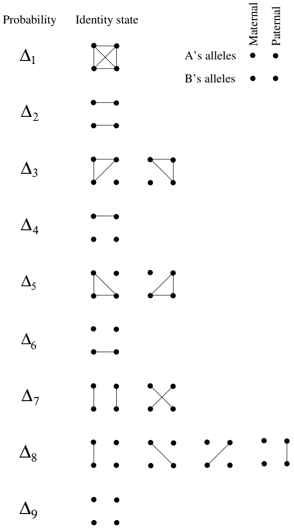
Genetic Covariance of Trait Values for Relatives

Coefficients of Coancestry

- We previously showed that for a pair of individuals that the kinship coefficient (or coefficient of coancestry) θ can be written in terms of Jacquard's 9 condensed coefficients of identity where

$$\theta = \Delta_1 + \frac{1}{2}(\Delta_3 + \Delta_5 + \Delta_7) + \frac{1}{4}\Delta_8$$

Jacquard's (1970) 9 Condensed Coefficients of Identity



Coefficients of Coancestry

- Consider an outbred population. For outbred populations we have that Δ_1 to Δ_6 are 0.
- it is convenient to let k_2, k_1 and k_0 represent the probability that a pair of outbred individuals sharing 2, 1, or 0 alleles IBD, respectively, in lieu of Δ_7, Δ_8, and Δ_9.
- For outbred populations the kinship coefficient for a pair of individuals can be written as

$$\theta = \frac{1}{2}k_2 + \frac{1}{4}k_1$$

- Note that the kinship coefficient is based on the probability of sharing 0, 1, or 2 alleles IBD. However, at a locus, a pair of individuals actually share either zero, one, or two alleles ibd at a locus.

Coefficients of Coancestry

- Let k_0^*, k_1^*, and k_2^* be the actual value at the locus.
- Exactly one of these three quantities is one (for that ibd state being true) and the other two are zero (for those ibd states being false).
- Calculate the following
  - $E[k_i^*]$
  - $Var[k_i^*]$
  - $E[k_i^* k_j^*]$ for $i \neq j$
  - $Cov[k_i^*, k_j^*]$ for $i \neq j$

Variance of actual Coancestry

- We have the following:
  - $E[k_i^*] = k_i$
  - $Var[k_i^*] = k_i(1 - k_i)$
  - $E[k_i^* k_j^*] = 0$ for $i \neq j$
  - $Cov[k_i^*, k_j^*] = -k_i k_j$ for $i \neq j$

Variance of actual Coancestry

- Now, the actual coancestry at a locus for two noninbred individuals is

$$\theta^* = \frac{1}{2}k_2^* + \frac{1}{4}k_1^*$$

- Calculate $Var(\theta^*)$

Variance of actual Coancestry

$$Var(\theta^*) = \frac{1}{4}Var(k_2^*) + \frac{1}{16}Var(k_1^*) + \frac{1}{4}Cov(k_1^*, k_2^*)$$
$$= \frac{1}{4}k_2(1-k_2) + \frac{1}{16}k_1(1-k_1) - \frac{1}{4}k_2 k_1$$

- First cousins have $k_2 = 0$, $k_1 = .25$ and $k_0 = .75$. Calculate the expected value, variance, and standard deviation of actual coancestry for this relative pair type at a locus.
- What is the variance of actual coancestry for parent-offspring?

Variance of actual Coancestry

$$Var(\theta^*) = \frac{1}{4}k_2(1-k_2) + \frac{1}{16}k_1(1-k_1) - \frac{1}{4}k_2 k_1$$

- First cousins have $k_2 = 0$, $k_1 = \frac{1}{4}$ and $k_0 = \frac{3}{4}$, so $\theta = \frac{1}{16} = .0625$.
- The variance of actual coancestry is $\left(\frac{1}{16}\right)\left(\frac{1}{4}\right)\left(\frac{3}{4}\right) = \frac{3}{256}$
- The standard deviation is $\frac{\sqrt{3}}{16} = .10825$
- For parent-offspring, the variance of actual coancestry is 0.

Genetic Covariance for Two Outbred Relatives

- We will now focus on obtaining the genetic covariance of trait values for two outbred relatives
- Consider a quantitative trait that is influence by a single locus.
- As before, we denote the genetic value for genotype A_iA_j as

$$G_{ij} = \mu_G + \alpha_i + \alpha_j + \delta_{ij}$$

where

$$\mu_G = \sum_i \sum_j p_i p_j G_{ij} = G_{..}$$

$$\alpha_i = \sum_j p_j G_{ij} - \mu_G = G_{i.} - G_{..}$$

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

- These imply that $\sum_i p_i \alpha_i = 0$ and $\sum_i p_i \delta_{ij} = 0$

Genetic Covariance for Two Outbred Relatives

- Consider two individuals X and Y. We will calculate the covariance of the genetic values for X and Y.
- Let X_1 and X_2 be the two alleles at the locus for individual X, and let Y_1 and Y_2 be the two alleles for individual Y
- We have the following:

$$Cov(G_{X_1X_2}, G_{Y_1Y_2}) =$$

$$Cov\left(\mu_G + \alpha_{X_1} + \alpha_{X_2} + \delta_{X_1X_2}, \mu_G + \alpha_{Y_1} + \alpha_{Y_2} + \delta_{Y_1Y_2}\right)$$

$$\begin{aligned}
&= Cov(\alpha_{X_1}, \alpha_{Y_1}) + Cov(\alpha_{X_1}, \alpha_{Y_2}) + Cov(\alpha_{X_1}, \delta_{Y_1Y_2}) \\
&+ Cov(\alpha_{X_2}, \alpha_{Y_1}) + Cov(\alpha_{X_2}, \alpha_{Y_2}) + Cov(\alpha_{X_2}, \delta_{Y_1Y_2}) \\
&+ Cov(\delta_{X_1X_2}, \alpha_{Y_1}) + Cov(\delta_{X_1X_2}, \alpha_{Y_2}) + Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2}) \\
&= 4Cov(\alpha_{X_1}, \alpha_{Y_1}) + 2Cov(\alpha_{X_1}, \delta_{Y_1Y_2}) + 2Cov(\delta_{X_1X_2}, \alpha_{Y_1}) \\
&+ Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2})
\end{aligned}$$

Since in outbred populations the two alleles within an individual are independent and identically distributed (iid)

Genetic Covariance for Two Outbred Relatives

- Now let's first focus on the terms involving the covariance of the additive and dominance effects: $2Cov(\alpha_{X_1}, \delta_{Y_1 Y_2})$ and $2Cov(\delta_{X_1 X_2}, \alpha_{Y_1})$
- Let's consider the covariance when X and Y are the monozygotic twins, or the genetic equivalence of $X = Y$. What do we know about $Cov(\alpha_{X_1}, \delta_{X_1 X_2})$

$$Cov(\alpha_{X_1}, \delta_{X_1 X_2}) = E(\alpha_{X_1}\delta_{X_1 X_2}) - E(\alpha_{X_1})E(\delta_{X_1 X_2})$$

$$= E(\alpha_{X_1}\delta_{X_1 X_2}) - 0$$

$$= \sum_i \sum_j p_i p_j \alpha_i \delta_{ij} = \sum_i p_i \alpha_i \sum_j p_j \delta_{ij} = \sum_i p_i \alpha_i (0) = 0$$

- We actually already know this to be true since the additive effects and the dominance effects are uncorrelated!

Genetic Covariance for Two Outbred Relatives

- It follows that for any pair of individuals X and Y, who obviously must have IBD sharing that is less than or equal to monozygotic twins, that the additive and dominance effects must also have a covariance of 0.
- So we have

$$Cov(G_{X_1X_2}, G_{Y_1Y_2}) =$$

$$4Cov(\alpha_{X_1}, \alpha_{Y_1}) + 2Cov(\alpha_{X_1}, \delta_{Y_1Y_2}) + 2Cov(\delta_{X_1X_2}, \alpha_{Y_1})$$

$$+ Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2})$$

$$= 4Cov(\alpha_{X_1}, \alpha_{Y_1}) + Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2})$$

- Now take a moment to calculate $4Cov(\alpha_{X_1}, \alpha_{Y_1})$. Hint: use the kinship coefficient θ for the two individuals for this calculation

Genetic Covariance for Two Outbred Relatives

- We have

$$Cov(\alpha_{X_1}, \alpha_{Y_1}) = E[\alpha_{X_1}\alpha_{Y_1}] - E[\alpha_{X_1}]E[\alpha_{Y_1}]$$

$$= E[\alpha_{X_1}\alpha_{Y_1}] - 0$$

- Now

$$E[\alpha_{X_1}\alpha_{Y_1}] = E[\alpha_{X_1}\alpha_{Y_1}|X_1 \text{and } Y_1 \text{ are IBD}]P(X_1 \text{and } Y_1 \text{ are IBD})$$

$$+E[\alpha_{X_1}\alpha_{Y_1}|X_1 \text{and } Y_1 \text{ are not IBD}]P(X_1 \text{and } Y_1 \text{ are not IBD})$$

$$= E[\alpha_{X_1}^2]\theta + 0(1-\theta)$$

$$= \frac{1}{2}\sigma_a^2\theta$$

where σ_a^2 is the additive variance for the trait since we previously define $\sigma_a^2 = 2Var(\alpha_i) = 2\sum_i p_i\alpha_i^2$

Genetic Covariance for Two Outbred Relatives

- So we have

$$Cov(G_{X_1X_2}, G_{Y_1Y_2}) =$$

$$= 4Cov(\alpha_{X_1}, \alpha_{Y_1}) + Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2})$$

$$= 4(\frac{1}{2}\sigma_a^2) + Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2}) = 2\theta\sigma_a^2 + Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2})$$

- Now take a moment to calculate $Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2})$. Hint: condition of the probabilities of the pair sharing zero, one, or two alleles IBD, i.e., k_0,k_1, and k_2

Genetic Covariance for Two Outbred Relatives

- We have

$$Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2}) = E[\delta_{X_1X_2}\delta_{Y_1Y_2}] - E[\delta_{X_1X_2}]E[\delta_{Y_1Y_2}]$$

$$= E[\delta_{X_1X_2}\delta_{Y_1Y_2}] - 0$$

- Now $E[\delta_{X_1X_2}\delta_{Y_1Y_2}] =$

$$E[\delta_{X_1X_2}\delta_{Y_1Y_2} | X \text{ and } Y \text{ share 2 alleles IBD}] \times$$

$$P(X \text{ and } Y \text{ share 2 alleles IBD})$$

$$+E[\delta_{X_1X_2}\delta_{Y_1Y_2} | X \text{ and } Y \text{ share 1 allele IBD}] \times$$

$$P(X \text{ and } Y \text{ share 1 alleles IBD})$$

$$+E[\delta_{X_1X_2}\delta_{Y_1Y_2} | X \text{ and } Y \text{ share 0 alleles IBD}] \times$$

$$P(X \text{ and } Y \text{ share 0 alleles IBD})$$

Genetic Covariance for Two Outbred Relatives

- We have that

$$E[\delta_{X_1X_2}\delta_{Y_1Y_2}|X \text{ and } Y \text{ share 2 alleles IBD}]\times$$
$$P(X \text{ and } Y \text{ share 2 alleles IBD}) = E[\delta^2_{X_1X_2}]k_2$$

- We also have that

$$E[\delta_{X_1X_2}\delta_{Y_1Y_2}|X \text{ and } Y \text{ share 1 allele IBD}]\times$$
$$P(X \text{ and } Y \text{ share 1 alleles IBD}) = k_1\sum_l\sum_i\sum_j p_lp_ip_j\delta_{il}\delta_{jl}$$
$$= k_1\sum_l p_l\sum_i p_i\delta_{il}\sum_j p_j\delta_{jl}$$
$$= k_1\sum_l p_l(0)(0)$$

since $\sum_i p_i\delta_{ij} = 0$.

Genetic Covariance for Two Outbred Relatives

- Finally, we have that

$$
\begin{aligned}
&E[\delta_{X_1X_2}\delta_{Y_1Y_2}|X \text{ and } Y \text{ share 0 alleles IBD}]\times \\
&P(X \text{ and } Y \text{ share 0 alleles IBD}) = E[\delta_{X_1X_2}]E[\delta_{Y_1Y_2}]k_0 \\
&= (0)(0)k_0 = 0
\end{aligned}
$$

Genetic Covariance for Two Outbred Relatives

- So, putting the three terms together we have that

$$Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2}) = E[\delta^2_{X_1X_2}]k_2 + (0)k_1 + (0)k_0 = \sigma^2_d k_2$$

where σ^2_d is the dominance variance for the trait that we previously define as

$$\sigma^2_d = Var(\delta_{ij}) = E[\delta^2_{ij}] = \sum_{ij} p_{ij}\delta^2_{ij}$$

Genetic Covariance for Two Outbred Relatives

- So we have
$$Cov(G_{X_1X_2}, G_{Y_1Y_2}) =$$
$$= 4Cov(\alpha_{X_1}, \alpha_{Y_1}) + Cov(\delta_{X_1X_2}, \delta_{Y_1Y_2})$$
$$= 2\theta\sigma_a^2 + k_2\sigma_d^2$$
- For inbred individuals, obtaining genetic covariance is a bit more complicated, but one can show that for X and Y inbreed we have
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$$Cov(G_{X_1X_1}, G_{Y_1Y_2}) =$$
$$= 2\theta\sigma_a^2 + \Delta_7\sigma_d^2$$
$$+D_1(4\Delta_1 + \Delta_3 + \Delta_5) + D_2\Delta_1 + H^2(\Delta_1 + \Delta_2 - F_XF_Y)$$

Terminology and Expressions for Variance of Trait

Components	Multi-allelic	Bi-allelic
Additive Variance	$\sigma_A^2 = 2\sum_i p_i \alpha_i^2$	$\sigma_A^2 = 2pq\alpha^2$
Dominance Variance	$\sigma_D^2 = \sum_i \sum_j p_i p_j \delta_{ij}^2$	$\sigma_D^2 = (2pqd)^2$
Inbreeding depression	$H = \sum_i p_i \delta_{ii}$	H=-2qpd
Covariance of α_i's and δ_{ii}'s	$D_1 = \sum_i p_i \alpha_i \delta_{ii}$	$D_1 = 2pqd\alpha(p-q)$
Variance of δ_{ii}'s	$D_2 = \sum_i p_i \delta_{ii}^2 - H^2$	$D_2 = 4pq(1-4pq)d^2$