Crimean state medical University named after S. I. Georgievsky

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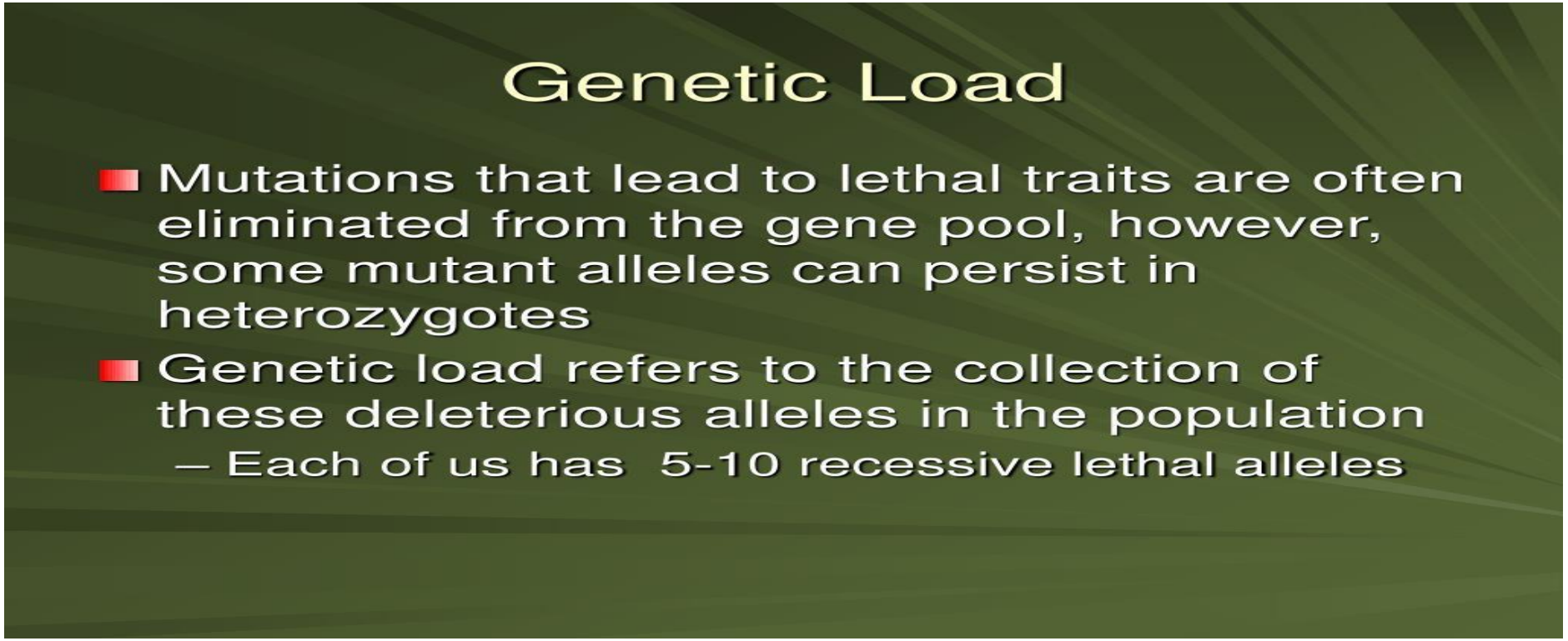
Key points to discuss about Genetic load.

- Key Concepts:
- 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 can also be caused by recombination breaking up beneficial combinations of alleles, segregation reducing the frequency of fit heterozygotes, or migration bringing less fit alleles into a local population.

What is genetic load ?



Genetic 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.[1][2] 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.[3] High genetic load may put a population in danger of extinction.

Genetic Load Sources

- The mutation load is the decrease in fitness or viability (or other trait of interest) caused by recurrent harmful mutations. As pointed out independently by J.B.S. Haldane and H.J. Muller, the effect of mutation on fitness is independent of the harmful effects of the individual mutations, but rather is equal to the total mutation rate per gamete, multiplied by a factor of 2 if the mutants are dominant. This formulation assumes that the mutations at different loci act independently. When there is epistasis the formula is modified (see Haldane–Muller Principle). The mutation load theory was used in the 1960s in an attempt to assess the total impact of mutation on the population, particularly the human population, and its possible increase from radiation and chemical mutagens.
- 1) Mutation Load.
- 2) Substitutional Load.
- 3) Segregation Load.

Direct Evidence of change in Mutational load in Humans.

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**.

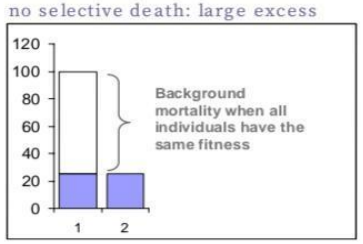
The extent to which selection has shaped present-day human populations has attracted intense scrutiny, and examples of local adaptations abound. However, the evolutionary trajectory of alleles that, today, are deleterious has received much less attention. To address this question, the genomes of 2,062 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.

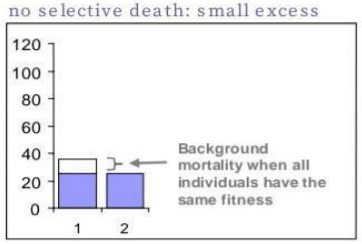
Genetic Load the Haldanes Dilemma.

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.





Population declines:

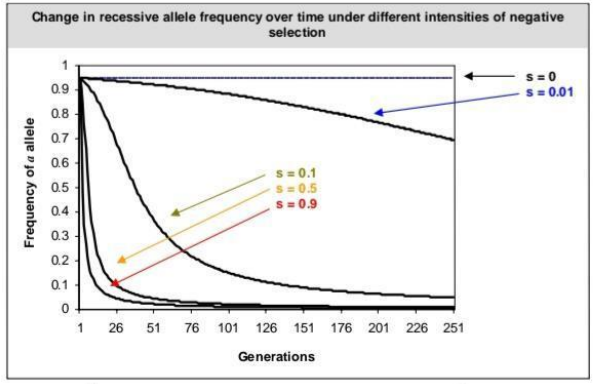
Genetic death > reproductive excess

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 muation to an beneficial domiant allele: it takes time for selection to remove the "old" [deleterious recessive] allele from the population.

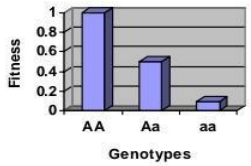


There is a cost to selection, in genetic death, during this time period

Directional Selection.

Defining directional selection

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



$w_{AA} > w_{Aa} > w_{aa}$

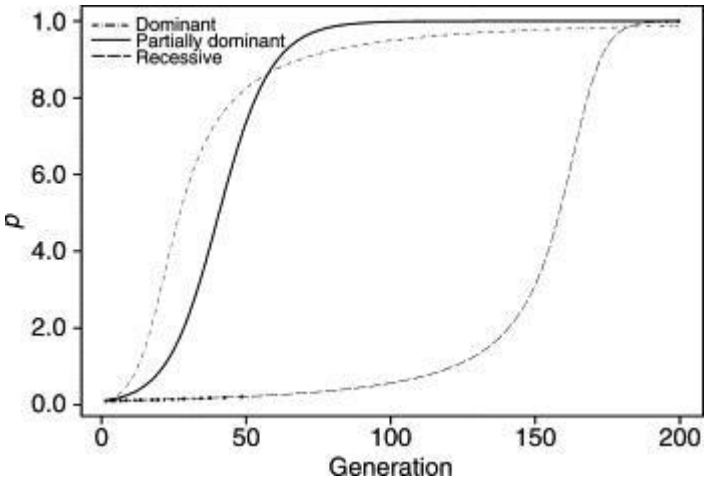
Directional selection: can be subdivided into two broad categories. These subtypes have been given different names, leading to a possible point of confusion. The next page is an attempt to clarify this issue.

In population genetics, **directional selection**, or positive **selection** is a mode of natural **selection** in which an extreme phenotype is favored over other phenotypes, causing the allele frequency to shift over time in the direction of that phenotype.

Some Key points About 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.

- 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.



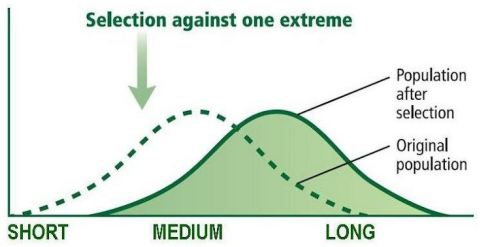
Effects of Sexual Selection on the Heritability of trait.

- Strong *directional selection* usually exhausts *additive genetic variance* for a trait in three to five generations. 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

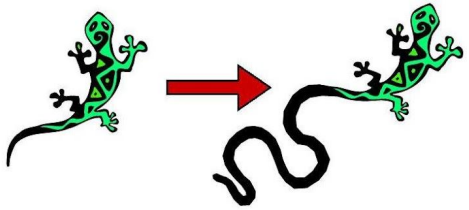
- There are a number of possible explanations for why selection does not eliminate all of the additive genetic variance for traits involved in mate choice. They include the following:
- 1.Sexual selection is strong only under extreme environmental conditions in which survivorship is low. Variance is maintained during periods of relaxed selection.
- 2.Interactions with other traits (e.g., linkage effects, viability effects) limit sexual selection before the additive variation is exhausted.
- 3.Mate choice relies on many factors, rather than one trait. When selection acts on multiple traits, they limit each other's evolution so that variation remains for each of the traits.
- 4.Counterbalancing selection for factors like protection from predators maintains additive genetic variance by limiting the elaborateness of a signal.[22,23] It is hard to overemphasize the complexity of mate choice and the need to consider multiple factors involved in any mate choice decision.

HOW does the trait change?

Directional Selection

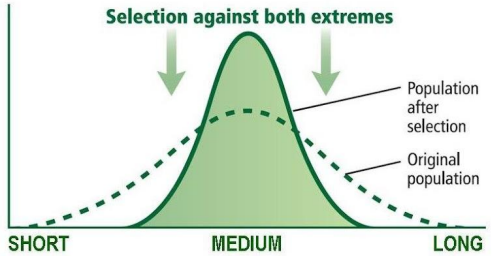


FOR: one extreme trait
AGAINST: the other extreme

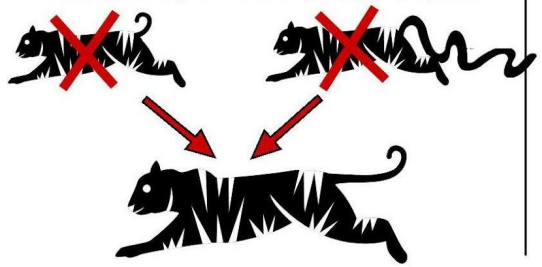


EX. Long wiggly tails look like a snake and scare predators. The longer the tail, the more it looks like a snake.

Stabilizing Selection

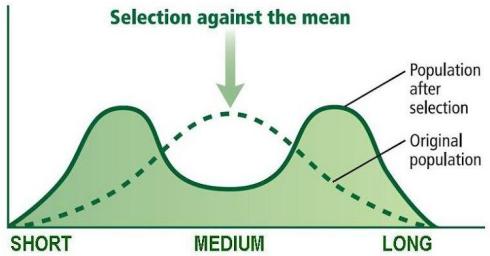


FOR: moderate traits
AGAINST: both extremes

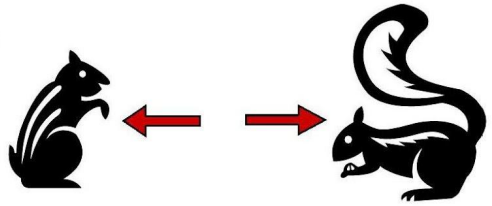


EX. Short tails mess up the cat's balance. Long tails drag on the ground. Medium tails are best.

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.

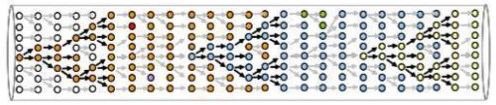
Plasmids role as an genetic Load

Plasmids represent an added genetic load to their host cell and must be maintained by positive selection, most often for a plasmid-encoded antibiotic resistance trait. Growth in the presence of antibiotics seems to have a generalized dampening effect on chemotactic performance in soft agar plates, perhaps owing to slowed growth rates. To ameliorate this effect as much as possible, we routinely halve the usual concentration of an antibiotic for use in soft agar plates.

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_{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.

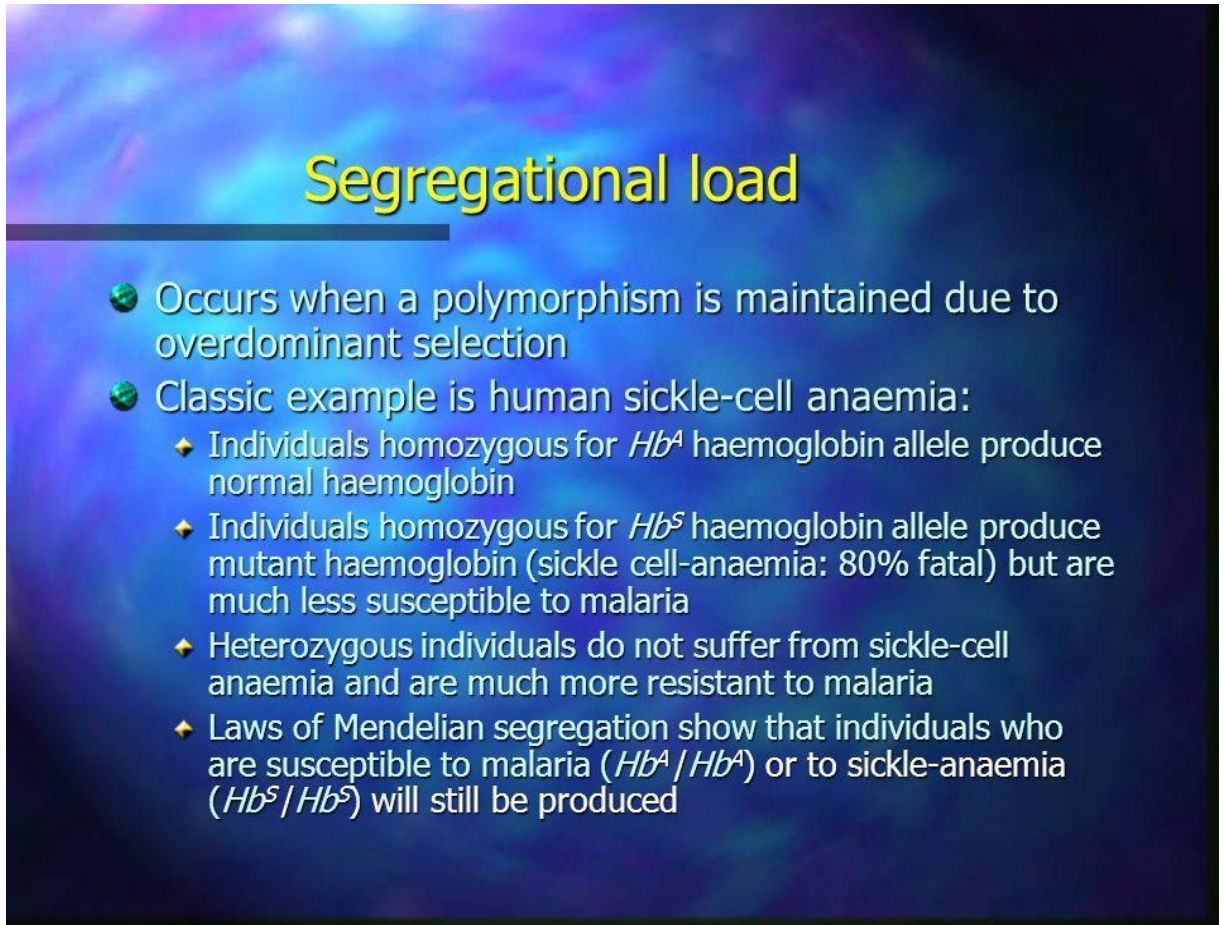
Haldane assumed this type of load to estimate that the maximum rate of fixation of mutations in humans could not exceed 1 in 300 generations

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**

Segregational or recombination load

high levels of heterozygosity could be maintained by **overdominant selection** at multiple loci, if alternative alleles at a locus were advantageous under different circumstances (e.g., environments, or tissue types).



Causes :

- **Deleterious mutation**
- Deleterious mutation load is the main contributing factor to genetic load overall.[5] Most mutations are neutral or slightly deleterious[*citation needed*], and occur at a constant rate[*citation needed*]. 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.[6] Specifically, relative to an ideal genotype of fitness 1, the mean population fitness is {\displaystyle \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.

Some New Beneficial Mutations.

- **Ne**w 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 substitutional load. The difference between the theoretical maximum (which may not actually be present) and the average is known as the "lag load".[ ] Motoo Kimura'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.[18] 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.[19]
- 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.[22] In a species that habitually inbreeds, e.g. through self-fertilization, recessive deleterious alleles are purged.

Thank You