Biometrical genetics

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Outline

1. Aim of this talk
2. Genetic concepts
3. Very basic statistical concepts
4. Biometrical model

1. Aim of this talk

- ▷ Revisit common genetic parameters - such as allele frequencies, genetic effects, dominance, variance components, etc

- ▷ Use these parameters to construct a biometrical genetic model

↓

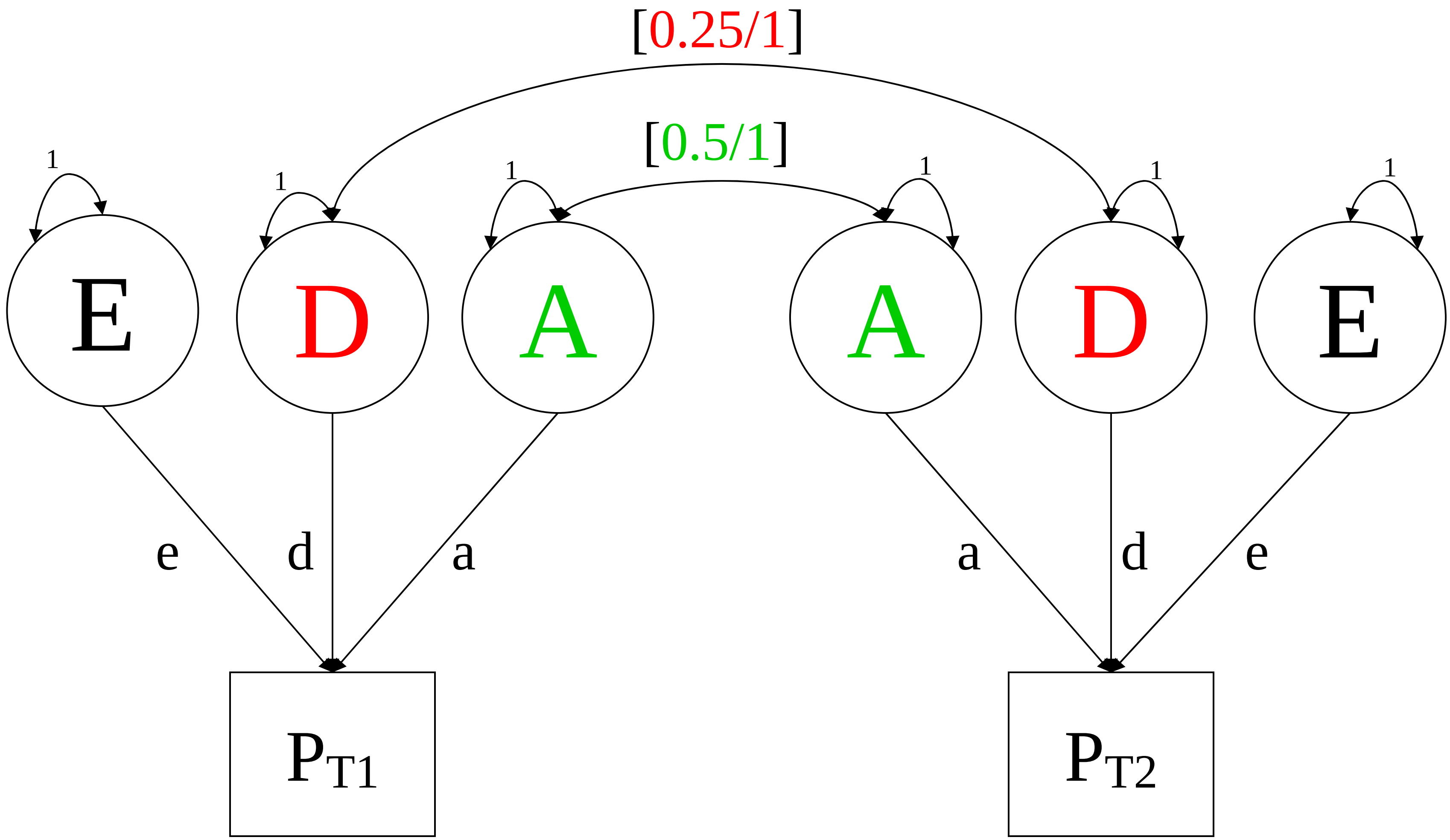
Model that expresses the:

(1) Mean

(2) Variance

(3) Covariance between individuals

for a quantitative phenotype as a function of genetic parameters.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P T1
P T2

2. Genetic concepts

▷ **Population level**

Allele and genotype frequencies

▷ **Transmission level**

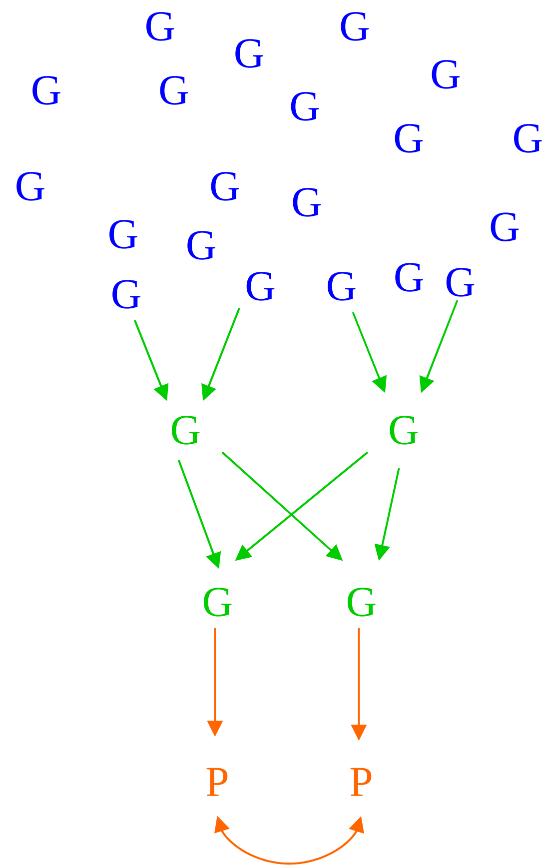
Mendelian segregation

Genetic relatedness

▷ **Phenotype level**

Biometrical model

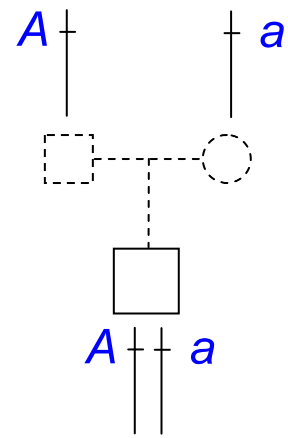
Additive and dominance components



Population level

1. Allele frequencies

▷ A single locus, with two alleles
- Biallelic / diallelic
- Single nucleotide polymorphism, SNP



▷ Alleles ***A*** and ***a***
- Frequency of ***A*** is ***p***
- Frequency of ***a*** is ***q*** = 1 – ***p***

▷ Every individual inherits two alleles
- A genotype is the combination of the two alleles
- e.g. ***AA***, ***aa*** (the homozygotes) or ***Aa*** (the heterozygote)

Population level

2. Genotype frequencies (Random mating)

Allele 1 (columns); Allele 2 (rows)

	A (p)	*a* (q)
A (p)	*AA* (p^2)	*Aa* (pq)
a (q)	*aA* (qp)	*aa* (q^2)

Hardy-Weinberg Equilibrium frequencies

$P(AA) = p^2$

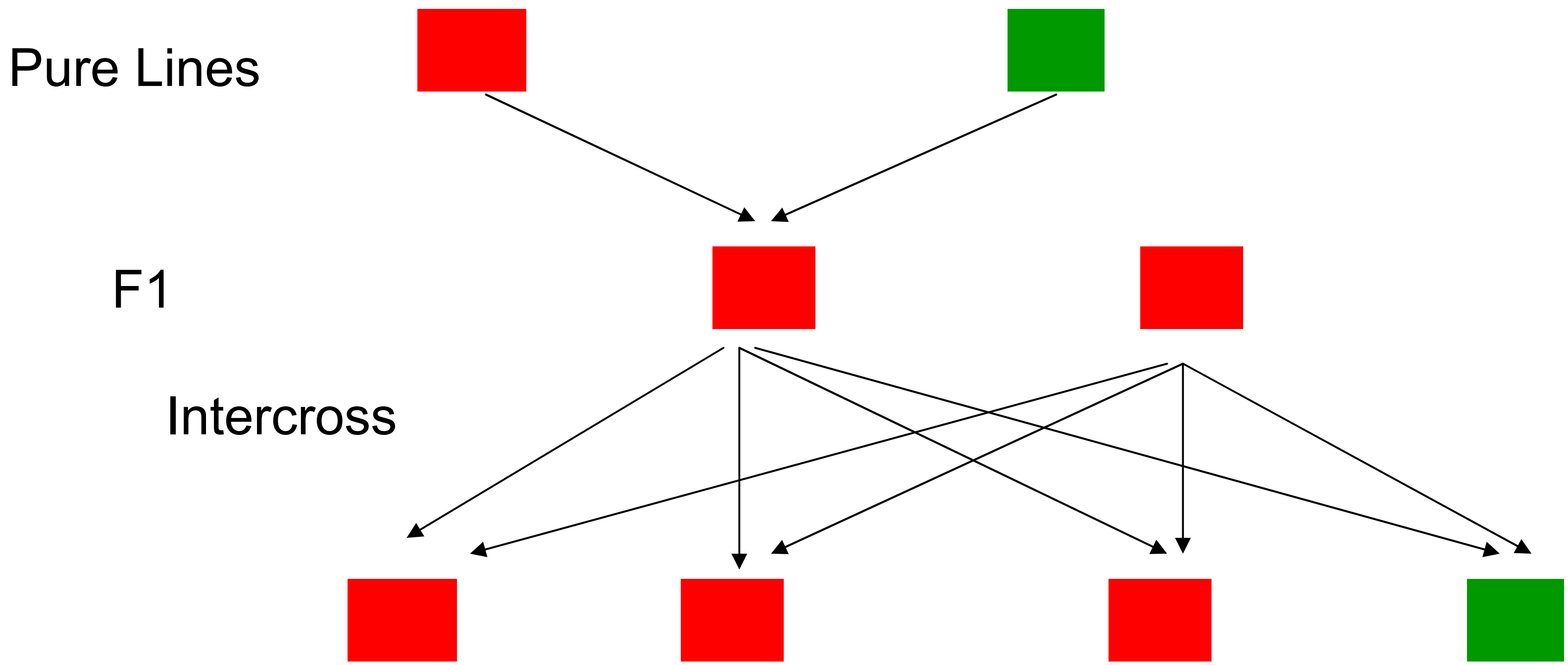
$P(Aa) = 2pq$

$P(aa) = q^2$

$$p^2 + 2pq + q^2 = 1$$

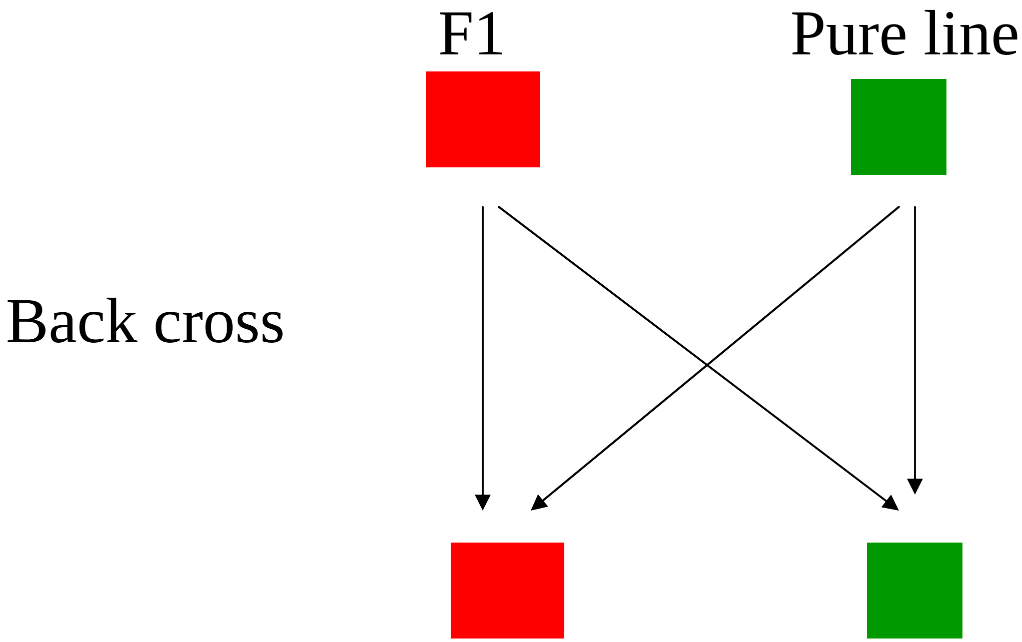
Transmission level

1. Mendel's experiments



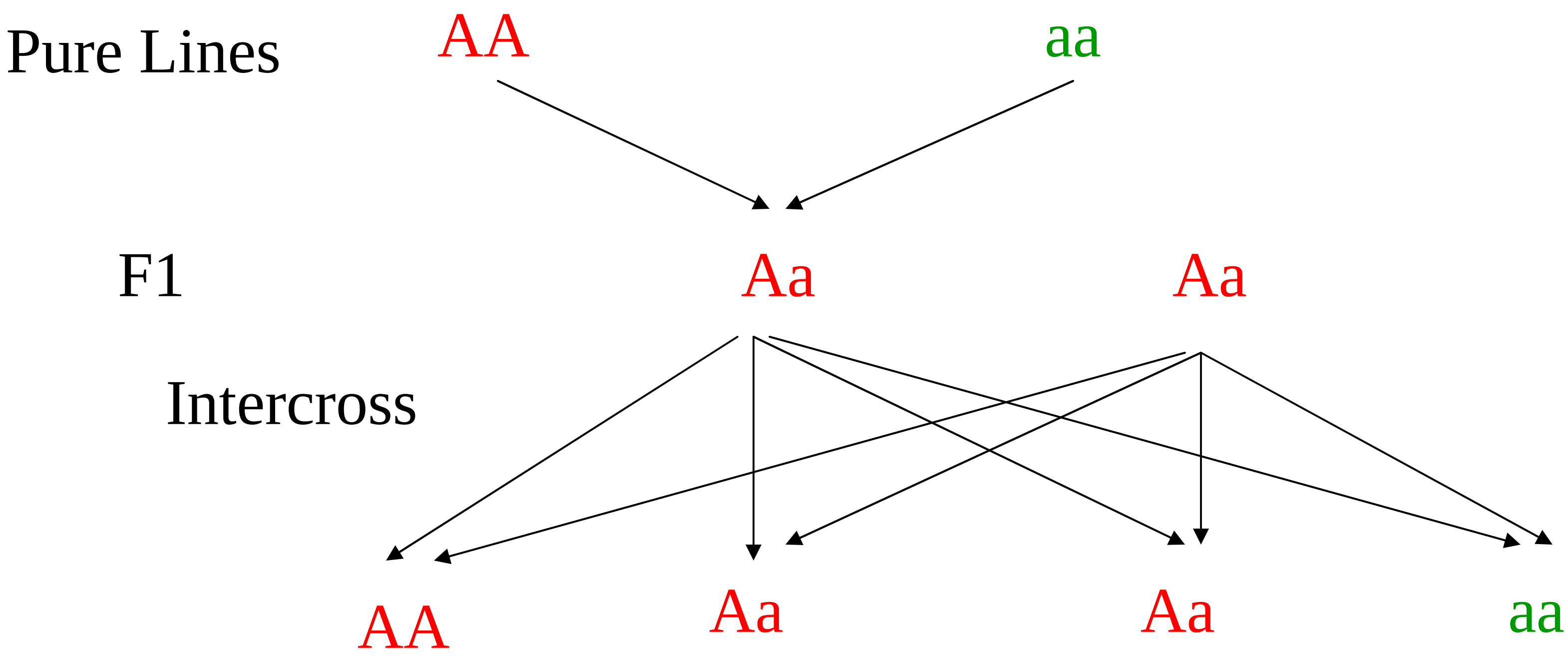
3:1 Segregation Ratio

Transmission level



1:1 Segregation ratio

Transmission level



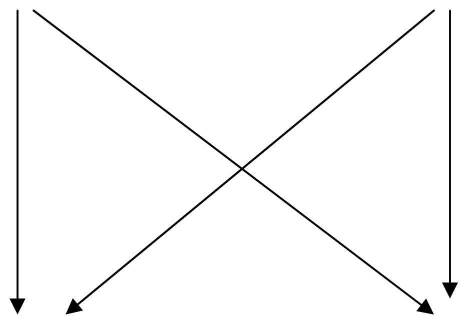
3:1 Segregation Ratio

Transmission level

F1 Pure line

Aa aa

Back cross



Aa aa

1:1 Segregation ratio

Transmission level

1. Mendel's law of segregation

Mother (A_3A_4)

Segregation, Meiosis

Gametes

Father (A_1A_2)

	A_3 (½)	A_4 (½)
A_1 (½)	A_1A_3 (¼)	A_1A_4 (¼)
A_2 (½)	A_2A_3 (¼)	A_2A_4 (¼)

Phenotype level

1. Classical Mendelian traits

- ▷ Dominant trait (**D** - presence, **R** - absence)
  - ***AA***, ***Aa*** **D**
  - ***aa*** **R**

- ▷ Recessive trait (**D** - absence, **R** - presence)
  - ***AA***, ***Aa*** **D**
  - ***aa*** **R**

- ▷ Codominant trait (**X, Y, Z**)
  - ***AA*** **X**
  - ***Aa*** **Y**
  - ***aa*** **Z**

Phenotype level

2. Dominant Mendelian inheritance

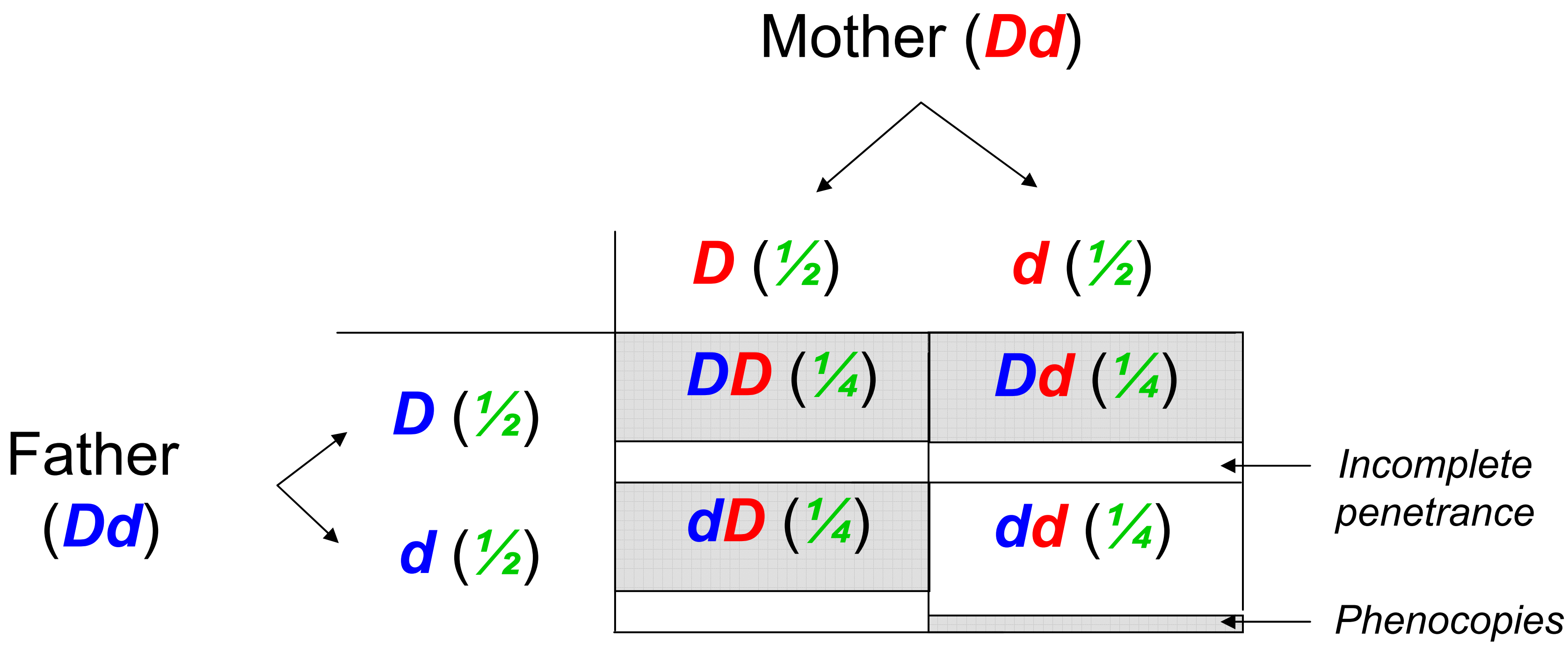
Mother (*Dd*)

Father (*Dd*)

	D **(½)**	***d*** **(½)**
D **(½)**	***DD*** **(¼)**	***Dd*** **(¼)**
d **(½)**	***dD*** **(¼)**	***dd*** **(¼)**

Phenotype level

3. Dominant Mendelian inheritance with incomplete penetrance and phenocopies



Phenotype level

4. Recessive Mendelian inheritance

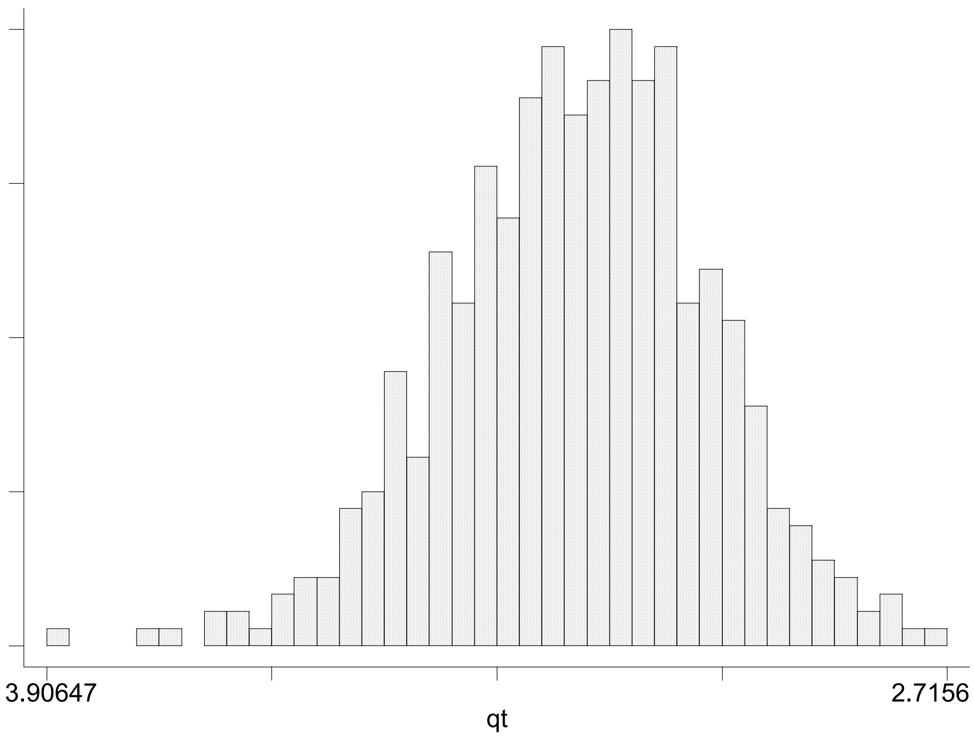
Mother (*Dd*)

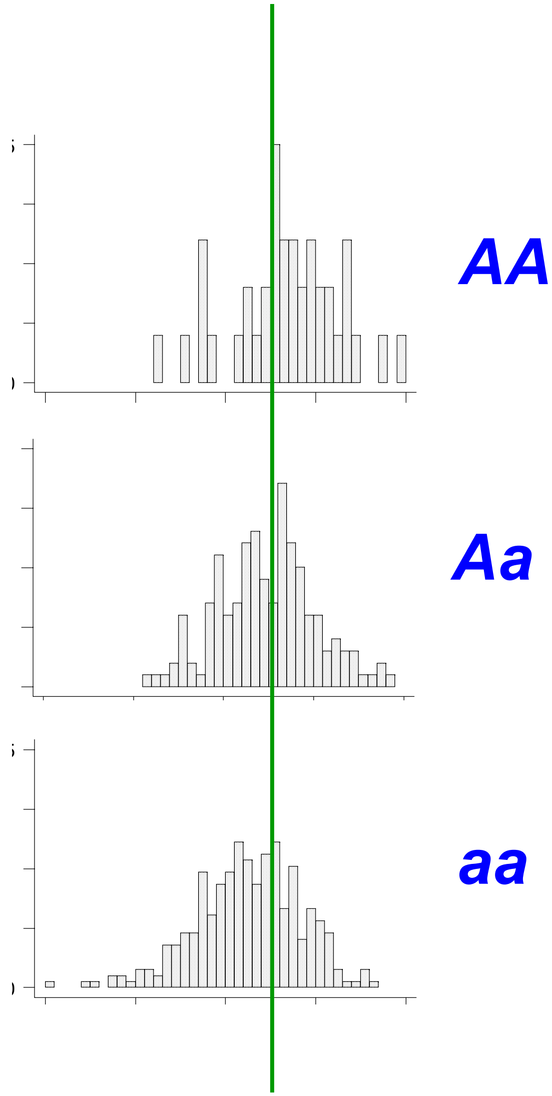
Father (*Dd*)

	D (½)	*d* (½)
D (½)	*DD* (¼)	*Dd* (¼)
d (½)	*dD* (¼)	*dd* (¼)

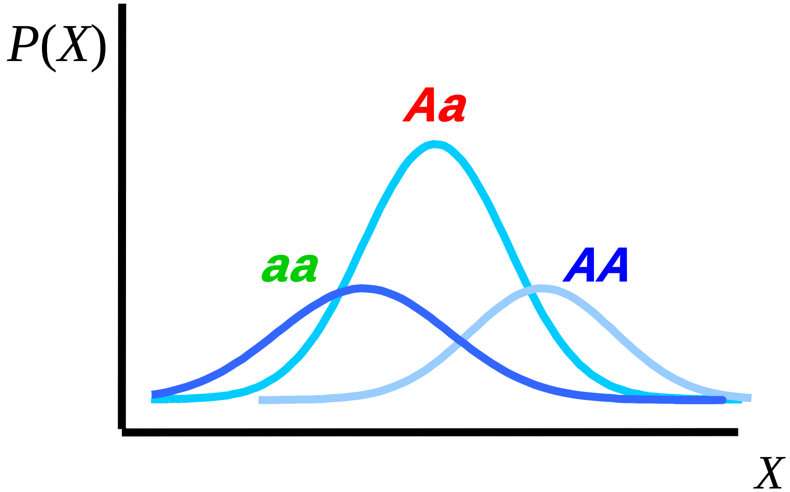
Phenotype level

5. Quantitative traits

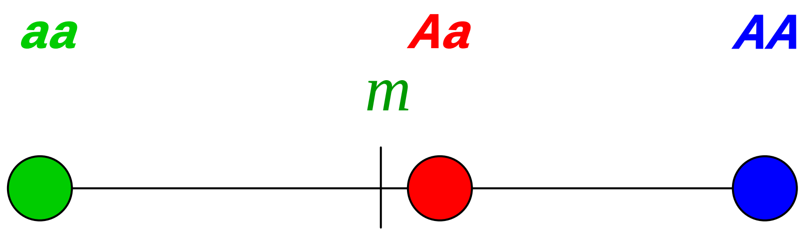




Phenotype level



Biometric Model



$-a$ d $+a$ ← Genotypic effect

$m-a$ $m+d$ $m+a$ ← Genotypic means

3. Very basic statistical concepts

Mean, variance, covariance

1. Mean (X)

$$\mu = E(X) = \frac{\sum_i x_i}{n} = \sum_i x_i f\left(x_i\right)$$

Mean, variance, covariance

2. Variance (X)

$$Var(X) = E(X-\mu)^2 = \frac{\sum_i (x_i-\mu)^2}{n-1} = \sum_i (x_i-\mu)^2 f(x_i)$$

Mean, variance, covariance

3. Covariance (X, Y)

$$Cov(X,Y) = E(X-\mu_X)(Y-\mu_Y) = \frac{\sum_i (x_i-\mu_X)(y_i-\mu_Y)}{n-1}$$

$$= \sum_i (x_i-\mu_X)(y_i-\mu_Y) f(x_i, y_i)$$

4. Biometrical model

Biometrical model for single biallelic QTL

- ▷ Biallelic locus
  - Genotypes: ***AA, Aa, aa***
  - Genotype frequencies: ***p^2, 2pq, q^2***

- ▷ Alleles at this locus are transmitted from P-O according to Mendel's law of segregation

- ▷ Genotypes for this locus influence the expression of a quantitative trait *X* (i.e. locus *is* a QTL)

↓

Biometrical genetic model that estimates the contribution of this QTL towards the **(1) Mean**, **(2) Variance** and **(3) Covariance between individuals** for this quantitative trait *X*

Biometrical model for single biallelic QTL

1. Contribution of the QTL to the Mean (*X*)

$$\mu = \sum_i x_i f\left(x_i\right)$$

Genotypes	***AA***	***Aa***	***aa***
Effect, *x*	***a***	***d***	***-a***
Frequencies, *f*(*x*)	p^2	$2pq$	q^2

$$Mean\ (X) = a(p^2) + d(2pq) - a(q^2) = a(p-q) + 2pqd$$

Biometrical model for single biallelic QTL

2. Contribution of the QTL to the Variance (*X*)

$$Var = \sum_i (x_i - \mu)^2 f(x_i)$$

Genotypes	***AA***	***Aa***	***aa***
Effect, *x*	***a***	***d***	***-a***
Frequencies, *f*(*x*)	p^2	$2pq$	q^2

$$Var(X) = (a-m)^2 p^2 + (d-m)^2 2pq + (-a-m)^2 q^2$$

$$= V_{QTL}$$

Broad-sense heritability of *X* at this locus = $V_{QTL} / V_{\text{Total}}$

Broad-sense total heritability of *X* = $\Sigma V_{QTL} / V_{\text{Total}}$

Biometrical model for single biallelic QTL

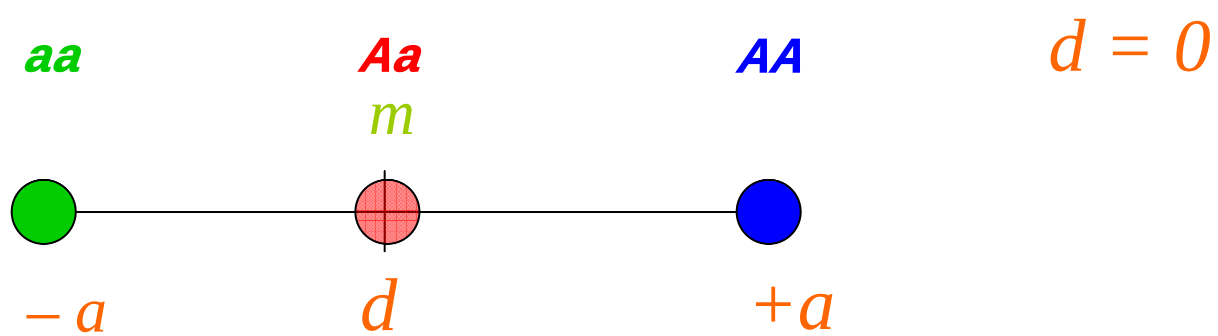
$$Var(X) = (a-m)^2 p^2 + (d-m)^2 2pq + (-a-m)^2 q^2$$

$$= \underline{2pq[a+(q-p)d]^2} + \underline{(2pqd)^2}$$

$$= V_{A_{QTL}} + V_{D_{QTL}}$$

Additive effects: the main effects of individual alleles

Dominance effects: represent the interaction between alleles



Biometrical model for single biallelic QTL

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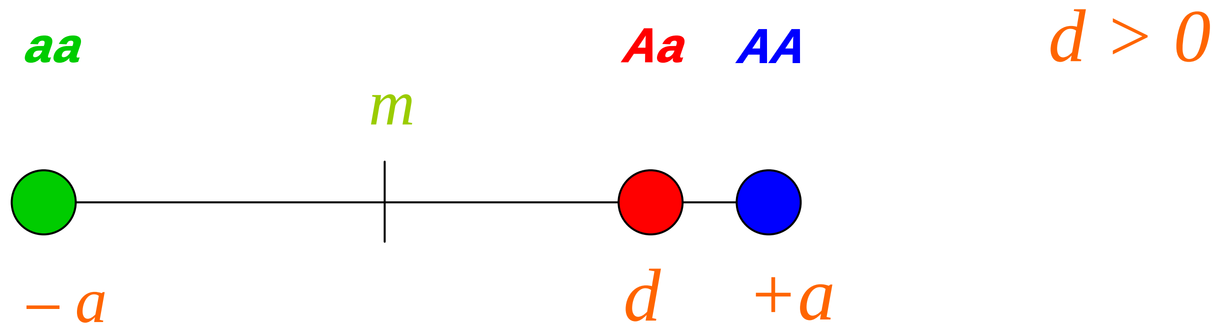

Biometrical model for single biallelic QTL

$$Var(X) = (a-m)^2 p^2 + (d-m)^2 2pq + (-a-m)^2 q^2$$

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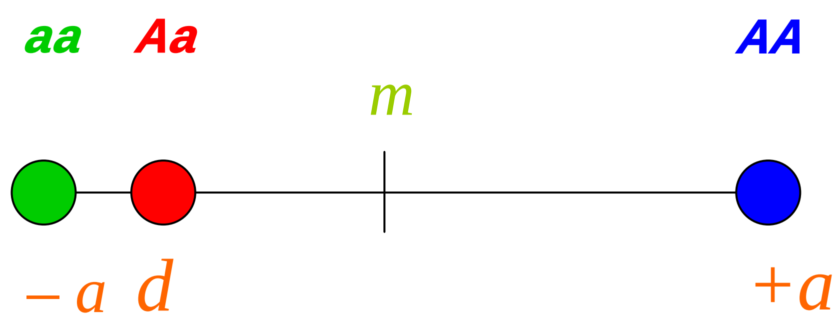
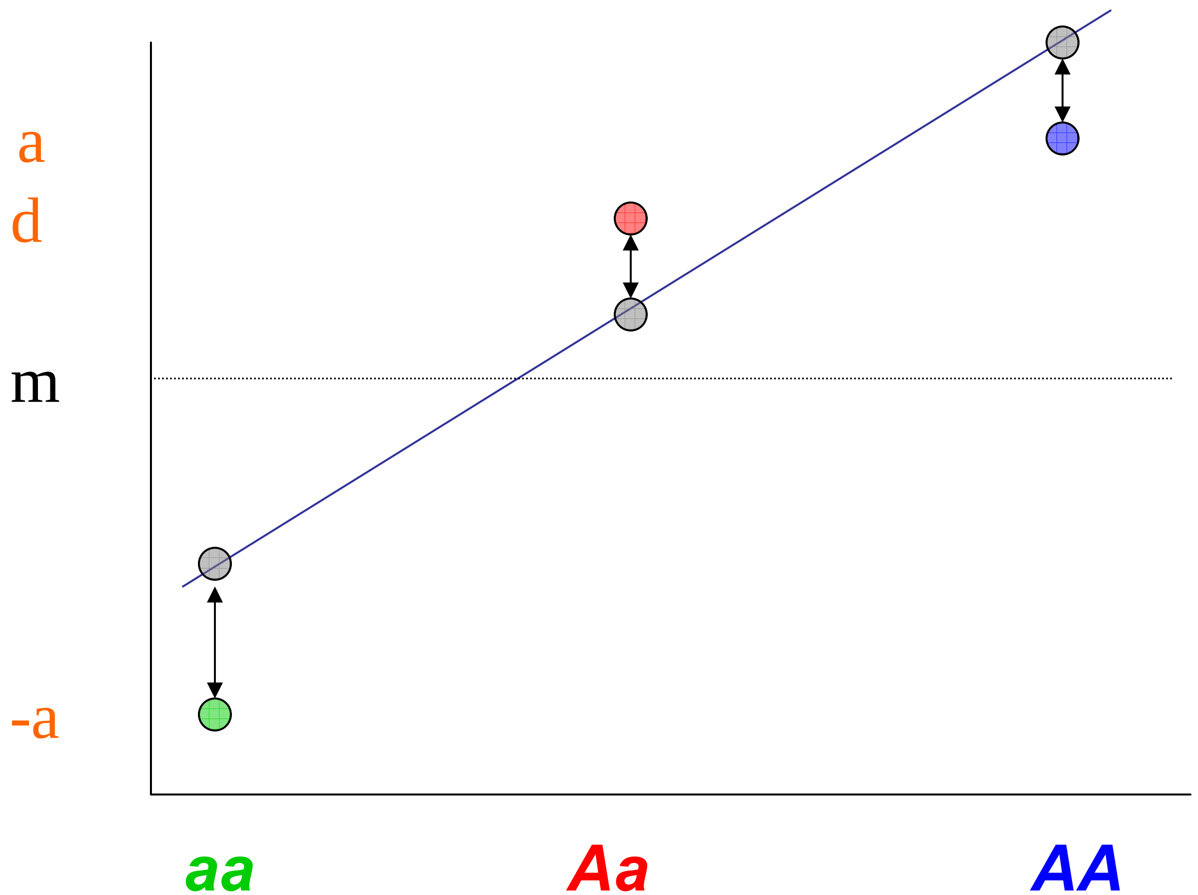
Additive effects: the main effects of individual alleles

Dominance effects: represent the interaction between alleles



$d < 0$

Biometrical model for single biallelic QTL



Var (X) = Regression Variance + Residual Variance
= Additive Variance + Dominance Variance

Practical

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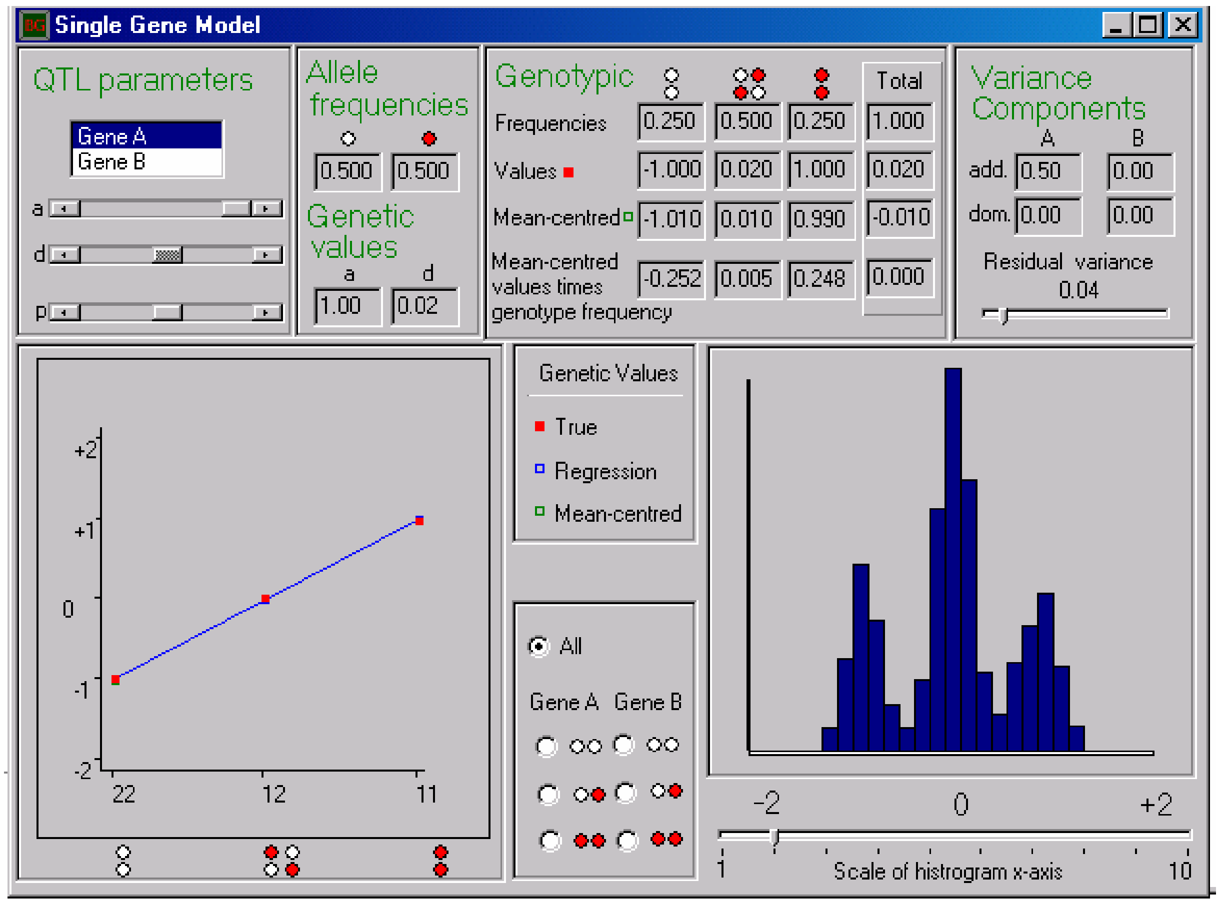


Practical

- **Aim** Visualize graphically how allele frequencies, genetic effects, dominance, etc, influence trait mean and variance

Ex1

a=0, d=0, p=0.4, Residual Variance = 0.04, Scale = 2.
Vary a from 0 to 1.

Ex2

a=1, d=0, p=0.4, Residual Variance = 0.04, Scale = 2.
Vary d from -1 to 1.

Ex3

a=1, d=0, p=0.4, Residual Variance = 0.04, Scale = 2.
Vary p from 0 to 1.

Look at scatter-plot, histogram and variance components.

Some conclusions

1. Additive genetic variance depends on

   allele frequency p

   & additive genetic value a

   as well as

   dominance deviation d

2. Additive genetic variance typically greater than dominance variance

Biometrical model for single biallelic QTL

$$Var(X) = \underline{2pq[a+(q-p)d]^2} + \underline{(2pqd)^2}$$

↓ *Demonstrate*

$$V_{A_{QTL}} + V_{D_{QTL}}$$

2A. Average allelic effect

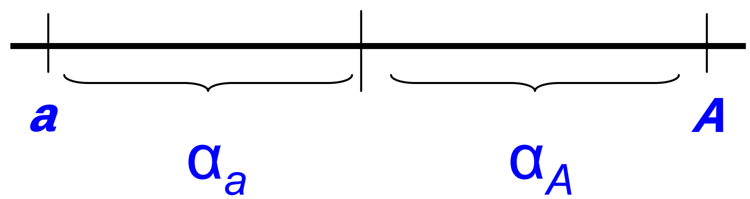
2B. Additive genetic variance

Biometrical model for single biallelic QTL

2A. Average allelic effect (α)

The deviation of the <u>allelic mean</u> from the <u>population mean</u>

	Allele ***a***	Population	Allele ***A***
Mean (*X*) →	?	$a(p-q) + 2pqd$	?



	AA ***a***	***Aa*** ***d***	***aa*** ***-a***	Allelic mean	Average allelic effect (α)
A	***p***	***q***		$ap+dq$	$q(a+d(q-p))$
a		***p***	***q***	$dp-aq$	$-p(a+d(q-p))$

Biometrical model for single biallelic QTL

- Denote the average allelic effects
  - $\alpha_A = q(a+d(q-p))$
  - $\alpha_a = -p(a+d(q-p))$

- If only two alleles exist, we can define the *average effect of allele substitution*
  - $\alpha = \alpha_A - \alpha_a$
  - $\alpha = (q-(-p))(a+d(q-p)) = (a+d(q-p))$

- Therefore:
  - $\alpha_A = q\alpha$
  - $\alpha_a = -p\alpha$

Biometrical model for single biallelic QTL

2A. Average allelic effect (α)

2B. Additive genetic variance

The variance of the average allelic effects

$\alpha_A = q\alpha$
$\alpha_a = -p\alpha$

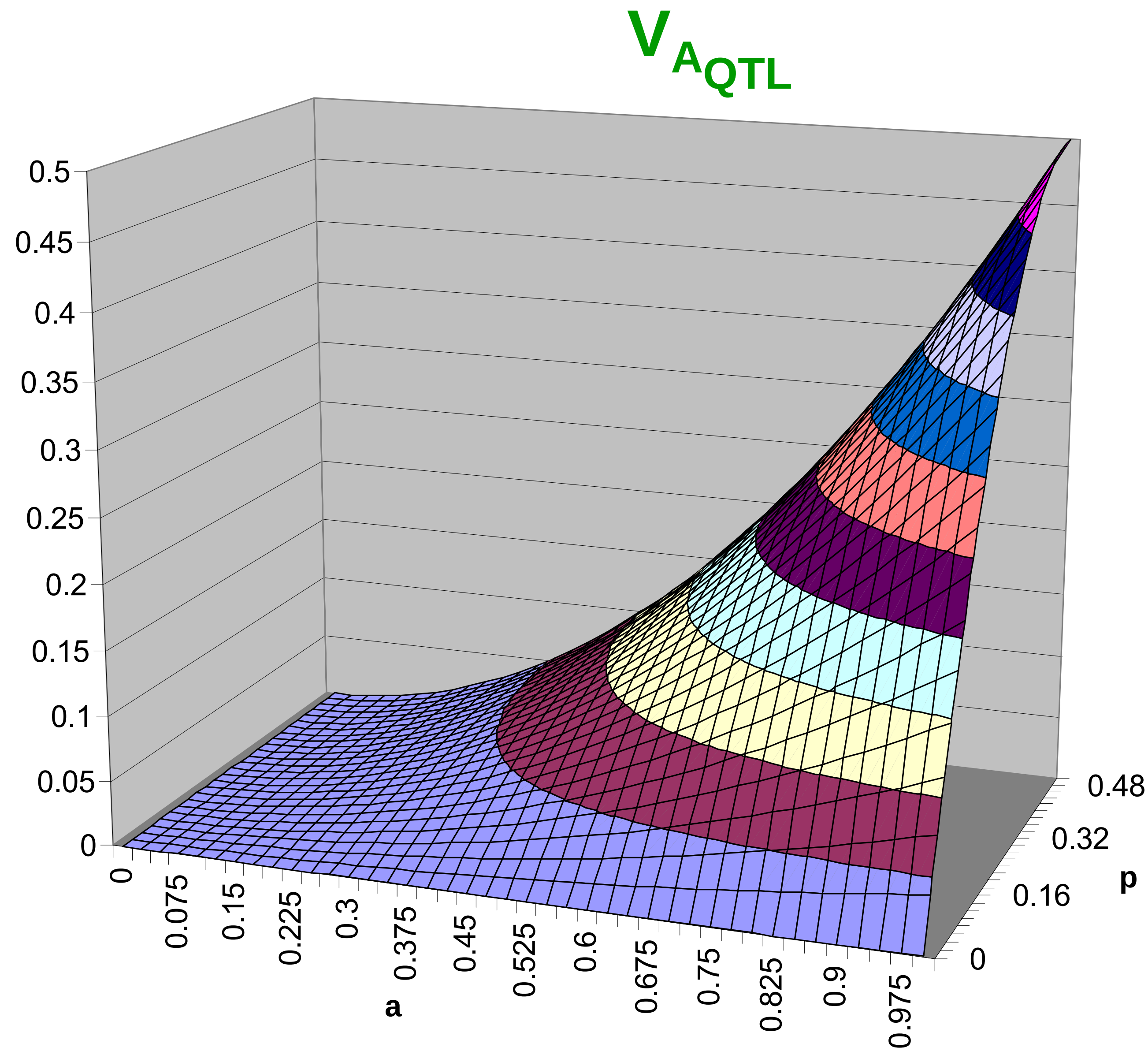
	Freq.	Additive effect	
AA	p^2	$2\alpha_A$	$= 2q\alpha$
Aa	$2pq$	$\alpha_A + \alpha_a$	$= (q-p)\alpha$
aa	q^2	$2\alpha_a$	$= -2p\alpha$

$$V_{A_{QTL}} = (2q\alpha)^2 p^2 + ((q-p)\alpha)^2 2pq + (-2p\alpha)^2 q^2$$
$$= 2pq\alpha^2$$
$$= 2pq[a+d(q-p)]^2$$

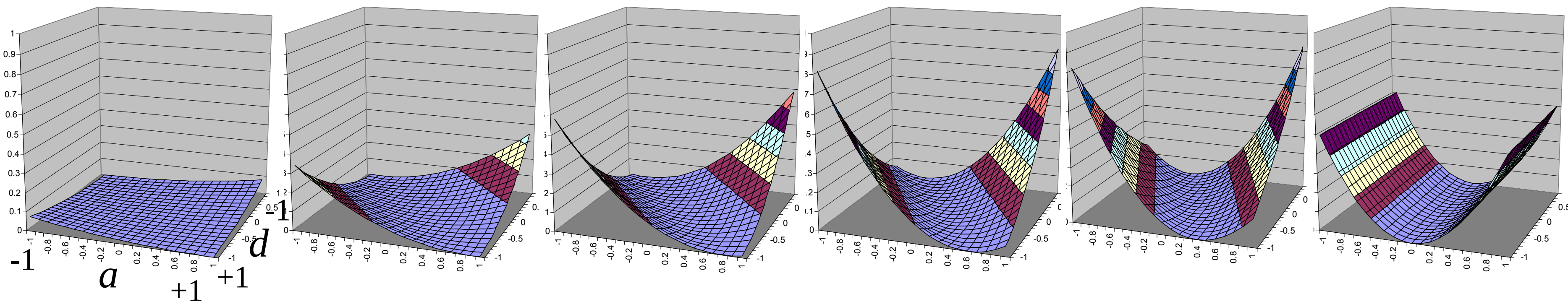
$d = 0$, $V_{A_{QTL}} = 2pqa^2$

$p = q$, $V_{A_{QTL}} = \frac{1}{2}a^2$

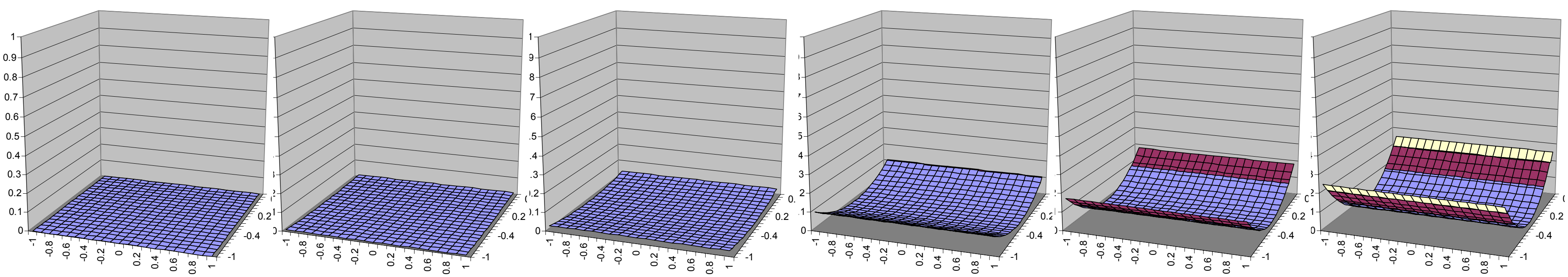
$d = 0$, $V_{A_{QTL}} = 2pqa^2$



Additive genetic variance V_A

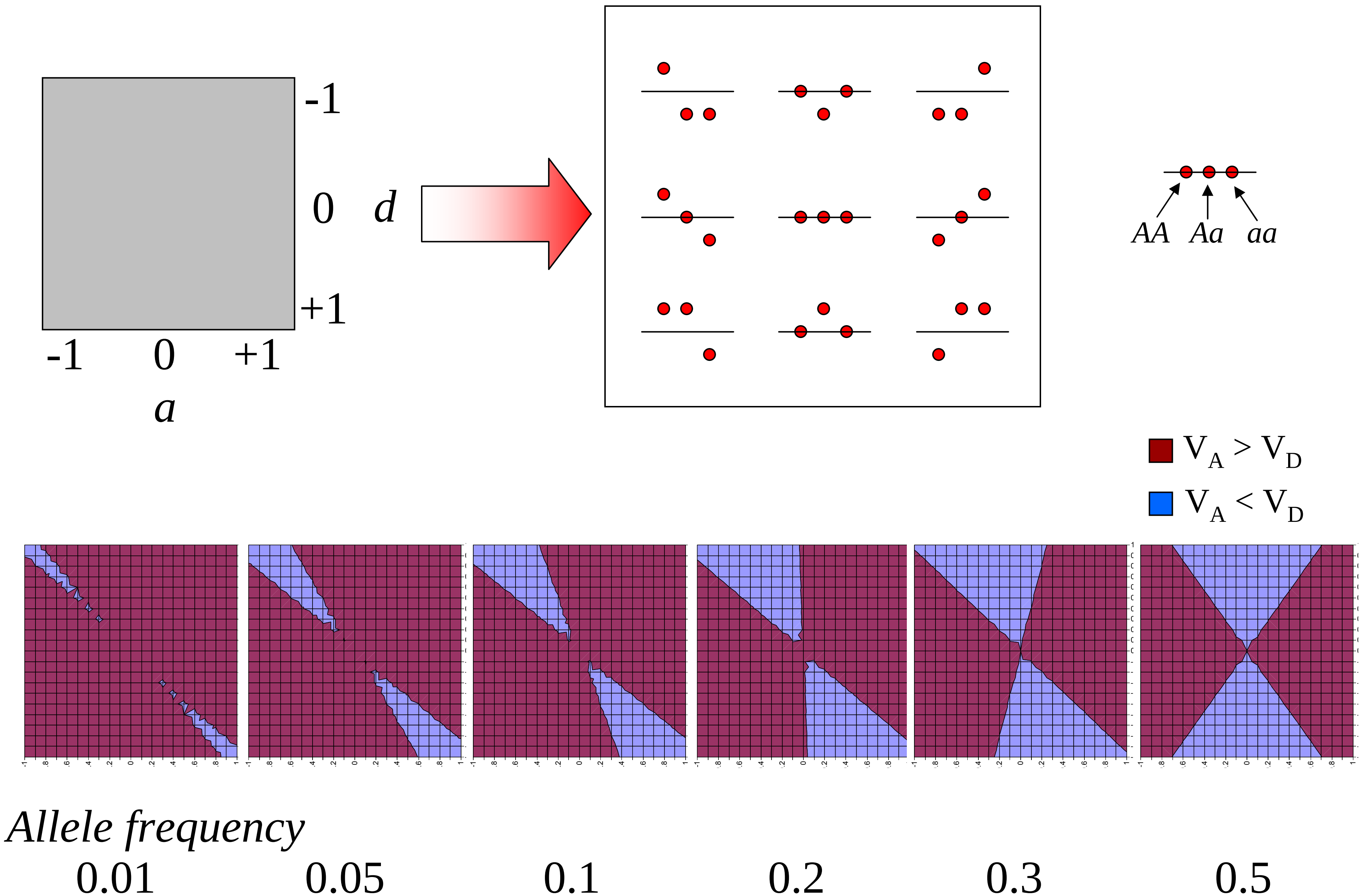


Dominance genetic variance V_D



Allele frequency

0.01 0.05 0.1 0.2 0.3 0.5


-1
0
+1
-1
0
+1
a
d
AA
Aa
aa
V_A > V_D
V_A < V_D
Allele frequency
0.01
0.05
0.1
0.2
0.3
0.5

Biometrical model for single biallelic QTL

1. Contribution of the QTL to the Mean (*X*)

2. Contribution of the QTL to the Variance (*X*)

2A. Average allelic effect (α)

2B. Additive genetic variance

3. Contribution of the QTL to the Covariance (*X*,*Y*)

Biometrical model for single biallelic QTL

3. Contribution of the QTL to the Cov *(X,Y)*

$$Cov(X,Y) = \sum_i (x_i - \mu_X)(y_i - \mu_Y) f(x_i, y_i)$$

	AA (*a*-*m*)	*Aa* (*d*-*m*)	*aa* (-*a*-*m*)
AA (*a*-*m*)	$(a-m)^2$		
Aa (*d*-*m*)	$(a-m)(d-m)$	$(d-m)^2$	
aa (-*a*-*m*)	$(a-m)(-a-m)$	$(d-m)(-a-m)$	$(-a-m)^2$

Biometrical model for single biallelic QTL

3A. Contribution of the QTL to the Cov *(X,Y)* – MZ twins

$$Cov(X,Y)=\sum_i (x_i-\mu_X)(y_i-\mu_Y)f(x_i,y_i)$$

	AA *(a-m)*	***Aa*** *(d-m)*	***aa*** *(-a-m)*
AA *(a-m)*	$p^2(a-m)^2$		
Aa *(d-m)*	$0\ (a-m)(d-m)$	$2pq(d-m)^2$	
aa *(-a-m)*	$0\ (a-m)(-a-m)$	$0\ (d-m)(-a-m)$	$q^2(-a-m)^2$

$$Covar(X_i,X_j) = (a-m)^2p^2 + (d-m)^2 2pq + (-a-m)^2 q^2$$

$$= 2pq[a+(q-p)d]^2 + (2pqd)^2 = V_{A_{QTL}} + V_{D_{QTL}}$$

Biometrical model for single biallelic QTL

3B. Contribution of the QTL to the Cov (X,Y) – Parent-Offspring

	AA $(a-m)$	***Aa*** $(d-m)$	***aa*** $(-a-m)$
AA $(a-m)$	$p^3(a-m)^2$		
Aa $(d-m)$	$p^2q\,(a-m)\,(d-m)$	$pq\,(d-m)^2$	
aa $(-a-m)$	$0\,(a-m)(-a-m)$	$pq^2\,(d-m)(-a-m)$	$q^3(-a-m)^2$

- *e.g.* given an *AA* father, an *AA* offspring can come from either *AA* x *AA* or *AA* x *Aa* parental mating types

AA x *AA* will occur $p^2 \times p^2 = p^4$

and have *AA* offspring Prob()=1

AA x *Aa* will occur $p^2 \times 2pq = 2p^3q$

and have *AA* offspring Prob()=0.5

and have *Aa* offspring Prob()=0.5

Therefore, P(*AA* father & *AA* offspring) $= p^4 + p^3q$

$= p^3(p+q)$

$= p^3$

Biometrical model for single biallelic QTL

3B. Contribution of the QTL to the Cov (X,Y) – Parent-Offspring

	AA $(a-m)$	**Aa** $(d-m)$	**aa** $(-a-m)$
AA $(a-m)$	$p^3(a-m)^2$		
Aa $(d-m)$	$p^2q\,(a-m)\,(d-m)$	$pq\,(d-m)^2$	
aa $(-a-m)$	$0\,(a-m)(-a-m)$	$pq^2\,(d-m)(-a-m)$	$q^3(-a-m)^2$

$$Cov\,(X_i,X_j) = (a-m)^2p^3 + \ldots + (-a-m)^2q^3$$

$$= pq[a+(q-p)d]^2 = \tfrac{1}{2}V_{A_{QTL}}$$

Biometrical model for single biallelic QTL

3C. Contribution of the QTL to the Cov (X,Y) – Unrelated individuals

	AA $(a-m)$	***Aa*** $(d-m)$	***aa*** $(-a-m)$
AA $(a-m)$	$p^4(a-m)^2$		
Aa $(d-m)$	$2p^3q\,(a-m)\,(d-m)$	$4p^2q^2\,(d-m)^2$	
aa $(-a-m)$	$p^2q^2(a-m)\,(-a-m)$	$2pq^3\,(d-m)(-a-m)$	$q^4\,(-a-m)^2$

$$Cov\,(X_i,X_j) = (a-m)^2p^4 + \ldots + (-a-m)^2q^4$$

$$= 0$$

Biometrical model for single biallelic QTL

3D. Contribution of the QTL to the Cov *(X,Y)* – DZ twins and full sibs

	¼ genome	¼ genome	¼ genome	¼ genome
# identical alleles inherited from parents	**2**	**1** (father)	**1** (mother)	**0**

¼ (2 alleles) + ½ (1 allele) + *¼ (0 alleles)*

MZ twins — *P-O* — *Unrelateds*

$$Cov(X_i,X_j) = ¼\ Cov(MZ) + ½\ Cov(P\text{-}O) + ¼\ Cov(Unrel)$$

$$= ¼(V_{A_{QTL}} + V_{D_{QTL}}) + ½\ (½\ V_{A_{QTL}}) + ¼\ (0)$$

$$= ½\ V_{A_{QTL}} + ¼ V_{D_{QTL}}$$

Summary

- Biometrical model predicts contribution of a QTL to the mean, variance and covariances of a trait

1 QTL

$$Var(X) = V_{A_{QTL}} + V_{D_{QTL}}$$

$$Cov(MZ) = V_{A_{QTL}} + V_{D_{QTL}}$$

$$Cov(DZ) = \tfrac{1}{2}V_{A_{QTL}} + \tfrac{1}{4}V_{D_{QTL}}$$

Multiple QTL

$$Var(X) = \Sigma(V_{A_{QTL}}) + \Sigma(V_{D_{QTL}}) = V_A + V_D$$

$$Cov(MZ) = \Sigma(V_{A_{QTL}}) + \Sigma(V_{D_{QTL}}) = V_A + V_D$$

$$Cov(DZ) = \Sigma(\tfrac{1}{2}V_{A_{QTL}}) + \Sigma(\tfrac{1}{4}V_{D_{QTL}}) = \tfrac{1}{2}V_A + \tfrac{1}{4}V_D$$

- Biometrical model underlies the variance components estimation performed in Mx

$$Var\,(X) = V_A + V_D + V_E$$

$$Cov\,(MZ) = V_A + V_D$$

$$Cov\,(DZ) = \tfrac{1}{2}V_A + \tfrac{1}{4}V_D$$