

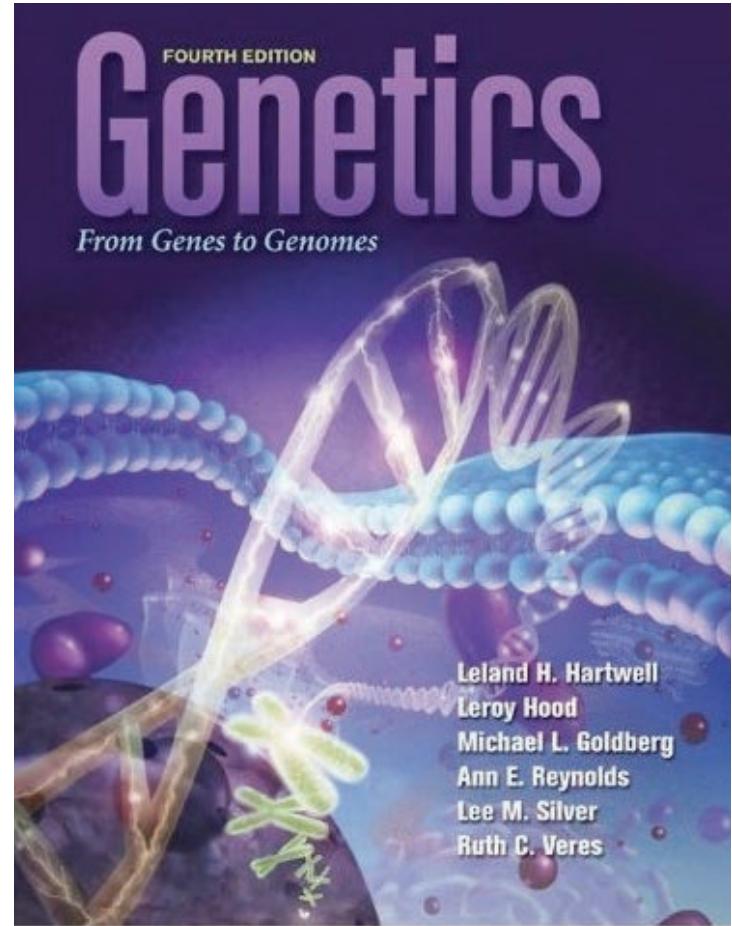
PowerPoint to accompany

Genetics: From Genes to Genomes

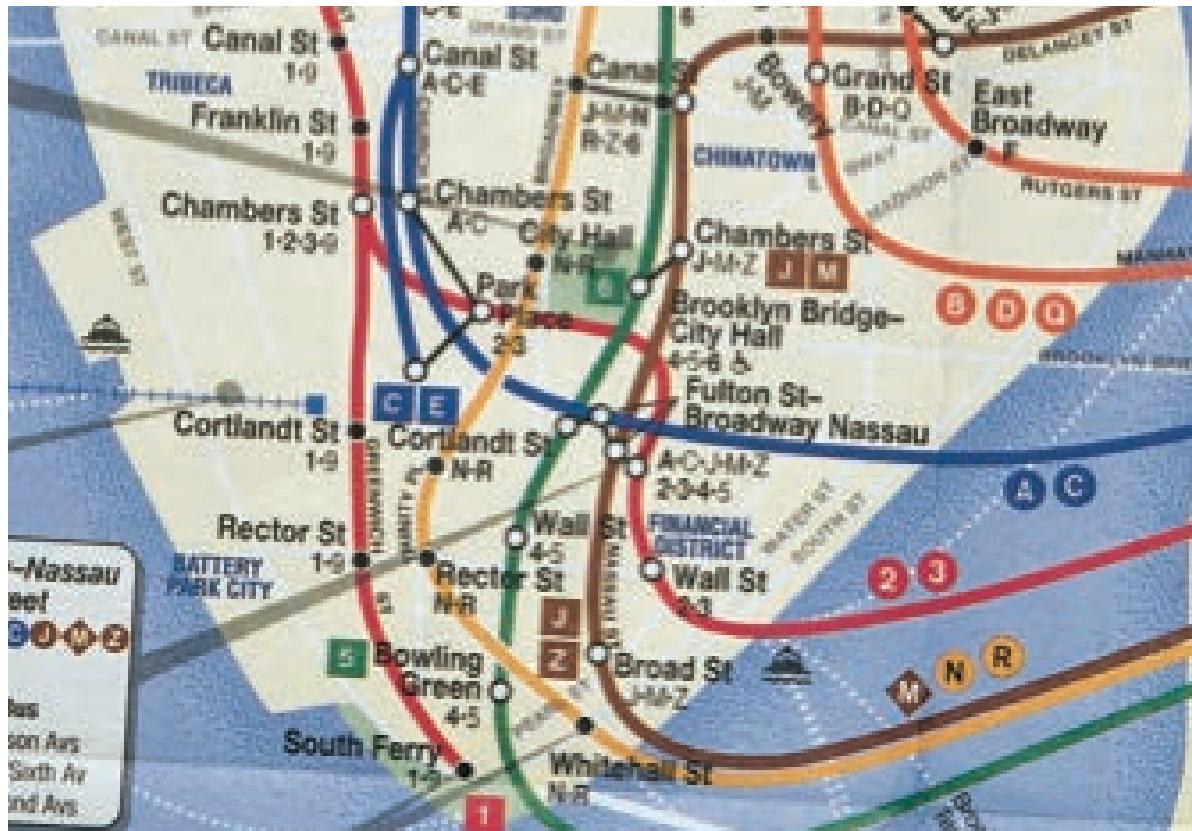
Fourth Edition

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Linkage, Recombination and the Mapping of Genes on Chromosomes



CHAPTER OUTLINE

- **5.1 Gene Linkage and Recombination**
- **5.2 The Chi-Square Test and Linkage Analysis**
- **5.3 Recombination: A Result of Crossing-Over During Meiosis**
- **5.4 Mapping: Locating Genes Along a Chromosome**
- **5.5 Tetrad Analysis in Fungi**
- **5.6 Mitotic Recombination and Genetic Mosaics**

Gene linkage and recombination

Genes linked together on the same chromosome usually assort together

Linked genes may become separated by recombination

Two themes in this chapter:

- 1.Further apart two genes are, the greater the probability of recombination**
- 2.Recombination data can be used to generate maps of relative locations of genes on chromosomes**

Detecting linkage by analyzing the progeny of dihybrid crosses: X-linked genes

Syntenic genes –genes located on the same chromosome

Two X-linked genes in Drosophila with recessive alleles

- w^+ (red eyes) and w (white eyes)
- y^+ (brown body) and y (yellow body)

Note that in this cross:

F_1 males get their only X chromosome from their mothers

F_1 females are dihybrids

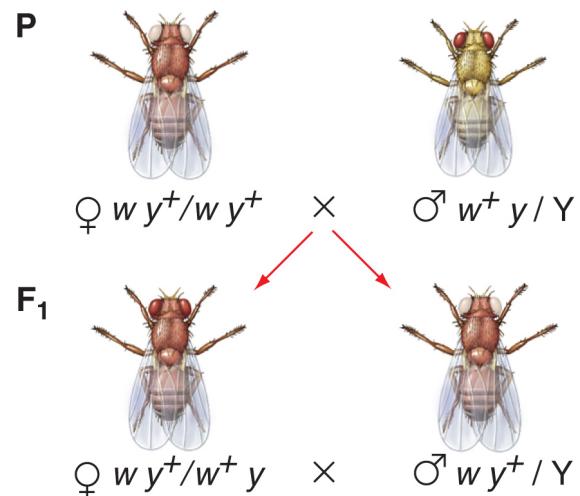


Fig. 5.2a

Detecting linkage by analyzing the progeny of dihybrid crosses: X-linked genes (cont)

Compare allele configurations in F₂ to P generation

Deviation from 1:1:1:1 segregation in F₂ indicates the genes are linked

Note that in this cross involving X-linked genes, only the F₂ male progeny were counted

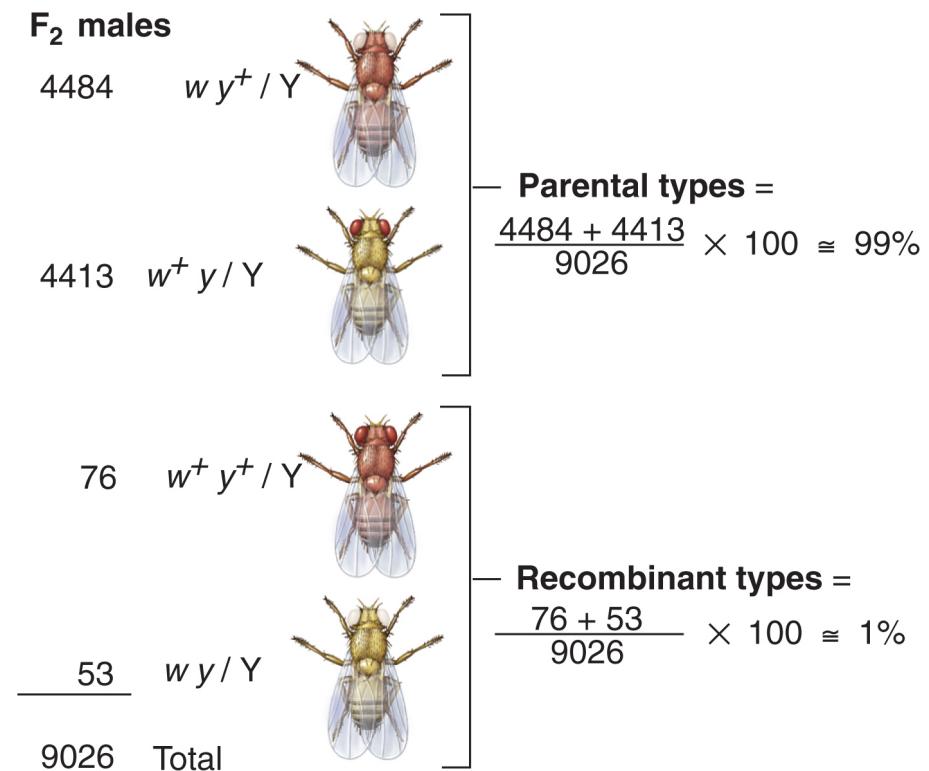


Fig. 5.2b

Designation of "parental" and "recombinant" relate to past history

Note that the parental configurations in these two crosses are the opposite of each other

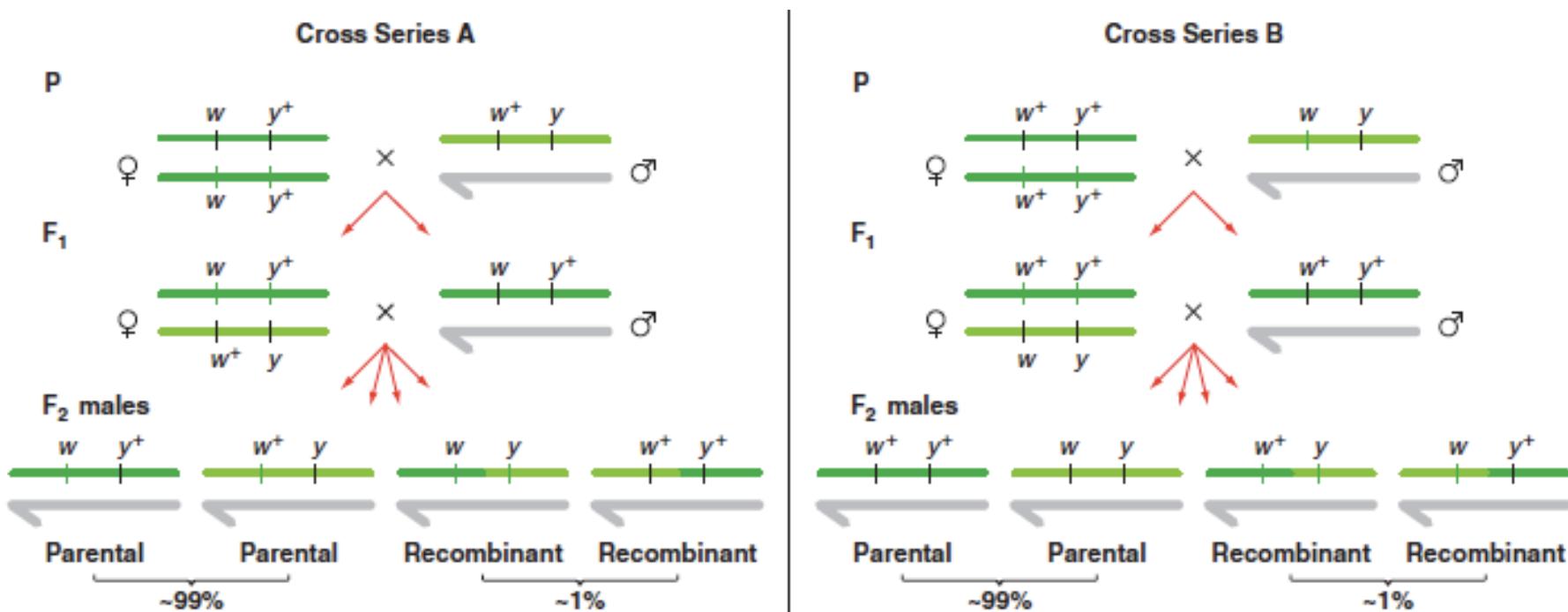


Fig. 5.3

Autosomal genes can also exhibit linkage

Detect linkage by generating a double heterozygote and crossing to homozygous recessive (testcross)

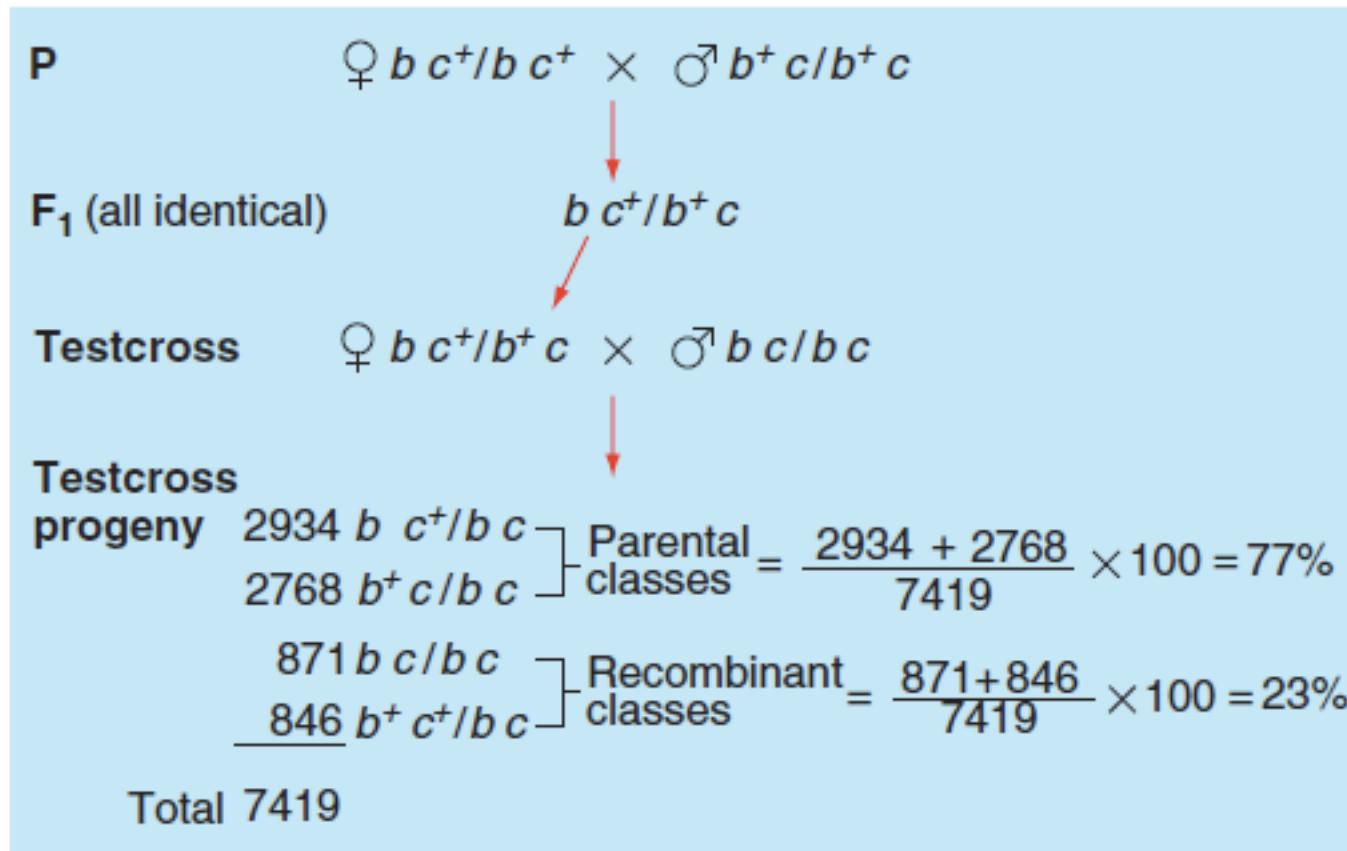


Fig. 5.4

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Chi square test pinpoints the probability that ratios are evidence of linkage

Deviations from 1:1:1:1 ratios can represent chance events or linkage

Chi square test measures "goodness of fit" between observed and expected values

Null hypothesis –observed values are no different from expected values

- In linkage studies, the null hypothesis is no linkage
- If genes are linked, expect 1:1:1:1 ratio in F_2 progeny
- Chi-square test can reject the null hypothesis, but it cannot prove a hypothesis

Information needed for the chi-square test

Use data from breeding experiment

- Total number of progeny
- How many classes of progeny
- Number of offspring observed in each class

Calculate number of offspring expected in each class if there is no linkage (1:1:1:1 segregation)

Applying the chi-square test

Calculate the chi-square:

$$\chi^2 = \sum \frac{(\text{no. observed} - \text{no. expected})^2}{\text{no. expected}} = \sum \frac{(O - E)^2}{E}$$

Consider degrees of freedom (df) in the experiment

- $df = N - 1$ (where N is the number of classes)

Determine a p value using chi-square value and df

- Probability that the deviation from expected numbers had occurred by chance
- Use table 5.1

Applying the chi-square test to see if genes *A* and *B* are linked

Progeny	Experiment 1		Experiment 2	
<i>A B</i>		17		34
<i>a b</i>		14		28
<i>A b</i>		8		16
<i>a B</i>		11		22
Total		50		100
Class	Observed / Expected		Observed / Expected	
Parentals	31	25	62	50
Recombinants	19	25	38	50

Fig. 5.5

Experiment 1: $\chi^2 = \sum \frac{(O - E)^2}{E} = \frac{(31 - 25)^2}{25} + \frac{(19 - 25)^2}{25} = 1.44 + 1.44 = 2.88$

Experiment 2: $\chi^2 = \sum \frac{(O - E)^2}{E} = \frac{(62 - 50)^2}{50} + \frac{(38 - 50)^2}{50} = 2.88 + 2.88 = 5.76$

Critical chi-square values

Use p value of 0.05 as cutoff

Chi-square values that lie in the yellow region of this table allow rejection of the null hypothesis with >95% confidence

If null hypothesis is rejected, then linkage can be postulated

Degrees of Freedom	p Values						
	Cannot Reject the Null Hypothesis				Null Hypothesis Rejected		
	0.99	0.90	0.50	0.10	0.05	0.01	0.001
χ^2 Values							
1	—	0.02	0.45	2.71	3.84	6.64	10.83
2	0.02	0.21	1.39	4.61	5.99	9.21	13.82
3	0.11	0.58	2.37	6.25	7.81	11.35	16.27
4	0.30	1.06	3.36	7.78	9.49	13.28	18.47
5	0.55	1.61	4.35	9.24	11.07	15.09	20.52

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Recombination: A result of crossing-over during meiosis

Frans Janssens –1909, observed chiasmata at chromosomes during prophase of meiosis I

T. H. Morgan – suggested chiasmata were sites of chromosome breakage and exchange

H. Creighton and B. McClintock (corn) and C. Stern (*Drosophila*) – 1931, direct evidence that genetic recombination depends on reciprocal exchanged of chromosomes

- **Physical markers were used to identify specific chromosomes**
- **Genetic markers were used as points of reference for recombination**

Evidence that recombination results from reciprocal exchanges between homologous chromosomes

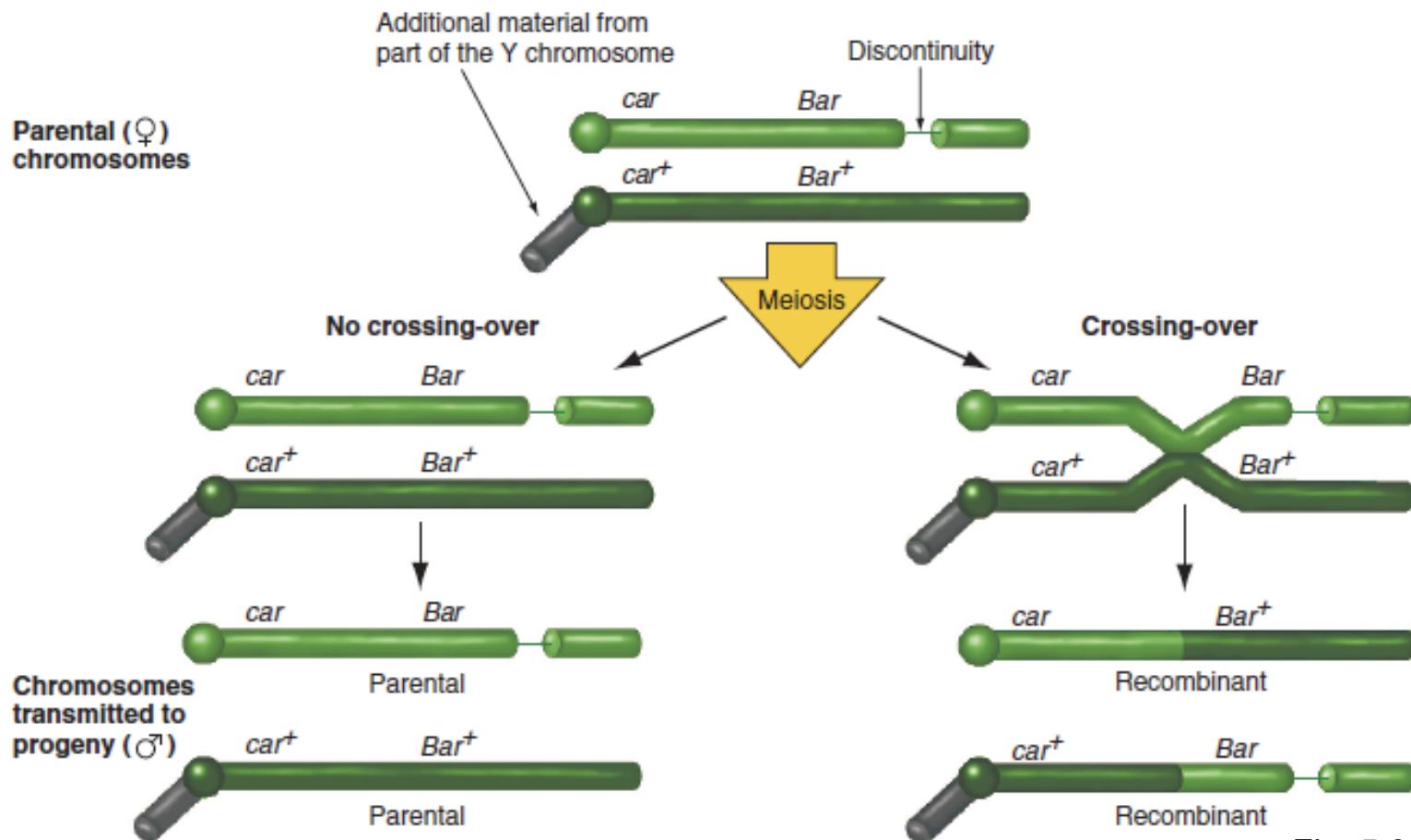


Fig. 5.6

Recombination during meiosis I visualized by light microscopy

Early Prophase

Leptotene and Zygote

Diplotene

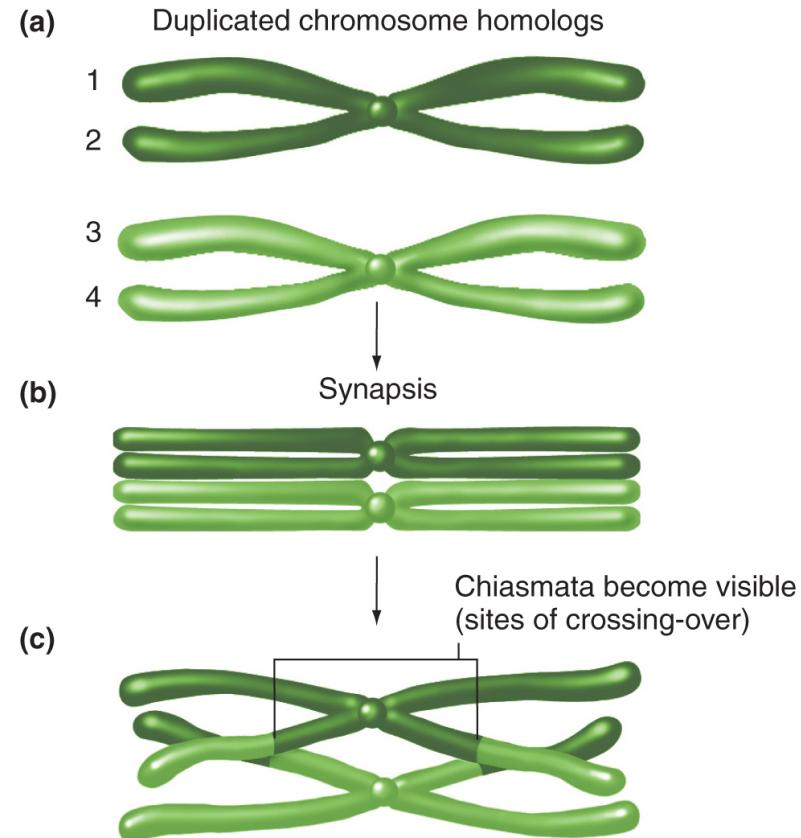


Fig. 5.7

Recombination during meiosis I visualized by light microscopy (cont)

Terminalization – movement of chiasmata

Anaphase – chromosome separation occurs after chiasmata reach the telomeres

Two recombinant and two parental gametes are produced

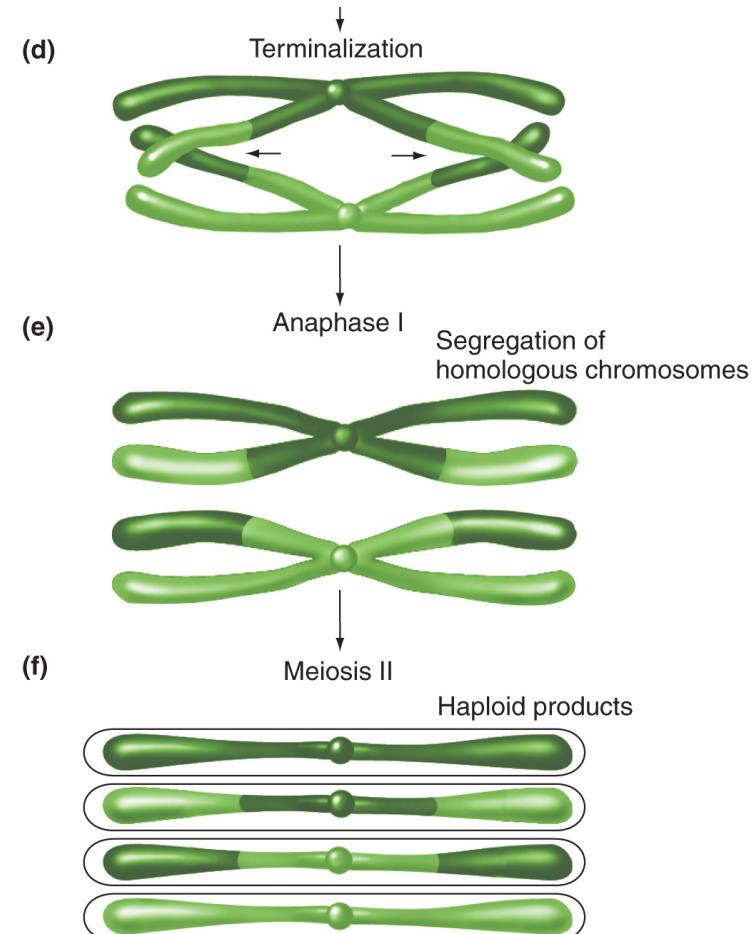


Fig. 5.7

Recombination frequencies are the basis of genetic maps

A. H. Sturtevant – proposed that **recombination frequencies (RF)** could be used as a measure of physical distance between two linked genes

1 percent recombination = 1 RF = 1 map unit (m.u.)

1 RF = 1 map unit (m.u.) – 1 centiMorgan (cM)

(a)



(b)

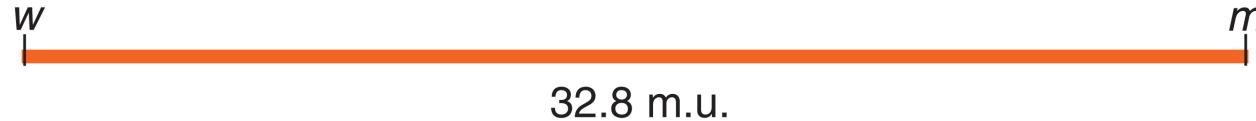


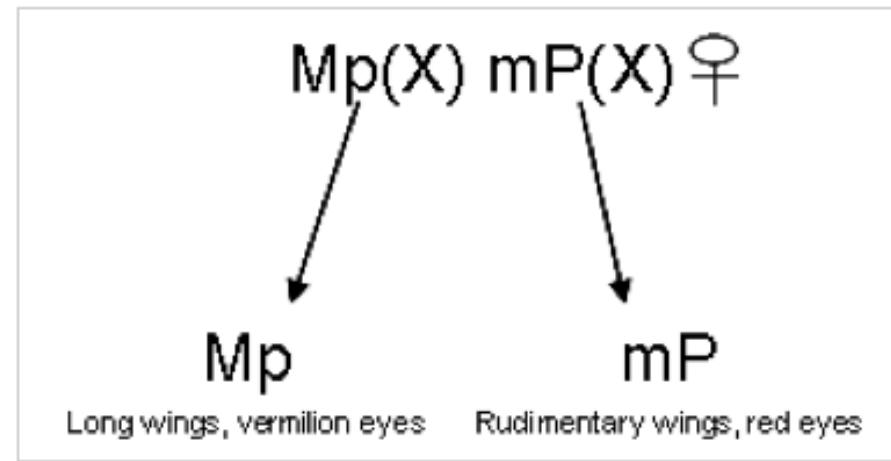
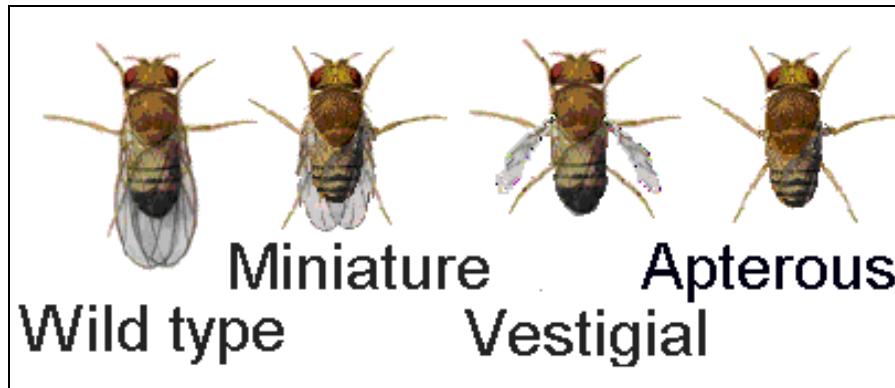
Fig. 5.8

Recombination frequencies are the basis of genetic maps

Sturtevant's map included five genes on the X chromosome of *Drosophila*.

The genes are yellow body (*y*), white eyes (*w*), vermilion eyes (*v*), miniature wings (*m*), and rudimentary wings (*r*).

Sturtevant's cross:



Properties of linked versus unlinked genes

Linked Genes

Parentals > recombinants ($RF < 50\%$)

Linked genes must be syntenic and sufficiently close together on the same chromosome so that they do not assort independently.

Unlinked Genes

Parentals = recombinants ($RF = 50\%$)

Occurs either when genes are on different chromosomes or when they are sufficiently far apart on the same chromosome.

Table 5.2

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Mapping genes by comparisons of two-point crosses

Left-right orientation of map is arbitrary

Most accurate maps obtained by summing many small intervening distances

(a) Gene pair	RF
$y-w$	1.1
$y-v$	33.0
$y-m$	34.3
$y-r$	42.9
$w-v$	32.1
$w-m$	32.8
$w-r$	42.1
$v-m$	4.0
$v-r$	24.1
$m-r$	17.8

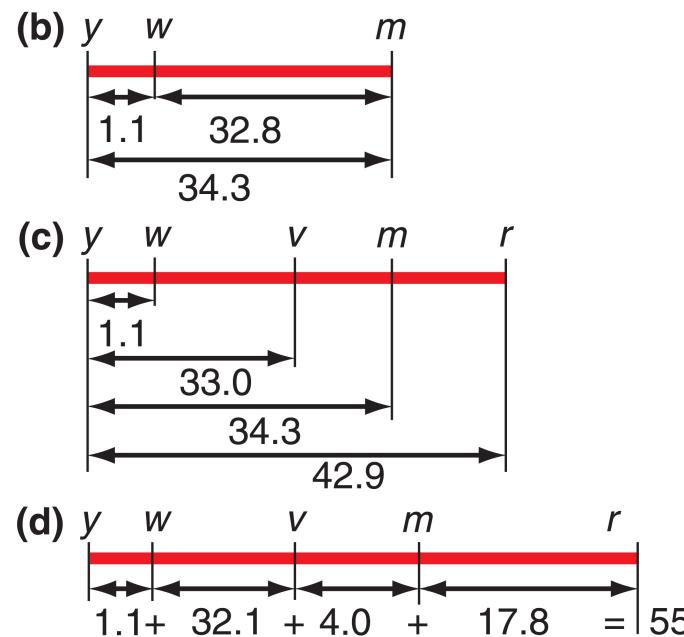


Fig. 5.9

Limitations of two point crosses

Difficult to determine gene order if two genes are close together

Actual distances between genes do not always add up

Pair-wise crosses are time and labor consuming

Three point crosses provide faster and more accurate mapping

Testcross of triply-heterozygous F₁

P ♀ $vg\ b\ pr / vg\ b\ pr$ × ♂ $vg^+\ b^+\ pr^+ / vg^+\ b^+\ pr^+$

F₁ (all identical) $vg\ b\ pr / vg^+\ b^+\ pr^+$

Testcross ♀ $vg\ b\ pr / vg^+\ b^+\ pr^+$ × ♂ $vg\ b\ pr / vg\ b\ pr$

Testcross progeny	Count	Genotype	Relative to	Description
	1779	$vg\ b\ pr$		Parental combinations for all three genes
	1654	$vg^+\ b^+\ pr^+$		
	252	$vg^+\ b\ pr$	$vg\ b\ pr$	Recombinants for vg relative to parental combinations for b and pr
	241	$vg\ b^+\ pr^+$	$vg\ b\ pr$	
	131	$vg^+\ b\ pr^+$	$vg^+\ b^+\ pr^+$	Recombinants for b relative to parental combinations for vg and pr
	118	$vg\ b^+\ pr$	$vg^+\ b^+\ pr^+$	
	13	$vg\ b\ pr^+$	$vg\ b\ pr$	Recombinants for pr relative to parental combinations for vg and b
	9	$vg^+\ b^+\ pr$	$vg^+\ b^+\ pr^+$	
	4197			

Fig. 5.10

Analyzing the results of a three-point cross

Testcross progeny have four sets of reciprocal pairs of genotypes

- Most frequent pair has parental configuration of alleles
- Least frequent pair results from double crossovers
- Examination of double crossover class reveals which gene is in the middle

1779	$vg\ b\ pr$	Parental combinations for all three genes
1654	$vg^+\ b^+\ pr^+$	
252	$vg^+\ b\ pr$	
241	$vg\ b^+\ pr^+$	
131	$vg^+\ b\ pr^+$	
118	$vg\ b^+\ pr$	
13	$vg\ b\ pr^+$	
9	$vg^+\ b^+\ pr$	

Recombinants for *vg* relative to parental combinations for *b* and *pr*

Recombinants for *b* relative to parental combinations for *vg* and *pr*

Recombinants for *pr* relative to parental combinations for *vg* and *b*

Fig. 5.10

Inferring the location of crossover event

Examine numbers of progeny

Compare configuration of alleles at two genes at a time to parental configuration

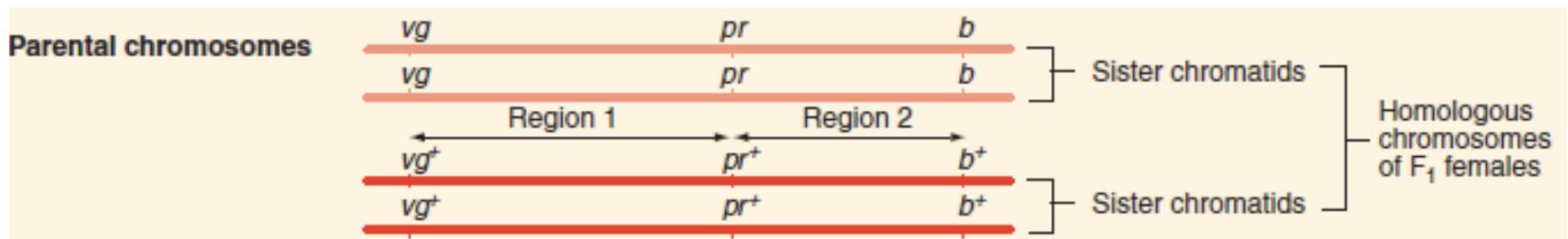


Fig. 5.11a

Inferring the location of crossover events (cont)

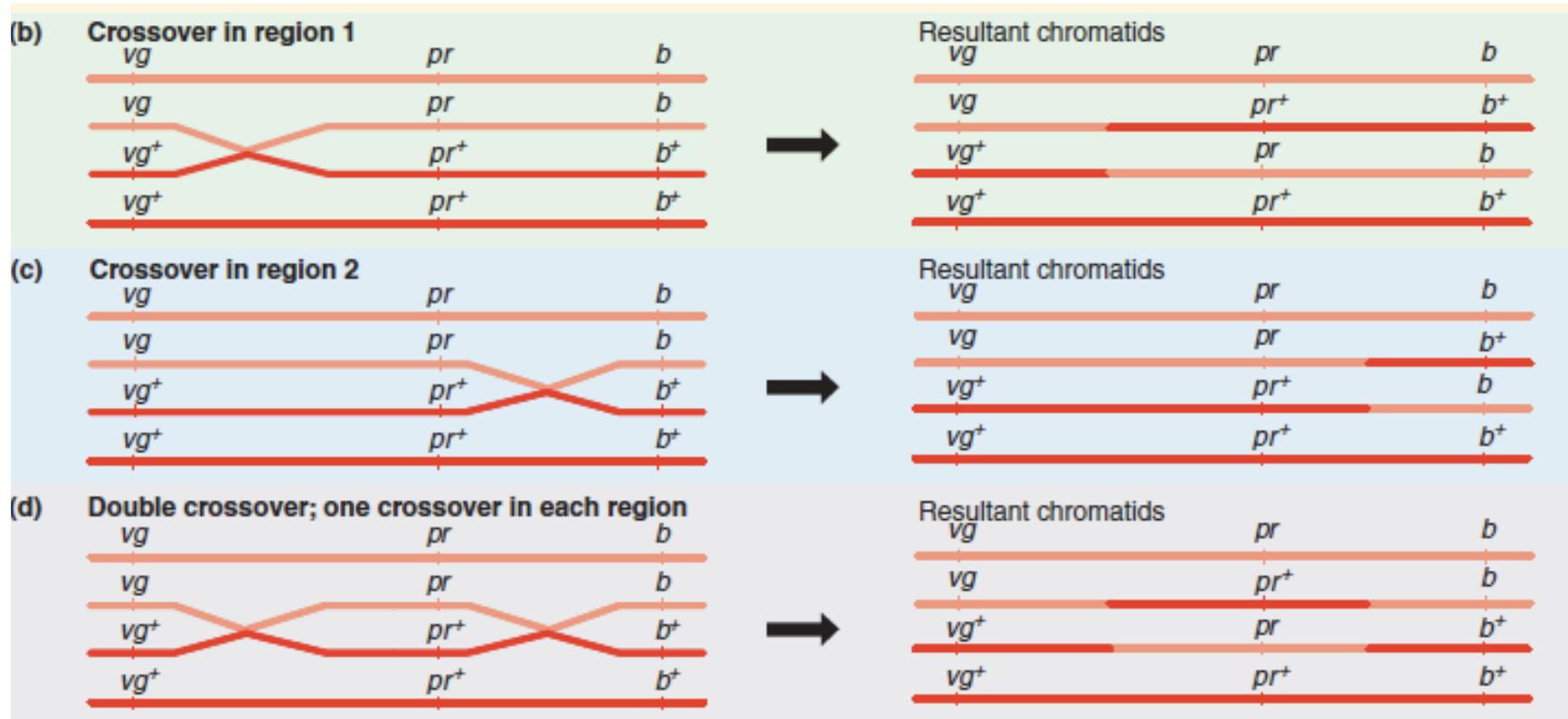


Fig. 5.11b-d

Genetic map deduced from three-point cross in Figure 5.10

$$vg - b \text{ distance} = \frac{(252 + 241 + 131 + 118)}{4197} \times 100 = 17.7$$

$$vg - pr \text{ distance} = \frac{(252 + 241 + 13 + 9)}{4197} \times 100 = 12.3$$

$$b - pr \text{ distance} = \frac{(131 + 118 + 13 + 9)}{4197} \times 100 = 6.4$$

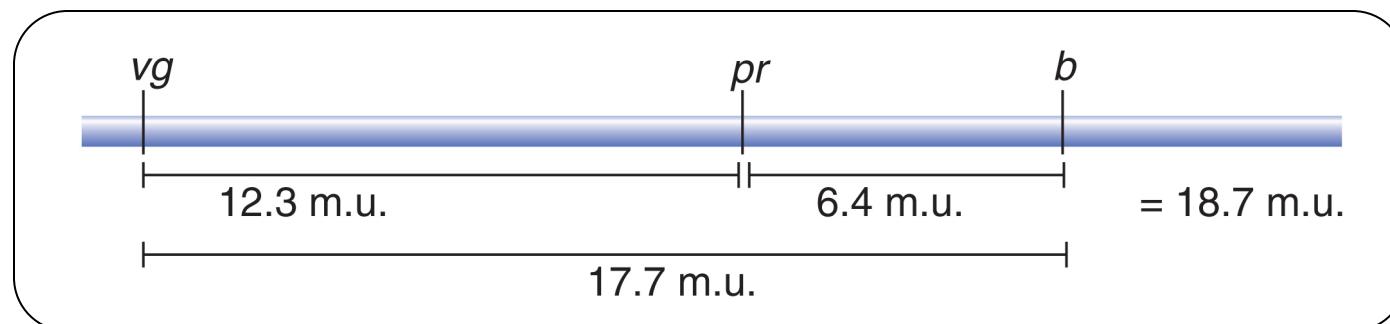


Fig. 5.10b

Correction for double crossovers

This calculation isn't accurate because it fails to account for double crossovers

$$vg - b \text{ distance} \frac{(252 + 241 + 131 + 118)}{4197} \times 100 = 17.7$$

Correct calculation that accounts for double crossovers

$$vg - b \text{ distance} \frac{(252 + 241 + 131 + 118 + 13 + 13 + 9 + 9)}{4197} \times 100 = 18.7$$

Interference: The number of double crossovers may be less than expected

Chromosomal interference – occurrence of crossover in one portion of a chromosome interferes with crossover in an adjacent part of the chromosome

Not uniform between chromosomes or within a chromosome

Compare observed and expected frequencies of double crossovers (DCO)

$$\text{Coefficient of coincidence} = \frac{\text{observed DCO frequency}}{\text{expected DCO frequency}}$$

$$\text{Interference} = 1 - \text{coefficient of coincidence}$$

Calculation of interference in the three-point cross in Figure 5.10

Expected probability of double crossovers is the product of the single crossover frequencies in each interval

- Probability of single crossover between *vg* and *pr* is 0.123 (12.3 m.u.)
- Probability of single crossover between *pr* and *b* is 0.064 (6.4 m.u.)

If interference = 0, crossovers in adjacent regions occur independently of each other

If interference = 1, no double crossovers occur

Calculation of interference in the three-point cross in Figure 5.10 (cont)

Expected probability of double crossovers

$$= 0.123 \times 0.064 = 0.0079 = 0.79\%$$

Observed proportion of double crossovers

$$= \frac{13 + 9}{4197} \times 100 = 0.52\%$$

$$\text{Coefficient of coincidence} = \frac{0.52}{0.79} = 0.66$$

$$\text{Interference} = 1 - 0.66 = 0.34$$

Drosophila melanogaster linkage groups

When many genes per chromosome have been mapped, a **linkage group** is synonymous with a chromosome

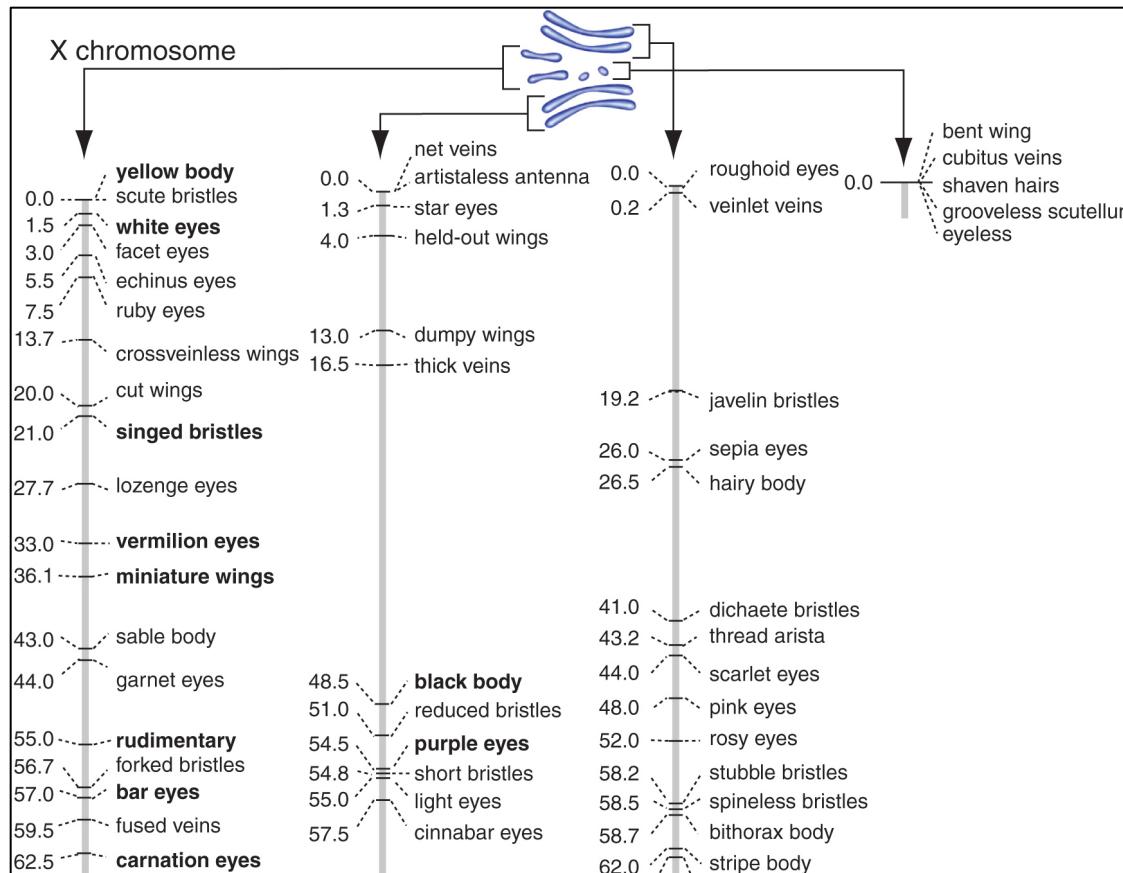


Fig. 5.13

Do genetic maps correlate with physical reality?

Order of genes revealed by genetic mapping corresponds to the actual order of genes along the chromosome

Actual physical distance (amount of DNA) does not always show direct correspondence to genetic distance

- Double, triple, and more crossovers
- 50% limit on observable recombination frequency
- Non-uniform recombination frequency across chromosomes
- Mapping functions compensate for some inaccuracies
- Recombination rates differ between species

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Tetrad analysis in fungi

- Two model organisms for understanding mechanisms of recombination
 - *Saccharomyces cerevisiae* – bakers yeast
 - *Neurospora crassa* – bread mold
- All four haploid products of each meiosis are contained within an ascus (sac)
- Ascospores (haplospores) can germinate and survive as viable haploids that divide by mitosis
- Tetrad - four ascospores in a single ascus
- Haploid strains of opposite mating type (*a* and *α*) can be mated and the resulting diploid induced to undergo meiosis

The life cycle of *Saccharomyces cerevisiae*

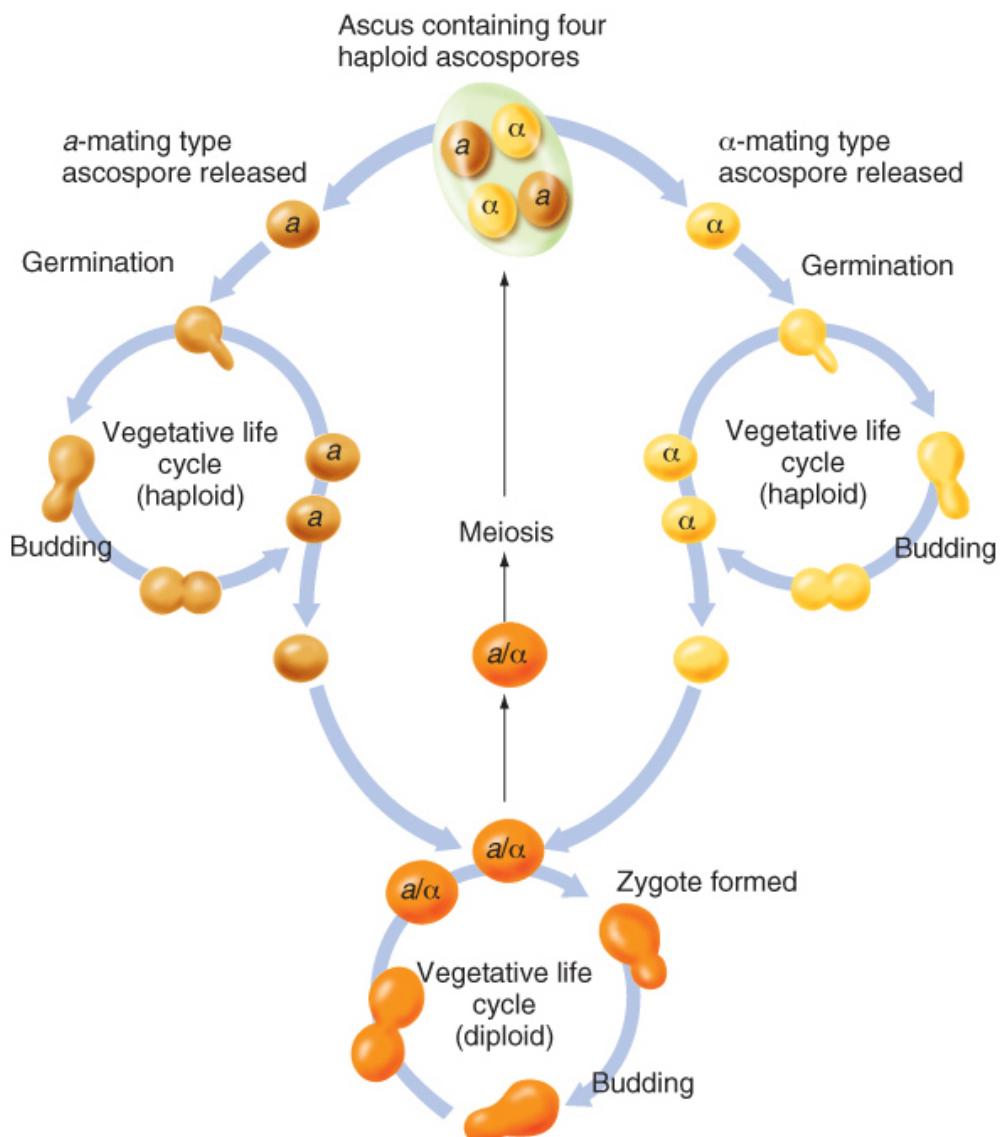
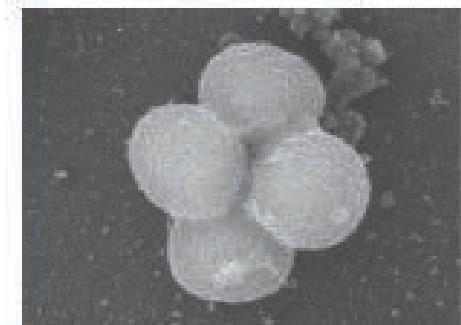
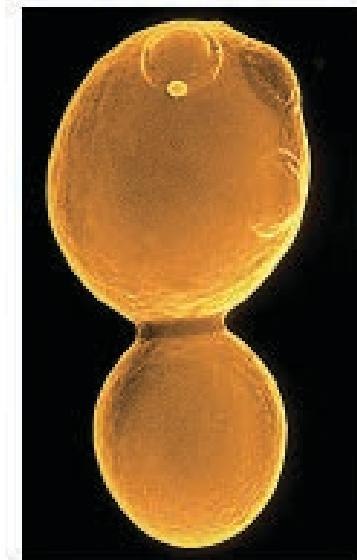


Fig. 5.14a

The life cycle of *Neurospora crassa*

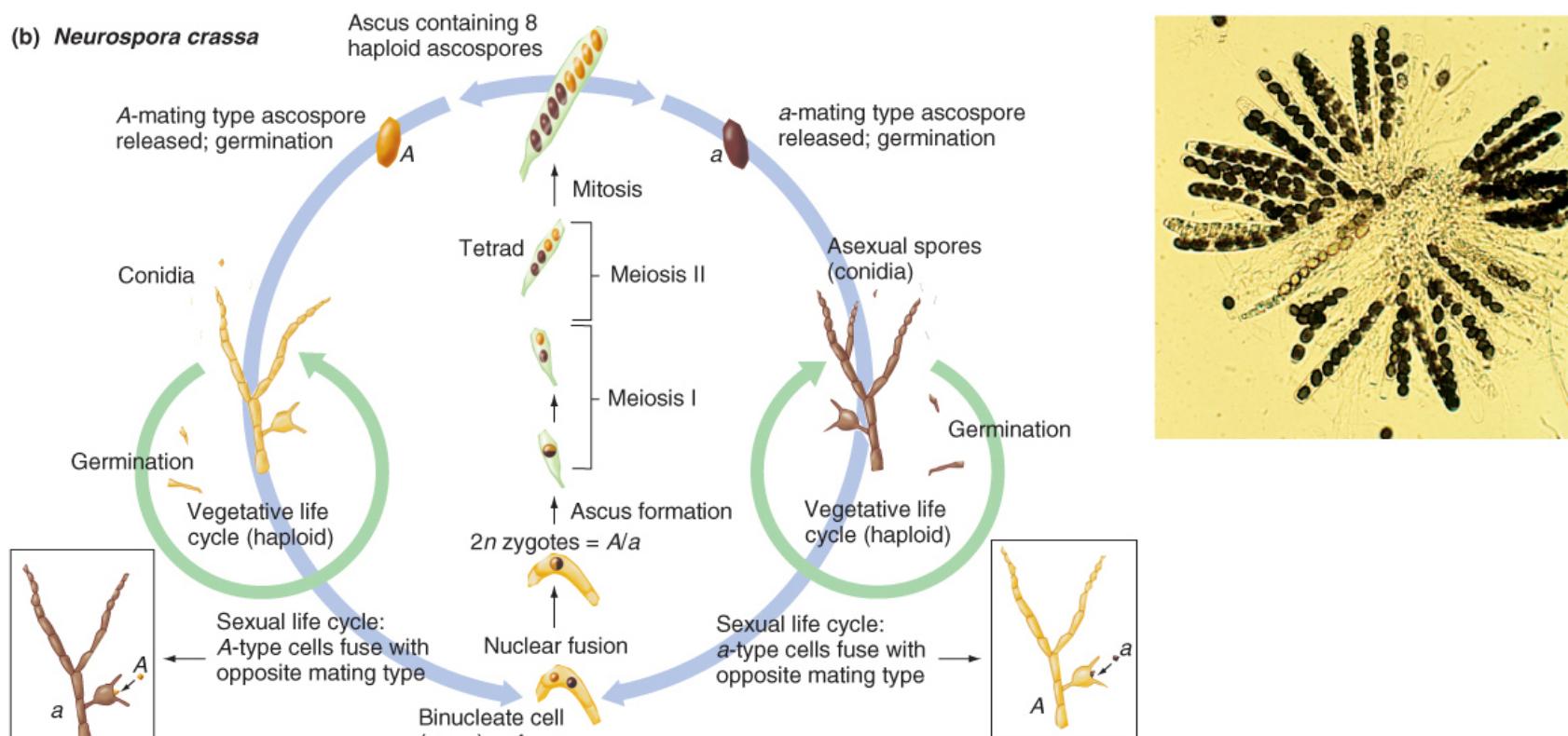


Fig. 5.14b

Genetic analysis in fungi

Phenotype of haploid fungi is direct representation of their genotype

Mutations in haploids can affect appearance of cells and ability to grow under certain conditions

- ***his4 mutant***; recessive, unable to grow in absence of histidine
- ***HIS4***; dominant, grows in presence or absence of histidine
- ***trp1 mutant***; recessive, unable to grow in absence of tryptophan
- ***TRP1***; dominant, grows in presence or absence of tryptophan

Generation of diploid yeast cells that are heterozygous for two unlinked genes

his4 TRP1 (a) x HIS4 trp1 (α) → his4/HIS4; trp1/TRP1 (a/ α)

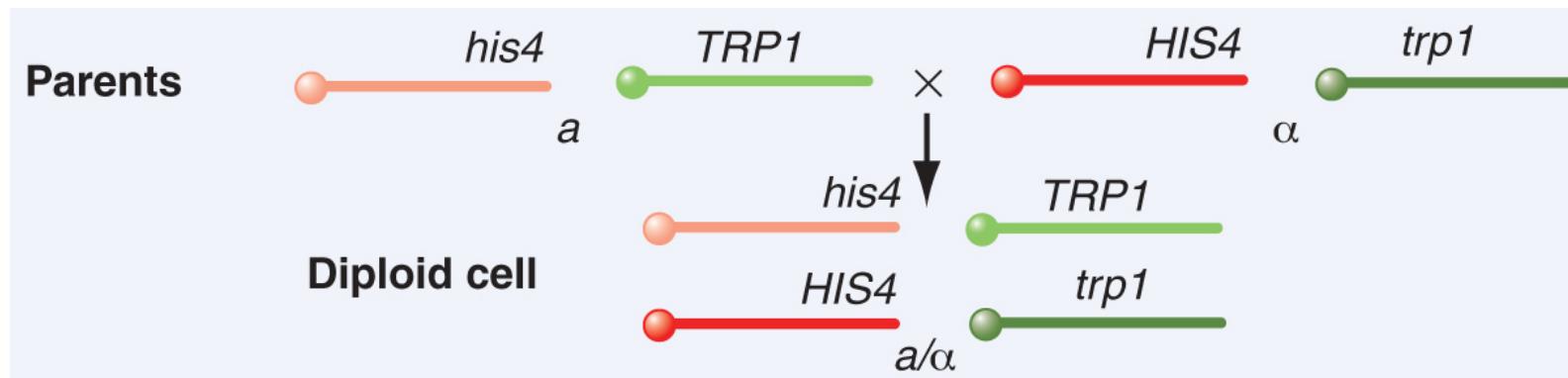


Fig. 5.15a

Meiosis can generate three kinds of tetrads:

(I) Parental ditype (PD)

his4 TRP1 (a) x HIS4 trp1 (α) → his4/HIS4; trp1/TRP1 (a/α)

Parental ditype (PD) - all spores with parental allele configurations (0/4 recombinants)

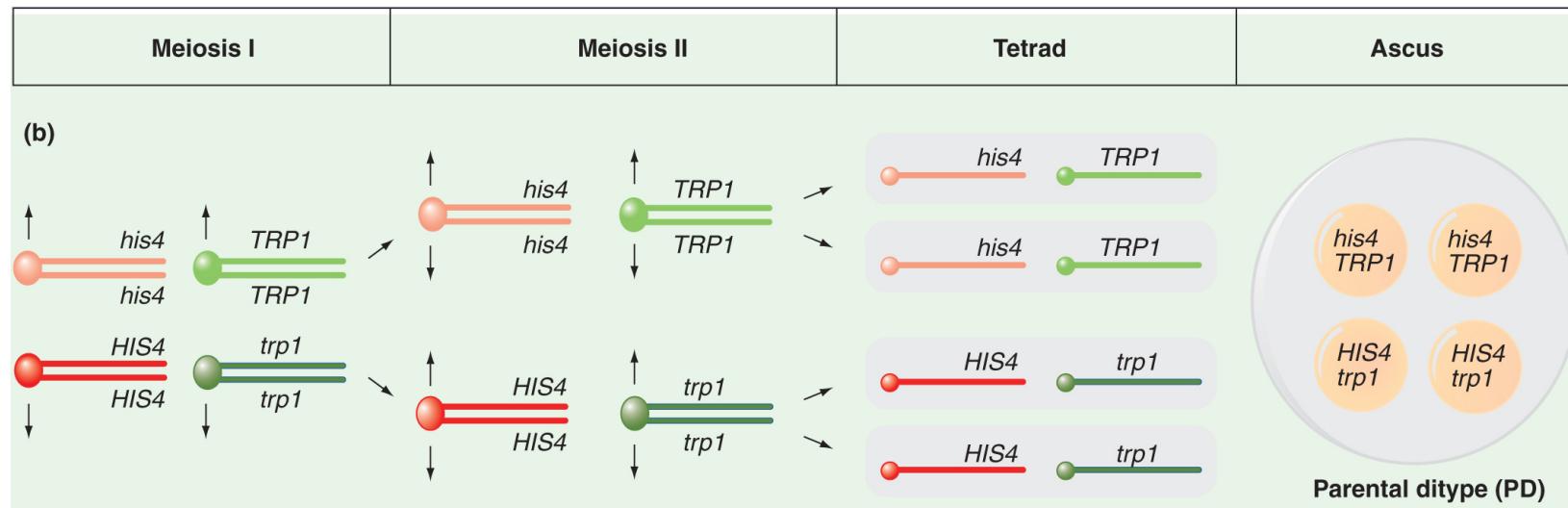


Fig. 5.15b

Meiosis can generate three kinds of tetrads:

(II) Nonparental ditype (NPD)

his4 TRP1 (a) x HIS4 trp1 (α) \rightarrow *his4/HIS4; trp1/TRP1 (a/ α)*

Nonparental ditype (NPD) - all spores with nonparental allele configuration (4/4 recombinants)

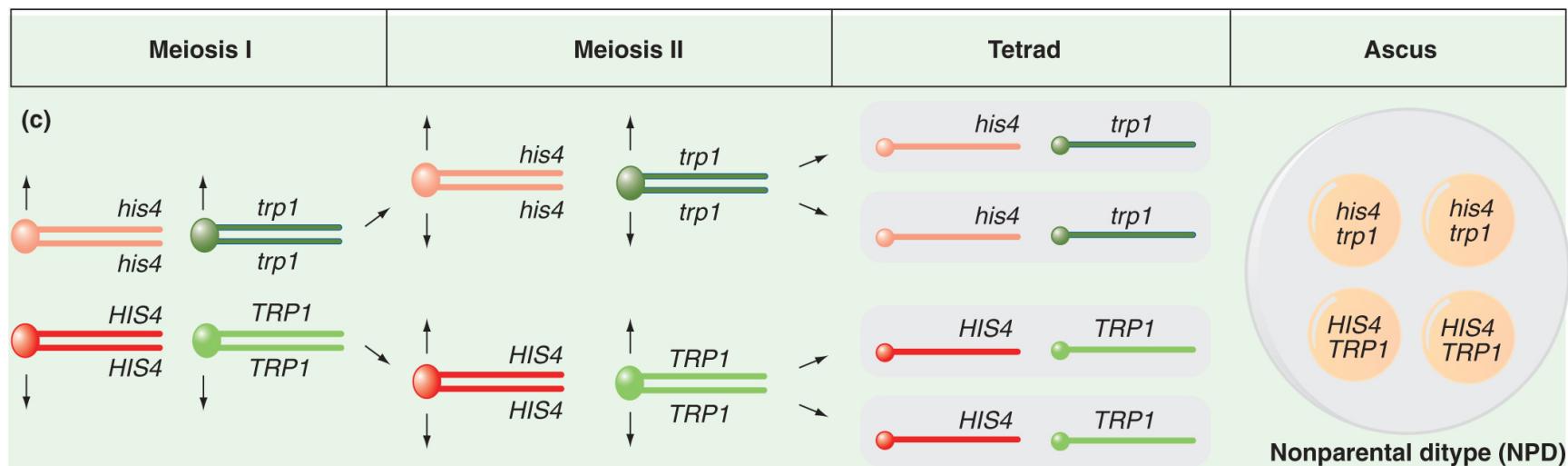


Fig. 5.15c

Meiosis can generate three kinds of tetrads:

(III) Tetratype (T)

his4 TRP1 (a) x HIS4 trp1 (α) → his4/HIS4; trp1/TRP1 (a/α)

Tetratype (T) - four kinds of spores (2/4 recombinants)

- Two have parental allele configurations
- Two have recombinant allele configurations
- Crossover between centromere and closest gene

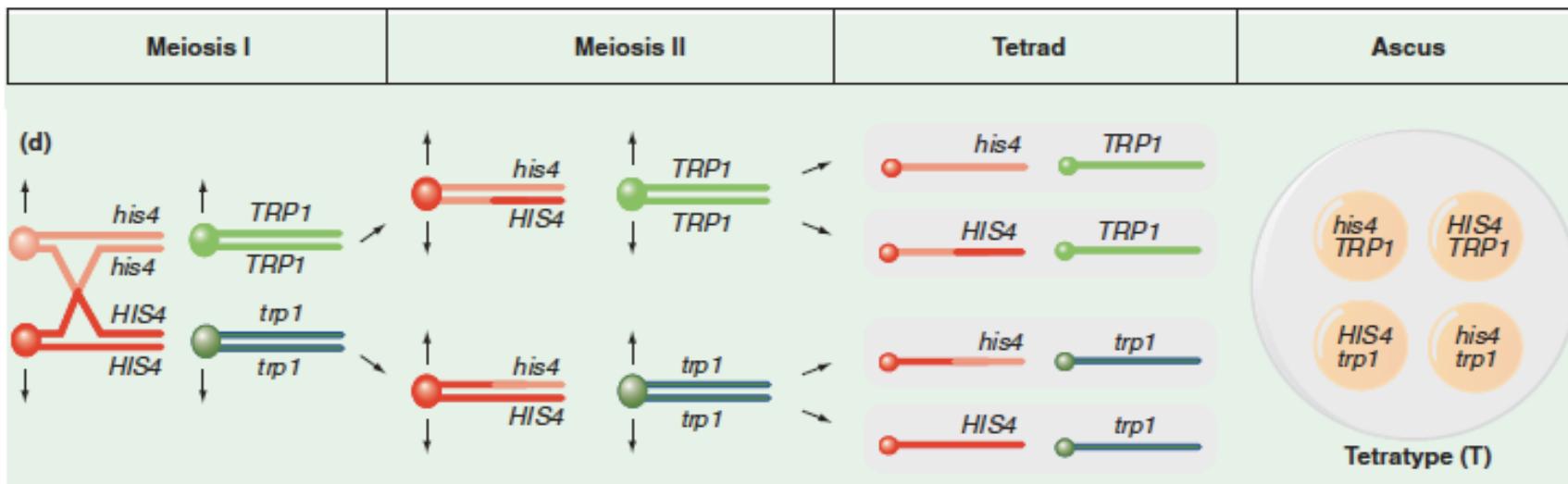


Fig. 5.15d

Tetrad analysis of unlinked genes

When genes are unlinked, number of PD = number of NPD

(e)	PD		NPD		T	
	<i>HIS4</i>	<i>trp1</i>	<i>his4</i>	<i>trp1</i>	<i>his4</i>	<i>trp1</i>
	<i>HIS4</i>	<i>trp1</i>	<i>his4</i>	<i>trp1</i>	<i>his4</i>	<i>TRP1</i>
	<i>his4</i>	<i>TRP1</i>	<i>HIS4</i>	<i>TRP1</i>	<i>HIS4</i>	<i>trp1</i>
	<i>his4</i>	<i>TRP1</i>	<i>HIS4</i>	<i>TRP1</i>	<i>HIS4</i>	<i>TRP1</i>
Number of tetrads	<hr/> 31		<hr/> 28		<hr/> 41	

Fig. 5.15e

Tetrad analysis of linked genes

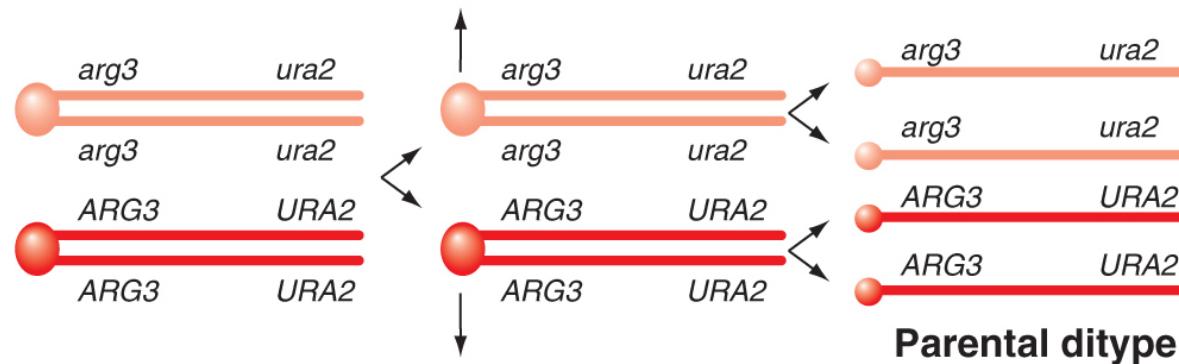
When genes are linked, number of PD >> number of NPD

P	<i>arg3 ura2</i> (α -mating type)	\times	<i>ARG3 URA2</i> (α -mating type)
Diploid cell	<i>arg3 ura2</i>	/	<i>ARG3 URA2</i>
		Meiosis	
Products of meiosis	PD	NPD	T
	<i>arg3 ura2</i>	<i>arg3 URA2</i>	<i>arg3 ura2</i>
	<i>arg3 ura2</i>	<i>arg3 URA2</i>	<i>arg3 URA2</i>
	<i>ARG3 URA2</i>	<i>ARG3 ura2</i>	<i>ARG3 ura2</i>
	<i>ARG3 URA2</i>	<i>ARG3 ura2</i>	<i>ARG3 URA2</i>
Number of tetrads	127	3	70

Fig. 5.16

How crossovers between linked genes generate different tetrads

(a) No crossing-over (NCO)



(b) Single crossover (SCO)

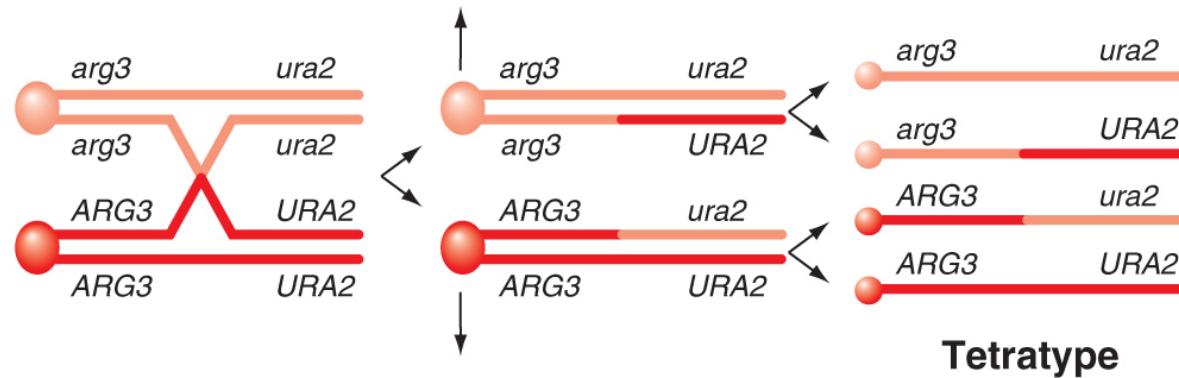
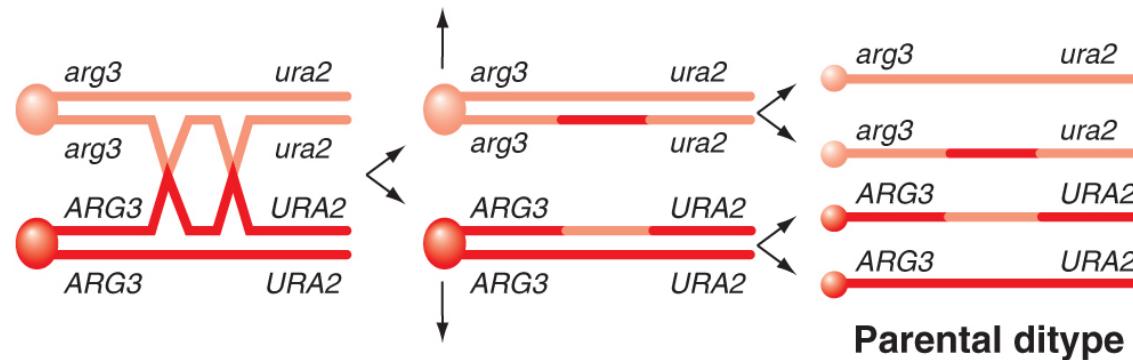


Fig. 5.17

How crossovers between linked genes generate different tetrads (cont)

(c) Double crossover (DCO)
2-strand



(d) DCO
3-strand

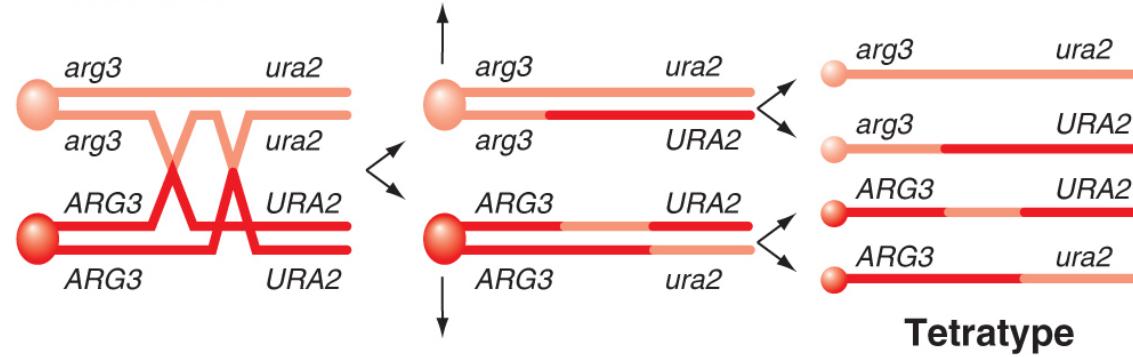
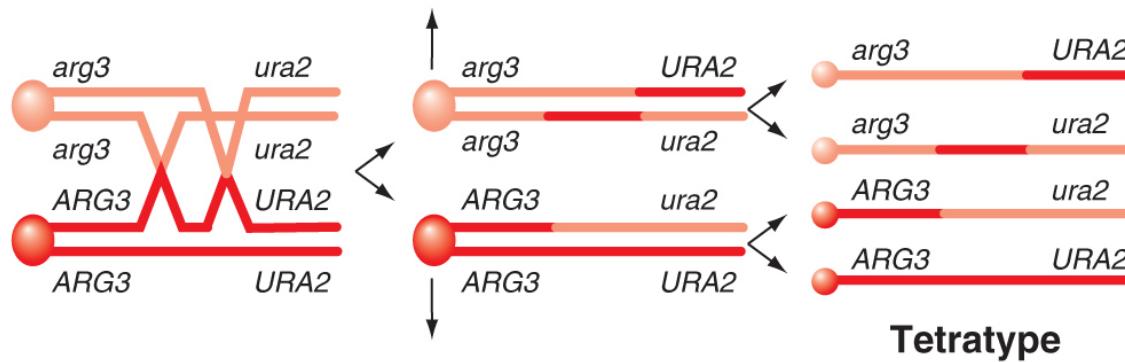


Fig. 5.17

How crossovers between linked genes generate different tetrads (cont)

(e) DCO
3-strand



(f) DCO
4-strand

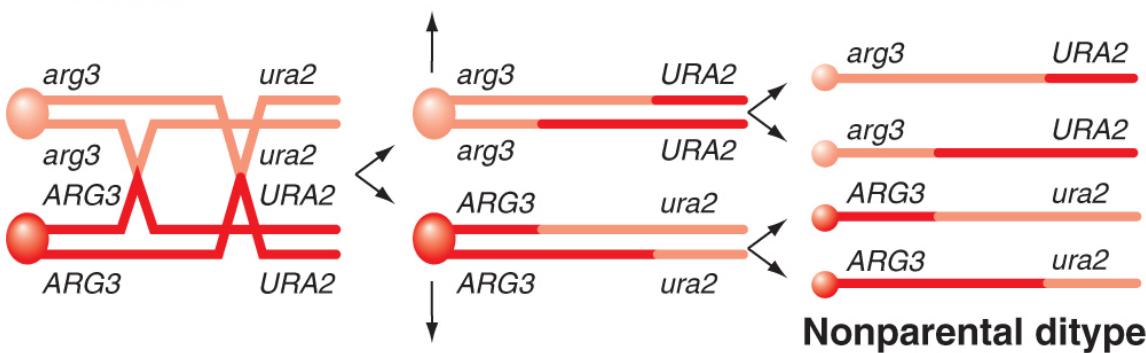


Fig. 5.17

Calculating Recombination Frequencies (RF) in Tetrad Analysis

$$RF = \frac{NPD + 1/2T}{\text{Total tetrads}} \times 100$$

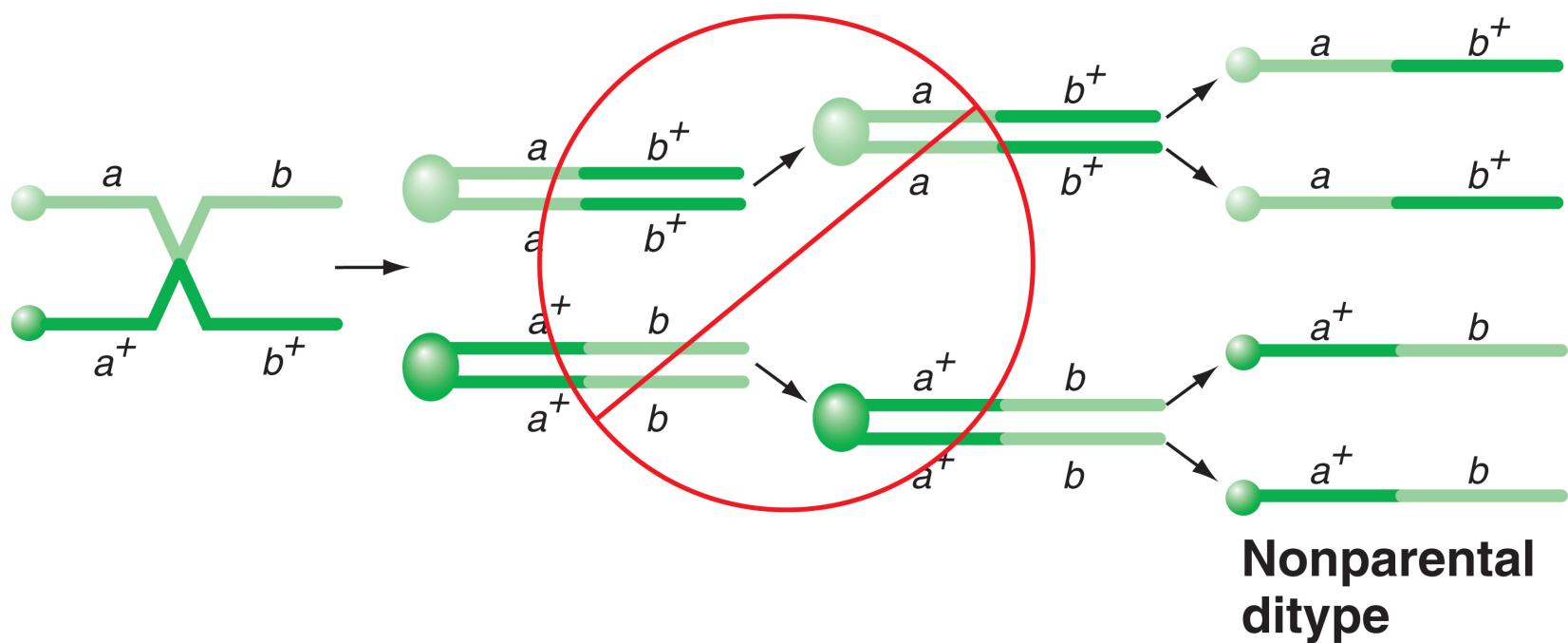
For the cross in Figure 5.16:

$$RF = \frac{3 + (1/2)(70)}{200} \times 100 = 19 \text{ m.u.}$$

P	<i>arg3 ura2</i> (α -mating type)	\times	<i>ARG3 URA2</i> (α -mating type)
Diploid cell	<i>arg3 ura2</i>	/	<i>ARG3 URA2</i>
		Meiosis	
Products of meiosis	PD	NPD	T
	<i>arg3 ura2</i> <i>arg3 ura2</i> <i>ARG3 URA2</i> <i>ARG3 URA2</i>	<i>arg3 URA2</i> <i>arg3 URA2</i> <i>ARG3 ura2</i> <i>ARG3 ura2</i>	<i>arg3 ura2</i> <i>arg3 URA2</i> <i>ARG3 ura2</i> <i>ARG3 URA2</i>
Number of tetrads	127	3	70

Tetrad Analysis: Evidence that recombination takes place at the four-strand stage

Recombination	Duplication	Meiosis I	Meiosis II
---------------	-------------	-----------	------------



Neurospora form ordered tetrads

Undergo meiosis I and II as usual, but a single round of mitosis after 2nd meiotic division – produces octad

Ascus is very narrow and spindle forms parallel to long axis

Two genetically identical ascospores are next to each other

Arrangement of chromatids can be inferred from position of ascospores

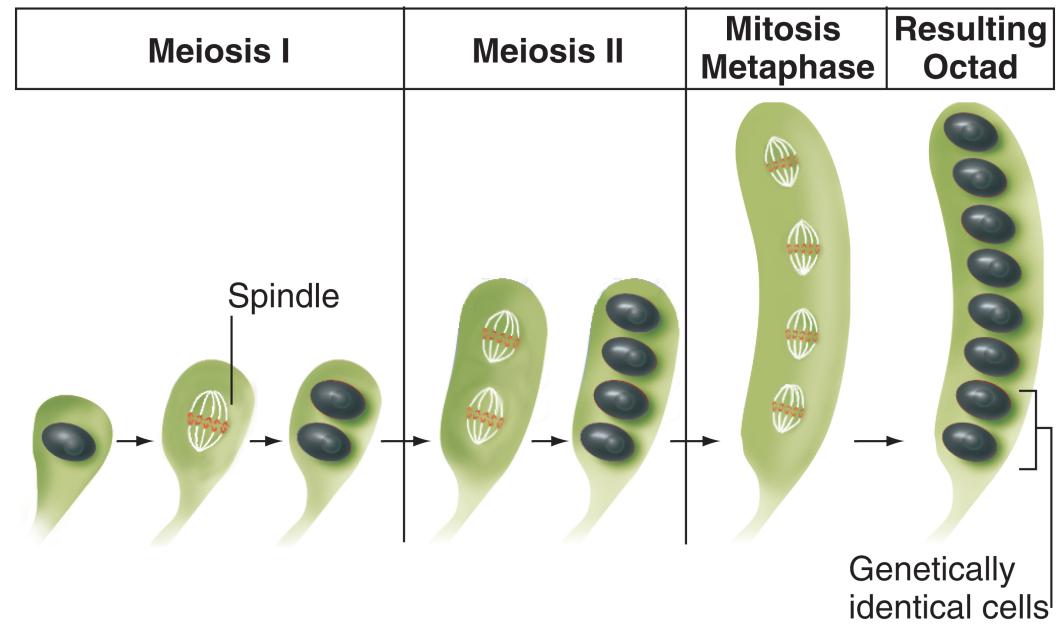


Fig. 5.20

Two segregation patterns in ordered ascospores: First-division segregation pattern

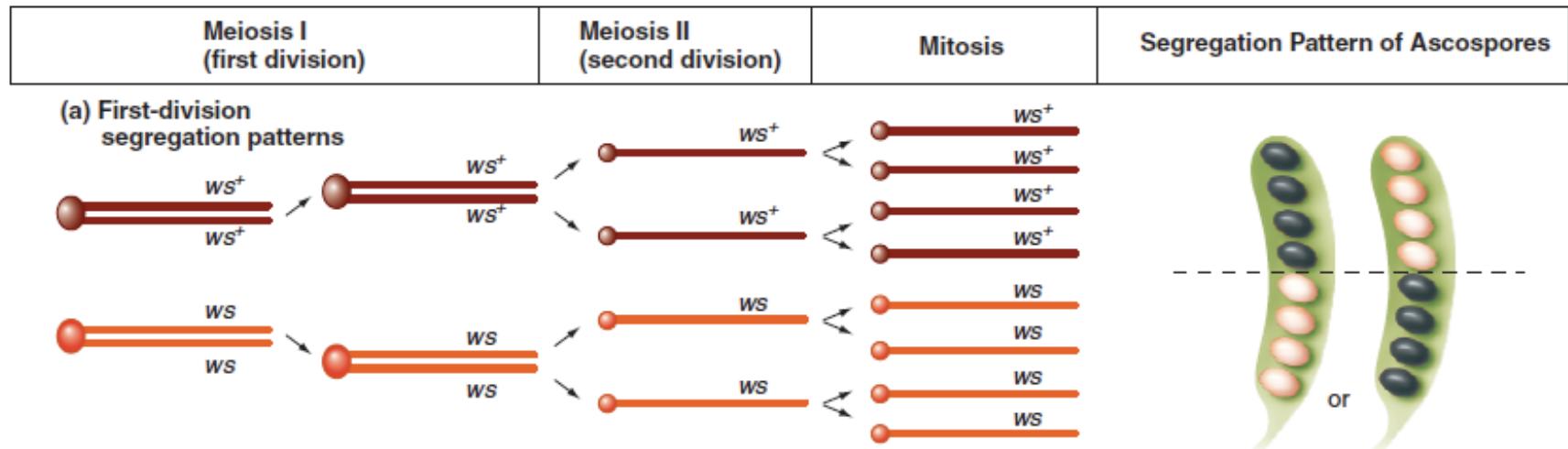


Fig. 5.21a

Two segregation patterns in ordered ascospores: Second-division segregation pattern

Number of second division tetrads is used to calculate the distance between a gene and a centromere

Centromere to Gene distance

$$= (\text{percentage of second division tetrads}) / 2$$

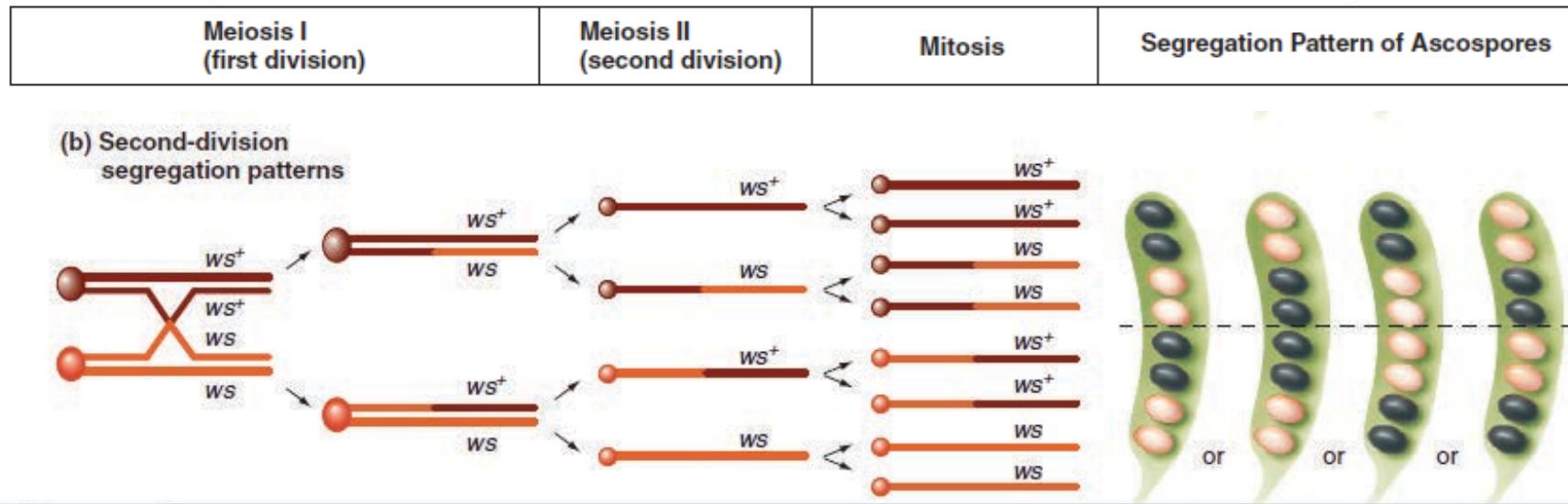


Fig. 5.21b

Ordered tetrads help locate genes in relation to the centromere

Neurospora cross $\text{thr}^+ \text{ arg}^+ \times \text{thr arg}$ → tetrads in 7 genotype classes

Centromere – thr distance:

$$\frac{(1/2)(16 + 2 + 2 + 1)}{105} \times 100 = 10 \text{ m.u.}$$

Centromere – arg distance:

$$\frac{(1/2)(11 + 2 + 2 + 1)}{105} \times 100 = 7.6 \text{ m.u.}$$

Tetrad group	A	B	C	D	E	F	G
Segregation pattern	thr arg thr arg $\text{thr}^+ \text{arg}^+$ $\text{thr}^+ \text{arg}^+$	thr arg $\text{thr}^+ \text{arg}$ $\text{thr}^+ \text{arg}^+$ $\text{thr}^+ \text{arg}^+$	thr arg thr arg^+ $\text{thr}^+ \text{arg}$ $\text{thr}^+ \text{arg}^+$	thr arg^+ $\text{thr}^+ \text{arg}$ $\text{thr}^+ \text{arg}^+$ thr arg	thr arg^+ $\text{thr}^+ \text{arg}$ $\text{thr}^+ \text{arg}$ thr arg^+	thr arg^+ $\text{thr}^+ \text{arg}$ $\text{thr}^+ \text{arg}$ thr arg	thr arg $\text{thr}^+ \text{arg}^+$ $\text{thr}^+ \text{arg}^+$ thr arg
Total in group	72	16	11	2	2	1	1

Fig. 5.22a

Determining linkage with ordered tetrads

Neurospora cross $thr^+ arg^+ \times thr\ arg$ → tetrads in 7 genotype classes

If *thr* and *arg* are linked, PD >> NPD

$$PD = 72 + 1 = 73 \gg NPD = 1 + 2 = 3$$

Tetrad group	A	B	C	D	E	F	G
Segregation pattern	<i>thr arg</i> <i>thr arg</i> <i>thr⁺arg⁺</i> <i>thr⁺arg⁺</i>	<i>thr arg</i> <i>thr⁺arg</i> <i>thr⁺arg⁺</i> <i>thr⁺arg⁺</i>	<i>thr arg</i> <i>thr arg⁺</i> <i>thr⁺arg</i> <i>thr⁺arg⁺</i>	<i>thr arg⁺</i> <i>thr⁺arg</i> <i>thr⁺arg⁺</i> <i>thr arg</i>	<i>thr arg⁺</i> <i>thr⁺arg</i> <i>thr⁺arg</i> <i>thr arg⁺</i>	<i>thr arg⁺</i> <i>thr arg⁺</i> <i>thr⁺arg</i> <i>thr⁺arg</i>	<i>thr arg</i> <i>thr⁺arg⁺</i> <i>thr⁺arg</i> <i>thr arg</i>
Total in group	72	16	11	2	2	1	1

Fig. 5.22a

Calculating map distance with ordered tetrads

arg – thr distance: $RF = \frac{3 + (1/2)(16 + 11 + 2)}{105} \times 100 = 16.7 \text{ m.u.}$

This calculation doesn't account for double crossovers

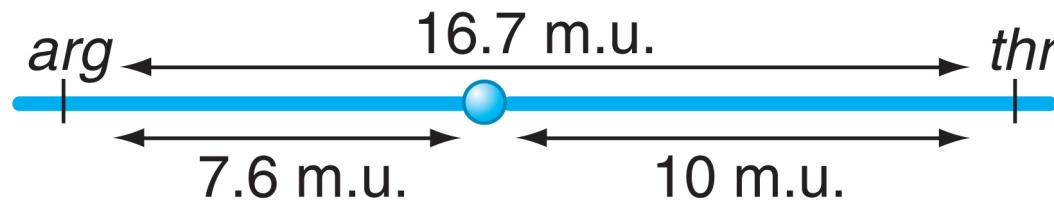


Fig. 5.22b

Rules for tetrad analysis in ordered and unordered tetrads

For Ordered and Unordered Tetrads

Considering genes two at a time, assign tetrads as PD, NPD, or T.

If $PD \gg NPD$, the two genes are genetically linked.

If $PD = NPD$, the two genes are genetically independent (unlinked).

The map distance between two genes if they are genetically linked

$$= \frac{NPD + (1/2)T}{\text{Total tetrads}} \times 100$$

For Ordered Tetrads Only

The map distance between a gene and its centromere

$$= \frac{(1/2) \times (\# \text{ of tetrads showing second-division segregation for this gene})}{\text{Total tetrads}} \times 100$$

Table 5.3

CHAPTER OUTLINE

- **5.1 Gene Linkage and Recombination**
- **5.2 The Chi-Square Test and Linkage Analysis**
- **5.3 Recombination: A Result of Crossing-Over During Meiosis**
- **5.4 Mapping: Locating Genes Along a Chromosome**
- **5.5 Tetrad Analysis in Fungi**
- **5.6 Mitotic Recombination and Genetic Mosaics**

Mitotic recombination can produce genetic mosaics

Rare occurrence through:

- Mistakes in chromosome replication
- Chance exposure to radiation

Can be observed in yeast and multicellular organisms

- Different genotypes in different cells

Have major repercussions to human health

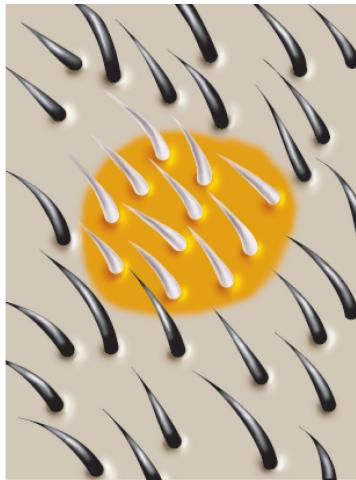
C. Stern (1936), inferred existence of **mitotic recombination** from observations of "twin spots" in *Drosophila*

- Patches of somatic tissue that have different genotypes

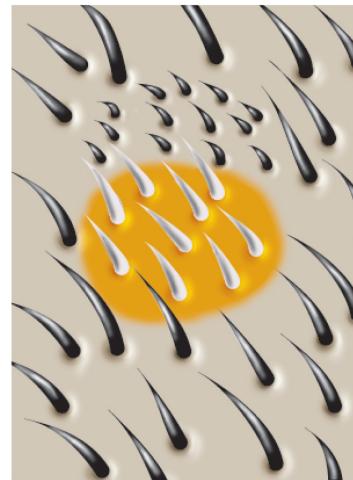
Twin spots are a form of genetic mosaicism

Double heterozygous *Drosophila* females $y\ sn^+/y^+ sn$

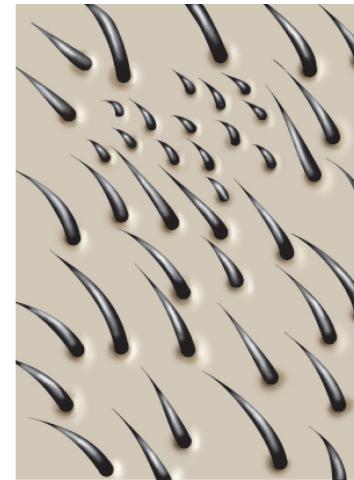
- yellow (*y*) mutant – yellow body
- wildtype (*y⁺*) – brown body
- singed (*sn*) mutant – short and curled bristles
- wildtype (*sn⁺*) – long and straight bristles



Single yellow spot



Twin spot



Single singed spot

Fig. 5.23

Origin of twin spots in *Drosophila*

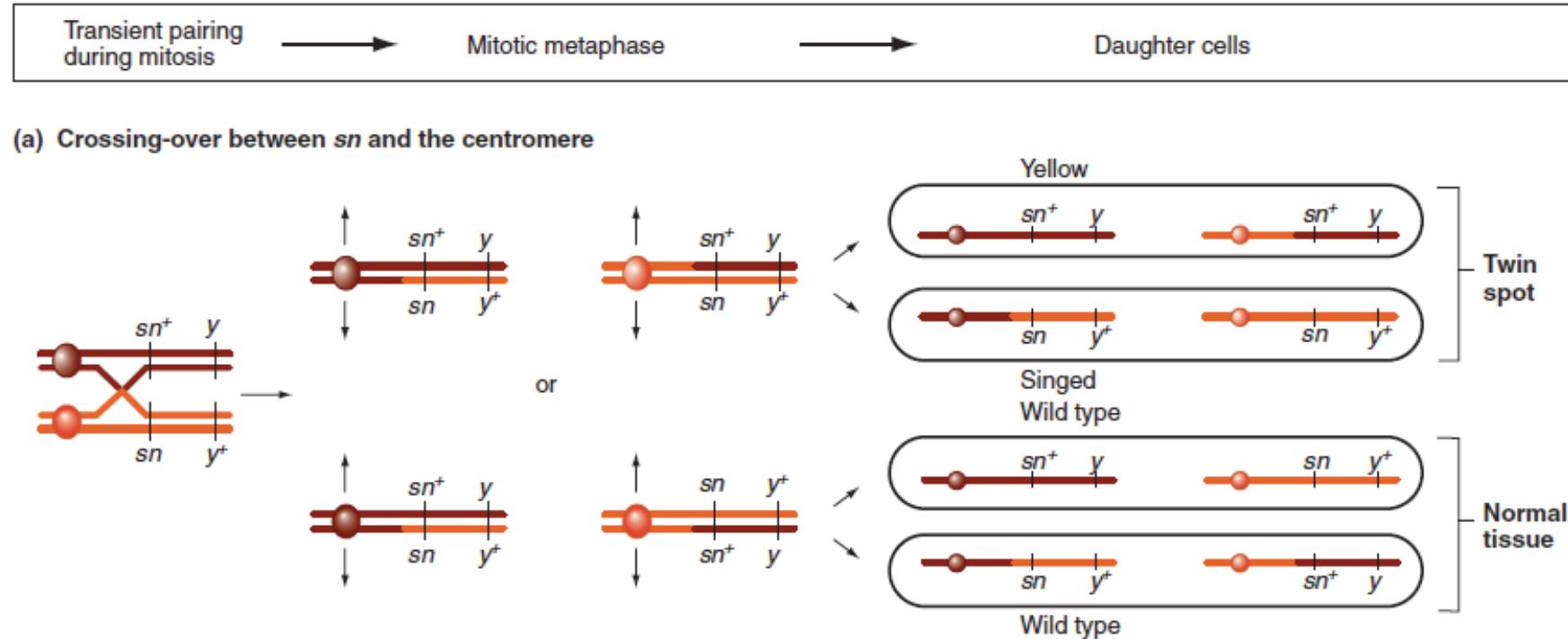


Fig. 5.24a

Origin of yellow spots in *Drosophila*

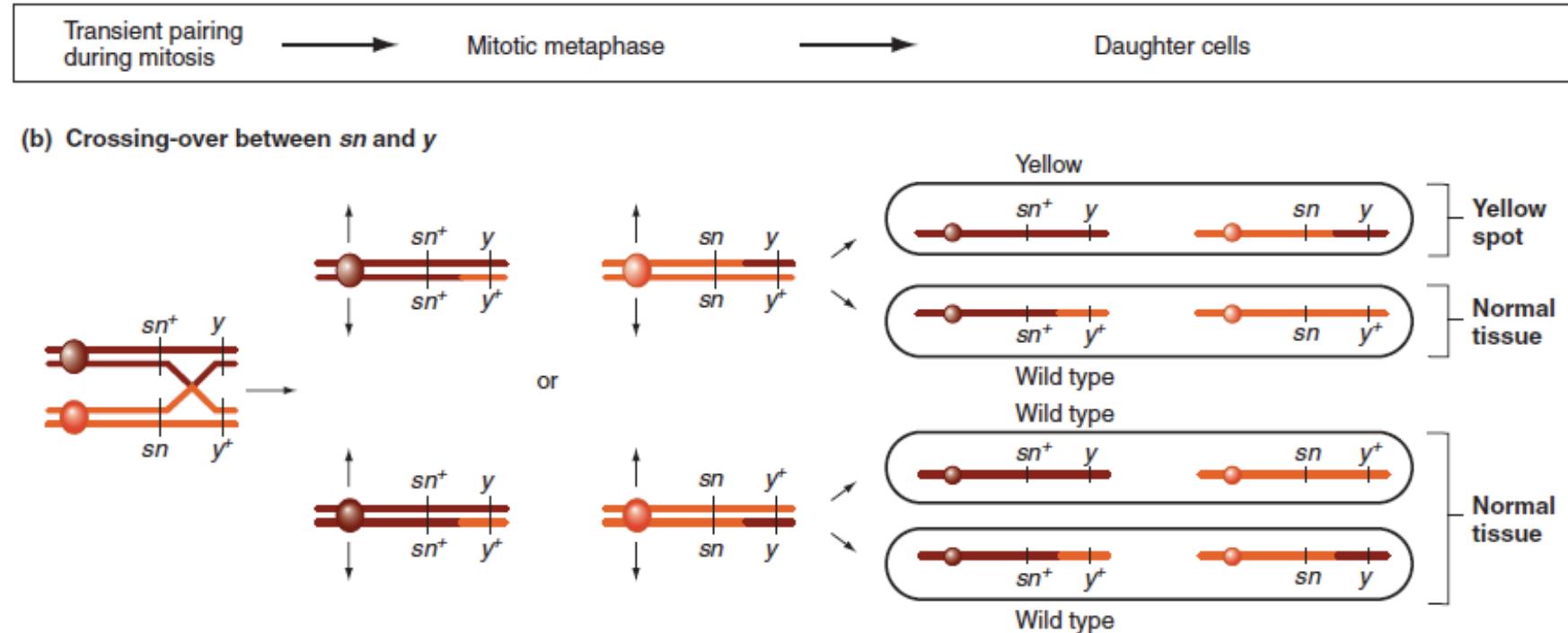


Fig. 5.24b

Chapter 5 Questions