Genetic Variation of Multilocus Traits

Intro to Multilocus Traits

- We previously discussed traits that are influenced by a single locus
- Most traits of interest, however, are expected to be influenced by numerous loci
- A number of factors must be considered for traits that are influenced by more than one locus including
  - Can genetic effects, including additive and dominance effects, defined for single locus be combined additively to explain the phenotypic variation association with multilocus genotypes?
  - Are there non-linear interactions?
  - Are the distribution of alleles at one locus independent of those at other loci?
  - What impact does environmental variability have on gene expression?

Intro to Multilocus Traits

- The joint occurrence of all of these sources of variation for most traits makes it unfeasible to identify the precise breeding value of any single individual

- Nevertheless, it is possible to characterize populations with respect to the relative magnitudes of different sources of phenotypic variation, i.e., we can partition the variance

- We previously showed that the genetic value and variance for a single locus with an arbitrary number of alleles (in both outbred and inbreed populations) can be partitioned into additive and dominance components.

- We will now use this same general approach to account for the contribution of all loci contributing to the expression a a quantitative trait

Epistasis

- We will focus on the two quantitative trait loci (QTL) case. The extension to higher number of QTL will be obvious.
- We previously defined the dominance effect at a single locus to be the deviation of the observed genotypic values from the expectation trait value based on the additive effects.
- So dominance is essentially a measure of non-additivity of allelic effects within loci
- When there are multiple quantitative trait loci, **epistasis** is defined to be the non-additivity of effects between loci.
- Epistasis can be viewed as the interaction of effects among loci.

General Expression for Quantitative Traits for Multi-Locus Traits

- Consider two loci that influence a quantitative trait were one locus has alleles A_i and A_j and the other locus has alleles B_k and B_l.
- We can define the genotypic value for an individual who has genotype $A_i A_j$ at locus 1 and $B_k B_l$ at locus 2 to be

$$G_{ijkl} = \mu_G + (\alpha_i + \alpha_j + \delta_{ij}) + (\alpha_k + \alpha_l + \delta_{kl}) + \varepsilon_{ijkl}$$

- The effect ε_{ijkl} can consist of very complex epistatic interactions!

General Expression for Quantitative Traits for Multi-allelic Locus

- With two loci there are three ways in which interactions between loci can arise

- There first is additive $\times$ additive interaction, which we will denote by $(\alpha\alpha)$ with superscripts for the different alleles at the two loci.

- There second is additive $\times$ dominance interaction, which we will denote by $(\alpha\delta)$ with subscripts for the alleles at one of the loci (for the additive effects) and the genotypes at the other locus (for the dominance effects)

- There third is dominance $\times$ dominance interaction, which we will denote by $(\delta\delta)$ with subscripts for the genotypes at the two loci.

- How many different types of epistasis are there with three QTLs?

Effects with multiple loci

- We defined earlier the genotypic value for an individual who has genotype $A_i A_j$ at locus 1 and $B_k B_l$ at locus 2 to be

$$G_{ijkl} = \mu_G + (\alpha_i + \alpha_j + \delta_{ij}) + (\alpha_k + \alpha_l + \delta_{kl}) + \varepsilon_{ijkl}$$

- We have that

$$\mu_G = \sum_{ijkl} P(ijkl) G_{ijkl} = G_{....}$$

- For the single locus case, the additive effect for an allele was shown to be equal to the deviation of the mean trait value for individuals with the allele from the population mean. The definition does not change with the addition of loci.

Additive Effects with Multiple Loci

- Let $G_{i...}$ represent the conditional mean phenotype value of individuals with allele i at the first locus such that

$$G_{i...} = \sum_{jkl} P(jkl|i) G_{ijkl}$$

- The additive effect for allele i at the first locus is

$$\alpha_i = G_{i...} - \mu_G = G_{i...} - G....$$

- The additive effect for allele k at the second locus is

$$\alpha_k = G_{..k.} - \mu_G = G_{..k.} - G....$$

where

$$G_{..k.} = \sum_{ijl} P(ijl|k) G_{ijkl}$$

Dominance Effects with Multiple Loci

- The dominance effects are defined by obtaining the conditional mean phenotype values for individuals with a given genotype at a locus. The dominance effect for genotype $A_i A_j$ and genotype $B_k B_l$ are

$$\delta_{ij} = G_{ij..} - \mu_G - \alpha_i - \alpha_j$$

$$\delta_{kl} = G_{..kl} - \mu_G - \alpha_k - \alpha_l$$

where

$$G_{ij..} = \sum_{kl} P(kl|ij) G_{ijkl}$$

$$G_{..kl} = \sum_{ij} P(ij|kl) G_{ijkl}$$

Mean Additive and Dominance Effects with Multiple Loci

- For the multilocus case, the expected (or mean) additive effects is 0 at each locus and the expected dominance deviance is 0 at each locus are, as in the single locus case

Epistatic Effects with Multiple Loci

- For the additive $\times$ additive effects, we define $G_{i.k.}$ to be the marginal phenotype mean for individuals who have an allele i at locus 1 and an allele k and locus 2 where

$$G_{i.k.} = \sum_{jl} P(jl|ik) G_{ijkl}$$

- Then the ikth additive $\times$ additive effect is

$$(\alpha\alpha)_{ik} = G_{i.k.} - \mu_G - \alpha_i - \alpha_k$$

- So $(\alpha\alpha)_{ik}$ is the deviation from the marginal mean $G_{i.k.}$ from the expected value based on the population mean and the additive effects α_i and α_k at the two loci.

Epistatic Effects with Multiple Loci

- The additive $\times$ dominance effects measures the interaction between an allele at one locus and a particular genotype at the other locus.
- It is defined to be the deviation of the conditional mean for an individual with a particular allele at one locus and a particular genotype at another locus from the expected value based on all lower-order effects. For the two loci case, we have the following lower-order effects:
  - the three additive effects
  - one dominance effect
  - the two additive $\times$ additive effects involving the allele at one locus and the two alleles at the other locus
- So that the additive $\times$ dominance effects for allele i and locus 1 and genotype kl at locus 2 is

$$(\alpha\delta)_{ikl} = G_{i.kl} - \mu_G - \alpha_i - \alpha_k - \alpha_l - \delta_{kl} - (\alpha\alpha)_{ik} - (\alpha\alpha)_{il}$$

Epistatic Effects with Multiple Loci

- The final epistatic effect is the dominance$\times$ dominance effect which can be written as

$$(\delta\delta)_{ijkl} = G_{ijkl} - \mu_G - \alpha_i - \alpha_j - \alpha_k - \alpha_l - \delta_{ij} - \delta_{kl}$$

$$-(\alpha\alpha)_{ik} - (\alpha\alpha)_{il} - (\alpha\alpha)_{jk} - (\alpha\alpha)_{jl}$$

$$-(\alpha\delta)_{ikl} - (\alpha\delta)_{jkl} - (\alpha\delta)_{ijk} - (\alpha\delta)_{ijl}$$

- The dominance$\times$ dominance effect is the effect that is not accounted for by the combined additive, dominance, additive $\times$ additive, and additive $\times$ dominance effects.

Partitioning Effects of Trait with Multiple Loci

- Summing up all of the effects, we have that the genotypic value for the two locus case can be written as

$$G_{ijkl} = \mu_G + [\alpha_i + \alpha_j + \alpha_k + \alpha_l] + [\delta_{ij} + \delta_{kl}]$$
$$+ [(\alpha\alpha)_{ik} + (\alpha\alpha)_{il} + (\alpha\alpha)_{jk} + (\alpha\alpha)_{jl}]$$
$$+ [(\alpha\delta)_{ikl} + (\alpha\delta)_{jkl} + (\alpha\delta)_{ijk} + (\alpha\delta)_{ijl}] + (\delta\delta)_{ijkl}$$

- So, similar to the single locus case, we have partitioned the genetic values for the two-loci case into various components

- In samples with random mating and loci segregating independently, the total genetic variance is the sum of the variances of the effects at each locus, where we have

$$\sigma_A^2 = \sigma^2(\alpha_i) + \sigma^2(\alpha_j) + \sigma^2(\alpha_k) + \sigma^2(\alpha_l)$$
$$\sigma_D^2 = \sigma^2(\delta_{ij}) + \sigma^2(\delta_{kl})$$

Partitioning Effects of Trait with Multiple Loci

$$\sigma_{AA}^2 = \sigma^2[(\alpha\alpha)_{ik}] + \sigma^2[(\alpha\alpha)_{il}] + \sigma^2[(\alpha\alpha)_{jk}] + \sigma^2[(\alpha\alpha)_{jl}]$$

- And similarly, individual epistatic variances across loci can be summed to obtain σ_{AD}^2 and σ_{DD}^2.
- So the total genetic variance can now be written as a series of components:

$$\sigma_G^2 = \sigma_A^2 + \sigma_D^2 + \sigma_{AA}^2 + \sigma_{AD}^2 + \sigma_{DD}^2$$

Partitioning Effects of Trait with Multiple Loci

- In many applications, epistatic effects are often ignored with the rationalization that the magnitude of higher order effects are likely to be small relative to the additive and dominance effects

- This assumption does not always hold and epistatic interactions likely play an important role in the expression of many quantitative traits.

- Also note that for a quantitative trait with n loci, the number of additive effects is of order n while the number of di-allelic epistatic effects could potentially be of order n^2. So even if the epistatic effects are small, the sum of these effects can be large.

- The question that has still not yet been affirmed as to whether or not epistasis is the rule or the exception for quantitative traits.

Example: Quantitative Trait Influenced by Two Loci

- A quantitative trait is influenced by two loci. Locus 1 has alleles A and a, and locus 2 has alleles B and b. The frequency of the A allele is .2 and the frequency of the B allele is .5 in a population. The two loci are unlinked and the population is in HWE at the two loci.

- Below is a table with the mean trait values for each of the genotype combinations at the two loci in the population:

	Locus 2		
Locus 1	BB	Bb	bb
AA	2	4.4	6.0
Aa	5.2	4.6	6.8
aa	4.8	8.6	11.7

- Calculate the population mean
- Calculate the additive effects for locus 1

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- Joint probability distribution of genotypes at the two loci:

	Locus 2		
Locus 1	BB	Bb	bb
AA	.01	.02	.01
Aa	.08	.16	.08
aa	.16	.32	.16

Example: Quantitative Trait Influenced by Two Loci

- $\mu_G = 7.256$
- $\alpha_A = -2.176$
- $\alpha_a = 0.544$