

# Gene Linkage and Genetic Mapping

## Key Concepts

- Genes that are located in the same chromosome and that do not show independent assortment are said to be linked.
- The alleles of linked genes present together in the same chromosome tend to be inherited as a group.
- Crossing-over between homologous chromosomes results in recombination, which breaks up combinations of linked alleles.
- A genetic map depicts the relative positions of genes along a chromosome.
- The map distance between genes in a genetic map is related to the rate of recombination between the genes.
- Physical distance along a chromosome is often, but not always, correlated with map distance.
- Tetrads are sensitive indicators of linkage because they include all the products of meiosis.
- At the DNA level, recombination is initiated by a double-stranded break in a DNA molecule. Use of the homologous DNA molecule as a template for repair can result in a crossover, in which both strands of the participating DNA molecules are broken and rejoined.

## Key Terms

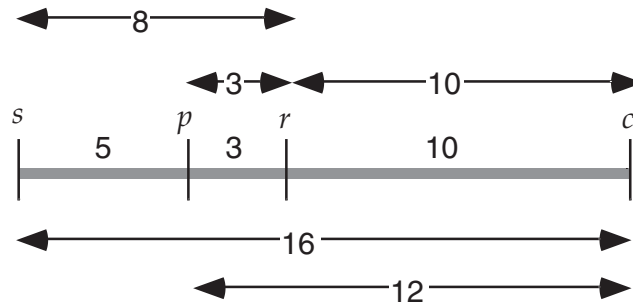
1. linkage
2. map unit
3. map distance
4. repulsion
5. coincidence
6. interference
7. restriction endonuclease
8. gene conversion
9. Holliday junction
10. second-division segregation
11. nonparental ditype (NPD)

## Concepts in Action

- 4.1. Genotype  $A B/a b$  has  $A$  present with  $B$  in one chromosome and  $a$  present with  $b$  in the homologous chromosome; genotype  $A b/a B$  has  $A$  present with  $b$  in one chromosome and  $a$  present with  $B$  in the homologous chromosome. The role of the slash is to serve as a separator for the list of alleles present in each homolog. The genotype  $A B/a b$  has  $A$  and  $B$  in coupling,  $A b/a B$  has them in repulsion.
- 4.2. Females produce gametes of types  $AB$ ,  $ab$ ,  $Ab$ , and  $aB$  in the proportions  $(1 - 0.08)/2 = 0.46$ ,  $0.08/2 = 0.04$ ,  $0.08/2 = 0.04$ , and  $0.08/2 = 0.04$ , respectively.

Males produce gametes of types  $AB$  and  $ab$  only (owing to the absence of crossing-over), in the proportions 0.50 and 0.50.

- 4.3. The map distance between widely separated genes is determined by summing the distances of shorter intervals between the genes. Hence, the accumulated map distances can (and often does) exceed 50 map units, even though the maximum observed frequency of recombination between any two genetic markers is 50 percent.
- 4.4. Only **(b)** is true; all of the others are false.
- 4.5. With genes that undergo independent assortment, PD and NPD tetrads are outcomes of equally probable orientations of two bivalents, each carrying one of the heterozygous genes. For linked genes, NPD tetrads are rare because a four-strand double crossover is required to form an NPD tetrad.
- 4.6. This is a testcross, so the phenotypes of the progeny reveal the ratio of meiotic products from the doubly heterozygous parent. The expected progeny are 86 percent parental (43 percent wildtype and 43 percent scarlet, spineless) and 14 percent recombinant (7 percent scarlet and 7 percent spineless).
- 4.7. The genetic map is shown in the accompanying illustration. The map distance between  $s$  and  $c$  is 18 cM, but there is only 16 percent recombination, and the map distance between  $p$  and  $c$  is 13 cM, but there is only 12 percent recombination. The fact that the frequency of recombination is smaller than the map distance results from double crossovers.



- 4.8. The data include  $59 + 52 = 111$  progeny with either both mutations or neither, and  $46 + 43 = 89$  with one mutation or the other. One of these groups consists of parental chromosomes and the other of recombinant chromosomes, and so the appropriate chi-square test compares the ratio 111:89 against an expected 100:100 with no linkage. The chi-square value equals 2.42 and there is one degree of freedom, from which  $P$  equals approximately 0.12. There is no evidence of linkage even though both genes are in the X chromosome.
- 4.9. The frequency of recombination between the genes is  $9/200 = 0.045$ , or 4.5 percent.
- 4.10. **(a)** They are not alleles because they fail to segregate; if they were alleles, all the progeny would be resistant to one insecticide or the other. **(b)** The alleles are not linked, The chi-square of 177 parental:205 recombinant types against 191:191 equals 2.05 with one degree of freedom, which is not significant. **(c)** The two genes must be far apart on the chromosome.
- 4.11. The most frequent classes indicate the alleles present in the parental chromosomes, and the “odd man out” in the least frequent classes indicates the order of the genes. In this case, the parental chromosomes are  $ABc/aBc$  and the gene  $C$  is in the middle; hence, the parental genotype was  $AcB/aCb$ .
- 4.12. **(a)** The parental types are evidently  $v^+prbm$  and  $vpr^+bm^+$  and the double-recombinant types  $v^+pr^+bm^+$  and  $vprbm$ . This puts  $v$  in the middle. The  $pr-v$  recombination frequency is  $(69 + 76 + 36 + 41)/1000 = 22.2$  percent, and the  $v-bm$  recombination frequency is  $(175 + 181 + 36 + 41)/1000 = 43.3$  percent. The expected number of double crossovers equals  $0.222 \times 0.433 \times 1000 = 96.13$ , so the coincidence is  $(36 + 41)/96.13 = 0.80$ . The interference is therefore  $1 - 0.80 = 0.20$ . **(b)** The true map distances are certainly larger than 22.2 and 43.3 cM. The frequencies of recombina-

tion between these genes are so large that there are undoubtedly many undetected double crossovers in each region.

**4.13. (a)** The mother of II-1 has genotype  $hd A/hd A$ , and the father of II-1 has genotype  $HD a/hd a$ . Therefore, II-1 must have the genotype  $HD a/hd A$ . **(b)** The male II-2 has genotype  $hd A/hd A$  and therefore must contribute an  $hd A$  gamete to each offspring. Among the gametes from II-1, the possible genotypes are:

1.  $HD A$  with frequency  $0.10/2 = 0.05$  (recombinant)
2.  $HD a$  with frequency  $(1 - 0.10)/2 = 0.45$  (nonrecombinant)
3.  $hd A$  with frequency  $(1 - 0.10)/2 = 0.45$  (nonrecombinant)
4.  $hd a$  with frequency  $0.10/2 = 0.05$  (recombinant)

Because individual III-1 has the RFLP genotype  $Aa$ , she must have resulted from an egg with genotype either  $HD a$  or  $hd a$ . Among these two possibilities, only the  $HD a$  gamete will result in Huntington disease. Therefore, the probability that III-1 will be affected is given by  $0.45/(0.45 + 0.05) = 0.90$ . **(c)** In this case, because III-2 is  $AA$ , the egg cell giving rise to III-2 would have to have the genotype either  $HD A$  or  $hd A$ . Only the  $HD A$  gamete will result in Huntington disease. Therefore, the probability that III-2 will be affected is  $0.05/(0.05 + 0.45) = 0.10$ .

**4.14. (a)** The three-allele hypothesis predicts that the matings will be  $FS \times FS$  and should yield  $FF:FS:SS$  offspring in a ratio of 1:2:1. **(b)** These ratios are not observed, and furthermore, some of the progeny show the “null” pattern. **(c)** One possibility is that the  $F$  and  $S$  bands are from unlinked loci and that there is a “null” allele of each, say,  $f$  and  $s$ . Because  $f$  and  $s$  are common and  $F$  and  $S$  are rare, most persons with two bands would have the genotype  $FfSs$ . The cross should therefore yield  $9/16 F-S-$  (two bands),  $3/16 F-ss$  (fast band only),  $3/16 ffS-$  (slow band only), and  $1/16 ffss$  (no bands). **(d)** The data are consistent with this hypothesis ( $\chi^2 = 2.67$  with three degrees of freedom,  $P$  value approximately 0.50).

**4.15.** Consider each gene in relation to first-division and second-division segregation. Gene  $a$  gives 1766 asci with first-division segregation and 234 with second-division segregation; the frequency of second-division segregation is  $234/(1766 + 234) = 0.117$ , which implies that the distance between  $a$  and the centromere is  $0.117/2 = 5.85$  percent. Gene  $b$  gives 1780 first-division and 220 second-division segregations, for a frequency of second-division segregation of  $220/(1780 + 220) = 0.110$ . The distance between  $b$  and the centromere is therefore  $0.110/2 = 5.50$  map units. If we consider  $a$  and  $b$  together, there are 1986 PD asci, 14 TT asci, and no NPD asci. Because  $NPD \ll PD$ , genes  $a$  and  $b$  are linked. By applying Equation (4-1), we find that the frequency of recombination between  $a$  and  $b$  is  $[(1/2) \times 14]/2000 = 0.35\%$ . Comparing this distance with the gene-centromere distances calculated earlier results in the map  $a-0.35-b-5.50$ -centromere.

**4.16.** In this case, one must start by calculating the number of double-crossover gametes that would be observed, given the interference. The number of observed doubles equals the number of expected doubles times the coincidence, or  $0.15 \times 0.20 \times 0.20 = 0.006$ , or among 1000 gametes, 3 each of  $o++$  and  $+cip$ . The single recombinants in the  $o-ci$  interval would therefore number  $0.15 \times 1000 - 6 = 144$ , or 72 each of  $o+p$  and  $+ci+$ . The single recombinants in the  $ci-p$  interval would number  $0.20 \times 1000 - 6 = 194$ , or 97 each of  $oci p$  and  $+++$ . The remaining 656 gametes are nonrecombinant, 328 each of  $oci+$  and  $+++p$ .

**4.17. (a)** To determine the linked genes, first consider each possible set of pairs and classify each tetrad type as PD, NPD, and TT with respect to the gene pairs. For  $a$  and  $b$ , the tetrad types 1 through 4 are PD, NPD, PD, and NPD, respectively, totaling 196 PD and 204 NPD; because  $PD \approx NPD$ , genes  $a$  and  $b$  are unlinked. For genes  $b$  and  $c$ , the tetrad types 1 through 4 are PD, NPD, TT, and TT, respectively, totaling 132 PD, 124 NPD, and 144 TT; because  $NPD \approx PD$ , genes  $b$  and  $c$  are unlinked. Finally, for genes  $a$  and  $c$ , the tetrad types 1 through 4 are PD, PD, TT, and TT, respectively, for a total of 256 PD and 144 TT. In this case,  $NPD \ll PD$ , and so genes  $a$  and  $c$  are linked. **(b)** Because  $NPD = 0$  for the  $a$  and  $c$  genes, the map distance between  $a$  and  $c$  is calculated as  $(1/2) \times ([TT]/Total) \times 100 = (1/2) \times 144/400 \times 100 = 18.0\%$ .

- 4.18.** The gene-centromere map distance equals 1/2 the frequency of second-division segregation, which also equals the frequency of crossing over in the region. In this problem, it is easiest to answer the questions by taking the cases out of order, considering the second-division segregations at the beginning. **(a)** The frequency of second-division segregation of *cys-1* must be 14 percent, because the map distance is 7 cM. Because of the complete interference, a crossover on one side of the centromere precludes a crossover on the other side, so these asci must have first-division segregation for *pan-2*. **(b)** Similarly, the frequency of second-division segregation of *pan-2* must be 6 percent, because the map distance is 3 cM; these asci must have first-division segregation for *cys-1*. **(c)** Because of the complete interference, second-division segregation of both markers is not possible. **(d)** The only remaining possibility is first-division segregation of both markers, which must have a frequency of  $1 - 0.14 - 0.06 = 80\%$ . **(e)** First-division segregation of both markers yields a PD tetrad, and second-division segregation for one of the markers yields a TT tetrad. Because there are no double crossovers, there can be no NPD tetrads. Hence, the frequencies are PD = 80% and TT = 20%.
- 4.19.** One parent contributes only *A B* gametes to the progeny. The doubly heterozygous parent contributes 155 *Ab* gametes, 44 *ab*, 36 *AB*, and 165 *aB*. The most frequent gametes are *Ab* and *aB*, indicating that the doubly heterozygous parent had *A* and *B* in repulsion. The frequency of recombination from these data equals  $80/400 = 0.20$ , or 20 percent.
- 4.20.** **(a)** This is like any other three-point cross problem once the genotypes of the progeny have been inferred from the gel patterns. One of the parents is triply heterozygous and one is homozygous *a b c*. The most frequent classes of gametes from the triply heterozygous parent are *A B C* and *a b c*, and the least frequent are *a B c* and *a B C*. Hence, gene *C* is in the middle. **(b)** *A C B/a c b*. **(c)**  $(54 + 45 + 5 + 3)/1000 = 0.107$ , or 10.7 map units. **(d)**  $(80 + 59 + 5 + 3)/1000 = 0.147$ , or 14.7 map units. **(e)** The coincidence =  $8/(0.107 \times 0.147 \times 1000) = 0.509$ . **(f)** The interference =  $1 - \text{coincidence} = 1 - 0.509 = 0.491$ .

## Study Questions

- 4.S1.** If recombination frequency between two genes is 2.8 percent, what is the distance between the genes in map units on the linkage map?
- A)** 1.4  
**B)** 2.8  
**C)** 5.6  
**D)** Impossible to determine, because the interference is not known
- 4.S2.** A coefficient of coincidence of 0.125 means that:
- A)** There were eight times as many single crossovers as double crossovers.  
**B)** The frequency of double crossovers is 1/8 of the number expected if there were no interference.  
**C)** There were eight times as many single crossovers in one region as there were in an adjacent region.  
**D)** There were eight times as many parental as recombinant progeny.  
**E)** The frequency of double crossovers is 1/8.  
**F)** The frequency of double crossovers is 1/8 of the number expected if there were no interference.
- 4.S3.** In tetrad analysis, if two genes are linked, then what?
- A)** PD = NPD  
**B)** PD < NPD  
**C)** NPD < PD  
**D)** TT = 6 NPD

- 4.S4.** In tetrad analysis, three-strand double crossing-over between two linked genes results in what?
- A)** PD tetrad
  - B)** NPD tetrad
  - C)** TT tetrad
  - D)** Type of tetrad depends on the distance between genes
  - E)** Type of tetrad depends on the distance between genes and the centromere
- 4.S5.** Genes that undergo independent assortment are said to be \_\_\_\_\_.
- 4.S6.** The genetic distance in map units equals the \_\_\_\_\_ so long as double crossovers do not occur.
- 4.S7.** The observed number of double recombinants divided by the \_\_\_\_\_ is the coefficient of coincidence.
- 4.S8.** What is the frequency of crossing-over between genes *A* and *B* if the distance between them is 5 map units?
- 4.S9.** One map unit is defined as the length of the chromosome in which, on the average, \_\_\_\_\_ crossover is formed in every \_\_\_\_\_ cells undergoing meiosis.
- 4.S10.** What is the map distance between two genes between which 70% of the meiotic cells have no crossover, 15% have one, 9% have two, and 6% have three.