

# **CRIMEAN STATE** **MEDICAL** **UNIVERSITY** **NAMED AFTER S.** **I. GEORGIEVSKY**

NAME – VIKRANT KUMAR MAURYA  
GROUP- 19IB  
GUIDED ANNA ZUKOVA–



# **Topic: Genetic load of human population**

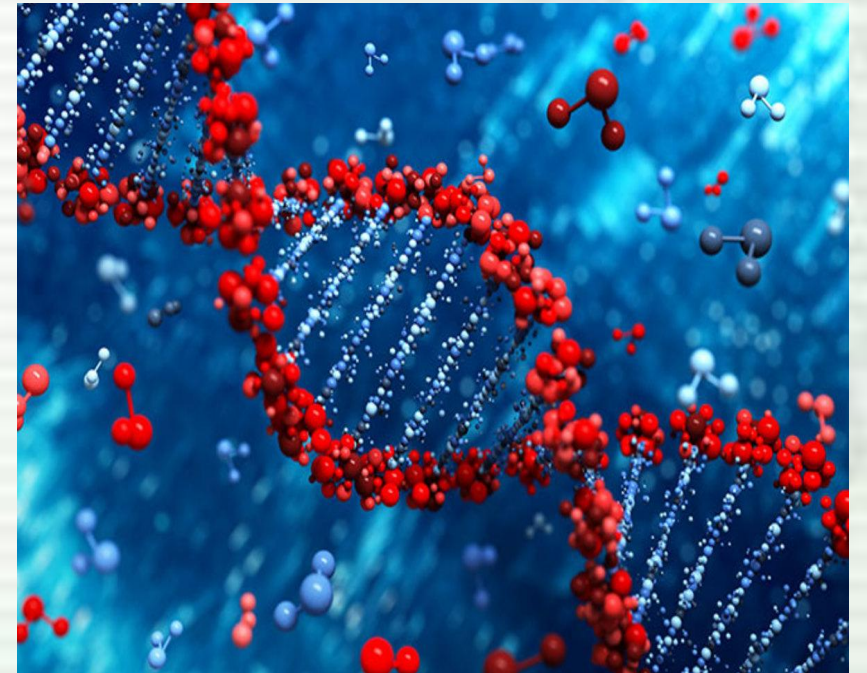
## **Some Important Points:-**

- ❖ Genetic load is the reduction in mean fitness of a population caused by some population genetic process.
- ❖ Mutation load is the reduction in fitness caused by recurrent deleterious mutations.
- ❖ Mutation load may be as great as 95% for the human population.
- ❖ Drift load is the reduction in mean fitness caused by genetic drift. In extreme cases, deleterious alleles can reach a frequency of one in a population because of genetic drift.



# GENETIC LOAD

- ❖ Mutation that leads to lethal traits are often eliminated from the gene pool, however some mutant alleles can persist in heterozygote's .
- ❖ Genetic load refers to collection of these deleterious alleles in the population

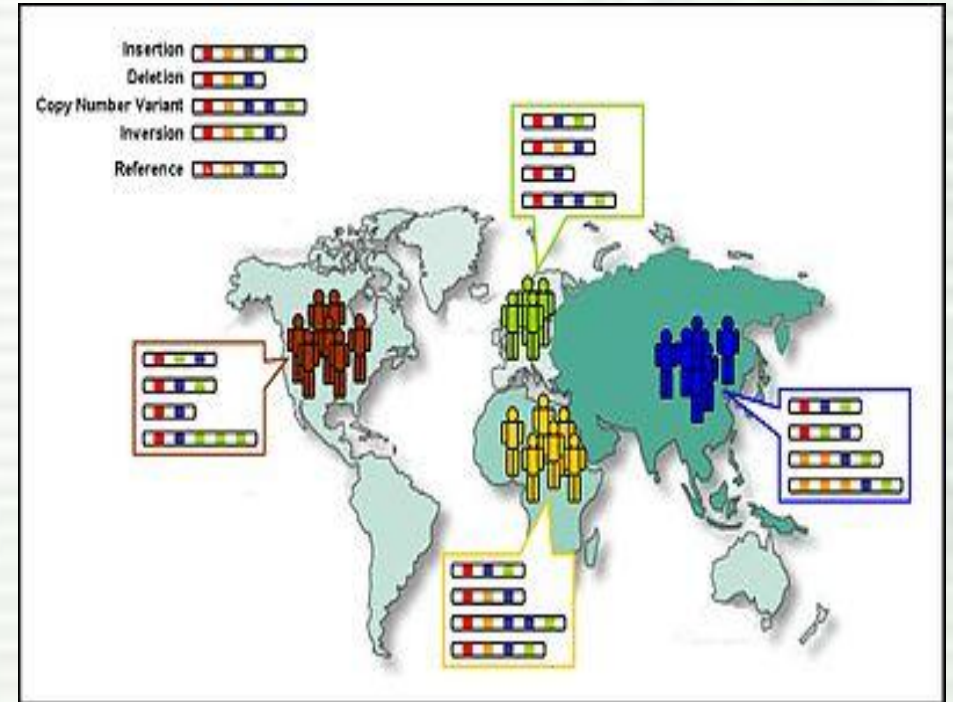


# **ABSTRACT**

- Genetic load is the reduction in the mean fitness of a population relative to a population composed entirely of individuals having optimal genotypes. Load can be caused by recurrent deleterious mutations, genetic drift, recombination affecting epistatically favourable gene combinations, or other genetic processes. Genetic load potentially can cause the mean fitness of a population to be greatly reduced relative to populations without sources of less fit genotypes. Mutation load can be difficult or impossible to measure. Many species have mutation rates low enough that substantial genetic load is not expected, but for others, such as humans, the mutation rate may be great enough that load can be substantial.
- In extremely small populations, drift load, caused by the fixation by drift of weakly deleterious mutations, can threaten the probability of persistence of the population. Migration from other populations adapted to different local conditions can bring in locally maladapted alleles, resulting in migration load.



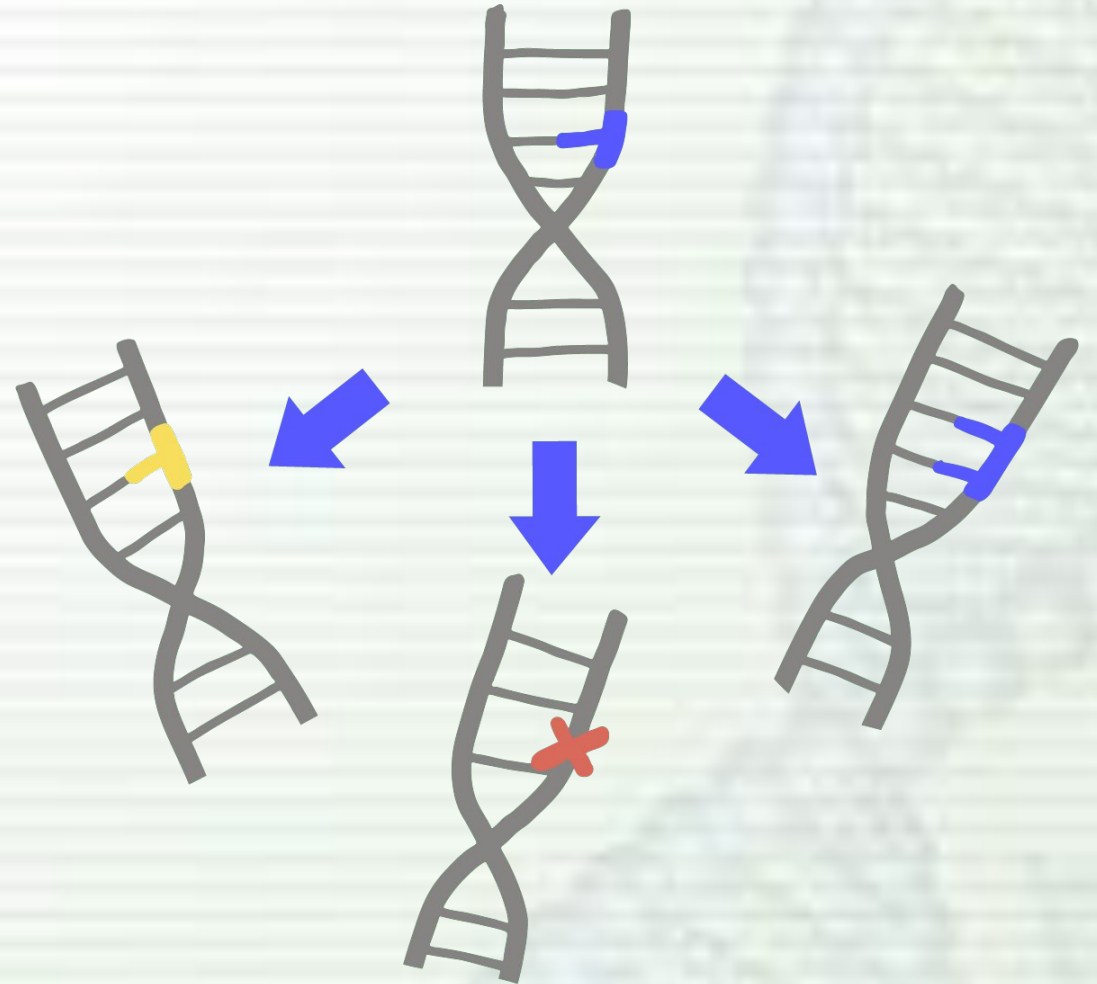
- **Genetic load** is the difference between the fitness of an average genotype in a population and the fitness of some reference genotype, which may be either the best present in a population, or may be the theoretically optimal genotype. The average individual taken from a population with a low genetic load will generally, when grown in the same conditions, have more surviving offspring than the average individual from a population with a high genetic load.<sup>[1][2]</sup> Genetic load can also be seen as reduced fitness at the population level compared to what the population would have if all individuals had the reference high-fitness genotype.<sup>[3]</sup> High genetic load may put a population in danger of extinction.



# GENETIC LOAD : SOURCES

Mainly form three sources:

1. Mutational Load
2. Substitution load
3. Segregation load



# **DIRECT EVIDENCE OF AN INCREASING MUTATIONAL LOAD IN HUMANS**

The extent to which selection has shaped present-day human populations has attracted intense scrutiny, and examples of local adaptations abound. However, the evolutionary trajectory of alleles that, today, are deleterious has received much less attention. To address this question, the genomes of 2,062 individuals, including 1,179 ancient humans, were reanalyzed to assess how frequencies of risk alleles and their homozygosity changed through space and time in Europe over the past 45,000 years. Although the overall deleterious homozygosity has consistently decreased, risk alleles have steadily increased in frequency over that period of time. Those that increased most are associated with diseases such as asthma, Crohn disease, diabetes, and obesity, which are highly prevalent in present-day populations. These findings may not run against the existence of local adaptations but highlight the limitations imposed by drift and population dynamics on the strength of selection in purging deleterious mutations from human populations.



# MUTATIONAL LOAD

**Mutational load** is the total genetic burden in a population resulting from accumulated deleterious mutations. It is a kind of genetic **load**. It can be thought of as a balance between selection against a deleterious gene and its production by **mutation**.

## Genetic load: mutational

Let's assume: (i) new mutations are deleterious alleles, and (ii) recessive.

Remember the approximation of the equilibrium frequency of deleterious alleles [See population genetics, Topic 5 for a review]:

$$q = (\mu/s)^{1/2}$$

Remember that population load is:

$$L = 1 - \bar{W}$$

And remember that the average fitness under these assumptions was:

$$\bar{W} = 1 - sq^2$$

We can make substitutions:

$$\begin{aligned} L &= 1 - \bar{W} \\ L &= 1 - (1 - sq^2) \\ L &= 1 - (1 - s(\mu/s)) \\ L &= 1 - (1 - \mu) \\ L &= \mu \end{aligned}$$

It is interesting that we estimate that the load is equal to the mutation rate. Because it suggests that the load is approximately independent of the reduction in fitness caused by the mutant ( $s$ ).

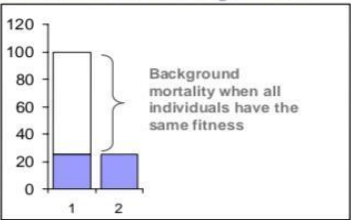




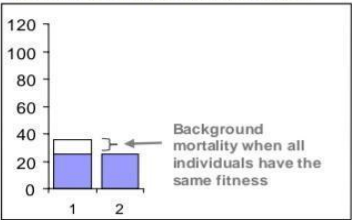
# Genetic load: the cost of selection [ or “Haldane’s dilemma”]

Genetic load has implications for the long term fate of a population.  
Haldane: the total load tolerated by a population is bounded by its excess reproductive capacity.

no selective death: large excess



no selective death: small excess



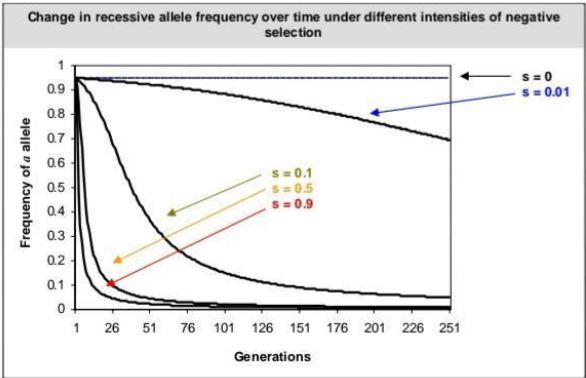
Population declines:  
Genetic death > reproductive excess



# Genetic load: the cost of selection [ or “Haldane’s dilemma”]

Genetic load has implications for the long term fate of a population.  
Haldane: the total load tolerated by a population is bounded by its excess reproductive capacity.

Consider a new mutation to an beneficial domiant allele: it takes time for selection to remove the “old” [deleterious recessive] allele from the population.



There is a cost to selection, in genetic death, during this time period



## Genetic load: the cost of selection [ or “*Haldane’s dilemma*”]

Genetic load has implications for the long term fate of a population.

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Population declines:  
Genetic death > reproductive excess

Haldane’s “Cost of selection”  
(1957)

$$C = \sum \underbrace{\frac{\text{proportion that die due to selection}}{\text{proportion that survive}}}_{\text{over all generations it takes to fix the allele}} = \sum \frac{l_i}{\bar{w}} \times N_e$$

Assume directional  
selection of a new  
mutation:

$C \times N_e$  gives the total  
selective death; this  
must be sum over  
generations it take to  
fix the allele



## Genetic load: the cost of selection [ or “*Haldane’s dilemma*”]

Genetic load has implications for the long term fate of a population.

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### Suppose $L = 0.1$

Load = 10% population reduction

Total size = 500 individuals

Reproductive size: 450

Cost of selection ( $C$ ) =  $L / \bar{w} = 0.1 / 0.9 = 0.111$

$C_1 \times N_e = 50$  extra individuals per **1<sup>st</sup>** generation

Total generation to fix allele = 100

Population 1:

Reproductive excess = 0

Generation = 53

- **Extinction:**  $C_{53} = 499.1$

Population 2:

Reproductive excess = 0.1

Generation = 100

- fixed beneficial allele

-  $C_{100} = 334.6$

- **survival:**  $N = 165.4$

Population 2:

Cost =  $C - R$

Cost =  $0.111 - 0.1 = 0.011$

... “soft selection”

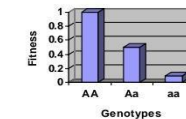


# DIRECTIONAL SELECTION

Directional selection occurs when individuals homozygous for one allele have a fitness greater than that of individuals with other genotypes and individuals homozygous for the other allele have a fitness less than that of individuals with other genotypes. At equilibrium the population will be composed entirely of individuals that are homozygous for the allele associated with the highest probability of survival. The rate at which the population approaches this equilibrium depends on whether the favored allele is dominant, partially dominant, or recessive with respect to survival probability. An allele is dominant with respect to survival probability if heterozygotes have the same survival probability as homozygotes for the favored allele, and it is recessive if heterozygotes have the same survival probability as homozygotes for the disfavored allele. An allele is partially dominant with respect to survival probability if heterozygotes are intermediate between the two homozygotes in survival probability. This pattern of selection is referred to as directional selection because one of the two alleles is always increasing in frequency and the other is always decreasing in frequency.

## Defining directional selection

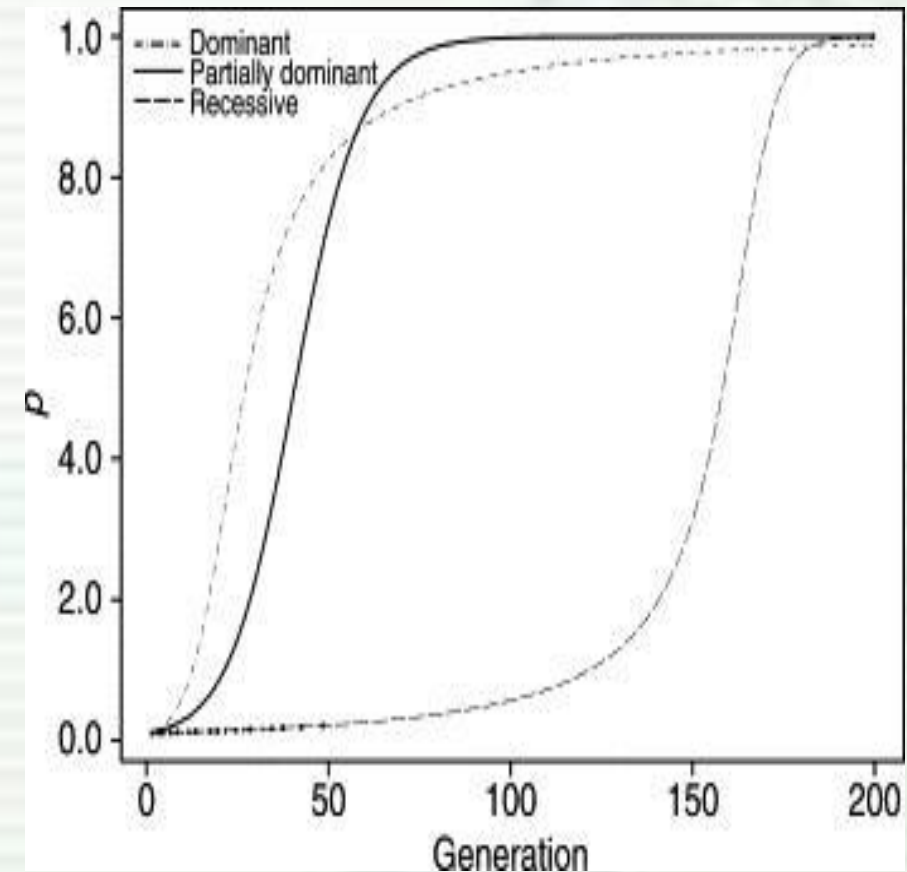
Directional selection: selection that favours the phenotype at an extreme of the range of phenotypes.



$$W_{AA} > W_{Aa} > W_{aa}$$

Directional selection: can be subdivided into two broad categories. These subtypes have been given different names, leading to a possible point of confusion. The next page is an attempt to clarify this issue.

- When a dominant favored allele is rare most individuals carrying it are heterozygous, and the large fitness difference between heterozygotes and disfavored homozygotes causes rapid changes in allele frequency. When the favored allele becomes common most individuals carrying the disfavored allele are heterozygous, and the small fitness difference between favored homozygotes and heterozygotes causes allele frequencies to change much more slowly (Figure 1). For the same reason changes in allele frequency occur slowly when an allele with recessive fitness effects is rare and much more rapidly when it is common. A deleterious recessive allele may be found in different frequencies in isolated populations even if it has the same fitness effect in every population, because natural selection is relatively inefficient when recessive alleles become rare, allowing the frequency to fluctuate randomly as a result of genetic drift.



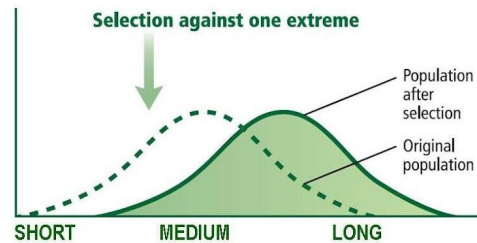


## ■ THE EFFECTS OF SEXUAL SELECTION ON THE HERITABILITY OF TRAIT

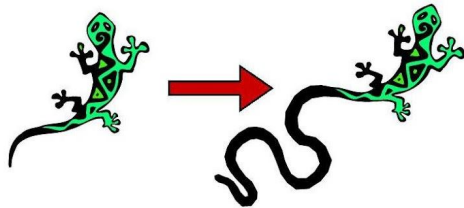
- Strong *directional selection* usually exhausts *additive genetic variance* for a trait in three to five generations. (In this context, this means traits governed by polygenic inheritance, or quantitative trait loci; see Chapter 3 on genetics.) This means that the proportion of variation in the phenotype due to genetic variation, or heritability, approaches zero. After that, there can be no further response to selection because the remaining phenotypic variation is from either environmental or nonadditive genetic variation. In theory, sexual selection on a trait such as antler size should rapidly eliminate the additive genetic variance for the trait. In other words, the trait will be genetically fixed. In practice, many traits that seem to be under strong sexual selection still have considerable heritability.

## HOW does the trait change?

### Directional Selection

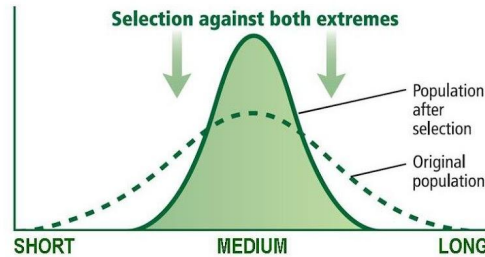


FOR: one extreme trait  
AGAINST: the other extreme

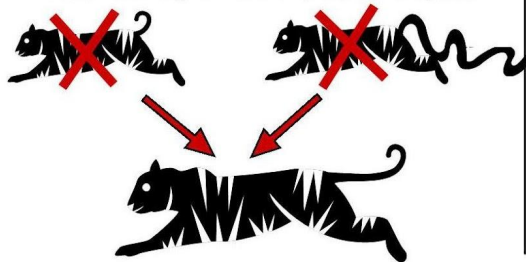


EX. Long wiggly tails look like a snake and scare predators. The longer the tail, the more it looks like a snake.

### Stabilizing Selection

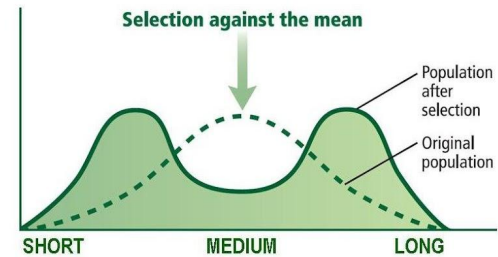


FOR: moderate traits  
AGAINST: both extremes

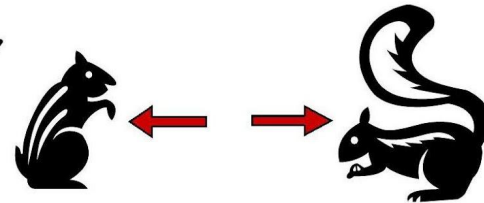


EX. Short tails mess up the cat's balance. Long tails drag on the ground. Medium tails are best.

### Disruptive Selection



FOR: both extremes  
AGAINST: moderate traits



EX. Short tails help keep predators from catching you on the ground. Long tails are good for balance in the trees. Medium tails don't help.

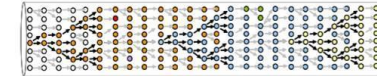


# SUBSTITUTIONAL LOAD

**Substitutional load** In genetics, the cost in genetic deaths to the population of replacing one allele by another (a mutation) in the course of evolutionary change. When **load** is calculated as the difference between the fittest genotype present and the average, this creates a **substitutional load**

Genetic load: substitutional

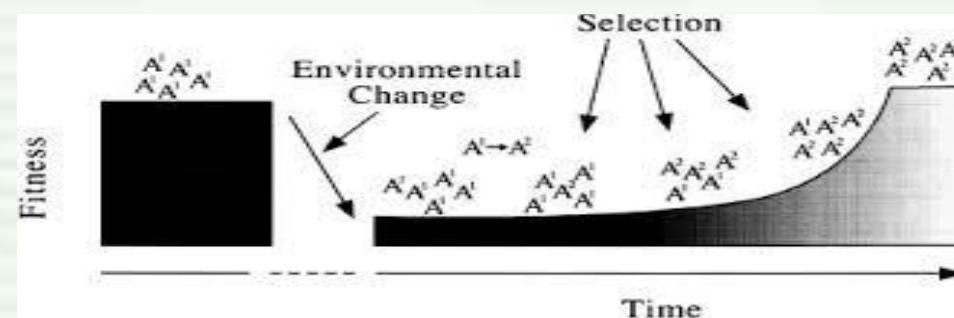
= substitution by "type 1" directional selection



Deleterious recessive			
Genotype	AA	Aa	aa
Frequency	$p_0^2$	$2p_0q_0$	$q_0^2$
$w_{\text{model}}$	1	1	$1 - s$
$w'$	1	1	0.66

Haldane's "cost of selection" is associated with fixation of an allele under a model such as the one above.

Haldane assumed this type of load to estimate that the maximum rate of fixation of mutations in humans could not exceed 1 in 300 generations



# SEGREGATIONAL OR RECOMBINATION LOAD

- Segregation load is the presence of under dominant heterozygote's (i.e. heterozygote's that are less fit than either homozygote).
- Recombination load arises through unfavorable combinations across multiple loci that appear when favorable linkage disequilibria are broken down.

HAZARDOUS MATERIALS LOAD AND SEGREGATION CHART

CLASS	HAZARD	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0
1	EXPLOSIVES very insensitive explosives	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0
	EXPLOSIVES insensitive explosives and insensitive gases	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0		
	EXPLOSIVES very insensitive explosives	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0			
	VERY INSENSITIVE EXPLOSIVES	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0				
	EXTREMELY INSENSITIVE EXPLOSIVES	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0					
2	FLAMMABLE GASES	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0										
	FLAMMABLE GASES	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0											
	POISONOUS GAS ZONE A	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0												
	POISONOUS GAS ZONE B	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0													
	FLAMMABLE LIQUIDS	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0														
	FLAMMABLE SOLIDS	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																														
	SPONTANEOUSLY COMBUSTIBLE MATERIALS	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																															
	DANGEROUS WHEN WET MATERIALS	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																																
5	OXIDIZERS	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																																								
	ORGANIC PEROXIDES	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																																									
	POISONOUS LIQUIDS PG I ZONE A	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																																																		
7	RADIOACTIVE MATERIALS	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																																																												
8	CORROSIVE LIQUIDS	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																																																																						

LEFT SIDE: HAZARDOUS LOADS (HOW THEY SEGREGATION) AND RIGHT SIDE: HAZARDOUS MATERIALS AND SEGREGATION

3	COMBUSTIBLE LIQUIDS	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0
6	OTHER POISONOUS LIQUIDS PG I ZONE A	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																														
9	MISCELLANEOUS	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0																																																												

1	EXPLOSIVES	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5
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# **CAUSES**

**Some causes are :-**

- ☐ Deleterious mutation**
- ☐ Beneficial mutation**
- ☐ Inbreeding**

# DELETERIOUS MUTATION

It is the main contributing factor to genetic load overall. Most mutations are neutral or slightly deleterious and occur at a constant rate. The Haldane-Muller theorem of mutation selection balance says that the load depends only on the deleterious mutation rate and not on the selection coefficient. Specifically, relative to an ideal genotype of fitness 1, the mean population fitness is  $\exp(-U)$  where  $U$  is the total deleterious mutation rate summed over many independent sites. The intuition for the lack of dependence on the selection coefficient is that while a mutation with stronger effects does more harm per generation, its harm is felt for fewer generations.

# **BENEFICIAL MUTATION**

- **New** beneficial mutations create fitter genotypes than those previously present in the population. When load is calculated as the difference between the fittest genotype present and the average, this creates a substitution load . The difference between the theoretical maximum (which may not actually be present) and the average is known as the "lag load".  
Kumar's original argument for the [neutral theory of molecular evolution](#) was that if most differences between species were adaptive, this would exceed the speed limit to adaptation set by the substitutional load. However, Kimura's argument confused the lag load with the substitutional load, using the former when it is the latter that in fact sets the maximal rate of evolution by natural selection.
- More recent "travelling wave" models of rapid adaptation derive a term called the "lead" that is equivalent to the substitutional load, and find that it is a critical determinant of the rate of adaptive evolution.



# INBREEDING

- Inbreeding increases homozygosity In the short run, an increase in inbreeding increases the probability with which offspring get two copies of a recessive deleterious alleles, lowering fitnesses via inbreeding depression In a species that habitually inbreeds, e.g. through self fertilization, recessive deleterious alleles are purged.

**THANK YOU**