Reading: Chapter 7.

Up until now we have described how the phenotypic variation can be partitioned into components due to genetics and environment given knowledge of a QTL. We have not discussed the important issue of how to estimate these components when we don't know the number and location of QTLs.

$\Rightarrow$ estimation can be accomplished by noting that the sources of variation contribute differentially between different types of relatives

Suppose for now that there is no gene by environment interaction and that we are considering two individuals:

$$z_x = G_x + E_x + e_x$$

and

$$z_y = G_y + E_y + e_y$$

What is the covariance between z_x and z_y?

$\sigma(z_x, z_y) =$

If we assume that there is no genotype-environment covariance,

$\sigma(z_x, z_y) =$

Measures of relatedness

In order to define relatedness between two individuals, we must select a reference population. For a pedigree, we will define our reference population to be the oldest generation within the pedigree.

$\Rightarrow$ once a reference population is selected we can begin to discuss whether two alleles chosen between or within individuals are **identical by descent**

$\Rightarrow$ two alleles are **identical by descent** if they are direct descendents of a specific gene carried in some ancestral individual

$\Rightarrow$ **identical by descent (ibd)** is different from **identical by state (ibs)**

Coefficients of Identity

There are 4 genes to consider between two individuals. This translates into 15 possible identity by descent configurations.

If we ignore the ordering of genes by maternal and paternal descent, then there are 9 identity states called the **condensed coefficients of identity**. Their probabilities are denoted by Δ_1 to Δ_9.

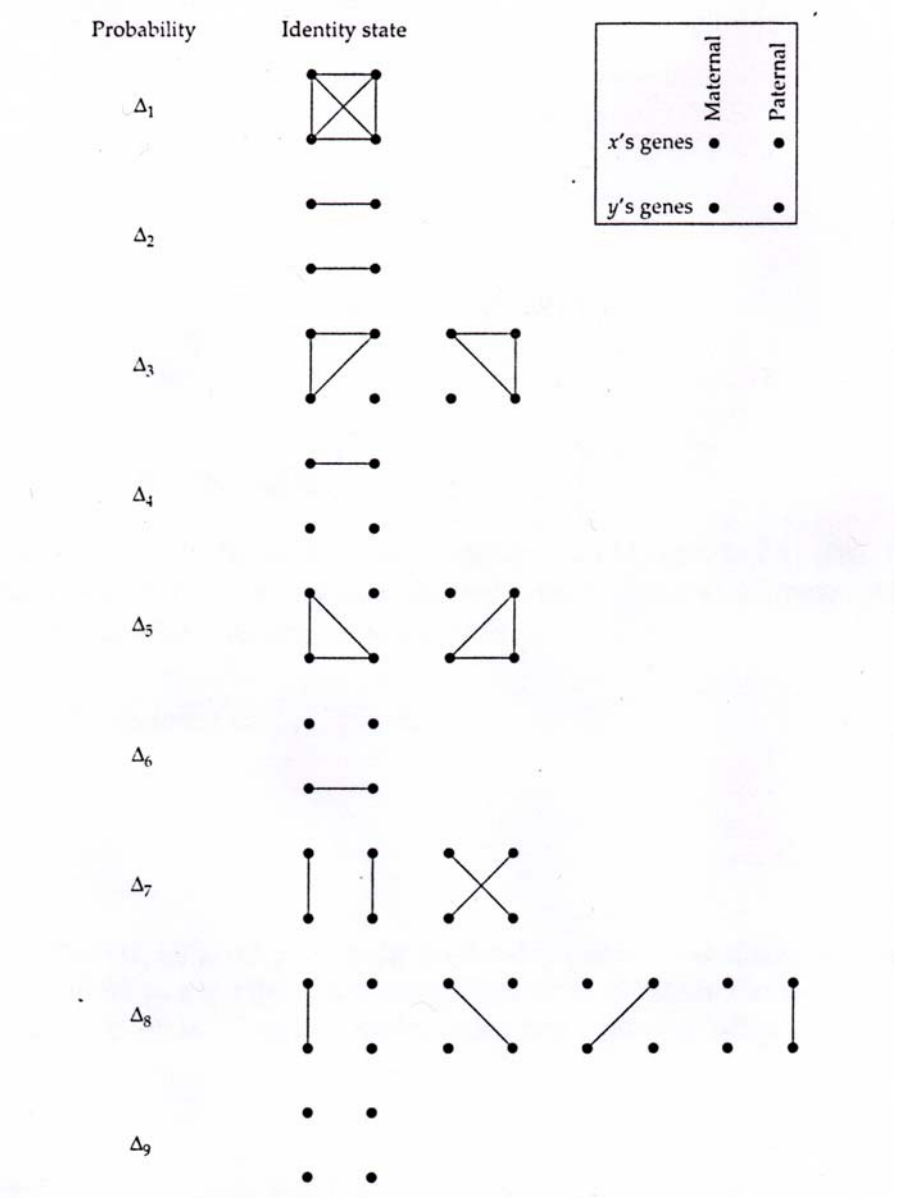


Figure 7.2 The 15 possible states of identity by descent for a locus in individuals x and y, condensed into nine classes. Genes that are identical by descent are connected by lines.

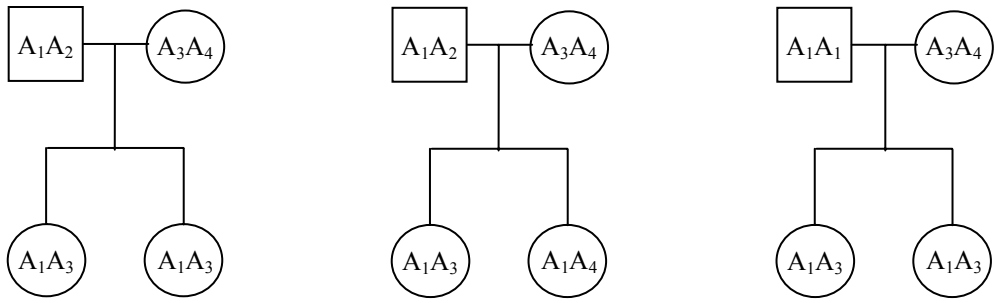
Coefficients of Coancestry and Inbreeding

Suppose that a gene is randomly drawn from both individual *x* and individual *y*. The probability that these two genes are identical by descent is the **coefficient of coancestry** (also called the coefficient of kinship) and denoted by Θ_{xy}.

Write Θ_{xy} in terms of $\Delta_1, \ldots, \Delta_9$:

Coefficient of Fraternity

The coefficient of fraternity for individuals *x* and *y*, denoted by Δ_{xy}, is the probability that individuals *x* and *y* share both of their alleles identical by descent.



Both
ibd?

There are two possible ways that a pair of individuals can share both of their alleles at a particular locus.

- they share their maternal alleles ibd and they share their paternal alleles ibd
- the maternal allele for individual *x* is ibd to the paternal allele for the individual *y* AND the paternal allele for individual *x* is ibd to the maternal allele for individual *y*

We can write this in terms of our coefficients of coancestry:

Δ_{xy}=

Table 7.1 of the text gives the condensed coefficients of identity and the coefficients of coancestry and fraternity for common relationships under the assumption of no inbreeding.

GENETIC Covariance between Relatives

We can now derive the genetic covariance between a pair of individuals. We will begin with several assumptions (a number of these can be relaxed):

- all of the genetic variation is due to diallelic autosomal loci
- mating is random
- loci are unlinked and in gametic phase equilibrium
- no genotype-environment covariance or interaction
- no genetic variation due to maternal effects
- no selection

Suppose we consider a trait that is influenced by two loci and that we are interested in the covariance between individuals *x* and *y*.

$G_{ijkl}^{x} =$

$G_{mnst}^{y} =$

Our formulation for the various genetic effects was such that effects within individuals are uncorrelated. Fisher (1918) showed that these effects are uncorrelated between individuals as well if the above assumptions are satisified.

This gives us a very nice expression for the genetic covariance:

$\sigma_G(x,y) =$

Another nice feature of our formulation for the various genetic effects is that each effect has mean 0. Thus

$\sigma_A(x,y) =$

Likewise,

$\sigma_D(x,y) =$

In general, the covariance due to higher-order epistatic effects is equal to the product of $2\Theta_{xy}$ for each additive component, Δ_{xy} for each dominant component and the variance component for the higher-order interaction.

For example, $\sigma_{AA}(x,y) = (2\Theta_{xy})^2\sigma^2_{AA}$ and $\sigma_{AD}(x,y) = (2\Theta_{xy})\Delta_{xy}\sigma^2_{AD}$.

Table 7.2 Coefficients for the components of genetic covariance between different types of relatives under the assumptions of random mating, free recombination, and gametic phase equilibrium.

Relationship	σ^2_A	σ^2_D	σ^2_{AA}	σ^2_{AD}	σ^2_{DD}
Parent–offspring	$\frac{1}{2}$		$\frac{1}{4}$		
Grandparent–grandchild	$\frac{1}{4}$		$\frac{1}{16}$		
Great grandparent–great grandchild	$\frac{1}{8}$		$\frac{1}{64}$		
Half sibs	$\frac{1}{4}$		$\frac{1}{16}$		
Full sibs, dizygotic twins	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{8}$	$\frac{1}{16}$
Uncle (aunt)–nephew (neice)	$\frac{1}{4}$		$\frac{1}{16}$		
First cousins	$\frac{1}{8}$		$\frac{1}{64}$		
Double first cousins	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{1}{16}$	$\frac{1}{64}$	$\frac{1}{256}$
Second cousins	$\frac{1}{32}$		$\frac{1}{1024}$		
Monozygotic twins (clonemates)	1	1	1	1	1

Note: To obtain the covariance expression for a particular type of relationship, multiply each variance component by its coefficient and sum. For example, the genetic covariance between half sibs is $(\sigma^2_A/4) + (\sigma^2_{AA}/16)$. Blanks indicate values of zero.

How might you go about estimating σ_A^2? How about σ_{AA}^2? What type of data would you need? What would be the most practical type of data that could be used? What us a major assumption that is being made concerning environmental effects?

Example: The following data is from Tregouet et al. (1999) Bivariate familial correlation analysis of quantitative traits by use of estimating equations: application to a familial analysis of the insulin resistance syndrome. Genet Epidem 16:69-83. What could you say about the genetic effects on each of these traits (if anything) from this data? How is the spouse correlation useful?

TABLE IV. Age- and Sex-Adjusted Family Intra-Trait Correlations (ρ)

	BMI	Insulin	TG	HDL-chol	DBP
Spouses	0.15**	0.18**	0.12*	0.28**	0.21**
Parent-offspring	0.33***	0.30***	0.23**	0.39***	0.25**
Sib-sib	0.36***	0.42***	0.34***	0.42***	0.27**

*$\rho < 0.15$; **$0.15 \leq \rho < 0.30$; ***$\rho \geq 0.30$; all correlations are significantly different from 0.

In our discussion of the genetic covariance between relatives, we made several assumptions. It is important to note that these can be relaxed. For instance, tables 7.3, 7.4 and 7.6 give adjustments for

- linkage between loci
- gametic phase disequilibrium
- assortative mating
- environmental effects (will discuss later)

Heritability

Heritability is the fraction of the total phenotypic variance attributable to additive genetic differences among individuals:

$$h^2 = \frac{\sigma_A^2}{\sigma_z^2}$$

Recall that the first component of the covariance between the trait for two individuals x and y is

$$2\Theta_{xy}\sigma_A^2.$$

If it is assumed that all other effects are negligible, then an estimate of the heritability could be obtained from:

$$\frac{Cov(z_x, z_y)}{2\Theta_{xy}Var(z)}$$

Great care must be taken with interpretation of this estimate. Violations of this assumption tend to lead to an upwardly biased estimate of heritability.