

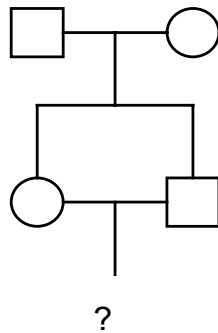
Class 29: Effects of Inbreeding

Today we will examine how inbreeding between close relatives (also known as consanguineous matings) influences the appearance of autosomal recessive traits.

Note that inbreeding will not make a difference for dominant traits because they need only be inherited from one parent or for X-linked traits passed on to male progeny since they are inherited only from the mother.

I. Brother-sister mating

Let's consider the extreme case of inbreeding by a brother-sister mating.



A useful concept is the **Inbreeding Coefficient = F** which is defined as the likelihood of **homozygosity by descent** at a given locus.

If we consider a locus with different alleles in each grandparent: A_1, A_2, A_3, A_4

F is the probability that the grandchild will be either $A_1/A_1, A_2/A_2, A_3/A_3, A_4/A_4$

$$p(A_1/A_1) = \frac{1}{2} \times \frac{1}{2} \times \frac{1}{4} = \frac{1}{16}$$

$$p(A_2/A_2) = \quad \quad \quad " \quad = \frac{1}{16}$$

$$p(A_3/A_3) = \quad \quad \quad " \quad = \frac{1}{16}$$

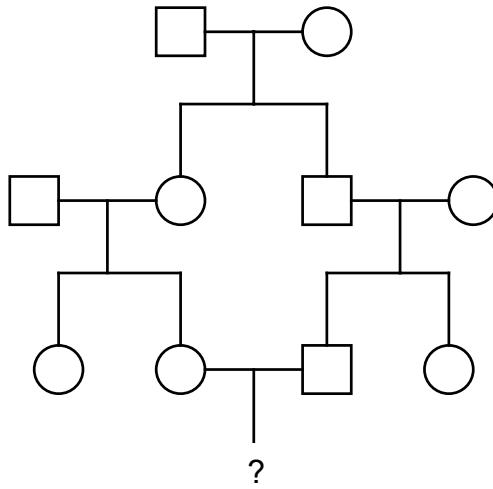
$$p(A_4/A_4) = \quad \quad \quad " \quad = \frac{1}{16}$$

$$p(\text{homozygous by descent}) = 4 \times \frac{1}{16} \quad \quad \quad \mathbf{F = \frac{1}{4}}$$

A brother-sister mating is the simplest case but is of little practical consequence in human population genetics since all cultures have strong taboos against this type of consanguineous mating and the frequency is extremely low.

I. 1st cousin marriages

First cousin marriages do happen at an appreciable frequency. Let's calculate **F** for offspring of 1st cousins.



$$p(A^1/A_1) = \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{4} = \frac{1}{64}$$

$$p(A^2/A_2) = \quad " \quad = 1/64$$

$$p(A^3/A_3) = \quad " \quad = 1/64$$

$$p(A^4/A_4) = \quad " \quad = 1/64$$

$p(\text{homozygous by descent}) = 4 \times 1/64$ **F** = $1/16$

Example: Consider a rare recessive allele **a** at frequency $f(\mathbf{a}) = q = 10^{-4}$

For **random mating** the frequency of homozygotes is $f(a/a) = q^2 = 10^{-8}$

Imagine a hypothetical situation where **only 1st cousins mated**. In that case the frequency of homozygotes would be:

$$\begin{array}{lcl} f(\mathbf{a}/\mathbf{a}) & = \text{p (homozygous by descent)} & \times \quad \text{p (allele is } \mathbf{a}) \\ & = \mathbf{F} & \times \quad \mathbf{q} \end{array}$$

$$f(\mathbf{a}/\mathbf{a}) = 1/16 \times \mathbf{q} = 6.3 \times 10^{-6}$$

Thus there would be 600 times more affected individuals for 1st cousin matings than for random mating. But 1st cousin marriages are rare and their actual impact on the frequency of homozygotes in a population will depend on the frequency of 1st cousin marriages.

III. Impact of consanguinity and genetic load

In the U.S. the frequency of 1st cousin marriages is ≈ 0.001

p (affected because of 1st cousin mating) = $\frac{1}{16} q 10^{-3} = 6.3 \times 10^{-9}$

p (affected because of random mating) = 10^{-8}

Thus, $\sim \frac{1}{3}$ of affected individuals will come from 1st cousin marriages

Note that this proportion **depends on allele frequency**. Thus, traits caused by very rare alleles will more often be the result of consanguinity

For rare diseases, it is often quite difficult to tell whether or not they are of genetic origin. A useful method to identify disorders that are likely to be inherited is to ask whether an unusually high proportion of affected individuals have parents that are related to one another.

Now let's consider the problem of recessive lethal mutations in the genome. We have already seen that the frequencies of recessive, loss-of-function alleles are usually in the range of 10^{-3} - 10^{-4} . This may seem like a comfortably small number but given that the total number of human genes is about 2×10^4 , each of us must be carrying many recessive alleles. Assuming that about 50% of genes are essential, each person should carry an average of approximately 1-10 recessive lethal mutations!

Genetic Load: lethal equivalents per genome.

Usually the genetic load is not a problem since it is very unlikely that both parents will happen to have lethal mutations in the same genes. However, that chance is considerably increased for parents that are 1st cousins.

As we have already calculated, the probability that a grandparental allele will become homozygous is $\frac{1}{64}$ for 1st cousins. Thus, each recessive lethal allele for which one of the grandparents in a carrier will contribute **an increased probability of ~ 0.016** that the grandchild will be homozygous and therefore be afflicted by a lethal inherited defect.

To look for this effect we will use the frequency of stillbirth or neonatal death from 1st cousin marriages. We must also be careful to subtract the background frequency of stillbirths and neonatal deaths that are not due to genetic factors. These frequencies can be obtained from the cases where parents are not related.

	unrelated parents	1st cousins	difference
Observed frequency of still-birth or neonatal death	0.04	0.11	0.07

Average number of recessive lethals in both grandparents = $\frac{0.07}{0.016} = 4.4$
Thus each grandparent has an average of 2.2 recessive lethal alleles.