ESTIMATION OF GENETIC PARAMETERS #5

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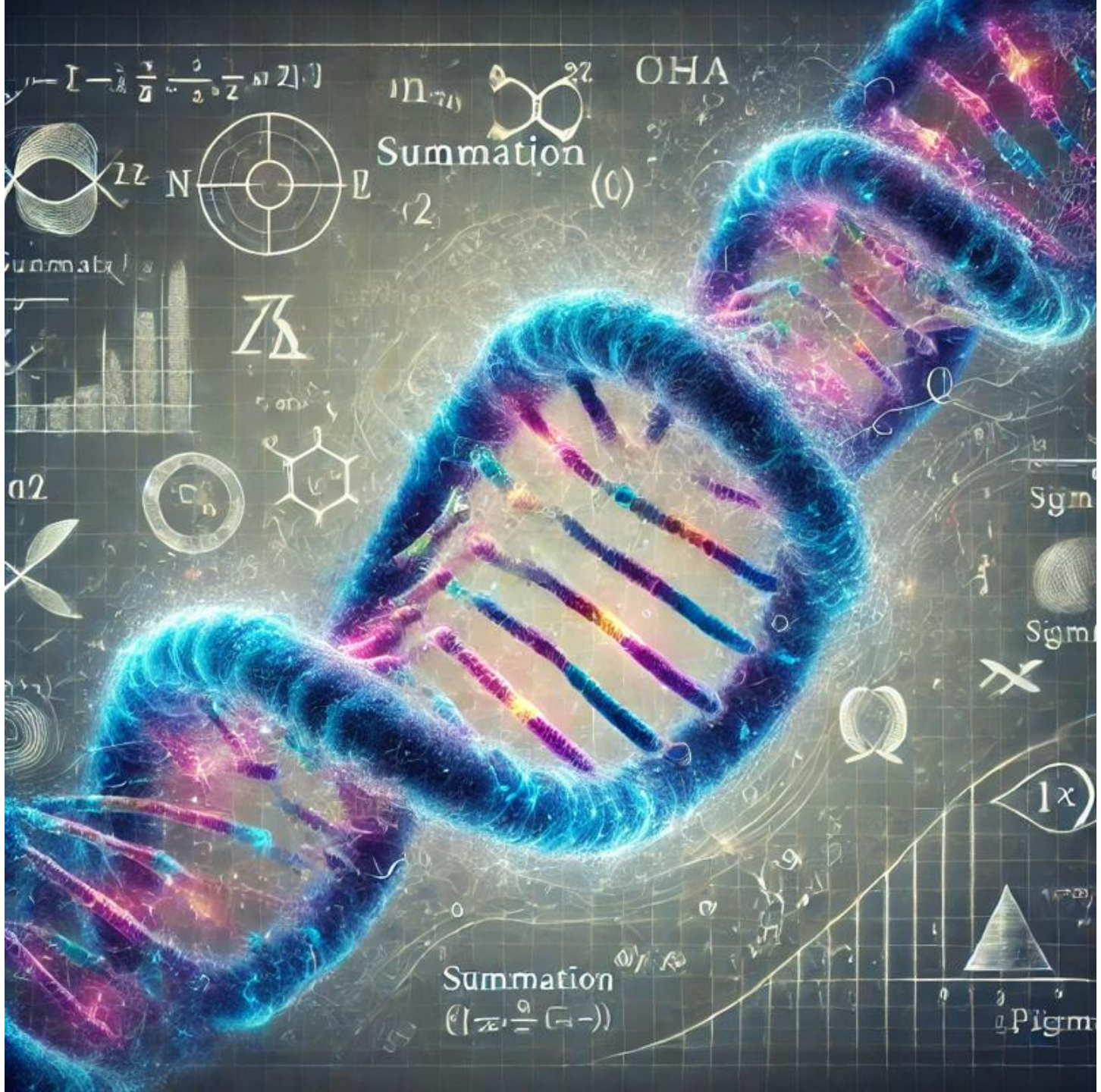
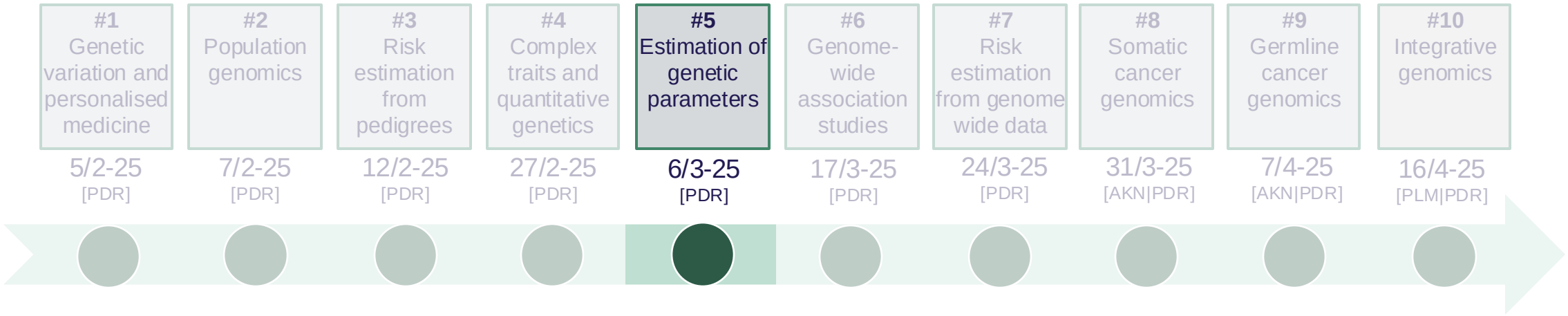


LETS GET STARTED



LINKAGE AND GENETIC TESTING

Today we will talk about

- Quantitative genetic parameters
  - Variance components
  - Heritability
  - Genetic correlation

AGENDA

08:15 – 09:00	Lecture 1 [*Quantitative genetic parameters*]
09:00 – 09:15	Break
09:15 – 10:00	Exercise
10:00 – 10:15	Break
10:15 – 11:00	Exercise continued
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11:00 – 11:55	Group work [*selfpaced*]
11:55 – 12:00	Evaluation at Moodle

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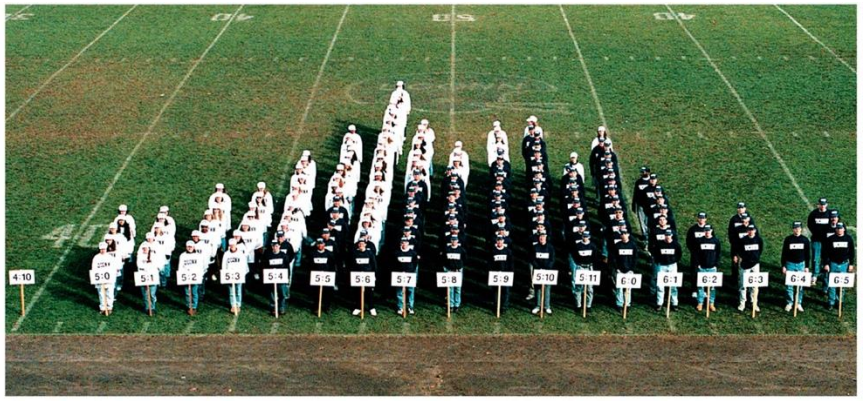
QUANTITATIVE TRAITS

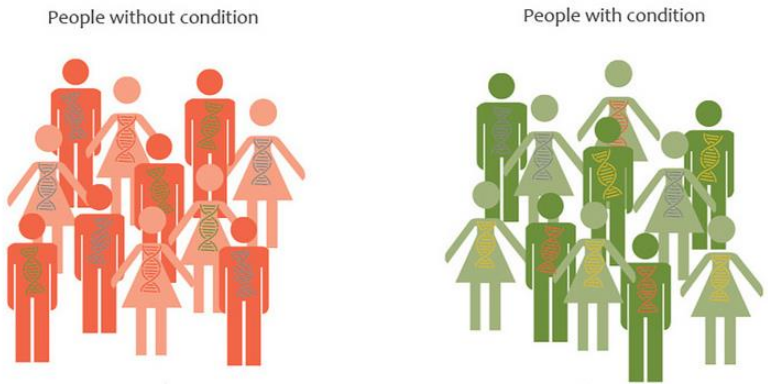
IN DIFFERENT SHAPES

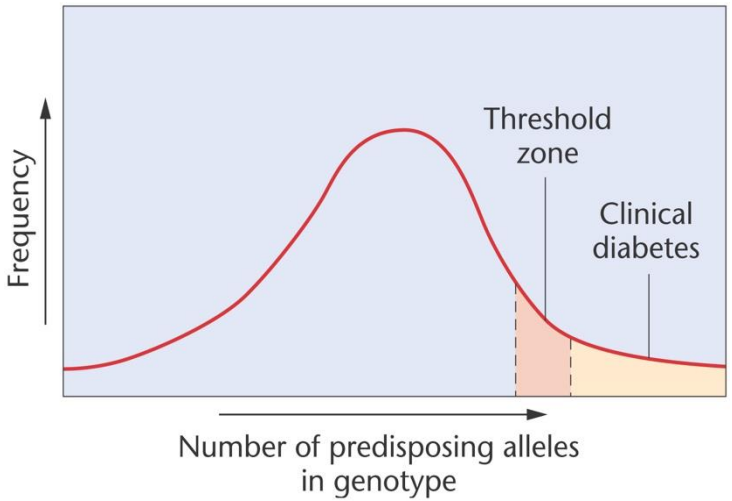
Continous variation



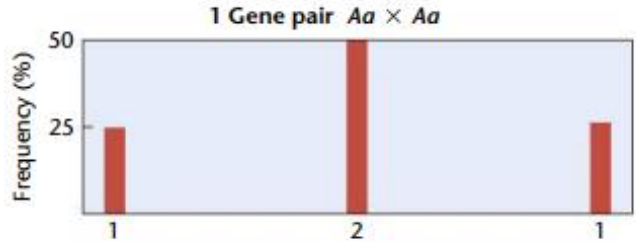
Categorical variation

Threshold traits

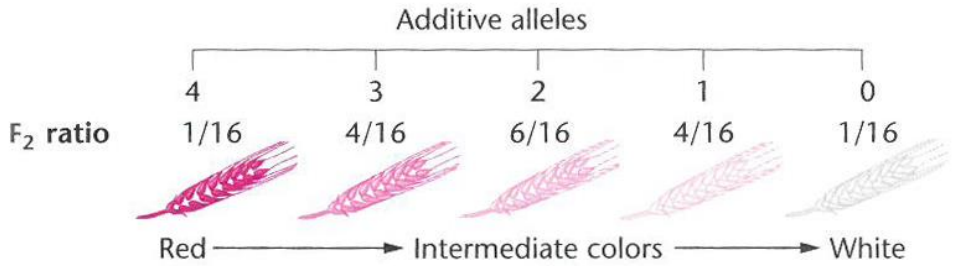


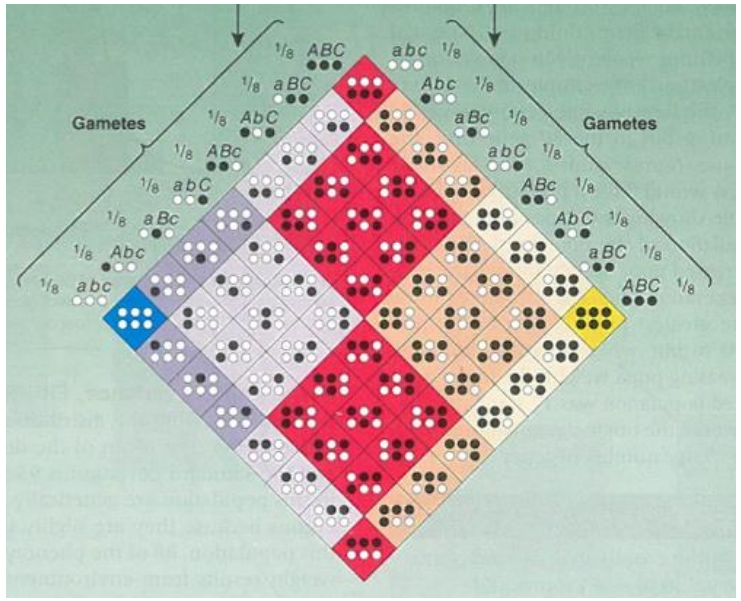


COMPLEX TRAITS



3 classes





PHENOTYPIC VARIANCE

GENETIC PARAMETERS

- Separate V_G and V_E
- Heritability
- Genetic correlation

PARTITION OF GENETIC VARIANCE

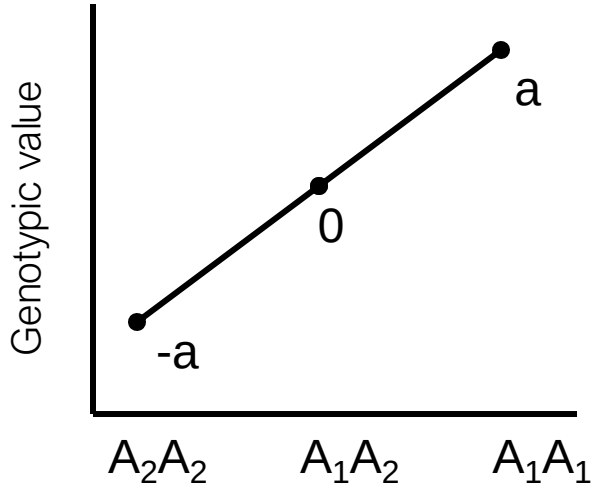
$$V_P = V_G + V_E$$

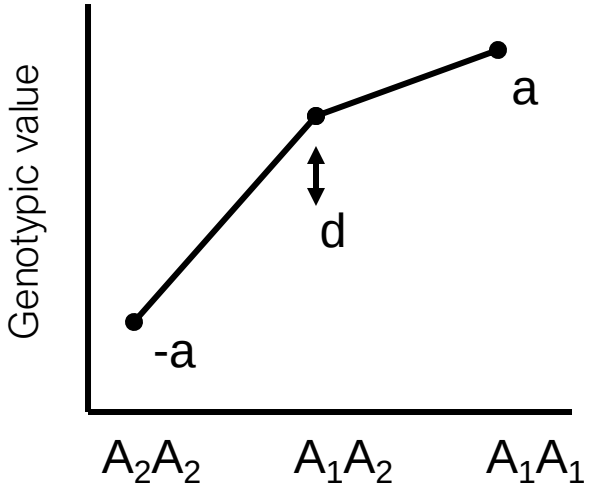
Additive variance

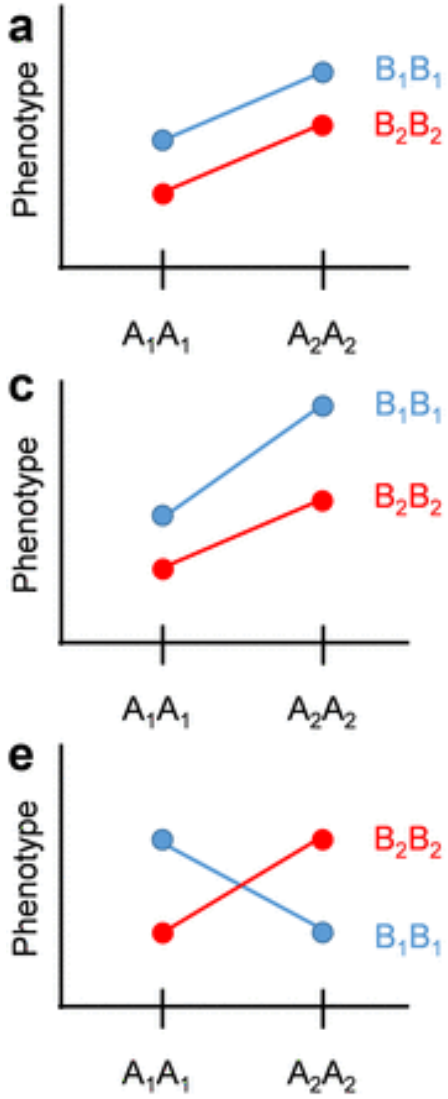
Interaction variance

$$V_G = V_A + V_D + V_I$$

Dominance variance







HERITABILITY

The concept heritability is an important concept as it describes the proportion of the ***phenotypic variance that is due to genetic variation***.

BROAD-SENSE HERITABILITY

Broad-sense heritability (H^2) describes the proportion of the phenotypic variance that is explained by genetic difference between individuals in the population.

$$V_P = V_G + V_E$$

$$H^2 = \frac{V_G}{V_P} = \frac{V_G}{V_G + V_E}$$

H^2 can take values between 0 and 1:

$H^2 = 0$→ all variation is due to environmental variation

$H^2 = 1$→ all variation is due to genetic variation

NARROW-SENSE HERITABILITY

$$V_P = V_G + V_E$$
$$V_P = V_A + V_D + V_I + V_E$$

Narrow-sense heritabilitet (h^2) is the proportion of the phenotypic variance that is explained by additive genetic variance

$$h^2 = \frac{V_A}{V_P}$$

H^2 VS h^2

Broad-sense heritability (H^2)
is an estimate for the proportion of phenotypic variation that is due to genetic variation

h^2 is always smaller than H^2

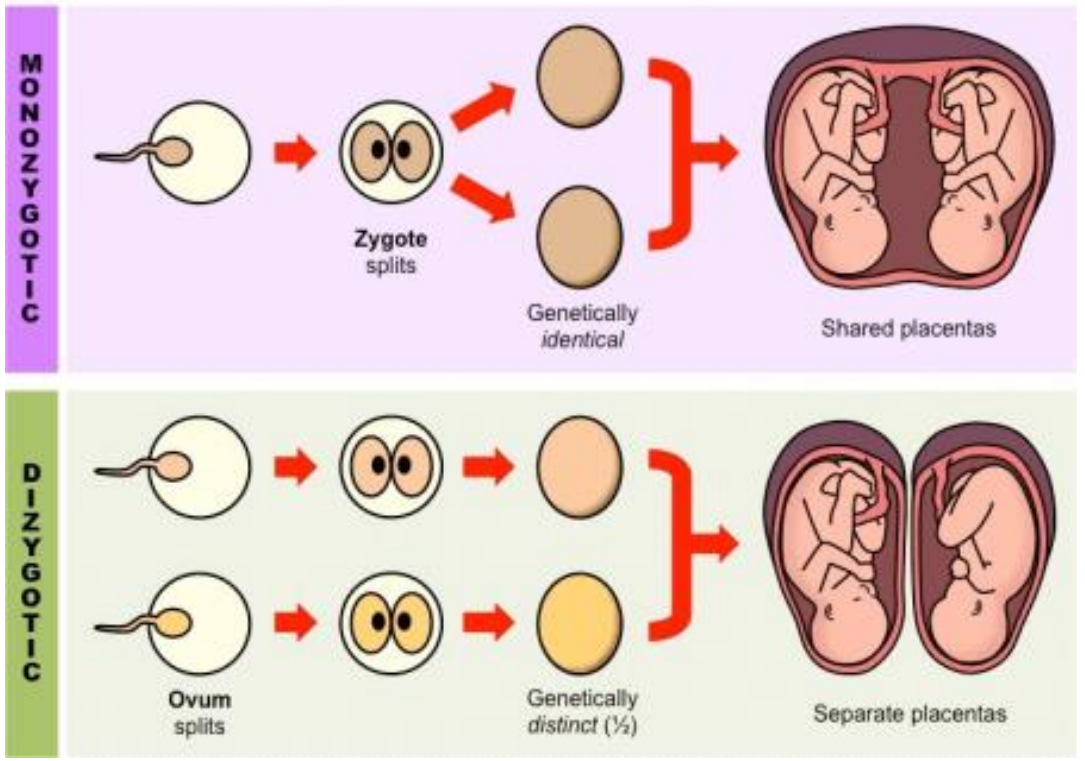
Narrow-sense heritability (h^2)
Is an estimate of the proportion of phenotypic variation that is caused by additive genetic variation – the part of the genetic variation that is directly transmitted from generation to generation

Additive genetic variance: hereditary | one allele from mom, one from dad
Dominance variance: is established after gamete formation
Interaction variance: is established after gamete formation

USING TWINS TO ESTIMATE H^2

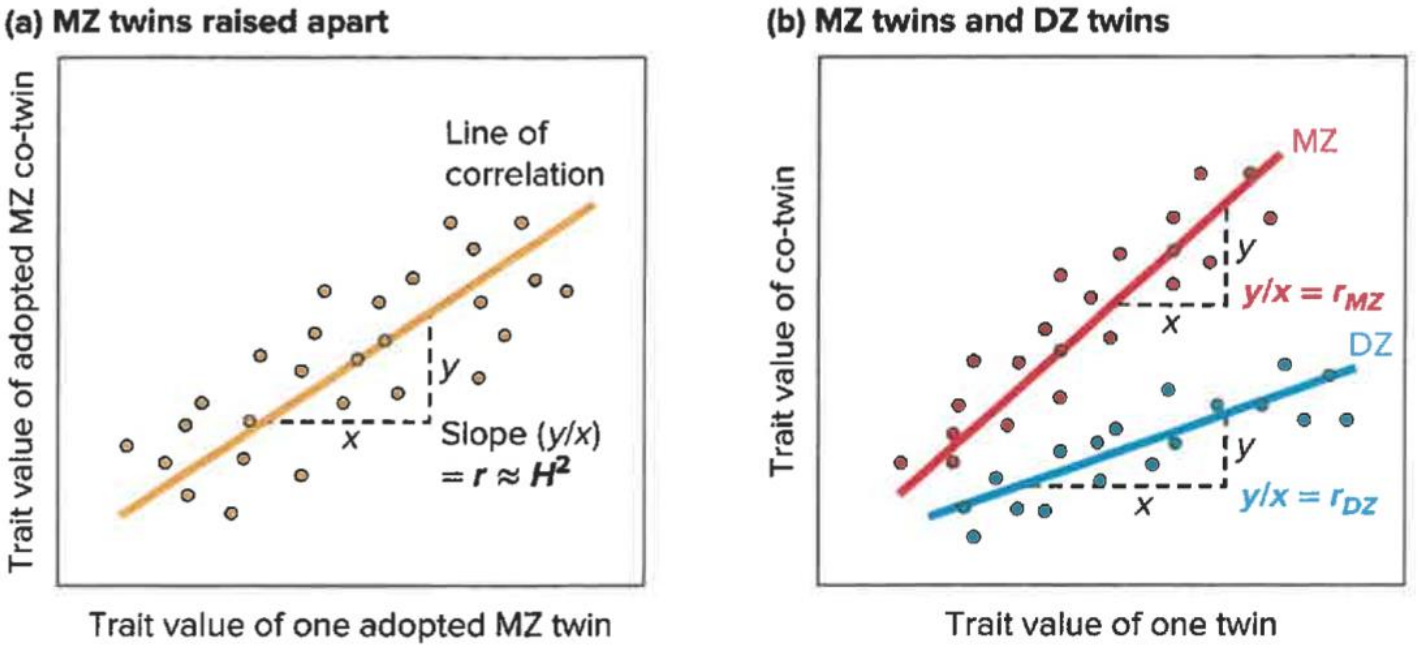
Monozygotic twins (MZ): Difference in V_P is V_E.

Dizygotic twins (DZ): Difference in V_P is $V_G + V_E$.



USING TWINS TO ESTIMATE H^2

QUANTITATIVE COMPLEX TRAITS



Because DZ share 50% of the genetic material

$$H^2 = 2(r_{MZ} - r_{DZ})$$

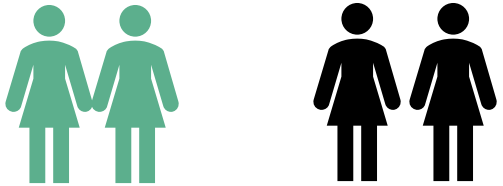
All phenotypic variation between MZ is environment, whereas all phenotypic variation between DZ is both

Thus, the difference is genetic variation

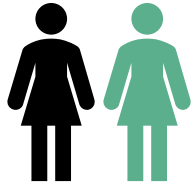
USING TWINS TO ESTIMATE H^2

DICHOTOMOUS COMPLEX TRAITS

Concordance rate (C) = the frequency with which the other twin has the trait



Concordant pair: same phenotype



Discordant pair: only one in the pair has the trait

$$H^2 = \frac{C_{MZ} - C_{DZ}}{1 - C_{DZ}}$$

Important

There must be a difference between C_{MZ} and C_{DZ} for a trait to be under genetic influence

The larger ratio $\frac{C_{MZ}}{C_{DZ}}$ the higher H^2

If $C_{MZ} < 1$ environmental exposures affect the trait

USING TWINS TO ESTIMATE H^2

TABLE 22.1 Heritability estimates from twin studies of quantitative traits

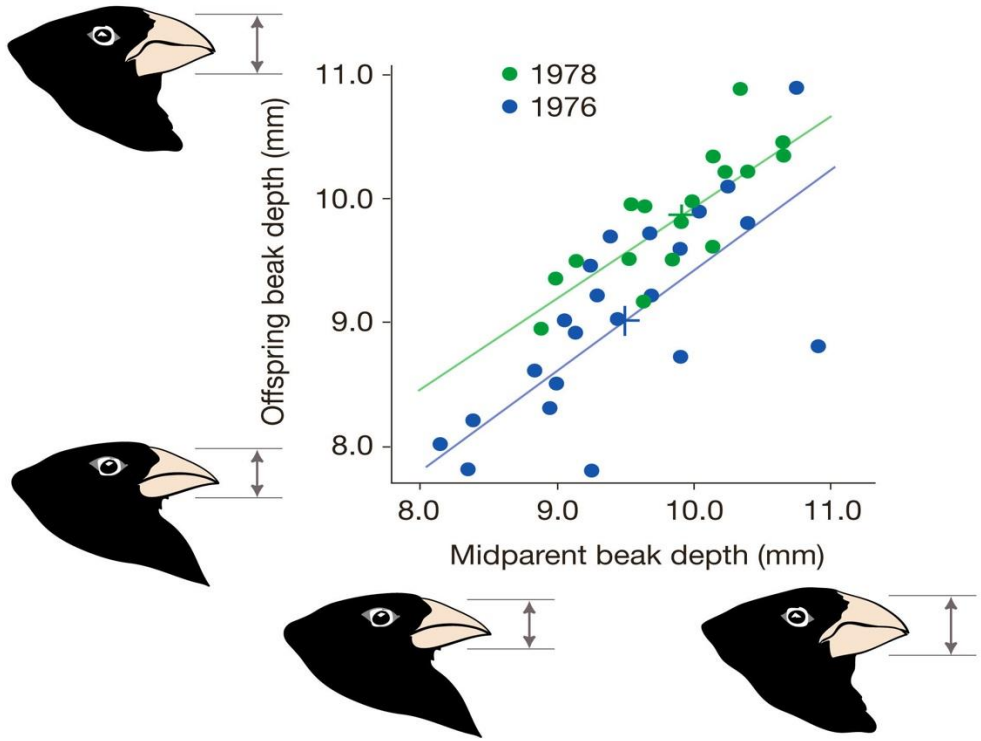
Trait	Heritability*
Height	0.68 – 0.90
Body mass index	0.64 – 0.84
Birth weight	0.64 – 0.84
Brain frontal lobe volume	0.90 – 0.95
Exercise participation	0.48 – 0.71
Dietary patterns	0.41 – 0.48

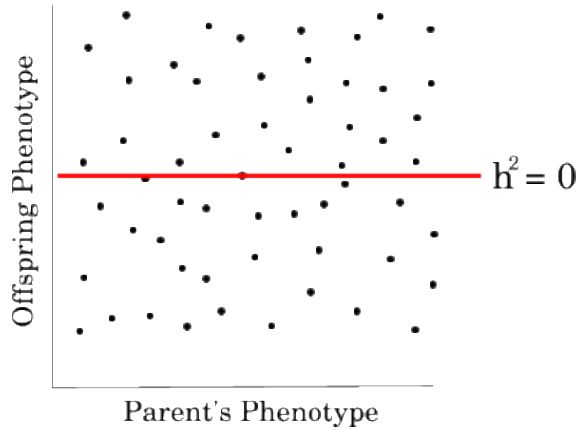
TABLE 22.2 MZ and DZ twin concordance for complex discrete traits

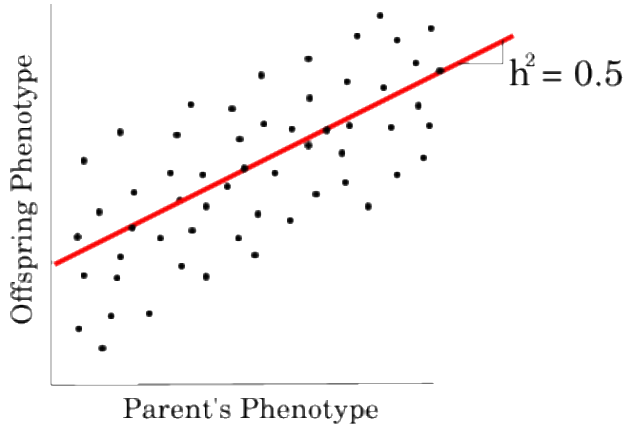
Trait	Concordance* MZ twins	DZ twins	H^2
Type 1 diabetes	0.43	0.074	0.38
Type 2 diabetes	0.34	0.16	0.21
Schizophrenia	0.41	0.053	
Autism spectrum	0.94	0.47	
Alzheimer's disease	0.32	0.087	
Parkinson's disease	0.16	0.11	0.06
Multiple sclerosis	0.25	0.054	
Crohn's disease	0.38	0.02	
Colorectal cancer	0.11	0.05	
Breast cancer	0.13	0.09	
Prostate cancer	0.18	0.03	

ESTIMATE h^2

Parent-offspring regression h^2 = slope = $\hat{\beta} = COV_{XY}/\sigma_X^2$







GENERAL APPROACH TO PARTITION VARIANCES

- Use a linear mixed model

$$\boldsymbol{y} = \boldsymbol{Xb} + \boldsymbol{Za} + \boldsymbol{e}$$

$\boldsymbol{y} = n \times 1$ vector of observations; n = number of records

$\boldsymbol{b} = p \times 1$ vector of **fixed effects**; p = number of levels for fixed effects

$\boldsymbol{a} = q \times 1$ vector of **random individual effects**, q = number of levels for random effect

$\boldsymbol{e} = n \times 1$ vector of **random residual**

$\boldsymbol{X}$ = design matrix of order $n \times p$ which relates records to fixed effects

$\boldsymbol{Z}$ = design matrix of order $n \times q$ which relates records to random effects

Variance components can be estimated with REML (residual maximum likelihood)

RELATIONSHIP MATRICES

- $var(a) = A\sigma_a^2, A$ =relationship matrix

A tabular pedigree for six individuals

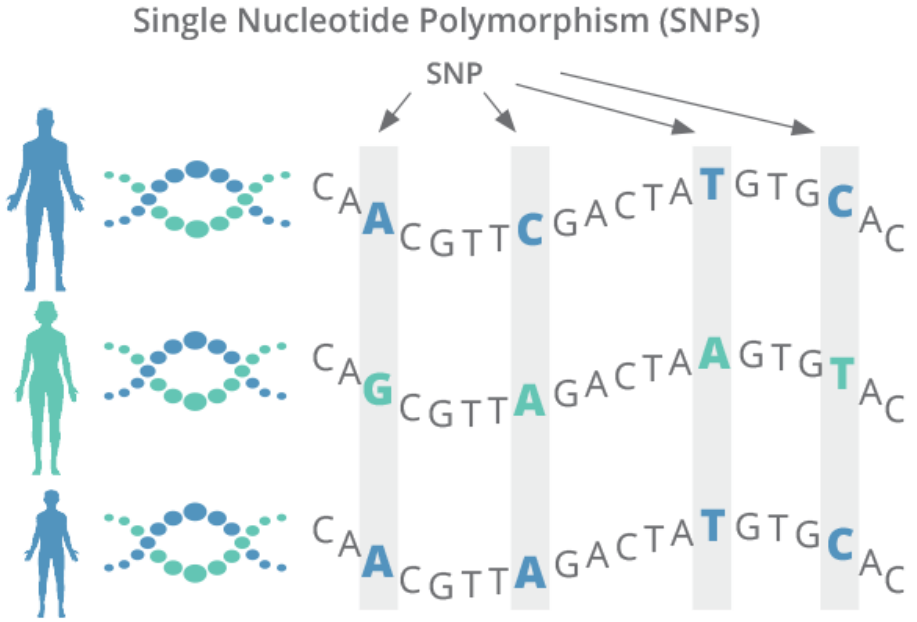
Individual	Dad	Mom
3	1	2
4	1	NA
5	4	3
6	5	2

	1	2	3	4	5	6
1	1	0	0.5	0.5	0.5	0.25
2	0	1	0.5	0	0.25	0.625
3	0.5	0.5	1	0.25	0.625	0.563
4	0.5	0	0.25	1	0.625	0.313
5	0.5	0.25	0.625	0.625	1.125	0.688
6	0.25	0.625	0.563	3.13	0.688	1.125

if both parents are known; $a_{i,j} = 0.5(a_{jd}+a_{jm})$ & $a_{i,i} = 1 + 0.5(a_{dm})$

if one parent is known; $a_{i,j} = 0.5(a_{jd})$

RELATIONSHIP MATRICES



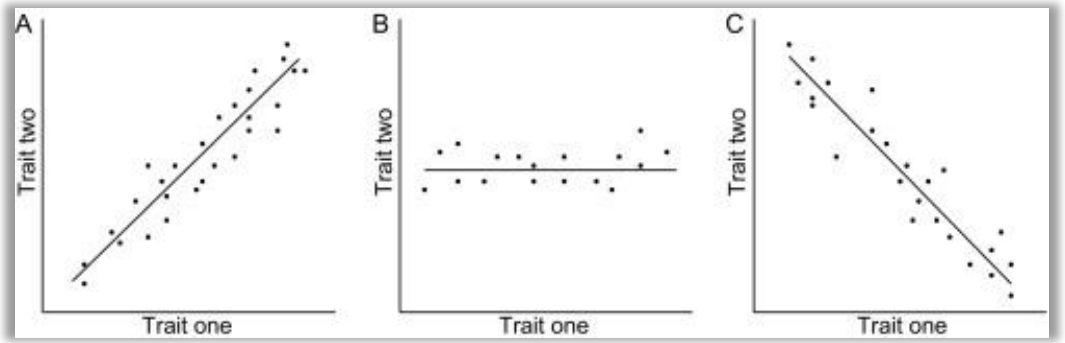
- If we don't have a pedigree but genetics…

Individual	SNP_1	SNP_2	..	...
1	0	2		
2	2	1		
3	1	1		
4	2	2		
5	0	0		
6	0	0		

$$\mathbf{GRM} = \frac{WW'}{m}$$

$$var(a) = G\sigma_a^2,$$

GENETIC CORRELATION



- The **genetic correlation** refers to the genetic link between two traits, which can help elucidate the shared biological pathways and/or causal relationships between them.

$$x = g_x + e_x$$

$$y = g_y + e_y,$$

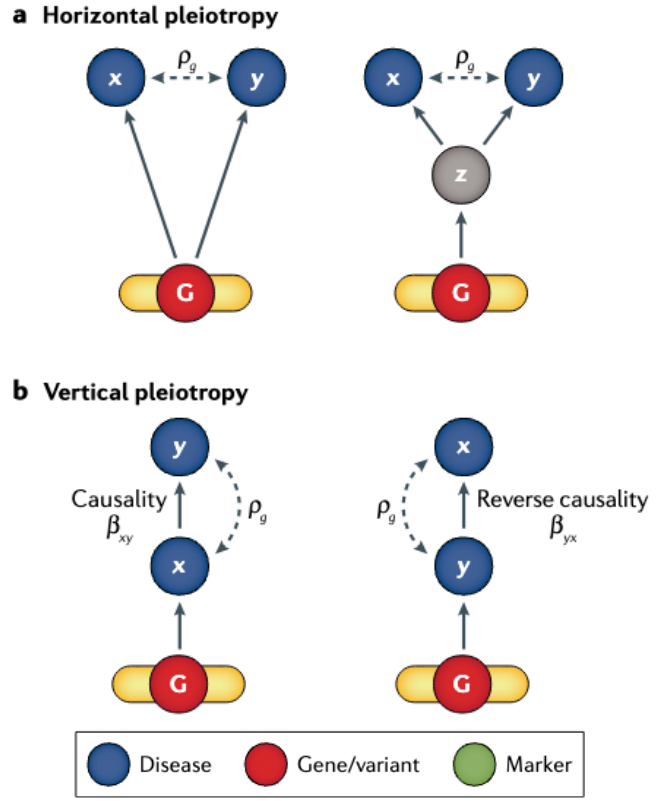
the genetic correlation (ρ_g) of the traits is:

$$\rho_g = \frac{\sigma_{g_x,g_y}}{\sqrt{\sigma^2_{g_x}\sigma^2_{g_y}}}$$

If traits are standardized to variance =1

$$\rho_g = \frac{h_{xy}}{\sqrt{h^2_x h^2_y}}$$

Pleiotropy is present when a genetic locus affects more than one trait



10.1038/s41576-019-0137-z

QUANTITATIVE GENETICS

- Unidentified genotypes but measured trait variability.
- Phenotypic vs Genotypic values
- Gene action
- Heritability

BREAK

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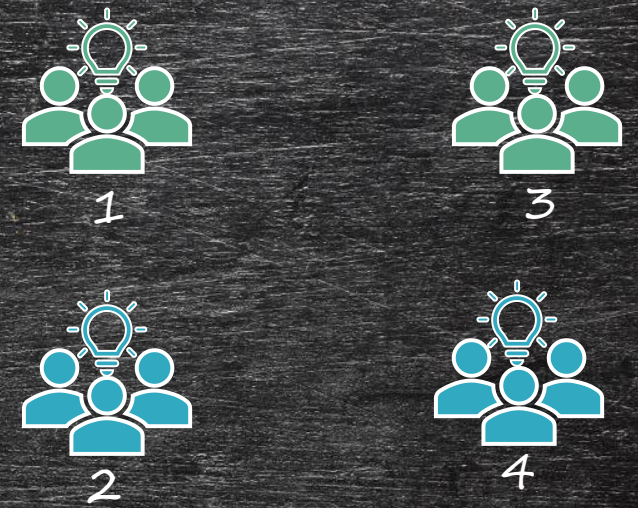
GROUP WORK

THE HERITABILITY OF HUMAN DISEASE

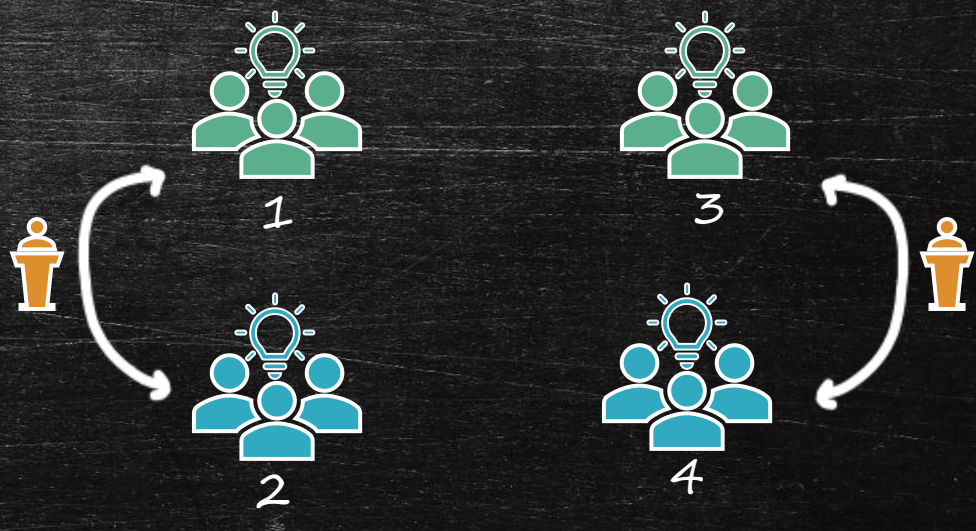
PART 1

1) Make 4 groups & prepare a 5-7 min presentation
   - ❑ Group 1 & 3 works with section 'Estimating heritability' p141-144
   - ❑ Group 2 & 4 works with section 'Biased heritability' p144-148



PART 2 – *next time (17/3)*

- ❑ Group 1 present to group 2 and *vise versa*
- ❑ Group 3 present to group 4 and *vise verse*



MOODLE EVALUATION

REMEMBER

List the two most important things you learned today	What did you find difficult?	What did you find easy?	Improvements for next session?
+	+	+	+