

Chapter 4: Properties of Single Loci

Introduction

too easy

Allele and genotype frequencies

too easy

The transmission of genetic information

The Hardy-Weinberg principle

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

where p = allele frequency of first allele at a locus and q = allele frequency of the second allele at that same locus.

Assumptions of H-W:

- No selection
- No mutation
- Random mating
- No differential migration
- No random drift

Even though these assumptions will never be met completely in the real world, for the majority of the time the H-W principle holds regardless.

Assuming assumptions are met, 2 important points from H-W:

1. It takes no more than a single generation equilibrate and stabilize gene frequencies in the two sexes.
2. Only one additional generation is required for the stabilisation of the genotype frequencies into the predictable Hardy-Weinberg proportions.

Sex-linked loci

Alleles on sex chromosomes in diploid organisms are obviously different. Sons can only receive an X chromosome from their mother so the frequency of X linked loci in the sons is equal to that of their mothers. Daughters receive both an X chromosome from Mum + from Dad.

Overall this means allele frequencies oscillate around an equilibrium state, but continually get closer to that state over the generations (see Figure 4.2 and page 56 for equation).

Polyploidy

Skipped over this section because it's not relevant to human quant gen. Buuut, essentially it just details how to derive allele frequencies under a certain case of polyploidy. Also, it should be noted that of course H-W does not hold under polyploidy!

Age structure

Age structure also complicates our idealised model of H-W. In populations composed of several age classes, the generations overlap, and this causes the approach of genotype frequencies towards the H-W expectations to be gradual (rather than just by 1/2 generations), even in the case of an autosomal locus. Doesn't explain this very much, but it's covered elsewhere. Importantly, when newly founded populations have significant age structure, fluctuations in both gene and genotype frequencies may occur for a substantial period of time even in the absence of selection!

Testing for Hardy-Weinberg proportions

Says in the book that LRT can be used to test for departures from HWE, buuuut I'm pretty sure that even now the most common method is the chi-squared test (or Fisher's exact test if the sample size is tiny and the allele is rare.). Essentially, in a population, at a specific locus, you can calculate the allele frequencies (and from that expected genotype frequencies) from the observed genotype frequencies then test if there is a difference between the observed and expected values. LRT equation for it given on page 60. **RECREATE THE CHI-SQUARED TEST IN CODE!!!!**

Should remember (as pointed out above), that just because some assumptions are violated, doesn't mean you'd get a departure from HWE!

Characterising the influence of a locus on the phenotype

If a trait is entirely influenced by a single locus then the genetic effect on that trait can be characterised pretty easily and the dominance and additive effects of the alleles can be calculated. So if a locus has genotypes B_1B_1 , B_1B_2 , B_2B_2 , then the values given to these genotypes can be said to be: $-a$, $(1+k)a$ and $+a$. Now if you have genotype data at that locus and data on the trait you can work out the effect of the B_2 allele by taking the mean phenotypic value of individuals with B_2B_2 and subtracting the mean phenotypic value of individuals with B_1B_1 and dividing by 2 i.e.

$$B_{2eff} = \frac{p_{B2} - p_{B1}}{2}$$

where B_{2eff} is the effect of allele B_2 , p_{B2} is the mean phenotypic value of individuals with B_2B_2 and p_{B1} is the mean phenotypic value of individuals with B_1B_1 .

As $B_{2eff} = a$ you can then substitute this in to $(1+k)a$ to get the dominance coefficient k . Of course if $k = 0$ then there is no dominance (in reality you would calculate probability of dominance).

The basis of dominance

Confusing part... Don't really get the enzyme activity bit...

Main point (I think) is that new deleterious mutations are very likely to be recessive and new mutations with a slight deleterious effect interact in an almost entirely additive fashion (no dominance!).

Fisher's decomposition of the genotypic value

Recalling that the phenotypic value can be partitioned like so:

$$z = G + E$$

where z is the phenotype, G is the genotypic value and E is the environmental value.

The genotypic value of a specific locus can be partitioned into its "expected" values based on there being only additive effects (\hat{G}) and the deviations from the expected values or dominance effects (δ). So for genotype B_iB_j :

$$G_{ij} = \hat{G}_{ij} + \delta_{ij}$$

This can be formalised (whatever the fuck that means) by regressing the genotypic values on the number of B_1 and B_2 alleles in the genotype (N_1 and N_2):

$$G_{ij} = \hat{G}_{ij} + \delta_{ij} = \mu_G + \alpha_1 N_1 + \alpha_2 N_2$$

μ_G = the mean genotypic value in the population, α_1 and α_2 are the slopes of the regression, N_1 and N_2 are the number of B_1 and B_2 alleles. So the regression is:

$$G_{ij} = \mu_G + \alpha_1 N_1 + \alpha_2 N_2$$

By noting that for any individual, $N_1 = 2 - N_2$ you can reduce the multiple regression model into an easier to work with univariate model. Give it a go:

$$G_{ij} = \mu_G + \alpha_1 (2 - N_2) + \alpha_2 N_2$$

If you plotted the genotypic value (G) against gene content (N_2 or number of B_2 alleles) and calculated residuals these residuals would be δ (see Figure 4.6).

The rest of the chapter uses this regression and what we know about genotype frequencies to derive a formula for the average effect of allelic substitution:

$$\alpha = a[1 + k(p_1 - p_2)]$$

where a = genotypic value of B_2 (see above), k is the dominance coefficient and p_1 and p_2 are the frequencies of B_1 and B_2 . This value α represents the average change in genotypic value that results when a B_2 allele is randomly substituted for a B_1 allele. If no dominance ($k = 0$) then $\alpha = a$. Except in the case of additivity, the average effect of allelic substitution is not simply a function of the inherent physiological properties of the allele. It can only be defined in the context of the population!

Partitioning the genetic variance.

Deriving variance of G :

$$G = \hat{G} + \delta$$

$$\sigma_G^2 = \sigma^2(\hat{G} + \delta)$$

$$\sigma_G^2 = \sigma^2(\hat{G}) + \sigma^2(\hat{G} + \delta) + \sigma^2(\delta)$$

The top equation is just like a regression, with δ being the residual error and we know that for least-squares there is no correlation between the residual error and the predictor. So there is no correlation between \hat{G} and δ . Therefore:

$$\sigma_G^2 = \sigma^2(\hat{G}) + \sigma^2(\delta)$$

OR more commonly

$$\sigma_G^2 = \sigma_A^2 + \sigma_D^2$$

σ_A^2 is the variance of G explained by regression on N_2 (or N_1), and σ_D^2 is the residual variance of that regression. The variance of the additive and dominance effects!

For a diallelic locus we can do some rearranging of equations in Table 4.1 of the book and get these equations:

$$\sigma_A^2 = 2p_1p_2\alpha^2$$

$$\sigma_D^2 = (2p_1p_2ak)^2$$

From these we can clearly see that both components depend on allele frequencies, the dominance coefficient and the homozygous effect (remember α is just the slope of the G N_2 regression!).

By plotting how genetic variance changes with gene frequency under different scenarios (**DEFINITELY DO THIS**). You see some interesting patterns. Firstly, at a single diallelic locus, you see that σ_A^2 reaches it's peak when $p_1 = p_2 = 0.5$. Secondly, it's clear that, even in the case of overdominance (which is rare!), additive genetic variance will almost always be much higher than genetic variance from dominance effects, even when the frequency of the dominant allele is high. (btw I think the scale on the top left graph is wrong...).

Additive effects, average excesses and breeding values

The dominance deviation of a parent, which is a function of the interaction between the two parental alleles, is eliminated when gametes are produced. Thus, one can think of \hat{G} and δ as the heritable and nonheritable components of an individual's genotypic value.

Fisher proposed two different measures of the effect of an allele: one being the additive effect (α_i) and then the average excess α_i^x . The average excess α_2^x of allele B_2 is the difference between the mean genotypic value of individuals carrying at least one copy of B_2 and the mean genotypic value of a random individual from the entire population:

$$\alpha_2^x = (G_{12}P_{12|2} + G_{22}P_{22|2}) - \mu_G$$

where P_{ij} is the conditional probability of a B_iB_j genotype given that one allele is B_i . Under random mating $P_{ij|i} = p_j$ (p_j = frequency of allele B_j). THINK ABOUT HARDY-WEINBERG AND IT MAKES SENSE!

So under random mating,

$$\alpha_2^x = G_{12}p_1 + G_{22}p_2 - \mu_G$$

$G_{12} = a(1 + k)$ and $G_{22} = 2a$. By substituting these into the equation above for α_1^x and α_2^x and then calculating α_1 and α_2 (additive effects) by the method previously mentioned (regressing genotypic value G on the number of B_2 alleles N_2), we will see they're equivalent (shown on page 72):

$$\alpha_2 = p_1\alpha$$

$$\alpha_1 = -p_2\alpha$$

The breeding value of an individual (A) is the sum of the additive effects of its genes. So the breeding value of a B_1B_1 homozygote is just $2\alpha_1$. In randomly mating populations the breeding value of a genotype is equivalent to twice the expected deviation of its offspring mean phenotype from the population mean. Soooo, no genotype information is needed to calculate the breeding value. All we have to do is mate an individual to many randomly chosen individuals from the population and taking twice the deviation of its offspring mean from the population mean. EASY IN HUMANS!!!

In Chapter 13 this will be discussed wrt candidate gene studies.

Extensions for multiple alleles and non random mating

So this section seems mostly irrelevant as we're unlikely to deal with situations with more than 2 alleles. Non-random mating could be encountered if we're interested in some phenotypes (e.g. alcohol intake). Buuuut, it's still good to note some of the generalised equations for what we've been discussing so far in the chapter.

Average excess

When n alleles are present, the average excess, α_i^x , for any allele B_i is given by

$$\alpha_i^x = \sum_{j=1}^n P_{ij|i} G_{ij} - \mu_G$$

Remember, under random mating $P_{ij|i} = p_j$

Additive effects

The genotypic value can also be obtained using regression as before, but in its generalised form is a multi-variate regression. For n alleles

$$G = \mu_G + \sum_{i=1}^n \alpha_i N_i + \delta$$

After some re-arranging can derive the regression coefficients and finally end with

$$\alpha_i = \sum_{j=1}^n p_j G_{ij} - \mu_G$$

i.e. under random mating, the average effects (α_i) are equal to the conditional mean deviations from the mean genotypic value of the population (μ_G).

For non-random mating we need the inbreeding coefficient, f to define our genotype frequencies:

$$\begin{aligned} P_{ii} &= (1-f)p_i^2 + fp_i \\ P_{ij} &= 2(1-f)p_i p_j \end{aligned}$$

Unsure of why, but this means

$$\alpha_i = \frac{\alpha_i^x}{1+f}$$

so f is the fractional reduction of heterozygote frequencies relative to those expected under random mating. This means you can kind of do a test for random mating by checking heterozygote and homozygote frequencies in a population!

Additive genetic variance

The additive genetic variance across n alleles is

$$\sigma_A^2 = 2 \sum_{i=1}^n p_i \alpha_i \alpha_i^x$$

In general inbreeding inflates the additive genetic variance by causing correlations among the effects of alleles within the same individuals.

The broad sense heritability, even under scenarios of non-random mating can be given by

$$\sigma_G^2 = \sigma^2(\alpha_i + \alpha_j) + \sigma^2(\delta_{ij})$$

although it should be noted that the definitions of α_i and δ_{ij} change with the degree of inbreeding! Random mating means α_i and α_j are uncorrelated so we get back to the good old equation

$$\sigma_G^2 = \sigma_A^2 + \sigma_D^2$$

Importantly, under random mating, σ_A^2 is equivalent to the variance of breeding values of individuals in the population.

Summarising some key terms

The homozygous effect, a , and the dominance coefficient, k , are intrinsic properties of allelic products. They are not functions of allele frequencies, but may vary with genetic background

The additive effect, α_i , and the average excess, α_i^x , are properties of alleles in a particular population. They are functions of a , k and genotype frequencies (p_i).

The breeding value, A , is a property of a particular individual in reference to a particular population. It's equivalent to the sum of the additive effects of an individual's alleles.

The additive genetic variance, σ_A^2 is a property of a particular population. It is equivalent to the variance of the breeding values of individuals within the population.
