

Review question:

Your mother has a rare genetic ataxia that is inherited as an autosomal dominant. The mutation is completely penetrant in that everyone with the mutant allele develops ataxia by age 45, but only 50% do so by your age. There is no genetic test. You do not (yet) have any symptoms. What is the probability that you have inherited this disease? (hint: consider how the data affect the sample space).

I didn't really go over the probability theory that serves as background to this (in past years, I somehow had more time, and gave a deeper background to probability before presenting lod scores). Consider the probabilities of three situations, at birth:

- A) The dominant allele is not inherited. The probability of this is 1/2.
- B) The dominant allele is inherited, but disease will not be observed by age 45. The probability of this is $(1/2)(50\%) = 25\%$.
- C) The dominant allele is inherited and the disease observed by age 45. The probability of this is also $(1/2)(50\%) = 25\%$.

The question can be rephrased as "What is the probability of B given that C can be ruled out. The answer is $0.25 / 0.75 = 1/3$. The numerator is the probability of B at birth. The denominator is the sum of the probabilities of A and C, those "events" that have not been ruled out.

This is very similar to the 2:1 ratio observed for transmission of alleles that are recessive-lethal. See Fig. 3.9 of Hartwell (3rd edition).

Consider two populations of a species, population 1 and population 2, that differ at two unlinked loci, A and B. In each population a specific allele is fixed at each locus (all individuals in population 1 have the genotype $A_{1,1} B_{1,1}$ while all individuals in population 2 have the genotype $A_{2,2} B_{2,2}$). You cross a single male from population 1 with a single female in population 2.

1. What is the expected frequency of **each** of the nine possible genotypes

$A_{1,1} B_{1,1}$	0
$A_{1,1} B_{1,2}$	0
$A_{1,1} B_{2,2}$	0
$A_{1,2} B_{1,1}$	0
$A_{1,2} B_{1,2}$	1
$A_{1,2} B_{2,2}$	0
$A_{2,2} B_{1,1}$	0
$A_{2,2} B_{1,2}$	0
$A_{2,2} B_{2,2}$	0

2. Is locus A at Hardy-Weinberg equilibrium in the F1 generation (your answer would be the same for locus B)?

No. At Hardy-Weinberg equilibrium $A_{1,1} : A_{1,1} : A_{1,1}$ should be present at frequencies of 25%, 50% and 25%. There is a deficit of homozygotes.

3. Do the two alleles A_1 and B_1 show linkage disequilibrium (association) in this F1 generation? (Please consider the frequency of the **haplotypes** transmitted by the F1 individuals).

No. The frequency of haplotypes generated will be

$A_1 B_1$	1/4
$A_1 B_2$	1/4
$A_2 B_1$	1/4
$A_2 B_2$	1/4

This is exactly as expected in the absence of linkage disequilibrium (the frequency of A_1 with B_1 is 1/2, which is identical to the frequency of A_1 with B_2)

4. What is the expected frequency of each of the nine possible genotypes in the F2 progeny (assuming random mating among the F1)?

$A_{1,1} B_{1,1}$	1/16
$A_{1,1} B_{1,2}$	2/16
$A_{1,1} B_{2,2}$	1/16
$A_{1,2} B_{1,1}$	2/16
$A_{1,2} B_{1,2}$	4/16
$A_{1,2} B_{2,2}$	2/16
$A_{2,2} B_{1,1}$	1/16
$A_{2,2} B_{1,2}$	2/16
$A_{2,2} B_{2,2}$	1/16

5. Is locus A at Hardy-Weinberg equilibrium in the F2 generation?

Yes. At Hardy-Weinberg equilibrium $A_{1,1} : A_{1,2} : A_{2,2}$ should be present at frequencies of 25%, 50% and 25%. That is observed.

6. Do the two alleles A_1 and B_1 show linkage disequilibrium in this F2 generation?

No. The frequency of haplotypes is still equal.

7. What is the frequency of each of the four possible haplotypes (A_1B_1 , A_1B_2 , A_2B_1 , and A_2B_2) in gametes transmitted from the F2 generation to the F3 generation?

$A_1 B_1$	1/4
$A_1 B_2$	1/4
$A_2 B_1$	1/4
$A_2 B_2$	1/4

Now (ques. 8-14) consider what happens if you allow a large and equivalent number of individuals from the two populations -- for example, 500 males and 500 females from population 1 and 500 males and 500 females from population 2 -- to mate at random (and they do mate at random).

8. What is the expected frequency of **each** of the nine possible genotypes

A _{1,1} B _{1,1}	1/4
A _{1,1} B _{1,2}	0
A _{1,1} B _{2,2}	0
A _{1,2} B _{1,1}	0
A _{1,2} B _{1,2}	1/2
A _{1,2} B _{2,2}	0
A _{2,2} B _{1,1}	0
A _{2,2} B _{1,2}	0
A _{2,2} B _{2,2}	1/4

9. Is locus A at Hardy-Weinberg equilibrium in the F1 generation (your answer would be the same for locus B)?

Yes. At Hardy-Weinberg equilibrium A_{1,1} : A_{1,1} : A_{1,1} should be present at frequencies of 25%, 50% and 25%. That is observed.

10. Do the two alleles A₁ and B₁ show linkage disequilibrium (association) in this F1 generation? (There are several ways to answer this; please consider the frequency of the **haplotypes** generated by the F1 individuals).

Frequencies:

A ₁ B ₁	3/8	(All of the gametes from A _{1,1} B _{1,1} plus 1/4 of those from A _{1,2} B _{1,2})
A ₁ B ₂	1/8	(1/4 of the gametes from A _{1,2} B _{1,2})
A ₂ B ₁	1/8	(1/4 of the gametes from A _{1,2} B _{1,2})
A ₂ B ₂	3/8	(All of the gametes from A _{2,2} B _{2,2} plus 1/4 of those from A _{1,2} B _{1,2})

There is linkage disequilibrium (the frequency of A₁ with B₁ is 3/4, which is different from the frequency of A₁ with B₂)

11. What is the expected frequency of each of the nine possible genotypes in the F2 progeny (assuming random mating among the F1)?

A _{1,1} B _{1,1}	9/64
A _{1,1} B _{1,2}	6/64
A _{1,1} B _{2,2}	1/64
A _{1,2} B _{1,1}	6/64
A _{1,2} B _{1,2}	20/64
A _{1,2} B _{2,2}	6/64
A _{2,2} B _{1,1}	1/64
A _{2,2} B _{1,2}	6/64
A _{2,2} B _{2,2}	9/64

12. Is locus A at Hardy-Weinberg equilibrium in the F2 generation?

Yes. At Hardy-Weinberg equilibrium $A_{1,1} : A_{1,1} : A_{1,1}$ should be present at frequencies of 25%, 50% and 25%. That is observed.

13. Do the two alleles A_1 and B_1 show linkage disequilibrium in this F2 generation?

Yes; there is linkage disequilibrium (there is still an excess of $A_1 B_1$ and $A_2 B_2$)

14. What is the frequency of each of the four possible haplotypes (A_1B_1 , A_1B_2 , A_2B_1 , and A_2B_2) in gametes transmitted from the F2 generation to the F3 generation?

$A_1 B_1$	5/16
$A_1 B_2$	3/16
$A_2 B_1$	3/16
$A_2 B_2$	5/16

15. Compare your results for questions 1-7 with your results for questions 8-14. What does this tell you about linkage disequilibrium (e.g. does it require linkage? What is the effect of demographic history?)

Linkage disequilibrium is observed in this case, which concerns two unlinked loci. The LD observed here is population stratification. You can see that it persists over several generations of random mating.