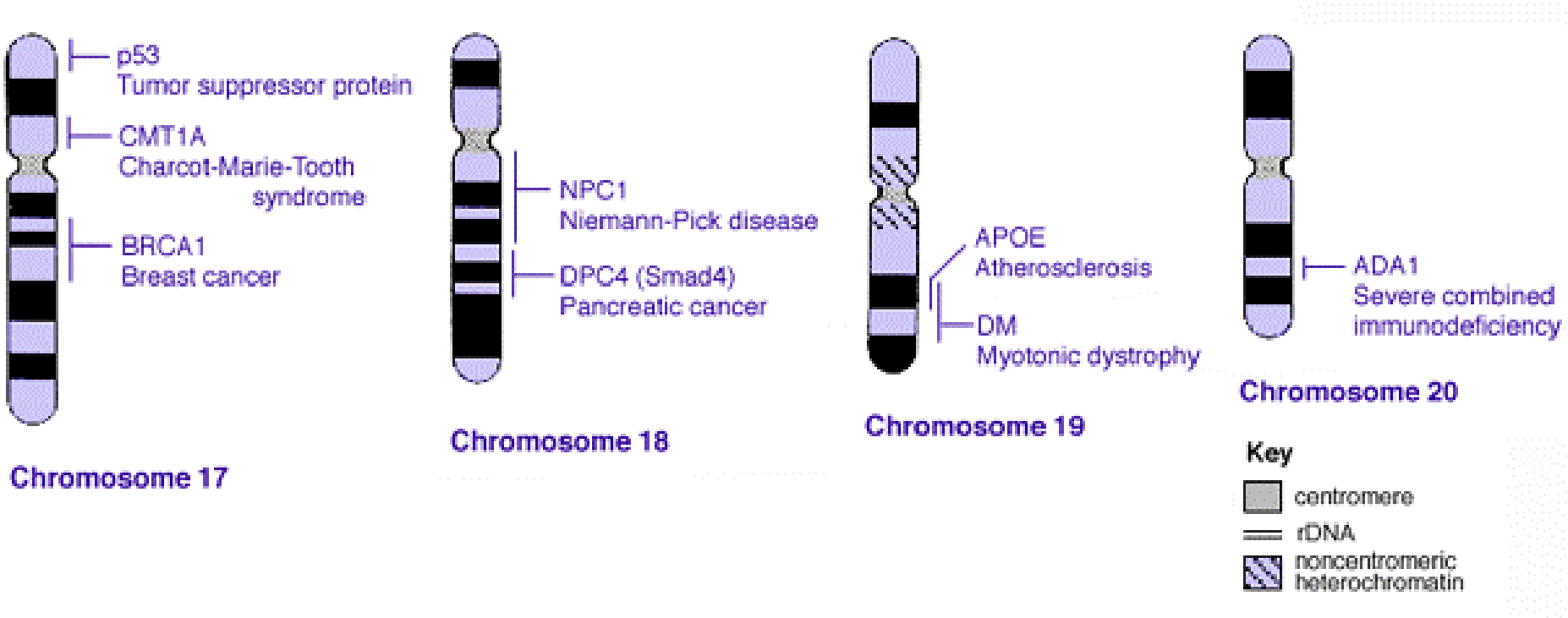
Linkage

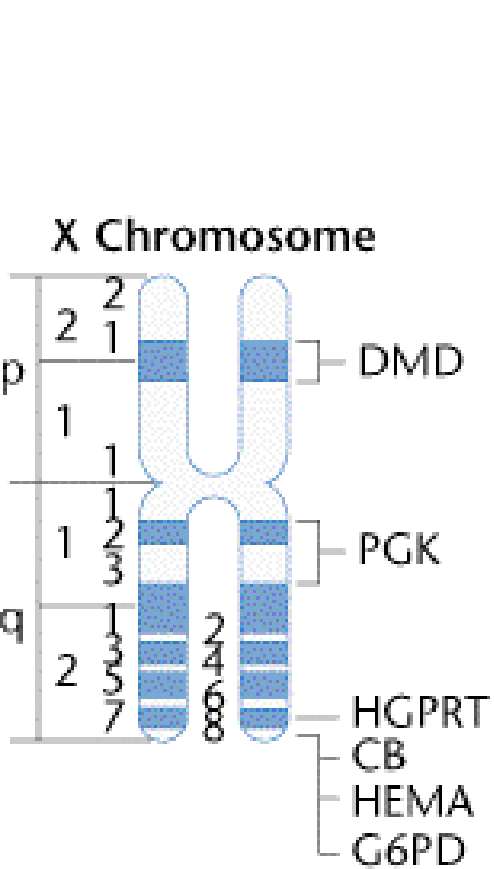
-Genes on the same chromosome are called linked

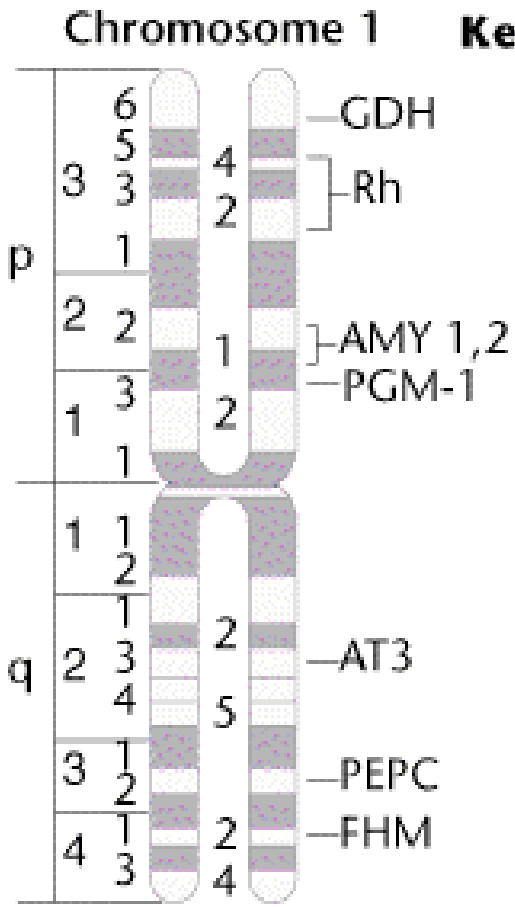
Human

-23 pairs of chromosomes, ~35,000 different genes expressed.

- average of 1,500 genes/chromosome


p53
Tumor suppressor protein
CMT1A
Charcot-Marie-Tooth syndrome
BRCA1
Breast cancer
Chromosome 17
NPC1
Niemann-Pick disease
DPC4 (Smad4)
Pancreatic cancer
Chromosome 18
APOE
Atherosclerosis
DM
Myotonic dystrophy
Chromosome 19
ADA1
Severe combined immunodeficiency
Chromosome 20
Key
centromere
rDNA
noncentromeric heterochromatin





Key

AMY	Amylase (Salivary and Pancreatic)
AT3	Antithrombin (Clotting Factor IV)
CB	Colorblindness
DMD	Duchenne Muscular Dystrophy
FHM	Fumarate Hydratase (Mitochondrial)
GDH	Glucose Dehydrogenase
G6PD	Glucose-6-Phosphate Dehydrogenase
HEMA	Hemophilia A (Classic)
HGPRT	Hypoxanthine-Guanine-Phosphoribosyl Transferase (Lesch–Nyhan Syndrome)
PEPC	Peptidase C
PGK	Phosphoglycerate Kinase
PGM	Phosphoglucomutase
Rh	Rhesus Blood Group (Erythroblastosis Fetalis)

Following Meiosis

Parental chromosomal types
- complete linkage and no crossing over. Seldom occurs.

Nonparental chromosomal types
- result from crossing-over, recombination of alleles.

Crossing-Over

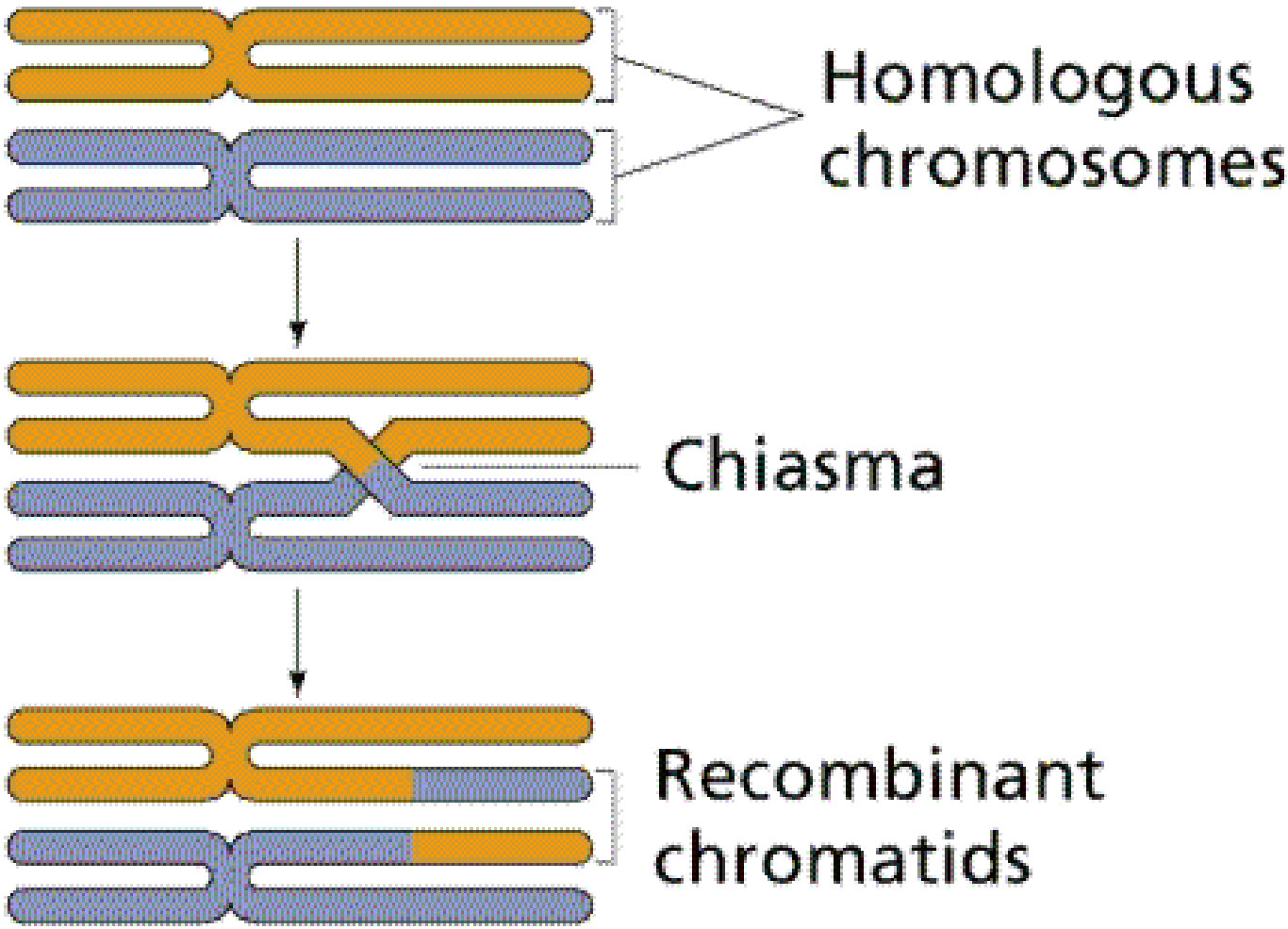
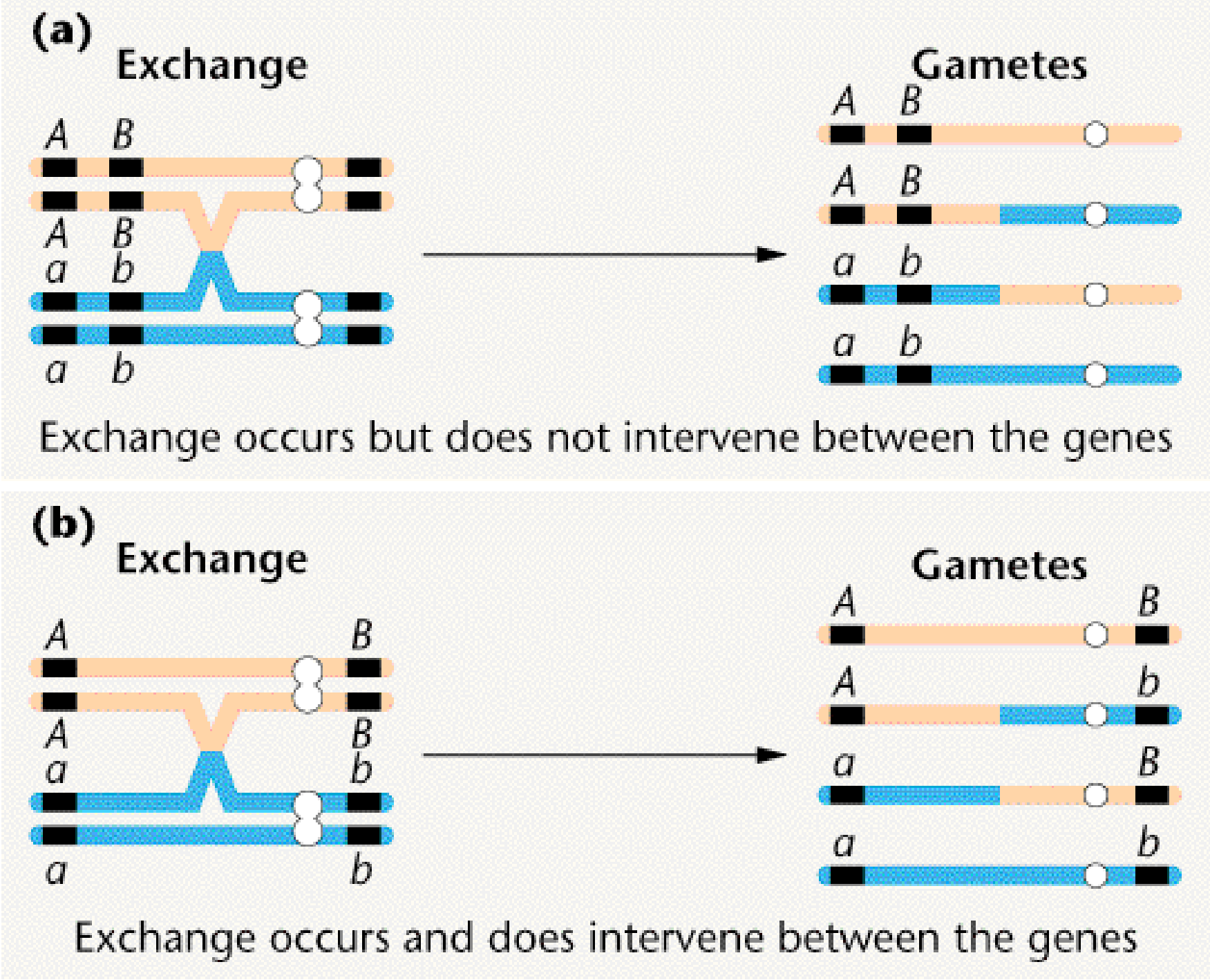


Figure 9.16


(a)
Exchange
A B
A B
a b
a b
Gametes
A B
A B
a b
a b
Exchange occurs but does not intervene between the genes
(b)
Exchange
A B
A B
a b
a b
Gametes
A B
A b
a B
a b
Exchange occurs and does intervene between the genes

-Frequency of crossing-over between linked genes is proportional to the distance between them.

-Possible if two genes are close that crossing-over will not be detected.

- crossing-over has been used to construct chromosome maps.

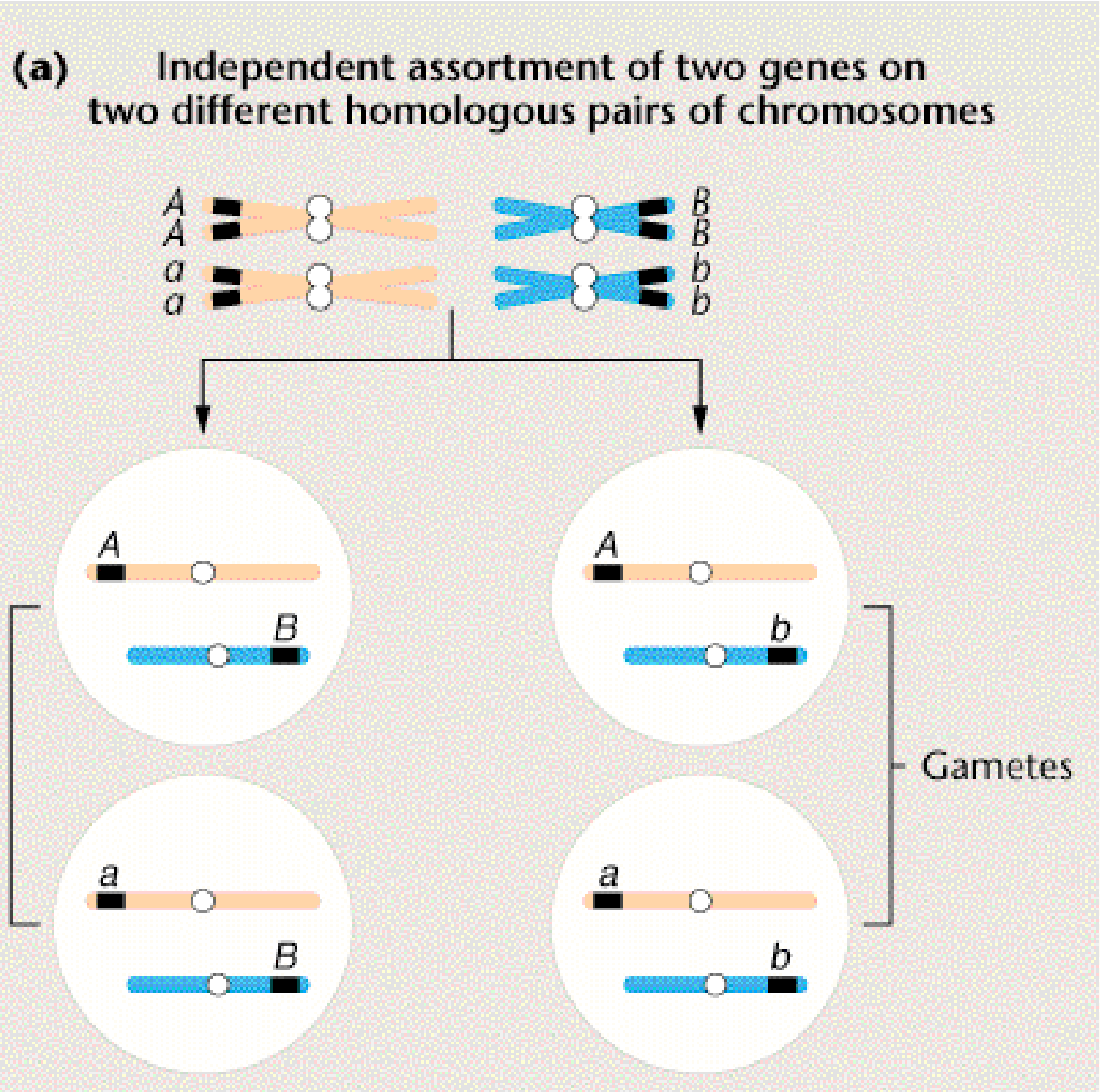
Three possibilities for two genes:

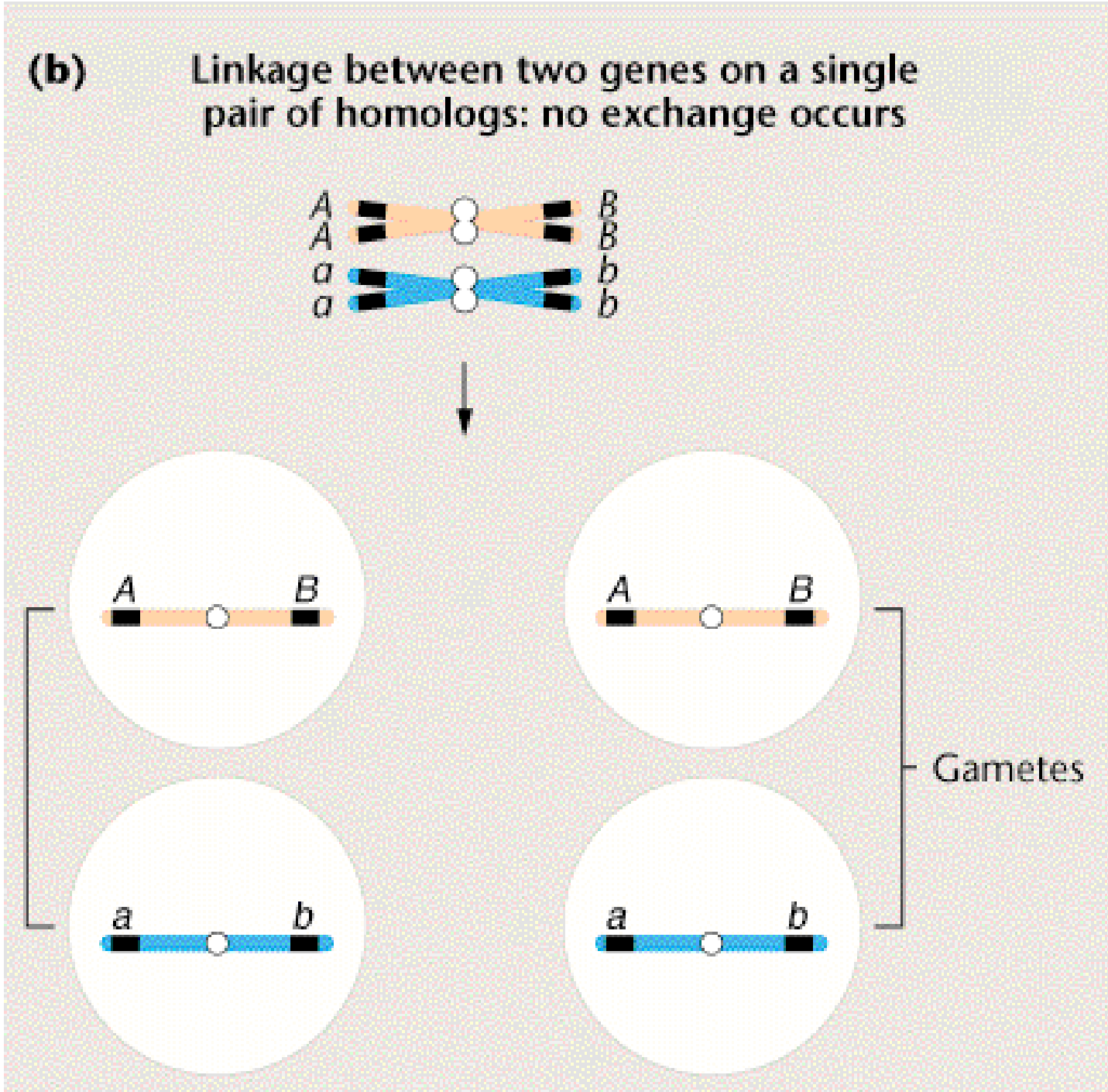
Fig. 6.1 in text.

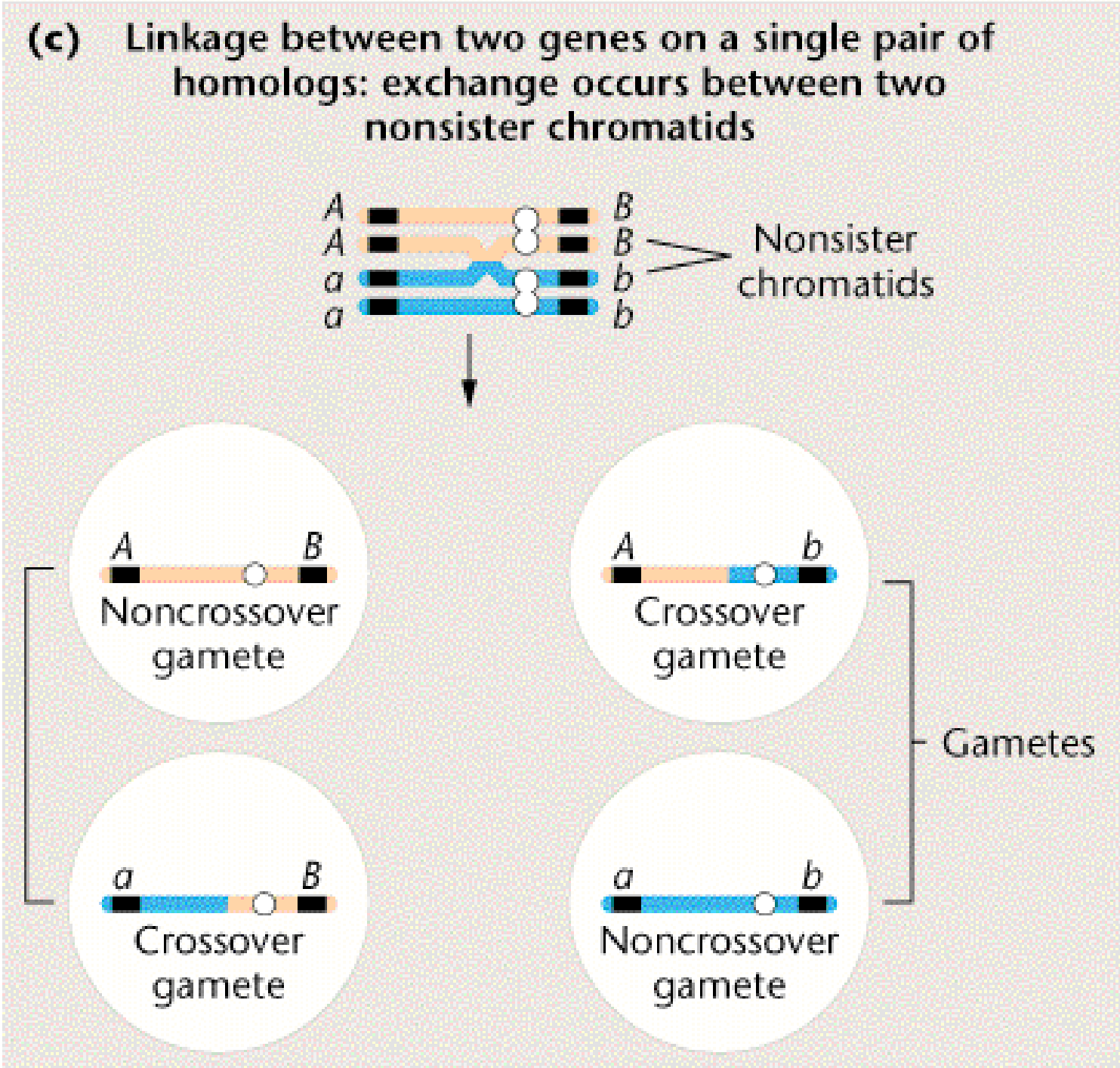
a. On separate chromosomes so segregate independently.

b. Both genes on same pair of chromosomes, no crossing-over so always stay together.

c. Both genes on same pair, crossing over, produces recombinant gametes.


(a) Independent assortment of two genes on two different homologous pairs of chromosomes
A
A
a
a
B
B
b
b
A
B
A
b
a
B
a
b
Gametes


(b)
Linkage between two genes on a single pair of homologs: no exchange occurs
A
A
a
a
B
B
b
b
A
B
A
B
a
b
a
b
Gametes


(c) Linkage between two genes on a single pair of homologs: exchange occurs between two nonsister chromatids
A
A
a
a
B
B
b
b
Nonsister chromatids
A B
Noncrossover gamete
A b
Crossover gamete
a B
Crossover gamete
a b
Noncrossover gamete
Gametes

Possible for two genes to be far enough apart so number of recombinants approaches 50%.

Four types of gametes produced in a 1:1:1:1 ratio.

Linkage ratio

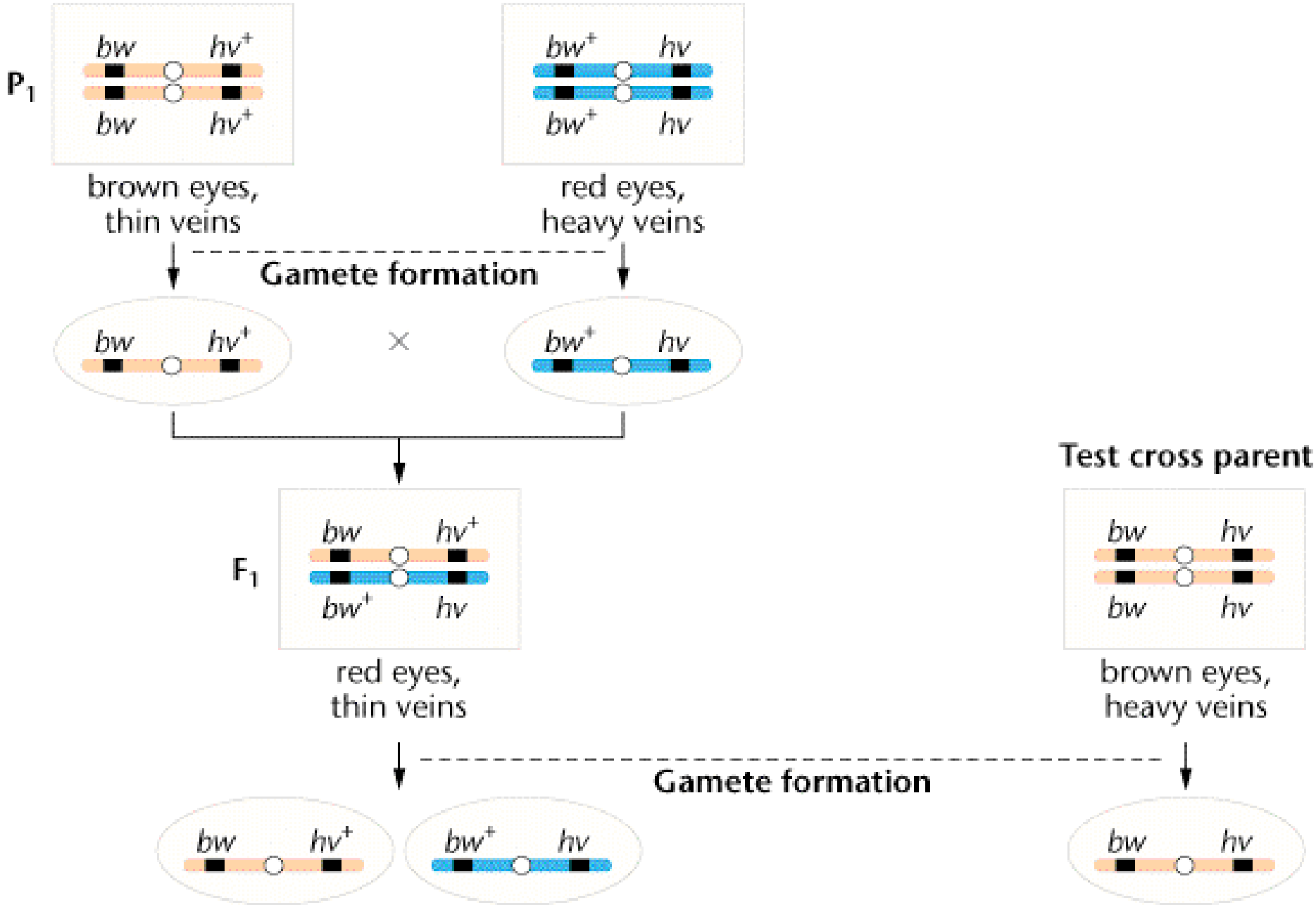
If complete linkage, a unique F_2 phenotypic ratio results.

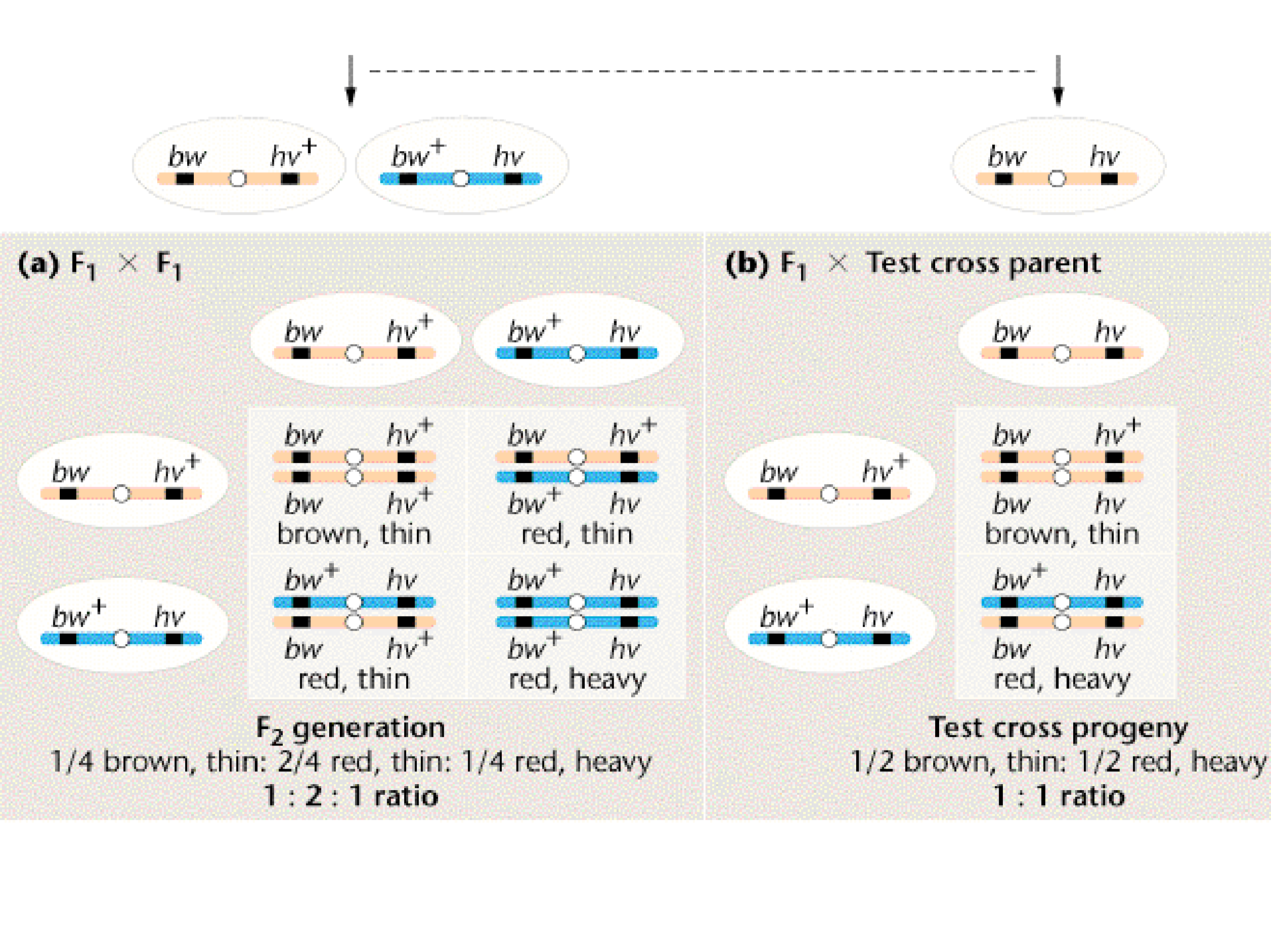
1:2:1 phenotypic and genotypic ratio

Test cross produces 1:1 ratio

Genetic Symbols

$$P_1: \quad \frac{bw \quad hv^+}{bw \quad hv^+} \quad X \quad \frac{bw^+ \quad hv}{bw^+ \quad hv}$$


P1
bw
hv+
bw
hv+
bw+
hv
bw+
hv
brown eyes,
thin veins
red eyes,
heavy veins
Gamete formation
bw
hv+
×
bw+
hv
F1
bw
hv+
bw+
hv
red eyes,
thin veins
Test cross parent
bw
hv
bw
hv
brown eyes,
heavy veins
Gamete formation
bw
hv+
bw+
hv
bw
hv


bw hv+
bw+ hv
bw hv
(a) F1 × F1
bw hv+
bw+ hv
bw hv+
bw hv+
brown, thin
bw hv+
bw+ hv
red, thin
bw+ hv
bw hv+
red, thin
bw+ hv
bw+ hv
red, heavy
F2 generation
1/4 brown, thin: 2/4 red, thin: 1/4 red, heavy
1 : 2 : 1 ratio
(b) F1 × Test cross parent
bw hv
bw hv+
bw+ hv
bw hv+
bw hv
brown, thin
bw+ hv
bw hv
red, heavy
Test cross progeny
1/2 brown, thin: 1/2 red, heavy
1 : 1 ratio

Genes located on same chromosome will show evidence of linkage.

Linkage groups
- number equals haploid number of chromosomes.

Complete linkage is rare, usually some crossing-over.

Thomas Hunt Morgan

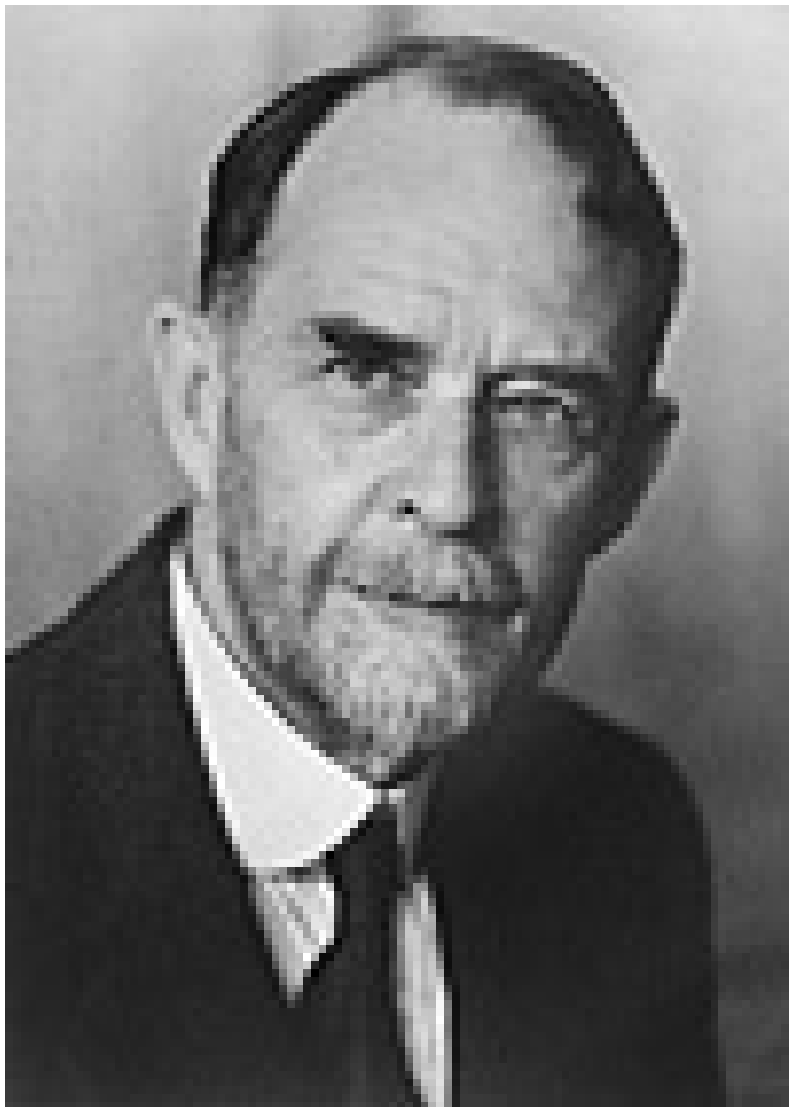
- first discovered sex-linkage.

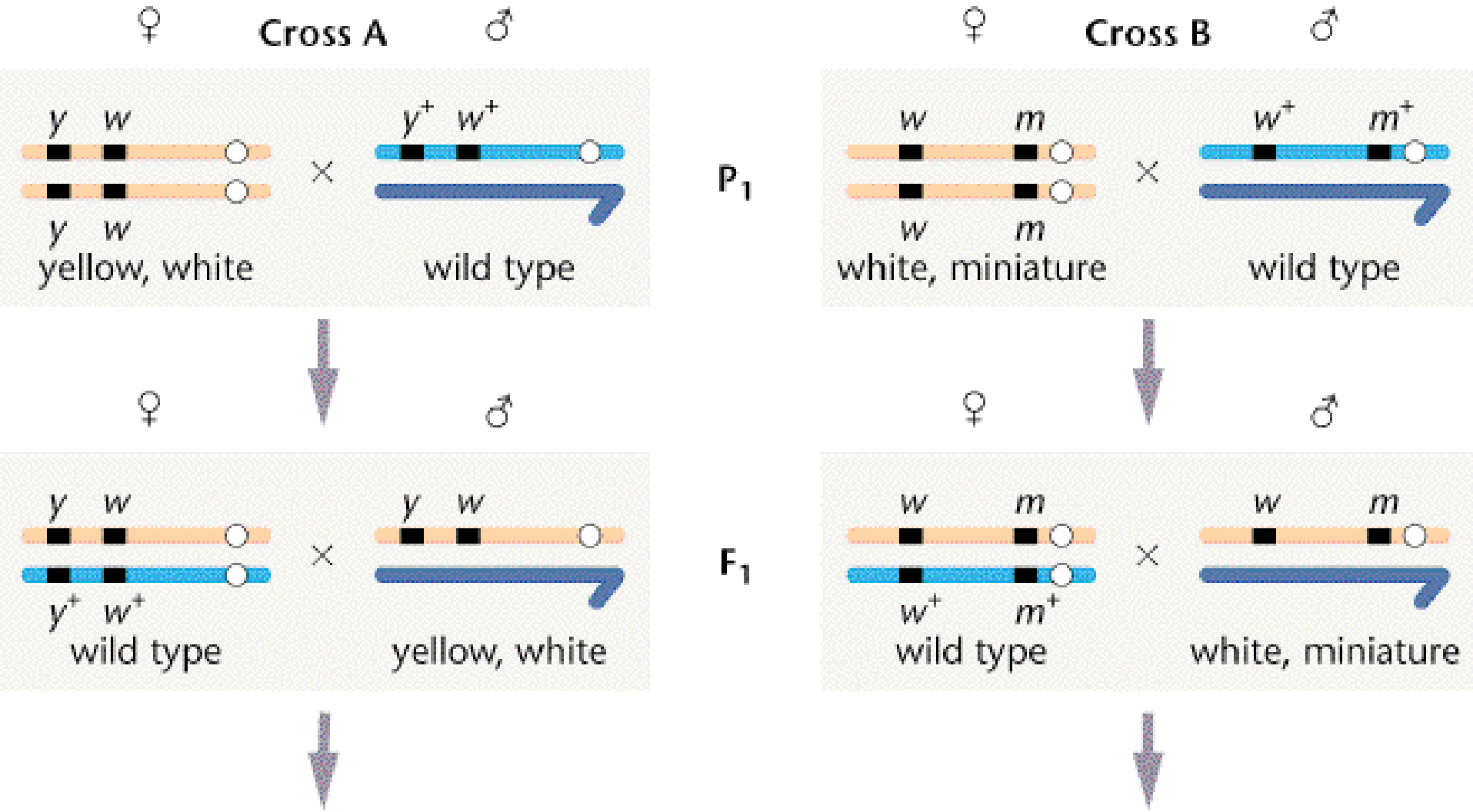
-linked genes can become separated

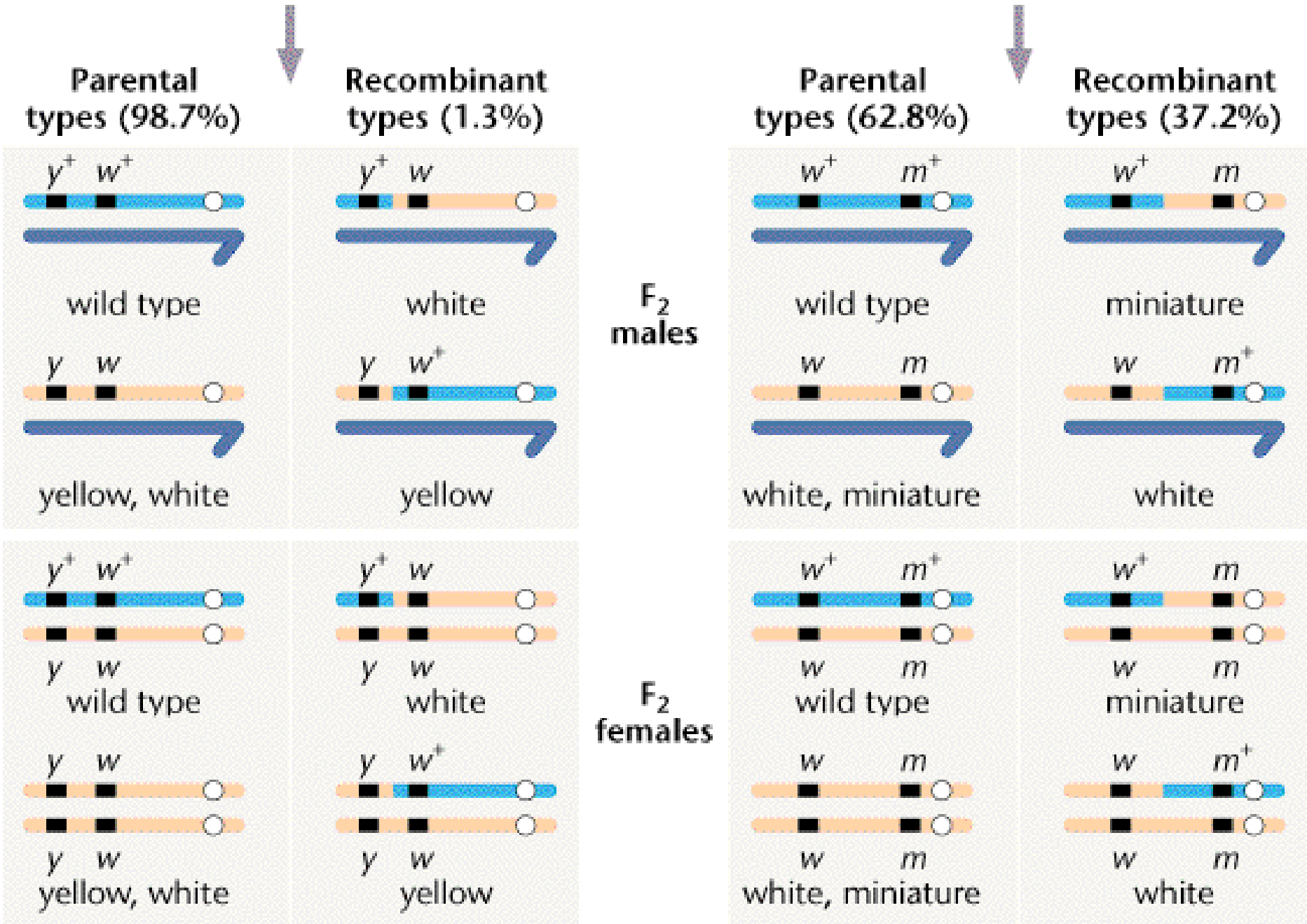
-How did genes that were linked become separated?

-Why did the frequency of separation vary depending on the gene?

Thomas Hunt Morgan




♀
Cross A
♂
y w
y w
yellow, white
y+ w+
wild type
P1
♀
Cross B
♂
w m
w m
white, miniature
w+ m+
wild type
♀
♂
y w
y+ w+
wild type
y w
yellow, white
F1
♀
♂
w m
w+ m+
wild type
w m
white, miniature


Parental types (98.7%)
Recombinant types (1.3%)
Parental types (62.8%)
Recombinant types (37.2%)
y+ w+
y+ w
w+ m+
w+ m
wild type
white
wild type
miniature
y w
y w+
w m
w m+
yellow, white
yellow
white, miniature
white
F2 males
F2 females
y+ w+
y+ w
w+ m+
w+ m
y w
wild type
white
wild type
miniature
y w
y w+
w m
w m+
yellow, white
yellow
white, miniature
white

Morgan proposed:

During Meiosis, synapsed chromosomes exchanged genetic material.

Chiasmatype theory.

Two genes located close to each other are less likely to form chiasamata between them. Crossing-over results the actual physical exchange.

Alfred H. Sturtevant - Morgan's student, crossing-over frequencies could be used to map the sequence of genes and the distance between genes.

Alfred H. Sturtevant

Compiled data on recombination
Listed frequency of crossing-over between pairs.

yellow, white	**0.5%**
white, minature	**34.5%**
yellow, minature	**35.4%**

yellow, white 0.5%
white, minature 34.5%
yellow, minature 35.4%

1. **yellow and white must be close**
   - recombiantion frequency is low.
2. **yellow and white must be far from minature**
   -high recombination frequency for both.
3. **Minature shows more recombination with yellow than white.**
   -White must be between yellow and minature.

0.5
34.5
y
w
m
35.4

one map unit = 1% recombination between genes.

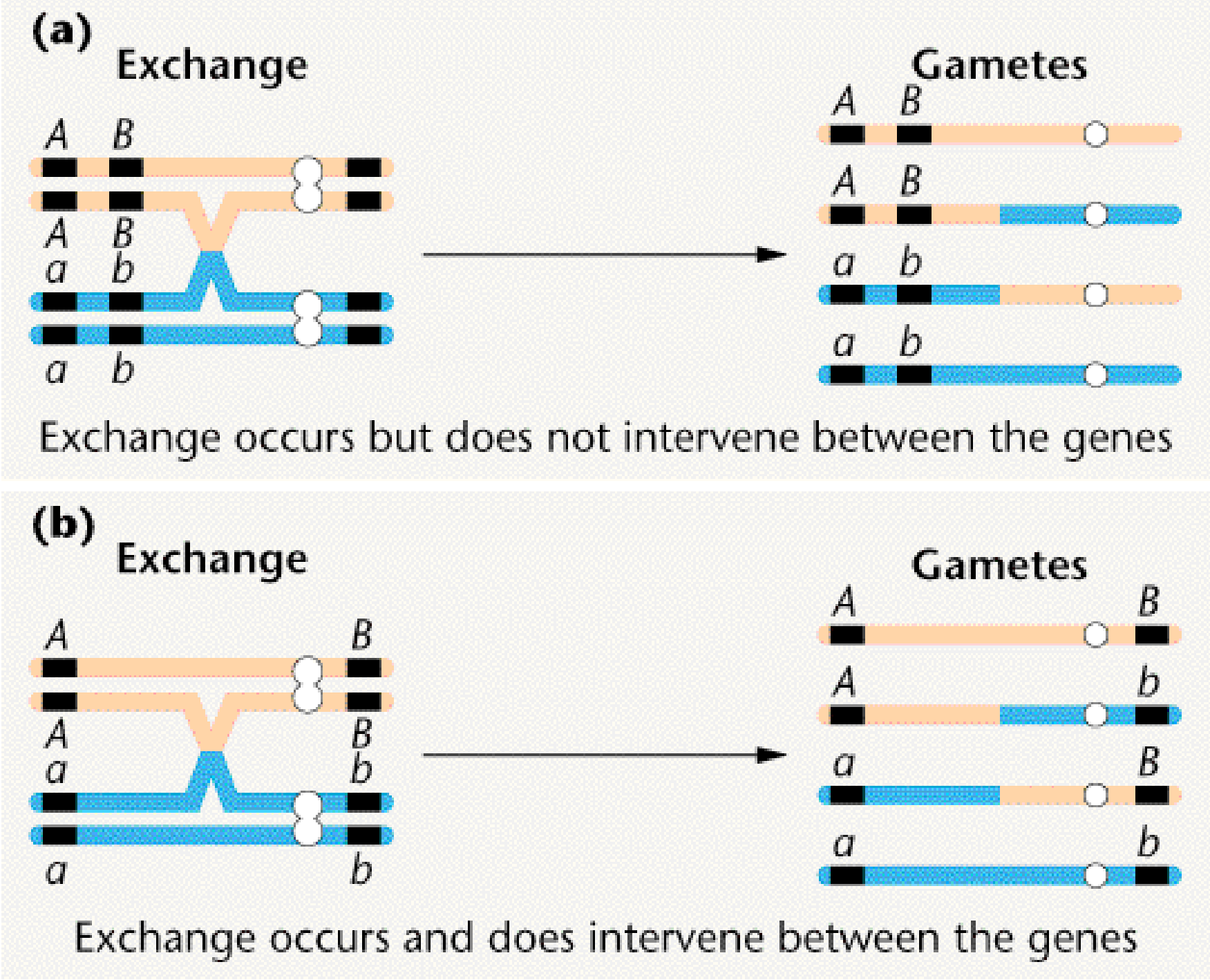
linkage also occurs on autosomes

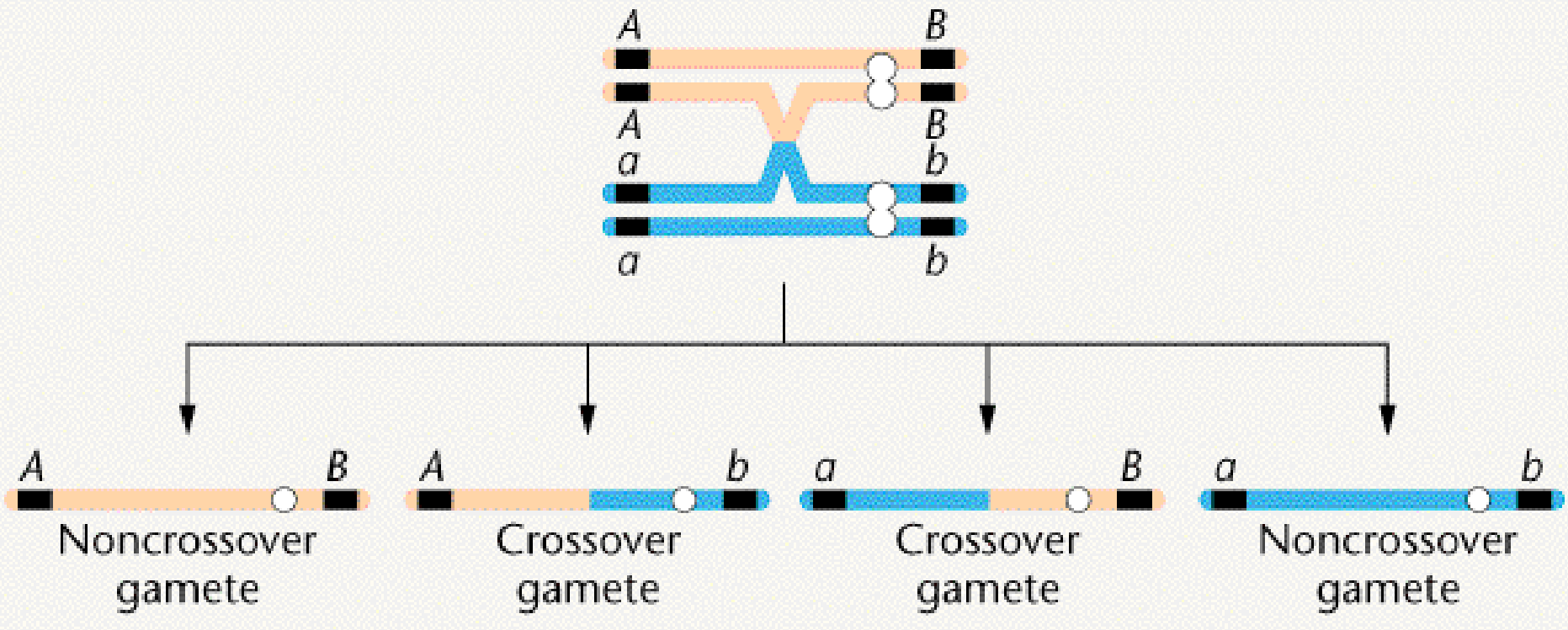
In Drosophila crossing-over occurs only in females.

Why should relative distance between loci affect recombination?

A limited number of random cross overs occur during meiosis.

The closer the two loci, the less likely that crossing-over will occur.


(a)
Exchange
A B
A B
a b
a b
Gametes
A B
A B
a b
a b
Exchange occurs but does not intervene between the genes
(b)
Exchange
A B
A B
a b
a b
Gametes
A B
A b
a B
a b
Exchange occurs and does intervene between the genes


A
B
A
B
a
b
a
b
A
B
A
b
a
B
a
b
Noncrossover gamete
Crossover gamete
Crossover gamete
Noncrossover gamete

Crossing-over occurs in four strand tetrad stage.

Single cross over between two nonsister chromatids, other two chromatids will be unchanged.

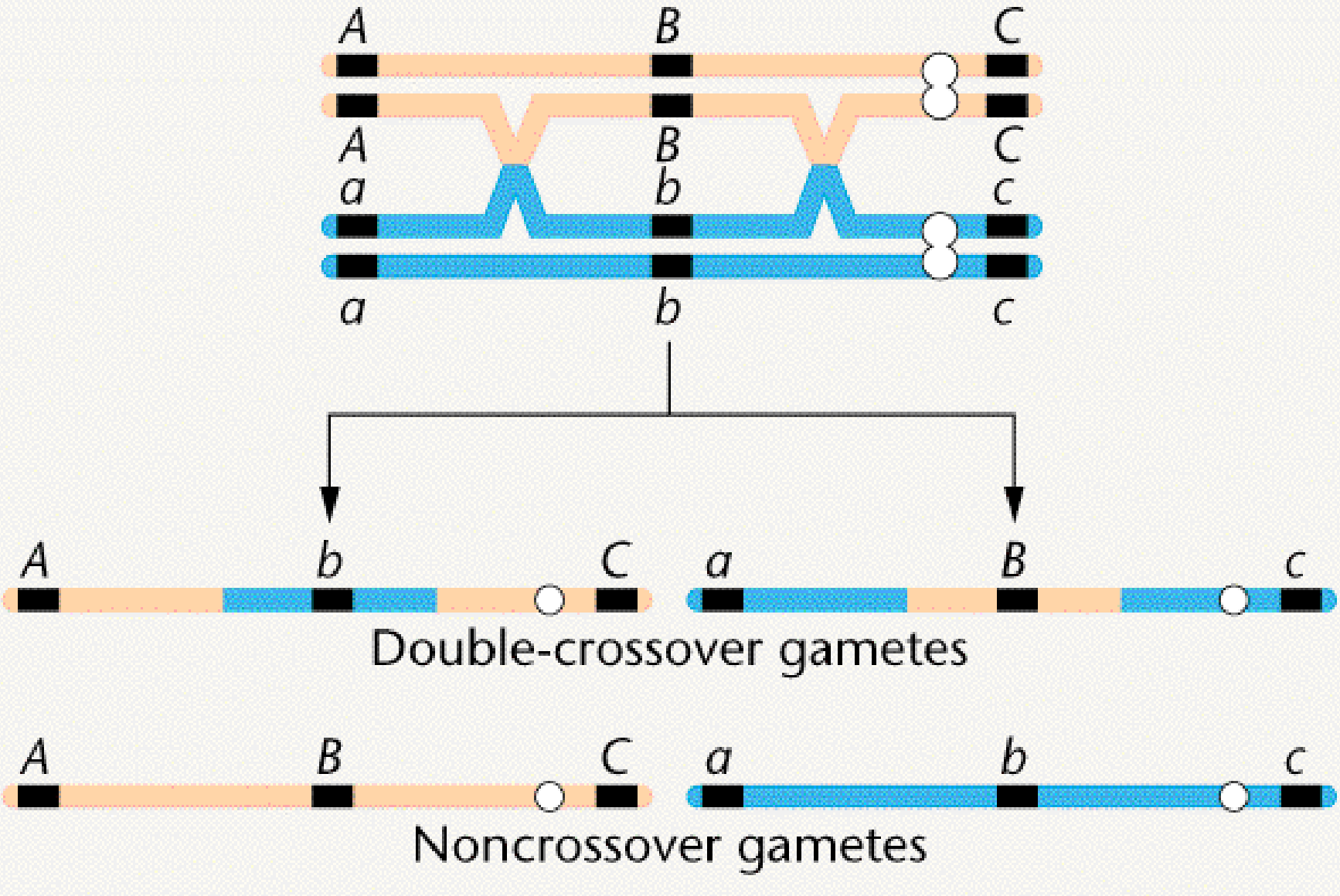
If single cross over occurs 100% of time, 50% of gametes formed affected.

For single cross over, maximum percentage of recombinant gametes is 50%.

Multiple crossovers

- multiple exchanges between nonsister chromatids.

Probability of double cross over between 2 loci is product of individual probabilities.


A
B
C
A
B
C
a
b
c
a
b
c
A
b
C
a
B
c
Double-crossover gametes
A
B
C
a
b
c
Noncrossover gametes

A and B = 20% recombinant
B and C = 30% recombinant

Probability of double crossover between A and C is:

.2 x .3 = .06 or 6%

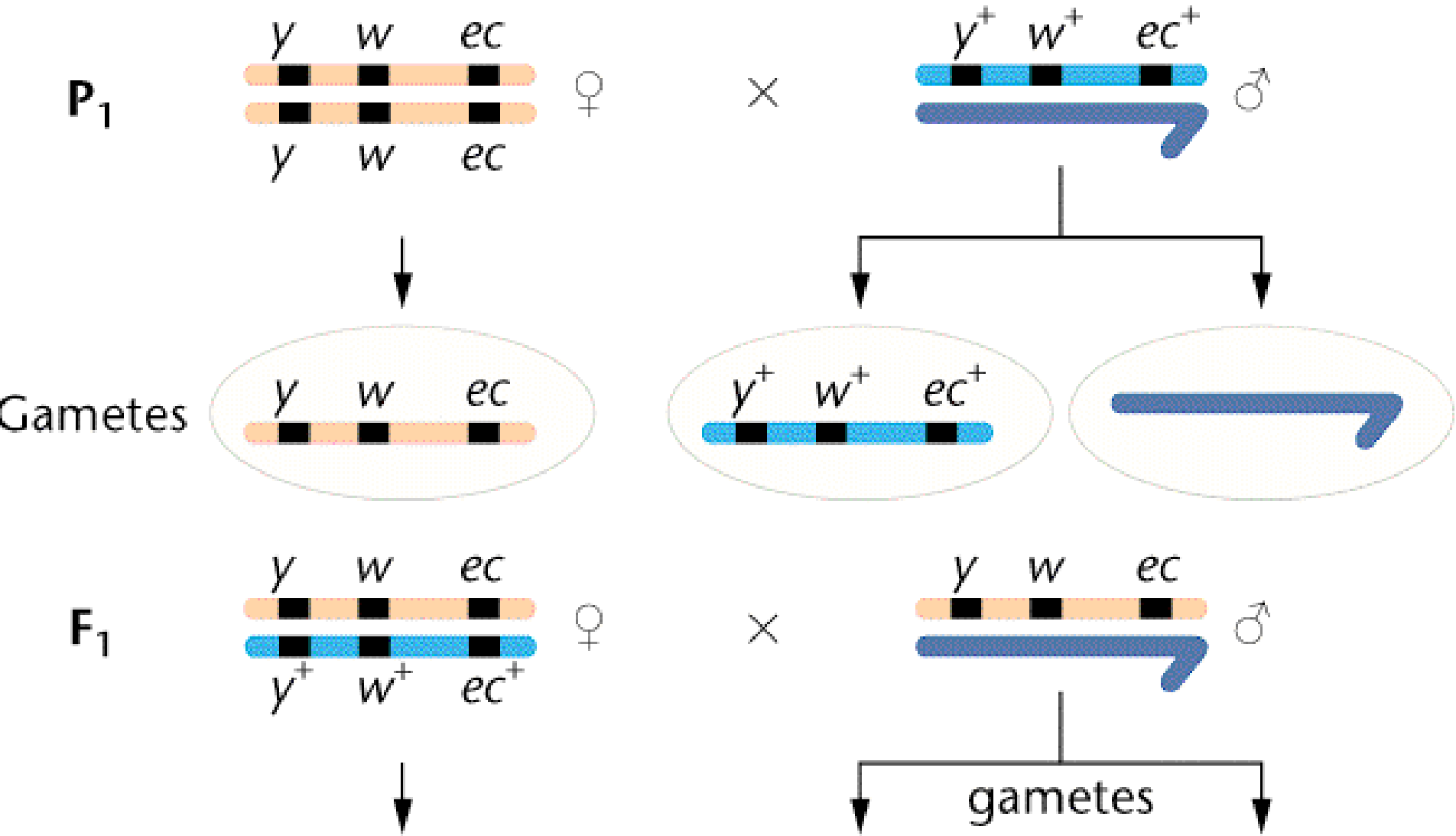
Three-Point Mapping

Have 3 genes and want to determine which gene is in the middle.

Three-Point Mapping

Three criteria must be met:

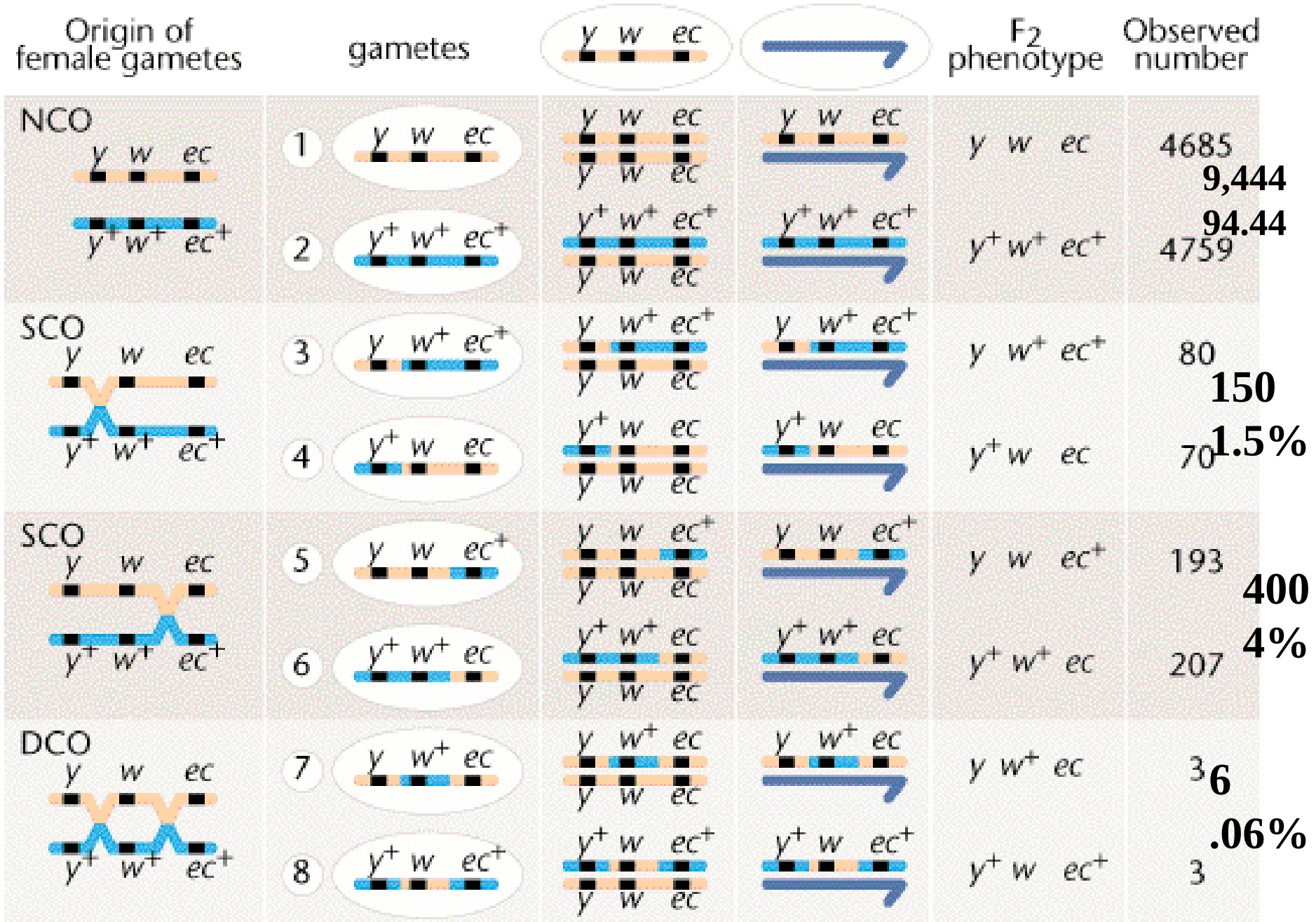
1. **Genotype of organism producing the crossover gametes must be heterozygous at the loci.**
2. **Each phenotypic class must reflect the genotype of the gametes of the parents producing it.**
3. **A sufficient number of offspring must be produced.**


P1
y w ec
y w ec
♀
×
y+ w+ ec+
♂
Gametes
y w ec
y+ w+ ec+
F1
y w ec
y+ w+ ec+
♀
×
y w ec
♂
gametes

Noncrossover F_2 phenotypes
- highest proportion.

double crossover
- least

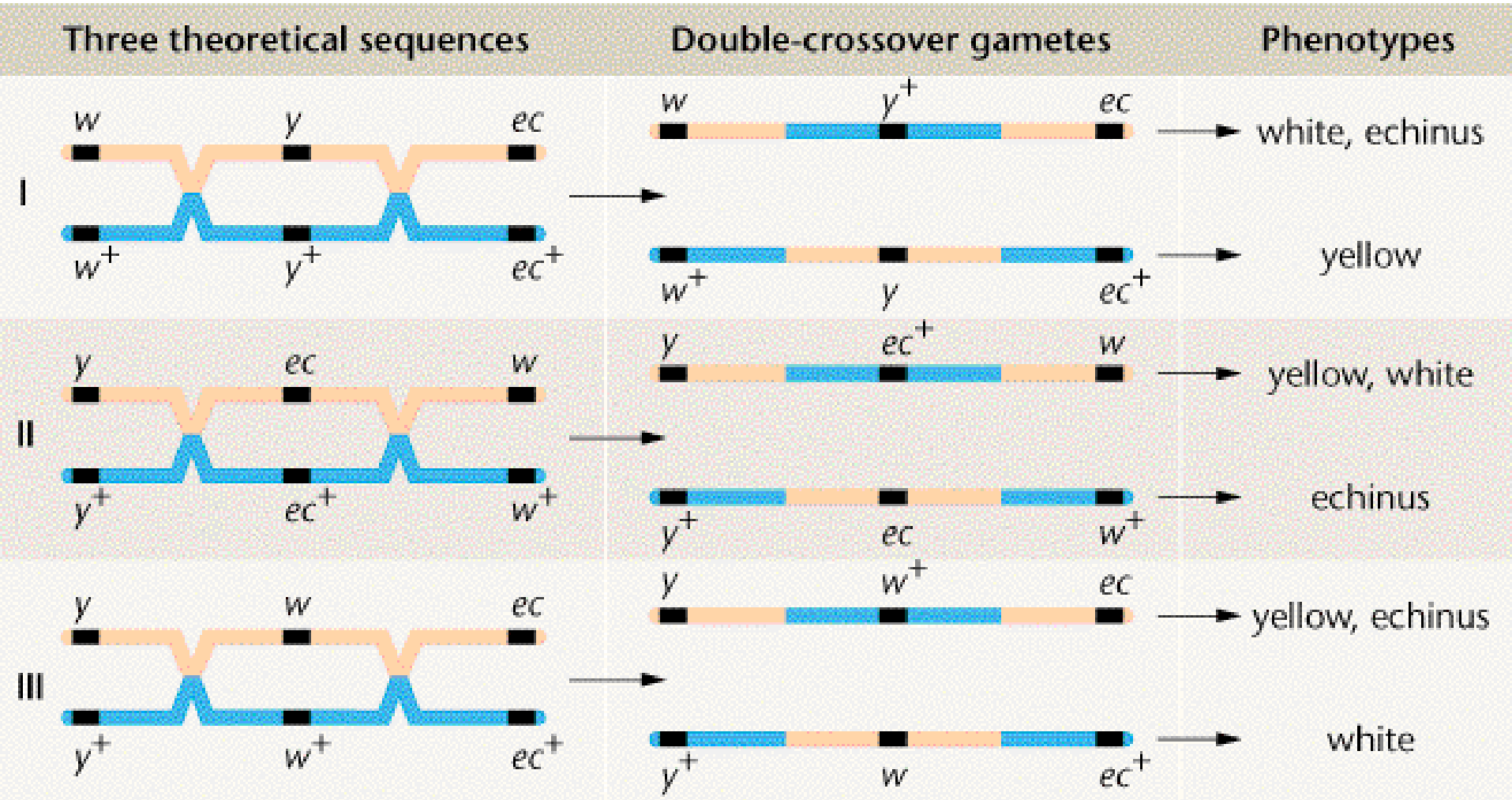
Remaining are from single crossovers.


Origin of female gametes
gametes
y w ec
F2 phenotype
Observed number
NCO
y w ec
y+ w+ ec+
1
y w ec
y w ec
y w ec
4685
2
y+ w+ ec+
y+ w+ ec+
y+ w+ ec+
4759
9,444
94.44
SCO
y w ec
y+ w+ ec+
3
y w+ ec+
y w+ ec+
y w+ ec+
80
4
y+ w ec
y+ w ec
y+ w ec
70
150
1.5%
SCO
y w ec
y+ w+ ec+
5
y w ec+
y w ec+
y w ec+
193
6
y+ w+ ec
y+ w+ ec
y+ w+ ec
207
400
4%
DCO
y w ec
y+ w+ ec+
7
y w+ ec
y w+ ec
y w+ ec
3
8
y+ w ec+
y+ w ec+
y+ w ec+
3
6
.06%

Determining the Gene Sequence

1. **Assign order of genes along each homologue of the heterozygous parent.**

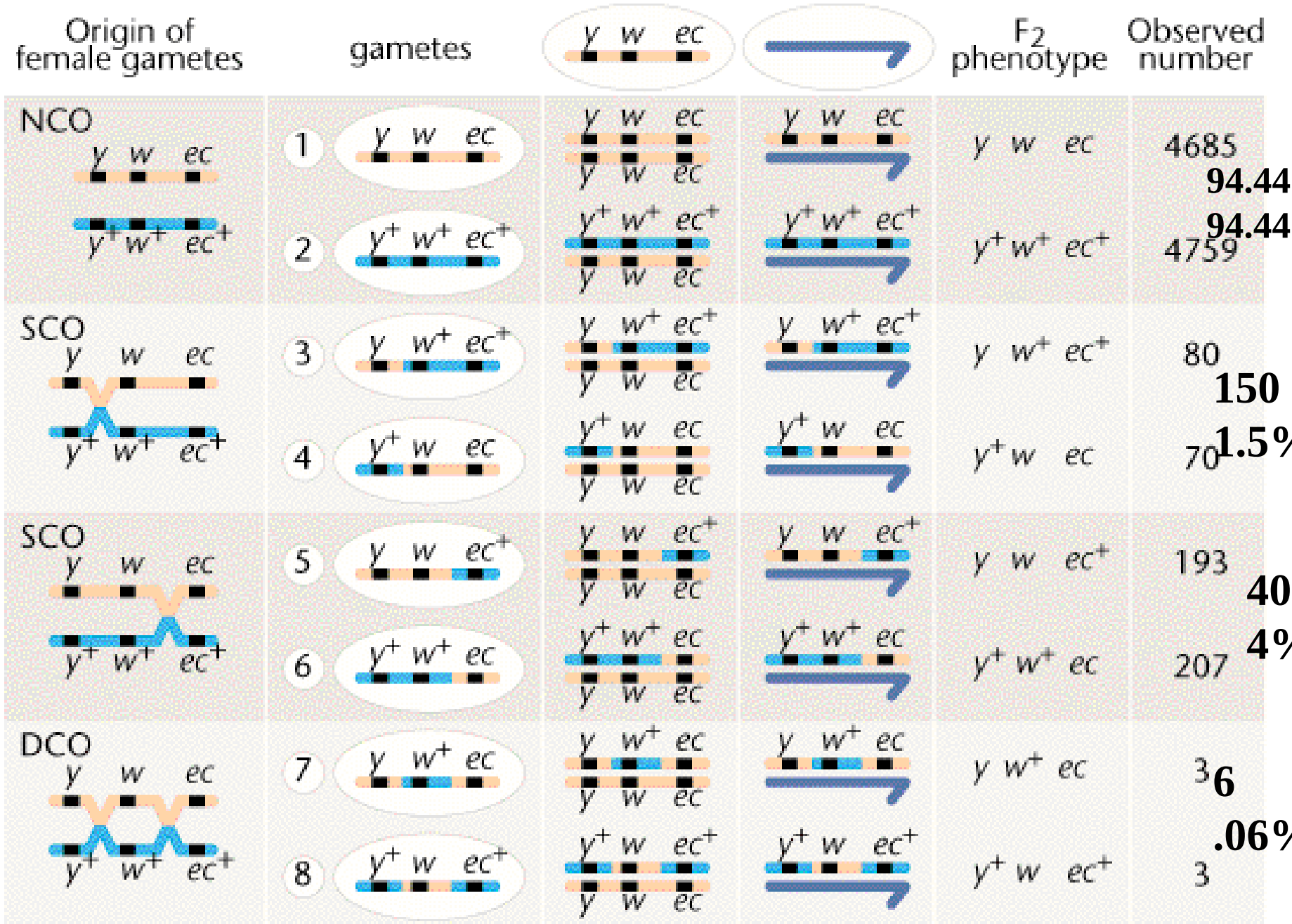
2. **Following a double crossover, the middle allele will end up in the middle of the other two alleles on the other homologue**


Three theoretical sequences
Double-crossover gametes
Phenotypes
I
w
y
ec
w+
y+
ec+
w
y+
ec
white, echinus
w+
y
ec+
yellow
II
y
ec
w
y+
ec+
w+
y
ec+
w
yellow, white
y+
ec
w+
echinus
III
y
w
ec
y+
w+
ec+
y
w+
ec
yellow, echinus
y+
w
ec+
white

w y ec	y ec w	y w ec
$w^+ y^+ ec^+$	$y^+ ec^+ w^+$	$y^+ w^+ ec^+$

double crossover phenotypes

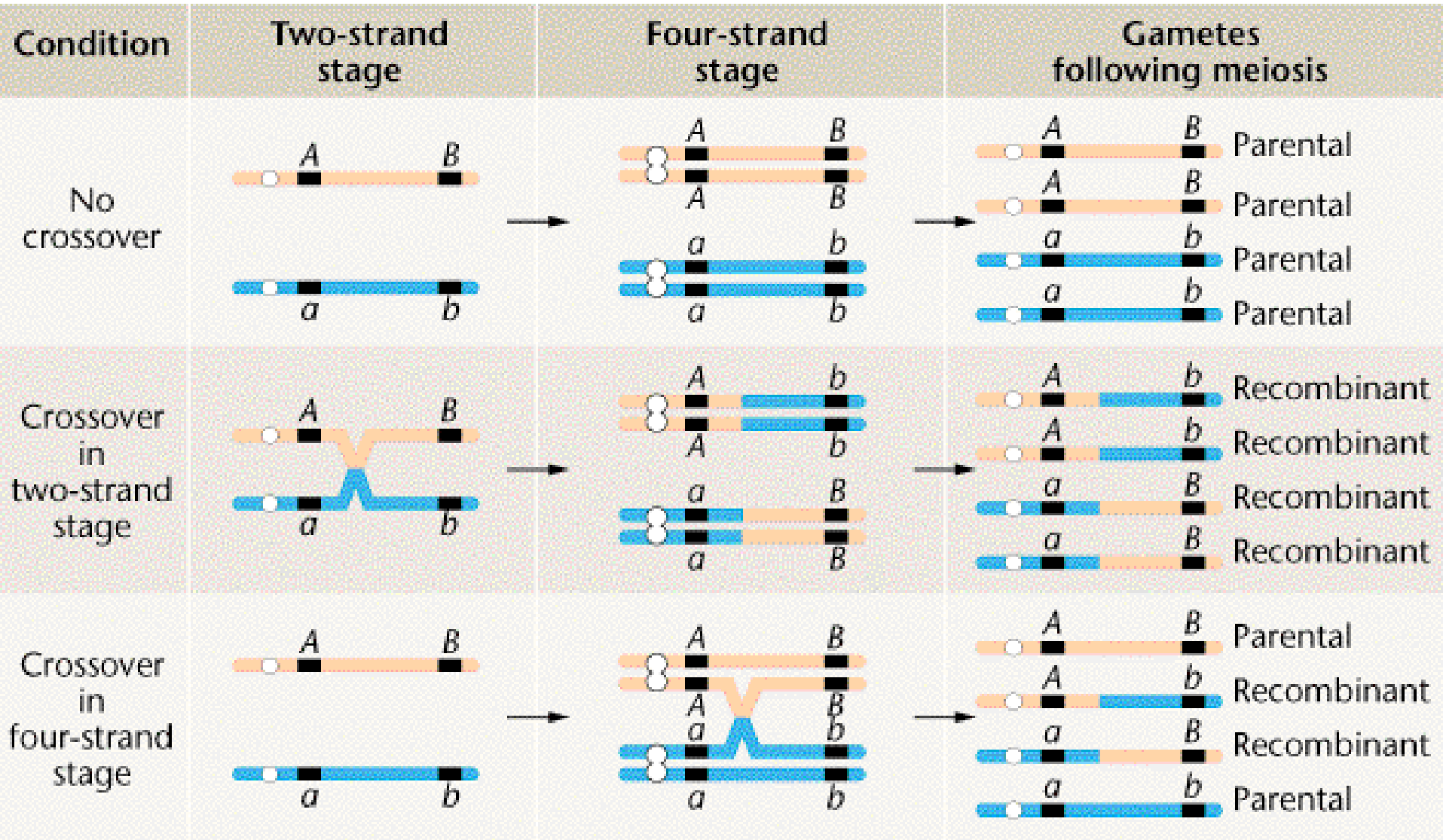
y w^+ ec and y^+ w ec^+


Origin of female gametes
gametes
y w ec
F2 phenotype
Observed number
NCO
y w ec
y+ w+ ec+
1
2
SCO
3
4
SCO
5
6
DCO
7
8
y w ec
y+ w+ ec+
4685
4759
80
70
193
207
3
3
94.44
94.44
150
1.5%
40
4%
6
.06%

Map distances - any two genes must consider all exchanges.

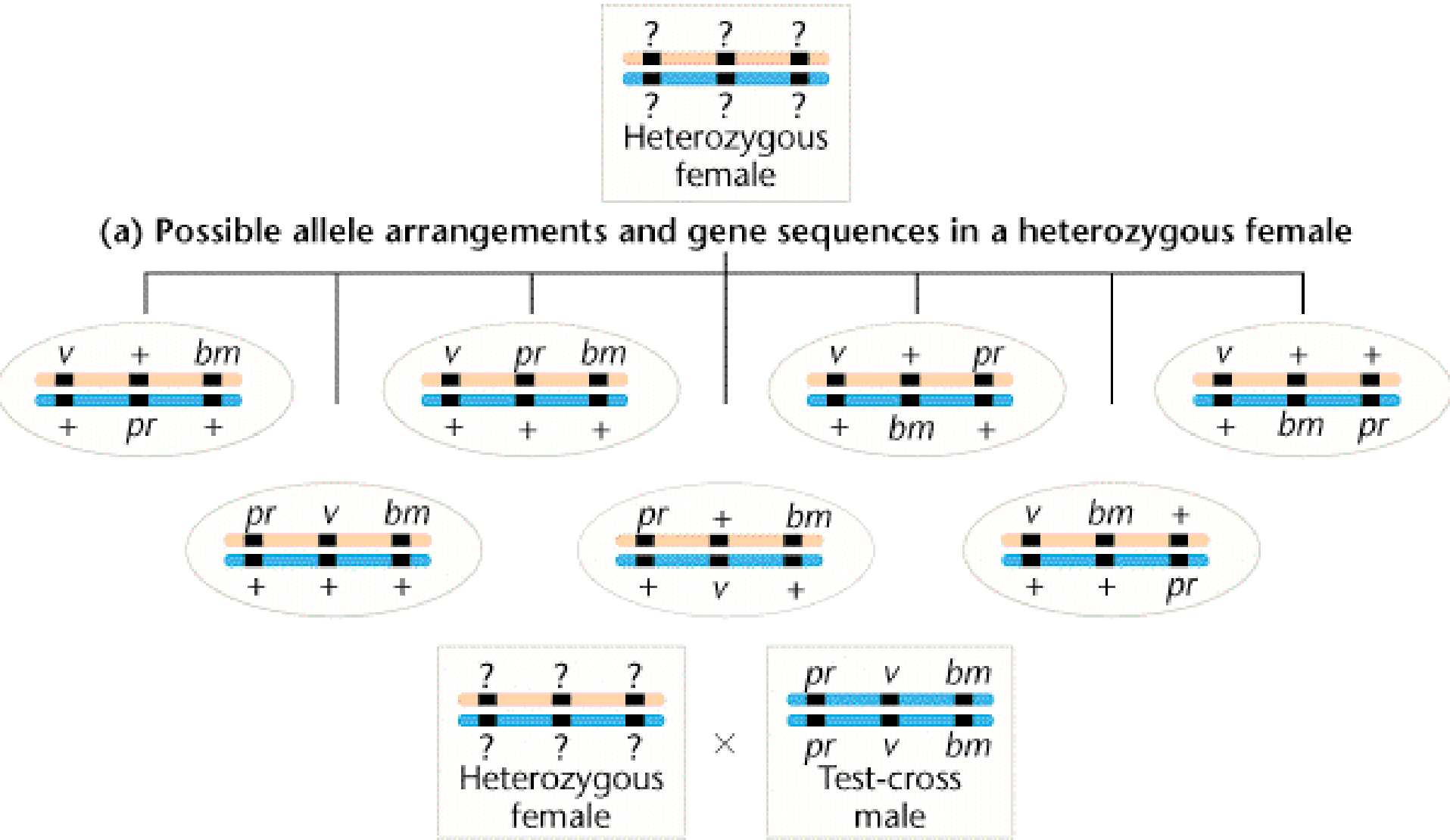
y and w = 1.5% + .06% = 1.56%

w and ec = 4.0% + .06% = 4.06%


Condition
Two-strand stage
Four-strand stage
Gametes following meiosis
No crossover
Crossover in two-strand stage
Crossover in four-strand stage
A
B
a
b
Parental
Recombinant

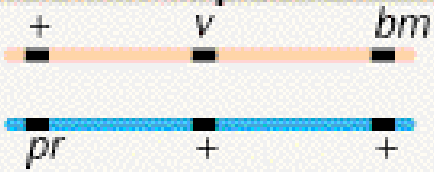
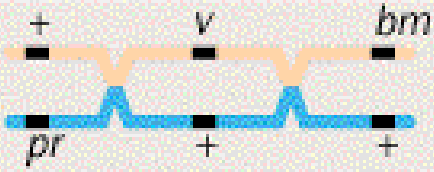
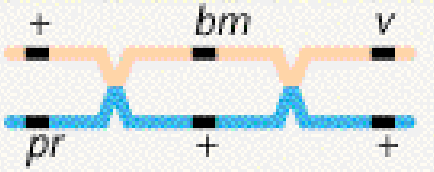
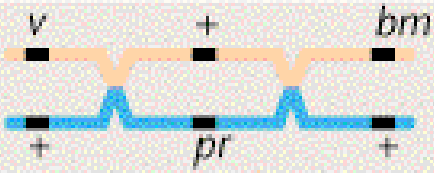
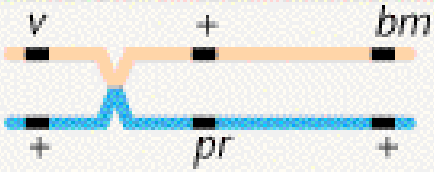
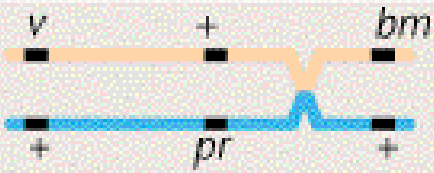
In maize, the recessive mutant genes bm (brown midrib), v (virescent seedling) and pr (purple aleurone) are linked on chromosome 5. Assume that a female plant is known to be heterozygous for all three traits. Nothing is known about the arrangement of the mutant alleles on the paternal and maternal homologs of this heterozygote, the sequence of the genes, or the map distances between the genes. What genotype must the male have to allow successful mapping?

1. **What is the correct heterozygous arrangement of the alleles in the female parent?**


? ? ?
? ? ?
Heterozygous female
(a) Possible allele arrangements and gene sequences in a heterozygous female
v + bm
+ pr +
v pr bm
+ + +
v + pr
+ bm +
v + +
+ bm pr
pr v bm
+ + +
pr + bm
+ v +
v bm +
+ + pr
? ? ?
? ? ?
Heterozygous female
×
pr v bm
pr v bm
Test-cross male

(b) Actual results of mapping cross

Phenotypes of offspring			Number	Total and percentage	Exchange classification
+	*v*	*bm*	230	467	Noncrossover
pr	+	+	237	42.1%	(NCO)
+	+	*bm*	82	161	Single crossover
pr	*v*	+	79	14.5%	(SCO)
+	*v*	+	200	395	Single crossover
pr	+	*bm*	195	35.6%	(SCO)
pr	*v*	*bm*	44	86	Double crossover
+	+	+	42	7.8%	(DCO)

	Allele arrangement and sequence	Test cross phenotypes	Explanation
(a)		+ v bm and pr + +	Noncrossover phenotypes provide the basis of determining the correct arrangement of alleles on homologs
(b)		+ + bm and pr v +	Expected double crossover phenotypes if *v* is in the middle
(c)		+ + v and pr bm +	Expected double crossover phenotypes if *bm* is in the middle
(d)		v pr bm and + + +	Expected double crossover phenotypes if *pr* is in the middle (actually realized)
(e)		v pr + and + + bm	Given that (a) and (d) are correct, single crossover product phenotypes when exchange occurs between *v* and *pr*
(f)		v + + and + pr bm	Given that (a) and (d) are correct, single crossover product phenotypes when exchange occurs between *pr* and *bm*
(g)	Final map		

2. **What is the correct sequence of the genes?**

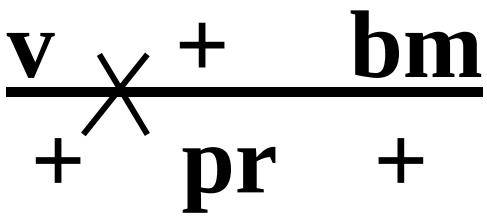
+	v	bm
pr	+	+

+	bm	v
pr	+	+

v	+	bm
+	pr	+

Only last choice will yield v pr bm and +++ following double cross-overs.

3.What is the distance between each pair of genes?

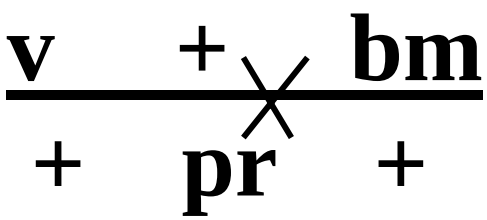


+ + bm 14.5%

+7.8

v pr + -------

22.3



v + + 35.6%

+7.8

+ pr bm -------

43.4

Linkage or genetic map

- use frequency of recombination to measure distant between genes.

Syntenic

- genes on the same chromosome