Genetics and Genomics

5. Evolution and Population Genetics

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The Human Evolutionary Tree
The Great Human Migrations

Human Population Structure
3 Giants of Population Genetics

RA Fisher’s “Genetical Theory of Natural Selection” (1930) founded the field, integrating mathematics with genetics.

JBS Haldane started to integrate evolutionary theory with population genetics in “The Causes of Evolution.”

Sewall Wright’s “Shifting Balance” theory initiated the Modern Synthesis.

The Hardy-Weinberg Principle

- $p^2 + 2pq + q^2 = 1$
- $p$: frequency of A allele
- $q$: frequency of a allele
- $p^2$: frequency of AA homozygotes
- $2pq$: frequency of Aa heterozygotes
- $q^2$: frequency of aa homozygotes

Equilibrium is reached in a single generation after two populations meet.

In the absence of selection, migration, mutation and inbreeding, allele frequencies do not change.
The Major Evolutionary Processes

- Genetic drift
- Natural selection
- Mutation
- Migration (gene-flow)
- Mating structure

- These processes are mechanisms of evolution

- Additional factors:
  - Recombination (and linkage), gene conversion, ploidy, dominance, epistasis, developmental constraints

Founder Effects, Migration, and Drift

Migration can lead to founder effects in which new populations have altered allele frequencies.
Drift reduces heterozygosity over time

- In small populations there is a decay of heterozygosity:
  \[ H_t = H_0 \left( 1 - \frac{1}{2N} \right)^t \]
- The net effect of drift is to reduce the amount of genetic variation segregating in a population

1000 Years of Drift has shaped Iceland

Genes mirror geography across Europe!


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**Natural Selection**

- **Natural selection**: The differential survival and/or reproduction of different genotypes due to unequal fitnesses
- Natural selection is not the same thing as evolution
- Selection coefficient ($s$)
  - $s = 0.01$ indicates a 1% fitness advantage
  - $|s|$ tends to be close to 0
- Operates on short time scales (~1/s generations)
- The outcome of natural selection depends on fitnesses and initial frequencies
- Probability of fixation: ~2s
  - Most advantageous mutations are not fixed
Drift and Inbreeding

\[ F_{ST} = \frac{Var(p)}{\bar{p}(1-\bar{p})} \]

- \( F_{ST} \) measures how much genetic variation can be explained by sub-populations within the total population

\[ F = 1 - \frac{H}{2pq} \]

- Inbreeding coefficient \( (F) \): Another F-statistic can be used to quantify the effects of inbreeding (the inbreeding coefficient)

- Inbreeding results in an excess of homozygotes

Inbreeding due to Consanguinity in Humans

- Consanguinity: closer than 2\textsuperscript{nd} cousin mating \( (F > 0.015625) \)
Types of Natural Selection

A (rare) Example of Natural Selection in Humans

- Figures from Gerbault et al. 2011 (*Phil Trans Roy Soc B*)
- Lactase persistence alleles show evidence of positive selection
- Different causal alleles in Africa (convergent phenotypic evolution)
Summary of the Evolutionary Processes

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Motoo Kimura’s Neutral Theory of Molecular Evolution

- Drift + mutation
- Most mutations are deleterious (bad)
- Most polymorphisms are neutral (neither good nor bad)
  - Synonymous changes (codon change, but same amino acid)
  - Pseudogenes: “dead genes” that are no longer expressed
  - Intergenic DNA
- A balance exists between a decrease in variation due to drift and an increase in variation due to mutation

$$\Delta H_{mutation} = 2\mu(1 - H)$$
$$\Delta H_{drift} = -\left(\frac{1}{2N}\right)H$$

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Mutation – Selection Balance

- Mutation + selection
- Deleterious mutants increase in frequency by mutation
- Deleterious mutants are reduced in frequency by selection
- There exists an equilibrium allele frequency where the magnitude of these two forces are balanced:
- Alleles under mutation-selection balance are rare

\[ \Delta p_\mu \approx \mu \quad \text{and} \quad \Delta p_s \approx -ps \]

Detection of Recent Selection

Compared to genomics
- Neutral: Non-synonymous, Synonymous
- Polymorphic: Fixed, Derived

Haplotype statistics
- Neutral: Derived, Genome position

Allele frequencies
- Proportion of positively selected alleles

Multiple populations
- Neutral: Population 1, 2, 3

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Adaptation to High Altitude

- Reduced $[O_2]$ is a strong selective pressure
- Allele frequencies compared between Tibetans (TIB) and Han Chinese from Beijing (HAN)
- Outlier SNPs are located near EPAS1, a hypoxia-induced transcription factor
- The Tibetan EPAS1 haplotype comes from Denisovans (Huerta-Sanchez et al. 2014)
- Positively selected EPAS1 haplotype contains a deletion that occurred 12kya (Lou et al. 2015)


Adaptation to prevalent Malaria (Hb S)
Population Differences in Polygenic Disease Risk

Lots of caveats to comparisons across populations!!

BUT, we think differences in allele frequency rather than allelic effects mostly differentiate populations

But don’t forget about the environment!

US Adult Obesity Maps from CDC