How to listen to the recorded lectures

- I'll be closely following the online notes, but will often skip (or speed) through some of the technical details (you can read these) and instead try to emphasize the key concerns/points.

- There are several places with "PAUSE" slides. Here, stop the lecture, and look over the questions and perhaps go back and review the notes for the material just covered.

- Also, at the PAUSE slides, you might want to take a quick 2-5 minute break (but no more). This will keep you a bit fresher, but if you take too long a break, it may be harder to get back into the material.

- You can also use these PAUSE slides as bookmarks if you want to go back to review material again.

- First PAUSE at slide 10

Lecture 1:
Introduction to Quantitative Genetics

Bruce Walsh lecture notes
Introduction to Quantitative Genetics
SISG (Module 9), Seattle
20 – 22 July 2020

Basic model of Quantitative Genetics

Phenotypic value -- we will occasionally
also use z for this value

Basic model: P = G + E

Environmental value

Genotypic value

G = average phenotypic value for that genotype
if we are able to replicate it over the universe
of environmental values, G = E[P]

Hence, genotypic values are functions of the
environments experienced.

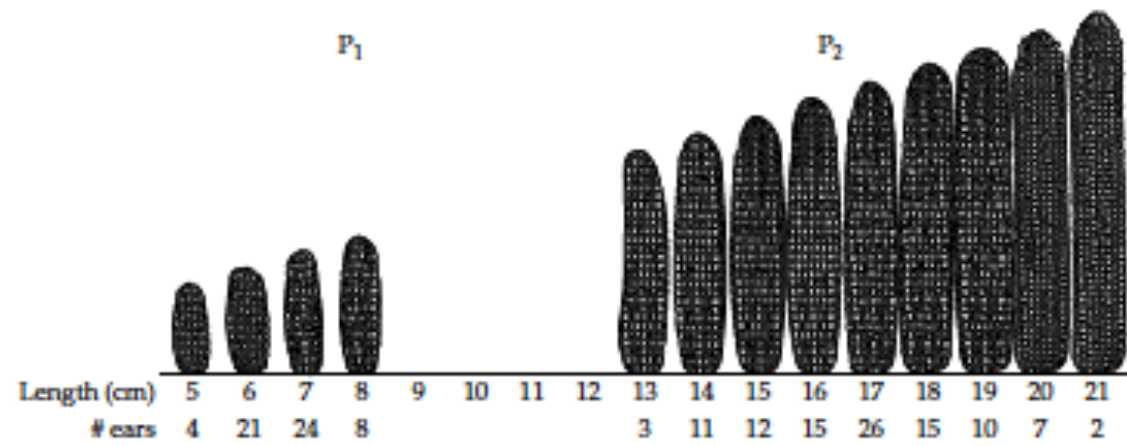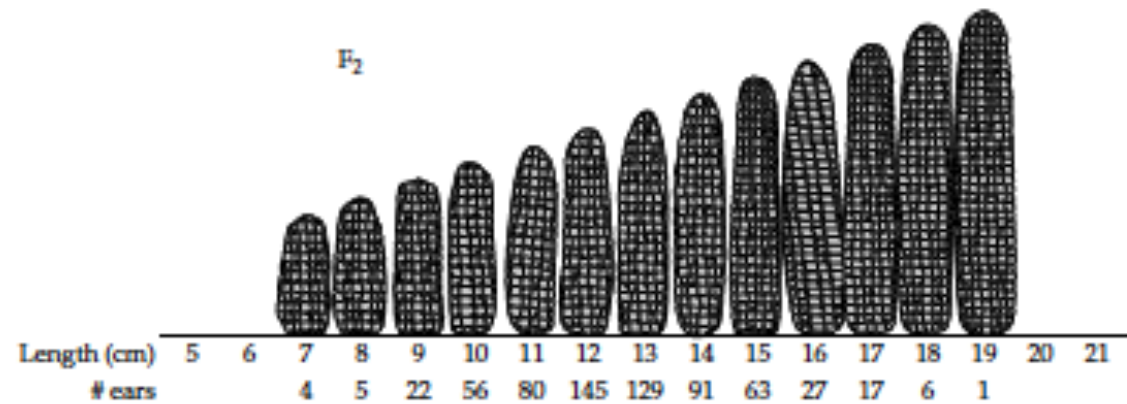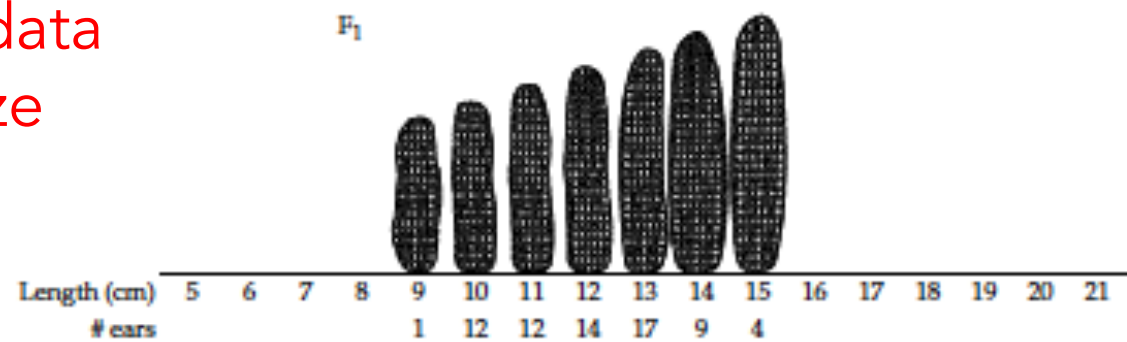# Basic model of Quantitative Genetics

Basic model: P = G + E

G = average phenotypic value for that genotype
if we are able to replicate it over the universe
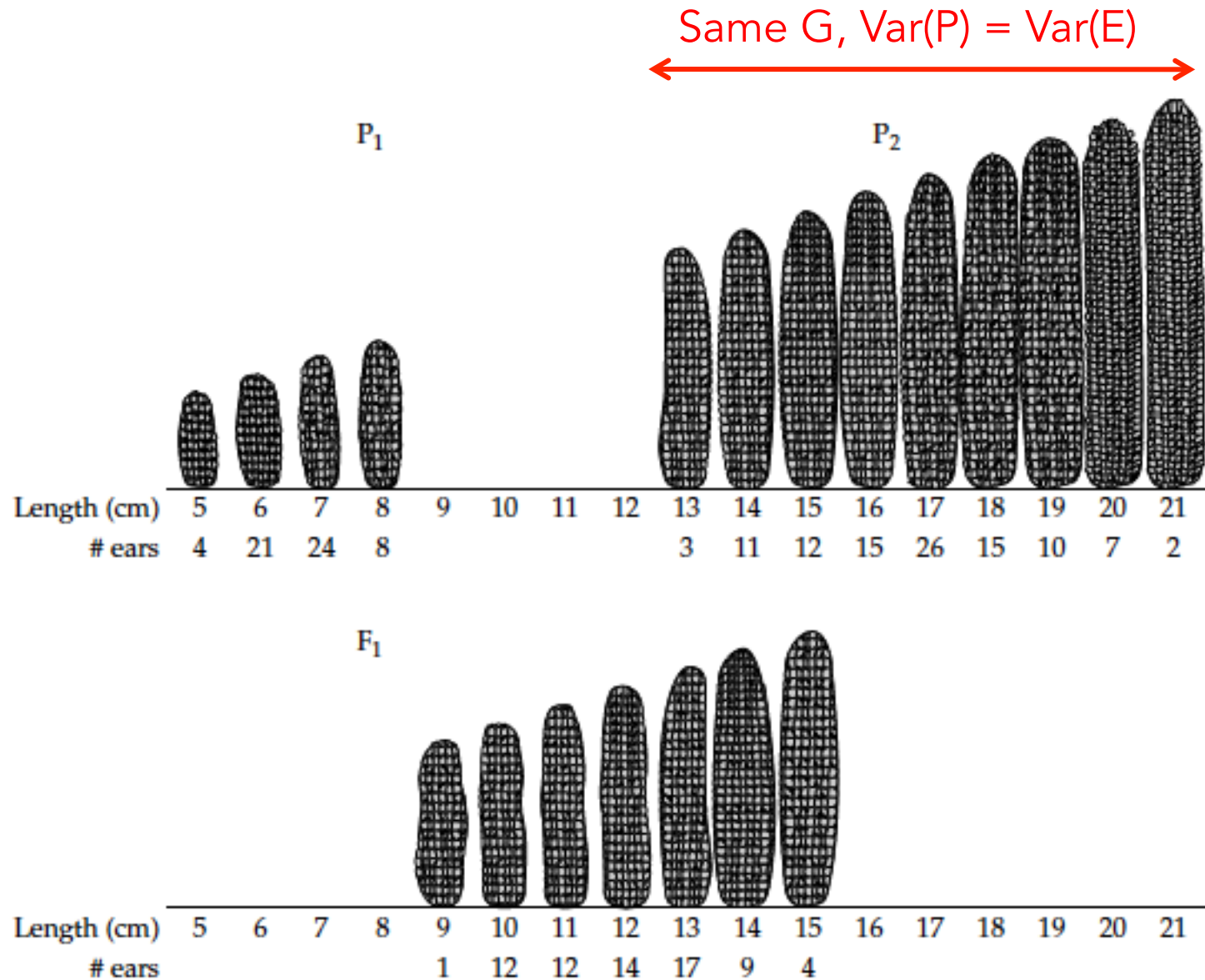of environmental values, G = E[P]

G = average value of an inbred line over a series
of environments

G x E interaction --- The performance of a particular
genotype in a particular environment differs from
the sum of the average performance of that
genotype over all environments and the average
performance of that environment over all genotypes.
Basic model now becomes P = G + E + GE

East (1911) data on US maize crosses

Length (cm)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
P₁ # ears	4	21	24	8					3	11	12	15	26	15	10	7	2
F₁ # ears					1	12	12	14	17	9	4						
F₂ # ears			4	5	22	56	80	145	129	91	63	27	17	6	1		

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Same G, Var(P) = Var(E)

P_1

P_2

Length (cm)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
# ears	4	21	24	8					3	11	12	15	26	15	10	7	2

F_1

Length (cm)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
# ears					1	12	12	14	17	9	4						

Each sample (P_1, P_2, F_1) has same G, all variation in P is due to variation in E

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F₁

Length (cm)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
# ears					1	12	12	14	17	9	4						
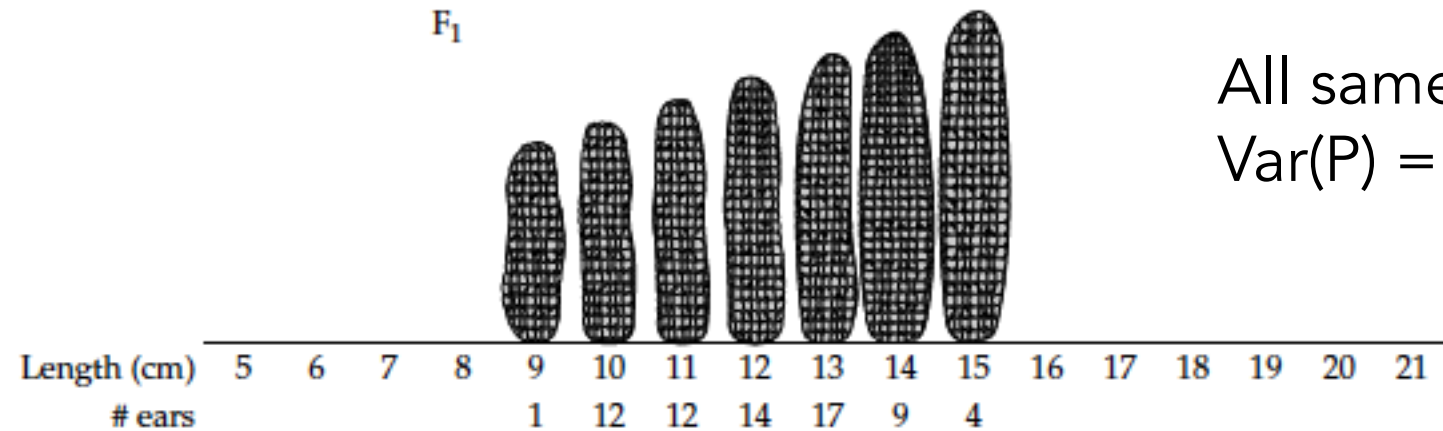
All same G, hence
Var(P) = Var(E)

F₂

Length (cm)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
# ears			4	5	22	56	80	145	129	91	63	27	17	6	1		
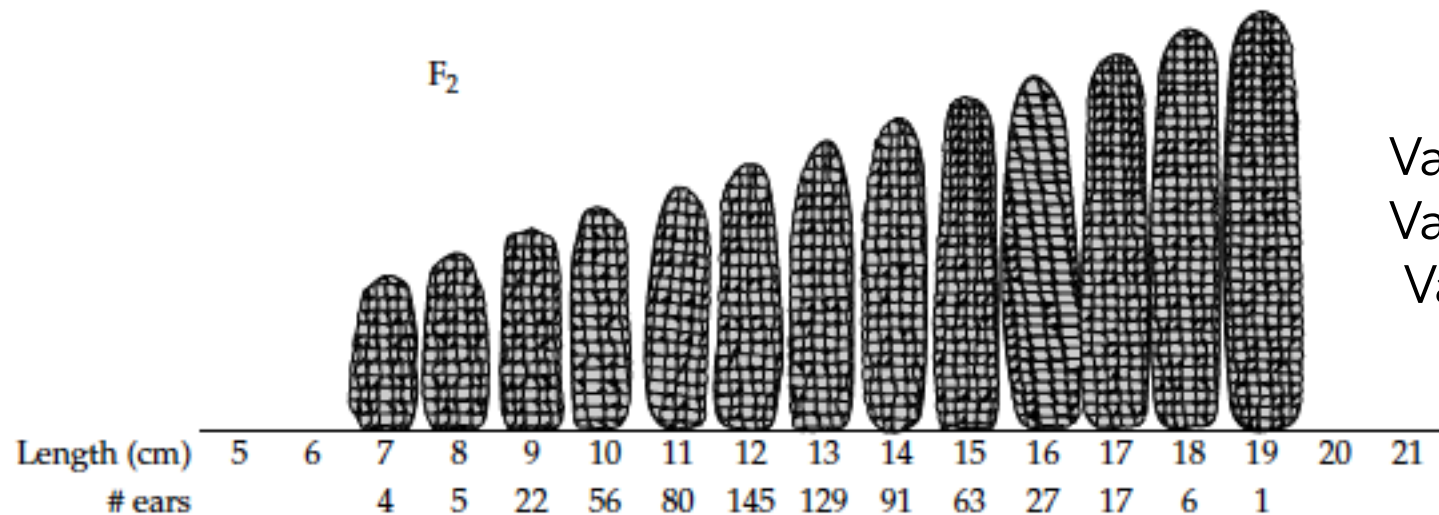
Variation in G
Var(P) = Var(G) +
 Var(E)

Var(F$_2$) > Var(F$_1$) due to Variation in G

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Johannsen (1903) bean data

- Johannsen had a series of fully inbred (= pure) lines.
- There was a consistent between-line difference in the mean bean size
  - Differences in G across lines
- However, <u>within</u> a given line, size of parental seed independent of size of offspring speed
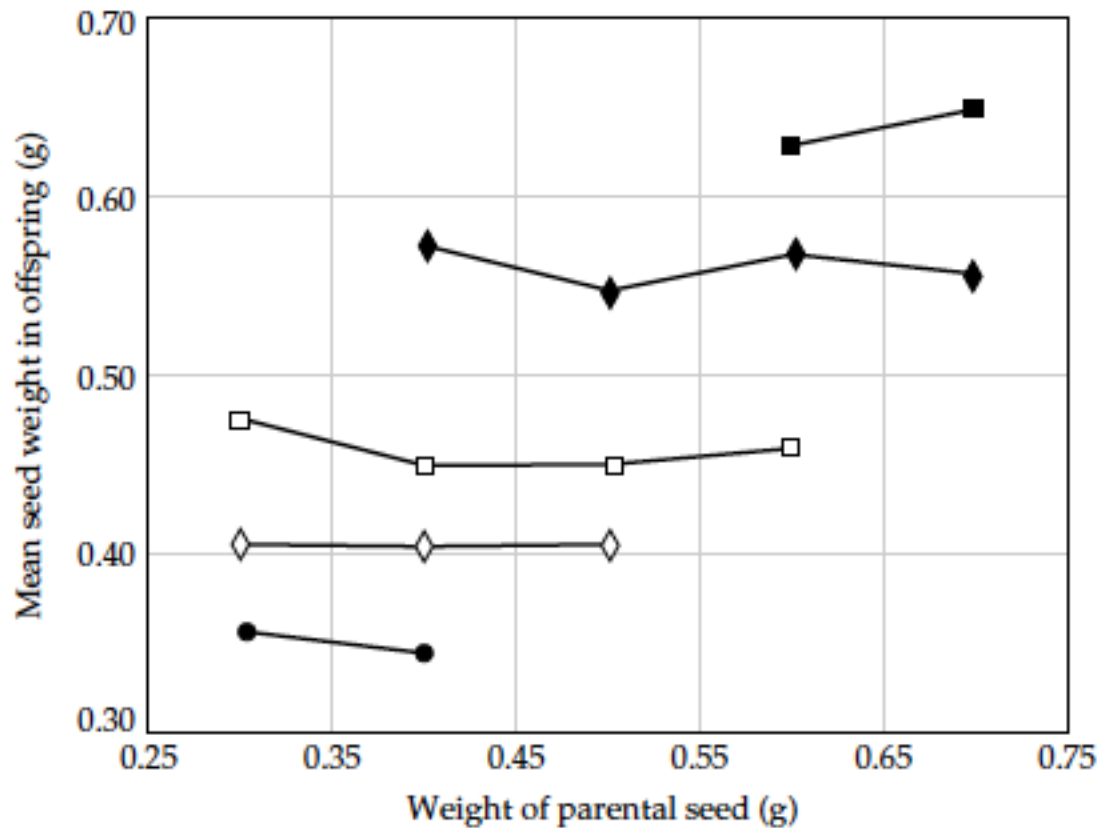 - No variation in G <u>within</u> a line

Figure 1.4 Mean offspring seed size as a function of parental seed size for some of Johannsen's pure lines. The data for the different lines are denoted by different symbols. If there is a heritable component to seed weight within a pure line, a line with positive slope is expected — larger parents should yield larger offspring. However, within each line, mean offspring size is essentially independent of the parental phenotype. (Data from Johannsen 1903.)

PAUSE

- Questions for consideration:
  - What the difference between genotypic and environmental effects?
  - How might you distinguish these
    - Using a set of clones
    - Using a set of (outbred) related individuals
  - We will return to these issues later (and in the breakout groups)
  - Next pause at slide 13

KEY

- <u>Relatives share alleles</u>, and this idea was exploited by R. A. Fisher (1918)
- If a trait has a genetic basis, the more genes that two individuals share (i.e., the closer the degree of relationship), the more similar they should be in trait value
  - The covariance in phenotypic trait values should be an increasing function of the amount of relatedness
    - E.g., Identical twins (clone) more similar than two non-identical sibs

The transmission of genotypes versus alleles

- With fully inbred lines, offspring have the same genotype as their parent, and hence the entire parental genotypic value G is passed along
  - Hence, favorable interactions between alleles (such as with dominance) are not lost by randomization under random mating but rather passed along.
- When offspring are generated by crossing (or random mating), each parent contributes a single allele at each locus to its offspring, and hence only passes along a PART of its genotypic value
- This part is determined by the average effect of the allele
  - Downside is that favorable interaction between alleles are NOT passed along to their offspring in a diploid (but, as we will see, are in an autoteraploid)

PAUSE

- Think about the implications of the last slide
- CLONES pass on their entire genotype (genotypic value G) to their offspring
- Sexual progeny pass on SINGLE alleles at each locus underlying the trait
  - Leads to the importance concepts of
    - <u>Average effects</u> of an allele
    - The <u>Breeding value</u> of an individual
    - The additive genetic variance
- We now address these in turn
- Next pause at slide 22

Genotypic values

It will prove very useful to decompose the genotypic value into the difference between homozygotes (2a) and a measure of dominance (d or k = d/a)

aa	Aa	AA
C - a	C + d	C + a
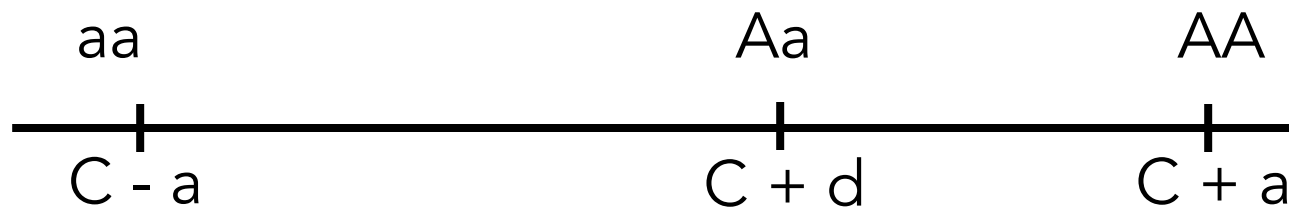
Note that the constant C is the average value of the two homozygotes.

If no dominance, d = 0, as heterozygote value equals the average of the two parents. Can also write d = ka, so that G(Aa) = C + ak

Computing a and d

Suppose a major locus influences plant height, with the following values

Genotype	aa	Aa	AA
Trait value	10	15	16

C = [G(AA) + G(aa)]/2 = (16+10)/2 = 13
a = [G(AA) - G(aa)]/2 = (16-10)/2 = 3
d = G(Aa)] - [G(AA) + G(aa)]/2
   = G(Aa)] - C = 15 - 13 = 2

Population means: Random mating

Let p = freq(A), q = 1-p = freq(a). Assuming random-mating (Hardy-Weinberg frequencies),

Genotype	aa	Aa	AA
Value	C - a	C + d	C + a
Frequency	q^2	$2pq$	p^2

Mean = q^2(C - a) + $2pq$(C + d) + p^2(C + a)

μ_{RM} = C + a(p-q) + d(2pq)

Contribution from homozygotes

Contribution from heterozygotes

Population means: Inbred cross F_2

Suppose two inbred lines are crossed. If A is fixed in one population and a in the other, then $p = q = 1/2$

Genotype	aa	Aa	AA
Value	C - a	C + d	C + a
Frequency	1/4	1/2	1/4

Mean = (1/4)(C - a) + (1/2)(C + d) + (1/4)(C + a)

μ_{RM} = C + d/2

Note that C is the average of the two parental lines, so when d > 0, F_2 exceeds this. Note also that the F_1 exceeds this average by d, so only half of this passed onto F_2.

The average effect of an allele

- The average effect α_A of an allele **A** is defined by the difference between offspring that get allele **A** and a random offspring.

  - α_A = mean(offspring value given parent transmits A) - mean(all offspring)

  - Similar definition for α_a.

- Note that while C, a, and d (the genotypic parameters) do not change with allele frequency, α_x is clearly a function of the frequencies of alleles with which allele x combines.

Random mating

Consider the average effect of allele A when a parent is randomly-mated to another individual from its population

Suppose parent contributes A

Allele from other parent	Probability	Genotype	Value
A	p	AA	C + a
a	q	Aa	C + d

Mean(A transmitted) = p(C + a) + q(C + d) = C + pa + qd

α_A = Mean(A transmitted) - μ = q[a + d(q-p)]

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Random mating

Now suppose parent contributes a

Allele from other parent	Probability	Genotype	Value
A	p	Aa	C + d
a	q	aa	C - a

Mean(a transmitted) = p(C + d) + q(C - a) = C - qa + pd

α_a = Mean(a transmitted) - μ = -p[a + d(q-p)]

α, the average effect of an allelic substitution

- $\alpha = \alpha_A - \alpha_a$ is the average effect of an allelic substitution, the change in mean trait value when an *a* allele in a random individual is replaced by an *A* allele

  - $\alpha = a + d(q-p)$. Note that

    - $\alpha_A = q\alpha$ and $\alpha_a = -p\alpha$.
    - $E(\alpha_X) = p\alpha_A + q\alpha_a = pq\alpha - qp\alpha = 0$,
    - The average effect of a random allele is zero, hence average effects are deviations from the mean

PAUSE

- Key concept from the last few slides
  - The <u>average effect</u> of an allele
    - For a given population, how much of a deviation from the mean in a trait is generated by getting the target allele
    - Property of a <u>particular trait</u> in a <u>particular population</u>.
      - The average effect of the same allele will change over traits
      - The average effect of the same allele will change over background populations.
  - The <u>average effects of a *substitution*</u> (swapping one allele for another)
  - Next pause at slide 33

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Dominance deviations

- Fisher (1918) decomposed the contribution to the genotypic value from a single locus as
  $$G_{ij} = \mu + \alpha_i + \alpha_j + \delta_{ij}$$

  - Here, μ is the mean (a function of p)
  - α_i are the average effects
  - Hence, $\mu + \alpha_i + \alpha_j$ is the predicted genotypic value given the average effect (over all genotypes) of alleles i and j.
  - The dominance deviation associated with genotype G_{ij} is the difference between its true value and its value predicted from the sum of average effects (essentially a residual)

Fisher's (1918) Decomposition of G

One of Fisher's key insights was that the genotypic value consists of a fraction that can be passed from parent to offspring and a fraction that cannot.

In particular, under sexual reproduction, parents only pass along SINGLE ALLELES to their offspring

Consider the genotypic value G_{ij} resulting from an $A_i A_j$ individual

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

Average contribution to genotypic value for allele i

Mean value $\mu_G = \Sigma \, G_{ij} \, Freq(A_i A_j)$

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

Since parents pass along single alleles to their offspring, the α_i (the average effect of allele i) represent these contributions

The average effect for an allele is POPULATION-SPECIFIC, as it depends on the types and frequencies of alleles that it pairs with

The genotypic value predicted from the individual allelic effects is thus
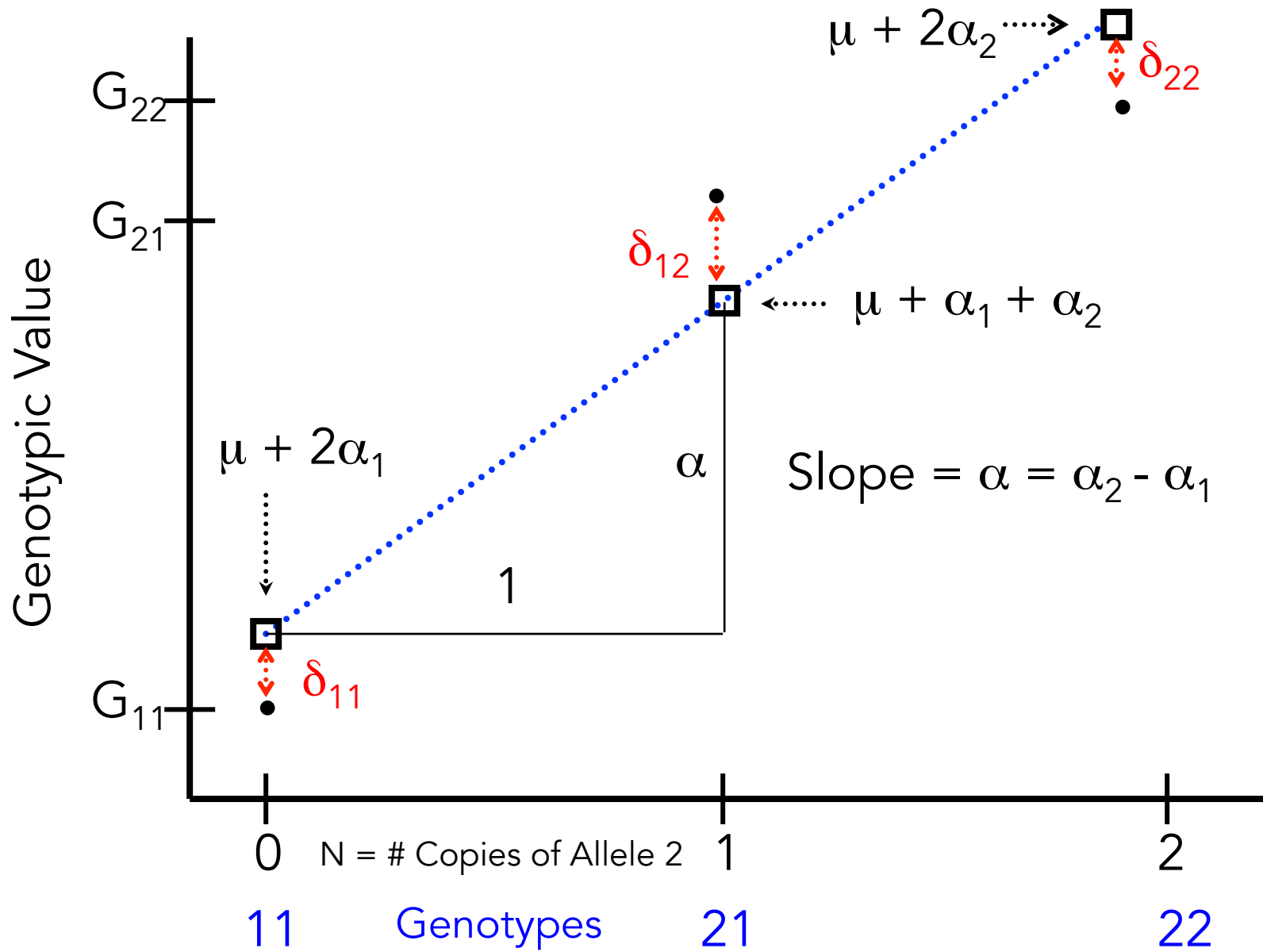
$$\hat{G}_{ij} = \mu_G + \alpha_i + \alpha_j$$

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

The genotypic value predicted from the individual allelic effects is thus

$$\hat{G}_{ij} = \mu_G + \alpha_i + \alpha_j$$

Dominance deviations --- the difference (for genotype A_iA_j) between the genotypic value predicted from the two single alleles and the actual genotypic value,

$$G_{ij} - \hat{G}_{ij} = \delta_{ij}$$

$\mu + 2\alpha_2$

δ_{22}

G_{22}

δ_{12}

$\mu + \alpha_1 + \alpha_2$

$\mu + 2\alpha_1$

α

Slope $= \alpha = \alpha_2 - \alpha_1$

G_{21}

1

δ_{11}

G_{11}

Genotypic Value

0   N = # Copies of Allele 2   1   2

11   Genotypes   21   22

Fisher's decomposition is a Regression

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

Predicted value

Residual error

A notational change clearly shows this is a regression,

$$\textcolor{blue}{G_{ij} = \mu_G + 2\alpha_1 + (\alpha_2 - \alpha_1)\, N} + \textcolor{blue}{\delta_{ij}}$$

Independent (predictor) variable N = # of A_2 alleles

Note that the slope $\alpha_2 - \alpha_1 = \alpha$, the average effect of an allelic substitution

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$$G_{ij} = \mu_G + 2\alpha_1 + (\alpha_2 - \alpha_1)\, N + \delta_{ij}$$

Intercept   Regression slope

$$2\alpha_1 + (\alpha_2 - \alpha_1)N = \begin{cases} 2\alpha_1 & \text{for } N = 0, \text{ e.g, } A_1 A_1 \\ \alpha_1 + \alpha_2 & \text{for } N = 1, \text{ e.g, } A_1 A_2 \\ 2\alpha_2 & \text{for } N = 2, \text{ e.g, } A_2 A_2 \end{cases}$$

A key point is that the average effects change with allele frequencies. Indeed, if overdominance is present they can change <u>sign</u> with allele frequencies.

Allele A_2 common, $\alpha_1 > \alpha_2$

G
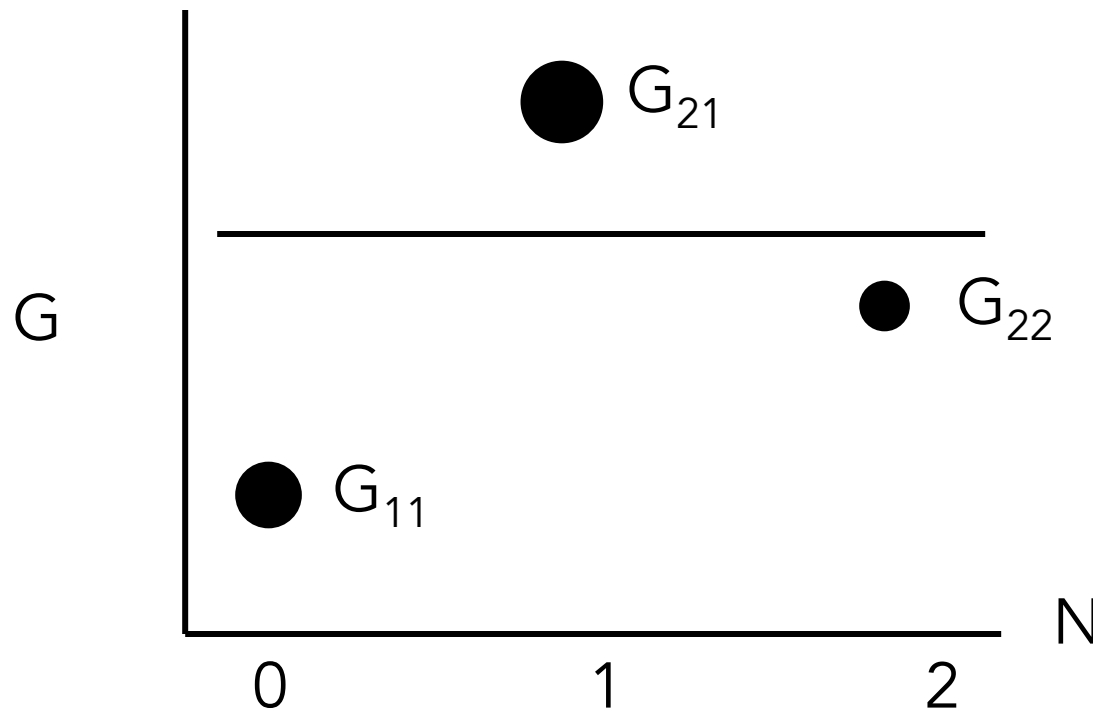
G_{21}

G_{22}

G_{11}

0   1   2

N
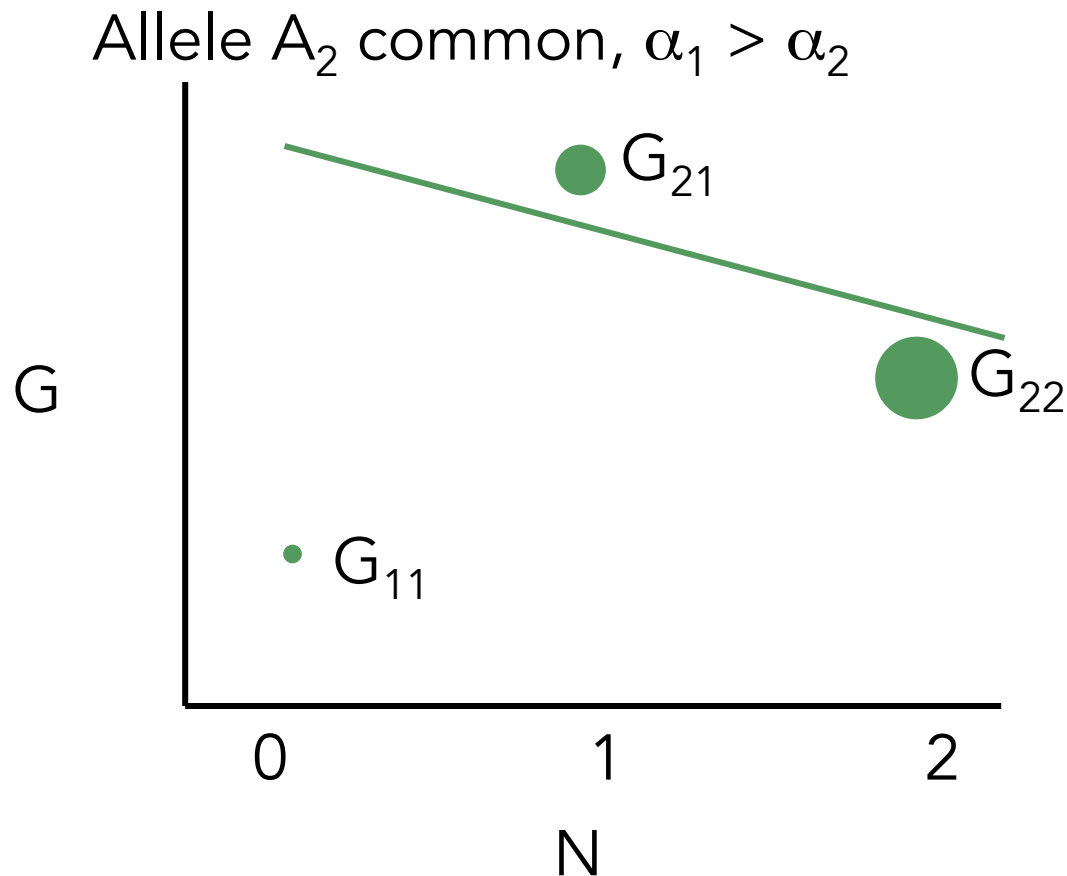
The size of the circle denotes the weight associated with that genotype. While the genotypic values do not change, their frequencies (and hence weights) do.
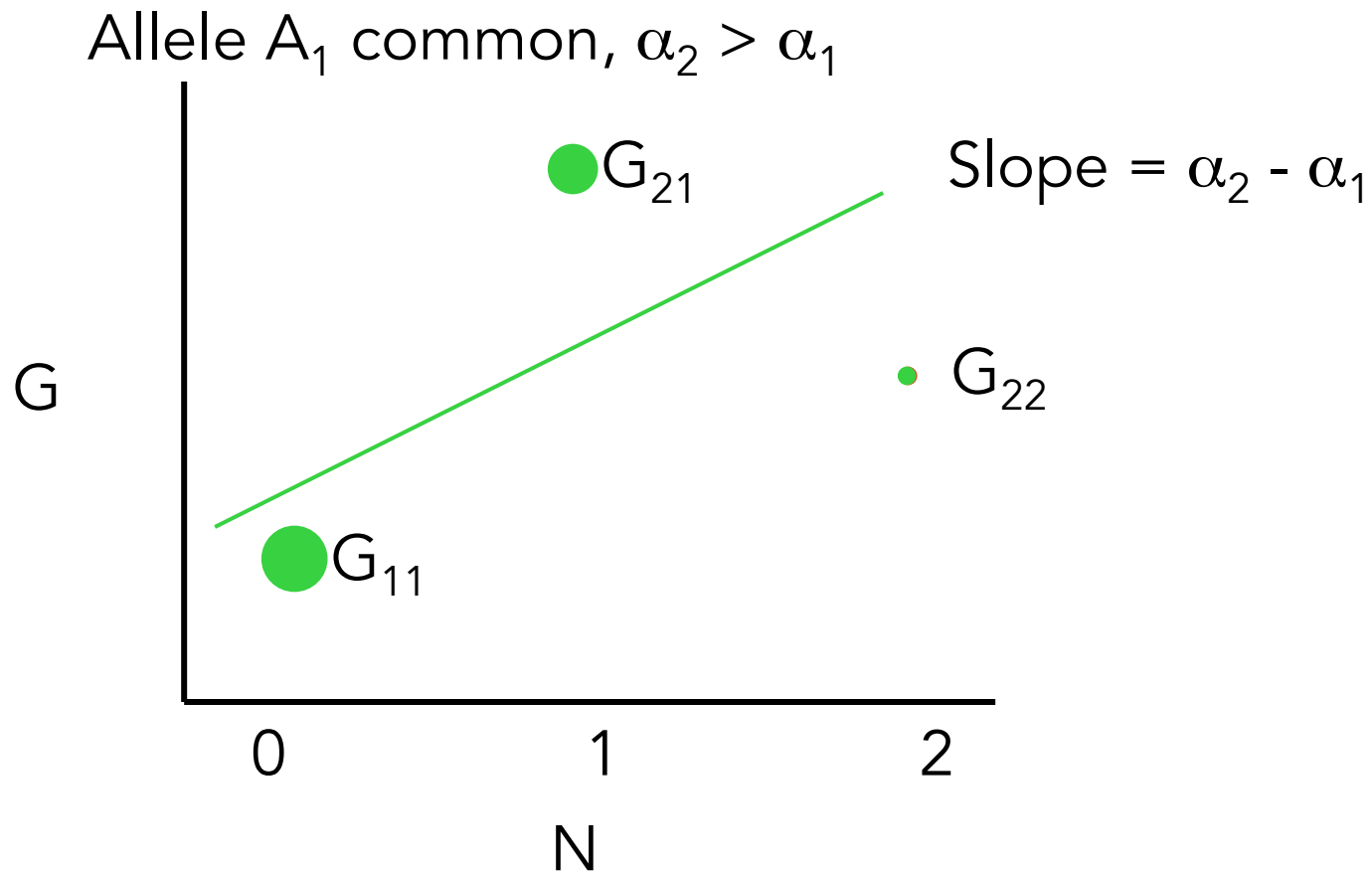
Again, same genotypic values as previous slide, but different weights, and hence a different slope (here a change in sign!)

Both A_1 and A_2 frequent, $\alpha_1 = \alpha_2 = 0$

With these allele frequencies, both alleles have the same mean value when transmitted, so that all parents have the same average offspring value -- no response to selection

PAUSE

- The last several slides were the technical details, so don't be too concerned (for now).
- We now examine the key concepts (related to these developments)
  - Average effects
  - Breeding (or additive-genetic) values
  - Genetic variances (such as the additive and dominance variance)
  - These are the quantities we work with in QG.
  - Next pause slide 38

Average Effects and Additive Genetic Values

The α values are the average effects of an allele

A key concept is the Additive Genetic Value (A) of an individual

$$A(G_{ij}) = \alpha_i + \alpha_j$$

$$A = \sum_{k=1}^{n} \left(\alpha_i^{(k)} + \alpha_j^{(k)} \right)$$

$\alpha_i^{(k)}$ = effect of allele i at locus k

A is called the Breeding value or the Additive genetic value

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$$A = \sum_{k=1}^{n} \left(\alpha_i^{(k)} + \alpha_j^{(k)} \right)$$

Why all the fuss over A?

Suppose pollen parent has A = 10 and seed parent has A = -2 for plant height

Expected average offspring height is (10 - 2)/2 = 4 units above the population mean. Offspring A = average of parental A's

KEY: parents only pass single alleles to their offspring. Hence, they only pass along the A part of their genotypic value G

Genetic Variances

Writing the genotypic value as

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

The genetic variance can be written as

$$\sigma^2(G) = \sum_{k=1}^{n} \sigma^2(\alpha_i^{(k)} + \alpha_j^{(k)}) + \sum_{k=1}^{n} \sigma^2(\delta_{ij}^{(k)})$$

This follows since

$$\sigma^2(G) = \sigma^2(\mu_g + (\alpha_i + \alpha_j) + \delta_{ij}) = \sigma^2(\alpha_i + \alpha_j) + \sigma^2(\delta_{ij})$$

As $\text{Cov}(\alpha, \delta) = 0$

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Key concepts (so far)

- α_i = average effect of allele i
  - Property of a single allele in a particular population (depends on genetic background)
- A = Additive Genetic Value (A)
  - A = sum (over all loci) of average effects
  - Fraction of G that parents pass along to their offspring
  - Property of an Individual in a particular population
- Var(A) = additive genetic variance
  - Variance in additive genetic values
  - Property of a population
- Can estimate A or Var(A) without knowing any of the underlying genetical detail (forthcoming)

PAUSE

- What is the expected breeding value for a random individual from a population?
  - Hint: A is a deviation from the mean
- You cross a single sire (male) to a large number of unrelated dams (females), with one daughter per cross
  - These are a collection of half-sibs
  - Suppose the mean milk yield of daughters from a given sire has a value of 10 units above the mean. What is the sire's BV?
  - Last PAUSE slide (last slide = 46)

- The BV for a randomly-chosen individual has an expected value of zero
- The expected offspring mean is
  - Overall mean + (1/2) BV(sire) + (1/2) BV(dam)
  - Hence, the expected mean with random dams is overall mean + (1/2) BV(Sire) + 0
  - Hence, if offspring are 10 units above the mean, then (1/2) BV(sire) = 10, or sire BV is 20.

Genetic Variances

$$\sigma^2(G) = \sum_{k=1}^{n} \sigma^2(\alpha_i^{(k)} + \alpha_j^{(k)}) + \sum_{k=1}^{n} \sigma^2(\delta_{ij}^{(k)})$$

Additive Genetic Variance
(or simply Additive Variance)

Dominance Genetic Variance
(or simply dominance variance)

Hence, total genetic variance = additive + dominance variances,

$$\sigma_G^2 = \sigma_A^2 + \sigma_D^2$$

$$\sigma_A^2 = 2E[\alpha^2] = 2\sum_{i=1}^{m}\alpha_i^2\, p_i$$

Q_1Q_1	Q_1Q_2	Q_2Q_2
0	a(1+k)	2a

Since E[α] = 0,

Var(α) = E[(α -μ_a)^2] = E[α^2]

One locus, 2 alleles:

$$\sigma_A^2 = 2p_1\, p_2\, a^2[\, 1 + k\, (p_1 - p_2)\,]^2$$

Dominance alters
additive variance

When dominance present, Additive variance is an
asymmetric function of allele frequencies

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Dominance variance

	Q_1Q_1	Q_1Q_2	Q_2Q_2
	0	a(1+k)	2a

$$\sigma_D^2 = E[\delta^2] = \sum_{i=1}^{m}\sum_{j=1}^{m} \delta_{ij}^2\, p_i\, p_j$$
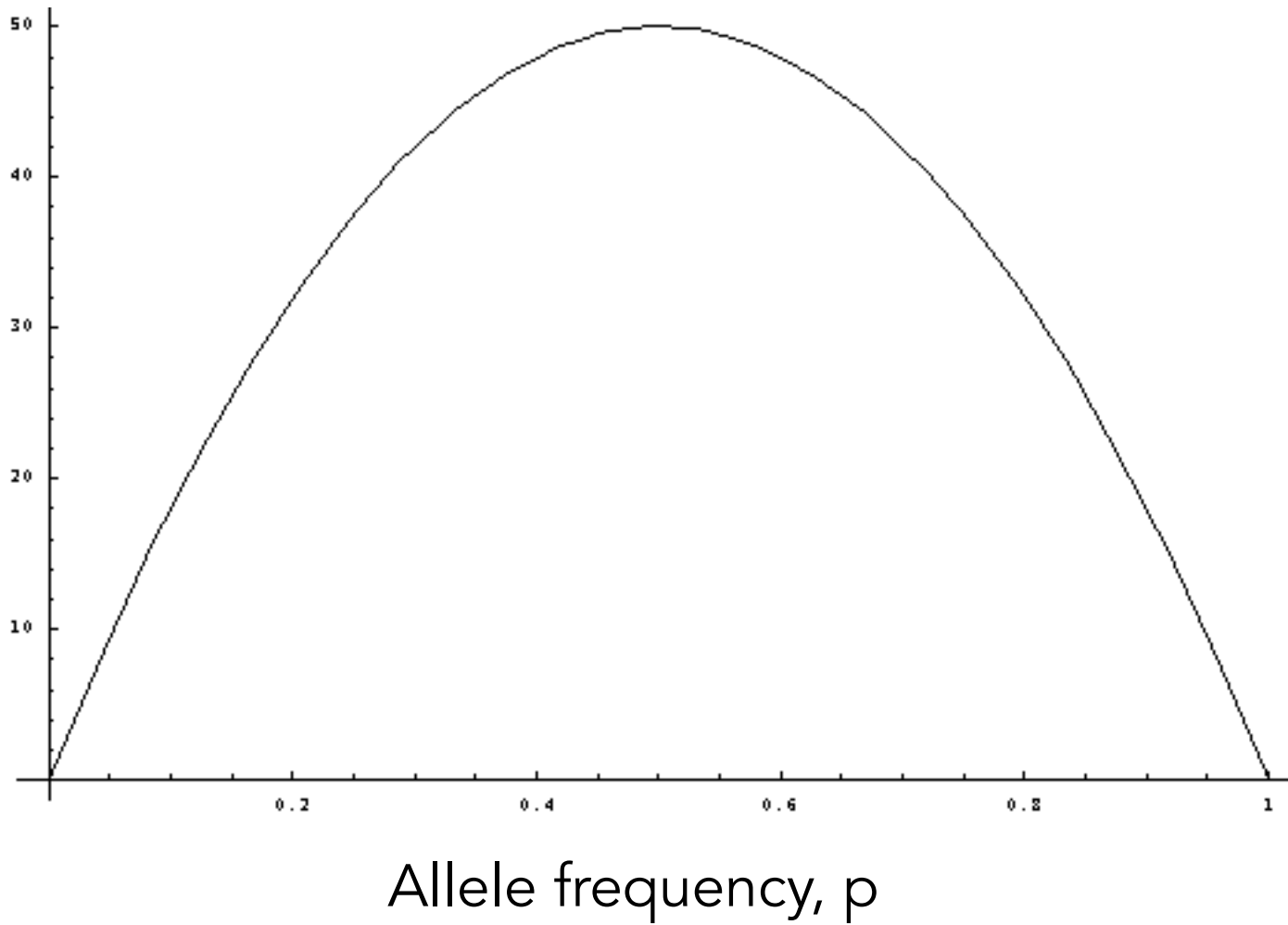
Equals zero if k = 0

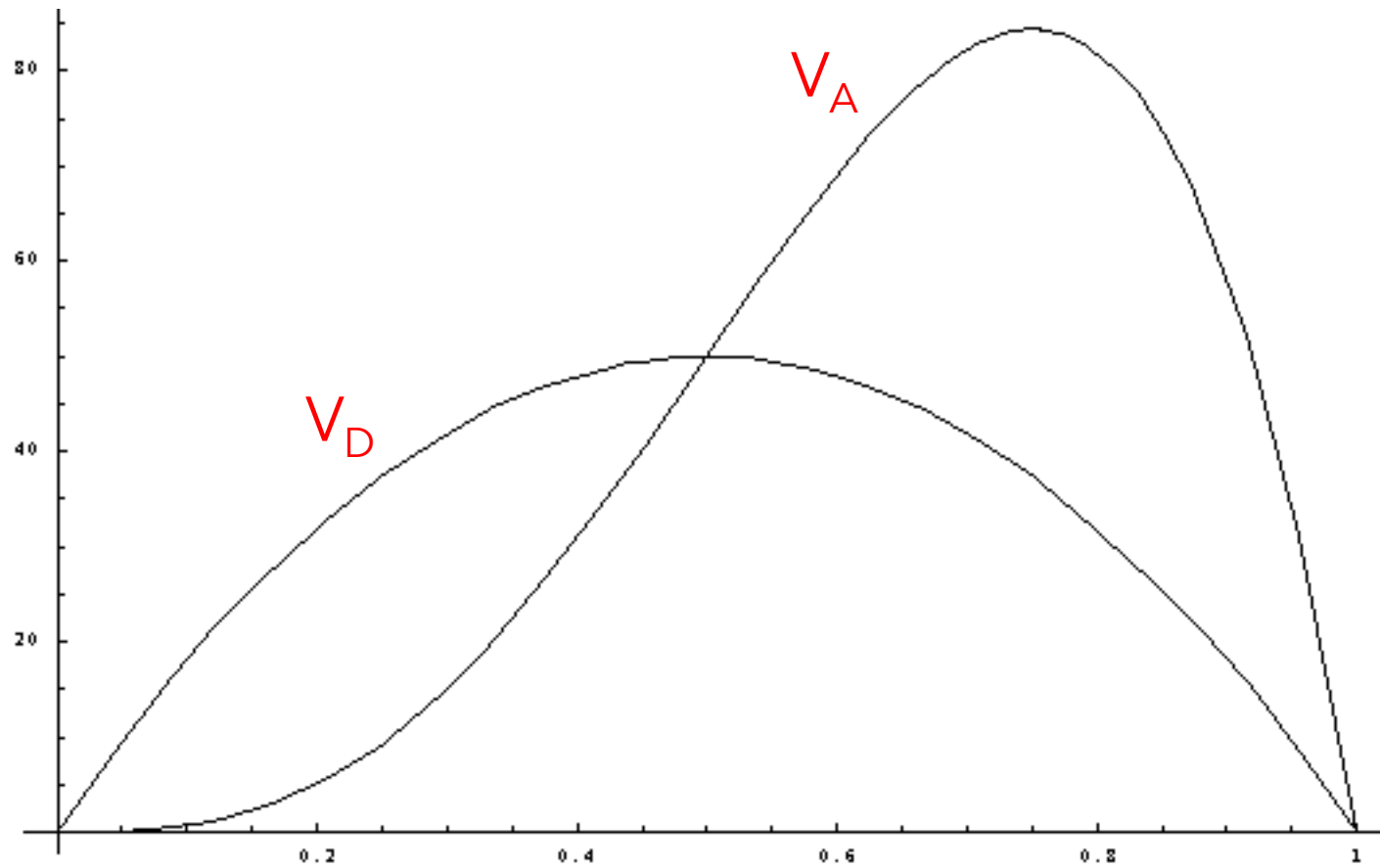One locus, 2 alleles: $\sigma_D^2 = (2p_1\, p_2\, ak)^2$

This is a symmetric function of allele frequencies

Can also be expressed in terms of d = ak

Additive variance, V_A, with no dominance (k = 0)

Allele frequency, p

Complete dominance (k = 1)

V_A

V_D

Allele frequency, p

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Epistasis

$$G_{ijkl} = \mu_G + (\alpha_i + \alpha_j + \alpha_k + \alpha_l) + (\delta_{ij} + \delta_{kj})$$
$$+ (\alpha\alpha_{ik} + \alpha\alpha_{il} + \alpha\alpha_{jk} + \alpha\alpha_{jl})$$
$$+ (\alpha\delta_{ikl} + \alpha\delta_{jkl} + \alpha\delta_{kij} + \alpha\delta_{lij})$$
$$+ (\delta\delta_{ijkl})$$
$$= \mu_G + A + D + AA + AD + DD$$

These components are defined to be uncorrelated, (or orthogonal), so that

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

$$G_{ijkl} = \mu_G + (\alpha_i + \alpha_j + \alpha_k + \alpha_l) + (\delta_{ij} + \delta_{kj})$$
$$+ (\alpha\alpha_{ik} + \alpha\alpha_{il} + \alpha\alpha_{jk} + \alpha\alpha_{jl})$$
$$+ (\alpha\delta_{ikl} + \alpha\delta_{jkl} + \alpha\delta_{kij} + \alpha\delta_{lij})$$
$$+ (\delta\delta_{ijkl})$$
$$= \mu_G + A + D + AA + AD + DD$$

Additive x Additive interactions -- $\alpha\alpha$, AA
interactions between a single allele
at one locus with a single allele at another

Additive x Dominance interactions -- $\alpha\delta$, AD
interactions between an allele at one
locus with the genotype at another, e.g.
allele A_i and genotype B_{kj}

Dominance x dominance interaction --- $\delta\delta$, DD
the interaction between the dominance
deviation at one locus with the dominance
deviation at another.

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