Consider a disease trait partially determined by an autosomal locus with two alleles 1 and 2 having frequencies \( p_1 \) and \( p_2 \). Let \( \phi_{k|l} \) be the probability that a person with genotype \( k/l \) manifests the disease.

For the sake of simplicity, assume that people mate at random and that the disease states of two relatives \( i \) and \( j \) are independent given their genotypes at the disease locus. Now let \( X_i \) and \( X_j \) be indicator random variables that assume the value 1 when \( i \) or \( j \) is affected, respectively. Show that

\[
\Pr(X_j = 1 \mid X_i = 1) = \frac{\sum_{g_i} \sum_{S_{ij}} \Pr(X_j = 1 \mid g_j) \Pr(g_j \mid S_{ij} \mid g_i) \times \Pr(S_{ij} \mid g_i) \Pr(g_i \mid X_i = 1)}{\Pr(S_{ij} \mid g_i) \Pr(g_i \mid X_i = 1)},
\]

where \( g_i \) and \( g_j \) are the possible genotypes of \( i \) and \( j \) and \( S_{ij} \) is a condensed identity state. This gives an alternative to computing risks by multiplying the relative risk ratio \( \lambda_k \) by the prevalence \( K \). Explicitly evaluate the risk (6.9) for identical twins and parent–offspring pairs.

4. Suppose that the two relatives \( i \) and \( j \) are inbred. Show that the covariance between their trait values \( X_i \) and \( X_j \) is

\[
\text{Cov}(X_i, X_j) = (4\Delta_1 + 2\Delta_2 + 2\Delta_3 + 2\Delta_4 + \Delta_5) \sum_k \sigma_k^2 p_k + (4\Delta_1 + \Delta_2 + \Delta_3) \sum_k \sigma_k^2 \delta_{kk} p_k
\]

\[
+ \Delta_1 \sum_k \delta_{kk}^2 p_k + \Delta_2 \sum_k \delta_{kk}^2 p_k p_k
\]

\[
+ (\Delta_3 - f_i f_j) \left( \sum_k \delta_{kk} p_k \right)^2.
\]

What is \( \text{Cov}(X_i, X_j) \) when \( \sigma_k^2 = 0 ?>
5. For a locus with two alleles, show that the additive genetic variance satisfies
\[
\sigma_a^2 = 2p_1p_2(a_1 - a_2)^2
\]
\[= 2p_1p_2[p_1(\mu_{11} - \mu_{12}) + p_2(\mu_{12} - \mu_{22})]^2. \quad (6.10)
\]
As a consequence of formula (6.10), \( \sigma_a^2 \) can be 0 only in the unlikely circumstance that \( \mu_{12} \) lies outside the interval with endpoints \( \mu_{11} \) and \( \mu_{22} \). (Hint: Expand \( 0 = 2(a_1p_1 + a_2p_2)^2 \) and subtract from the expression defining \( \sigma_a^2 \).)

Show that the dominance genetic variance satisfies
\[
\sigma_d^2 = p_1^2p_2^2(\mu_{11} - 2\mu_{12} + \mu_{22})^2.
\]
It follows that if either \( p_1 \) or \( p_2 \) is small, then \( \sigma_d^2 \) will tend to be small compared to \( \sigma_a^2 \). Hint: Let \( \bar{p} = p_1(\mu_{11} + 2\mu_{12} + \mu_{22}) + p_2(\mu_{12} + \mu_{22}) \). Since \( \bar{p} = 0 \), it follows that
\[
\begin{align*}
\delta_{11} &= \mu_{11} - 2\mu_{12} + \mu \\
&= p_1^2(\mu_{11} - 2\mu_{12} + \mu_{22}) \\
\delta_{12} &= -p_1p_2(\mu_{11} - 2\mu_{12} + \mu_{22}) \\
\delta_{22} &= p_2^2(\mu_{11} - 2\mu_{12} + \mu_{22}).
\end{align*}
\]

8. Let \((X_1, \ldots, X_n)\) and \((Y_1, \ldots, Y_n)\) be measured values for two different \( \vee \) traits on a pedigree of \( n \) people. Suppose that both traits are determined by the same locus. Show that there exist constants \( \sigma_{axy} \) and \( \sigma_{dxy} \) such that
\[
\text{Cov}(X_i, Y_j) = 2\sigma_{i,j}\delta_{axy} + \Delta_{i,j}\delta_{dxy}
\]
for any two non-inbred relatives \( i \) and \( j \) [8]. Prove that the two matrices
\[
\begin{pmatrix}
\sigma_{axx} & \sigma_{axy} \\
\sigma_{axy} & \sigma_{axy}
\end{pmatrix}
\quad \text{and} \quad
\begin{pmatrix}
\sigma_{dxx} & \sigma_{dxy} \\
\sigma_{dxy} & \sigma_{dxy}
\end{pmatrix}
\]
are covariance matrices, where \( \sigma_{axx}^2, \sigma_{dxx}^2, \sigma_{dxy}^2 \), and \( \sigma_{axy}^2 \) are the additive and dominance genetic variances of the \( X \) and \( Y \) traits, respectively. (Hints: For the first part, consider the artificial trait \( W = X + Y \) for a typical person. For the second part, prove that
\[
\sigma_{axy} = 2\text{Cov}(A_1, B_1)
\]
\[
\sigma_{dxy} = \text{Cov}(X - A_1 - A_2, Y - B_1 - B_2),
\]
where \( A_k = E(X \mid Z_k) \) and \( B_3 = E(Y \mid Z_3) \), \( Z_1 \) and \( Z_2 \) being the maternal and paternal alleles at the common locus.)