

## 2005 7.03 Problem Set 6 KEY

Due before 5 PM on WEDNESDAY, November 23, 2005.

Turn answers in to the box outside of 68-120.

PLEASE WRITE YOUR ANSWERS ON THIS PRINTOUT.

**1.** Two populations (Population One and Population Two) send a randomly selected group of their inhabitants to settle on a new and previously uninhabited island. Before sending anyone off to the island, both populations are at Hardy-Weinberg Equilibrium for an autosomal recessive trait displayed by individuals with the genotype  $bb$ . In Population One, 1 out of 2,000 people express the trait. In Population Two, the frequency of the  $b$  allele is 0.1.

(a) What is the allele frequency of the  $b$  allele in Population One?

**0.022**

The allele “ $b$ ” is recessive, so the frequency of “ $b$ ” is equal to “ $q$ ” in the Hardy-Weinberg equation. We know that 1 out of 2,000 people in Population 1 express the trait, which means that 1 / 2,000 people are  $b/b$  homozygotes.  $1 / 2,000 = 0.0005 = q^2$ . The frequency of  $b$ , therefore, is the square root of  $q^2$ , which is 0.022.

The two populations send off their settlers to the island, where the 100,000 settlers randomly mate. Each couple has two children, and thereby creates a new generation of 100,000 people (500 of whom express the trait).

(b) What is the allele frequency of the  $b$  allele in the new merged population on the island?

**0.071**

**500 / 100,000 people are  $b/b$ , so  $q^2 = 500 / 100,000 = 0.005$ . The value of  $q$  is 0.071.**

Answer the next parts assuming that the two populations of settlers have merged on the island and have reached Hardy Weinberg equilibrium.

(c) If you selected a female at random, what would the probability be that she was a carrier?

**0.132**

The frequency of  $b$  (“ $q$ ”) on the island is 0.071. The frequency of  $B$  (“ $p$ ”), therefore, must be  $1 - q = 0.929$ .

**$p$  (carrier) =  $2pq = 0.132$**

(d) What proportion of all b alleles are present in carriers?

**93%**

The total number of b alleles in the population =  $q$  \* the total number of alleles in the population (which is 200,000 because there are 100,000 people and each person has 2 alleles at this autosomal locus). Thus the total number of b alleles in the population is  $200,000 * 0.071 = 14200$ .

The total number of heterozygotes in the population =  $2pq$  \* the number of individuals in the population =  $0.132 * 100,000 = 13200$ . Each heterozygote possesses one b allele.

Thus the fraction of b alleles that are present in heterozygotes =  $13200/14200 = 93\%$ .

Note that 93% is actually the value of p.

(e) What fraction of all matings are between parents who are the same genotype as each other?

**76.2%**

Since the island's population is in Hardy-Weinberg equilibrium, we know that mating is random:

$$p \text{ (B/B mating with B/B)} = p^2 * p^2 = 0.929^4 = 0.745$$

$$p \text{ (B/b mating with B/b)} = 2pq * 2pq = 0.13^2 = 0.017$$

$$p \text{ (b/b mating with b/b)} = q^2 * q^2 = 0.071^4 \approx 0$$

$$\Rightarrow p \text{ (mating between parents with same genotype)} = 0.745 + 0.017 + \sim 0 = 0.762$$

**2.** A rare X-linked recessive trait affects 1/5000 males in a certain population.

(a) What is the allele frequency of the allele associated with the recessive trait?

**1/5000**

Since this is an X-linked trait, males are haploid at the locus for this gene (males only have one X chromosome). In this case, the frequency of affected males is equal to the frequency of males with the recessive allele:  $1 / 5000 = q = 0.0002$ .

(b) How many affected men are there for each affected woman?

**5000**

$q = 0.0002 =$  proportion of men affected

$q^2 = 0.00000004 =$  proportion of women affected

Ratio of affected men : affected women =  $0.0002 / 0.00000004 = 5000 : 1$

(c) In what proportion of matings would this trait affect half of the children of each sex?

**0.00000008**

Half of all offspring will show the trait only if the mother is a heterozygous carrier, and the father has the trait. The mother would pass on the recessive allele 1/2 of the time, and the father would pass on the recessive allele every time.

$p = 1 - q = 0.9998$

With random mating,

$p$  (mother is a carrier) =  $2pq = 2 * 0.0002 * 0.9998 = 0.0004$

$p$  (father is affected) =  $q = 0.0002$

$\Rightarrow p$  (half of offspring affected) =  $2pq * q = 0.0004 * 0.0002 = 0.00000008$

(d) In what proportion of matings would no children have the trait?

**99.96%**

In order for no children to be affected, there are two possible matings: (1) a wild-type mother and a wild-type father, and (2) a wild-type mother and an affected father.

With random mating,

$p$  (1) =  $p^2 * p = 0.9998^3 = 0.9994$

$p$  (2) =  $p^2 * q = 0.9998^2 * 0.0002 = 0.0002$

$\Rightarrow p$  (no offspring affected) =  $p(1) + p(2) = 0.9994 + 0.0002 = 99.96\%$

(e) Now assume that individuals showing the trait have a fitness of 70% as compared to individuals that do not show the trait. There are no other factors affecting the frequency of the trait. By how much would the allele frequency change between the current generation and the next generation?

**It would decrease by 0.00002.**

The current frequency of the allele is  $q = 0.0002$ . The change in frequency in the next generation is equal to  $\Delta q_{sel} = -(1/3)Sq$ , where  $S$  is the selective disadvantage. The fitness is 0.7 in this case, so  $S = 1 - 0.7 = 0.3$ . Since the overwhelming majority of individuals with the trait will be male, only affected males will be subjected to decreased fitness. The proportion of males subject to selection is the proportion of males that have the trait, which is  $q$ . Thus the effect of selection acting on males is  $-Sq$ . However you must then

multiply  $-Sq$  by  $1/3$ , because  $1/3$  of all X chromosomes in the population will be in males. This means that only  $1/3$  of the total recessive alleles are actually acted on by selection. The other  $2/3$  of X chromosomes with the recessive allele will be in females, who will not be subjected to decreased fitness. Therefore,

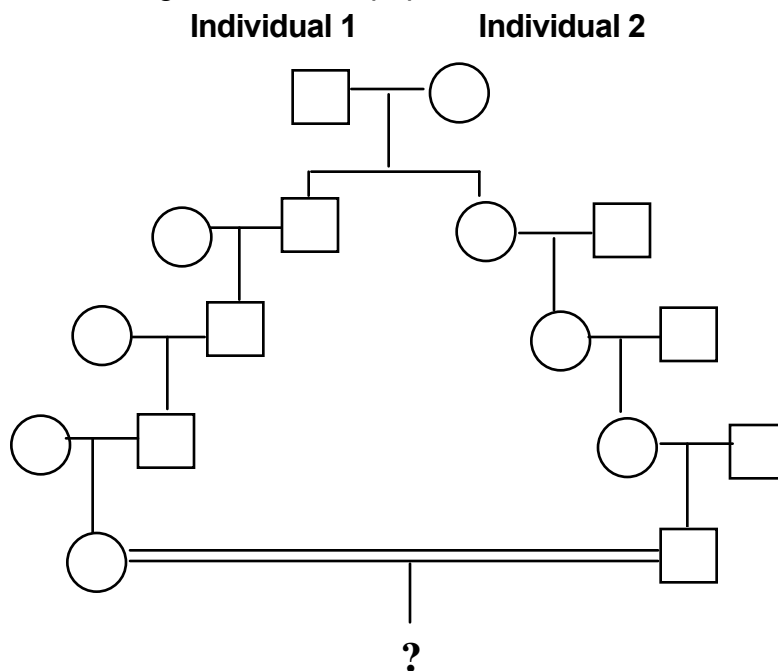
$$\Delta q_{\text{sel}} = - (1/3) 0.0002 * 0.3 = - 0.00002.$$

(f) Now assume that there are new mutations being introduced into the population. The mutation rate at the locus associated with this trait is  $10^{-4}$ . What would the allele frequency of the allele associated with the trait equal when a steady state between mutation and selection is reached?

The new  $q$  would be 0.001

At the steady state, the  $\Delta q_{\text{sel}} + \Delta q_{\text{mut}} = 0$ .  $\Delta q_{\text{mut}}$  is equal to the mutation rate  $\mu$ .  $\Delta q_{\text{sel}}$  is equal to  $-Sq/3$ , and so at steady state,  $-Sq/3 + \mu = 0$ . The mutation rate  $\mu$  is  $10^{-4}$  and  $S = 0.3$ . Solving for  $q$ , we get a new  $q$  at steady state = 0.001.

**3.** Consider the following pedigree, which illustrates a family in a very large population. The two relatives shown are considering having a child, and if they do, they will be the first example of inbreeding in the entire population.



Assume no new mutations occur, that penetrance is complete, and that selection is negligible. Also assume that all traits are rare.

(a) What is the inbreeding coefficient for this pedigree?

$$F = 1/256$$

The great great great grandparents of the child have a total of four alleles at any autosomal locus in the genome. We can label the great great grandfather as being A1/A2 and the great great grandmother as being A3/A4. We use these non-specific allele notations because we have no idea which alleles these grandparents possess. Now we can consider the probability that the child in the pedigree will be homozygous by descent at that locus. The child could become homozygous by descent for any of the four alleles possessed by the great great grandparents.

$$p(A1/A1) = 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/4 = 1/1024$$

$$p(A2/A2) = 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/4 = 1/1024$$

$$p(A3/A3) = 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/4 = 1/1024$$

$$p(A4/A4) = 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/2 * 1/4 = 1/1024$$

$$p(\text{homozygous at A locus by descent}) = 4 * 1/1024 = 1/256 = F$$

(b) For the child indicated by a question-mark, how many genes on average will he/she be homozygous by descent (i.e. the child has inherited two alleles of a gene, both of which came from the same DNA in one of the great great great grandparents)? (There are about 20,000 genes in the human genome)

about 78

There is a 1/256 chance that each gene will be homozygous by descent, so the number of homozygous loci would be about 1/256 \* 20,000, which is equal to about 78 loci in the genome.

(c) Assume that you do not know the genotypes of the great great great grandparents, but that you do know that neither exhibits an **autosomal recessive** trait with an incidence in the population of  $10^{-6}$ . What is the chance that Individual 2 is a carrier of the allele for the trait, **and** Individual 1 is not a carrier?

0.002

$$q^2 = 10^{-6}$$

therefore

$$q = 0.001, p = 0.999$$

$$p(\text{Individual 2 is a carrier}) = 2pq = 2 * 0.001 * 0.999 = 0.002$$

$$p(\text{Individual 1 is not a carrier}) = p^2 = 0.999 * 0.999 = 0.998$$

$$\Rightarrow p(2 \text{ carrier and } 1 \text{ not carrier}) = 0.002 * 0.998 = 0.002$$

Note that these are approximations. In fact, since we know that Individual 2 and Individual 1 are not affected, the most precise way to calculate their chances of being the respective genotypes are:

$$p(\text{Individual 2 is a carrier}) = [2pq / (2pq + p^2)] \approx 2 * 0.001 * 0.999 \approx 0.002$$

$$p(\text{Individual 1 is not a carrier}) = [p^2 / (2pq + p^2)] \approx 0.999 * 0.999 \approx 0.998$$

This is an example of a simple conditional probability – e.g. what is the probability that Individual 1 is AA given that Individual 1 is NOT aa?

(d) For the same trait described in part (c), if Individual 2 is a carrier of the allele for the trait, and Individual 1 is not a carrier (and does not show the trait), what is the chance that the unborn child denoted in the pedigree by a question-mark will have the trait?

**1/1024**

This question is asking for the chance that the child will be homozygous aa. Individual 2 is Aa, and Individual 1 is AA, so the answer to this question is really 1/4 F. This is because F is the chance that the child is homozygous by descent for any of the four alleles possessed by the great great grandparents, while we are asking here what is the chance that the child will be homozygous for 1/4 of the 4 alleles possessed by the great great grandparents (i.e. only for the “a” allele possessed by the great great grandmother).

$$p(\text{child is aa}) = p(\text{“A4”/”A4”}) = 1/1024$$

(e) Assume that an **autosomal recessive** trait in this population has an incidence of  $10^{-6}$ . Imagine that, in the next generation of the population, every person decides to inbreed with a person of the same degree of relatedness as the two relatives who are mating in the pedigree shown above. What will the frequency of the trait be in the next generation?

**The new incidence would be  $4 * 10^{-6}$**

$$q^2 = 10^{-6}$$

$$q = 0.001$$

Mating is no longer random; instead, now the probability of homozygosity by descent in each individual of the next generation is  $F = 1/256$ . The frequency of the allele in the previous generation was  $q$ , so the frequency of affected individuals in the population will be  $p(\text{affected by trait}) = Fq$ . This is because  $q$  is the chance that any child will receive a “a” allele, and  $F$  is the chance that any child will be homozygous. Thus the chance that any child will have “a” AND be homozygous =  $p(\text{child is aa}) = F * q$ .

$q^2$  does not enter into this calculation, because  $q^2$  would be the frequency of affected individuals as a result of random mating, and no random mating is occurring any more in this population.

$$\Rightarrow p(\text{affected by trait in next generation}) = Fq = (1/256) * 0.001 = 4 * 10^{-6}$$

(f) Assume that an **autosomal dominant** trait in this population has an incidence of  $10^{-6}$ . Now say that you know that Individual 2 is heterozygous for the allele for the trait, and Individual 1 does not have the trait. What is the chance that the unborn child denoted in the pedigree by a question-mark will have the trait?

**6.15%**

Designating the dominant trait allele as “A”, and the wild-type allele as “a,” there are 3 combinations of the parental genotypes that could produce a child with the trait:

	Mom	Dad
(mating 1)	aa	x Aa
(mating 2)	Aa	x aa
(mating 3)	Aa	x Aa

The probability of one of the parents of “child ?” having the “A” allele passed down from individual 2 is 1/16. Thus the probability that the mom of “child ?” is Aa = 1/16. The probability that the dad of “child ?” is Aa = 1/16.

Neither the mom or the dad of “child ?” can be AA (realistically speaking, because this would require that someone mating into the family has the A allele, and the chance of that is 1/1,000,000). Thus the probability of the mom of “child ?” being aa is 15/16 and the probability that the dad of “child ?” is aa is 15/16.

Therefore:

$p(\text{mating 1}) = (15/16) * (1/16)$   
 $p(\text{mating 2}) = (1/16) * (15/16)$   
 $p(\text{mating 3}) = (1/16) * (1/16)$

The probability of having a child who displays the dominant trait is equal to 1/2 in (mating 1) and (mating 2), and is equal to 3/4 in (mating 3). The final probability of having an affected “child ?” is:

$p(\text{affected child}) =$   
 $(15/16) * (1/16) * (1/2)$   
 $(1/16) * (15/16) * (1/2) +$   
 $(1/16) * (1/16) * (3/4)$   
 $= 0.0615$

Note that the chance of a person mating into the family randomly contributing the “A” allele is much much lower than the chance that the A allele is passed on to “child ?” from the first generation of the pedigree. This is why we can ignore the possibility that rare alleles can be contributed from people marrying into a pedigree for all rare traits.