Introduction to Biometrical Genetics {in the classical twin design}

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Slide acknowledgement: Manuel Ferreira, Pak Sham, Shaun Purcell, Sarah Medland, and Sophie van der Sluis

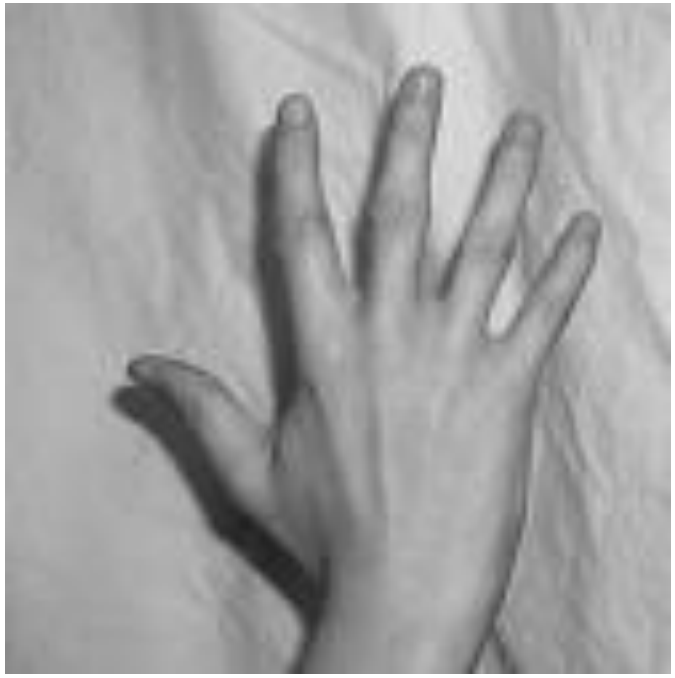
Slides: 3-7 .... what's it all about? individual differences
Slides: 8-15 ..... how to quantify individual differences
Slides: 16-18 .... genetic terminology, QTL

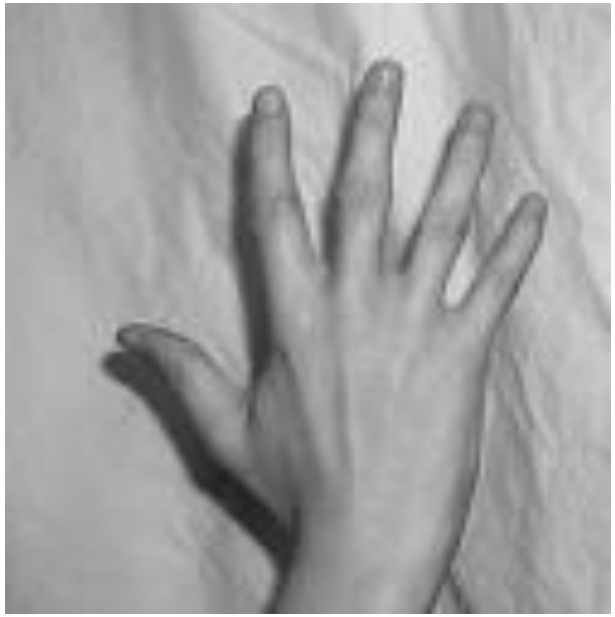
Slides: 19-27 ... mean & variance as function of QTL
Slides: 28- 30... interpretation of variance components in regression
Slides: 31- 43 ... covariance as function of QTL and IBD

Slides: 44-48 ... intro to practical (there is no practical!)

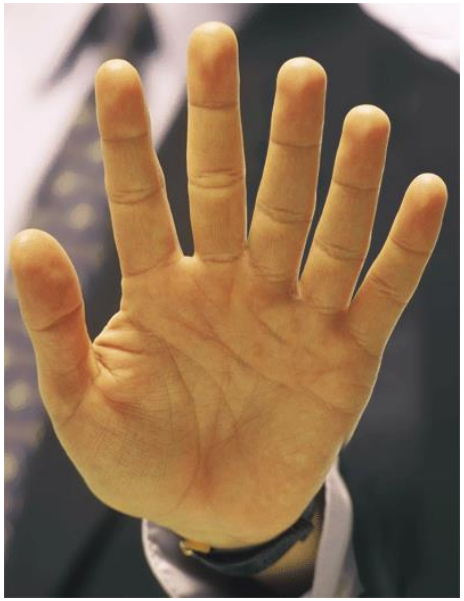
“Having 5 fingers genetically determined”

“*DNA includes a blueprint to build a hand*”





normal

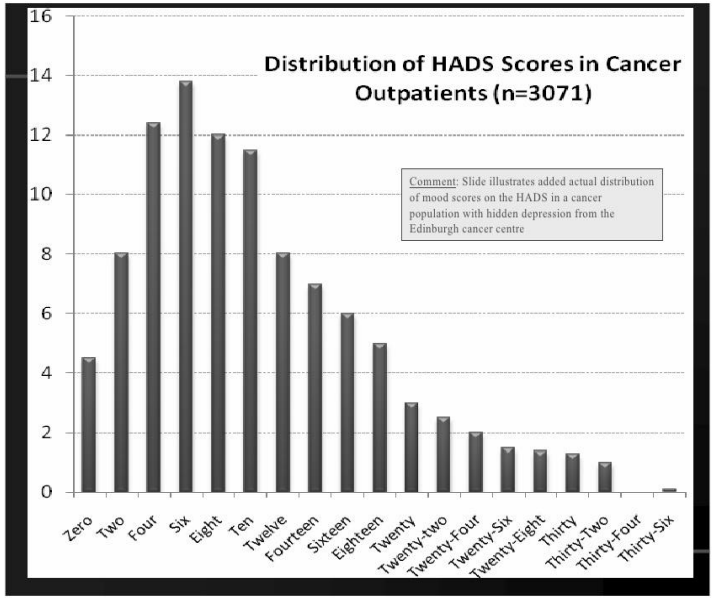


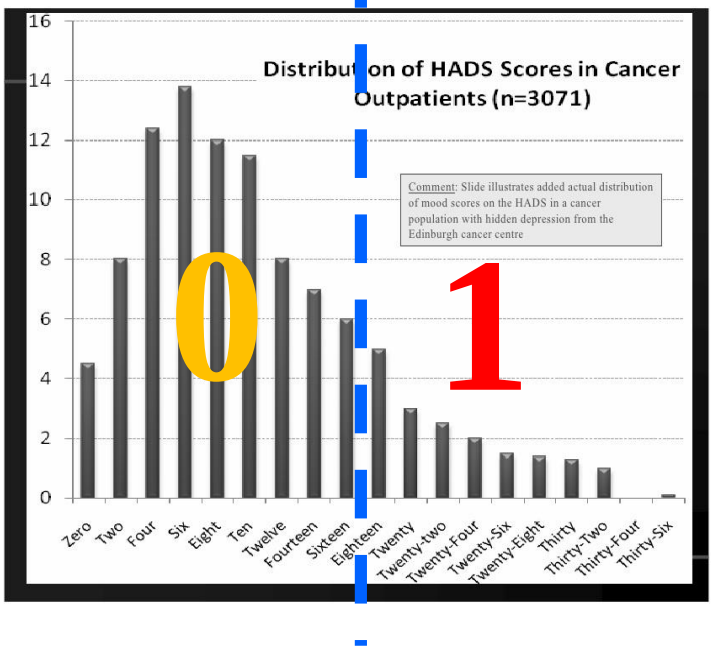
polydactyly

angry dog

Behavior genetic research is concerned with relating individual differences in phenotypes to individual differences at the genetic level and individual differences in environmental influences

Phenotype**: continuously varying, genetically complex,**
e.g. (ideally) normally distributed
e.g., binary (dichotomous, 0-1 coded) phenotype
(based on continuous phenotype; liability threshold model).





The phenotype is a **quantitative** trait, a **metric** trait, a **complex** trait

Genetically complex:

Individual differences in the phenotype are subject to the effects of many genes of small effects, a.k.a. **polygenes, minor genes**. How many? Hundreds (Educational Attainment, Height) … Thousands….?

Phenotypic individual differences are attributable to genetic individual differences in a large number of polygenes, a.k.a. **QTLs (quantitative trait loci).**

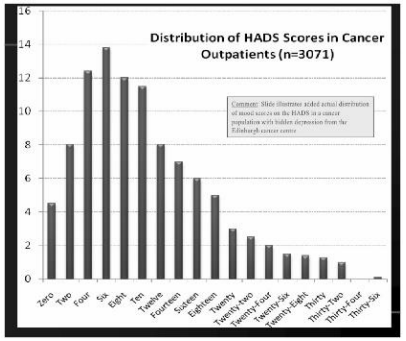
Polygenicity implies phenotypic continuous distributions (Nick Martin's intro talk)

People differ phenotypically

Q. How to quantify individual differences?

The variance: s^2, σ^2, σ^2_X , var(X), V_X

mean (X) $$\mu = \frac{1}{N}\sum_{i=1}^{N} x_i$$



variance (X) $$\sigma^2 = \frac{1}{N}\sum_{i=1}^{N} (x_i - \mu)^2$$

x_i is the phenotypic value of person i (i=1,...,N)

Formula to find the mean for X

$$\mu_x = \frac{\sum_{i=1}^{n} x_i}{n}$$

$$\mu = \frac{1}{N}\sum_{i=1}^{N} x_i$$

Formula to find the mean for Y

$$\mu_y = \frac{\sum_{i=1}^{n} y_i}{n}$$

Formula to find covariance of X & Y

$$cov(X,Y) = \frac{\sum_{i=1}^{n}(x_i - \mu_x)(y_i - \mu_y)}{(n-1)}$$

We need the covariance: express the phenotypic relatedness among family members

Means, Variances and Covariances

$$\mu = E(X) = \sum_i x_i f(x_i)$$

$$\mu = \frac{1}{N}\sum_{i=1}^{N} x_i$$

$$Var(X) = E(X-\mu)^2$$

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

$$\sigma^2 = \frac{1}{N}\sum_{i=1}^{N} (x_i - \mu)^2$$

$$Cov(X,Y) = E(X-\mu_X)(Y-\mu_Y)$$

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

1,1,2,2,3,4,5,5,6,6

mean = (1+1+2+2+3+4+5+5+6+6)/10
= 36/12 = 3.5

$$\mu = \frac{\sum_{i=1}^{N} x_i}{N}$$

f(1) = 2/10 = .2 .2*1 +
f(2) = 2/10 = .2 .2*2 +
f(3) = 1/10 = .1 .1*3 +
f(4) = 1/10 = .1 .1*4 +
f(5) = 2/10 = .2 .2*5 +
f(6) = 2/10 = .2 .2*6

3.5

$$\mu = E(X) = \sum_i x_i f(x_i)$$

```
# in R
x=c(1,1,2,2,3,4,5,5,6,6)
mean(x)
```

1,1,2,2,2,3,4,5,5,5,6,6

mean = 3.5

$$\mu = E(X) = \sum_i x_i f(x_i)$$

f(1) = 2/10 = .2 .2*(1-3.5)^2 +
f(2) = 2/10 = .2 .2*(2-3.5)^2 +
f(3) = 1/10 = .1 .1*(3-3.5)^2 +
f(4) = 1/10 = .1 .1*(4-3.5)^2 +
f(5) = 2/10 = .2 .2*(5-3.5)^2 +
f(6) = 2/10 = .2 .2*(6-3.5)^2

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

variance = 3.45
stdev = √variance
stdev = √3.45 = 1.857

```
# in R
x=c(1,1,2,2,3,4,5,5,6,6)
var(x)
```

covariance

$$Cov(X,Y) = E\left(X - \mu_X\right)\left(Y - \mu_Y\right)$$

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

correlation

Cor(X,Y) = Cov(X,Y) / √ [Var(X)*var(Y)] =
= Cov(X,Y) / [stdev(X)*stdev(Y)]

Cor(X,Y) is – stand-alone - interpretable

MZ covariance is 291.... uninterpretable
MZ correlation is .80 .... interpretable

To what extent, and how, are
individual differences in genetic makeup, and
individual differences in environmental factors, related to
phenotypic (observed) ***individual differences*** *?*

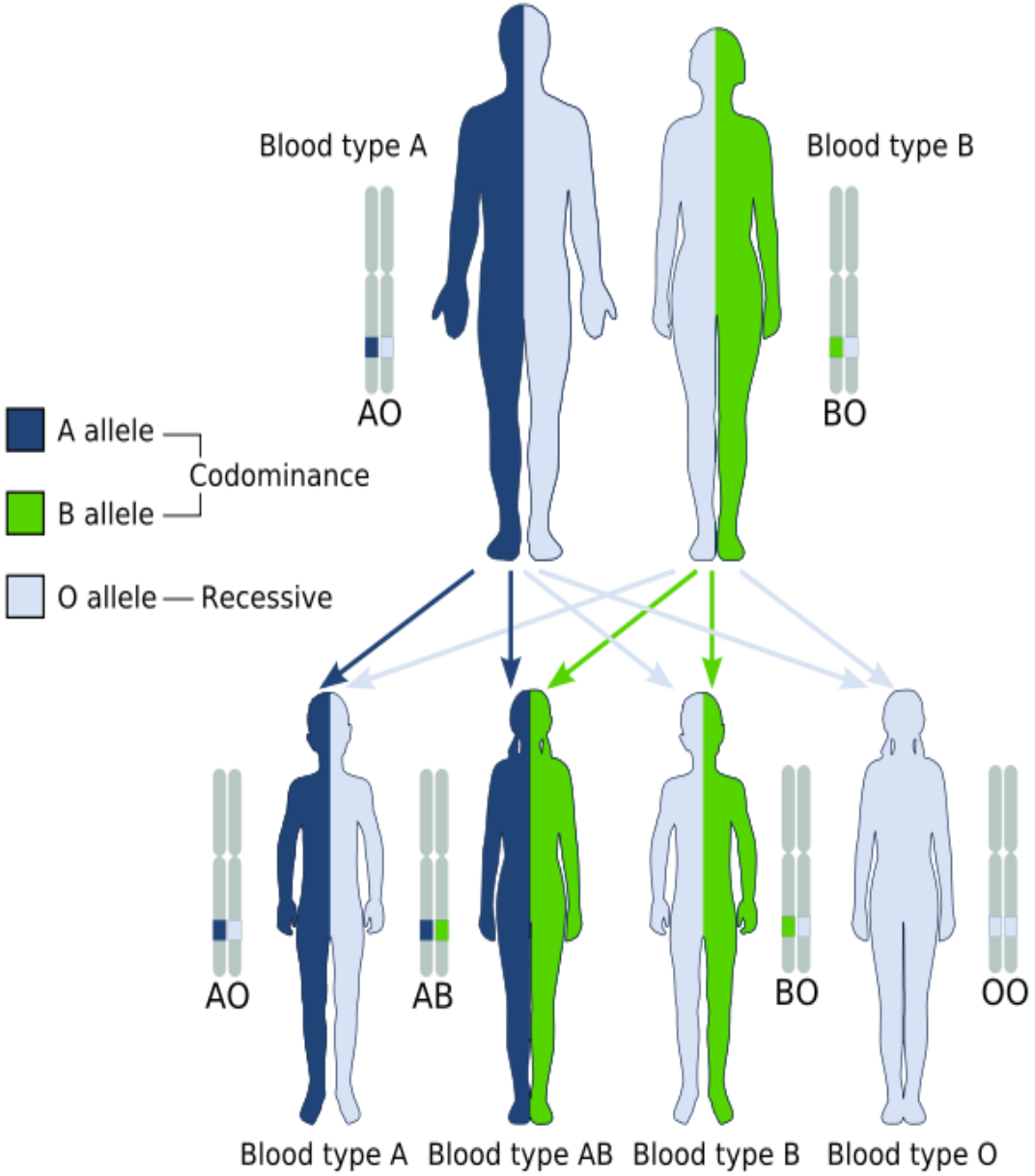
To what extent, and how, do
individual differences in genetic makeup, and
individual differences in environmental factors, explain
phenotypic (observed) ***variance****?*

$$\sigma_x^2 = \frac{\sum_{i=1}^{N} (x_i - \mu)^2}{N - 1}.$$

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

terminology

- **QTL Quantative trait locus**: a sequence of DNA base pairs (may be a SNP: single base pair).
- **Locus**: the site of the specific QTL on a chromosome (22 pairs + XY). Humans are dipoid (22 pairs autosomal chromosomes + sex chromosomes XY or XX).
- **Allele**: an alternative form of a gene at a locus
- **Genotype**: the combination of alleles at a particular locus
- **Phenotype**: an observed characteristic, which displays individual differences (in part due to genetic differences)



chromosome 9
location 9q34.2

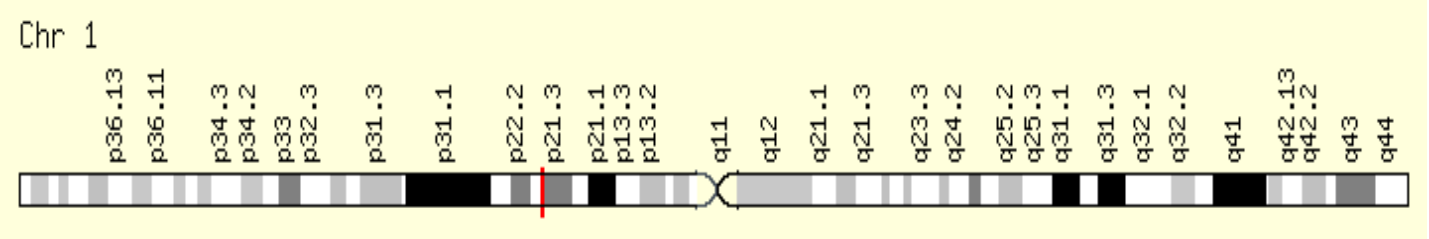
Mendel's law of segregration

Example of a QTL: FNBP1L gene

The FNBP1L gene has been associated with intelligence in two studies:

* "Genome-wide association studies establish that human intelligence is highly heritable and polygenic". 2011, *Mol. Psychiatry* **16** (10): 996–1005.doi:10.1038/mp.2011.85)
* "Childhood intelligence is heritable, highly polygenic and associated with FNBP1L". *Mol. Psychiatry* **19**(2): 2538. doi:10.1038/mp.2012.184.
Authors include Sarah Medland & Nick Martin.

This gene is on chromosome 1 (1p22,1), and it comprises 106531 bases (106.5Kb). Within this gene the SNP rs236330 specifically is associated with intelligence.



Population level

1. Allele frequencies (QTL: diallelic autosomal; e.g., SNP rs236330)

- A single locus, with two alleles
  - Biallelic a.k.a. diallelic
  - in GWAS: Single nucleotide polymorphism, SNP

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

} frequencies in the population

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

……genotype frequencies?

Biometrical model for single biallelic QTL

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

Genotype frequencies (Random mating)

Father's gametes (sperm) \ Mother's gametes (egg)	***A*** (***p***)	***a*** (***q***)
A (***p***)	***AA*** (p^2)	***Aa*** (pq)
a (***q***)	***aA*** (qp)	***aa*** (q^2)

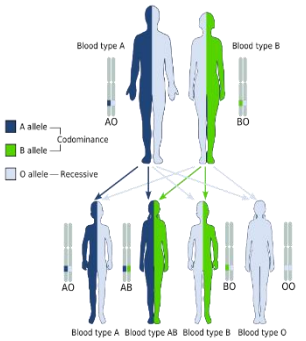
Hardy-Weinberg Equilibrium frequencies

P (***AA***) = p^2

P (***Aa***) = $2pq$

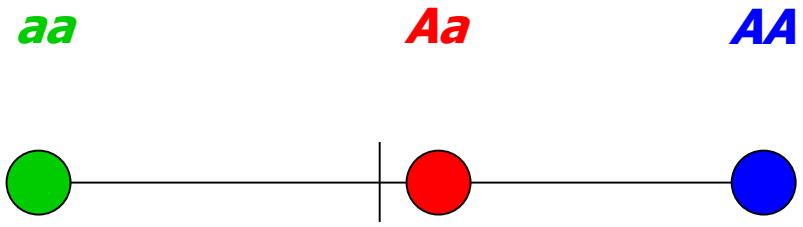
P (***aa***) = q^2

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



Phenotype level: contribution to continuous variation

Biometric Model



← Genotypic effect

$\mu - a$ $\mu + d$ $\mu + a$ ← means within each genotype (aa, Aa, AA) .....conditional on genotype

take all ***aa*** individuals and calculate their mean phenotypic value: $\mu - a$ (the phenotypic mean **conditional** on genotype ***aa***)

Biometrical model for single biallelic QTL

1. Contribution of the QTL to the Mean

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

$(\mu+a)(p^2) + (\mu+d)(2pq) + (\mu-a)(q^2) =$
$\mu + a(p^2) + d(2pq) - a(q^2) =$
$\mu + a(p-q) + 2pqd$. *(pop pheno mean)*

$$\mu = E(X) = \sum_i x_i f(x_i)$$

contribution of the QTL to the population phenotypic mean

$m = a(p-q) + 2pqd$

Biometrical model for single biallelic QTL

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

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

$$s^2_{QTL} = (a-m)^2p^2 + (d-m)^2 2pq + (-a-m)^2q^2$$

$$m = a(p-q) + 2pqd$$

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

Biometrical model for single biallelic QTL

$$s^2_{QTL} = (a-m)^2p^2 + (d-m)^2 2pq + (-a-m)^2q^2$$

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

$$= s^2_{QTL(A)} + s^2_{QTL(D)}$$

Additive or linear effects give rise to variance component

$s^2_{QTL(A)} = 2*pq[a+(q-p)d]^2$

Dominance or *within local allelic interaction* effects give rise to variance component

$s^2_{QTL(D)} = (2pqd)^2$

Biometrical model for single biallelic QTL

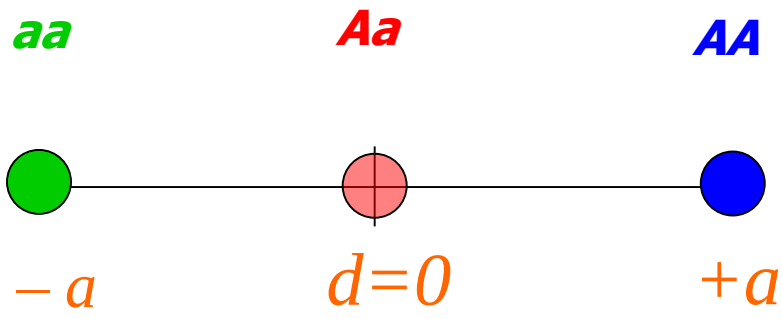
$$s^2_{QTL} = (a-m)^2p^2 + (d-m)^2 2pq + (-a-m)^2q^2$$

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

$$= s^2_{QTL(A)} + s^2_{QTL(D)}$$

Additive effects: $s^2_{QTL(A)} = 2*pq[a]^2$

Dominance effects: $s^2_{QTL(D)} = 0$



Biometrical model for single biallelic QTL

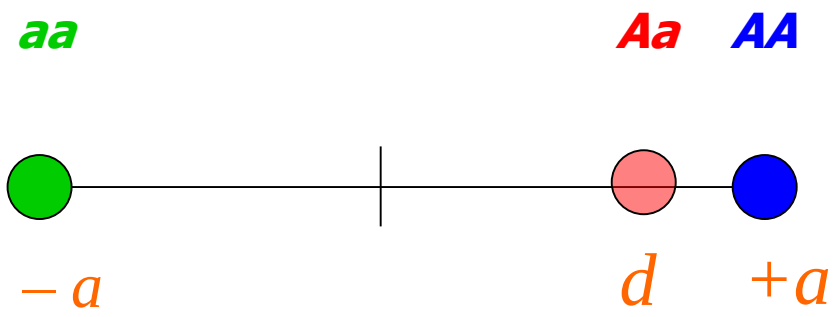
$$s^2_{QTL} = (a-m)^2p^2 + (d-m)^2 2pq + (-a-m)^2q^2$$

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

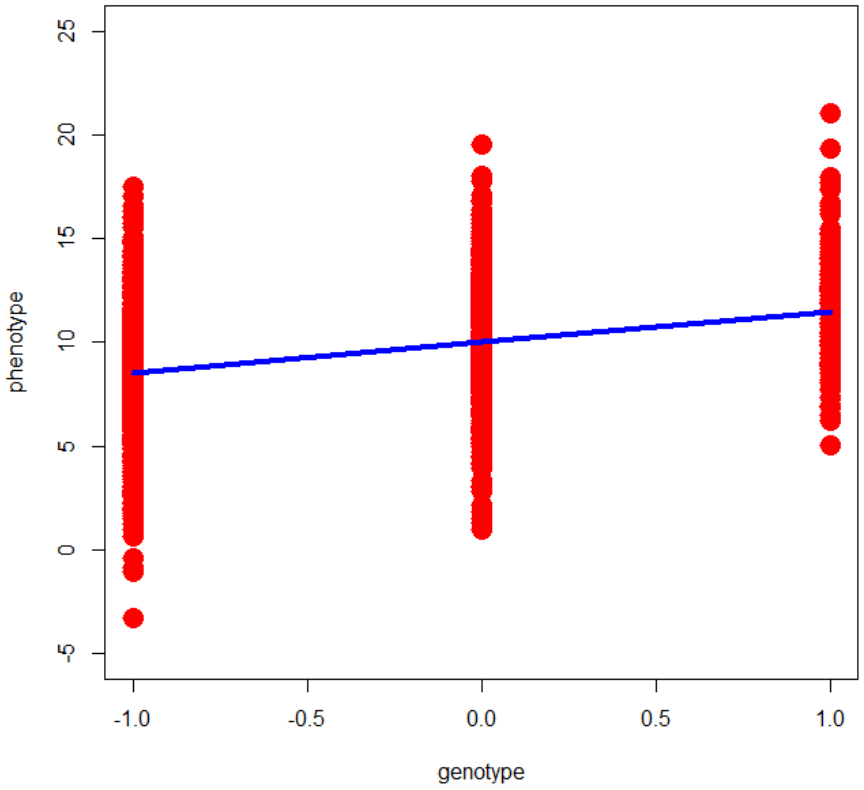
$$= s^2_{QTL(A)} + s^2_{QTL(D)}$$

Additive effects: $s^2_{QTL(A)} = 2*pq[a+(q-p)d]^2$

Dominance effects: $s^2_{QTL(D)} = (2pqd)^2$

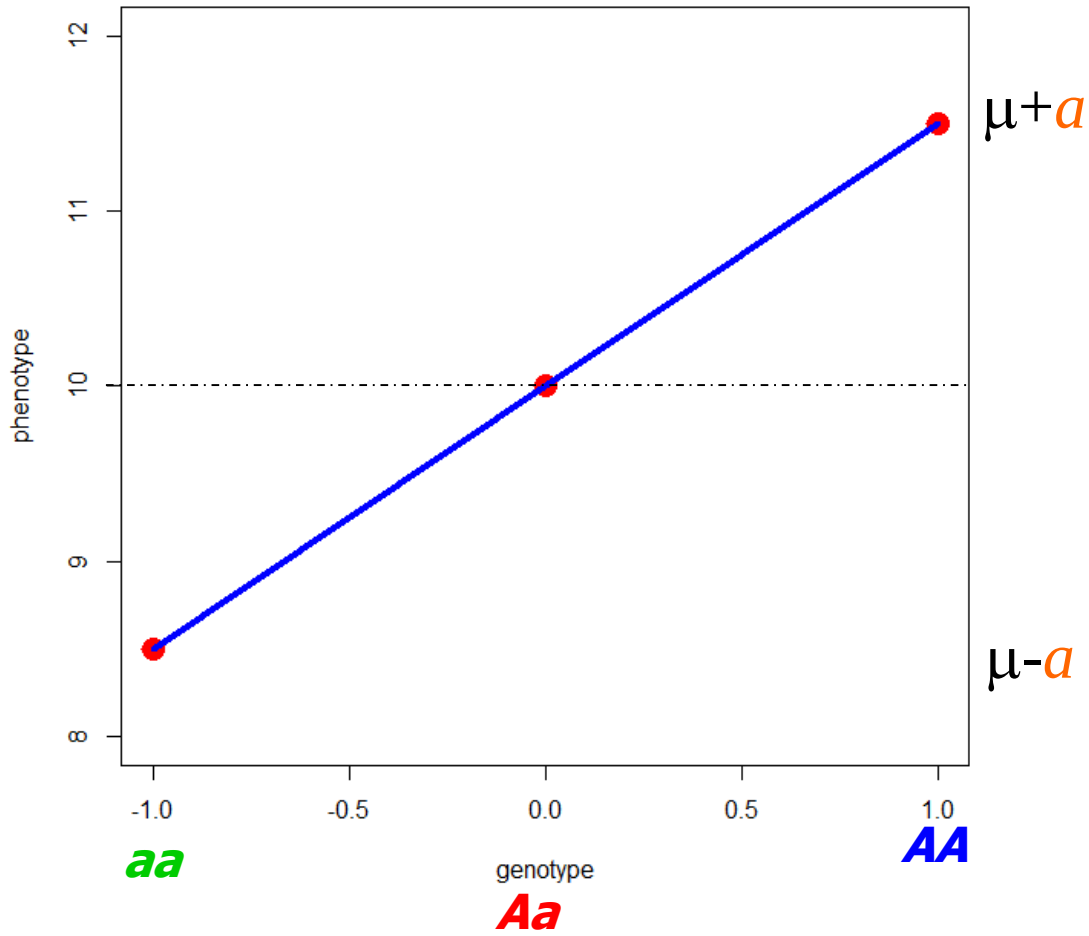


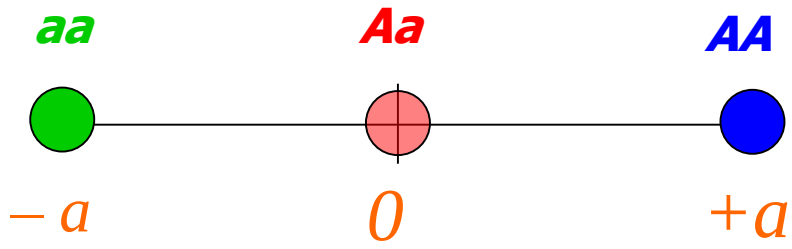
Suppose we measure the QTL and the phenotype and regress X on QTL.The scatterplot of the data
(aa coded -1; Aa coded 0; AA coded 1).



we ask:
how much of the phenotypic variance is explained by the predictor (QTL)

In the following slides we look at the regression lines only (not plotting the residuals – just to avoid clutter).

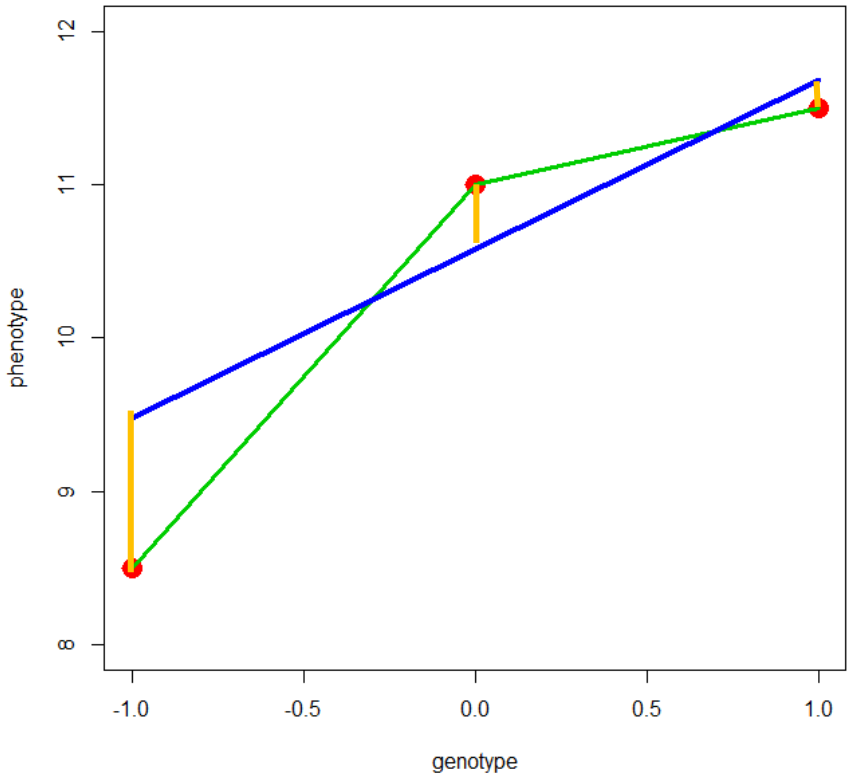




Explained variance:

$$s^2_{QTL(A)} = 2*pq[a]^2$$

$$s^2_{QTL(D)} = 0$$



$\mu+a$

$\mu+d$

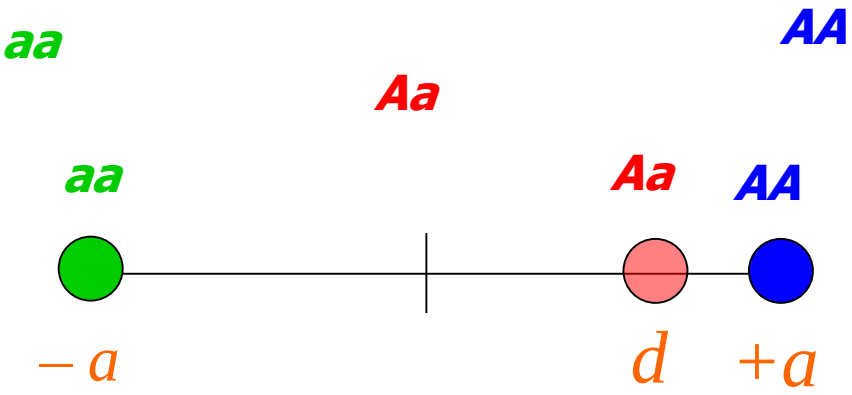
$\mu-a$

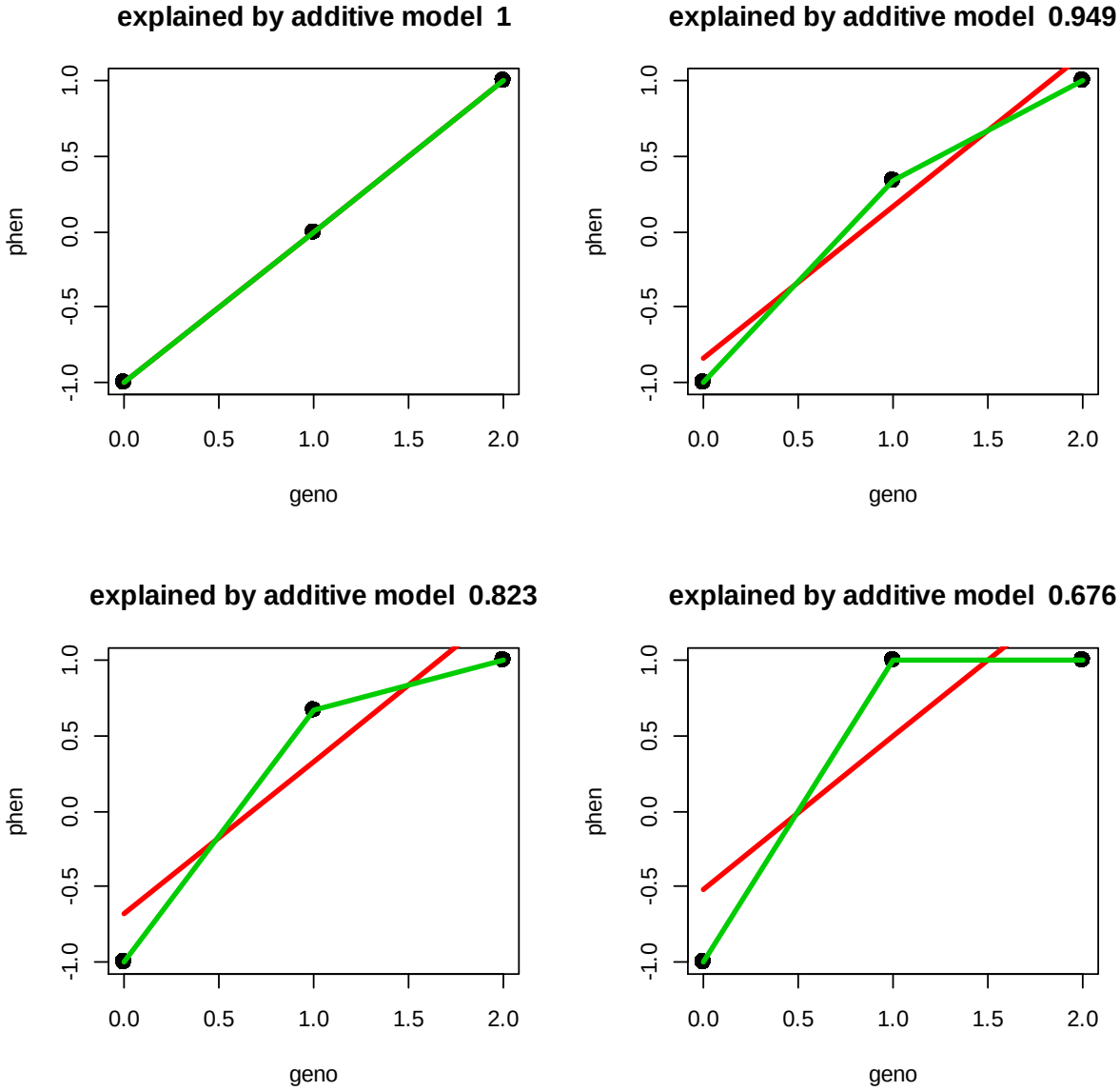
Explained variance (blue line):

$$s^2_{QTL(A)} = 2*pq[a+(q-p)d]^2$$

Not explained

$$s^2_{QTL(D)} = (2pqd)^2$$





$s^2_{QTL(A)}$ *always greater than zero*

$s^2_{QTL(D)}$ *can be zero (additive model d=0)*

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

$m = a(p-q) + 2pqd$

What about the f(xi, y_i)?

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

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

$$= 2pq[a+(q-p)d]^2 + (2pqd)^2 = s^2_{QTL(A)} + s^2_{QTL(D)}$$

Biometrical model for single biallelic QTL

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

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

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

given an *AA* parent, 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(AA)=1

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

and have *AA* offspring Prob(AA)=0.5

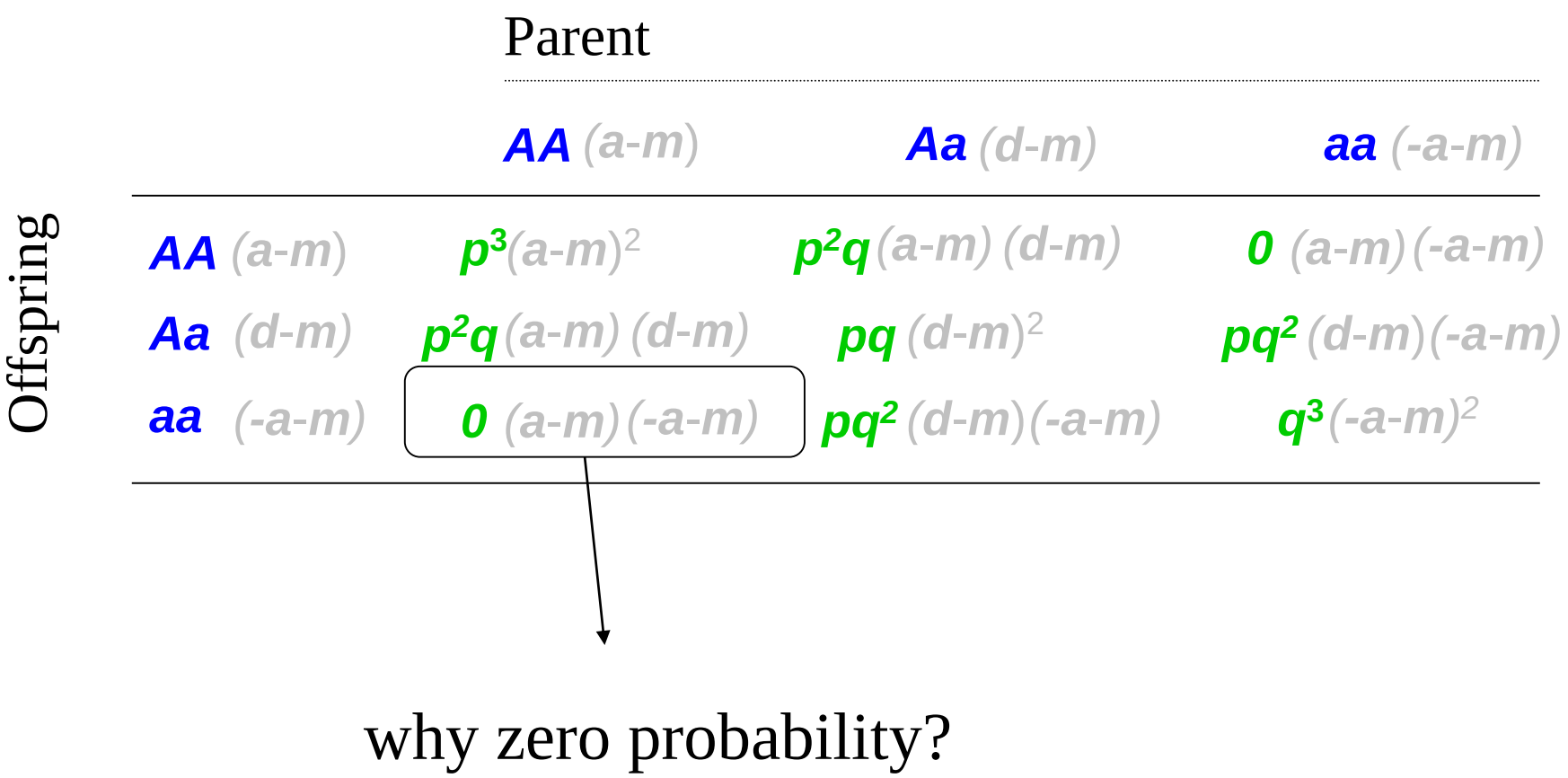
and have *Aa* offspring Prob(Aa)=0.5

Therefore, P(*AA* parent & *AA* offspring) $= p^4 + .5*2*p^3q$

$= p^3(p+q)$

$= p^3$

So can be complicated, but can also be simple ….



why zero probability?

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

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

$$= pq[a+(q-p)d]^2 = \tfrac{1}{2}\,s^2_{QTL(A)}$$

Biometrical model for single biallelic QTL

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

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

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

$$= 0$$

Follow same method for full sibs and DZ twins
Derive genotype frequences ....

s1	s2	eff	eff		frequency (p(A)=p, p(a)=1-p)
AA	AA	a	a	r1	p**4+p**3*q+p**2*q**2/4
aa	aa	-a	-a	r2	p**2*q**2/4+p*q**3+q**4
Aa	Aa	d	d	r3	p**3*q+3*p**2*q**2+p*q**3
AA	Aa	a	d	r4	p**3*q+p**2*q**2/2
Aa	AA	d	a	r4	p**3*q+p**2*q**2/2
Aa	aa	d	-a	r5	p**2*q**2/2+p*q**3
aa	Aa	-a	d	r5	p**2*q**2/2+p*q**3
AA	aa	a	-a	r6	p**2*q**2/4
aa	AA	-a	a	r6	p**2*q**2/4

Biometrical model for single biallelic QTL

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

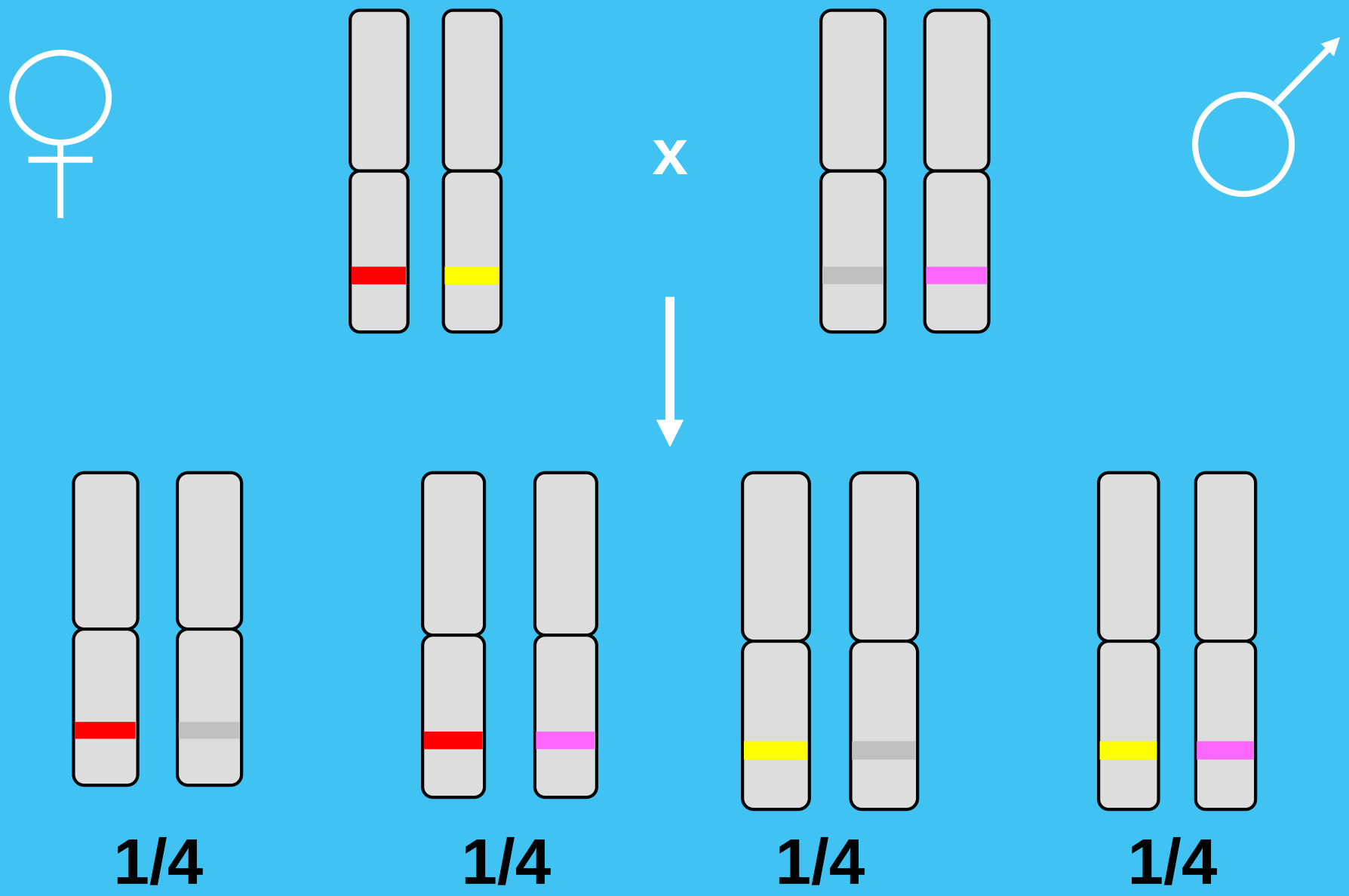
	AA *(a-m)*	***Aa*** *(d-m)*	***aa*** *(-a-m)*
AA *(a-m)*	***r1*** $(a-m)^2$	***r4*** $(a-m)(d-m)$	***r6*** $(a-m)(-a-m)$
Aa *(d-m)*	***r4*** $(a-m)(d-m)$	***r2*** $(d-m)^2$	***r5*** $(d-m)(-a-m)$
aa *(-a-m)*	***r6*** $(a-m)(-a-m)$	***r5*** $(d-m)(-a-m)$	***r3*** $(-a-m)^2$

$$Cov\,(X_i,X_j) \quad = \quad (a-m)^2 r1 + \ldots + (-a-m)^2 r3$$

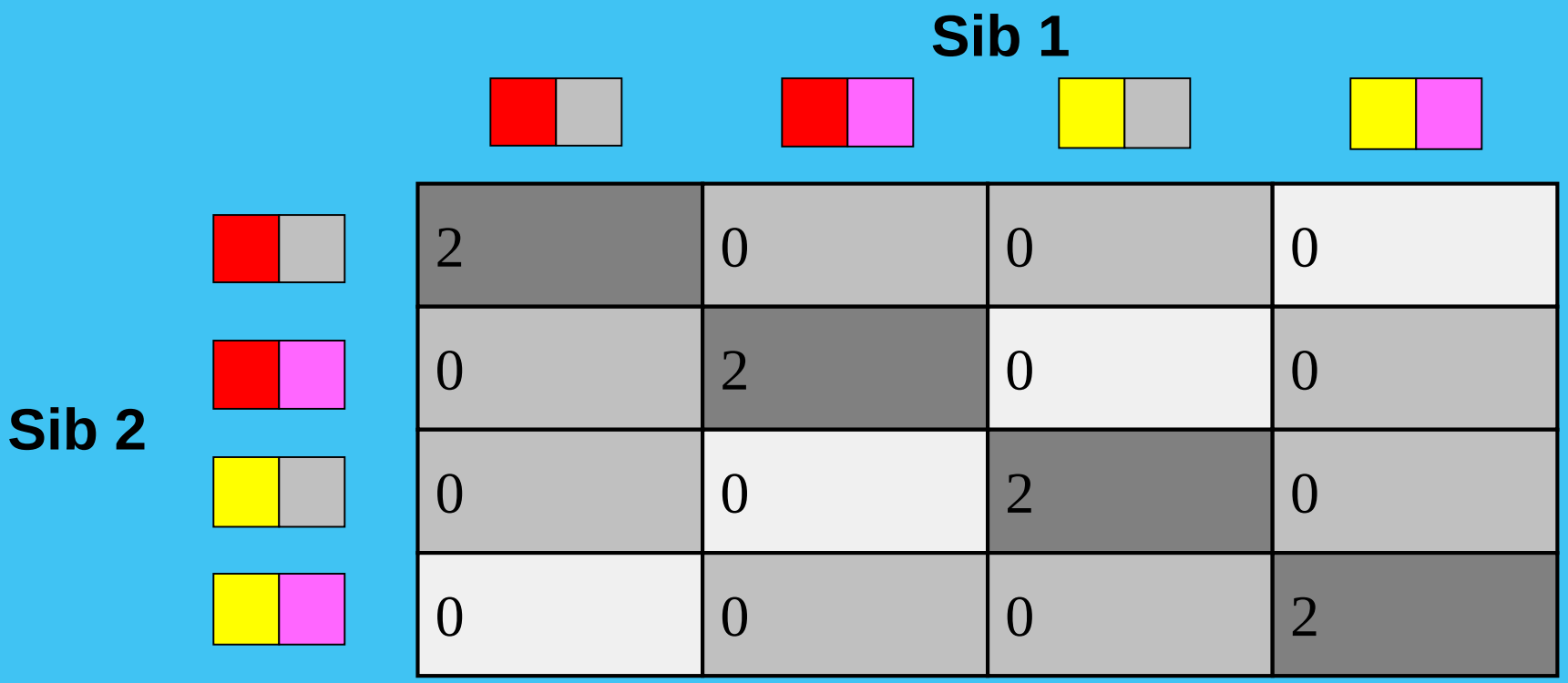
$$= \tfrac{1}{2}\, 2pq[a+(q-p)d]^2 + \tfrac{1}{4}(2pqd)^2 \quad = \quad \tfrac{1}{2}\, s^2_{QTL(A)} + \tfrac{1}{4}\, s^2_{QTL(D)}$$

John Cleese ... A famous British person

Random segregation and identity-by-descent (IBD) in sibpairs



IDENTITY BY DESCENT (IBD) MZs



100% MZ sibs share BOTH parental alleles IBD = 2

0 sibs share ONE parental allele IBD = 1

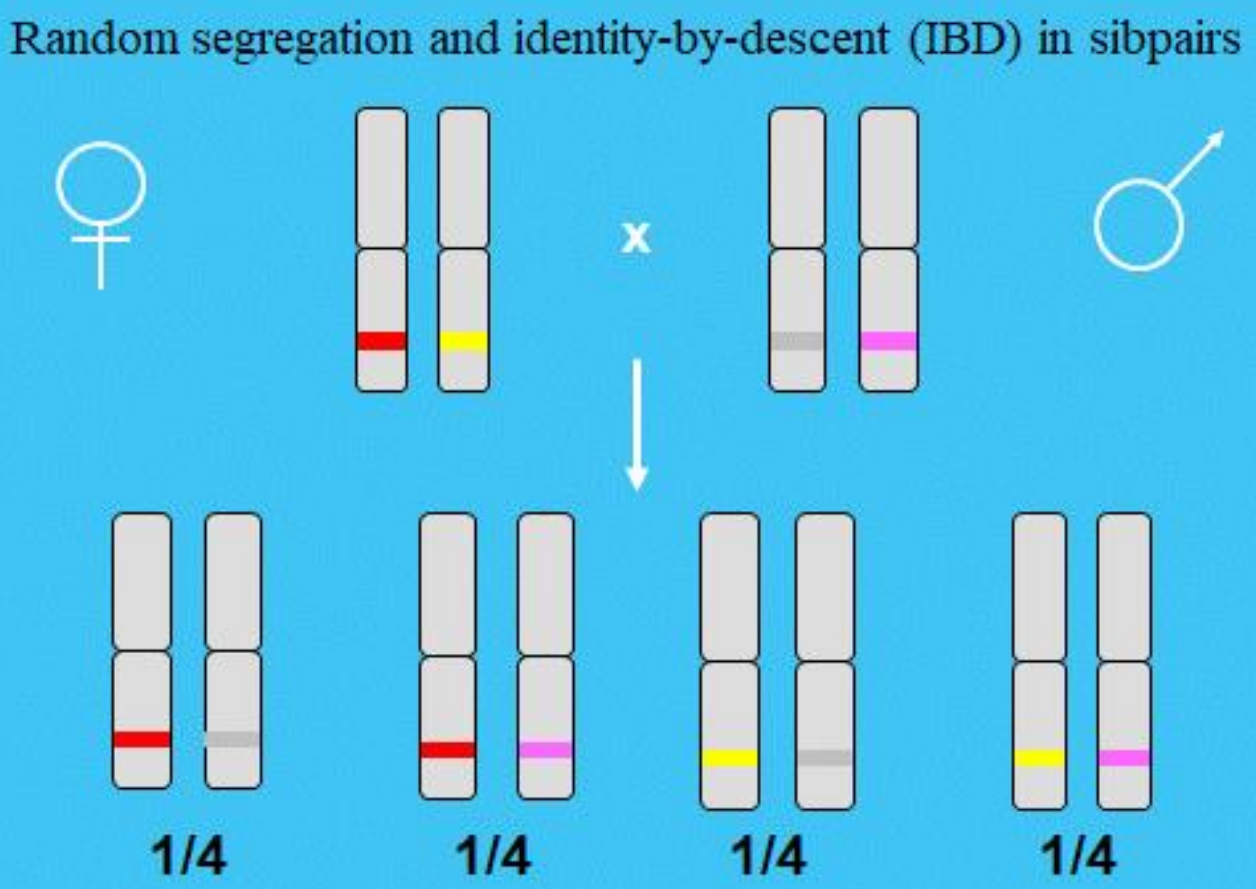
0 sibs share NO parental alleles IBD = 0

IDENTITY BY DESCENT (IBD) DZs

4/16 = 1/4 sibs share BOTH parental alleles IBD = 2

8/16 = 1/2 sibs share ONE parental allele IBD = 1

4/16 = 1/4 sibs share NO parental alleles IBD = 0



What about parent offsping?
many alleles do they share IBD?

Biometrical model for single biallelic QTL

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

# 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*

$$
\begin{aligned}
DZ\ Cov\ (X_i,X_j) &= \tfrac{1}{4}\,Cov(MZ) + \tfrac{1}{2}\,Cov(P\text{-}O) + \tfrac{1}{4}\,Cov(Unrel) \\
&= \tfrac{1}{4}(s^2_{QTL(A)} + s^2_{QTL(D)}) + \tfrac{1}{2}(\tfrac{1}{2}\,s^2_{QTL(A)}) + \tfrac{1}{4}\,(0) \\
&= \tfrac{1}{2}\,s^2_{QTL(A)} + \tfrac{1}{4}\,s^2_{QTL(D)}
\end{aligned}
$$

Biometrical model predicts contribution of a QTL to the mean, variance and covariances of a trait (discarding environmental effects)

1 QTL

$$Var\,(X) = s^2_{QTL(A)} + s^2_{QTL(D)}$$

$$Cov\,(MZ) = s^2_{QTL(A)} + s^2_{QTL(D)}$$

$$Cov\,(DZ) = \tfrac{1}{2}\, s^2_{QTL(A)} + \tfrac{1}{4}\, s^2_{QTL(D)}$$

$$Cov\,(P\text{-}O) = \tfrac{1}{2}\, s^2_{QTL(A)}$$

Multiple QTL

$$Var\,(X) = \Sigma(s^2_{QTL(A)}) + \Sigma(s^2_{QTL(D)}) = V_A + V_D$$

$$Cov\,(MZ) = \Sigma(s^2_{QTL(A)}) + \Sigma(s^2_{QTL(D)}) = V_A + V_D$$

$$Cov\,(DZ) = \Sigma(\tfrac{1}{2}\, s^2_{QTL(A)}) + \Sigma(\tfrac{1}{4}\, s^2_{QTL(D)\,L}) = \tfrac{1}{2}V_A + \tfrac{1}{4}V_D$$

$$Cov\,(P\text{-}O) = \Sigma(\tfrac{1}{2}\, s^2_{QTL(A)}) = \tfrac{1}{2}V_A$$

Contributions of V_A and V_D to covariances between relatives

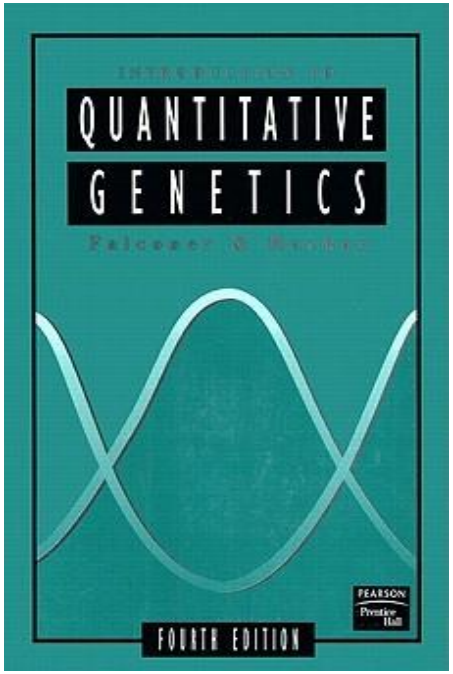
Relationship	contribution of QTL to covariance	
	V_A	V_D
Sibling (DZ twin)	½	¼
MZ twin	1	1
Half-sibling	¼	0
First cousin	1/8	0
Parent-offspring	½	0
Avuncular	¼	0
Grand-parent	1/8	0
Unrelated	0	0

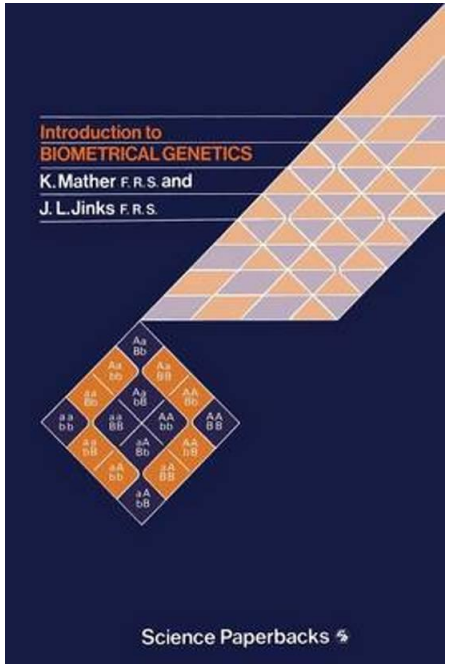
average proportion of alleles shared identically by descent

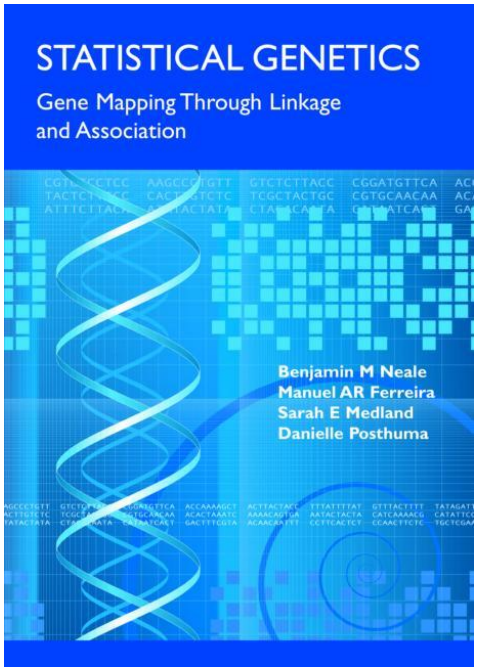
proportion of IBD=2

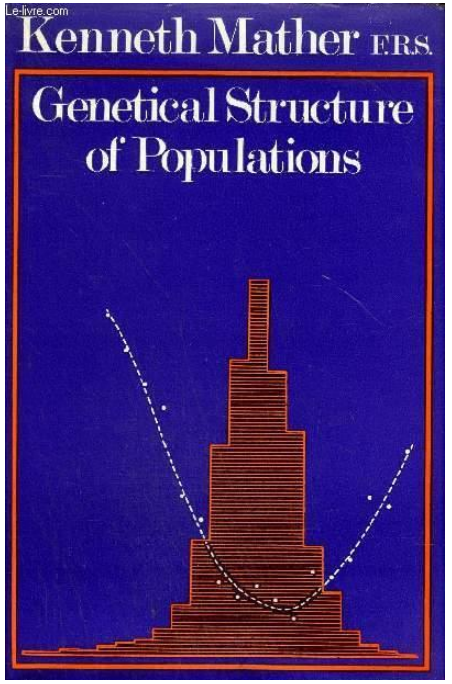
These proportions tell use how much of V_A &V_D contribute to the phenotypic covariance among family members (useful info in extended twin design / extended pedigrees

Slide acknowledgement: Manuel Ferreira, Pak Sham, Shaun Purcell, Sarah Medland, and Sophie van der Sluis



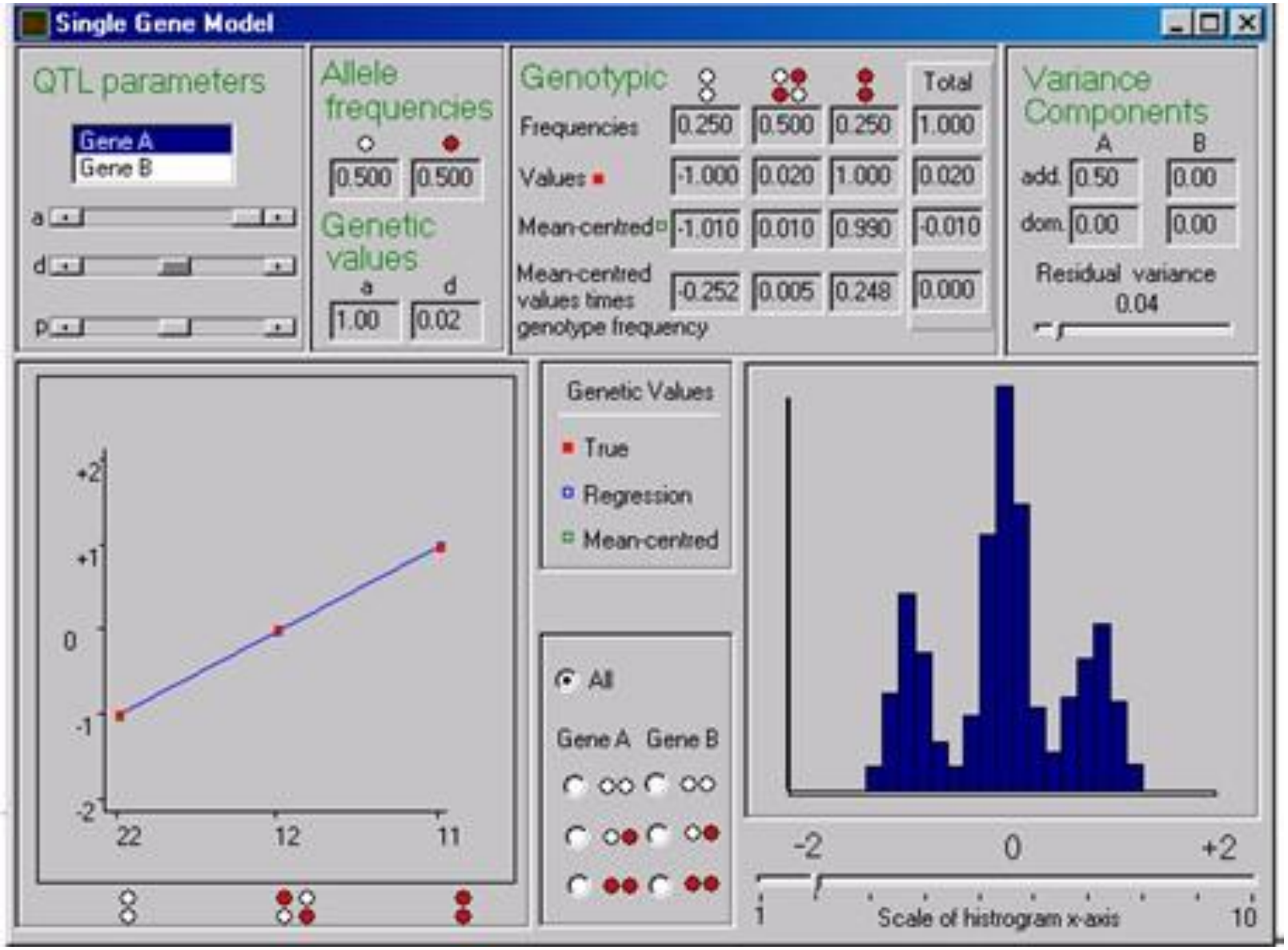






see also Manuel AR Ferreira's
http://slidegur.com/doc/4322268/biometrical-genetics

sgene.exe


Single Gene Model
QTL parameters
Gene A
Gene B
a
d
p
Allele frequencies
0.500
0.500
Genetic values
a
d
1.00
0.02
Genotypic
Total
Frequencies
0.250
0.500
0.250
1.000
Values
-1.000
0.020
1.000
0.020
Mean-centred
-1.010
0.010
0.990
-0.010
Mean-centred values times genotype frequency
-0.252
0.005
0.248
0.000
Variance Components
A
B
add.
0.50
0.00
dom.
0.00
0.00
Residual variance
0.04
+2
+1
0
-1
-2
22
12
11
Genetic Values
True
Regression
Mean-centred
All
Gene A
Gene B
-2
0
+2
1
Scale of histogram x-axis
10