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Tropical Livestock
Genetics and Health

# Conceptual model of phenotypic values


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Slides adapted from Gregor Gorjanc and Gabriela Mafra Fortuna

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# The Roslin Institute

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The Royal (Dick) School of Veterinary Studies

Biotechnology and Biological Sciences Research Council

https://vet.ed.ac.uk/roslin

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## Sustainable Agriculture

Improving the health, productivity and welfare of farmed animals while mitigating impacts on the climate and environment.

## Infectious Diseases

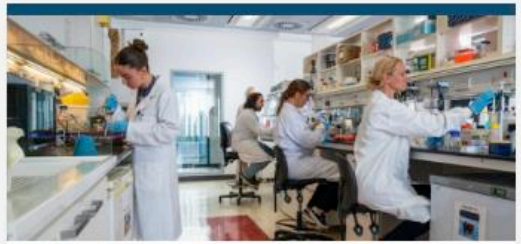
Improving the detection, prevention and treatment of infectious diseases of animals, and those that pass from animals to people.

## Enhancing Health

Leveraging our unique expertise, infrastructure and resources to understand animal and human health, ageing and disorders.


## Research

Animal research



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# Conceptual model of phenotypic values

Learning objectives

- Understanding how some types of variation in DNA looks like and how we work with that variation in computers (allele dosages)
- Connect variation in DNA and environment with the variation in phenotypic values
- Familiarise with the processes of mutation, recombination, segregation of DNA within pedigrees that give rise to DNA lottery
- Train common vector & matrix operations in R

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# Conceptual model of phenotypic values

Materials

- These slides (shared PDF) & lecture
- Exercises
- Reading material (shared PDF)
- AlphaSimR on-line course (for later)

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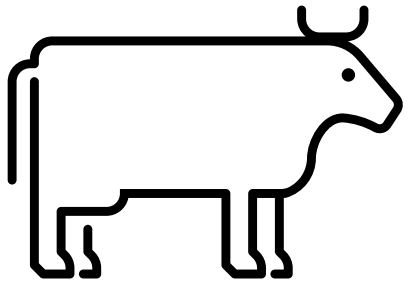
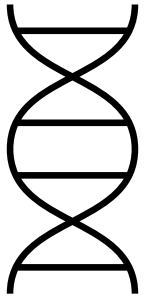
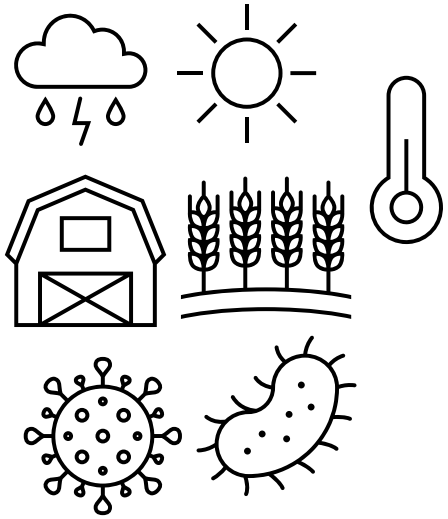
# Phenotypic variation



Phenotype = Genetics + Environment





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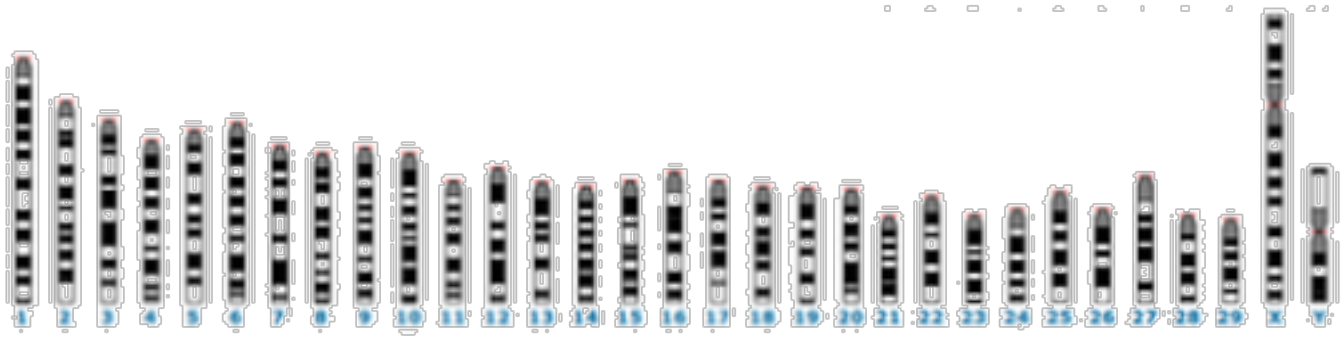
# Genome (cattle example)

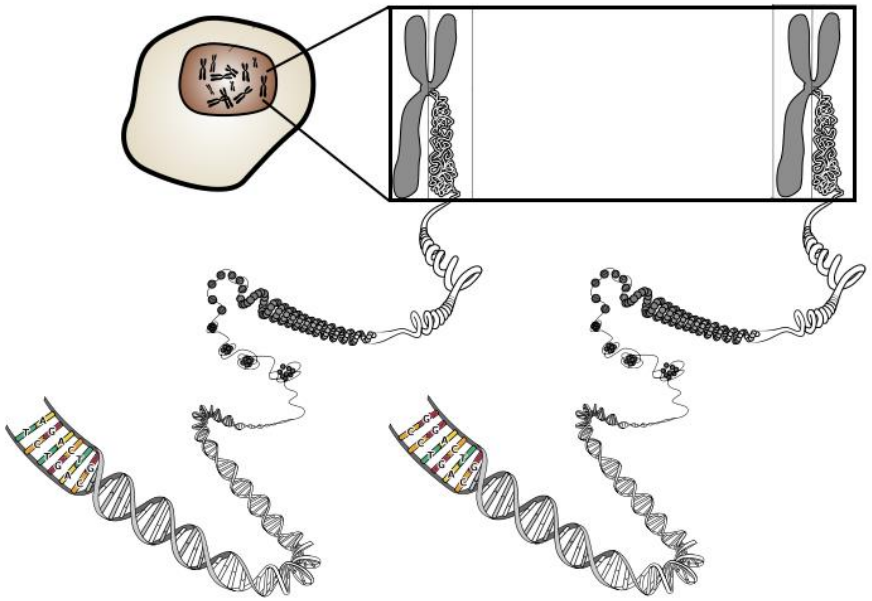
2 x 30 chromosomes



DNA, 2 x 3 billion (3,000,000,000) base pairs

Adenine
Thymine
A
T

Cytosine
Guanine
C
G



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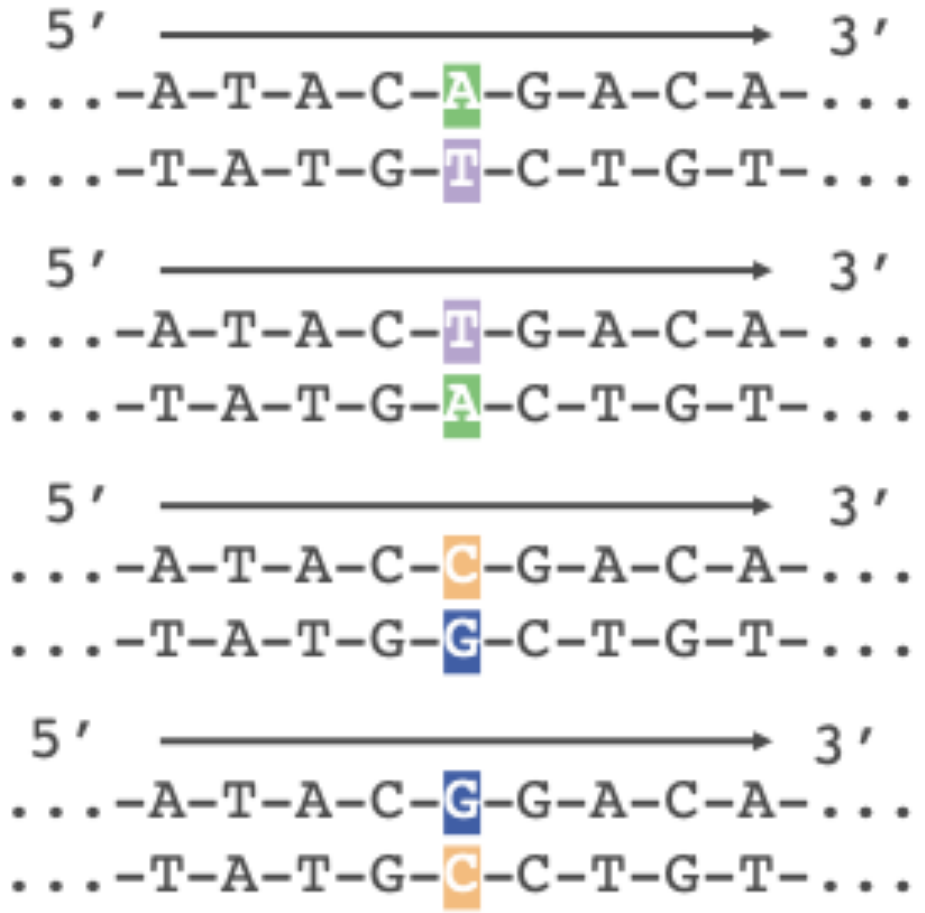
# Single Nucleotide Polymorphism

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# How many SNPs and other variants

The sequences of >150,119 genomes in the UK biobank

https://doi.org/10.1038/s41586-022-04965-x

~600M SNPs (representing 7% of all possible human SNPs)

~60M indels

~1M structural variants

~3M microsatellites

MEGA-SCALE DATA

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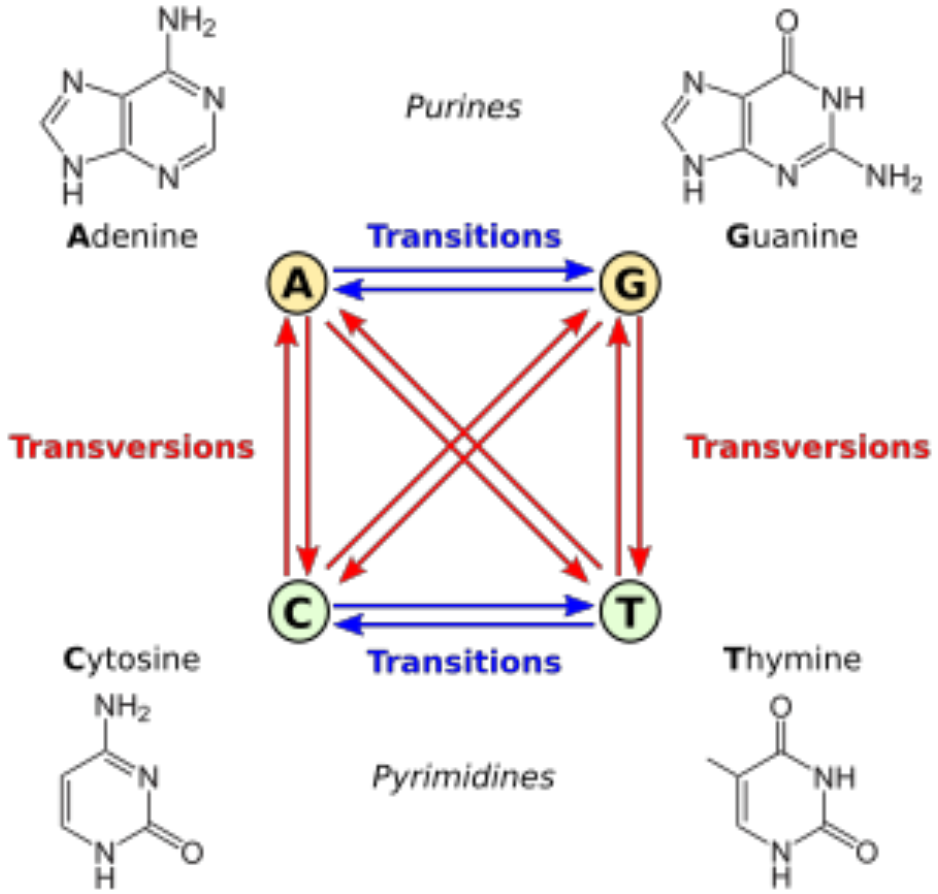
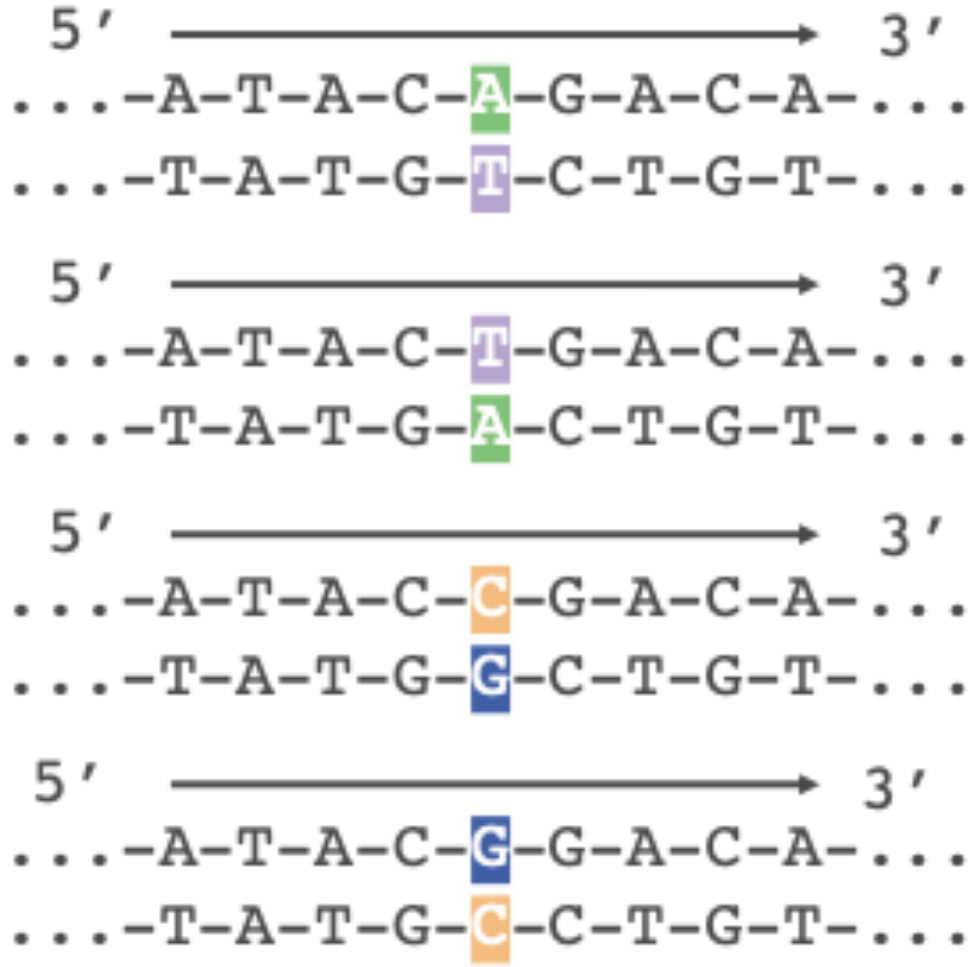
# Single Nucleotide Polymorphism (SNP)

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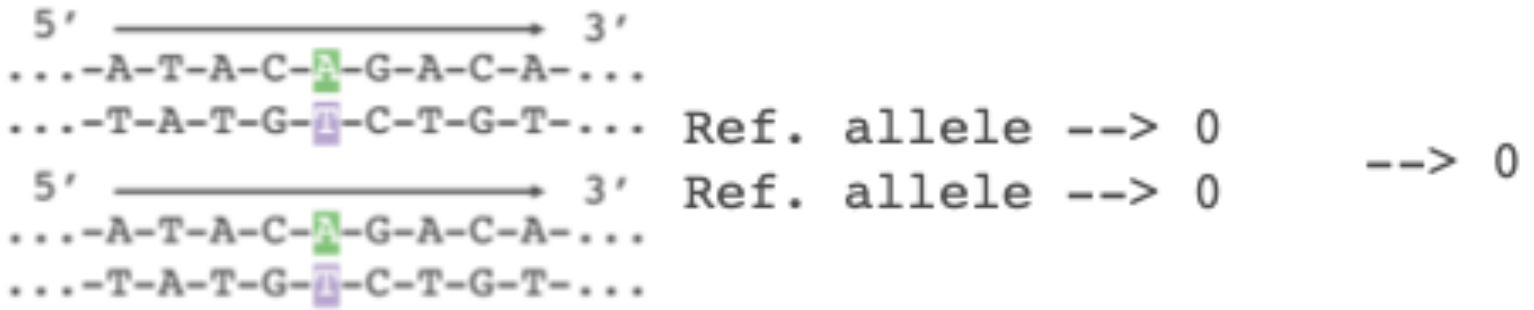
# Bi-allelic SNP alleles, genotypes & dosages

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# Bi-allelic SNP alleles, genotypes & dosages


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# Genome-wide haplotypes & genotype

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 1 | 0 | 1 | 1 | 0 | 0 | 1 |
| Haplotype 2 | 1 | 1 | 1 | 1 | 0 | 0 |
| Genotype | 1 | 2 | 2 | 1 | 0 | 1 |

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# Take home message 1:

Encoding haplotypes as a series of 0 & 1

Encoding genotypes as a series of 0, 1, & 2

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# SNP allele dosages in haplotypes and genotypes

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 3 | 0 | 0 | 1 | 1 | 0 | 1 |
| Haplotype 4 | 0 | 0 | 0 | 0 | 1 | 1 |
| Genotype | | | | | | |

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# SNP allele dosages in haplotypes and genotypes

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 3 | 0 | 0 | 1 | 1 | 0 | 1 |
| Haplotype 4 | 0 | 0 | 0 | 0 | 1 | 1 |
| Genotype | 0 | 0 | 1 | 1 | 1 | 2 |

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# SNP allele dosages in haplotypes and genotypes

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 5 | 1 | 1 | 1 | 0 | 1 | 1 |
| Haplotype 6 | 1 | 1 | 0 | 0 | 1 | 1 |
| Genotype | | | | | | |

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# SNP allele dosages in haplotypes and genotypes

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 5 | 1 | 1 | 1 | 0 | 1 | 1 |
| Haplotype 6 | 1 | 1 | 0 | 0 | 1 | 1 |
| Genotype | 2 | 2 | 1 | 0 | 2 | 2 |

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# Summarising SNP genotype data

Table 1: Genotype allele dosages at two loci in five animals and corresponding summary

| Animal | SNP1 | SNP2 |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 1 |
| 3 | 2 | 0 |
| 4 | 1 | 1 |
| 5 | 0 | 0 |
| Mean | 1.0 | 0.40 |
| Standard deviation | 1.0 | 0.55 |
| Variance | 1.0 | 0.30 |
| Allele frequency | 0.50 | 0.20 |
| Genic variance | 0.50 | 0.32 |
| Correlation | 0.46 | |

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# Summarising SNP genotype data

Table 1: Genotype allele dosages at two loci in five animals and corresponding summary

| Animal | SNP1 |
|---|---|
| 1 | 0 |
| 2 | 2 |
| 3 | 2 |
| 4 | 1 |
| 5 | 0 |
| Mean | 1.0 |
| Standard deviation | 1.0 |
| Variance | 1.0 |
| Allele frequency | 0.50 |
| Genic variance | 0.50 |
| Correlation | |

$$\bar{x} = \frac{\sum x_i}{N}$$

$$\sigma^2 = \frac{\sum (x_i - \bar{x})^2}{N - 1}$$

$$\sigma = \sqrt{\sigma^2}$$

$$\frac{\sum x_i}{2N}$$

$$\bar{x}\left(1 - \frac{\bar{x}}{2}\right)$$

$$r = \frac{\sum (x_i - \bar{x})\,(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$$

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# Summarising SNP genotype data

Table 1: Genotype allele dosages at two loci in five animals and corresponding summary

| Animal | SNP1 |
|---|---|
| 1 | 0 |
| 2 | 2 |
| 3 | 2 |
| 4 | 1 |
| 5 | 0 |
| Mean | 1.0 |
| Standard deviation | 1.0 |
| Variance | 1.0 |
| Allele frequency | 0.50 |
| Genic variance | 0.50 |
| Correlation | |

$$\bar{x} = \frac{\sum x_i}{N} = \frac{0+2+2+1+0}{5}$$

$$\sigma^2 = \frac{\sum (x_i - \bar{x})^2}{N-1} = \frac{(0-1)^2 + (2-1)^2 + (2-1)^2 + (1-1)^2 + (0-1)^2}{5-1}$$

$$\sigma = \sqrt{\sigma^2} = \sqrt{1}$$

$$\frac{\sum x_i}{2N} = \frac{0+2+2+1+0}{2(5)} \qquad \bar{x}\left(1 - \frac{\bar{x}}{2}\right) = 1\left(1 - \frac{1}{2}\right)$$

$$r = \frac{\sum (x_i - \bar{x})\,(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$$

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# Genotype summary (2)

| Animal | SNP3 | SNP4 |
|---|---|---|
| 1 | 1 | 0 |
| 2 | 0 | 1 |
| 3 | 2 | 2 |
| 4 | 0 | 1 |
| 5 | 0 | 0 |
| Mean | | |
| Standard deviation | | |
| Variance | | |
| Allele frequency | | |
| Genic variance | | |
| Correlation | | |

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# Genotype summary (2)

| Animal | SNP3 | SNP4 |
|---|---|---|
| 1 | 1 | 0 |
| 2 | 0 | 1 |
| 3 | 2 | 2 |
| 4 | 0 | 1 |
| 5 | 0 | 0 |
| Mean | 0.6 | 0.8 |
| Standard deviation | 0.89 | 0.84 |
| Variance | 0.8 | 0.7 |
| Allele frequency | 0.3 | 0.4 |
| Genic variance | 0.42 | 0.48 |
| Correlation | 0.55 | |

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# Genotype summary (3)

| Animal | SNP5 | SNP6 |
|---|---|---|
| 1 | 1 | 0 |
| 2 | 0 | 1 |
| 3 | 1 | 0 |
| 4 | 0 | 1 |
| 5 | 0 | 0 |
| Mean | | |
| Standard deviation | | |
| Variance | | |
| Allele frequency | | |
| Genic variance | | |
| Correlation | | |

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# Genotype summary (3)

| Animal | SNP5 | SNP6 |
|---|---|---|
| 1 | 1 | 0 |
| 2 | 0 | 1 |
| 3 | 1 | 0 |
| 4 | 0 | 1 |
| 5 | 0 | 0 |
| Mean | 0.6 | 0.4 |
| Standard deviation | 0.55 | 0.55 |
| Variance | 0.3 | 0.3 |
| Allele frequency | 0.3 | 0.2 |
| Genic variance | 0.42 | 0.32 |
| Correlation | -1 | |

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# Variation in phenotypic values

$$y_i = \mu + g_i + e_i + g_i \times e_i$$

$y_i$ - Phenotypic value

$\mu$ - Population mean(s)

$g_i$ - Genetic value (deviation from mean)

$e_i$ - Environmental value (deviation from mean)

$g_i \times e_i$ - Genotype-by-environment interaction (deviation from mean)

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# Genetic values comprise individual DNA locus effects

$$g_i = g_{i,1} + g_{i,2} + \cdots + g_{i,k} + g_{i,1} \times g_{i,2} + \cdots$$

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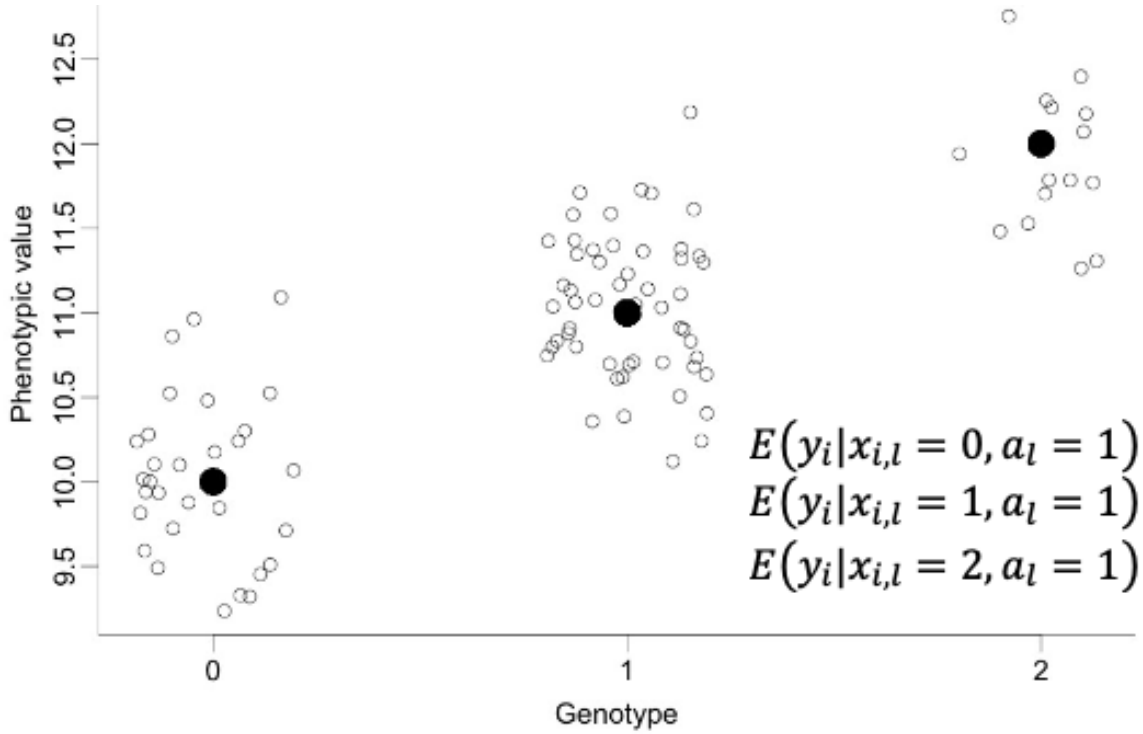
# Example

$$y_i = \mu + g_i + e_i$$




$$E(y_i|x_{i,l} = 0, a_l = 1) = \mu + x_{i,l}a_l = 10 + 0 \times 1 = 10,$$
$$E(y_i|x_{i,l} = 1, a_l = 1) = \mu + x_{i,l}a_l = 10 + 1 \times 1 = 11,$$
$$E(y_i|x_{i,l} = 2, a_l = 1) = \mu + x_{i,l}a_l = 10 + 2 \times 1 = 12.$$

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# Exercise 4

3 genotypes (0, 1, 2)

Allele substitution effect (-2)

Population mean (15)

$$y = 15 + 0 \times (-2)$$
$$y = 15 + 1 \times (-2)$$
$$y = 15 + 2 \times (-2)$$

Produce expected phenotype

Sample environment effect ($\sigma_e$=1)

Produce realised phenotype

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# Multi-locus version

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 1 | 0 | 1 | 1 | 0 | 0 | 1 |
| Haplotype 2 | 1 | 1 | 1 | 1 | 0 | 0 |
| Genotype | 1 | 2 | 2 | 1 | 0 | 1 |

X

| | | | | | | |
|---|---|---|---|---|---|---|
| | +1 | +2 | -1 | +1 | +1 | -2 |

Allele substitution effect

↓

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Haplotype 1 | 0 | +2 | -1 | 0 | 0 | -2 | -1 |
| Haplotype 2 | +1 | +2 | -1 | +1 | 0 | 0 | +3 |
| Genotype | +1 | +4 | -2 | +1 | 0 | -2 | +2 |

Values

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# Allele dosage to genetic value

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 3 | 0 | 0 | 1 | 1 | 0 | 1 |
| Haplotype 4 | 0 | 0 | 0 | 0 | 1 | 1 |
| Genotype | 0 | 0 | 1 | 1 | 1 | 2 |

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# Allele dosage to genetic value

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 3 | 0 | 0 | 1 | 1 | 0 | 1 |
| Haplotype 4 | 0 | 0 | 0 | 0 | 1 | 1 |
| Genotype | 0 | 0 | 1 | 1 | 1 | 2 |

X

| | | | | | |
|---|---|---|---|---|---|
| +1 | +1 | -3 | +2 | -2 | -1 |

↓

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 3 | | | | | | |
| Haplotype 4 | | | | | | |
| Genotype | | | | | | |

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# Allele dosage to genetic value

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Haplotype 3 | 0 | 0 | 1 | 1 | 0 | 1 | |
| Haplotype 4 | 0 | 0 | 0 | 0 | 1 | 1 | |
| Genotype | 0 | 0 | 1 | 1 | 1 | 2 | |

Allele dosage to genetic X

| | | | | | | |
|---|---|---|---|---|---|---|
| +1 | +1 | -3 | +2 | -2 | -1 | |

↓

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Haplotype 3 | 0 | 0 | -3 | +2 | 0 | -1 | -2 |
| Haplotype 4 | 0 | 0 | 0 | 0 | -2 | -1 | -3 |
| Genotype | 0 | 0 | -3 | +2 | -2 | -2 | -5 |

Values

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# Allele dosage to genetic value

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 5 | 1 | 1 | 1 | 0 | 1 | 1 |
| Haplotype 6 | 1 | 1 | 0 | 0 | 1 | 1 |
| Genotype | | | | | | |

X

| | | | | | |
|---|---|---|---|---|---|
| +1 | +1 | -3 | +2 | -2 | -1 |

↓

| | | | | | | |
|---|---|---|---|---|---|---|
| Haplotype 5 | | | | | | |
| Haplotype 6 | | | | | | |
| Genotype | | | | | | |

Values

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# Allele dosage to genetic value

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Haplotype 5 | 1 | 1 | 1 | 0 | 1 | 1 | |
| Haplotype 6 | 1 | 1 | 0 | 0 | 1 | 1 | |
| Genotype | 2 | 2 | 1 | 0 | 2 | 2 | |
| | | | | X | | | |
| | +1 | +1 | -3 | +2 | -2 | -1 | |
| | | | | ↓ | | | |
| Haplotype 5 | +1 | +1 | -3 | 0 | -2 | -1 | -4 |
| Haplotype 6 | +1 | +1 | 0 | 0 | -2 | -1 | -1 |
| Genotype | +2 | +2 | -3 | 0 | -4 | -2 | -5 |

Values

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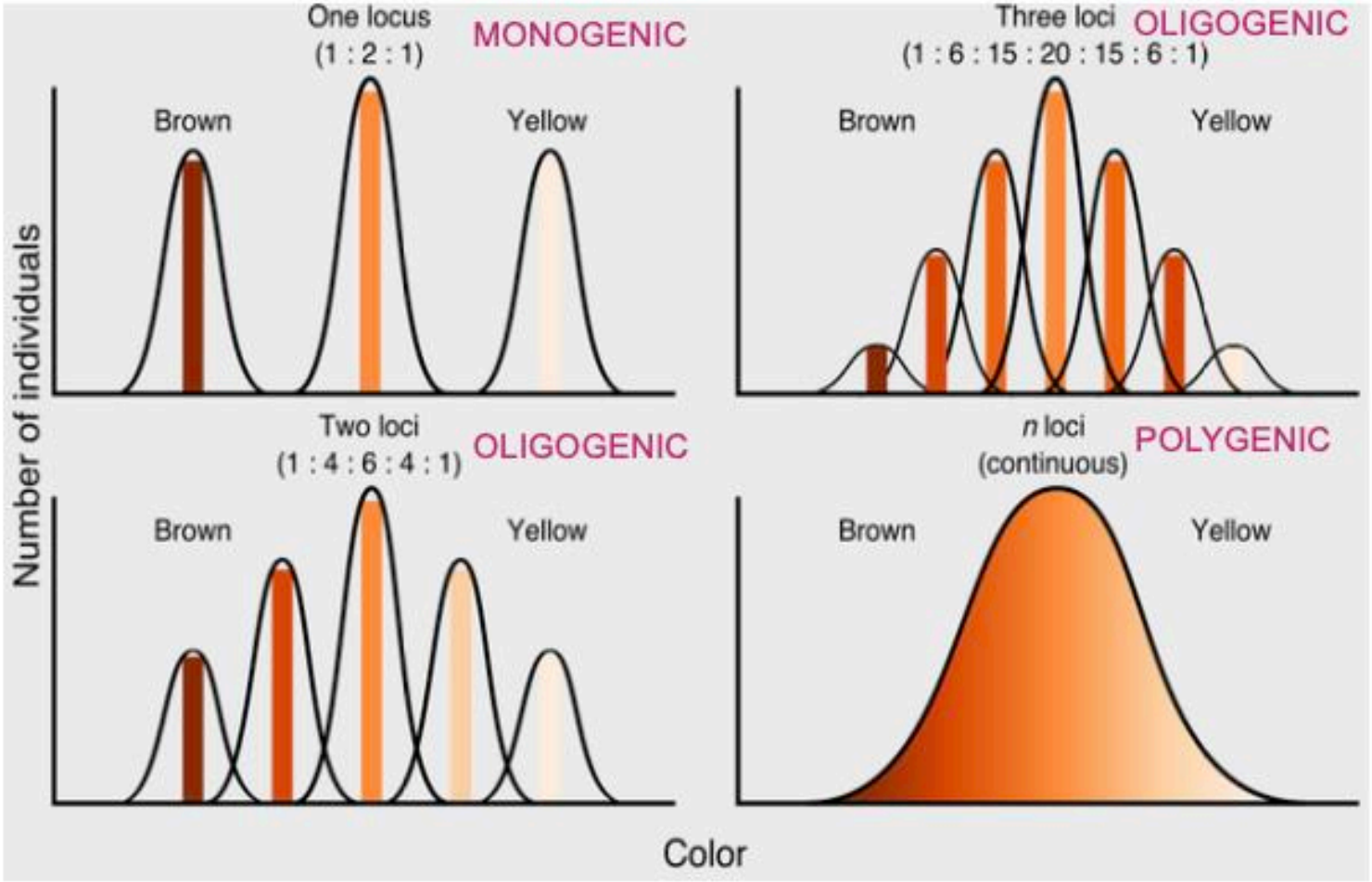
# Hypothetical architecture for cattle coat colour

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# Sources of variation between individuals

Discuss!

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# Sources of variation between individuals

Different DNA

- Due to different mutations
- These were inherited from parents following recombination and segregation of parental genomes
- Individual mutations can have effects
- Combinations of mutations can have effects (dominance and epistasis)

Different environment

- Nutrition, water, health, …

Different combination of DNA and environment

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# Sources of quantitative genetic variation within family

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# Sources of quantitative genetic variation within family

https://www.poultryclub.org/breeds/

F – frizzled
f – normal

Frizzle

Probability of each offspring being frizzled:

50%

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Ng et al., 2012 doi: 10.1371/journal.pgen.1002748

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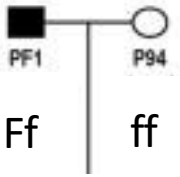
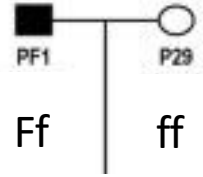
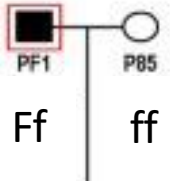
# Sources of quantitative genetic variation within family

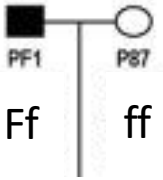
https://www.poultryclub.org/br

F – frizzled
f – normal





Frizzle

Probability of each offspring being frizzled:

50%

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Ng et al., 2012 doi: 10.1371/journal.pgen.1002748

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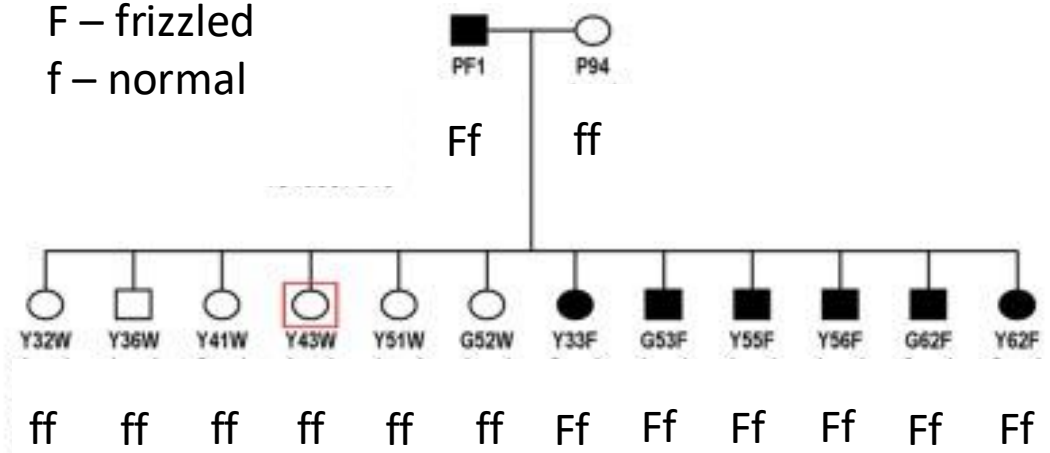
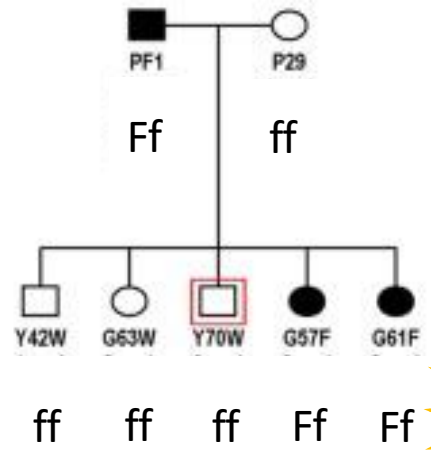
# Sources of quantitative genetic variation within family

https://www.poultryclub.org/br

F – frizzled
f – normal



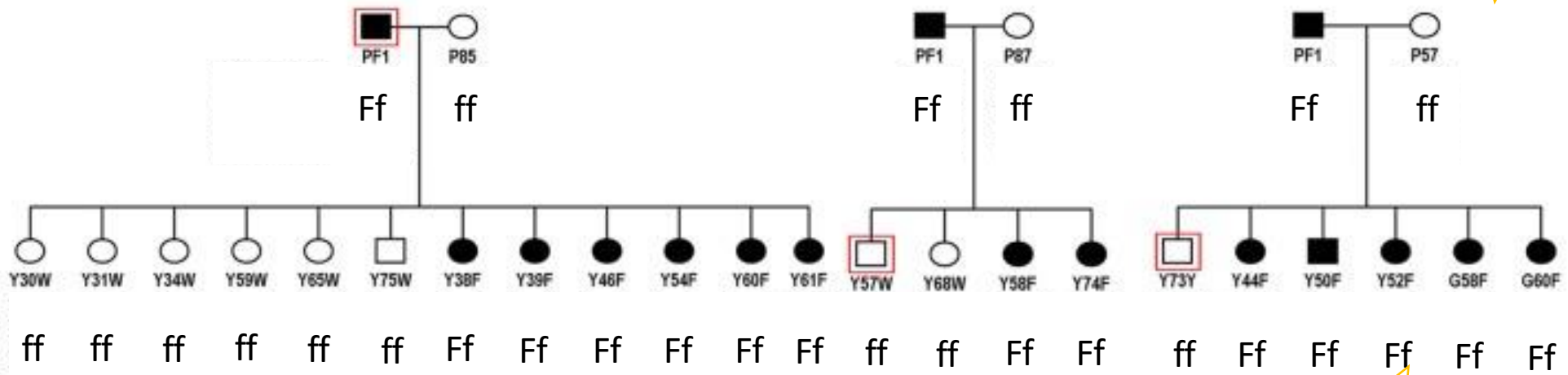




40%

Frizzle

Probability of each offspring being frizzled:

50%




83%

Ng et al., 2012 doi: 10.1371/journ[illegible]02748

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# Exercise

Generate combinations of father's chromosomes in his gametes

- 1 chromosome pair [1L 1D]
- 2 chromosome pairs [1L 1D, 2L 2D]
- 3 chromosome pairs [1L 1D, 2L 2D, 3L 3D]

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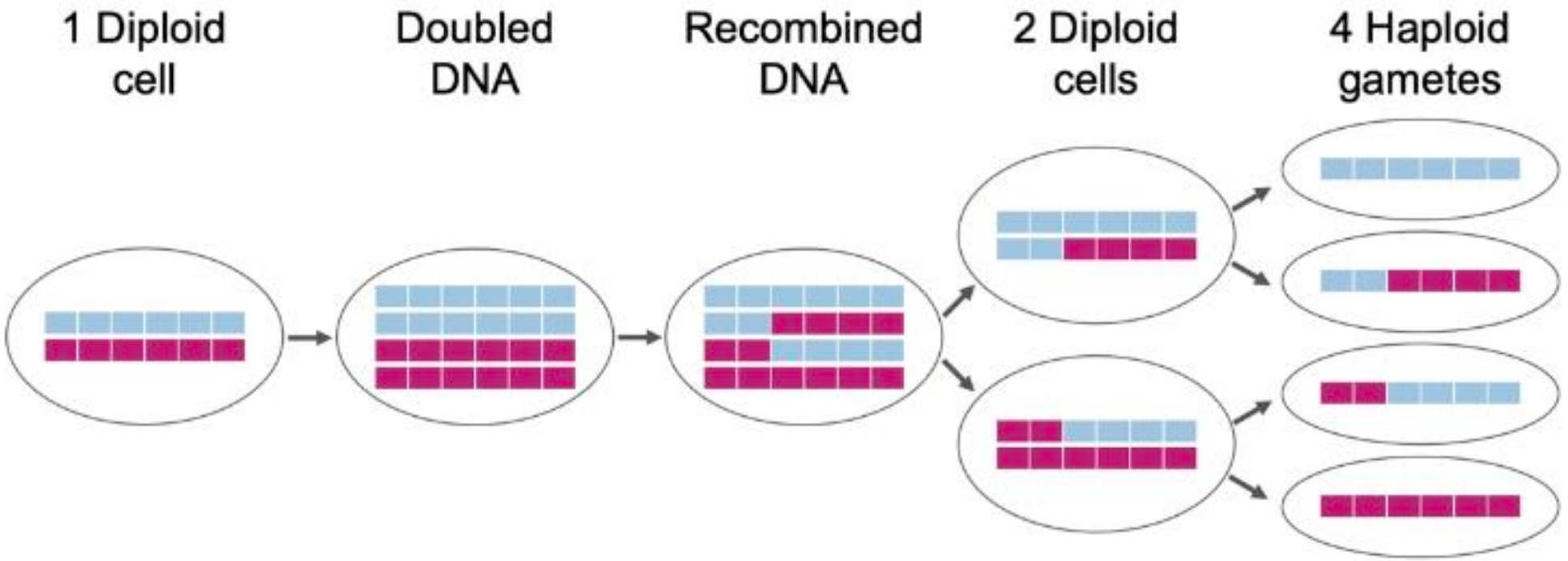
# Meiosis



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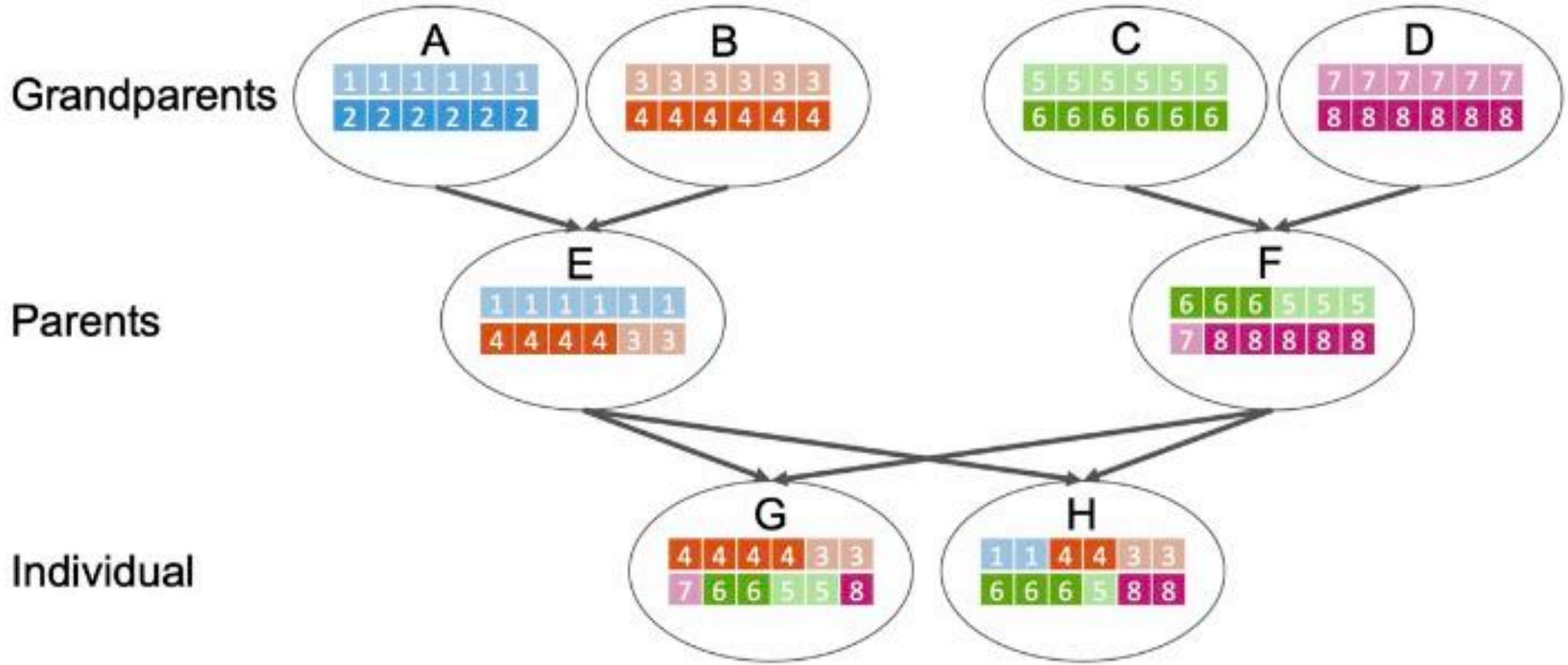
# Meiosis in a pedigree (IBS and IBD)

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# Exercise

Generate more progeny with parents E & F

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# Parent average and Mendelian sampling terms

$$g_i = \frac{1}{2} g_{f(i)} + \frac{1}{2} g_{m(i)} + r_i$$

$$g_i = g_{i,1} + g_{i,2},$$

$$g_{i,1} = \frac{1}{2} g_{f(i),1} + \frac{1}{2} g_{f(i),2} + r_{i,1},$$

$$g_{i,2} = \frac{1}{2} g_{m(i),1} + \frac{1}{2} g_{m(i),2} + r_{i,2}.$$

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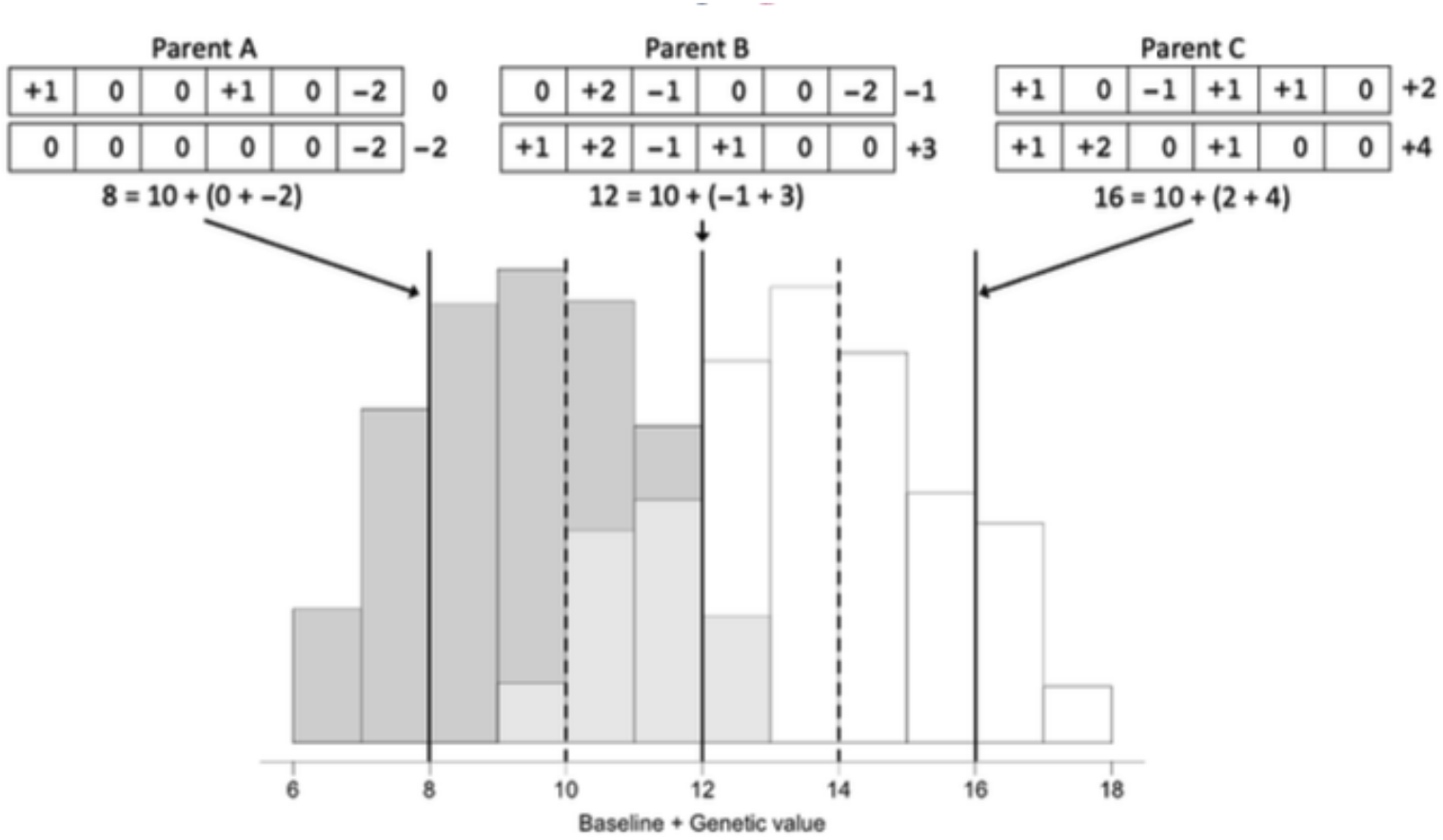
# Between and within family genetic variation

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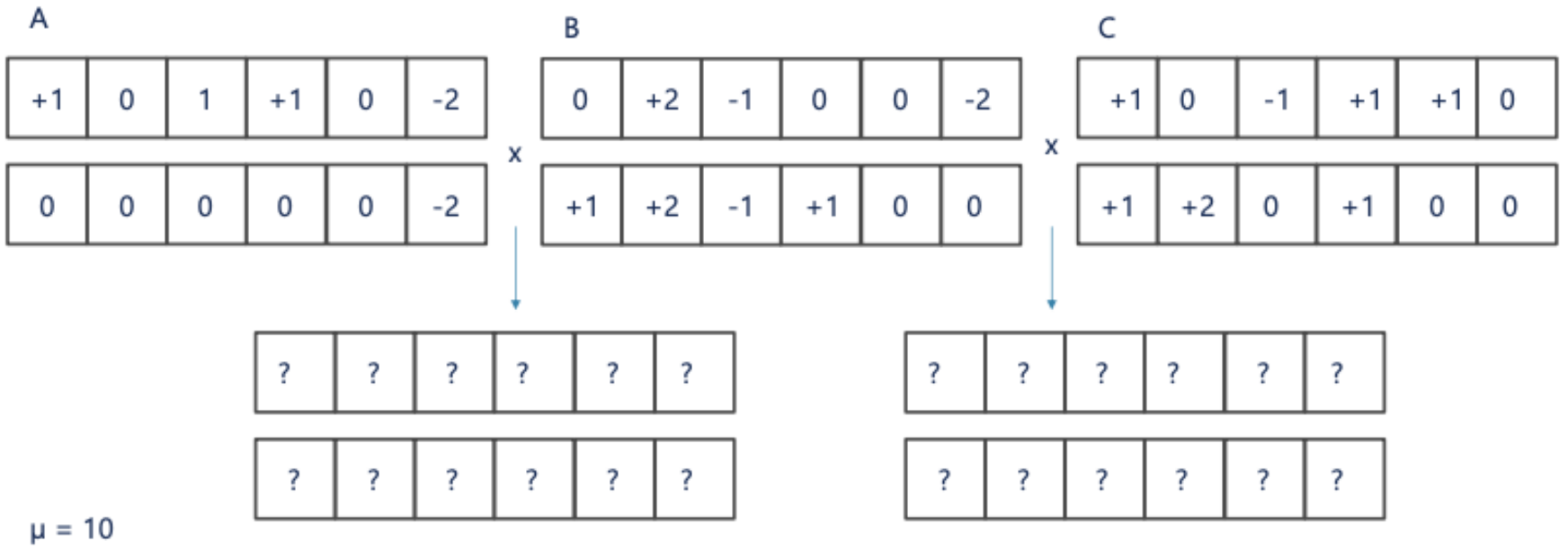
# Exercise

Generate progeny from the pairs and calculate their genetic value

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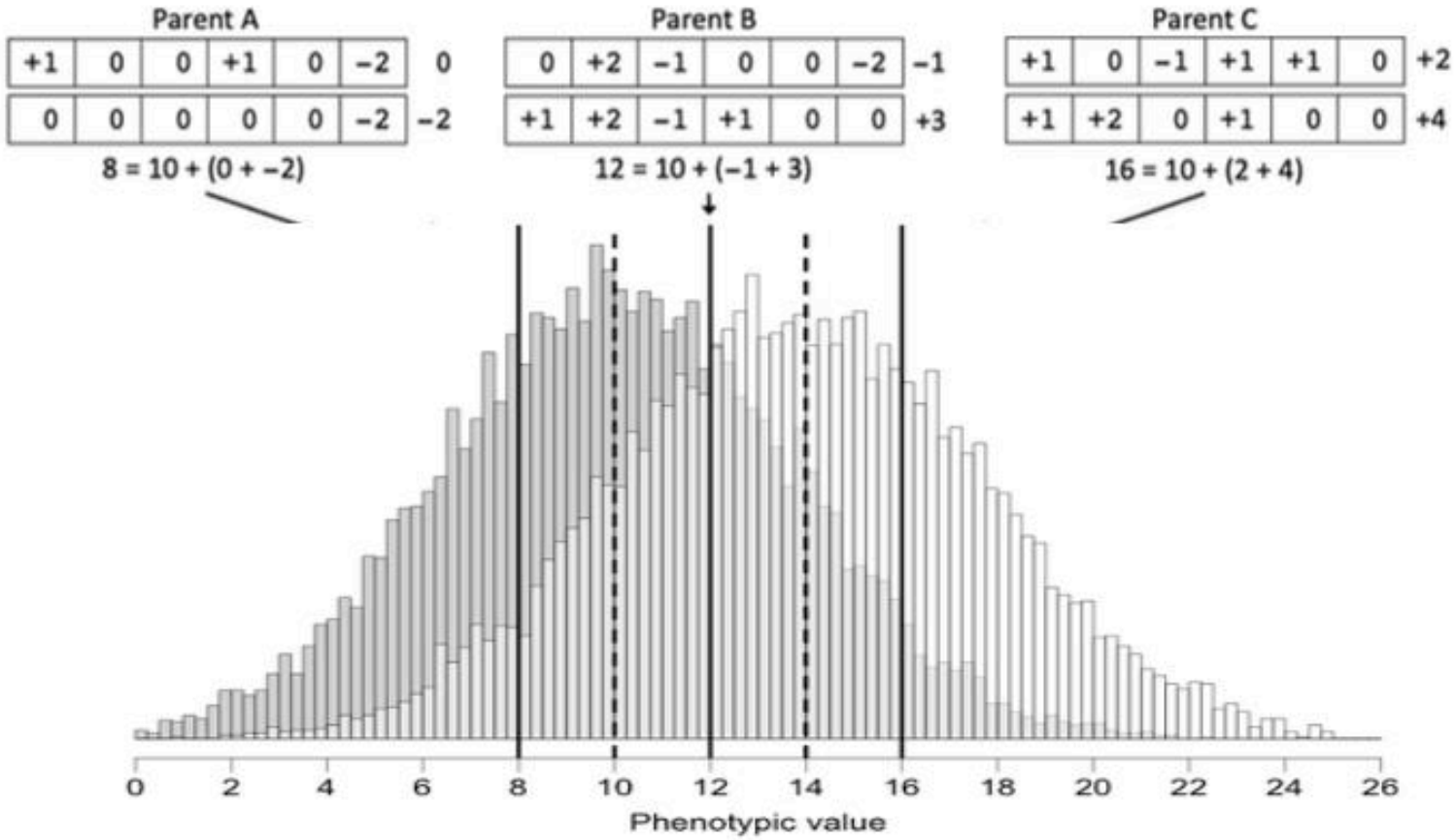
# Between and within family phenotypic variation

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# Exercise

Take the 4 genetic values from the previous example and add environment effect (can use the rnorm())



Free short online course

# Breeding Programme Modelling with AlphaSimR

THE UNIVERSITY of EDINBURGH

THE DATA LAB
value from data

DDI Data-Driven Innovation
Part of the Edinburgh & South East Scotland City Region Deal

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# Free online course on AlphaSimR

edX platform

https://www.edx.org/learn/animal-breeding/the-university-of-edinburgh-breeding-programme-modelling-with-alphasimr

5 weeks (~20+ hours)

1. The big question
2. Simulation of DNA and phenotypes
3. DNA lottery
4. Selection
5. Breeding programme

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# Conceptual model of phenotypic values

Learning objectives

- Understanding how some types of variation in DNA looks like and how we work with that variation in computers (allele dosages)
- Connect variation in DNA and environment with the variation in phenotypic values
- Familiarise with the processes of mutation, recombination, segregation of DNA within pedigrees that give rise to DNA lottery
- Train common vector & matrix operations in R