Chapter 2 – Genotype Frequencies

Mendelian Genetics

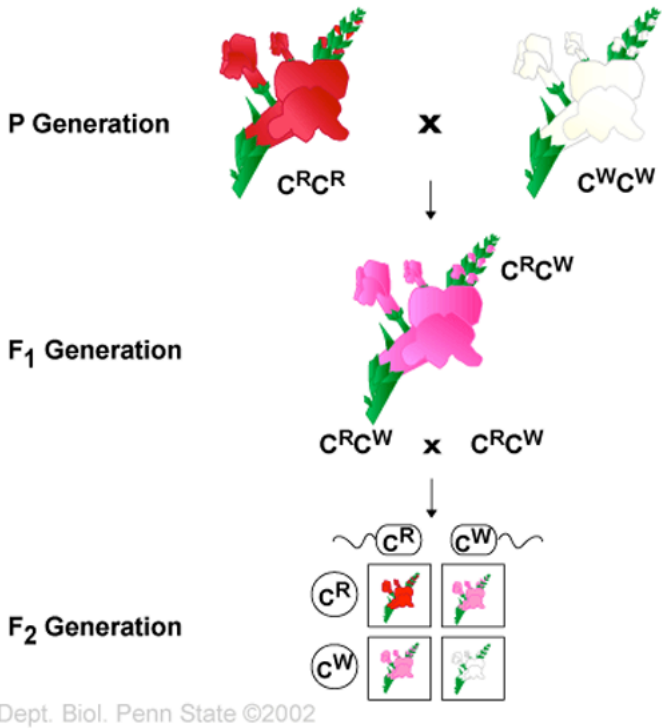
Hardy-Weinberg Equilibrium

Heterozygosity & Inbreeding

Linkage and Recombination

Mendel's "Laws"

- Independent segregation
  - two members of a gene pair (alleles) segregate separately into gametes so that half of the gametes carry one allele and the other half carry the other allele
- Independent assortment
  - during gamete formation, the segregation of alelles of one gene is independent of the segregation of alleles of another gene



“Population”

- “a group of organisms of the same species living within a … restricted geographical area so that any member can potentially mate with any other member of the same species”
  - Hartl & Clark, 2006
- “a population is a group of plants, animals, or other organisms, all of the same species, that live together and reproduce”
  - N.J. Gotelli, 1998
- “local population” = “deme” = “subpopulation”
  - fundamental unit of population genetics

Hardy-Weinberg Assumptions

- theoretical population genetics relies on a set of simplifying assumptions about the structure of populations
  - random mating*
  - non-overlapping generations*
  - migration (gene flow), mutation, and natural selection have negligible effects
  - **"large"** population size (= no genetic drift)
  - sexual reproduction
  - two alleles at a locus
  - allele frequencies equal in two sexes

Hardy-Weinberg Equilibrium (1908)

- relates allele and genotype frequencies assuming random mating
- Hardy considered the principle obvious…
- but presented it to refute an argument that 3:1 phenotypic ratios should be common in nature if inheritance was really Mendelian
  - phenotypic ratios depend on allele frequencies
- also shows that genetic variation is maintained in the absence of selection, drift, mutation
  - contrast to earlier notions of "blending inheritance"

Hardy-Weinberg Equilibrium (1908)

$$(p+q)^2 = p^2 + 2pq + q^2$$

$$(A+a)^2 = AA + 2Aa + aa$$

- HW model separates life history into two stages:
  - gametes combining to form zygotes
  - zygotes maturing into adults which produce more gametes
- more complex models including selection, drift, mutation, etc., still apply the HW principle in the formation of zygotes each generation

H-W Inferences:

- random mating of genotypes yields the same result as random union of gametes (see pg. 18 in text and do the math!)
- a population out of HW equilibrium reaches HW equilibrium in a single generation of random mating
- differences between sexes in allele frequencies at autosomal loci are eliminated in a single generation of random mating

Statistical Tests

- Chi-squared test
  - estimate allele frequencies from phenotypes or directly from genotypes
  - use to calculate "expected" genotype frequencies
  - compare with observed genotype frequencies

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

- What does a "statistically significant" result tell us?

http://faculty.vassar.edu/lowry/csfit.html

Dominance

- with dominance and allele frequencies estimated from phenotypes, there are no degrees of freedom left for a statistical test
- $\hat{q} = \sqrt{R}$, where R is the frequency of the recessive phenotype

Other Statistical Tests

- Chi-squared test not valid for small sample sizes, corrections available but may be too conservative
- Alternatives:
  - Exact test

$$\Pr\{n_{12} \mid n_1, n_2\} = \frac{n!/(n_{11}!n_{12}!n_{22}!)}{(2n)!/(n_1!n_2!)} 2^{n_{12}}$$

  - Permutation test

Multiple tests

- Testing multiple loci for HWE increases the likelihood of false positives
- Remedies:
  - Bonferroni correction: $p < 0.05/m$, where m is the number of independent tests
    - much too conservative!
  - Control of "false discovery rate"
    - e.g., Benjamini & Hochberg (1995,J. Roy. Stat. Soc.)
    - order p-values from smallest to largest, then find the largest i for which:

$$P_i \leq \frac{i}{m} q^*$$

Additional points…

- rarity of homozygotes for rare allele
  - most copies of rare alleles (e.g., recessive deleterious alleles) are in heterozygotes
- X-linked genes
  - male genotypes = allele frequencies
    - in XY systems
  - X-linked diseases
- multiple alleles
  - frequency of A_iA_i homozygotes = p_i^2
  - frequency of A_iA_j heterozygotes = $2p_ip_j$