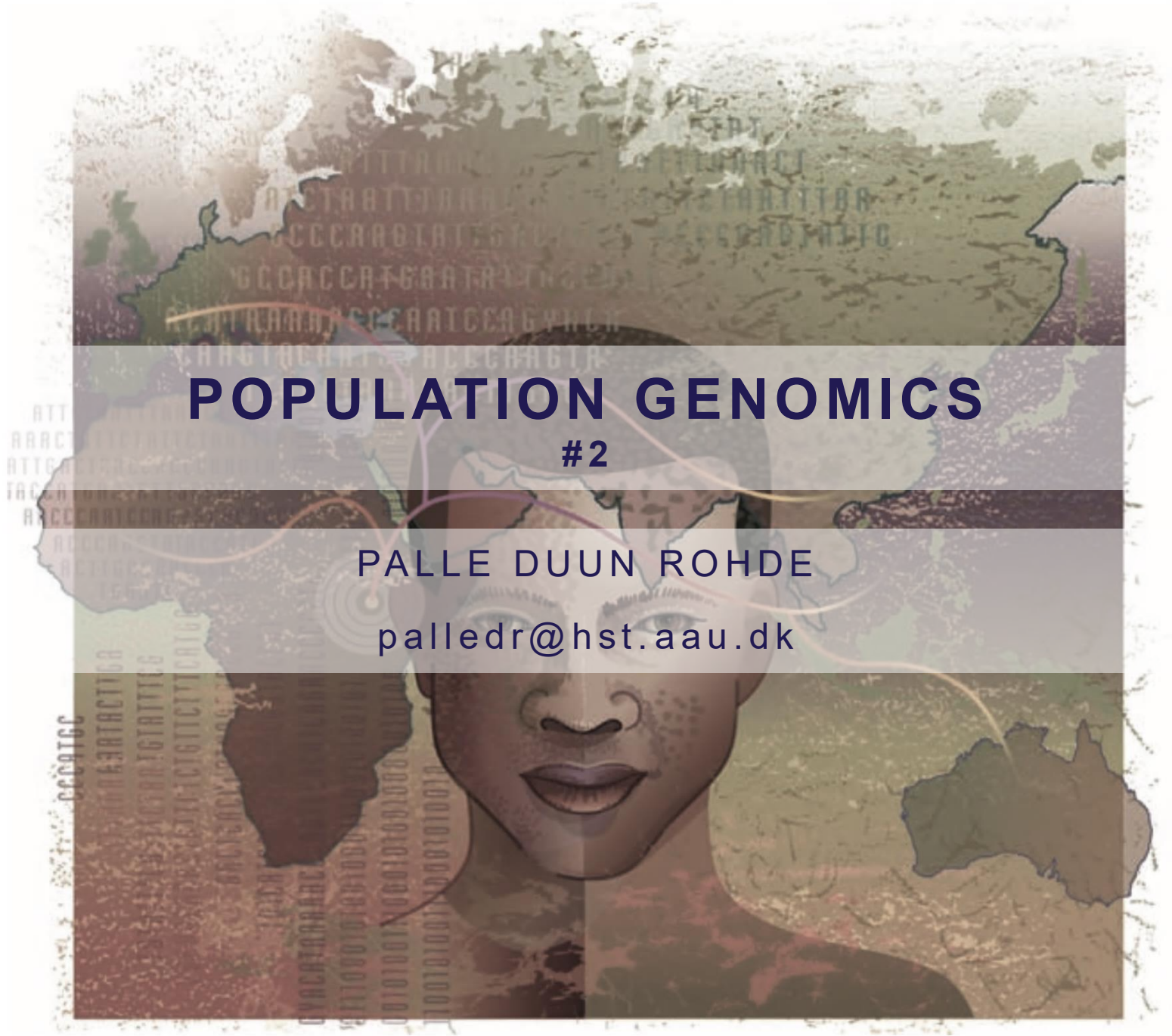


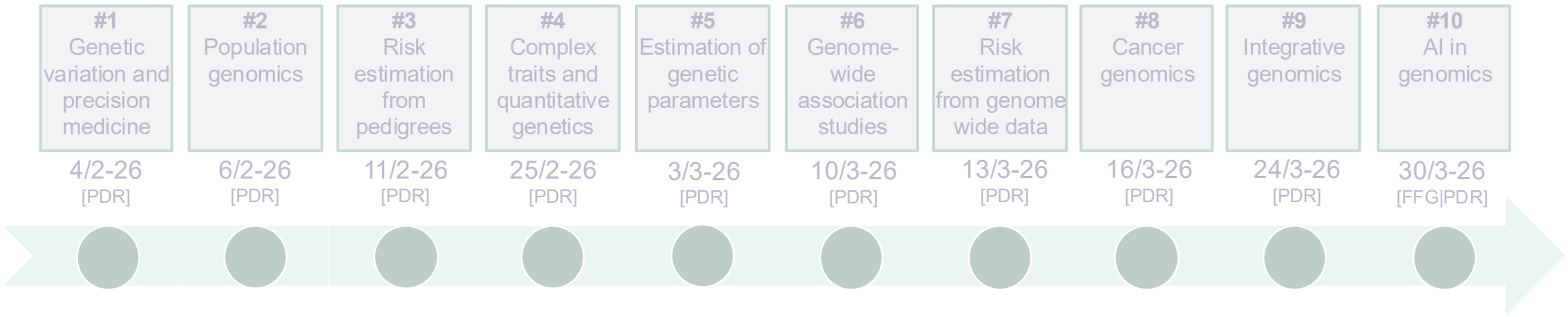
POPULATION GENOMICS

#2

PALLE DUUN ROHDE

palledr@hst.aau.dk

LETS GET STARTED



POPULATION GENOMICS

Today we will talk about

- Allele and genotype frequencies
- Hardy-Weinberg proportions
- Forces affecting genetic variation

OUTLINE

12:30 – 13:00	Recap + Exercise Answers
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The remaining exercises are also curriculum; thus, you must do them on your own.

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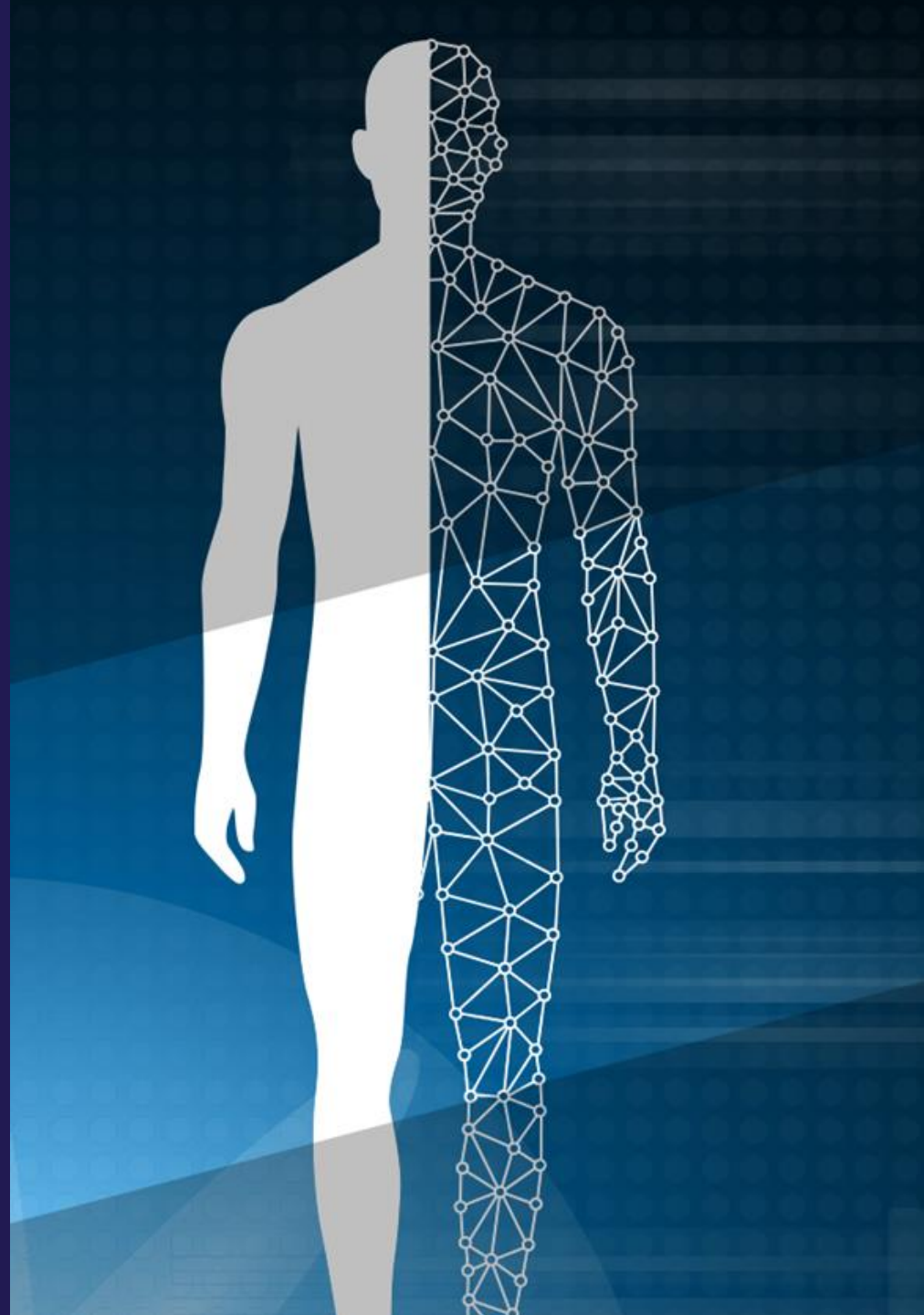
SHORT RECAP FROM LAST

- Precision medicine
- Genetic variation



WHAT IS PRECISION MEDICINE?

Evidence based medicine

Personalised medicine

Precision medicine

Genomic medicine

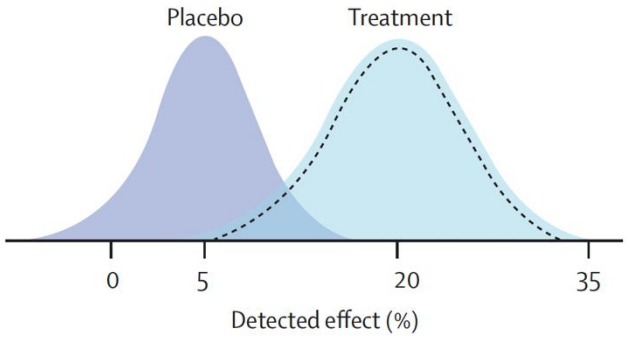
Individualised medicine

IMPLEMENTATION OF PRECISION MEDICINE

EPPOS [evidence-based precision personalised objective subjective]

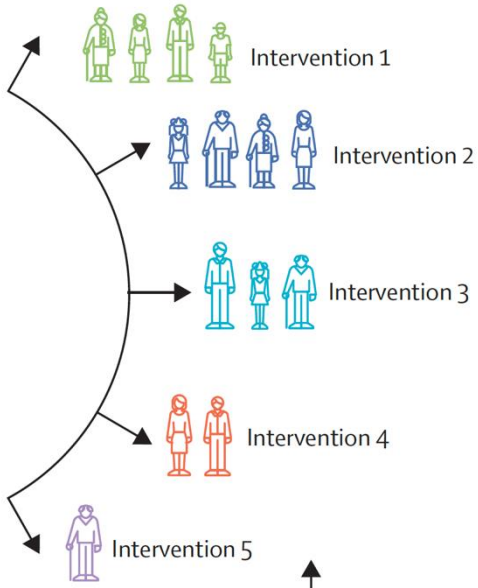
Evidence-based Medicine

(1) Contemporary evidence-based medicine
Estimate average risk or response using epidemiological and clinical trial cohorts



Precision Medicine

(2) Probability scoring and stratification
Maximise response and minimise risk using subclassification

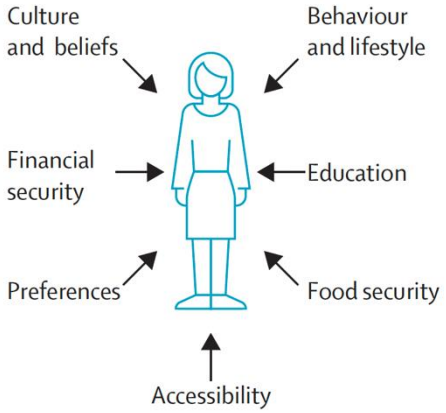


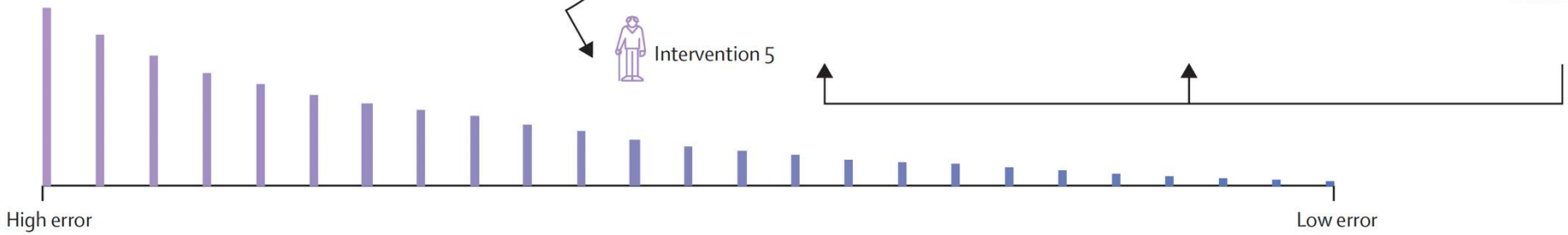
Personalised Medicine

(3) Personalisation (objective)
Monitor response to optimise dose, timing, and delivery

Individualised Medicine

(4) Personalisation (subjective)
Adapt intervention to fit the person's needs, capabilities, and preferences





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The Novo Nordisk Foundation, Precision medicine for cardiometabolic disease 2022

Franks et al, 2023, Lancet Diabetes Endocrinol; 11: 822–35

WHY PRECISION MEDICINE?

Because people are different

→ different disease risk

→ respond differently to medication

→ different side effects

Diagnostics, prognosis, treatment

FOCUS ON GENOMICS IN PRECISION MEDICINE

1) DNA is the *Blueprint* – identical from cradle-to-grave

2) Driven by *technological development*

3) One way causation [sickle cell disease]

4) A genetic test early in life have the potential to guide people

5) Other ‘omics also captures “environmental exposures”

GENETIC DIVERISTY

Human evolution is driven by several different (evolutionary) factors

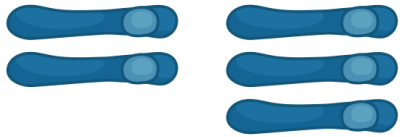
- Genetic mutations
- Migration
- Natural selection
- Genetic drift

The product is genetic diversity within a population.

Understanding the genetic diversity and how it has arisen is a necessary precursor to understand the genetics of complex traits.

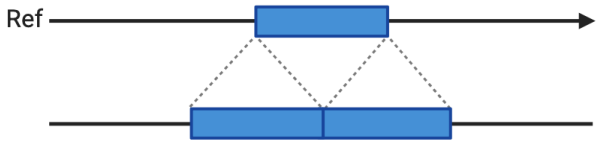
GENETIC VARIATION AT DIFFERENT RESOLUTION

Chromosome abnormality



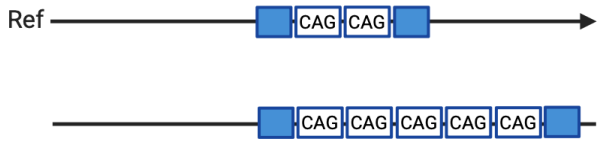
~Chromosome size

Copy number variants



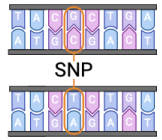
1000 - chromosome

Tandem repeats



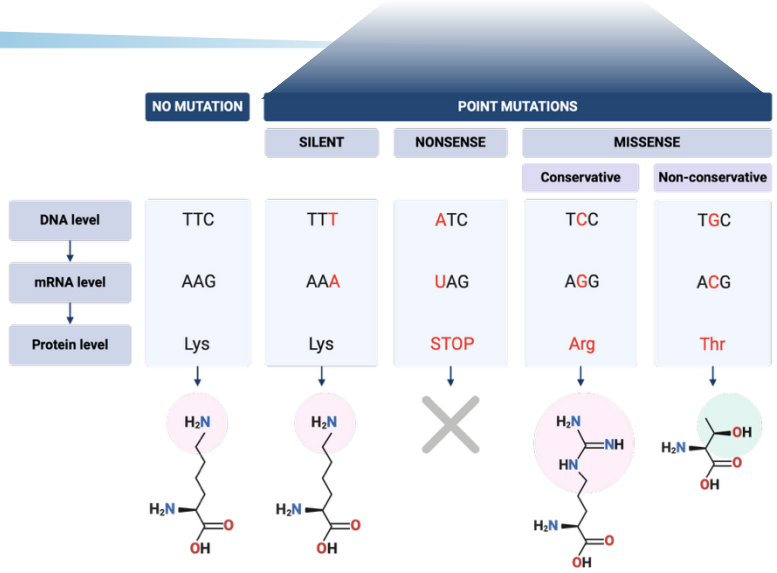
2-5 | 15-100 base pairs

Single nucleotide polymorphism (SNP)



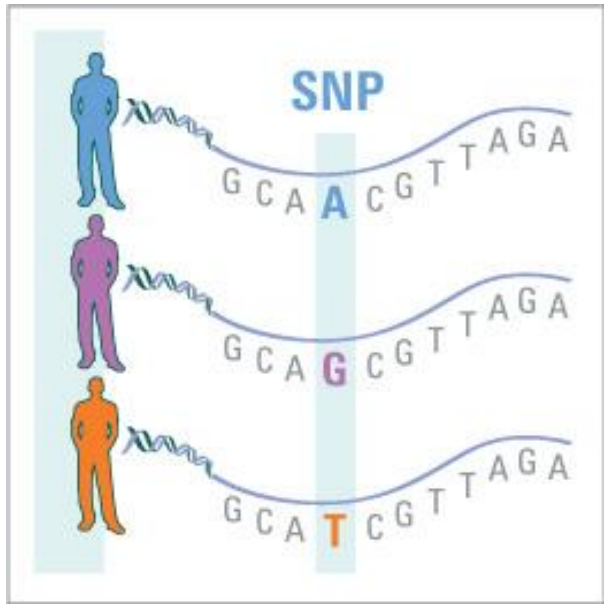
1 base pair

Size of the genetic variant



GENETIC VARIATION

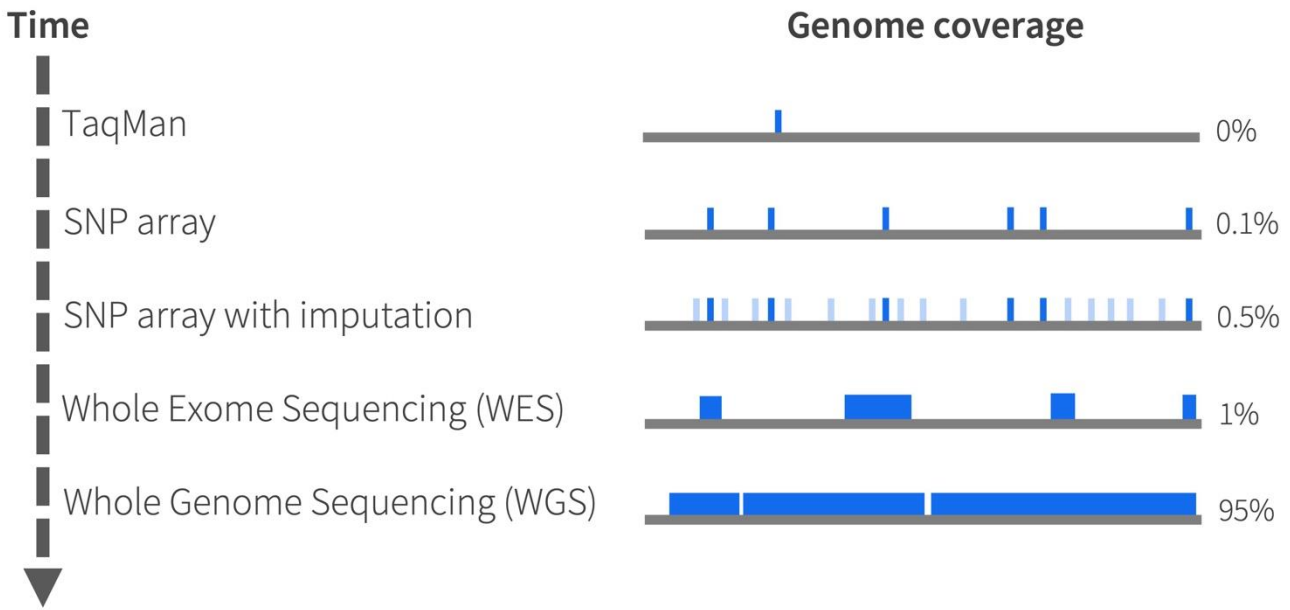
SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)

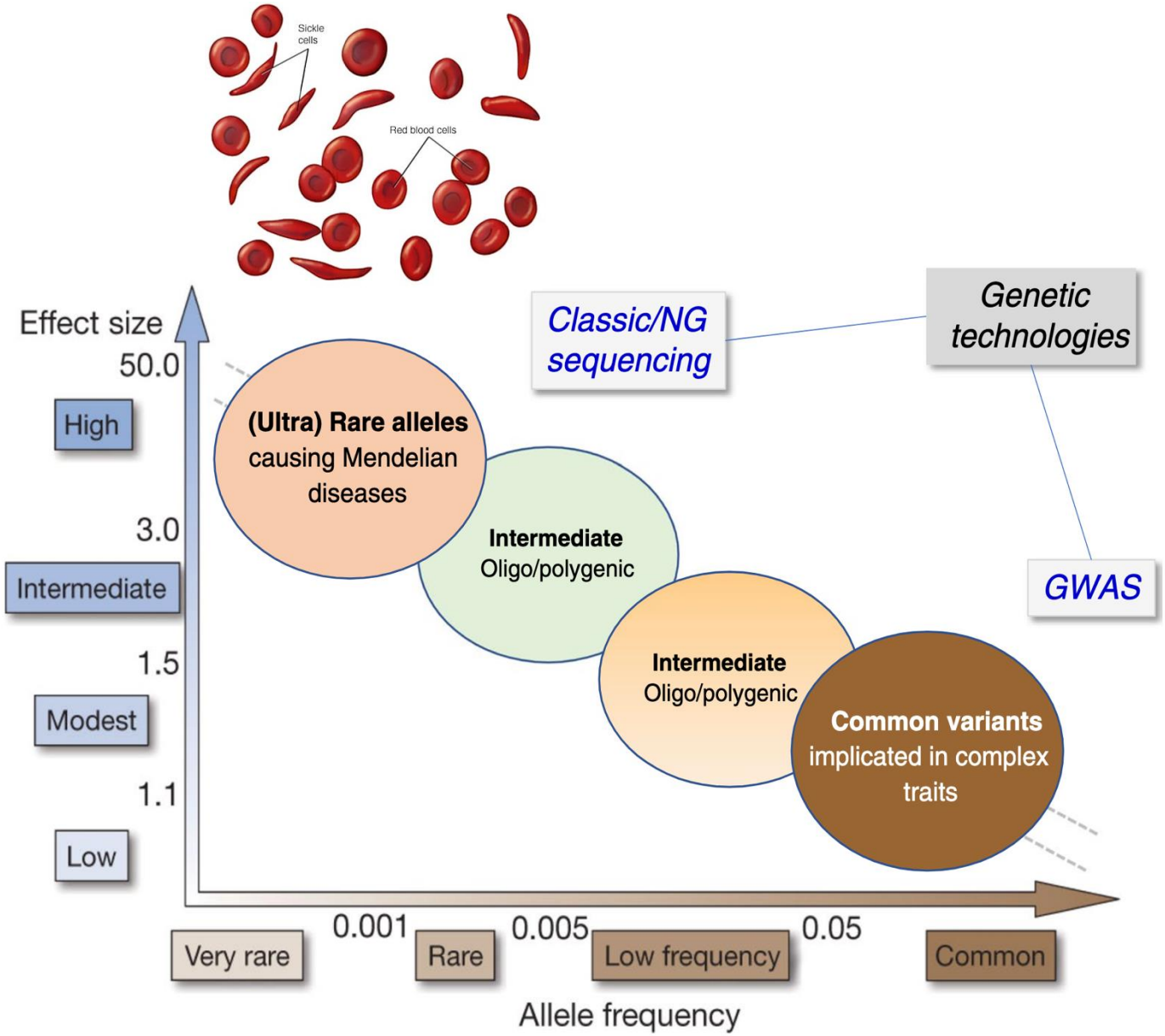


Variation in the human genome

~3 billion base pairs

~90 million variants





Devuyst et al European Journal of Physiology (2022) 474:771-781

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POPULATION GENOMICS

The study of the distribution of hereditary variation across time and space in species and populations [Bugge, F. 2008]

WHY IS POPULATION GENETICS IMPORTANT?

Population genomics tackles questions about genetic diversity

0.08% of nucleotide base pair in human DNA vary among individuals

Humans and orangutans are ~97% similar

Why this little genetic diversity?

- Selection favour functionally different DNA alleles in different circumstances
- DNA variation is tolerated when the alleles of a gene are functionally equivalent

The **aim of population genomics** is to model the dynamics of **evolutionary change within and between populations**.

THE FOUR FORCES

Mutation Copying errors during DNA replication, which introduce new alleles into the population

Natural selection differential transmission of alleles into the next generation due to the consequences of functional differences on an individual's survival and reproductive success

Genetic drift differential transmission of alleles into the next generation as a result of random sampling, and has the greatest potential impact in small populations

Gene flow spreads alleles from one population into another via migration, making them more genetically similar to each other, and countering genetic differentiation by drift

SIGNIFI
FORCES

NORMAL β-GLOBIN

DNA..... TGA

mRNA..... ACU

Amino acid..... – Thr

4

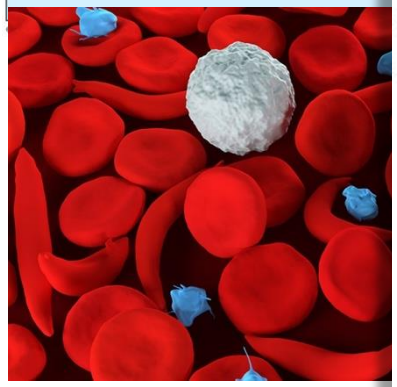
MUTANT β-GLOBIN

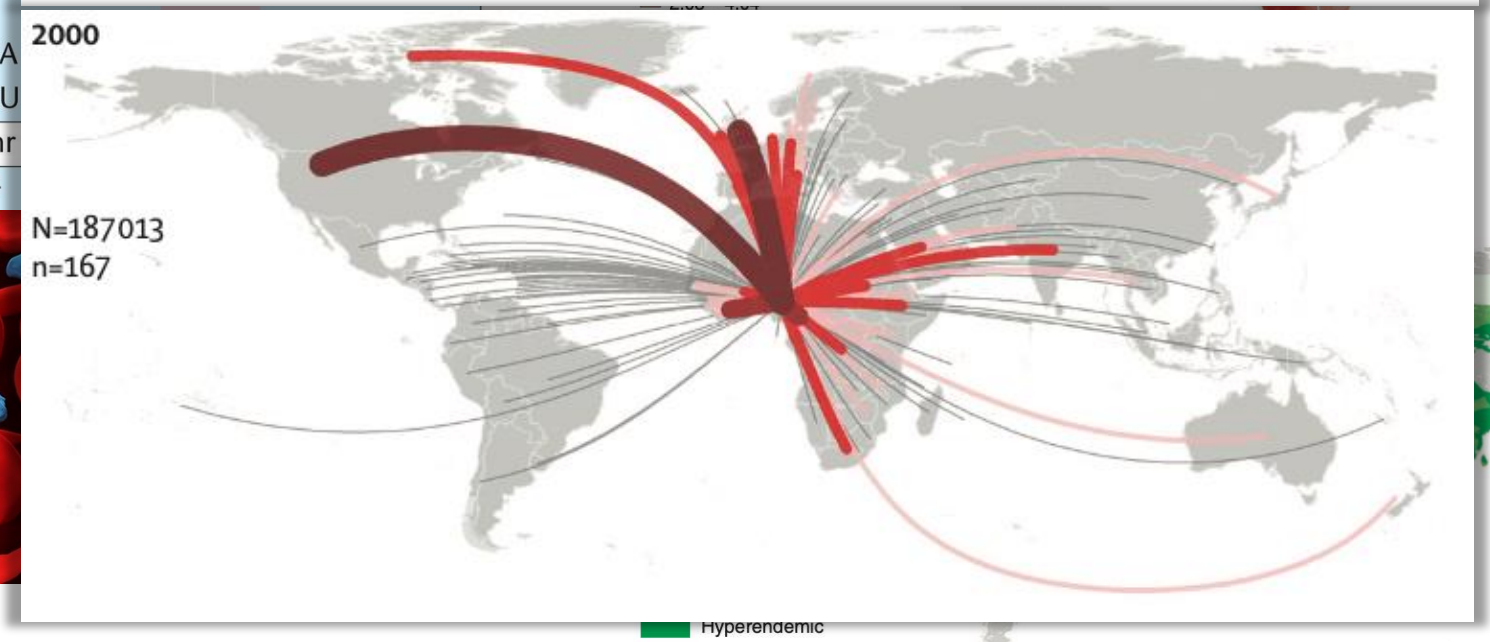
DNA..... TGA

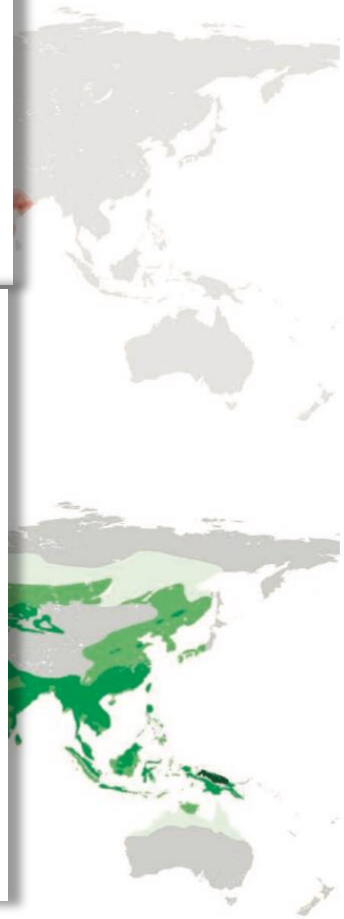
mRNA..... ACU

Amino acid..... – Thr

4







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GENETIC VARIATION IN A SINGLE LOCUS

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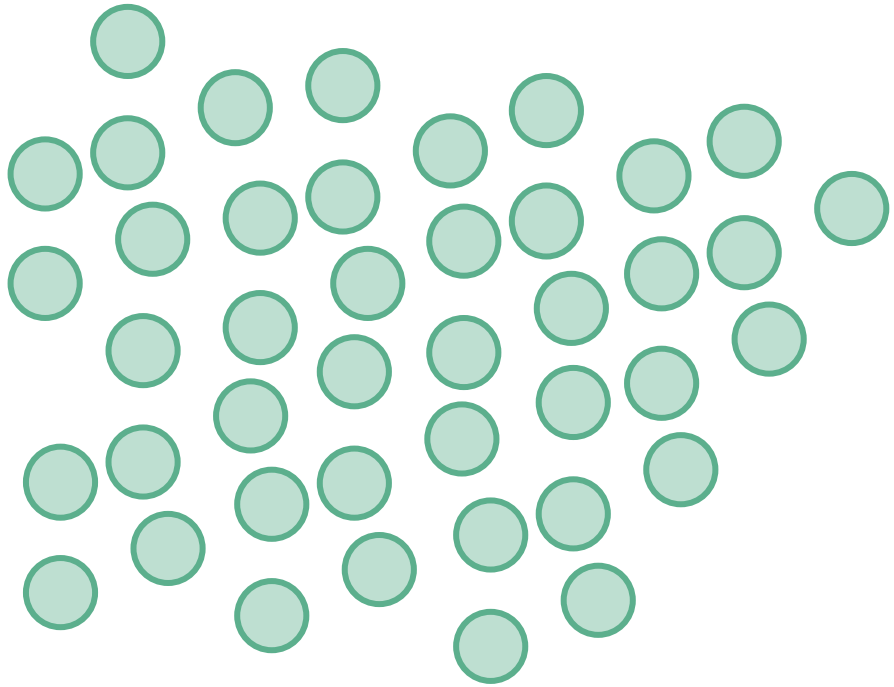
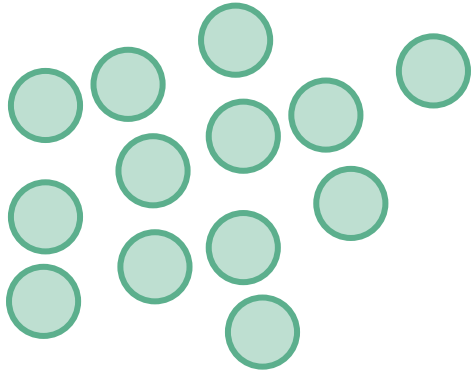
GENETIC VARIATION

IN A SINGLE LOCUS



A diploid (2*n* alleles) population

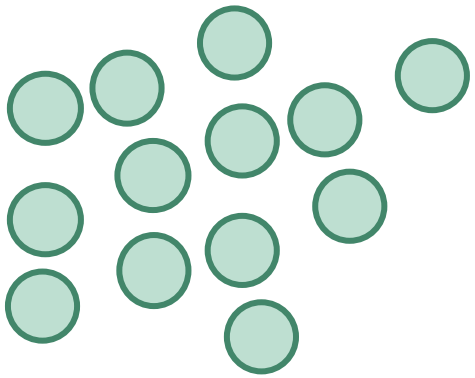
Random sampling



A random sample of individuals of whom we know the genotype of in a single locus

GENETIC VARIATION

IN A SINGLE LOCUS



A random sample of individuals of whom we know the genotype of in a single locus

Co-dominant (i.e., we can observe both alleles in heterozygote individuals).

The population is polymorph in one autosomal locus with the alleles **A** and **a**, and three genotypes, **AA**, **Aa** and **aa**.

The frequencies of the alleles are denoted **p** and **q**, and the frequency of the genotypes are P_{AA}, P_{Aa} and P_{aa}.

Note! There is a difference between $\hat{\mathbf{p}}$ and $\mathbf{p}$. The hat ($\widehat{\ }$) indicates that it is an estimate ($\hat{\mathbf{p}}$) over the true parameter ($\mathbf{p}$). For simplicity we ignore $\widehat{\ }$.

FREQUENCIES

Genotype	AA	Aa	aa	Σ
Count	n_{AA}	n_{Aa}	n_{aa}	N
Genotype frequency	n_{AA}/N	n_{Aa}/N	n_{aa}/N	1

Allele frequency of A: $p = (2 \times n_{AA} + n_{Aa})/2 \times N$

Allele frequency of a: $q = (2 \times n_{aa} + n_{Aa})/2 \times N$

We are counting the alleles

Check! $p + q = 1$

All alleles are counted

EXAMPLE

MN blod group system is controled by one locus with two co-dominante alleles L^M og L^N.

Genotype	**MM**	**MN**	**NN**	**Σ**
Count	64	120	16	200
Genotype frequency	$64/200 = 0.32$	$120/200 = 0.6$	$16/200 = 0.08$	1

Allele frequency of M: $p = (2 \times n_{MM} + n_{MN})/2 \times N = \frac{(2\times64+120)}{(2\times200)} = 0.62$

Allele frequency of N: $q = (2 \times n_{NN} + n_{Mn})/2 \times N = \frac{(2\times16+120)}{(2\times200)} = 0.38$

Check $p + q = 0.62 + 0.38 = 1$

YOUR TURN

In a random sample of 100 individuals, we observe whether they can roll their tongue or not.

R = can roll tongue
r = cannot roll tongue

Genotype	**RR**	**Rr**	**rr**
Count	49	42	9

What is the frequency of the R allele?

YOUR TURN

In a random sample of 100 individuals, we observe whether they can roll their tongue or not.

R = can roll tongue
r = cannot roll tongue

Genotype	**RR**	**Rr**	**rr**
Count	49	42	9

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HARDY-WEINBERG LAW

So far, we have computed allele frequencies by counting genotypes

Genotype frequencies → Allele frequencies

Under certain conditions, we can compute genotype frequencies in the next generation

Allele frequencies→ Genotype frequencies

However, that requires some assumptions.

THE NEUTRAL POPULATION

- Random mating
- No selection
- No genetic drift (infinite population size)
- No migration
- No mutation

Hardy-Weinberg principal describes the relationship allele- and genotype frequencies in the neutral population

HARDY-WEINBERG LAW

Known population parameters

AA	Aa	aa
P_{AA}	P_{Aa}	P_{aa}

What is the frequency in the next generation?

Using HW priciple

		Males		
		AA	Aa	aa
Females	AA	P_{AA}^2	$P_{AA}P_{Aa}$	$P_{AA}P_{aa}$
	Aa	$P_{Aa}P_{AA}$	P_{Aa}^2	$P_{Aa}P_{aa}$
	aa	$P_{aa}P_{AA}$	$P_{aa}P_{Aa}$	P_{aa}^2

HARDY-WEINBERG EQUILIBRIUM

		Genotypes of offspring		
Parental combinations	**Frequency**	**AA**	**Aa**	**aa**
AA x AA	P_{AA}^2	P_{AA}^2		
AA x Aa	$2 \times P_{AA} P_{Aa}$	$P_{AA} P_{Aa}$	$P_{AA} P_{Aa}$	
AA x aa	$2 \times P_{AA} P_{aa}$		$2 \times P_{AA} P_{aa}$	
Aa x Aa	P_{Aa}^2	$1/4\, P_{Aa}^2$	$1/2\, P_{Aa}^2$	$1/4\, P_{Aa}^2$
Aa x aa	$2 \times P_{Aa} P_{aa}$		$P_{Aa} P_{aa}$	$P_{Aa} P_{aa}$
Aa x aa	P_{aa}^2			P_{aa}^2

	A	**a**
A	AA	Aa
A	AA	Aa

	A	**a**
A	AA	Aa
a	Aa	aa

HARDY-WEINBERG EQUILIBRIUM

		Genotypes of offspring		
Parental combinations	**Frequency**	**AA**	**Aa**	**aa**
AA x AA	P_{AA}^2	P_{AA}^2		
AA x Aa	$2 \times P_{AA}P_{Aa}$	$P_{AA}P_{Aa}$	$P_{AA}P_{Aa}$	
AA x aa	$2 \times P_{AA}P_{aa}$		$2 \times P_{AA}P_{aa}$	
Aa x Aa	P_{Aa}^2	$1/4\,P_{Aa}^2$	$1/2\,P_{Aa}^2$	$1/4\,P_{Aa}^2$
Aa x aa	$2 \times P_{Aa}P_{aa}$		$P_{Aa}P_{aa}$	$P_{Aa}P_{aa}$
Aa x aa	P_{aa}^2			P_{aa}^2

$$\sum AA = P_{AA}^2 + P_{AA}P_{Aa} + 1/4\,P_{Aa}^2$$
$$= (P_{AA} + 1/2P_{Aa})^2 = p^2$$

$$\sum aa = P_{aa}^2 + P_{aa}P_{Aa} + 1/4\,P_{Aa}^2$$
$$= (P_{aa} + 1/2P_{Aa})^2 = q^2$$

$$\sum Aa = P_{AA}P_{Aa} + 2P_{AA}P_{aa} + 1/2\,P_{Aa}^2 + P_{Aa}P_{aa}$$
$$= 2(P_{AA} + 1/2P_{Aa})(P_{aa} + 1/2P_{Aa})$$
$$= 2pq$$

$$p = \frac{2N_{AA} + N_{Aa}}{2N} = \frac{N_{AA} + 1/2N_{Aa}}{N} = P_{AA} + 1/2P_{Aa}$$

$$q = \frac{2N_{aa} + N_{Aa}}{2N} = \frac{N_{aa} + 1/2N_{Aa}}{N} = P_{aa} + 1/2P_{Aa}$$

HARDY-WEINBERG EQUILIBRIUM

After one generation under HW assumptions the genotype frequencies will be in equilibrium:

Genotype	AA	Aa	aa
Frequency	p^2	$2pq$	q^2

Allele frequencies do not change!

		Males	
		A (p)	**a (q)**
Females	**A (p)**	p^2	pq
	a (q)	pq	q^2

TESTING H-W PROPORTIONS

Genotype	**AA**	**Aa**	**aa**
Observed	$\mathrm{N_{AA}}$	$\mathrm{N_{Aa}}$	$\mathrm{N_{aa}}$
Expected	$\mathrm{E_{AA}} = \mathrm{p^2N}$	$\mathrm{E_{Aa}} = \mathrm{2pqN}$	$\mathrm{E_{aa}} = \mathrm{q^2N}$

$$\chi^2 = \frac{(\mathrm{N_{AA}} - \mathrm{E_{AA}})^2}{\mathrm{E_{AA}}} + \frac{(\mathrm{N_{Aa}} - \mathrm{E_{Aa}})^2}{\mathrm{E_{Aa}}} + \frac{(\mathrm{N_{aa}} - \mathrm{E_{aa}})^2}{\mathrm{E_{aa}}}$$

General ≥ 2 alleles

$$\chi^2 = \sum_{i=1}^{m} \frac{(Obs - Exp)^2}{Exp}$$

P-value is obtained from χ^2-distribution and degrees of freedom (df):

$df = \frac{n(n-1)}{2}$, *n*= number of alleles

EXAMPLE

HIV-1

HIV-1 is the virus giving AIDS.
Being homozygote for the *CCR5* mutation Δ32 protects against HIV-1 virus, whereas heterozygotes are susceptible, and the disease progress slowly.

Genotype	**1/1**	**1/Δ32**	**Δ32/Δ32**	**Σ**
Observed	79	20	1	100
Expected	p^2N	$2pqN$	q^2N	N

Allele frequency of 1: $p = \frac{2\times79+20}{2\times100} = 0.89$

Allele frequency of Δ32 : $q = \frac{2\times1+20}{2\times100} = 0.11$

Expected	$0.89^2 \times 100 = 79.21$	$2 \times 0.89 \times 0.11 \times 100 = 19.58$	$0.11^2 \times 100 = 1.21$	100

$$\chi^2 = \frac{(79-79.21)^2}{79.21} + \frac{(20-19.58)^2}{19.58} + \frac{(1-1.21)^2}{1.21} = 0.046$$

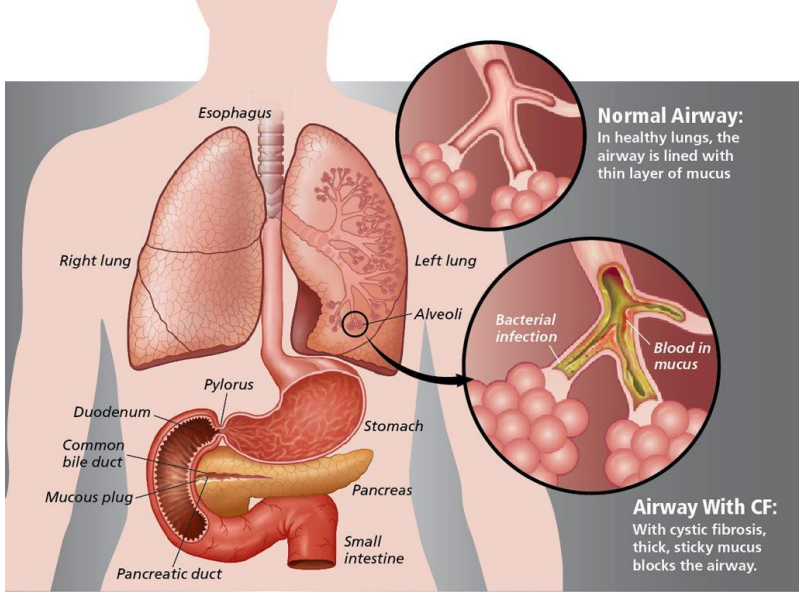
This population is in HW proportions

EXAMPLE

HIV-1

```
> NAA <- 79
> NAa <- 20
> Naa <- 1
> N <- NAA+NAa+Naa
>
> p <- (2*NAA+NAa)/(2*N)
> q <- (2*Naa+NAa)/(2*N)
>
> EAA <- p^2*N
> EAa <- 2*p*q*N
> Eaa <- q^2*N
>
> X <- (NAA-EAA)^2/EAA + (NAa-EAa)^2/EAa + (Naa-Eaa)^2/Eaa
> pchisq(q=X, df=1, lower.tail=FALSE)
[1] 0.8301536
>
```

YOUR TURN



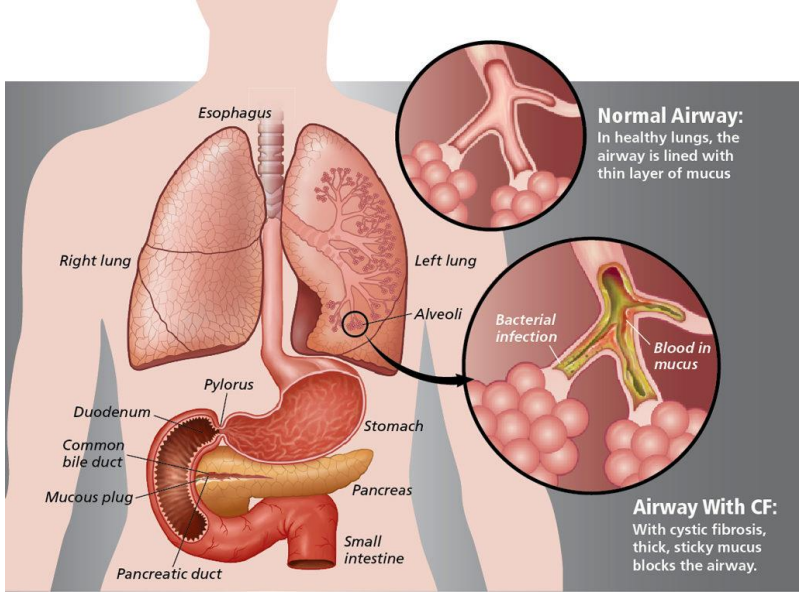
Cystic fibrosis (CF) is a hereditary autosomal recessive disease, that, among other things, affects the lungs causing chronic/frequent lung infections.

In Europe, the prevalence of children born with cystic fibrosis (CF) is approximately 1/2500.

What is the frequency of the CF-allele?

Assume Hardy-Weinberg proportions.

YOUR TURN



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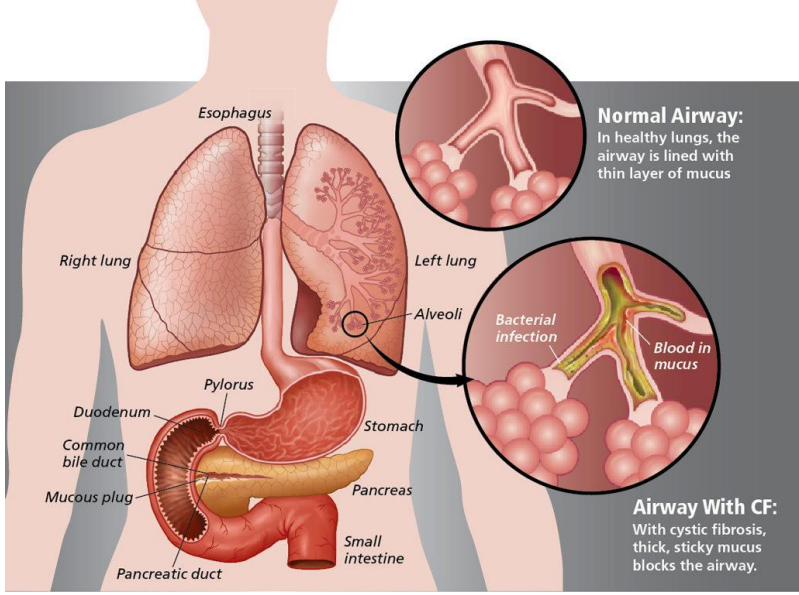

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In Europe, the prevalence of children born with cystic fibrosis (CF) is approximately 1/2500.

What is the frequency of healthy CF-carriers?

YOUR TURN AGAIN

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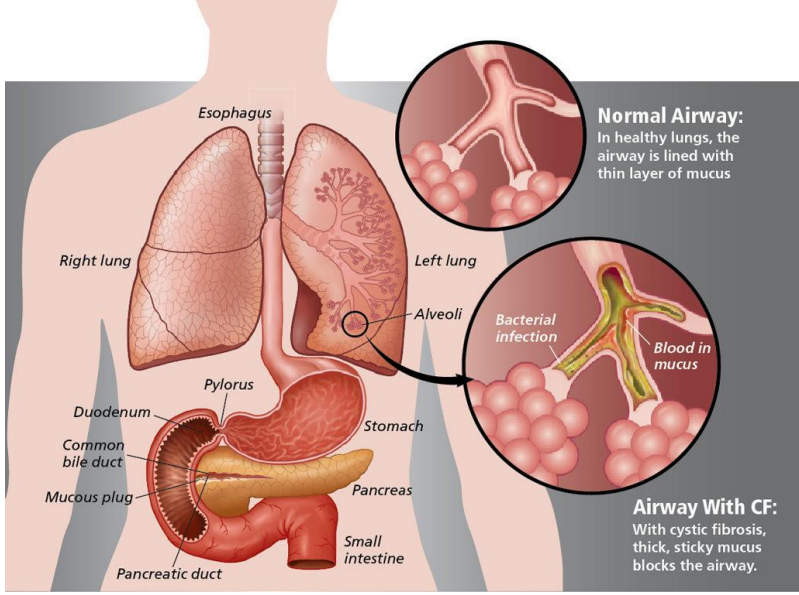


HARDY-WEINBERG PROPORTIONS

>2 ALLES

		Males		
		A_1 (p_1)	A_2 (p_2)	A_3 (p_3)
Females	A_1 (p_1)	A_1A_1 (p_1^2)	A_1A_2 (p_1p_2)	A_1A_3 (p_1p_3)
	A_2 (p_2)	A_2A_1 (p_2p_1)	A_2A_2 (p_2^2)	A_2A_3 (p_2p_3)
	A_3 (p_3)	A_3A_1 (p_3p_1)	A_3A_2 (p_3p_2)	A_3A_3 (p_3^2)

HARDY-WEINBERG PROPORTIONS

>2 ALLES

Genotype frequencies after random mating:

A_1A_1: p_1^2 $\quad$ A_1A_2: $2p_1p_2$
A_2A_2: p_2^2 $\quad$ A_1A_3: $2p_1p_3$
A_3A_3: p_3^2 $\quad$ A_2A_3: $2p_2p_3$

Allele frequencies after random mating:

$p_1(p_1+p_2+p_3)=p_1(p_1+(1-p_1-p_3)+p_3)$

$$p_1 = p_1^2 + 0.5 \times 2p_1p_2 + 0.5 \times 2p_1p_3 = p_1(p_1 + p_2 + p_3) = p_1$$
$$p_2 = p_2^2 + 0.5 \times 2p_1p_2 + 0.5 \times 2p_2p_3 = p_1(p_1 + p_2 + p_3) = p_2$$
$$p_3 = p_3^2 + 0.5 \times 2p_1p_3 + 0.5 \times 2p_2p_3 = p_1(p_1 + p_2 + p_3) = p_3$$

HARDY-WEINBERG PROPORTIONS

>2 ALLES

One locus with tre co-dominante alleles; A_1, A_2 og A_3

Genotypes	A_1A_1	A_1A_2	A_1A_3	A_2A_2	A_2A_3	A_3A_3	Σ
Observed	51	56	76	2	34	15	234

$$p_1 = \frac{2 \times 51 + 56 + 76}{2 \times 324} = 0.5$$

$$p_2 = \frac{2 \times 2 + 56 + 34}{2 \times 324} = 0.2$$

$$p_3 = \frac{2 \times 15 + 76 + 34}{2 \times 324} = 0.3$$

Expected	58.5	46.8	70.2	9.36	28.08	21.06	234

$$\chi^2 = \sum {}^{(\mathrm{Obs}-\mathrm{Exp})^2}/_{\mathrm{Exp}} = 12.028,\ \mathrm{df} = \frac{n(n-1)}{2} = \frac{3(3-1)}{2} = 3,\ p=0.0072$$

Deviation from HW proportions

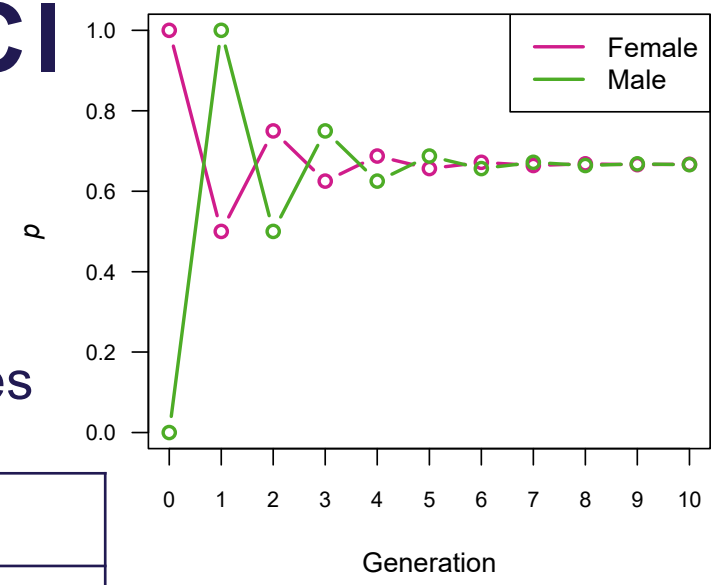
VARIATION IN SEX-LINKED LOCI

When allele frequencies are **THE SAME** between males and females

		Males		
		X_A (p)	X_a (q)	Y (1)
Females	X_A (p)	X_AX_A (p^2)	X_AX_a (pq)	X_AY (p)
	X_a (q)	X_aX_A (qp)	X_aX_a (q^2)	X_aY (q)

… then, the genotype frequency for males is the allele frequency.

VARIATION IN SEX-LINKED LOCI



When allele frequencies are **DIFFERENT** between males and females

		Males		
		X_A (p^m)	X_a (q^m)	Y (1)
Females	X_A (p^f)	X_AX_A (p^fp^m)	X_AX_a (p^fq^m)	X_AY (p^f)
	X_a (q^f)	X_aX_A (q^fp^m)	X_aX_a (q^fq^m)	X_aY (q^f)

At equlibrium: $p=(p^m+p^f)/3$

OUTLINE

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THE NEUTRAL POPULATION?

The **constancy of allele frequencies** from generation to generation only holds under the assumptions of HW-law.

- Random mating
- No selection
- No genetic drift (infinite population size)
- No migration
- No mutation

Does the neutral population exists

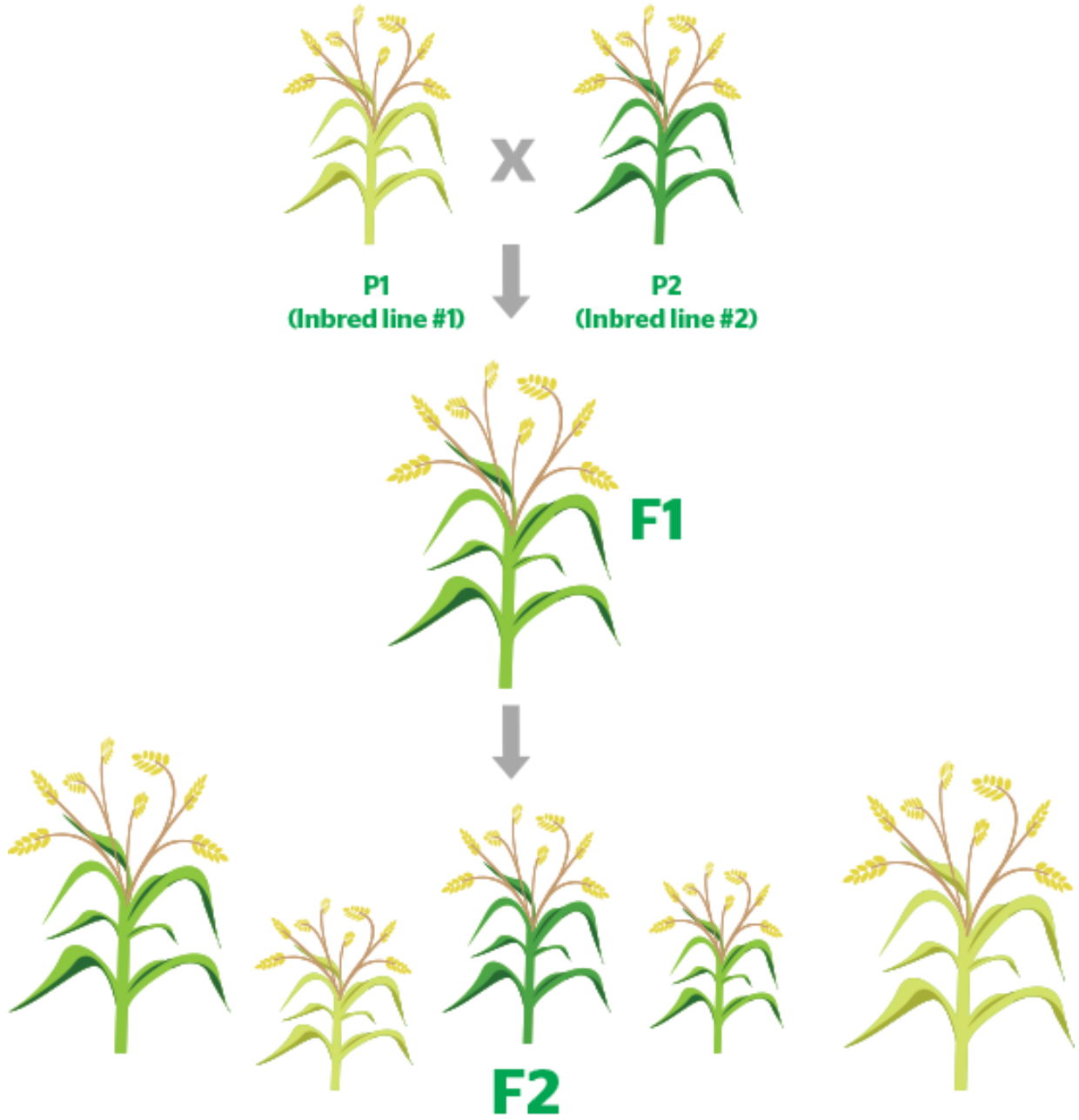
?

THE NEUTRAL POPULATION

- **Random mating**
- No selection
- No genetic drift (infinite population size)
- No migration
- No mutation

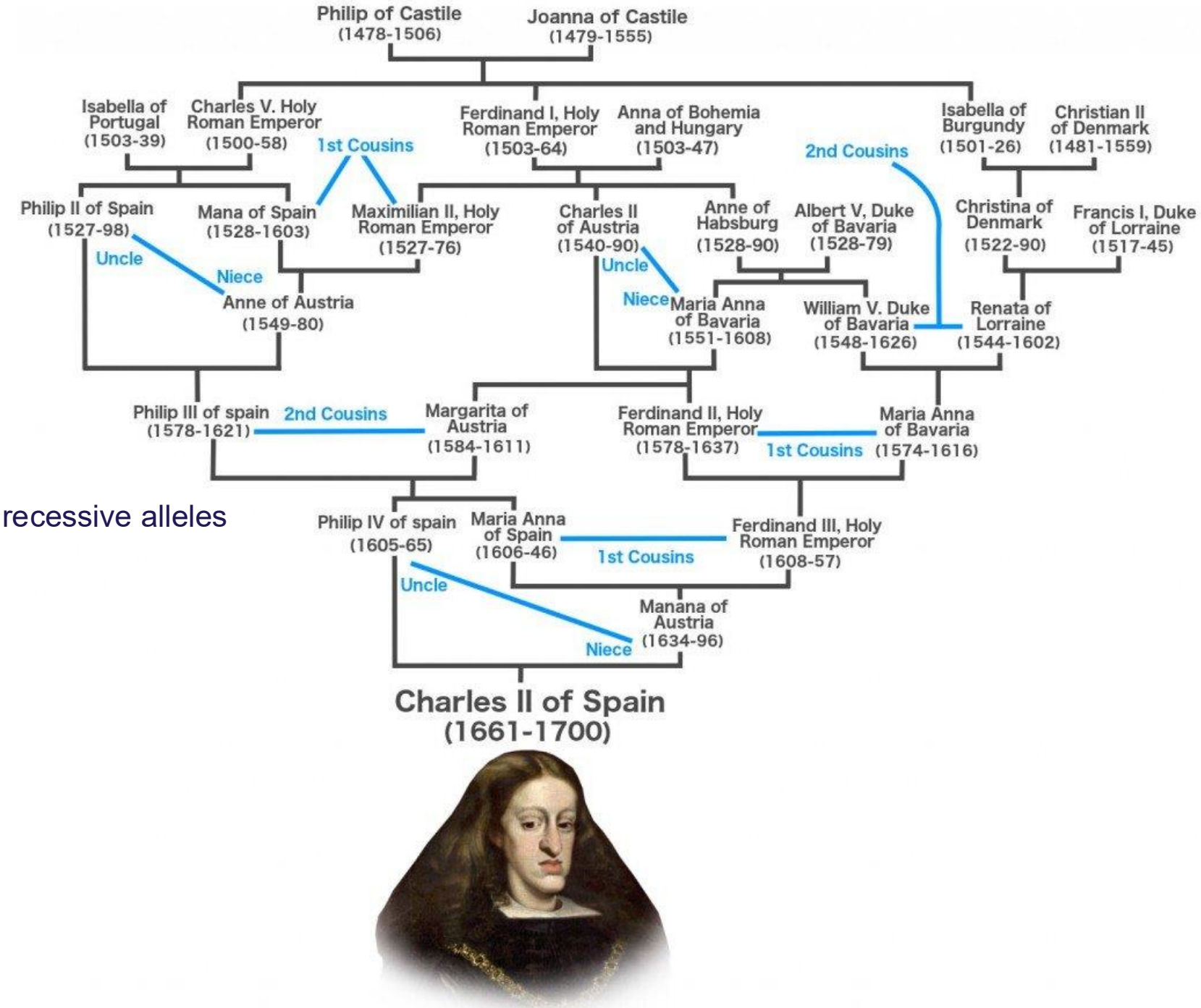
INBREEDING

- Mating between relatives
  - Heterosis | Hybrid vigor



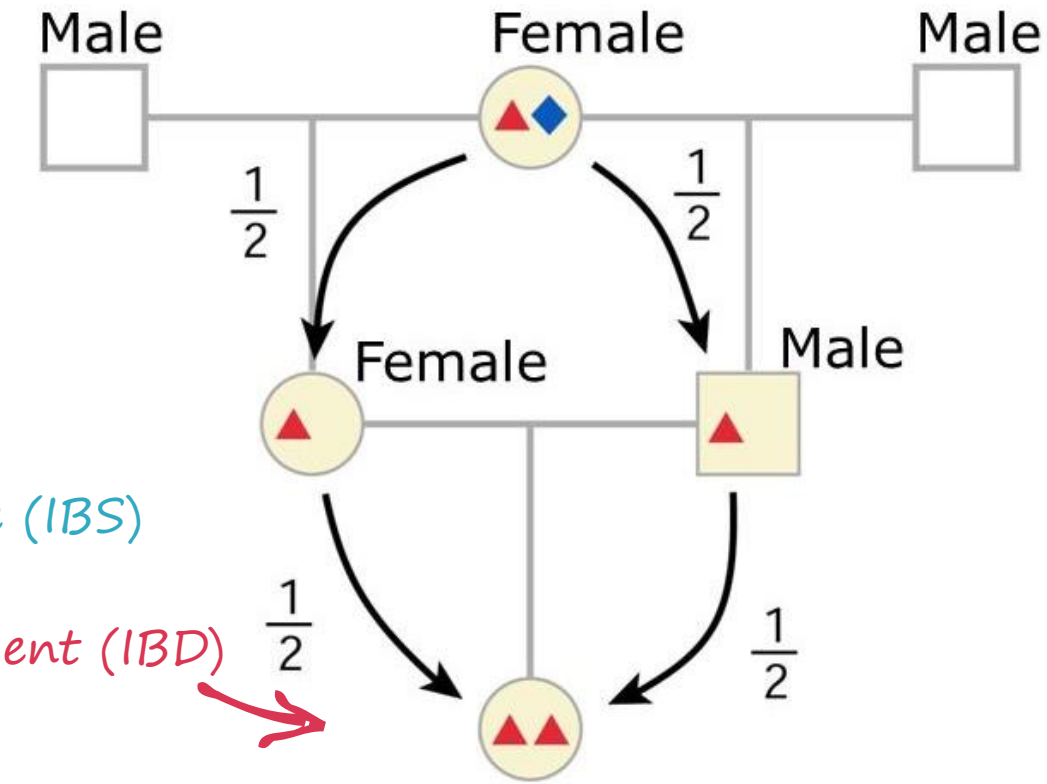
INBREEDING

- Mating between relatives
  - Heterosis | Hybrid vigor
  - Inbreeding depression
    - Accumulation of deleterious recessive alleles



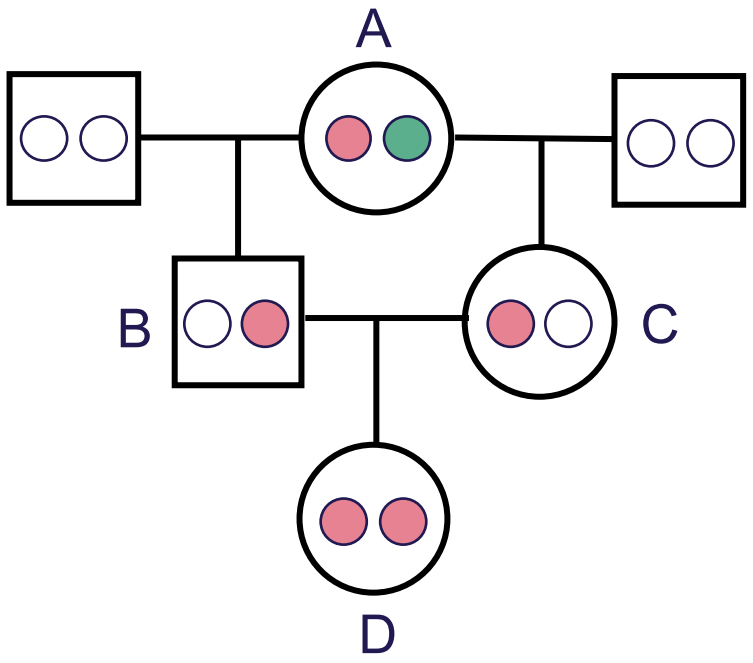
THE INBREEDING COEFFICIENT

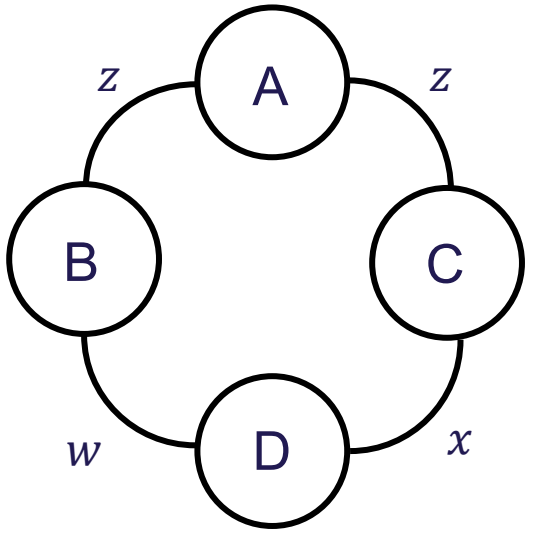
The inbreeding coefficient (F) is the probability that two alleles in an individual trace back to the same copy in a common ancestor.



Identical by state (IBS)
VS
Identical by descent (IBD)

THE INBREEDING COEFFICIENT





Follow the transmission of alleles.

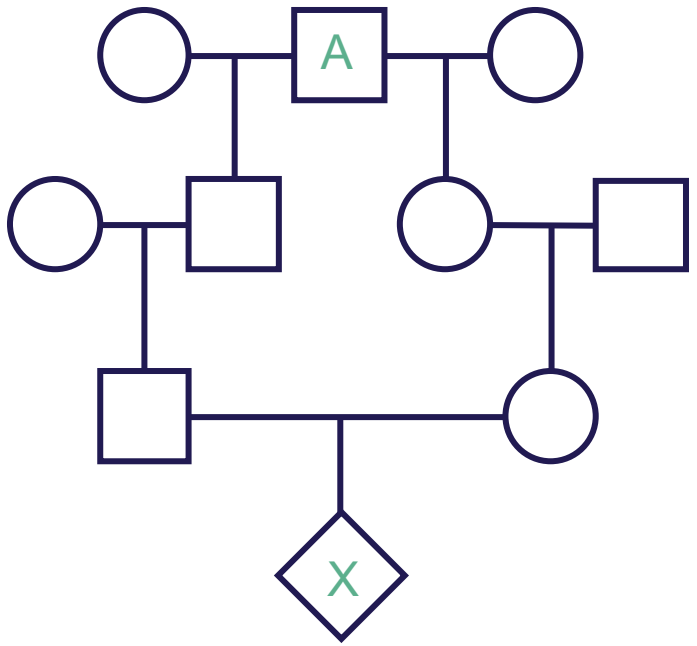
$$F_D = \left(\frac{1}{2}\right)^n (1 + F_A)$$

where n is the number of individuals in the loop without the individual we are computed F for.

$$F_D = \left(\frac{1}{2}\right)^3 (1 + F_A)$$

YOUR TURN

What is the inbreeding coefficient for individual X assuming individual A is not inbred ($F_A = 0$)?



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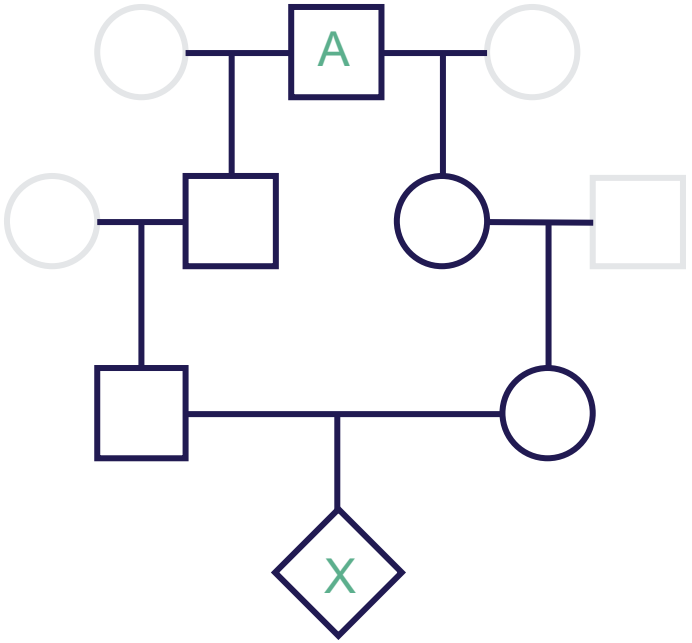
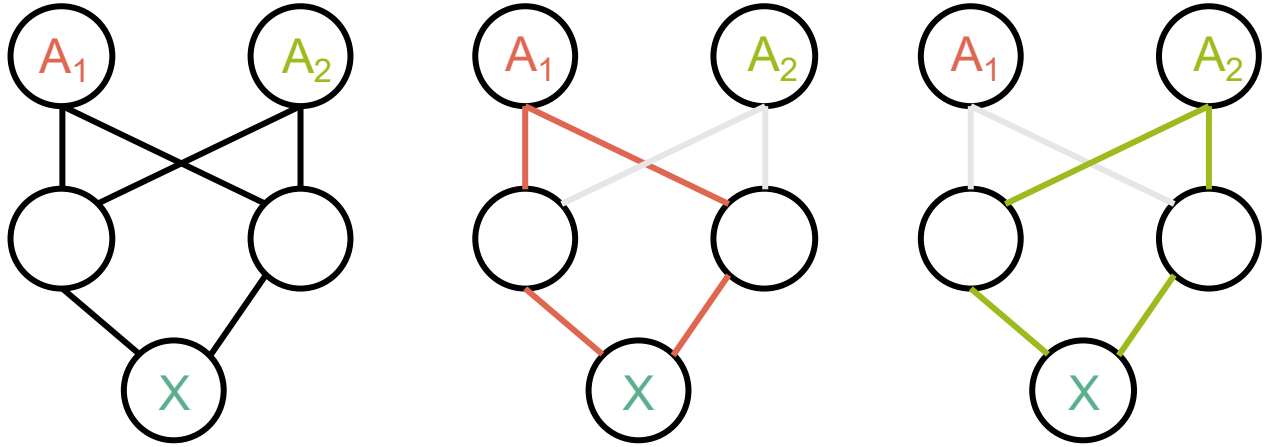


WHEN THERE ARE MULTIPLE ANCESTORS



Follow the transmission of alleles over multiple loops.

$$F_X = \sum_{loops} \left(\frac{1}{2}\right)^n (1 + F_A)$$

INBREEDING

CHANGES GENOTYPE FREQUENCIES

If the population is in HW proportions

Genotype	AA	Aa	aa
Frequency	p^2	$2pq$	q^2

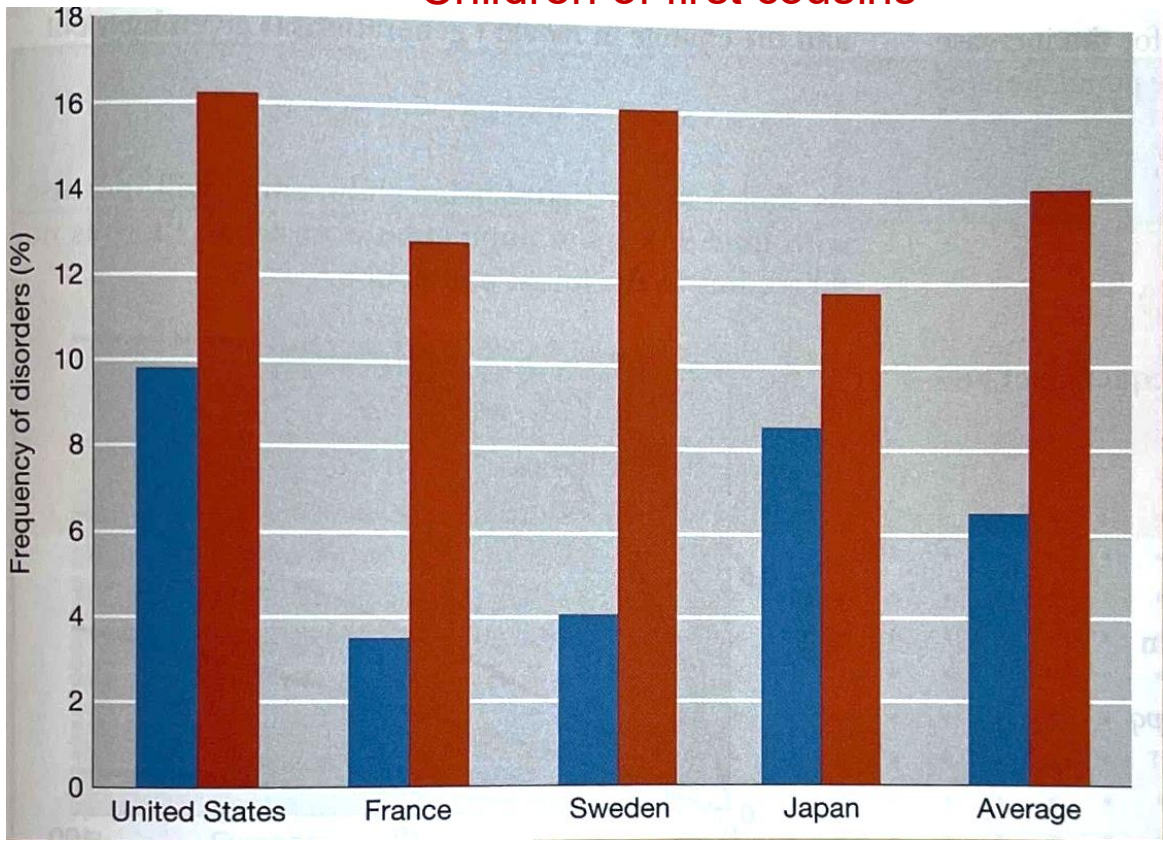
If there is inbreeding

Genotype	AA	Aa	aa
Frequency	p^2+pqF	$2pq-2pqF$	q^2+pqF

Results in excess in homozygotes

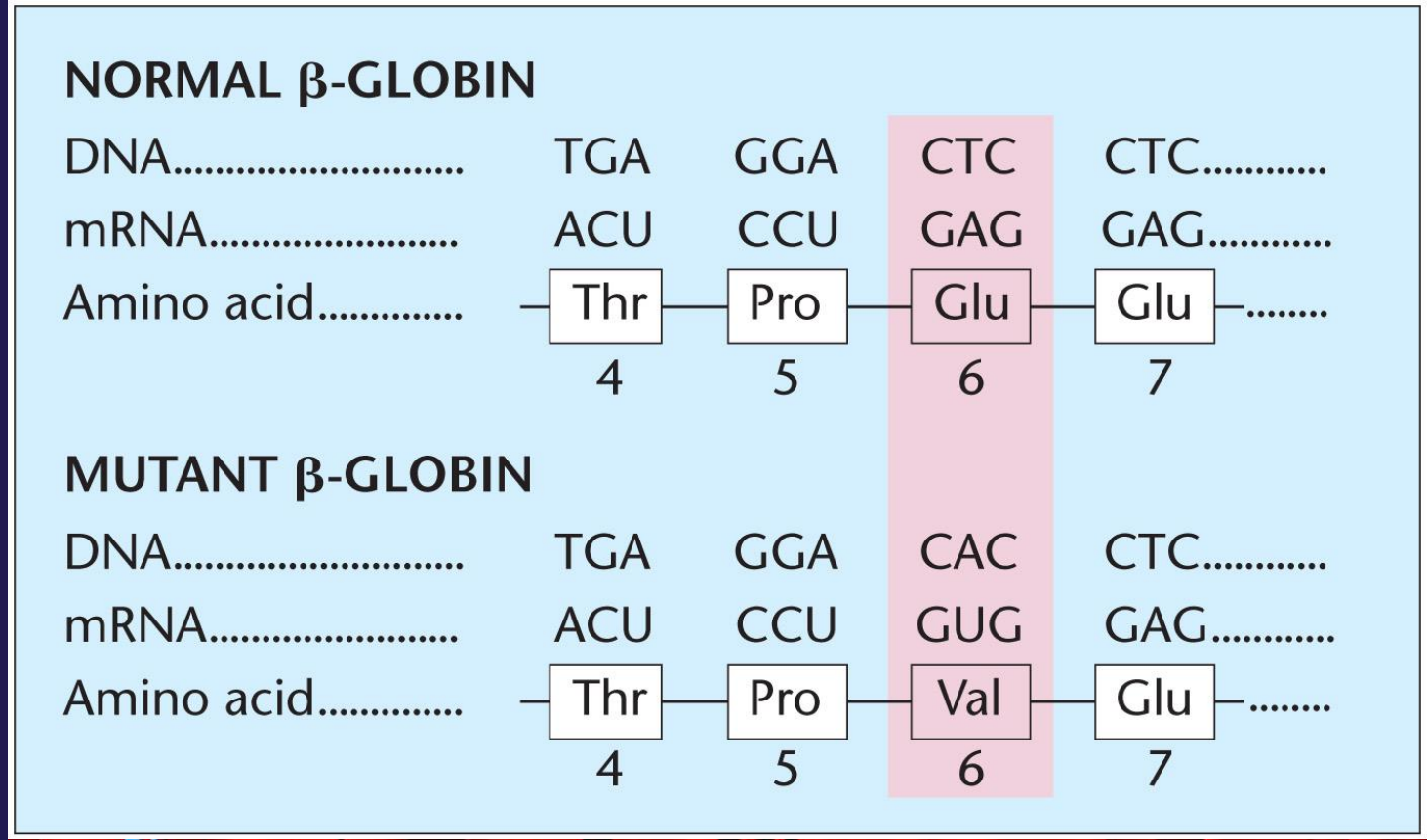
Children of unrelated parents

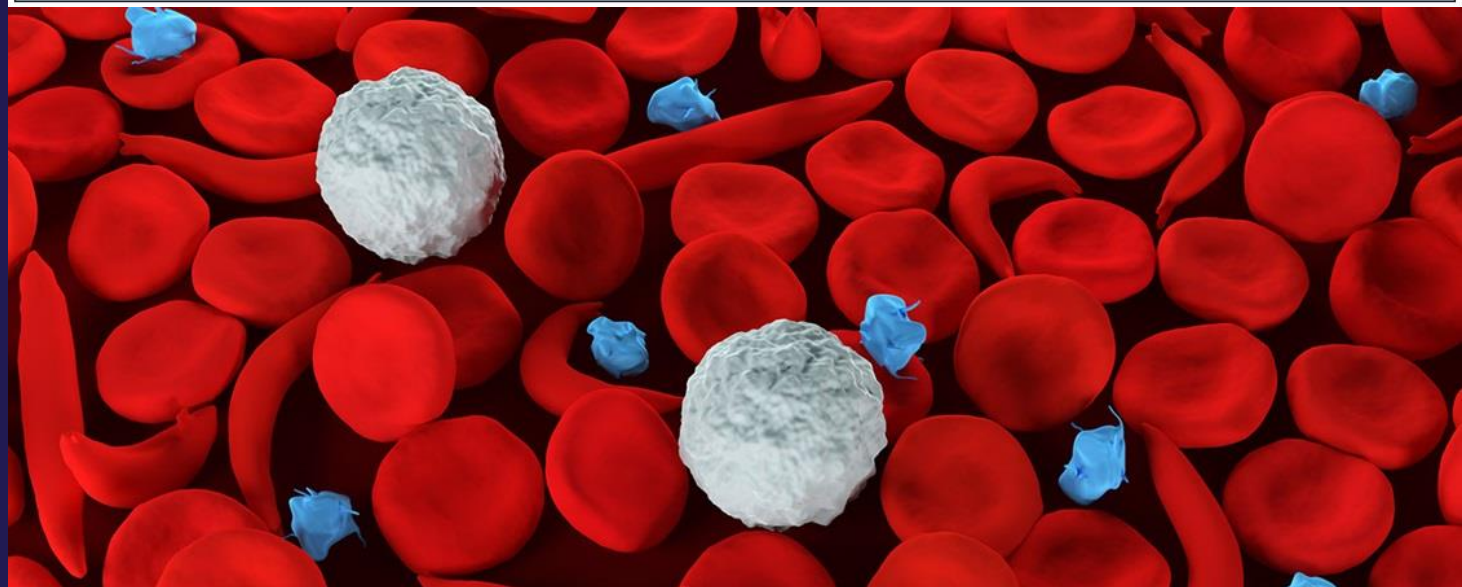
Children of first cousins



THE NEUTRAL POPULATION

- Random mating
- No selection
- No genetic drift (infinite population size)
- No migration
- **No mutation**





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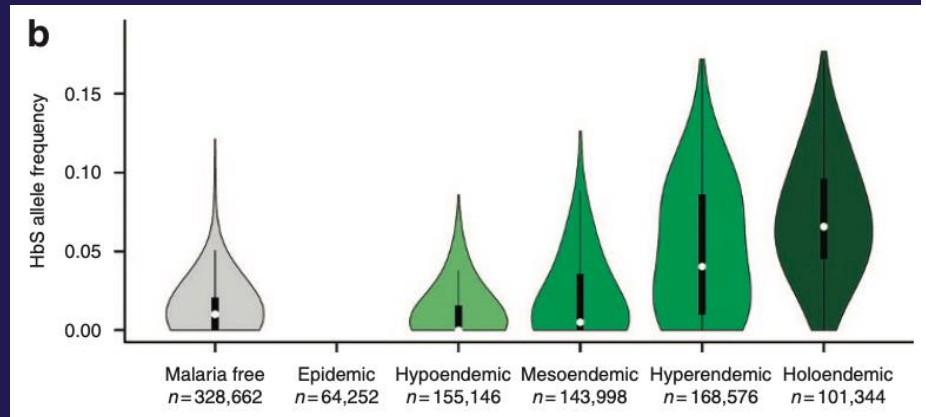
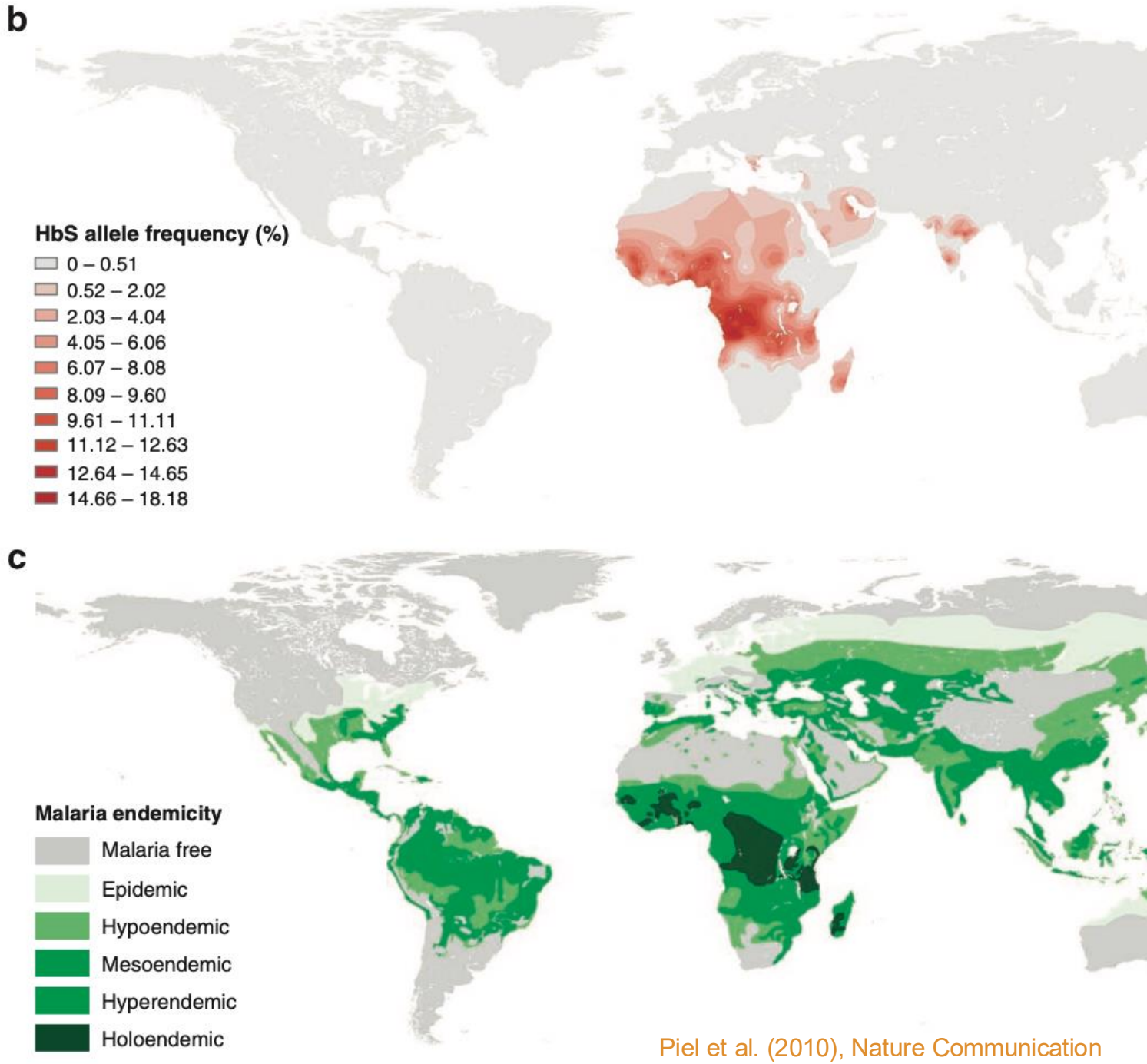




Piel et al. (2010), Nature Communication

MUTATION AND SELECTION $a^+ \xrightarrow{\mu} a$

Number wildtype alleles in a population of *2N* is $2Np$, which with the raten μ mutates to harmfull allele.

In the next generation the proportion of new harmfull alleles are: $\Delta q_\mu = 2Np\mu$

Recessive harmfull

$$\Delta q_\mu = 2Nsq^2$$

$$q = \sqrt{\frac{\mu}{s}}$$

Genotype	a^+a^+	a^+a	**aa**
Fitness	*1*	*1*	*1-s*

Dominant harmfull

$$\Delta q_\mu = Ns2pq + 2Nsq^2$$

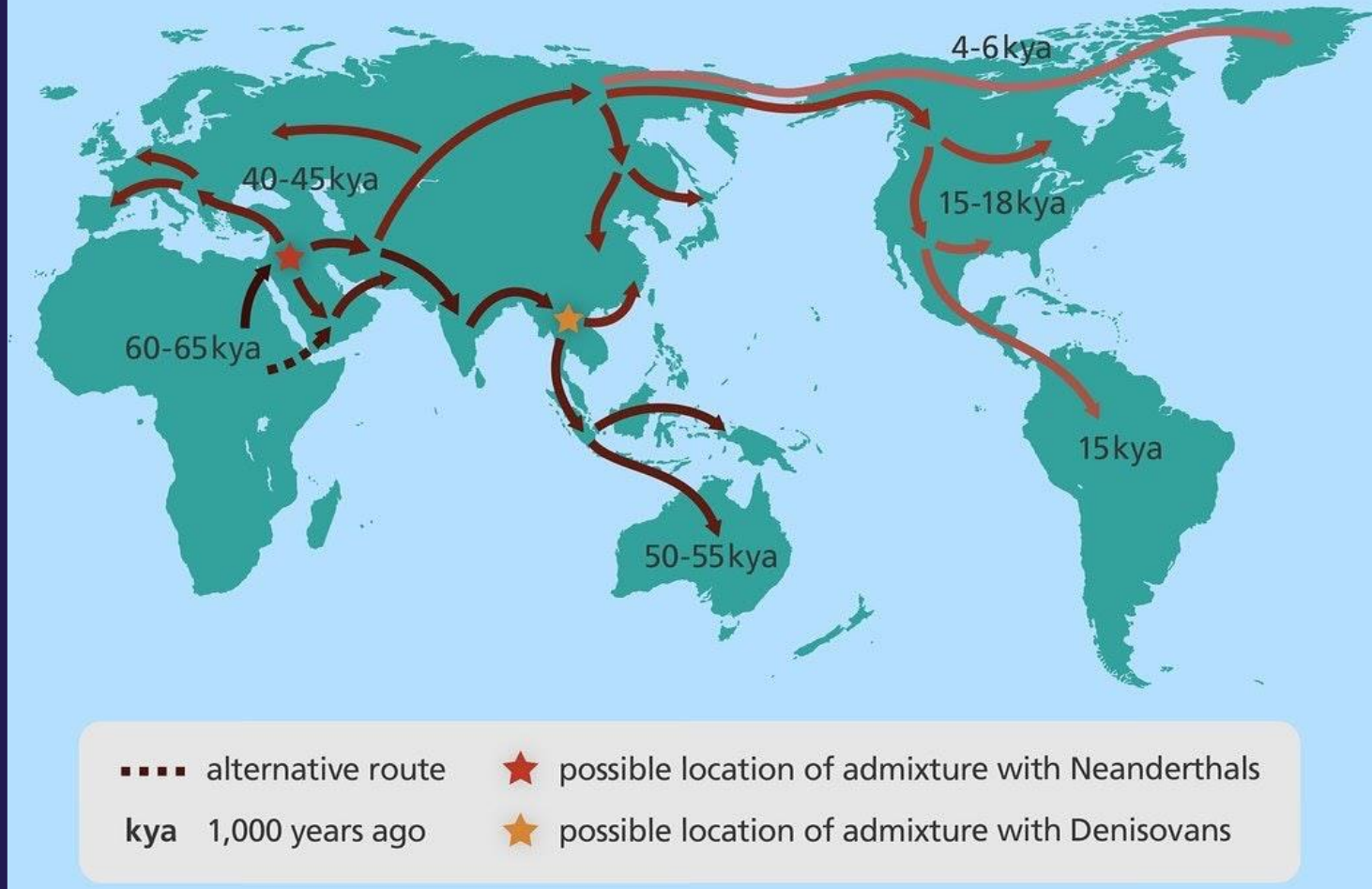
$$q = \frac{\mu}{s}$$

Genotype	a^+a^+	a^+a	**aa**
Fitness	*1*	*1-s*	*1-s*

THE NEUTRAL POPULATION

- Random mating
- No selection
- No genetic drift (infinite population size)
- **No migration**
- No mutation

$$q_1 = mq_m + (1 - m)q_1$$



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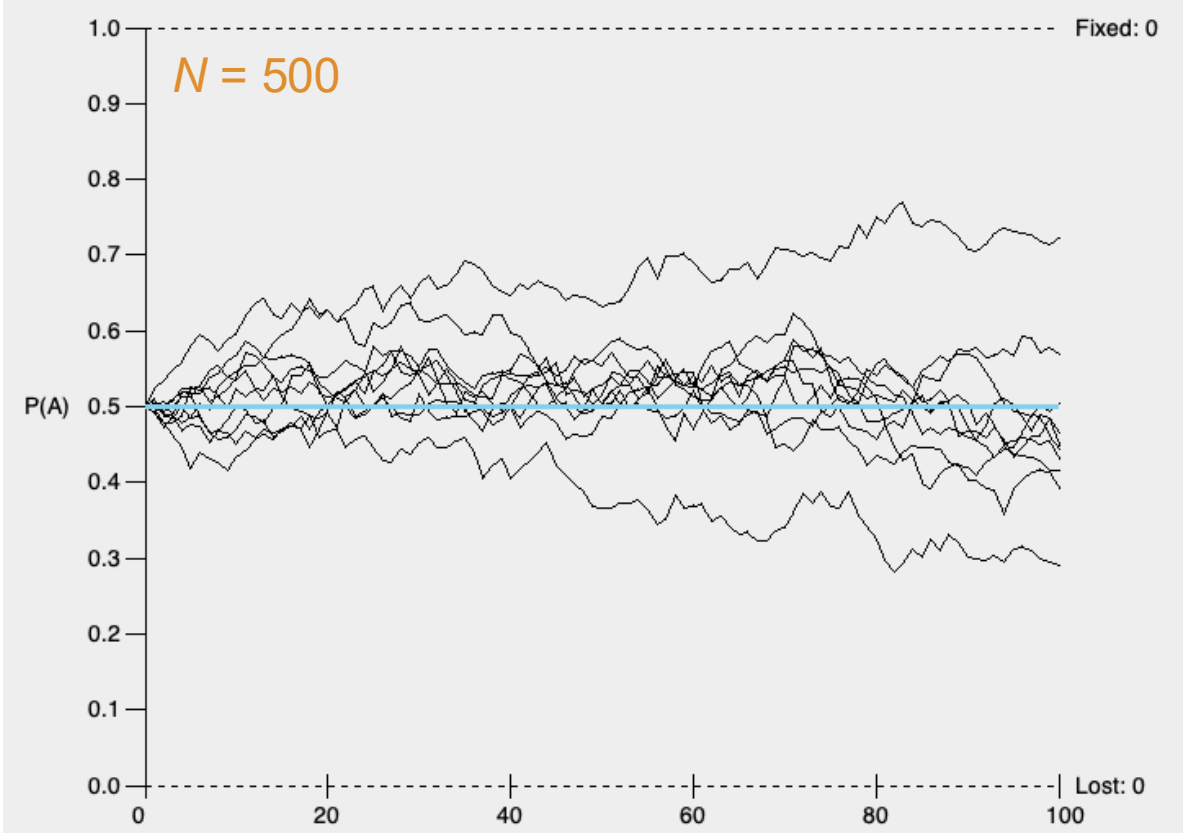
- No mutation

Genetic drift is changes in allele frequencies between generations due to sampling error



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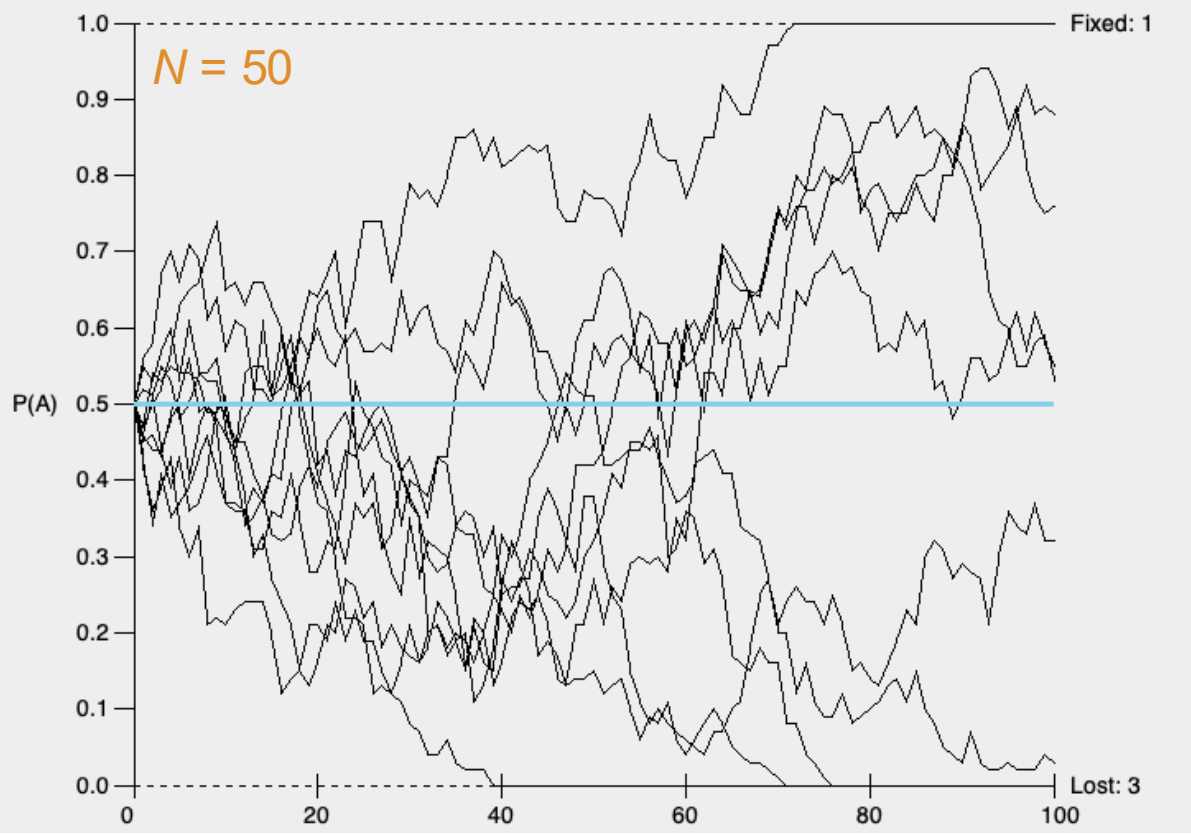

GENETIC DRIFT AND INBREEDING

Genetic drift entails loci in a sub-population becomes fixed, thus, the degree of homozygosity increases (thus, *F* increase).

The probability of selecting two gametes carrying the same allele is *1/(2N).*

The degree of inbreeding increase with time

$$F_t = 1 - (1 - \frac{1}{2N})^t$$

The rate of loss of heterozygosity (H) per generation

$H_t = (1 - \frac{1}{2N})^t H_0$, the rate depend on N

If there is inbreeding

Genotype	AA	Aa	aa
Frequency	p^2+pqF	2pq-2pqF	q^2+pqF

Results in excess in homozygotes

MODULATION OF FREQUENCIES

Mutation
introduces new alleles
diversity within populations ↑

Migration
introduces new alleles
diversity within populations ↑
diversity between populations ↓

Genetic drift
loss of alleles
diversity within populations ↓
diversity between populations ↑

Selection
removes harmfull alles
diversity within populations ↓
diversity between populations ↓↑

Non-random mating
do not change alleles, but change genotype frequencies

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REFLECT TOGETHER 2 AND 2

- What will you remember from today?
- What do you need to follow-up on?