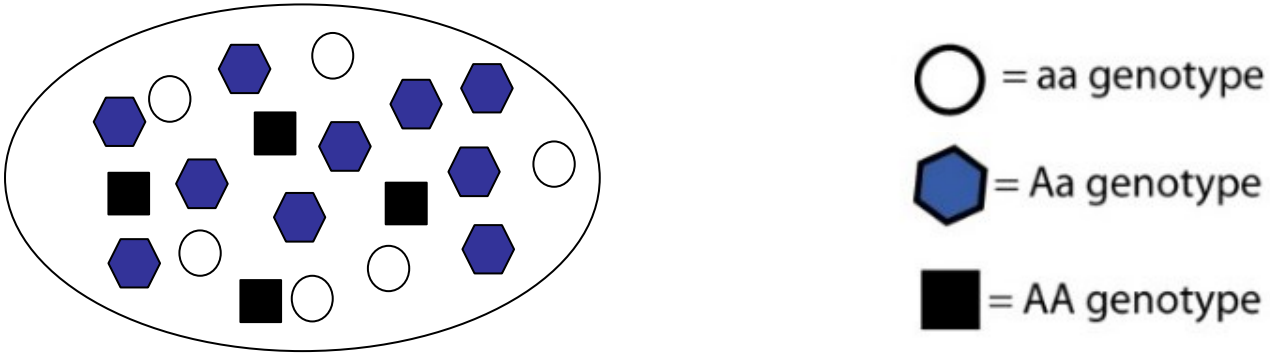
p^2 = 2/10 = 0.2
q^2 = 3/10 = 0.3
2pq = 5/10 = 0.5

$p = \sqrt{0.2} = 0.45$
$q = \sqrt{0.3} = 0.55$

Assumptions of Hardy-Weinberg equilibrium

Panmictic population

- Large population.
- All individuals contribute equally to the gamete pool (no selection)
- Random mating (in respect to particular genotype, spatial or temporal distribution).
- One generation of random mating can restore HW equilibrium.

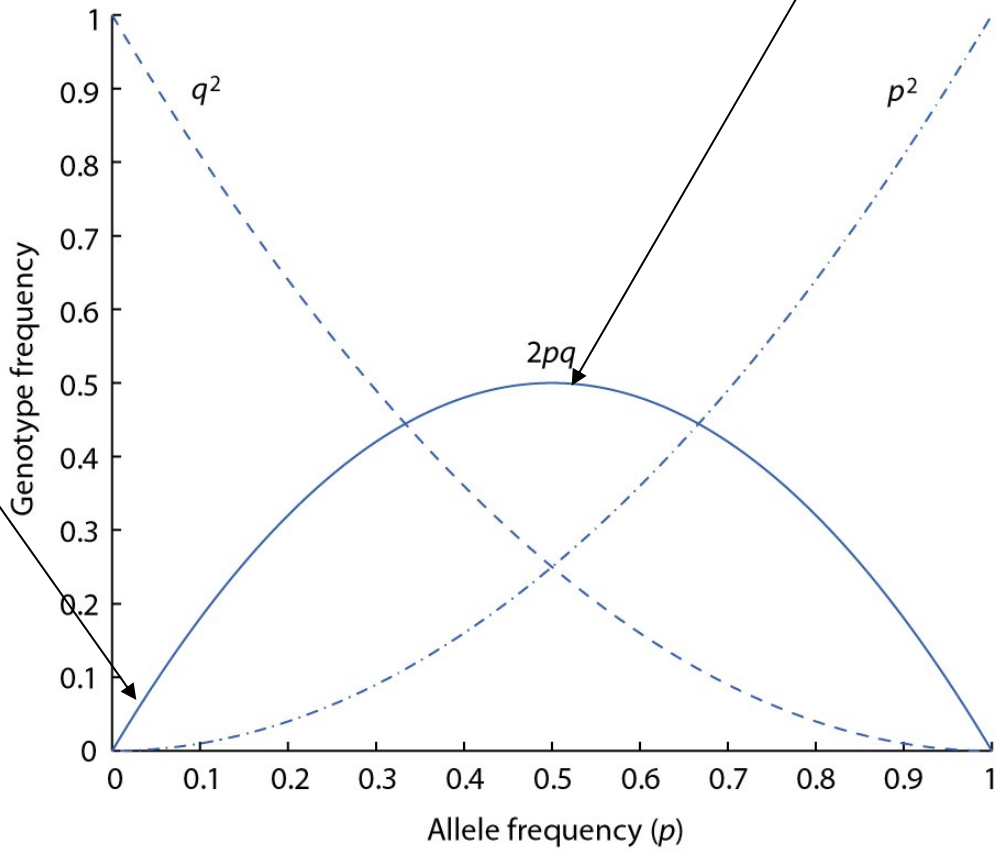


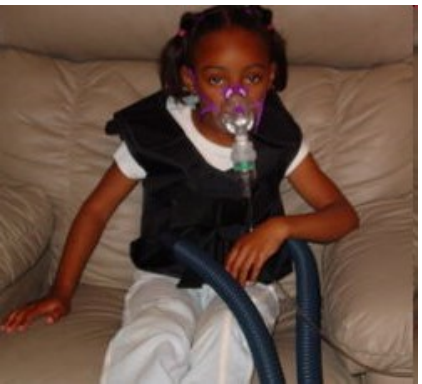
Hardy-Weinberg law

The recessive disadvantageus alleles can persist in population in very low frequencies.

The highest frequency of heterozygotes

The rare alleles hidden in heterozygotes.





Cystic fibrosis

Heterozygous carriers up to 1 from 25 individuals

Only about one from 3000 newbords affected

Hardy-Weinberg law

2 alleles

$(p + q)^2 = 1$

$p^2 + 2pq + q^2 = 1$

3 alleles

$(p + q + r)^2 = 1$

$p^2 + q^2 + r^2 + 2pq + 2pr + 2qr = 1$

4 alleles

$(p + q + r + s)^2 = 1$

$p^2 + q^2 + r^2 + s^2 + 2pq + 2pr + 2ps + 2qr + 2qs + 2rs = 1$

etc.

How to test whether population is in the Hardy-Weinberg equilibrium?

Genotypes	Observed numbers
AA	125
Aa	550
aa	325

Test of Hardy-Weinberg equilibrium

Calculation of allele frequencies

Genotypes	Observed numbers
AA	125
Aa	550
aa	325
all	1000

$$f_A = \frac{2 \times 125 + 550}{2 \times 1000} = 0.4$$

$$f_a = 1 - A = 0.6$$

Estimation of expected numbers of genotypes

AA $1000 \times (0.4)^2 = 160$
Aa $1000 \times 2(0.4)(0.6) = 480$
aa $1000 \times (0.6)^2 = 360$

Difference between observed and expected no. of genotypes

AA $125 - 160 = -35$
Aa $550 - 480 = 70$
aa $325 - 360 = -35$

Chi-square statistics (X^2)

$$X^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}}$$

Degree of freedom (df)
number of different genotypes
– 1 (no. of estimated variables)
– 1

Chi-square test

$$X^2 = \frac{(-35)^2}{160} + \frac{(70)^2}{480} + \frac{(-35)^2}{360} = 21.27$$

df = 3-1-1=1 **p < 0.01**

Population is not in HW equilibrium.

Mechanisms causing deviations from HW equilibrium

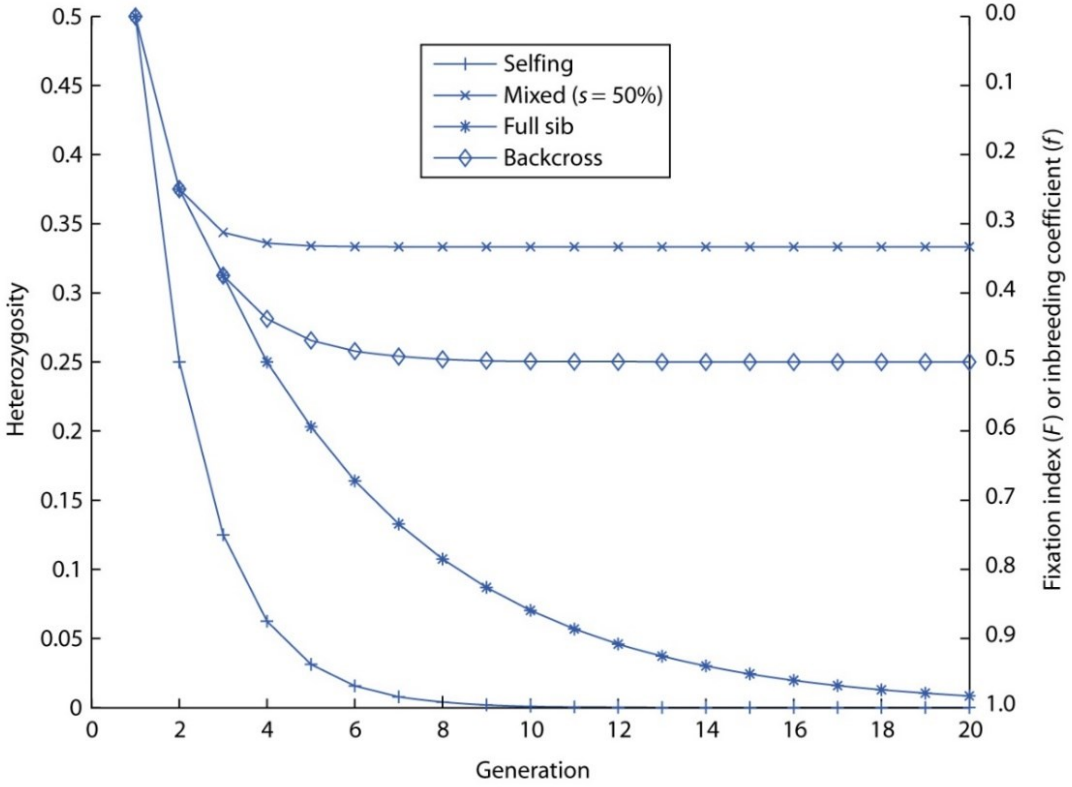
Assortative mating

Positive assortative mating

- Individuals with similar phenotypes (genotypes) mate with one another more frequently than would be expected under a random mating.
- Inbreeding
- Excess of homozygotes in population.
- Recesive disadvantageous alleles can be manifested (inbreeding depression).

Inbreeding

Establishment of laboratory inbred lines.

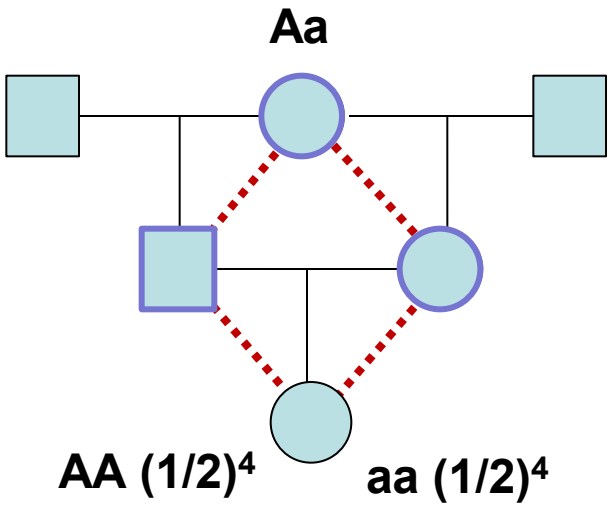


Coeficient of inbreeding (F)

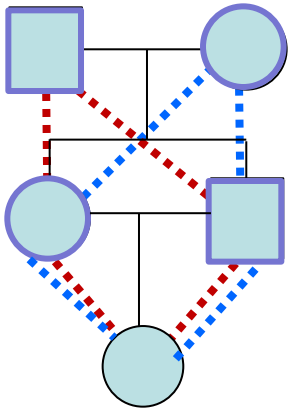
The probability that two alleles at any locus in an individual are identical by descent, i.e. inherited from the common ancestor.

$F = (1/2)^n$

n = number of individuals in the genealogy from the given individual to the common ancestor.



$F = (1/2)^3 = 1/8$



$F = 1/8 + 1/8 = 1/4$

Coeficient of inbreeding (F)

The probability that two alleles at any locus in an individual are identical by descent, i.e. inherited from the common ancestor.

$F = (1/2)^n$

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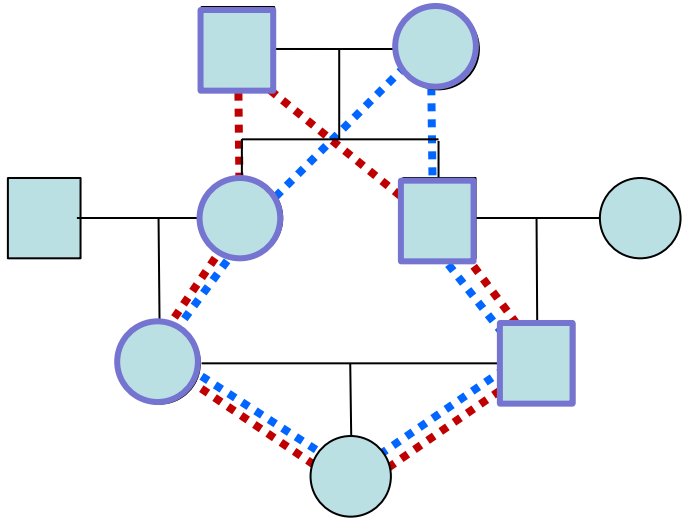
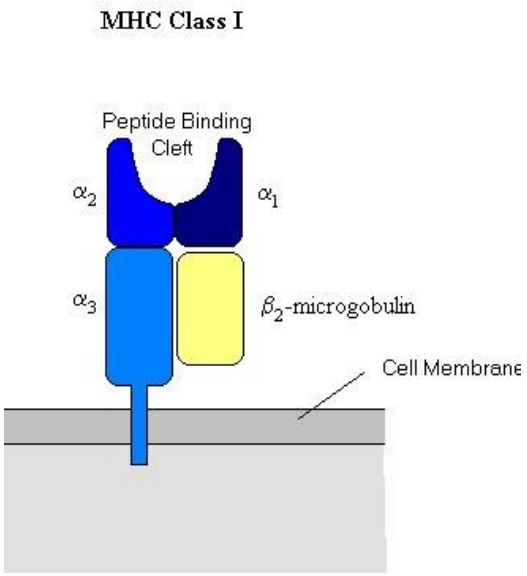


$F = (1/2)^5 + (1/2)^5$

$F = 1/32 + 1/32 = 1/16$

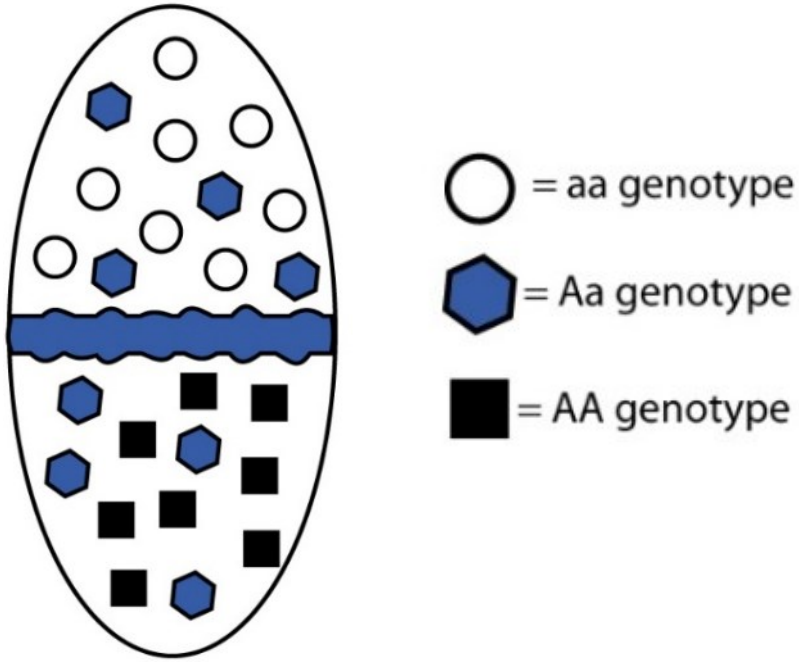
Negative assortative (disassortative) mating

- Individuals with dissimilar phenotypes (genotypes) mate with one another more frequently than would be expected under a random mating.
- Excess of heterozygotes.
- Example: MHC I (*Major Histocompatibility Complex I*) genes



Geographic population structure

- Geographic barriers prevent random mating.
- Reduces frequency of heterozygotes = **Wahlund effect.**



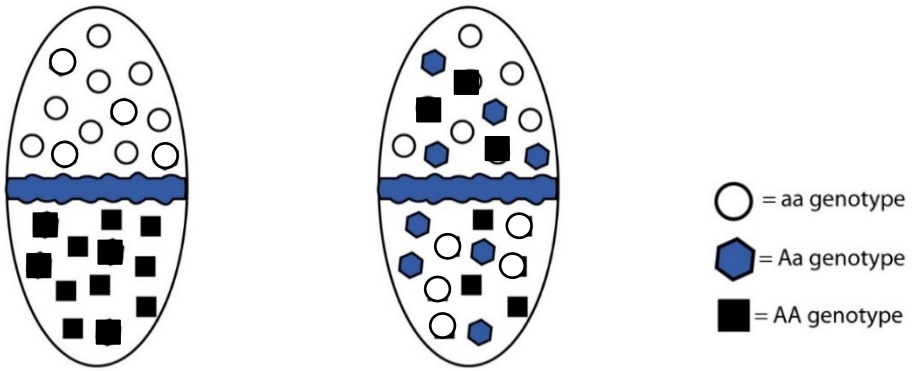
Estimation of levels of population structure

F_{ST} statistics (fixation index)

The expected degree of a reduction in heterozygosity when compared to Hardy–Weinberg expectation.

$$F_{ST} = \frac{H_T - H_S}{H_T}$$

H_T expected heterozygosity for whole population
H_S expected heterozygosity for subpopulations



$F_{ST} = 1$ $F_{ST} = 0$

Calculation of F_{ST} between two subpopulations

	Genotype numbers				Allele frequencies	
	AA	**Aa**	**aa**		**p**	**q**
subpopulation 1	25	50	25	100	0.5	0.5
subpopulation 2	49	42	9	100	0.7	0.3
whole population	74	92	34	200	0.6	0.4

$H_T = 2pq = 2 \cdot 0.6 \cdot 0.4 = 0.48$

$H_S = p_1q_1 + p_2q_2 = 0.25 + 0.21 = 0.46$

$F_{ST} = 0.0416$

$$F_{ST} = \frac{H_T - H_S}{H_T}$$

Isolation by distance

Genetic differentiation (Fst) increases with geographic distance.

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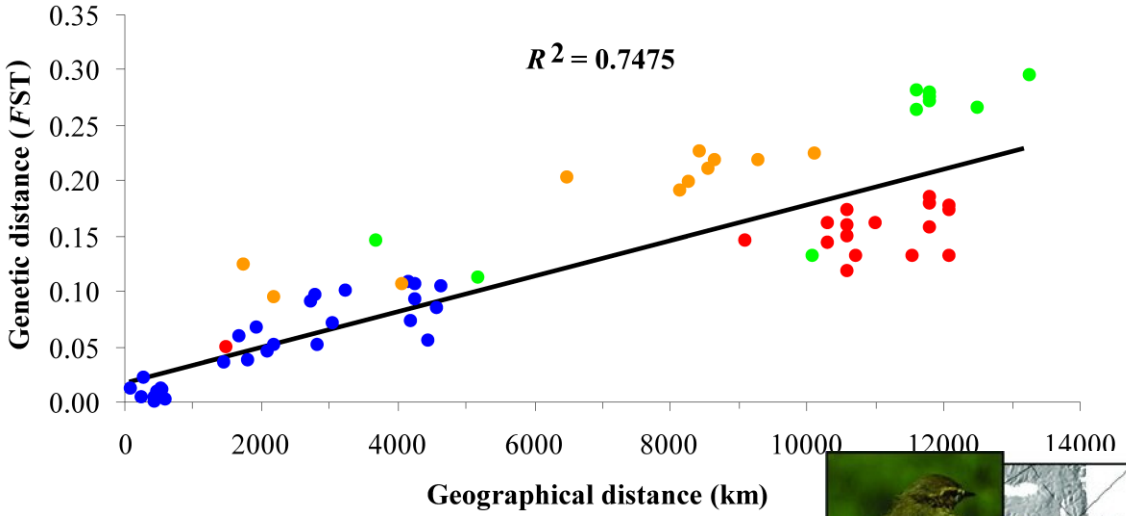
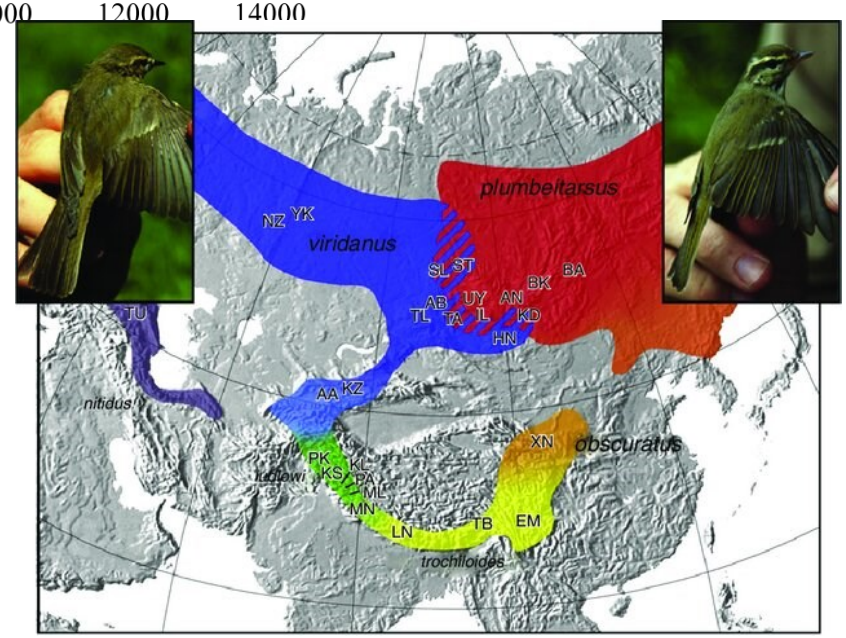


Pairs of populations involving *H. pylori* in

- West Africa only
- South Africa
- Madagascar
- San

Ring species

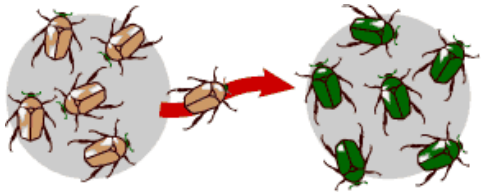
Greenish warblers (Phylloscopus trochiloides)



Mechanisms changing allele frequencing

mutation

drift

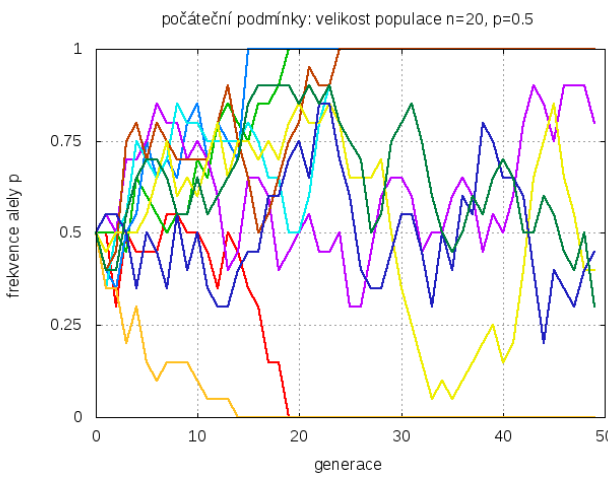


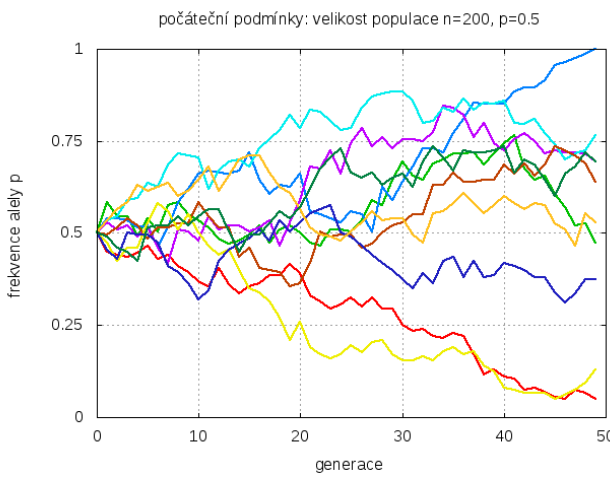
migration

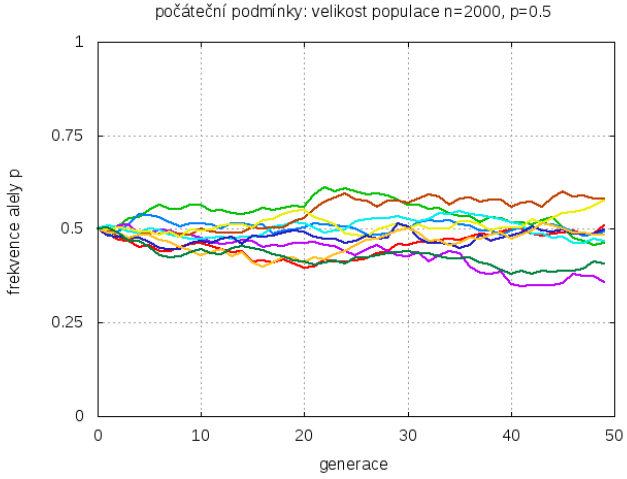
selection

Genetic drift

- Random changes in allele frequencies.
- Stronger in smaller populations.
- Reduces genetic variation.
- Probability of fixation is given by the allele frequency.
- Time to fixation is 4N (generations).

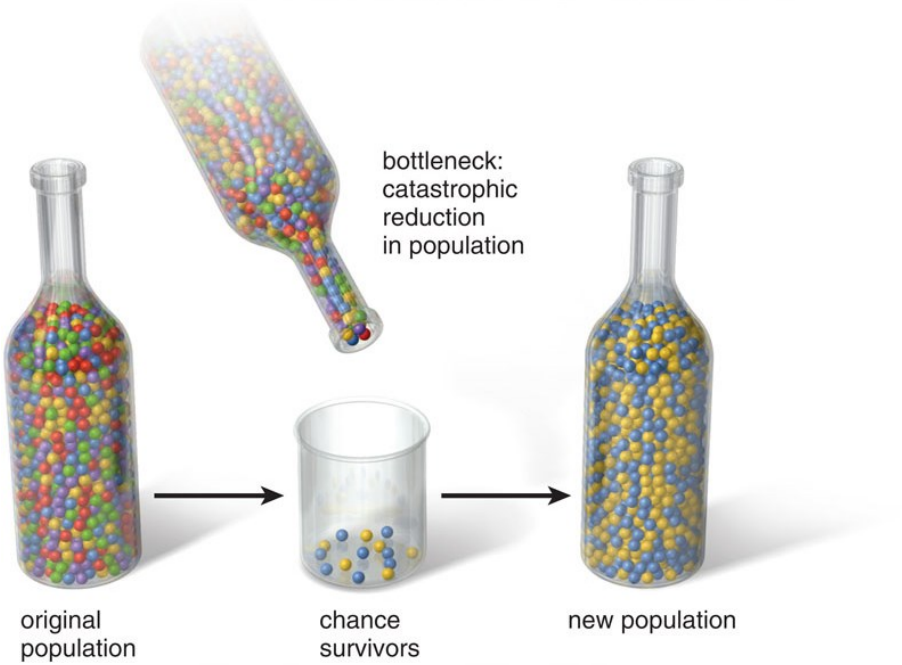




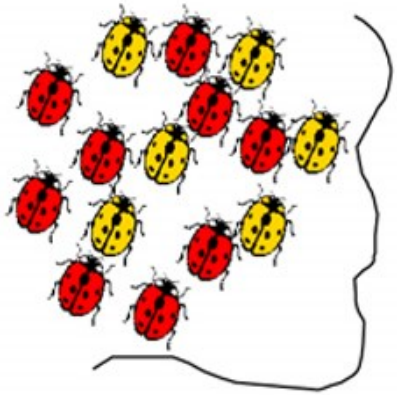


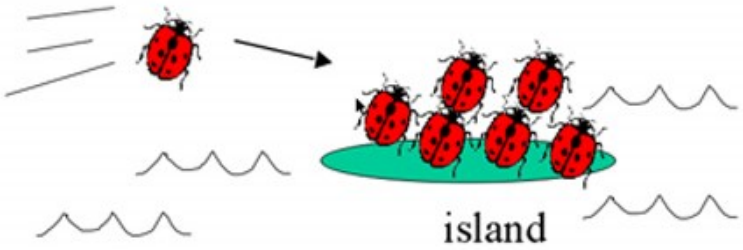
Genetic drift

Bottleneck effect

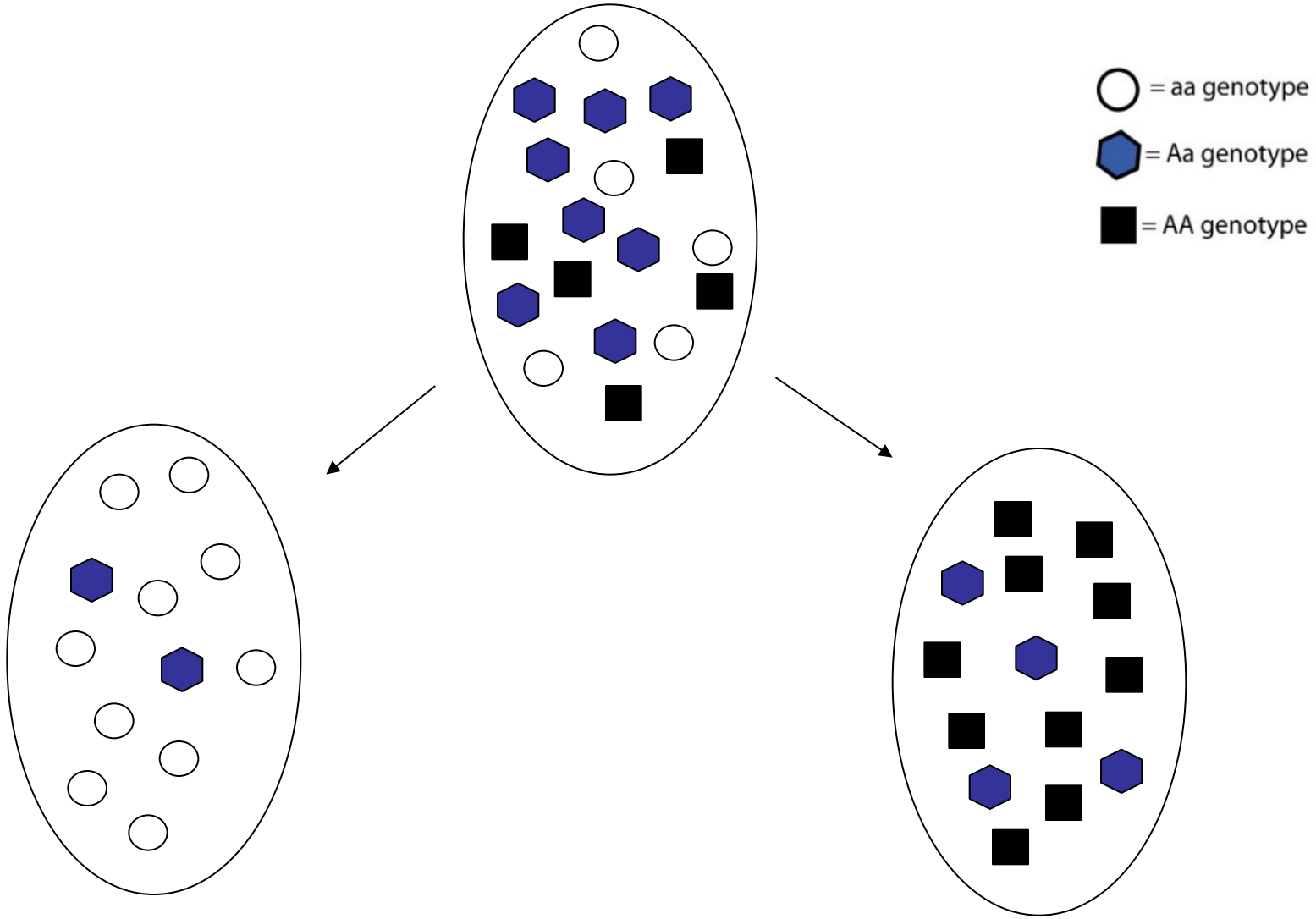


Founder effect





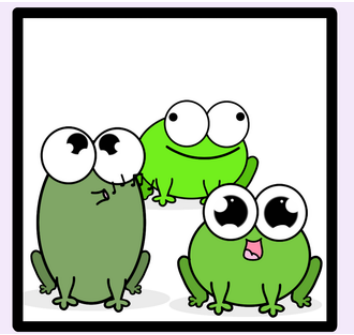
Genetic drift leads to differentiation of isolated populations



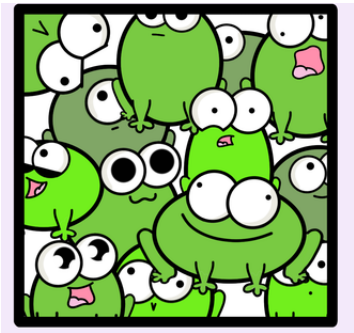
Effective population size (N_e)

- Number of breeding individual in the population.
- Is the size of ideal panmictic population (that meet all the HW assumptions), in which genetic proceses (e.g. genetic drift) have the same effects as in the real population.

Ideal population
N = 100



Real population
?

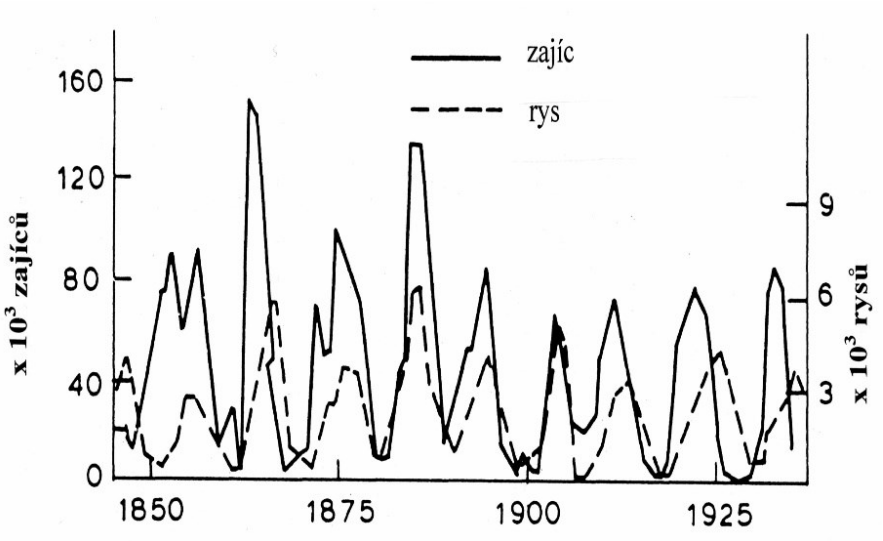


The strength of genetic drift is the same.

Factors affecting N_e

Changes in population size

- N_e reflects past changes in the population size.
- Correspond more to lower population sizes than higher population sizes.



Factors affecting N_e

Different number of reproducing males and females

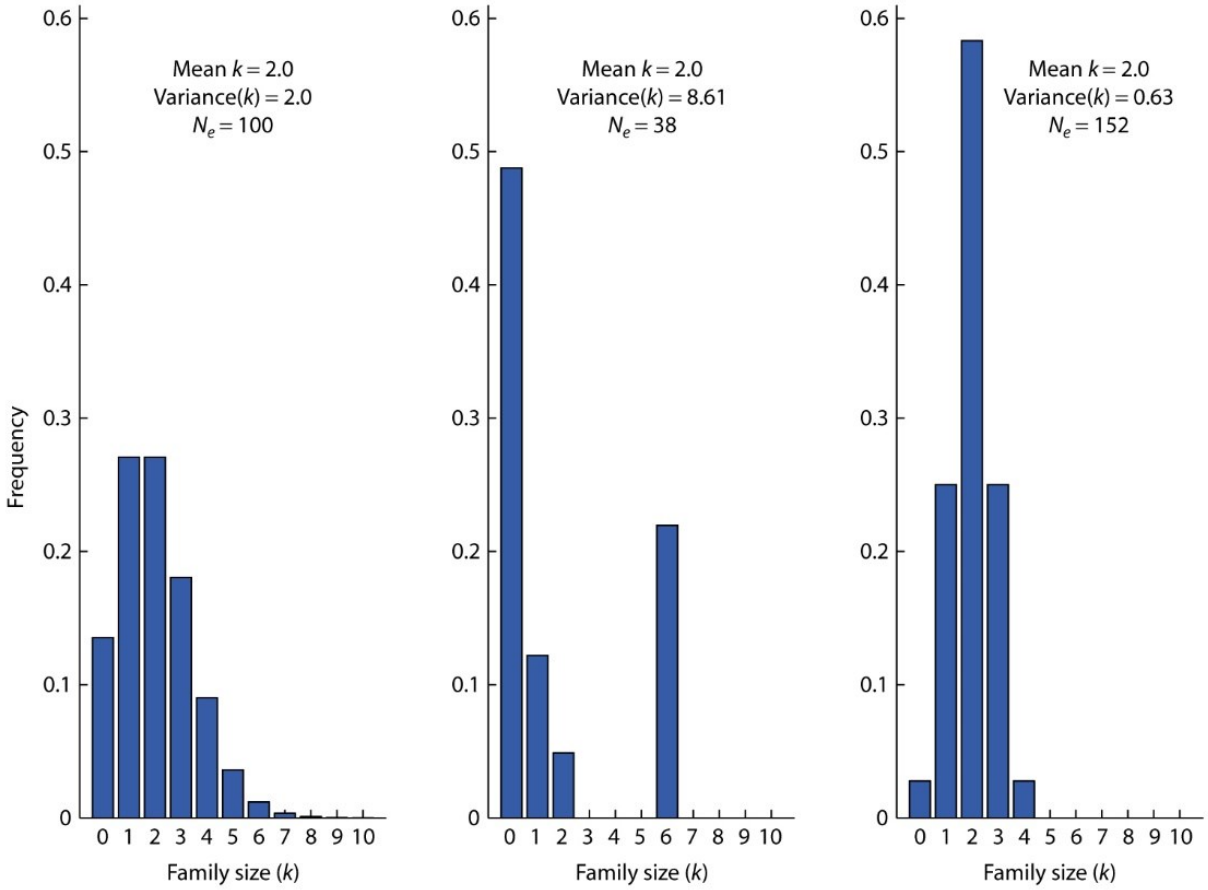
$$N_e = \frac{4N_mN_f}{N_m + N_f}$$

Elephant seal

Factors affecting N_e

Selection (variation in number of progeny among individuals)

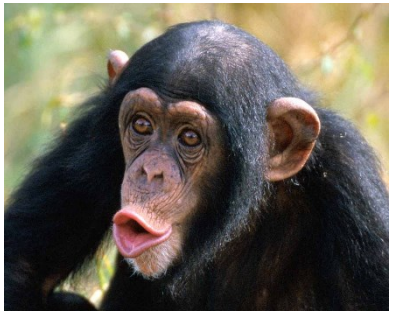
- Large variation in number of progeny among individuals reduces N_e



Estimates of N_e

~ 10 000

~ 30 000

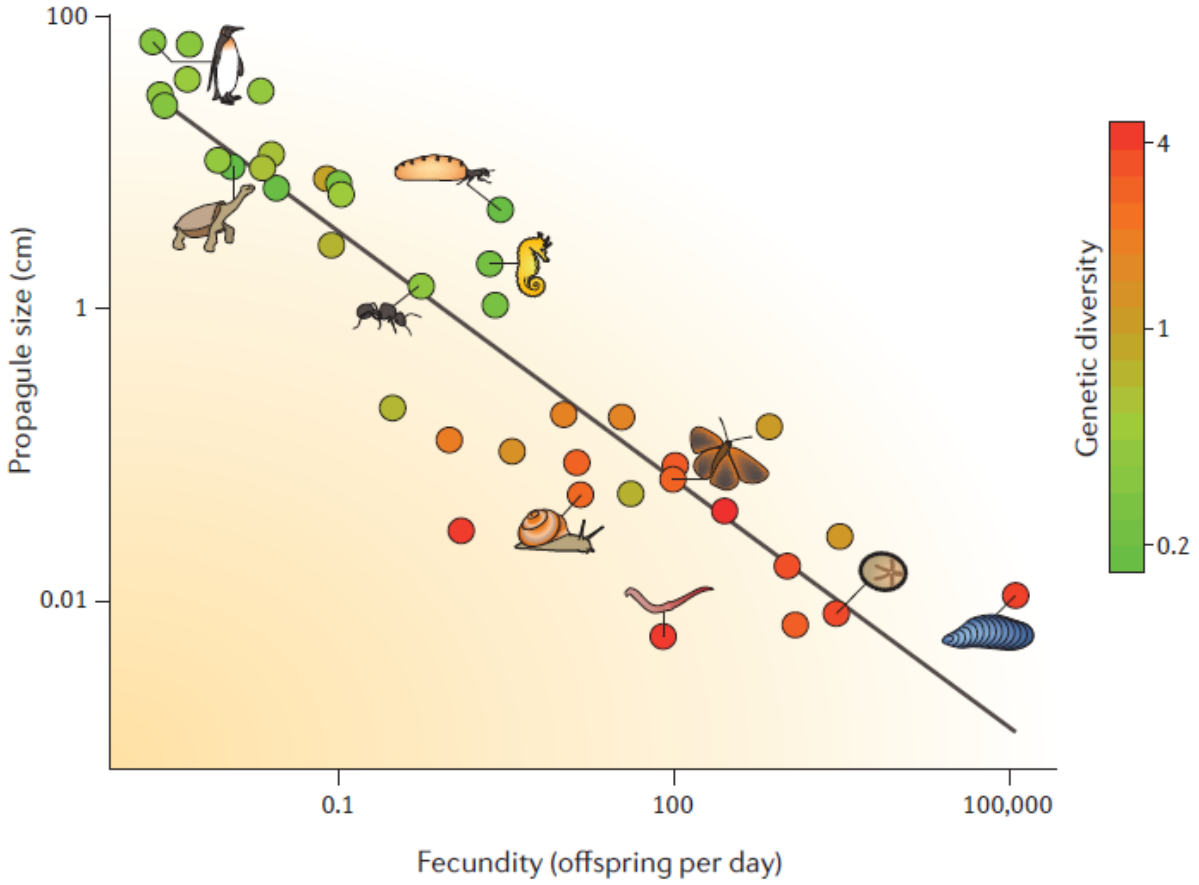


~ 2 000 000

~ 1 000 000

~ 100 000

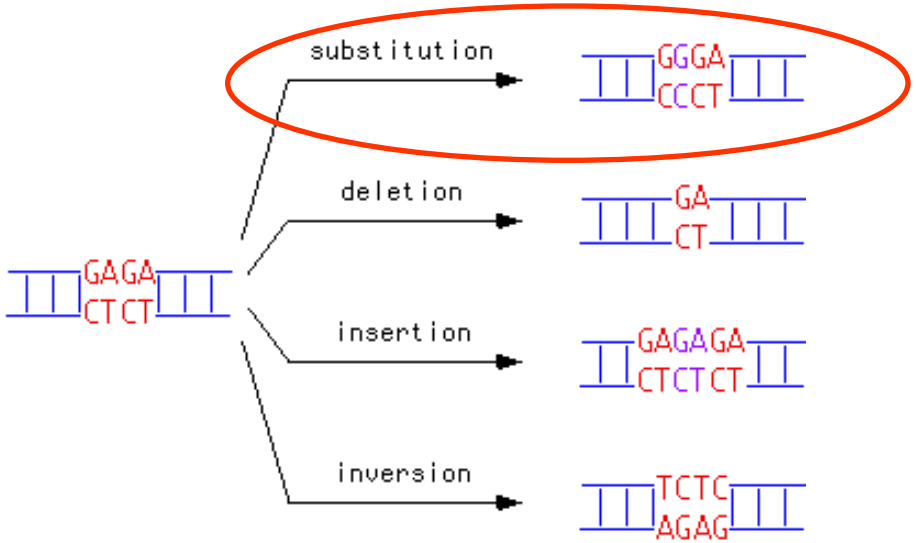
Effective population size and life strategies



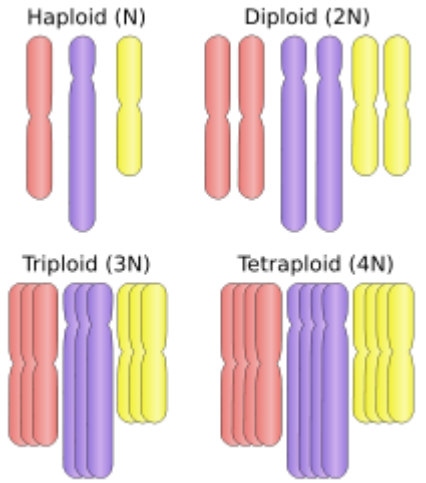
Ellegren and Galtier, 2016

Mutations: the source of genetic variation

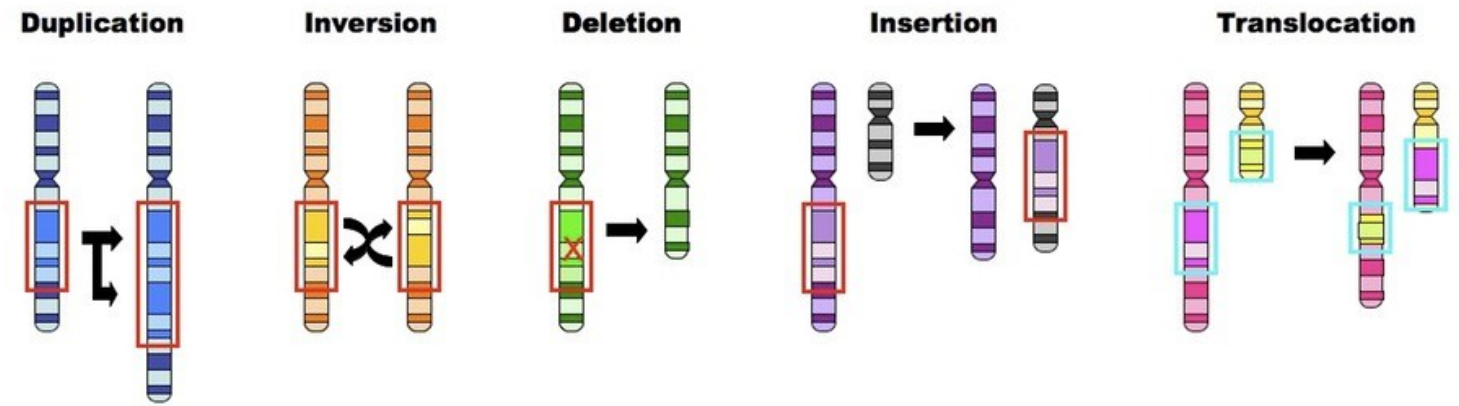
Point/gene mutations



Genome mutations



Chromosomal mutations (structural variations)



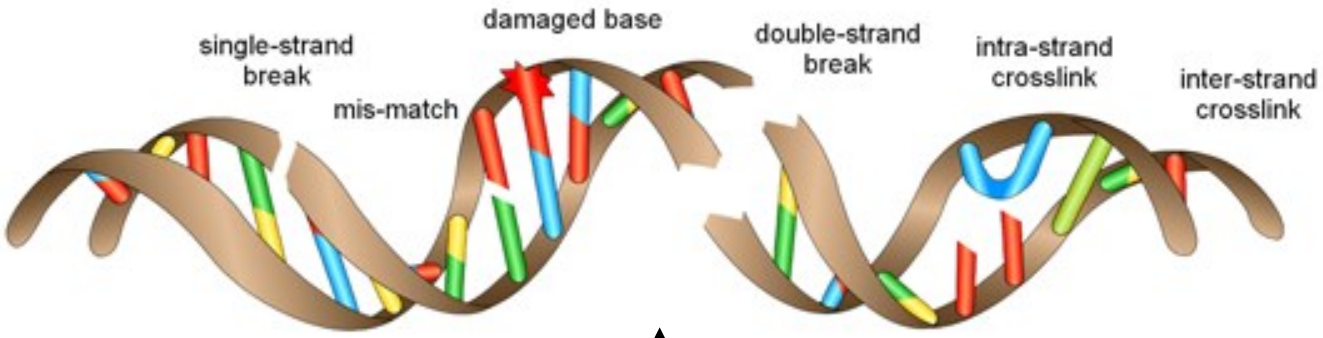
Mutations

Cell metabolism

Physical mutagens (UV light, gamma rays)

Chemical mutagens

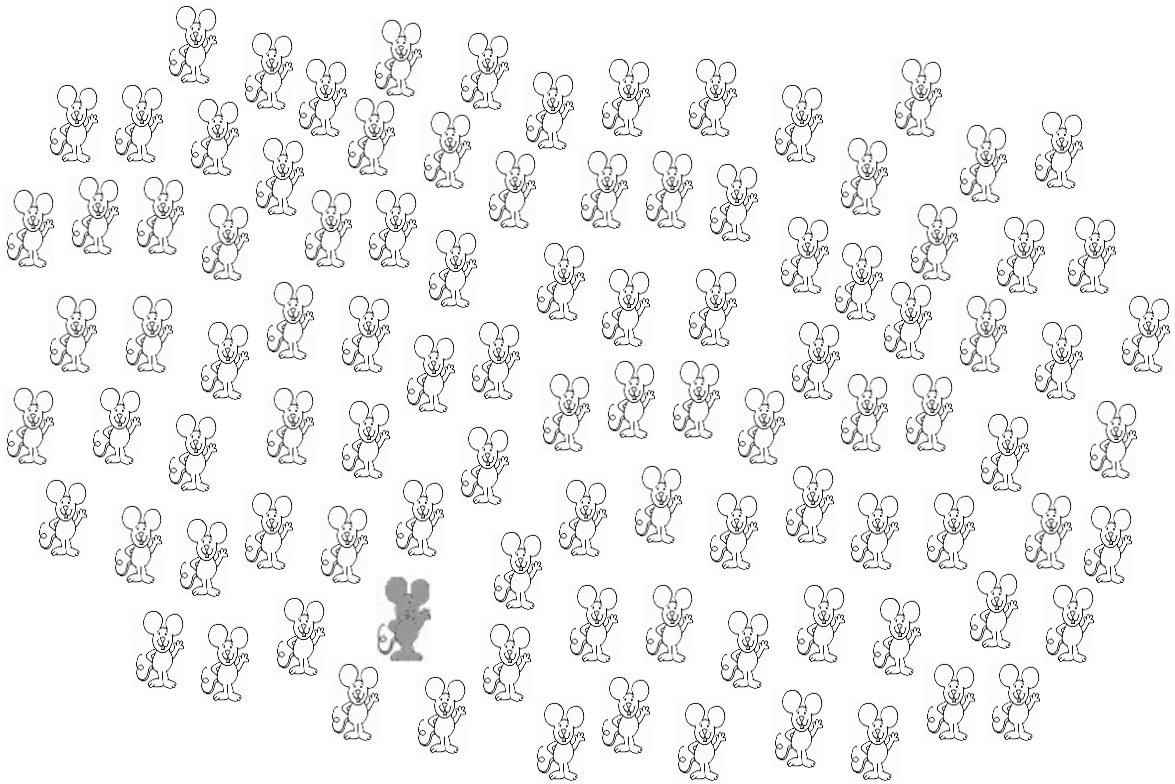
Replication errors



DNA reparation mechanisms

Mutation rate (μ)

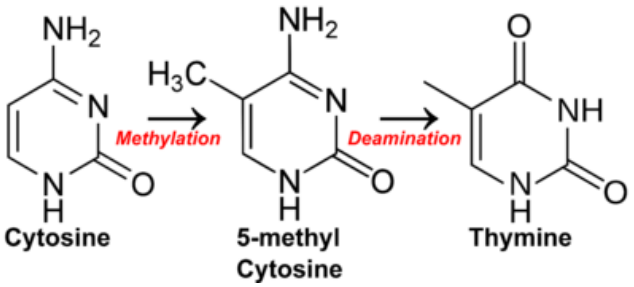
- Frequency of new mutations per generation
- μ = 0.01 (1 mutation per 100 individuals in 1 generation)



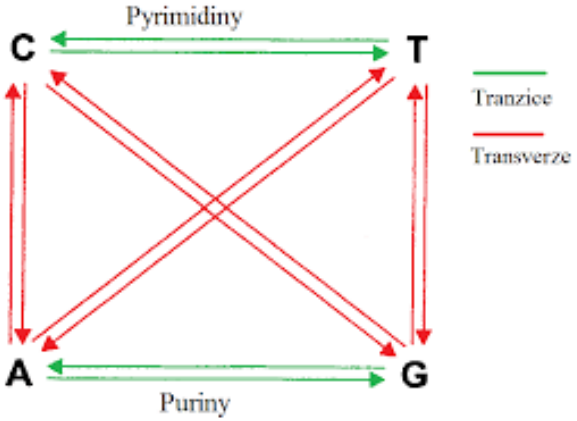
- Average mutation rate (for nucleotide substitutions) in humans is cca $1x10^{-8}$. (cca 60 new substitutions in the diploid genome of the individual each generation)

Mutation rate

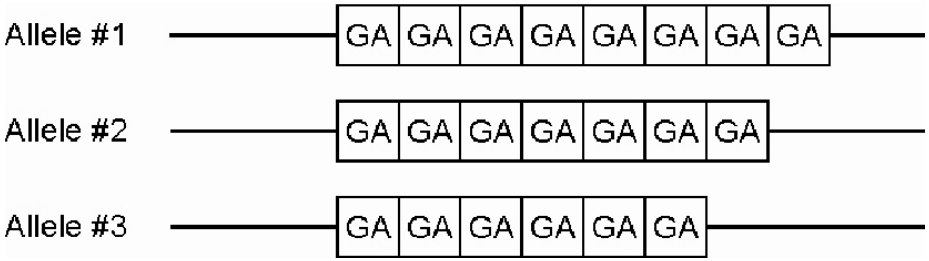
Different for various mutation types



- Transitions are more frequent than transversions
- mutation „hotspots“: CpG islands, mikrosatelites



mikrosatelit



Mutation rate

Different for various genes in the genome

- Affected by transcription rate, epigenetic modifications of DNA (a possible mechanism of genetic assimilation), meiotic breaks, distance to replication origin, nucleosome position etc.

Presentation

RESEARCH

RESEARCH ARTICLE SUMMARY

HUMAN GENETICS

Meiotic DNA breaks drive multifaceted mutagenesis in the human germ line

Robert Hinch, Peter Donnelly, Anjali Gupta Hinch*

INTRODUCTION: The creation of eggs and sperm in meiosis requires the chromosomes in each homologous pair to physically exchange genetic material through recombination and crossing over. This process is essential for proper segregation of chromosomes into haploid gametes, and it generates new patterns of genetic variation in populations, thereby creating the substrate for evolution through natural selection. Recombination is initiated by the induction of hundreds of programmed DNA double-strand breaks (DSBs). However, only a small proportion result in the formation of crossovers.

in meiosis. Most meiotic DSBs occur in narrow regions of the genome called "hotspots." We generated high-resolution maps of human mutation relative to hotspots by leveraging population-scale resources of human diversity. These mutations comprise hundreds of millions of single-base substitutions, short insertions and deletions (collectively indels), and large-scale genome changes known as structural variants (SVs). We characterized sequence features of these mutations ("signatures") and compared their positions with the localization of molecular processes involved in meiotic break repair ("footprints").

somes, we observed 100- to 400-fold increas
short indels and 400- to 1000-fold incre
in SVs per break. The impact of meiotic breaks on the X chromosome is larger and distinct from that on the autosomes. Although SVs are biased toward insertions on the autosomes, deletions are particularly strongly elevated on the X chromosome, exhibiting a 1300-fold increase in rate per break.

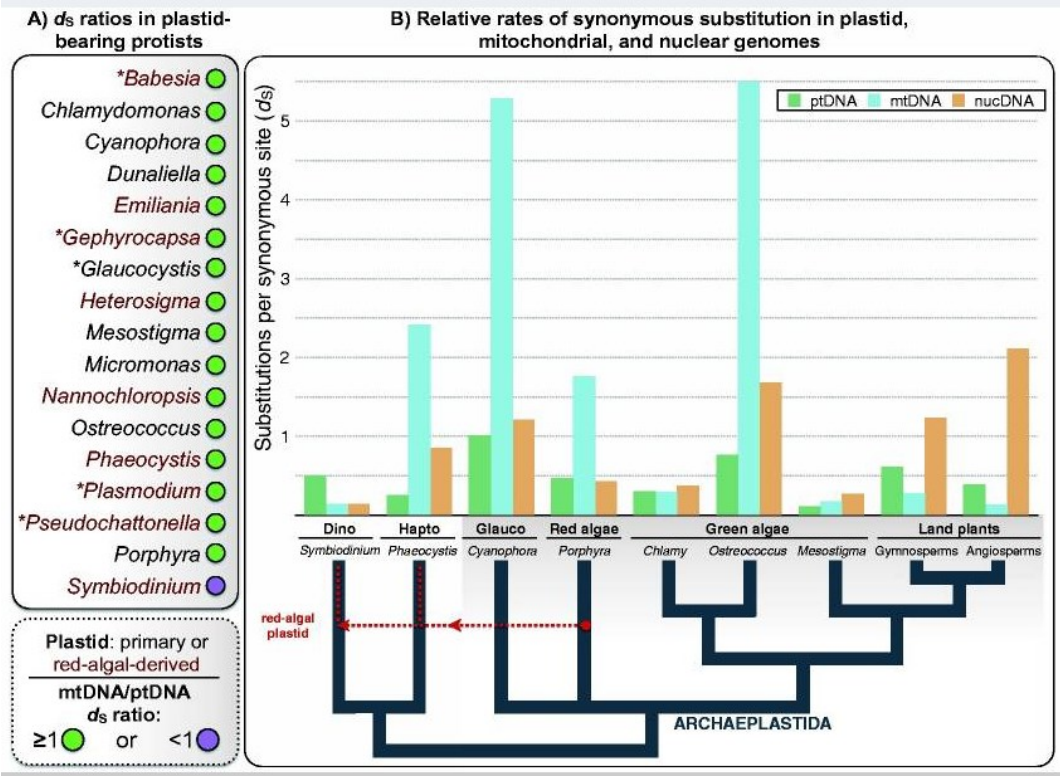
Some of these mutations have an impact on human health. We observed a 41% increase in pathogenic mutations in exonic regions overlapping hotspots, with >350 genes genome wide affected by pathogenic or loss-of-function mutations attributed to meiotic break repair. These genes are associated with a range of X-linked and autosomal developmental disorders, neurological and autoimmune conditions, and cancers.

We uncovered multiple new mutational footprints and signatures, which implicate unexpected biochemical processes in meiotic break repair and provide evidence that a range of error-prone DNA repair pathways normally associated with somatic and cancer cells are active in meiosis. For example, the nature and

Mutation rate

Different in nucleus, mitochondria and plastids

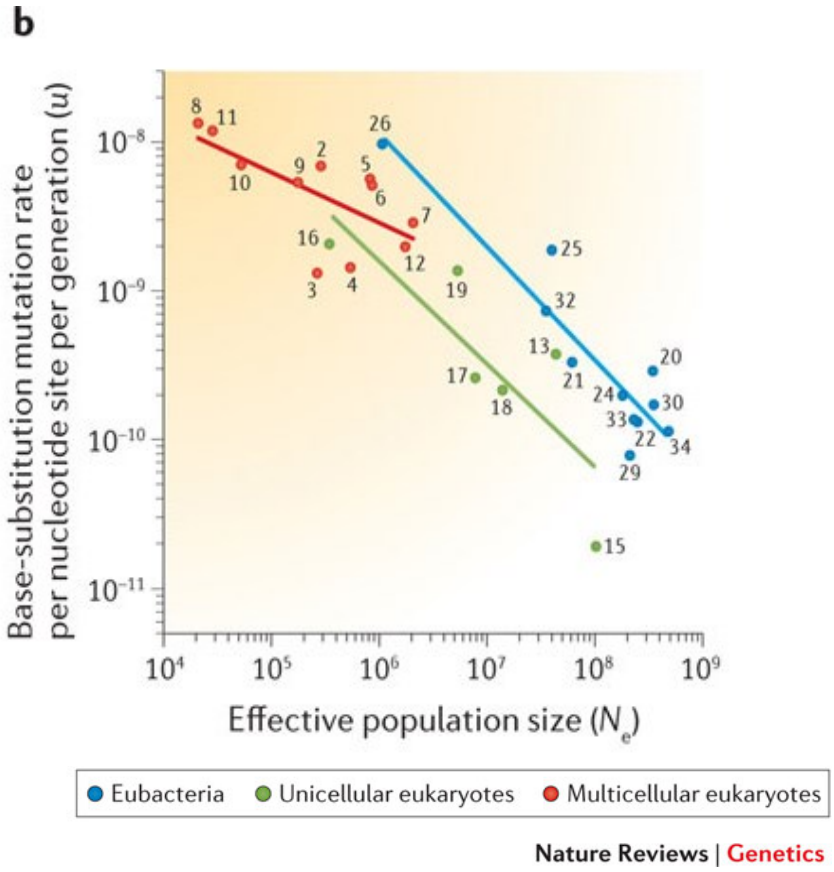
- In animals cca 10x higher in mtDNA than in nuclear DNA.
- In plants:



Mutation rate

Different in various organisms

- RNA viruses, DNA viruses, multicelular eukaryota, bacteria, unicellular eukaryota



Lynch et al. 2016

Germline mutation rate

Table 1. Mutation rates per nucleotide site ($\times 10^{-9}$) in different tissues[a]

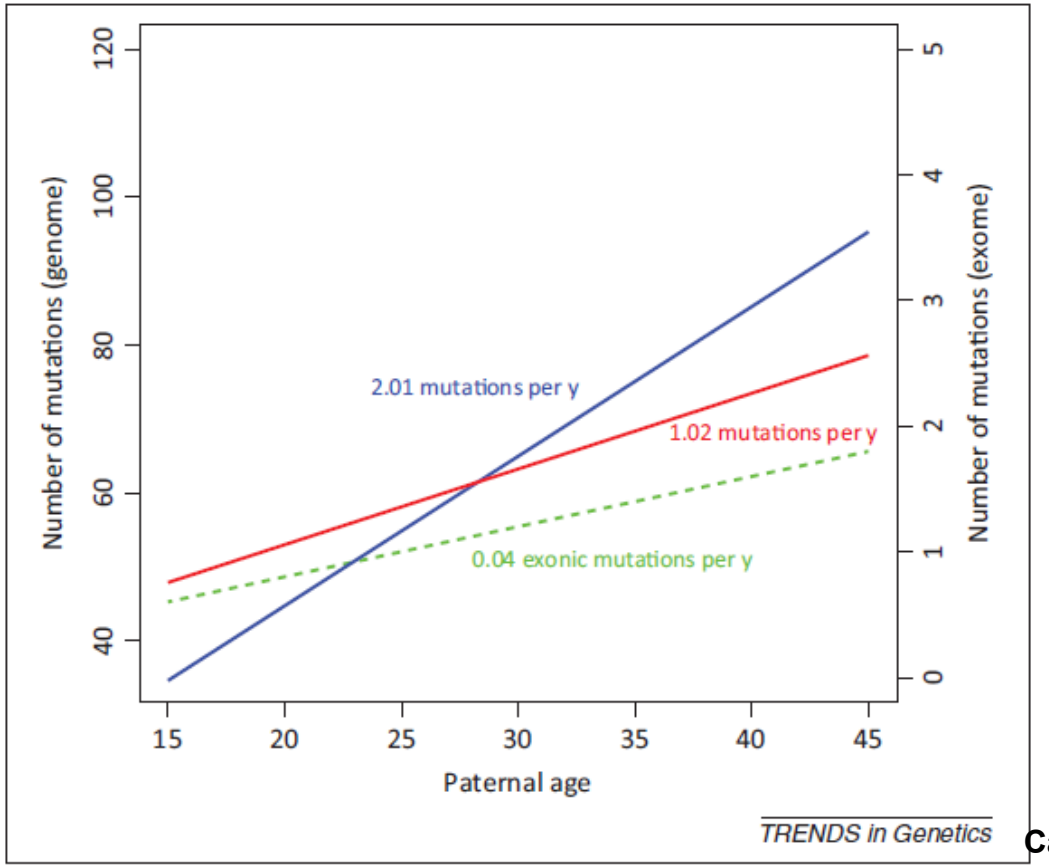
Species	Tissue	Cell divisions per generation[a]	Mutation rates[b]	
			Per generation	Per cell division
Homo sapiens	Germline	216	12.85	0.06
	Retina	55	54.45	0.99
	Intestinal epithelium	600	162.00	0.27
	Fibroblast (culture)			1.34
	Lymphocytes (culture)			1.47
Mus musculus	Male germline	39	38.00	0.97
	Brain		76.94	
	Colon		83.35	
	Epidermis		90.38	
	Intestine		117.69	
	Liver		237.88	
	Lung		166.83	
	Spleen		130.00	
Rattus norvegicus	Colon		178.38	
	Kidney		167.45	
	Liver		179.92	
	Lung		223.22	
	Mammary gland		57.70	
	Prostate		448.90	
	Spleen		101.62	
Drosophila melanogaster	Germline	36	4.65	0.13
	Whole body		380.92	
Caenorhabditis elegans	Germline	9	5.60	0.62
Arabidopsis thaliana	Germline	40	6.50	0.16
Saccharomyces cerevisiae		1	0.33	0.33
Escherichia coli		1	0.26	0.26

[a]References to data on numbers of germline cell divisions: human [Crow 2000]; *D. melanogaster* and mouse [57]; *C. elegans* [58]; and *A. thaliana* [59]. Numbers of cell divisions are unknown for the mouse and rat rates.

[b]Mammalian tissue-specific rates are given only for tissues in which at least two independent estimates have been acquired. All data on human mutation rates are taken from Lynch [36]. Data for somatic mutation rates in mouse and rat are derived from references contained within the supplementary material online. References to data on germline mutation rates are: *D. melanogaster* [5], *C. elegans* [4], *A. thaliana* [Ossowski *et al.*, 2009], *S. cerevisiae* [3], and *E. coli* [24].

Most mutations are inherited from fathers

- Male driven evolution
- Paternal age effect.
- Different mutation rate on sex chromosomes and autosomes.



Campbell and Eicher, 2013