Lecture 3
Resemblance Between Relatives

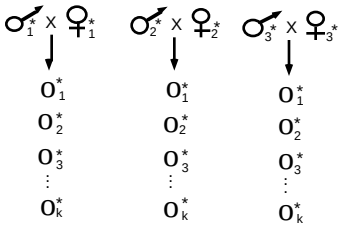
The **heritability** of a trait, a central concept in quantitative genetics, is the proportion of variation among individuals in a population that is due to variation in the additive genetic (i.e., breeding) values of individuals:

$$h^2 = \frac{V_A}{V_P} = \frac{\text{Variance of breeding values}}{\text{Phenotypic Variance}}$$

Since an individual's phenotype can be directly scored, the phenotypic variance V_P can be estimated from measurements made directly on the random breeding population.

In contrast, an individual's breeding value cannot be observed directly, but rather must be inferred from the mean value of its offspring (or more generally using the phenotypic values of other known relatives). Thus estimates of V_A require known collections of relatives. The most common situations (which we focus on here) are comparisons between parents and their offspring or comparisons among sibs. We can classify relatives as either ancestral or collateral, and we focus here on designs with just one type of relative. In a more general pedigree, information from both kinds of relatives is present.

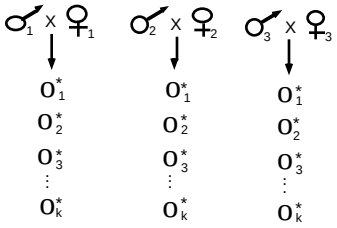
Ancestral relatives: e.g., parent and offspring



* Measure phenotypes of one or both parents, $+k$ offspring of each

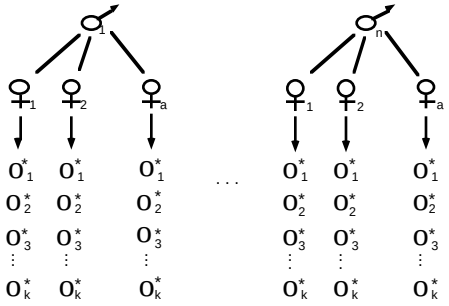
Collateral relatives:

Full Sibs have both parents in common



*Measure k offspring in each family, but not the parents.

Half Sibs have one parent in common



* Measure phenotype of k progeny of each family, but not the parents.

Key observation: *The amount of phenotypic resemblance among relatives for the trait provides an indication of the amount of genetic variation for the trait.*

Covariances and Regressions

In order to analyze this resemblance, we first digress to discuss some standard statistical measures of association.

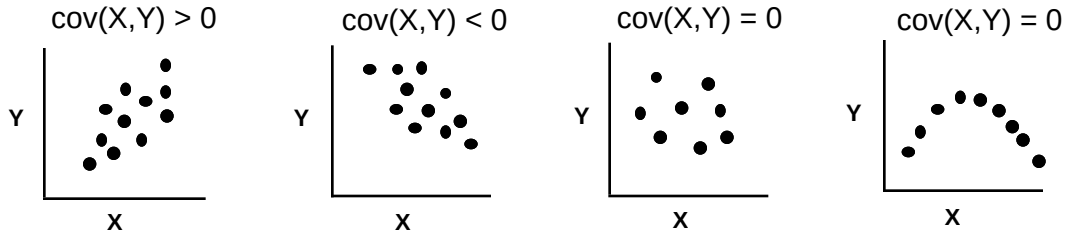
The Covariance:

One of the most useful measures in quantitative genetics is the **covariance** between two variables, which is a (linear) measure of association. Formally, the covariance, $Cov(x, y)$, of two random variables x and y is defined by

$$\begin{aligned} Cov(x, y) &= E[(\, x - \mu_x \,) * (\, y - \mu_y \,)] \\ &= E(\, xy \,) - \mu_x \mu_y \\ &= \text{mean of the product} - \text{product of the means} \end{aligned} \tag{1}$$

Here $E()$ denotes the **expected value** or population mean of the quantity of interest.

As the figure (below) shows, if x and y are positively associated, then $Cov(x, y) > 0$, while if they are negatively associated, then $Cov(x, y) < 0$. Note that the covariance is a measure of the *linear* association between two variables — even though x perfectly predicts y is the far right panel, there is no *linear* trend, so that $Cov(x, y) = 0$. While $Cov(x, y) = 0$ when x and y are independent, the converse is NOT true, as $Cov(x, y) = 0$ does not necessarily imply that x and y are independent (again, as evidenced by the last panel).



The covariance is estimated for a sample of n paired observations (x_i, y_i) by

$$\begin{aligned} Cov(x,y) &= \frac{1}{n-1}\sum_{i=1}^{n}(\,x_i - \overline{x}\,)(\,y_i - \overline{y}\,) \\ &= \frac{1}{n-1}\left(\sum_{i=1}^{n} x_i\,y_i - n\,\overline{x}\,\overline{y}\right) \end{aligned} \tag{2}$$

[In the literature, $\sigma(x,y) = \sigma_{xy}$ is often used to denote the population covariance (Equation 1), while $Cov(x)$ denotes its estimated value (Equation 2). In these notes, we will use Cov interchangeably for both.]

The **correlation**, $r(x,y)$ [the notation $\rho(x,y)$ and ρ_{xy} is also used] is a scaled measure of the covariance, where

$$r(x,y) = \frac{Cov(x,y)}{\sqrt{Var(x)\,Var(y)}}$$

Since the range of correlation is restricted between to -1 and $+1$, it provides a standard metric for comparing the amount of association between pairs of variables that show different levels of variation. For example, a covariance of 10 implies a relatively small association if both variables have a variance of 100 ($r = 10/100 = 0.1$), but complete association if both variables have a variance of 10 ($r = 10/10 = 1$).

Covariance and Regressions:

There is a very close connection between the regression of one variable on another and the covariance between the two variables. The slope $b_{y\,|\,x}$ for the best linear fit of y given an observed value of x, is given by

$$b_{y\,|\,x} = \frac{Cov(x,y)}{Var(x)}$$

The predicted value $\widehat{y}$ for y given we know x is

$$\widehat{y} = \overline{y} + b_{y\,|\,x}(\,x - \overline{x}\,)$$

Useful Properties of Variances and Covariances:

- The covariance function is symmetric, $Cov(x,y) = Cov(y,x)$
- The covariance of a variable with itself is the variance, e.g., $Cov(x,x) = Var(x)$
- If a is a constant, then $Cov(ax,y) = a \cdot Cov(x,y)$
- $Var(ax) = a^2 Var(x)$. This follows since
  $Var(ax) = Cov(ax,ax) = a^2 Cov(x,x) = a^2 Var(x)$
- $Cov(x+y,z) = Cov(x,z) + Cov(y,z)$, i.e., the covariance of a sum is the sum of covariances. More generally,

$$Cov\left(\sum_{i=1}^{n} x_i, \sum_{j=1}^{m} y_j\right) = \sum_{i=1}^{n}\sum_{j=1}^{m} Cov(x_i, y_j)$$

- $Var(x+y) = Var(x) + Var(y) + 2Cov(x,y)$. Hence, the variance of a sum, $Var(x+y)$, equals the sum of the variances, $Var(x) + Var(y)$, only when the variables have a covariance of zero.

Phenotypic Resemblance Between Relatives

We now will use the covariance (and the related measures of correlations and regression slopes) to quantify the phenotypic resemblance between relatives. Quantitative genetics as a field traces back to R. A. Fisher's 1918 paper showing how to use the phenotypic covariances to estimate genetic variances, whereby the phenotypic covariance between relatives is expressed in terms of genetic variances, as we detail below.

1. Parent-offspring regressions

There are three types of parent-offspring regressions: two **single parent - offspring regressions** (plotting offspring mean versus either the trait value in their father P_f or their mother P_m), and the **midparent-offspring regression** (the offspring mean regressed on the mean of their parents, the midparent $MP = (P_f + P_m)/2$).

The slope of the (single) parent-offspring regression is estimated by

$$b_{OP} = \frac{Cov(O,P)}{Var(P)}, \quad \text{where} \quad Cov(O,P) = \frac{1}{n-1}\left(\sum_{i=1}^{n} O_i\, P_i - n\,\overline{O}\cdot\overline{P}\right)$$

where O_i is the mean trait value in the offspring of parent i and we examine n pairs of parent-offspring. One could compute separate regressions using males (P_m) and females (P_f), although the later potentially includes maternal effect contributions and hence single-parent regressions usually restricted to fathers.

The midparent-offspring regression slope is estimated by

$$b_{OMP} = \frac{Cov(O,MP)}{Var(MP)}, \quad \text{where} \quad Cov(O,MP) = \frac{1}{n-1}\left(\sum_{i=1}^{n} O_i\, P_{mp,i} - n\,\overline{O}\cdot\overline{MP}\right)$$

where O_i is the mean trait value in the offspring of parents in pair i, where these parents have an average trait value MP_i and we examine n parent-offspring pairs .

Notice that all of the three regressions involve the covariance between parents and their offspring.

2. Collateral relationships: ANOVA

With collateral relatives, the above formulae for the sample covariance is not appropriate, for two reasons. First, there are usually more than two collateral relatives per family. Second, even if families consist of only two relatives, the order of the two is arbitrary — i.e., there is no natural distinction between "X" and "Y", as exists in the case of parents and offspring.

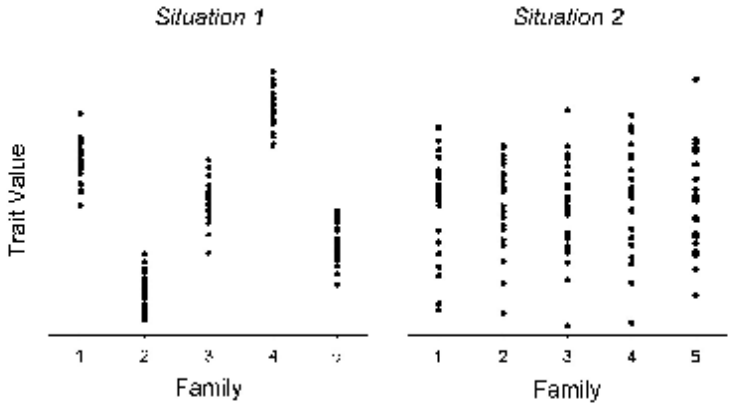
Another way of stating the second point is that collateral relatives belong to the same class or category. In contrast, parents and offspring belong to different classes. The covariance between parents and offspring is an **interclass** (between-class) covariance, while the covariance between collateral relatives is an **intraclass** (within-class) covariance. The analysis of variance (ANOVA), first proposed in Fisher's 1918 paper, is used to estimated intraclass covariances.

Under the simplest ANOVA framework, we can consider the total variance of a trait to consist of two components: a **between-group** (also called the **among-group**) component (for example, differences in the mean value of different families) and a **within-group** component (the variation in trait value within each family). The total variance is the sum of the between and within group variances,

$$Var(T) = Var(B) + Var(W)$$

A key feature of ANOVA is that *the between-group variance equals the within-group covariance*. Thus, the larger the covariance between members of a family, the larger the fraction of total variation that is attributed to differences between family means.

To see this point, consider the following extreme patterns of phenotypes in full sib families:



Situation 1

Here the between group variance $Var(B) = 2.5$, and the within-group variance $Var(W) = 0.2$. This gives a total phenotypic variance of $V_P = Var(T) = Var(B) + Var(W) = 2.7$. Here:

- members of a family resemble each other more closely than they do members of other families
- there are large differences in average phenotype between families

The resulting intraclass correlation t is

$$t = \frac{Cov(\text{full sibs})}{V_P} = \frac{Var(B)}{V_P} = 0.93$$

where we have used the ANOVA identity that the between-group variance equals the within-group covariance (here, the covariance between full sibs).

Situation 2

Suppose the total (phenotypic) variance is the same as in situation 1, with $Var(T) = V_P = 2.7$. However, suppose there is no between-group variance ($Var(B) = 0$), implying that $Var(W) = 2.7$ and the intraclass correlation is $t = 0$. Here:

- members of a family resemble each other no more than they do members of other families
- there are no significant differences in average phenotype between families
- phenotypic resemblance is low, so genetic variation is low

Note that phenotypic resemblance among relatives can equivalently be consider as a measure of the *similiary* among a group of relatives for the phenotype of a quantitative trait (the covariance of family members), or the *difference* in phenotype between different families (the between-group variance).

Causes of Phenotypic Covariance Among Relatives

Relatives resemble each other for quantitative traits more than they do unrelated members of the population for two potential reasons:

- relatives share genes. The closer the relationship, the higher the proportion of shared genes
- relatives share the same environment

The Genetic Covariance Between Relatives

The Genetic Covariance $Cov(G_x, G_y)$ = covariance of the genotypic values (G_x, G_y) of the related individuals x and y.

We will first show how the genetic covariances between parent and offspring, full sibs, and half sibs depend on the genetic variances V_A and V_D. We will then discuss how the covariances are estimated in practice.

Genetic covariances arise because two related individuals are more likely to share alleles than are two unrelated individuals. Sharing alleles means having alleles that are **identical by descent** (IBD): both are copies of the same allele in a recent common ancestor. Alleles can also be **identical in state** but not identical by descent.

For example, consider the offspring of two parents and label the four allelic copies in the parents by 1 - 4, independent of whether or not any are identical in state.

$$\text{Parents: } A_1A_2 \times A_3A_4$$

$$\text{Offspring: } o_1 = A_1A_3 \quad o_2 = A_1A_4 \quad o_3 = A_1A_3 \quad o_4 = A_2A_4$$

Here, o_1 and o_2 share one allele IBD, o_1 and o_3 share two alleles IBD, o_1 and o_4 share no alleles IBD.

1. Offspring and one parent.

What is the covariance of genotypic values of an offspring (G_o) and its parent (G_p)? Denoting the two parental alleles at a given locus by A_1A_2, since a parent and its offspring share *exactly* one allele, one allele in the offspring came from the parent (say A_1), while the other offspring allele (denoted A_3) came from the other parent. To consider the genetic contributions from a parent to its offspring, write the genotypic value of the parent as $G_p = A + D$. We can further decompose this by considering the contribution from each parental allele to the overall breeding value, with $A = \alpha_1 + \alpha_2$, and we can write the genotypic value of the parent as $G_p = \alpha_1 + \alpha_2 + D_{12}$ where D_{12} denotes the dominance deviation for an A_1A_2 genotype. Likewise, the genotypic value of its offspring is $G_o = \alpha_1 + \alpha_3 + D_{13}$, giving

$$Cov(G_o, G_p) = Cov(\alpha_1 + \alpha_2 + D_{12}, \alpha_1 + \alpha_3 + D_{13})$$

We can use the rules of covariances to expand this into nine covariance terms,

$$\begin{aligned} Cov(G_o, G_p) =& Cov(\alpha_1, \alpha_1) + Cov(\alpha_1, \alpha_3) + Cov(\alpha_1, D_{13}) \\ &+ Cov(\alpha_2, \alpha_1) + Cov(\alpha_2, \alpha_3) + Cov(\alpha_2, D_{13}) \\ &+ Cov(D_{12}, \alpha_1) + Cov(D_{12}, \alpha_3) + Cov(D_{12}, D_{13}) \end{aligned}$$

From the construction of the α and D,

$$Cov(\alpha_x, \alpha_y) = \begin{cases} 0 & \text{if } x \neq y, \text{ i.e., not IBD} \\ Var(A)/2 & \text{if } x = y, \text{ i.e., IBD} \end{cases} \tag{3a}$$

The last identity follows since $Var(A) = Var(\alpha_1 + \alpha_2) = 2Var(\alpha_1)$, so that

$$Var(\alpha_1) = Cov(\alpha_1, \alpha_1) = Var(A)/2$$

Hence, when individuals share one allele, they share half the additive genetic variance. Likewise,

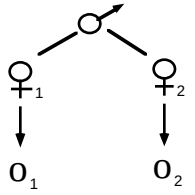
$$Cov(D_{xy}, D_{wz}) = \begin{cases} 0 & \text{if } xy \neq wz, \quad \text{i.e., both alleles are not IBD} \\ Var(D) & \text{if } xy = wz, \quad \text{both alleles are IBD} \end{cases} \tag{3b}$$

Two individuals only share the dominance variance when they share both alleles. Using the above identities (3a and 3b), eight of the above nine covariances are zero, leaving

$$Cov(G_o, G_p) = Cov(\alpha_1, \alpha_1) = Var(A)/2$$

2. Half-sibs.

Here, one parent is shared, the other is drawn at random from the population;



The genetic covariance between half-sibs is the covariance of the genetic values between o_1 and o_2.

To compute this, consider a single locus. First note that o_1 and o_1 share either one allele IBD (from the father) or no alleles IBD (since the mothers are assumed unrelated, these sibs cannot share both alleles IBD as they share no maternal alleles IBD). The probability that o_1 and o_2 both receive the same allele from the male is one-half (because whichever allele the male passes to o_1, the probability that he passes the same allele to o_2 is one-half). In this case, the two offspring have one allele IBD, and the contribution to the genetic covariance when this occurs is $Cov(\alpha_1, \alpha_1) = Var(A)/2$. When o_1 and o_2 share no alleles IBD, they have no genetic covariance.

Summarizing:

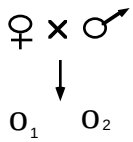
Case	Probability	Contribution
o_1 and o_2 have 0 alleles IBD	1/2	0
o_1 and o_2 have 1 allele IBD	1/2	$Var(A)/2$

giving the genetic covariance between half sibs as

$$Cov(G_{o_1}, G_{o_2}) = Var(A)/4$$

3. Full-Sibs.

Both parents are in common,



What is the covariance of genotypic values of two full sibs?

As illustrated previously, three cases are possible when considering pairs of full sibs: they can share either 0, 1, or 2 alleles IBD. Applying the same approach as for half sibs, if we can compute: 1) the probability of each case; and 2) the contribution to the genetic covariance for each case.

Each full sib receives one paternal and one maternal allele. The probability that each sib receives the same paternal allele is 1/2, which is also the probability each sib receives the same maternal allele. Hence,

$$\Pr(\text{2 alleles IBD}) = \Pr(\text{ paternal allele IBD})\ \Pr(\text{ maternal allele IBD}) = \frac{1}{2} \cdot \frac{1}{2} = \frac{1}{4}$$

$$\Pr(0\ \text{alleles IBD}) = \Pr(\text{ paternal allele not IBD})\ \Pr(\text{ maternal allele not IBD}) = \frac{1}{2} \cdot \frac{1}{2} = \frac{1}{4}$$

$$\Pr(\text{1 allele IBD}) = 1 - \Pr(\text{2 alleles IBD}) - \Pr(\text{0 alleles IBD}) = \frac{1}{2}$$

We saw above that when two relatives share one allele IBD, the contribution to the genetic covariance is $Var(A)/2$. When two relatives share both alleles IBD, each has the same genotype at the locus being considered, and the contribution is

$$Cov(\alpha_1 + \alpha_2 + D_{12}, \alpha_1 + \alpha_2 + D_{12}) = Var(\alpha_1 + \alpha_2 + D_{12}) = Var(A) + Var(D)$$

Putting these results together gives

Case	Probability	Contribution
o_1 and o_2 have 0 alleles IBD	1/4	0
o_1 and o_2 have 1 allele IBD	1/2	$Var(A)/2$
o_1 and o_2 have 2 allele IBD	1/4	$Var(A) + Var(D)$

This results in a genetic covariance between full sibs of

$$Cov(G_{o_1}, G_{o_2}) = \frac{1}{2}\,\frac{Var(A)}{2} + \frac{1}{4}\,(Var(A) + Var(D)) = \frac{Var(A)}{2} + \frac{Var(D)}{4}$$

4. General degree of relationship.

The above results for the contribution when relatives share one and two alleles IBD suggests the general expression for the covariance between (noninbred) relatives.

If r_{xy} = (1/2) Prob(relatives x and y have one allele IBD) + Prob(relatives x and y have both alleles IBD), and u_{xy} = Prob(relatives x and y have both alleles IBD), then the genetic covariance between x and y is given by

$$Cov(G_x, G_y) = r_{xy}V_A + u_{xy}V_D$$

If epistatic genetic variance is present, this can be generalized to

$$Cov(G_x, g_y) = r_{xy}V_A + u_{xy}V_D + r_{xy}^2 V_{AA} + r_{xy}u_{xy}V_{AD} + u_{xy}^2 V_{DD} + \cdots$$

Environmental Causes of Relationship Between Relatives

Shared environmental effects (such as a common maternal environment) also contribute to the covariance between relatives, and care must be taken to distinguish these environmental covariances from genetic covariances.

If members of a family are reared together they share a common environment. If the common environmental circumstances are different for each family, the variance due to common environmental effects, V_{Ec}, causes greater similarity among members of a family, and greater differences among families, than would be expected from the proportion of genes they share. Thus, V_{Ec} inflates the phenotypic covariance of sibs over what is expected from their genotypic covariance.

Just as we decomposed the total genotypic value into components, some shared, others not transmitted between relatives, we can do the same for environmental effects. In particular, we can write the total environmental effect E as the sum of a common environmental effect shared by the relatives E_c, a general environmental effect E_g, and a specific environmental effect E_s. Hence, we can write $E = E_c + E_g + E_s$, partitioning the environmental variance as

$$V_E = V_{Ec} + V_{Eg} + V_{Es}$$

We can further consider different possible sources of the common environmental effect E_c:

- E_{cS} or E_{cL}: Shared effects due to sharing the space/location (different farms, cages)
- E_{cT}: Temporal (changes in climactic or nutritional conditions over time)
- E_{cM} Maternal (pre- and post-natal nutrition)

Thus, we can partition the environmental variance as

$$\begin{aligned} V_E &= V_{Ec} + V_{Eg} + V_{Es} \\ &= V_{EcS} + V_{EcT} + V_{EcM} + V_{Ec} + V_{Eg} + V_{Es} \end{aligned}$$

Common environment effects mainly contribute to resemblance of sibs, but maternal environment effects can contribute to resemblance between mother and offspring as well.

V_{EcS} and V_{EcT} can be eliminated, or estimated, by using the correct experimental design, but it is very difficult (except by cross-fostering) to eliminate or estimate V_{EcM} from the covariance of full sibs. Further, cross-fostering only removes post-natal (past birth) maternal effects, it does not remove shared pre-natal maternal effects.

Phenotypic Covariance Among Relatives and h^2

Summarizing the above results,

Relative Pair	Cov	t or b	h^2
Parent-offspring (P-O)	$V_A/2$	$b_{OP} = \frac{1}{2} V_A/V_P$	$2b_{OP}$
Midparent-offspring (MP-O)	$V_A/2$	*$b_{OMP} = V_A/V_P$	b_{OMP}
Half-sibs (HS)	$V_A/4$	$t_{HS} = (1/4)V_A/V_P$	$4t_{HS}$
Full-sibs (FS)	$V_A/2 + V_D/4 + V_{Ecm}$	$t_{FS} = \dfrac{V_A/2 + V_D/4 + V_{Ecm}}{V_P}$	$2t_{FS} > h^2$

*The midparent-offspring slope is computed as follows: using the properties of covariances,

$$\begin{aligned} Cov(O, MP) &= Cov(0, [P_f + P_m]/2) = \frac{Cov(0, P_f)}{2} + \frac{Cov(0, P_m)}{2} \\ &= \frac{V_A/2}{2} + \frac{V_A/2}{2} = V_A/2 \end{aligned}$$

The variance of the midparent values also follows from the properties of covariances, with

$$Var(MP) = Var\left(\frac{P_f + P_m}{2}\right) = \frac{Var(P_f)}{4} + \frac{Var(P_m)}{4} = V_P/2$$

The last equality assumes equal trait variances in both parents and that parental values are uncorrelated (i.e., no assortative mating). The regression slope equals the covariance between midparent and offspring divided by the midparent variance,

$$b_{OPmp} = \frac{Cov(O, MP)}{Var(MP)} = \frac{V_A/2}{V_P/2} = \frac{V_A}{V_P}$$

Resemblance Between Relatives Problems

1. Recall that the sm allele affecting *Drosophila* bristle number that segregates in an Australian population. The environmental variance of bristle number is 6, and there are no common environmental effects due to maternal environment or rearing families together is vials. Assuming the sm locus is the only source of genetic variance, compute the regressions or intraclass correlations of bristle number between the following relatives:

a: Offspring and midparent

b: Half sibs

c: Full sibs

Do the calculations for (i) populations where freq(sm) = 0.1 and (ii) populations where freq(sm) = 0.9.

2. What is the covariance between an individual's breeding value A and its phenotypic value P? Hint, use the properties of the covariance and decompose P into its various genetic and environmental components.

3. Using your result from (2), what is the best linear predictor of an individual's breeding value A given that we observe their phenotypic value P (i.e., the regression of A on P). (Recall that, by construction, the mean breeding value is zero.)

Solutions to Resemblance Between Relatives Problems

1. Recall for the sm locus that the genotypes $++ : +sm : smsm$ have values of $44 : 40 : 22$. Rescaling these to $a : d : -a$ gives $11 : 7 : -11$, or $a = 11, d = 7$. Hence, the genetic variances are given by

$$V_A = 2pq(a + d(q - p)) = 2pq(11 + 7(q - p))$$

and

$$V_D = (2pqd)^2 = q^2p^2\,196$$

where $q = \text{freq}(sm)$. Hence:

q	V_A	V_D	V_G
0.1	0.97	1.59	2.56
0.9	2.99	1.59	4.58

Here $V_E = 6$, giving $V_P = V_G + 6$.

a) Parent-offspring regression: $b = V_A/V_p$, or 0.11 for $q = 0.1$, 0.28 for $q = 0.9$.

b) Half-sib correlation: $t_{HS} = (1/4)V_A/V_P$, or 0.03 for $q = 0.1$, 0.07 for $q = 0.9$.

c) Full-sib correlation: $t_{FS} = (V_A/2 + V_D/4)/V_P$, or 0.10 for $q = 0.1$, 0.19 for $q = 0.9$.

2.

$$Cov(P, A) = Cov(G + E, A) = Cov(A + D + E, A) = Cov(A, A) = Var(A)$$

3. The regression is $A = \mu_A + b_{A\,|\,P}(P - \mu_p)$. The slope is

$$b_{A\,|\,P} = \frac{Cov(P, A)}{V_P} = \frac{Cov(A, A)}{V_P} == \frac{Var(A)}{V_P} = h^2$$

Hence, the best predictor of an individual's breeding value given that we only observe their phenotypic value P is

$$A = h^2(P - \mu_p)$$

as the mean breeding value (by construction) is zero, i.e.., $\mu_A = 0$