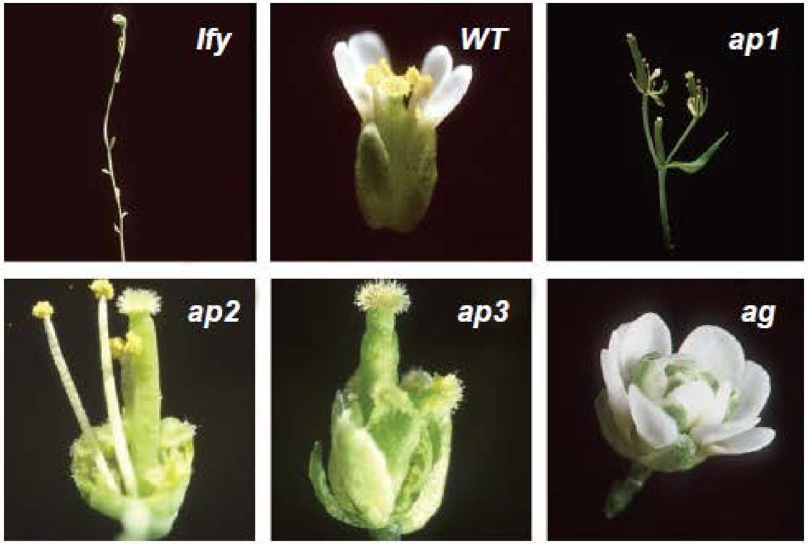
第一章 孟德尔遗传学及孟德尔定律的延伸

Mendelian Genetics and Extensions to Mendelism

Genetic analysis begins with mutants



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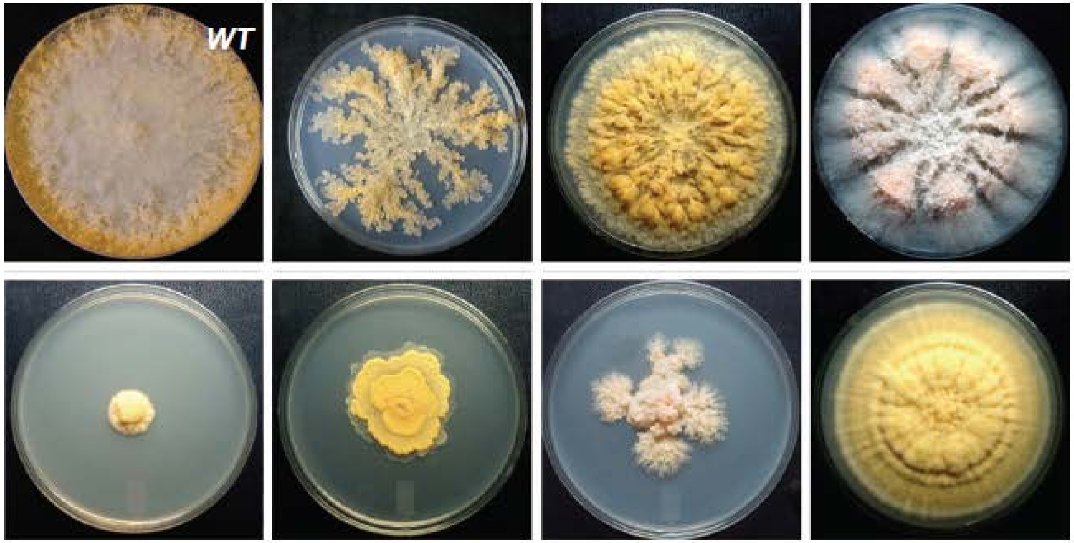
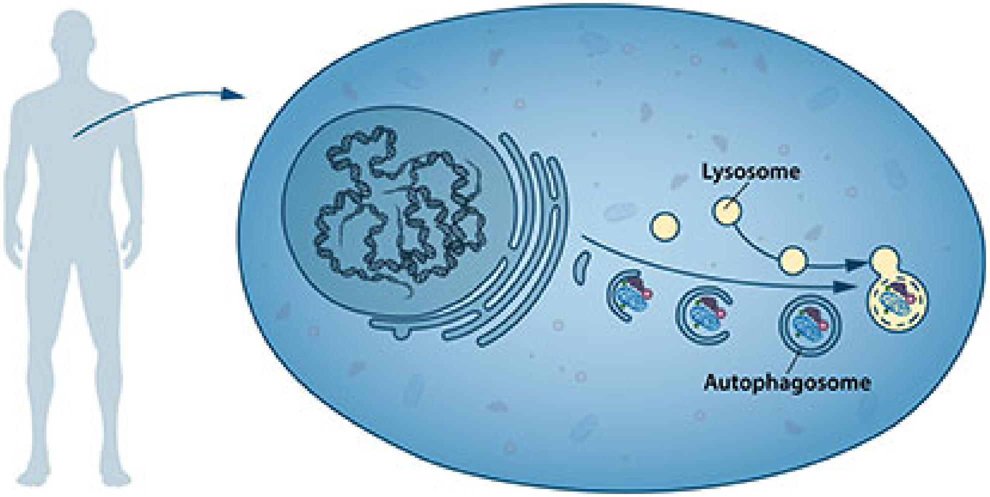
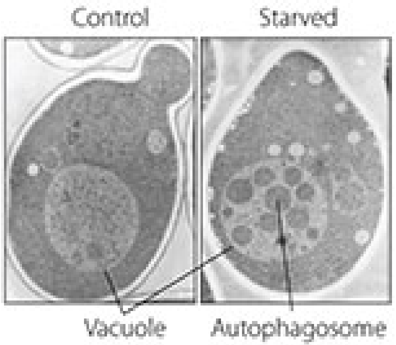


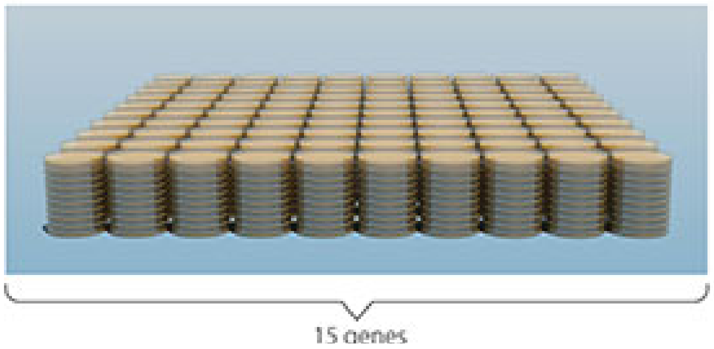
(b)

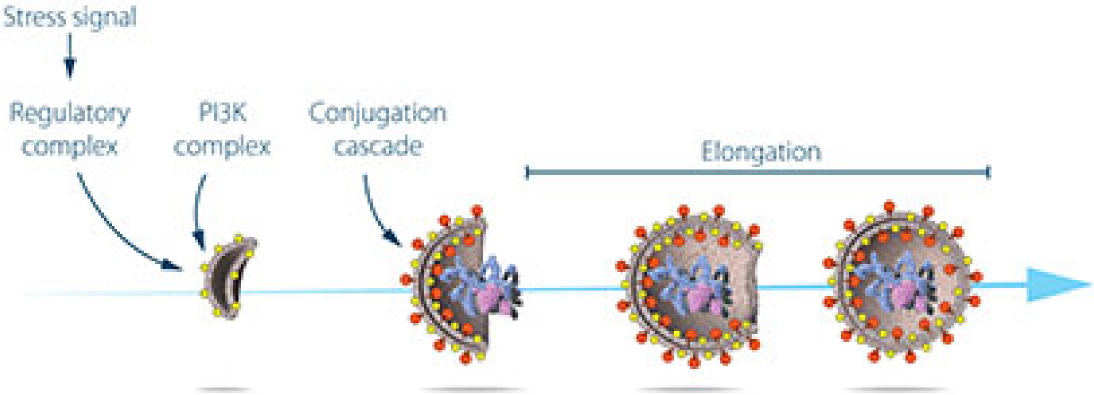
Wild type / Mutants

2016年诺贝尔奖关于突变与基因







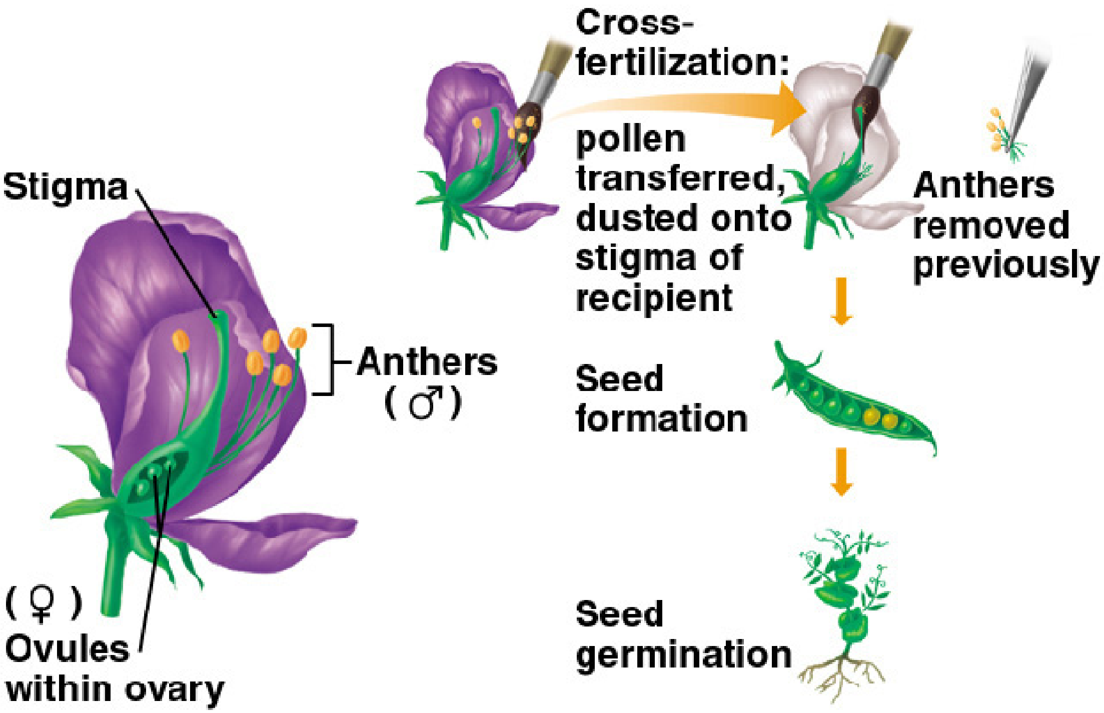


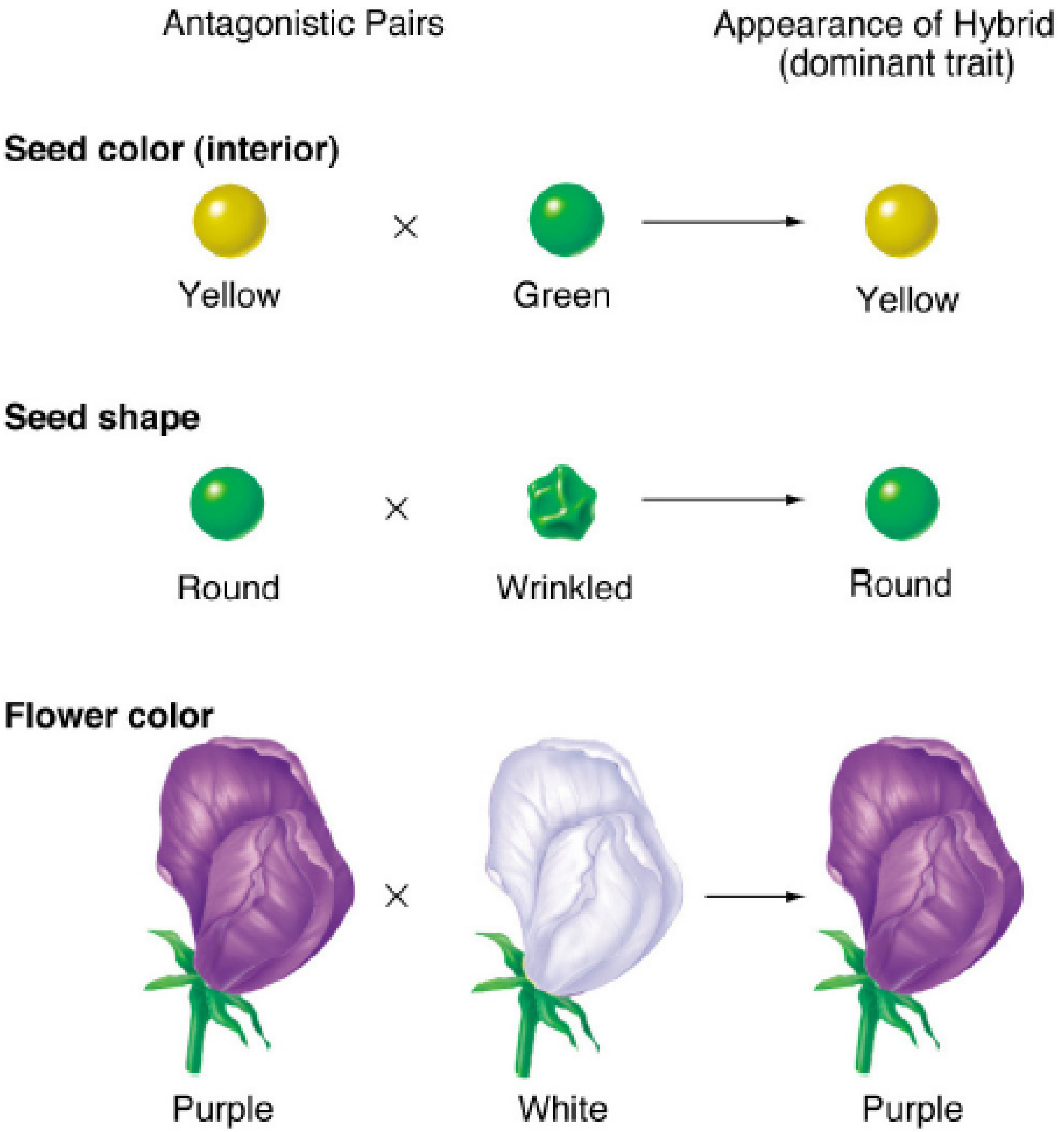
- Takeshige, K., Baba, M., Tsuboi, S., Noda, T. and Ohsumi, Y. (1992). Autophagy in yeast demonstrated with proteinase-deficient mutants and conditions for its induction. Journal of Cell Biology 119, 301-311
- Tsukada, M. and Ohsumi, Y. (1993). Isolation and characterization of autophagy-defective mutants of *Saccharomyces cervisiae*. FEBS Letters 333, 169-174
- Mizushima, N., Noda, T., Yoshimori, T., Tanaka, Y., Ishii, T., George, M.D., Klionsky, D.J., Ohsumi, M. and Ohsumi, Y. (1998). A protein conjugation system essential for autophagy. Nature 395, 395-398
- Ichimura, Y., Kirisako T., Takao, T., Satomi, Y., Shimonishi, Y., Ishihara, N., Mizushima, N., Tanida, I., Kominami, E., Ohsumi, M., Noda, T. and Ohsumi, Y. (2000). A ubiquitin-like system mediates protein lipidation. Nature, 408, 488-492

Section I:

Mendelian Genetics

Experiments with garden peas





Antagonistic Pairs

Appearance of Hybrid (dominant trait)

Seed color (interior)

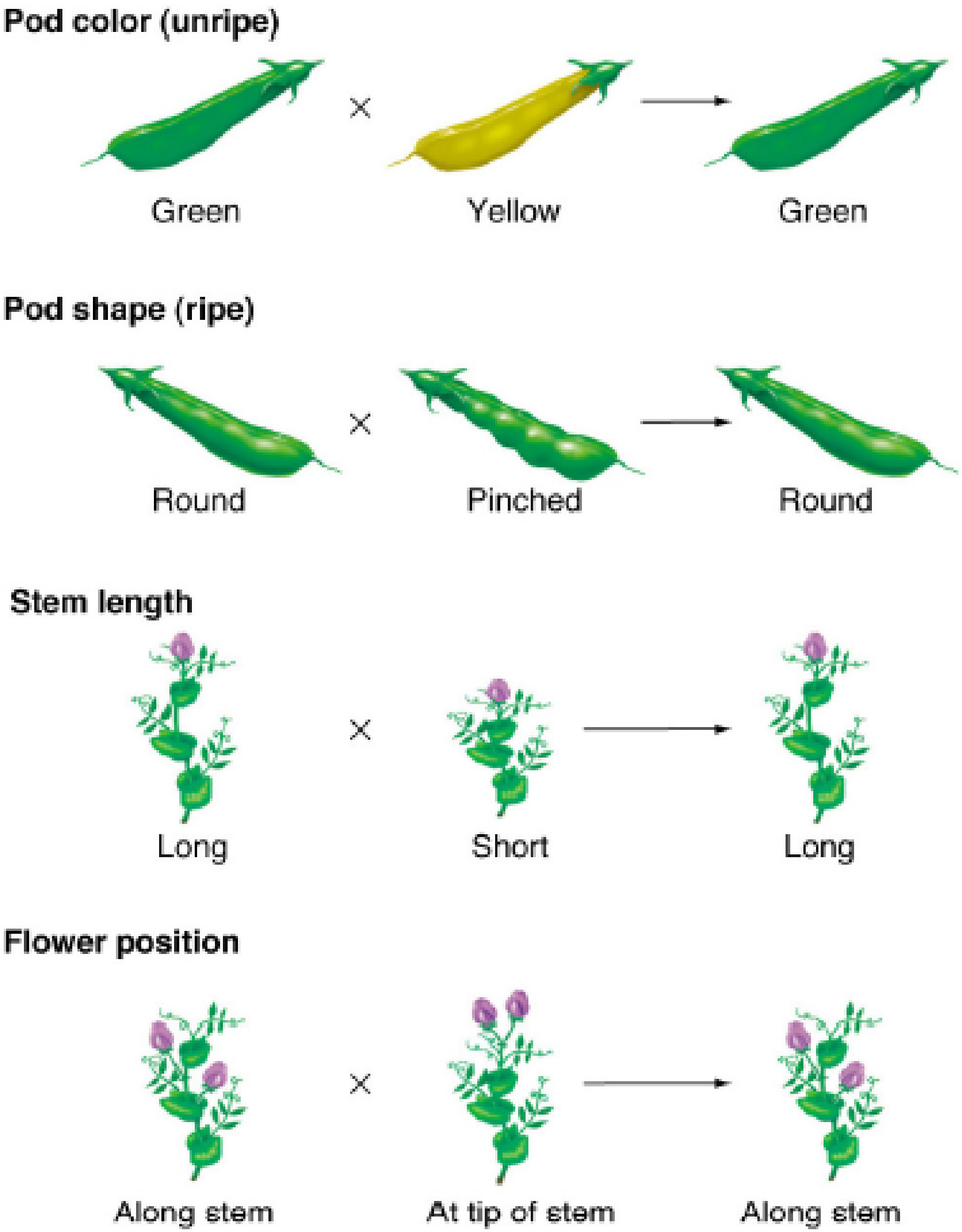
Yellow × Green → Yellow

Seed shape

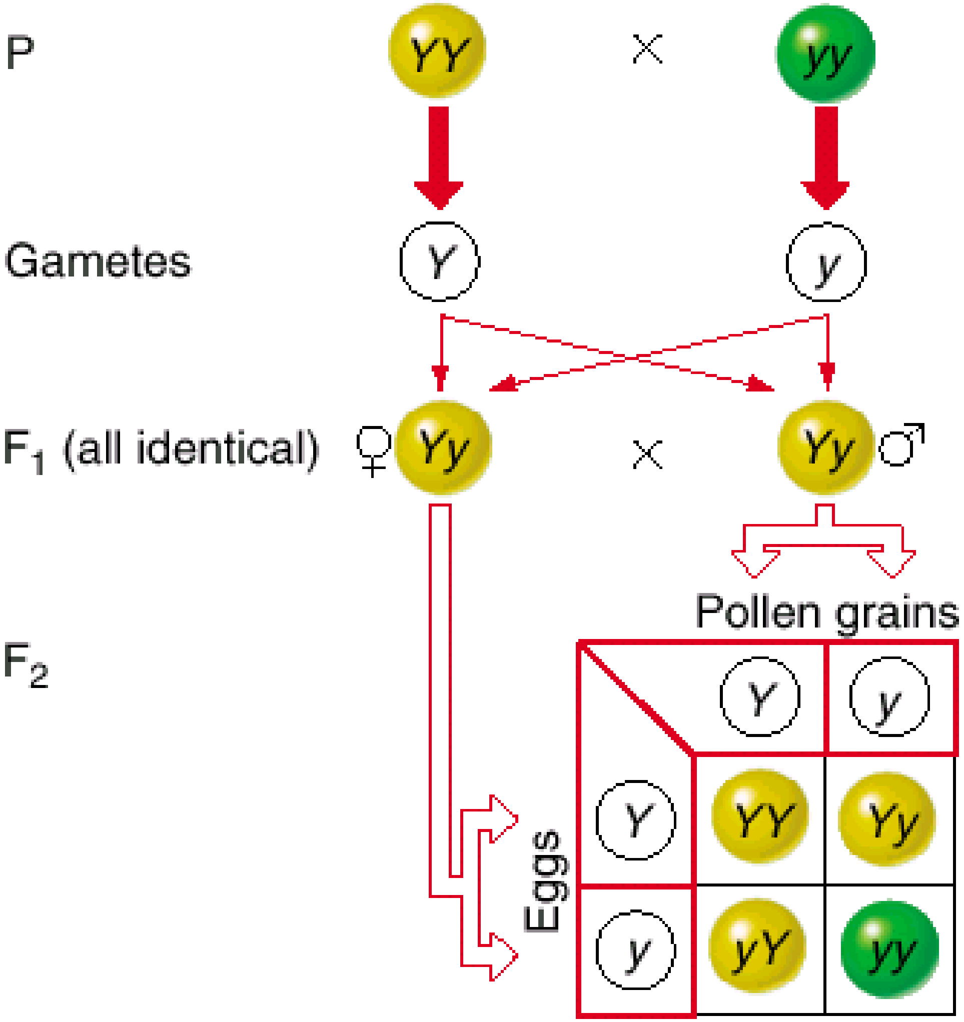
Round × Wrinkled → Round

Flower color

Purple × White → Purple


Pod color (unripe)
Green
×
Yellow
Green
Pod shape (ripe)
Round
×
Pinched
Round
Stem length
Long
×
Short
Long
Flower position
Along stem
×
At tip of stem
Along stem

Monohybrid cross



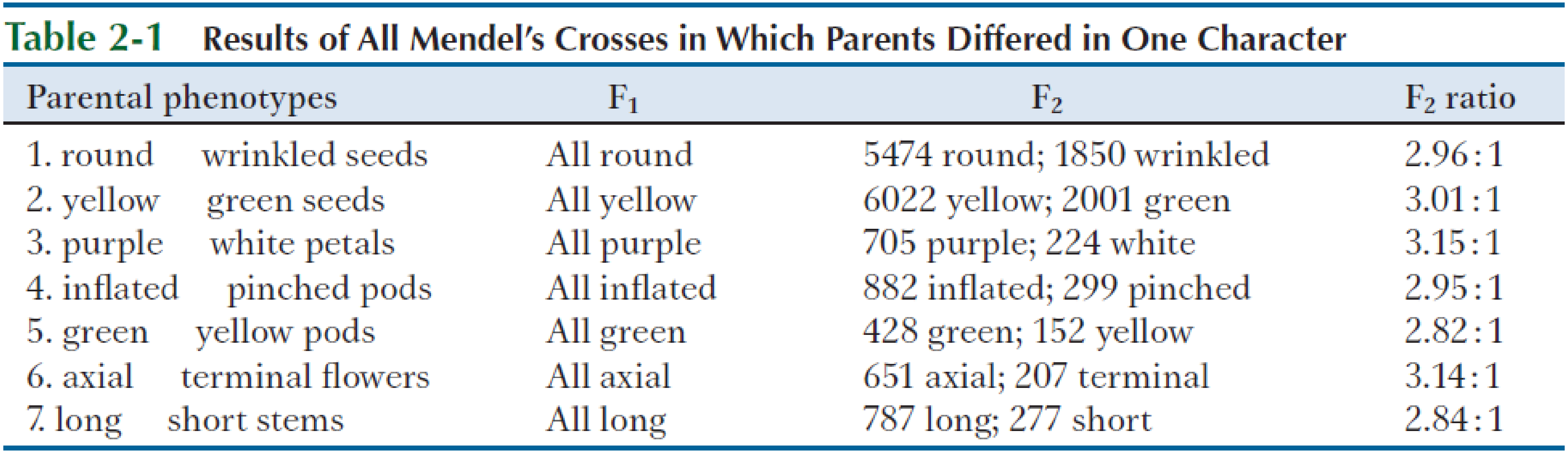
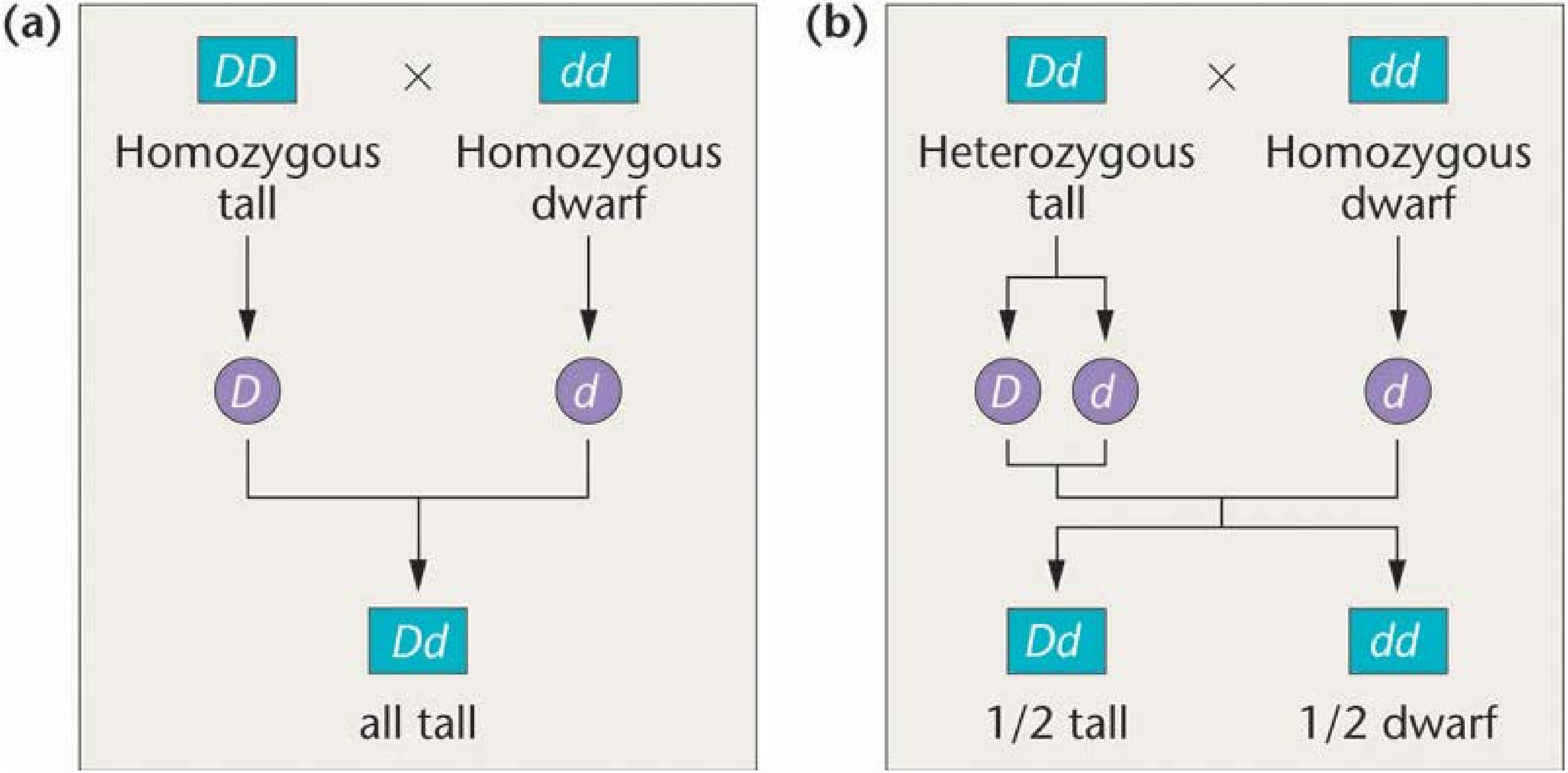


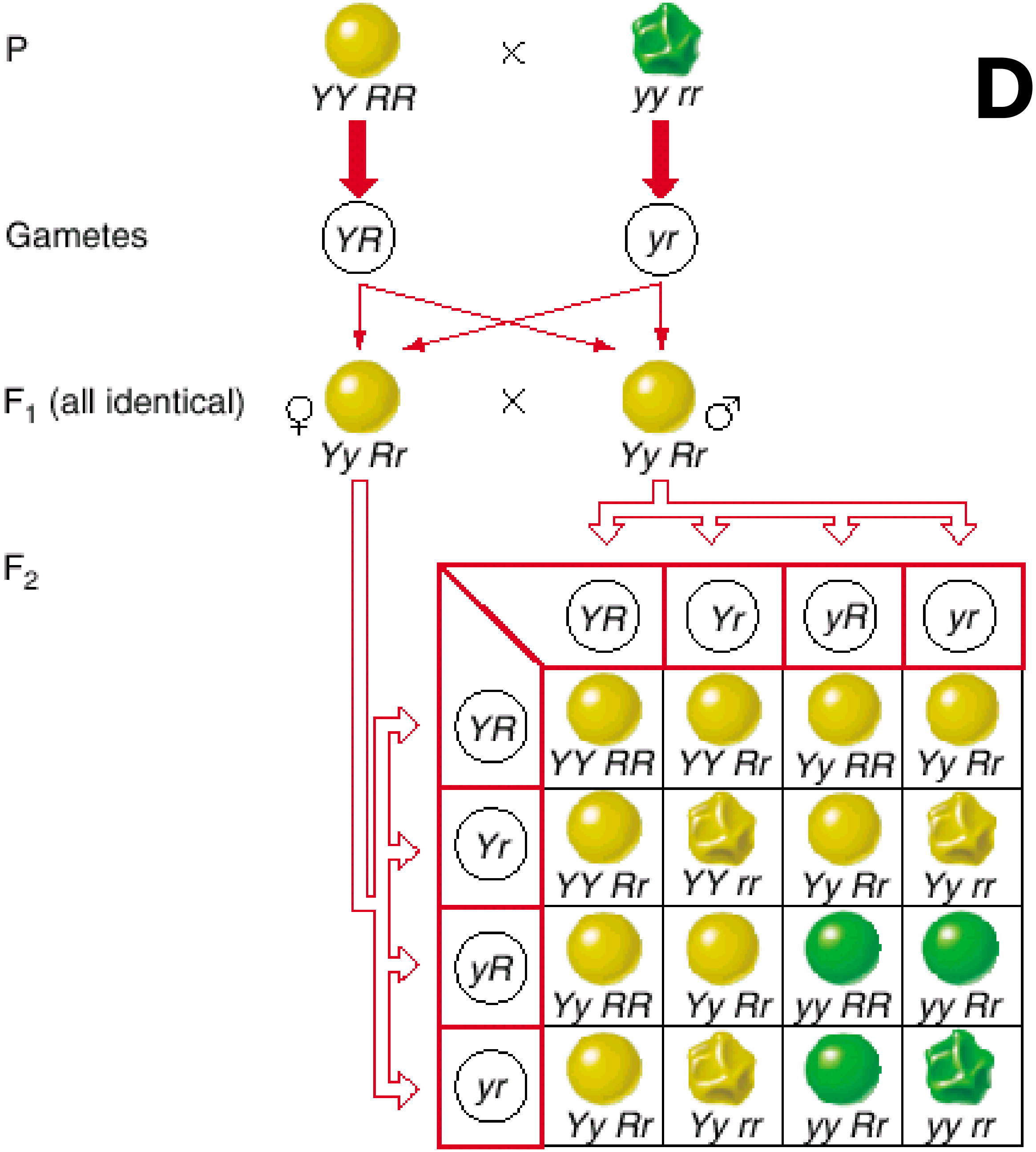
Table 2-1 **Results of All Mendel's Crosses in Which Parents Differed in One Character**

Parental phenotypes	F_1	F_2	F_2 ratio
1. round wrinkled seeds	All round	5474 round; 1850 wrinkled	2.96 : 1
2. yellow green seeds	All yellow	6022 yellow; 2001 green	3.01 : 1
3. purple white petals	All purple	705 purple; 224 white	3.15 : 1
4. inflated pinched pods	All inflated	882 inflated; 299 pinched	2.95 : 1
5. green yellow pods	All green	428 green; 152 yellow	2.82 : 1
6. axial terminal flowers	All axial	651 axial; 207 terminal	3.14 : 1
7. long short stems	All long	787 long; 277 short	2.84 : 1

Test Cross


(a)
DD
×
dd
Homozygous tall
Homozygous dwarf
D
d
Dd
all tall
(b)
Dd
×
dd
Heterozygous tall
Homozygous dwarf
D
d
d
Dd
dd
1/2 tall
1/2 dwarf

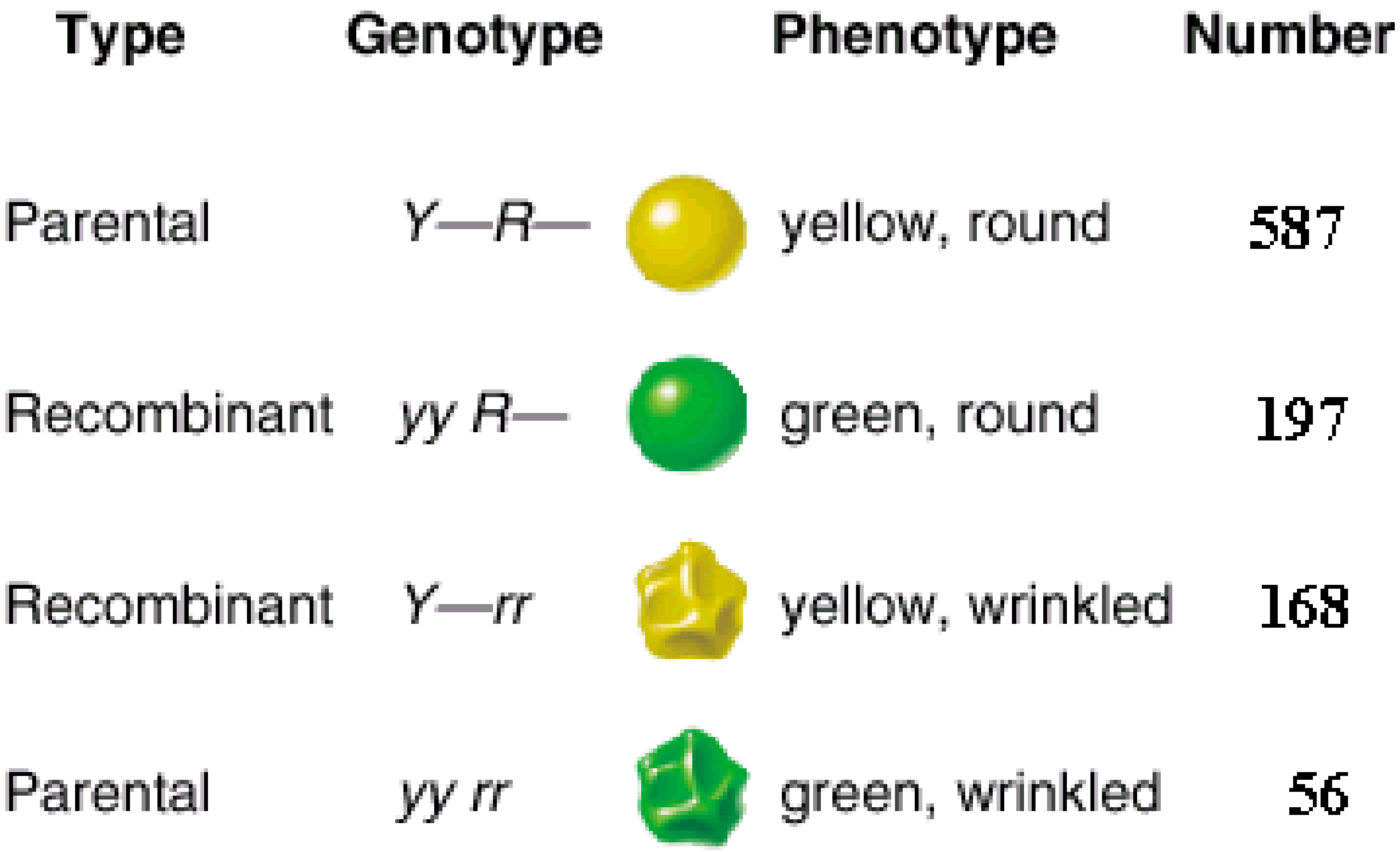
Dihybrid cross



	YR	Yr	yR	yr
YR	YY RR	YY Rr	Yy RR	Yy Rr
Yr	YY Rr	YY rr	Yy Rr	Yy rr
yR	Yy RR	Yy Rr	yy RR	yy Rr
yr	Yy Rr	Yy rr	yy Rr	yy rr

Punnett square

Evaluating Genetic Data



Type	Genotype	Phenotype	Number	
Parental	*Y—R—*	yellow, round	587	**10.5**
Recombinant	*yy R—*	green, round	197	**3.5**
Recombinant	*Y—rr*	yellow, wrinkled	168	**3**
Parental	*yy rr*	green, wrinkled	56	**1**

Goodness of fit

Chi-square(χ^2) test

- A statistical test used to determine the probability that the difference between the observed and the expected values is due to **chance**.

$$\chi^2 = \sum \frac{(O - E)^2}{E}$$

O：observed　E：expected

$$\chi^2 = \sum \frac{(O-E)^2}{E}$$

Expected Ratio	Observed	Expected	o-e	$(o-e)^2$	$(o-e)^2/e$
9/16	587	9/16(1008) =567	20	400	0.71
3/16	197	3/16 (1008) =189	8	64	0.34
3/16	168	3/16 (1008) =189	-21	441	2.33
1/16	56	1/16 (1008) =63	-7	49	0.78
	Total 1008				$\chi^2 = 4.16$

Degrees of freedom (*df*)

Df is a measure of the number of *independently varying parameters* in the experiment

$$df = n - 1$$

Chi square values

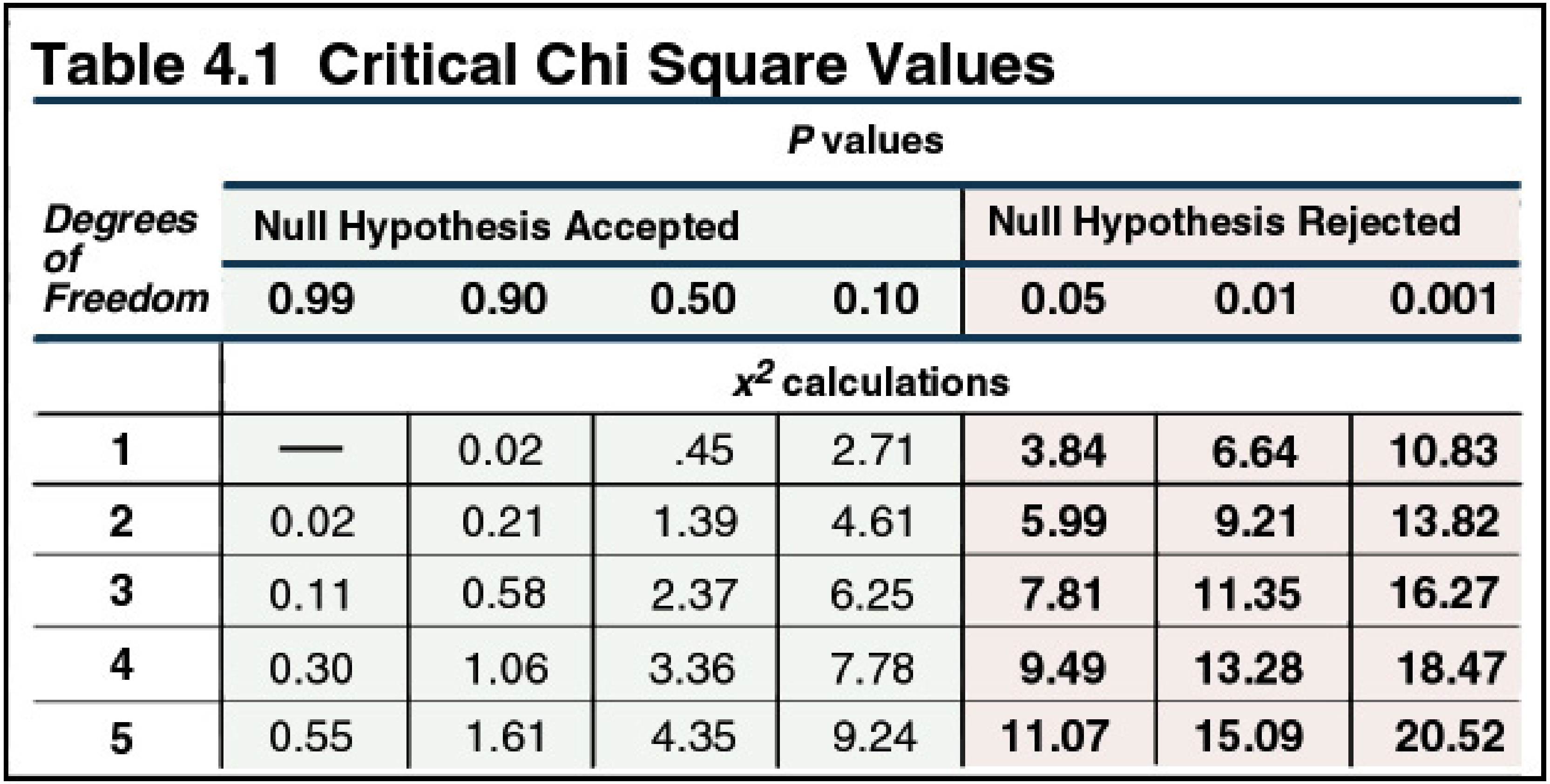


Table 4.1 Critical Chi Square Values

Degrees of Freedom	*P* values						
	Null Hypothesis Accepted				Null Hypothesis Rejected		
	0.99	0.90	0.50	0.10	0.05	0.01	0.001
	x^2 calculations						
1	—	0.02	.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**

$df=3$, $X^2=4.16$ → $P=0.26$

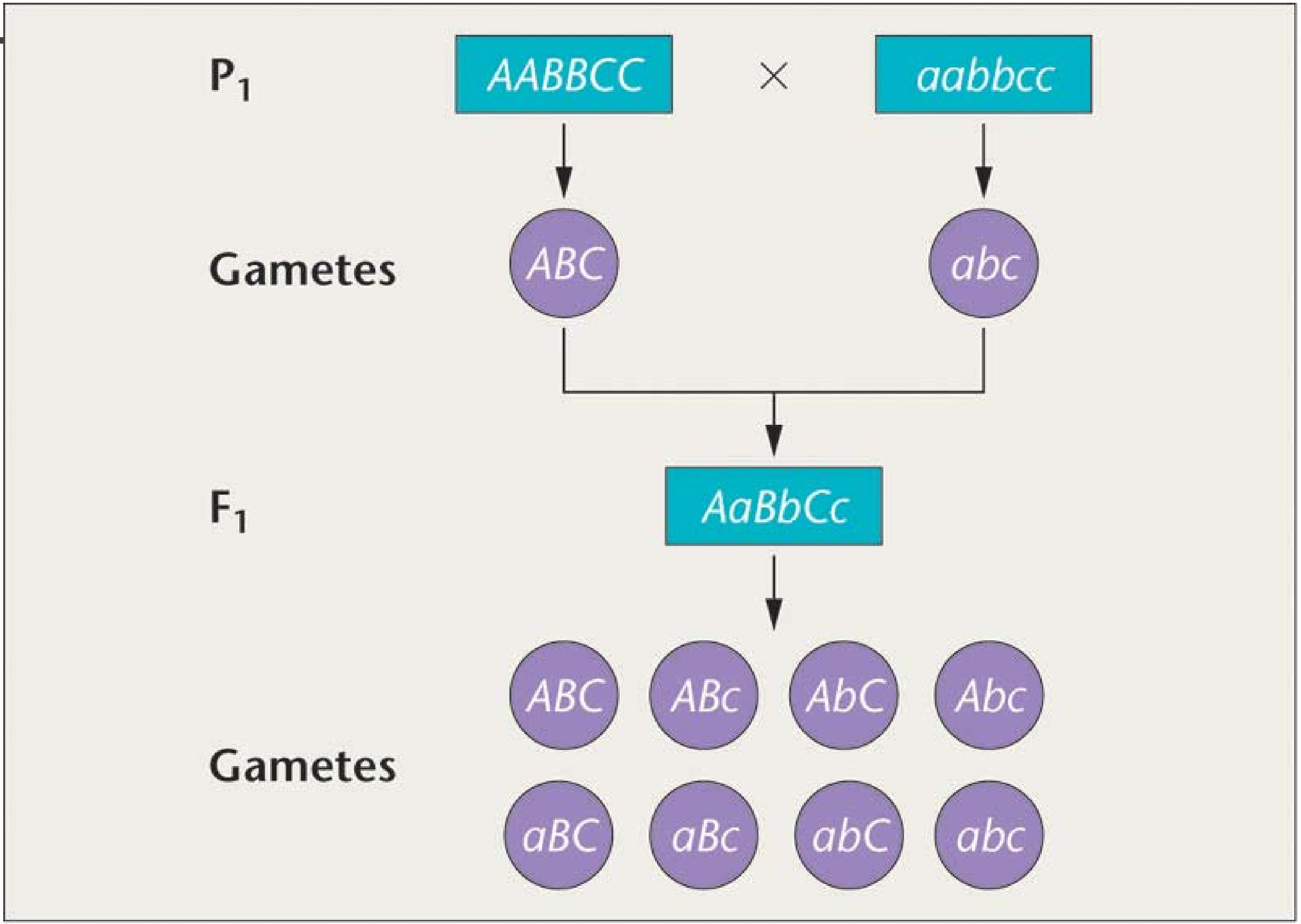
P value

- **Probability value: percentage**
  - **P** =0.26 means, if we repeat the same experiment many times, 26% of the trials would be expected to exhibit chance derivation as great as or greater than that seen in the initial trials.
- **P=0.05 as a relative standard**
  - P>0.05 the hypothesis is correct
  - P<0.05 reject the null hypothesis

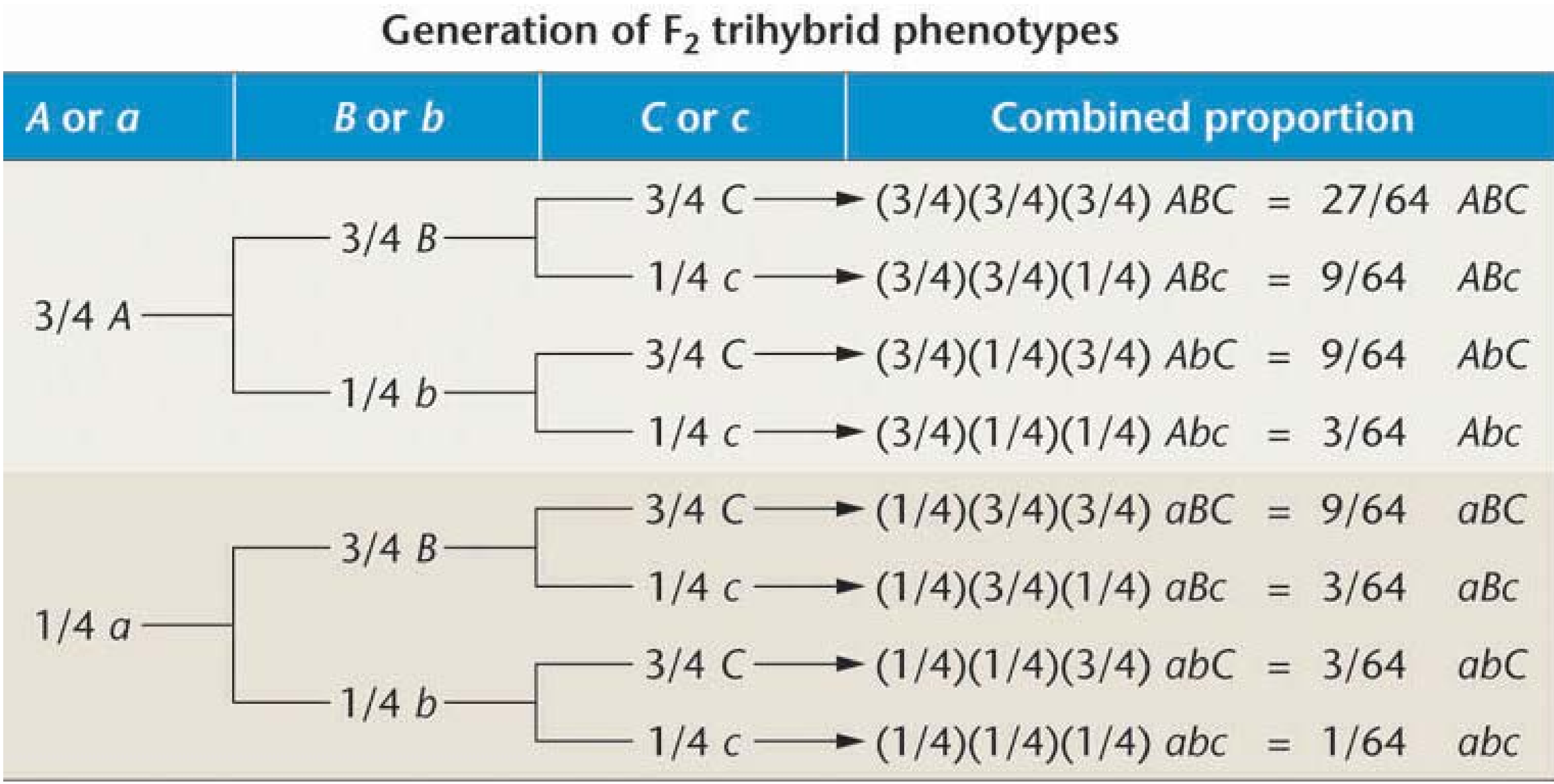
df =3 ,X^2= 4.16, P=0.26

The two genes assort independently.

Trihybrid cross



Fork-line method



Generation of F_2 trihybrid phenotypes

A or *a*	*B* or *b*	*C* or *c*	Combined proportion
3/4 *A*	3/4 *B*	3/4 *C*	(3/4)(3/4)(3/4) *ABC* = 27/64 *ABC*
		1/4 *c*	(3/4)(3/4)(1/4) *ABc* = 9/64 *ABc*
	1/4 *b*	3/4 *C*	(3/4)(1/4)(3/4) *AbC* = 9/64 *AbC*
		1/4 *c*	(3/4)(1/4)(1/4) *Abc* = 3/64 *Abc*
1/4 *a*	3/4 *B*	3/4 *C*	(1/4)(3/4)(3/4) *aBC* = 9/64 *aBC*
		1/4 *c*	(1/4)(3/4)(1/4) *aBc* = 3/64 *aBc*
	1/4 *b*	3/4 *C*	(1/4)(1/4)(3/4) *abC* = 3/64 *abC*
		1/4 *c*	(1/4)(1/4)(1/4) *abc* = 1/64 *abc*

AaBbCcddEe×AabbCcDdEe

↓

AaBbCcDdEe

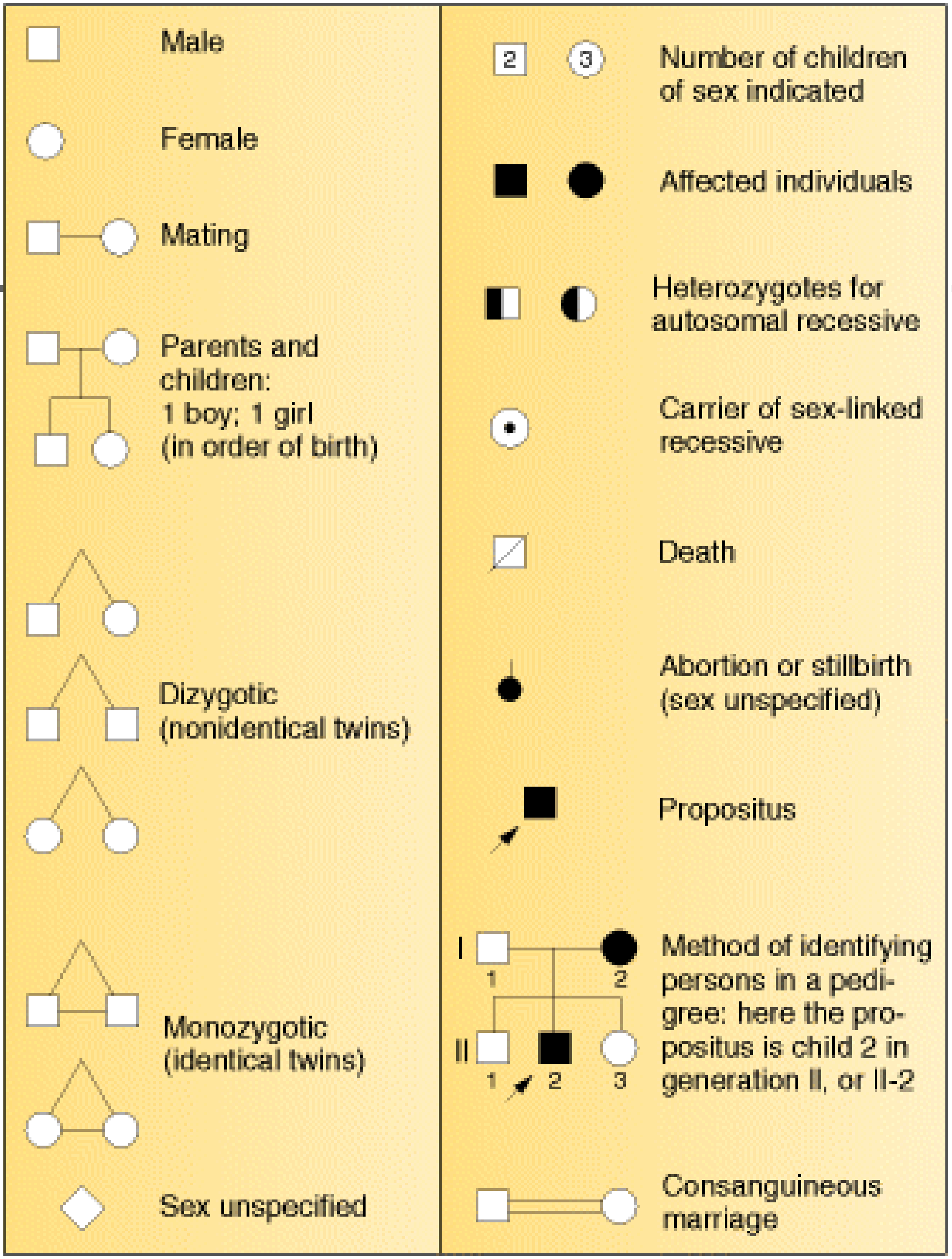
aabbccddee

- **Monohybrid** crosses reveals **the law of segregation**

- **Dihybrid** crosses reveals **the law of independent assortment**

Mendelian Inheritance in Human

- Pedigree analysis



Male

Female

Mating

Parents and children: 1 boy; 1 girl (in order of birth)

Dizygotic (nonidentical twins)

Monozygotic (identical twins)

Sex unspecified

Number of children of sex indicated

Affected individuals

Heterozygotes for autosomal recessive

Carrier of sex-linked recessive

Death

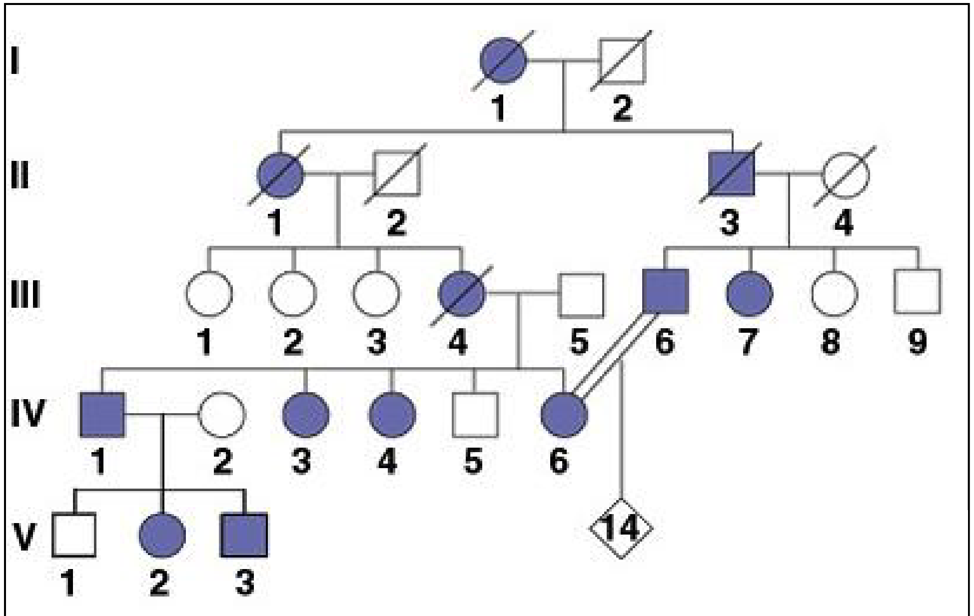
Abortion or stillbirth (sex unspecified)

Propositus

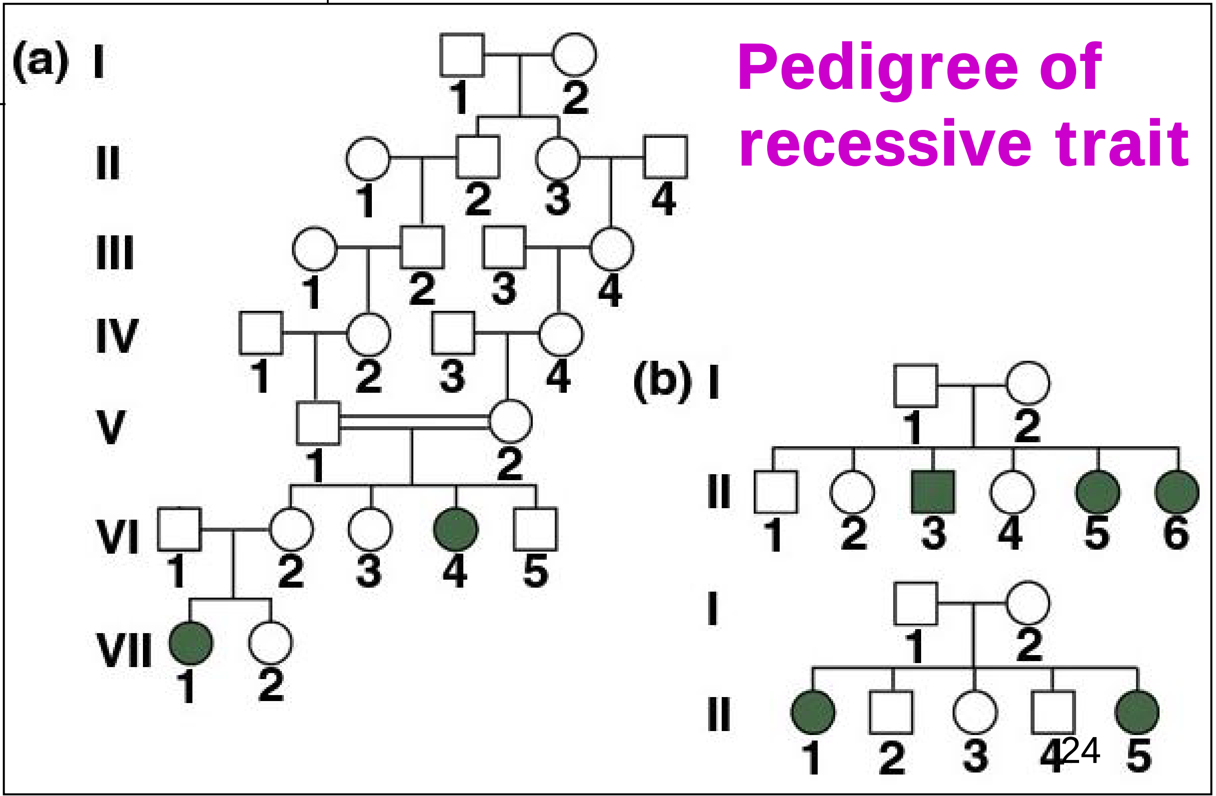
Method of identifying persons in a pedigree: here the propositus is child 2 in generation II, or II-2

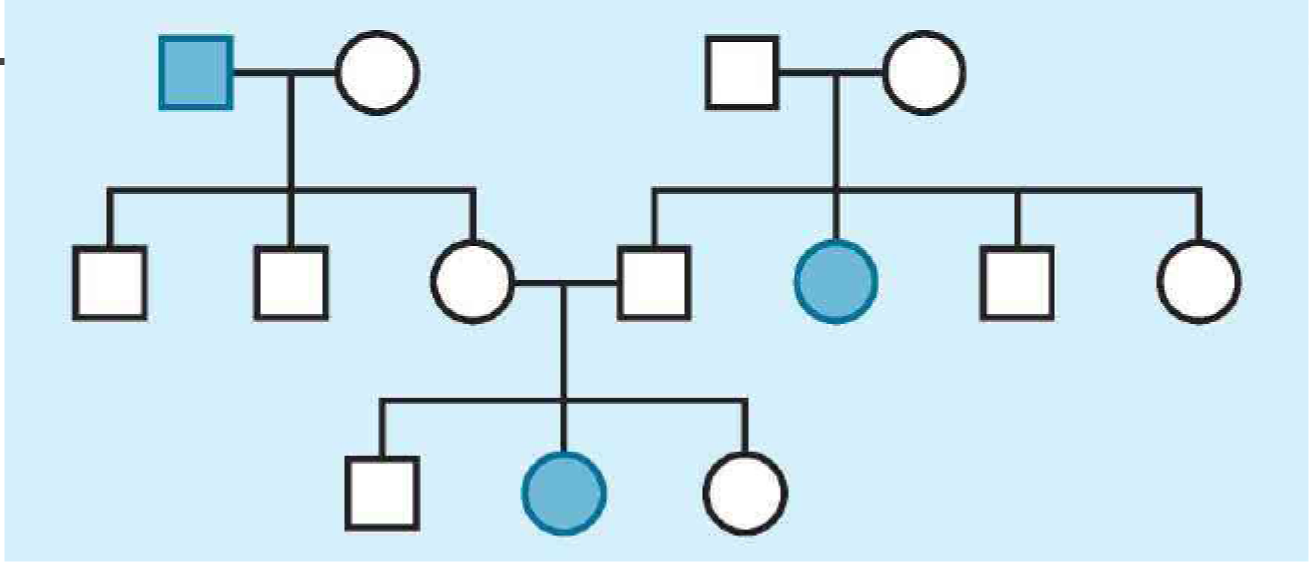
Consanguineous marriage

Pedigree of dominant trait

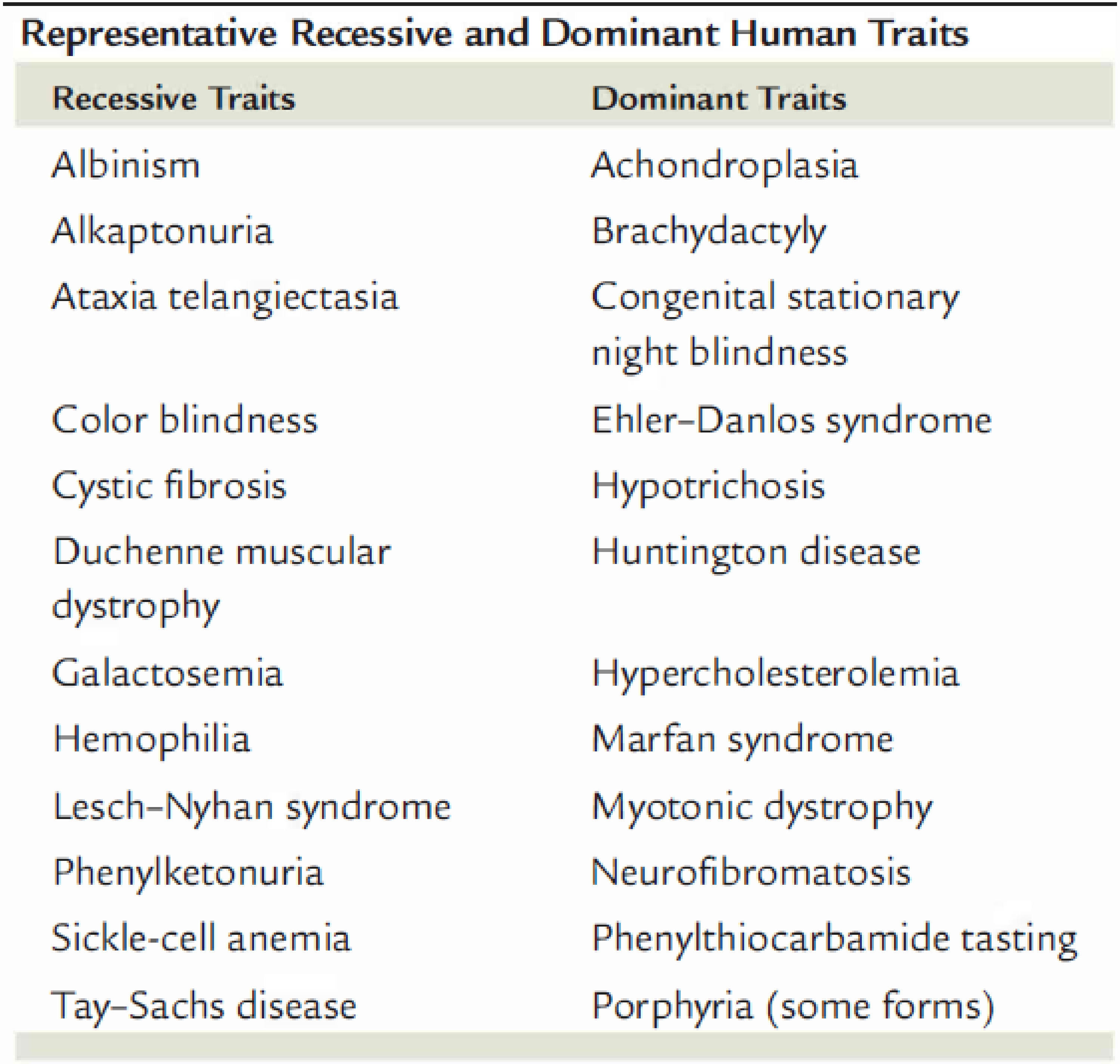


Pedigree of recessive trait





The key to predict dominant or recessive traits is …….



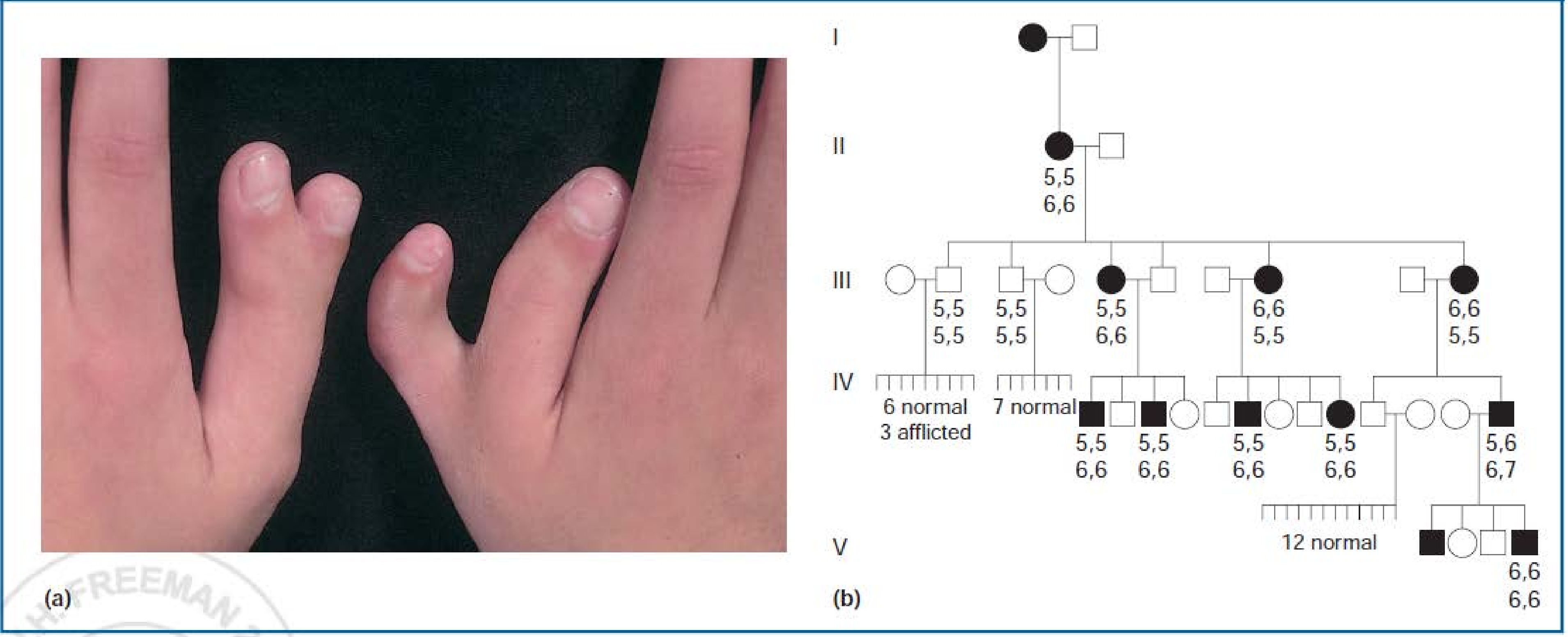
Representative Recessive and Dominant Human Traits

Recessive Traits	Dominant Traits
Albinism	Achondroplasia
Alkaptonuria	Brachydactyly
Ataxia telangiectasia	Congenital stationary night blindness
Color blindness	Ehler–Danlos syndrome
Cystic fibrosis	Hypotrichosis
Duchenne muscular dystrophy	Huntington disease
Galactosemia	Hypercholesterolemia
Hemophilia	Marfan syndrome
Lesch–Nyhan syndrome	Myotonic dystrophy
Phenylketonuria	Neurofibromatosis
Sickle-cell anemia	Phenylthiocarbamide tasting
Tay–Sachs disease	Porphyria (some forms)

Pseudoachondroplasia phenotype

假性软骨发育不全（显性）

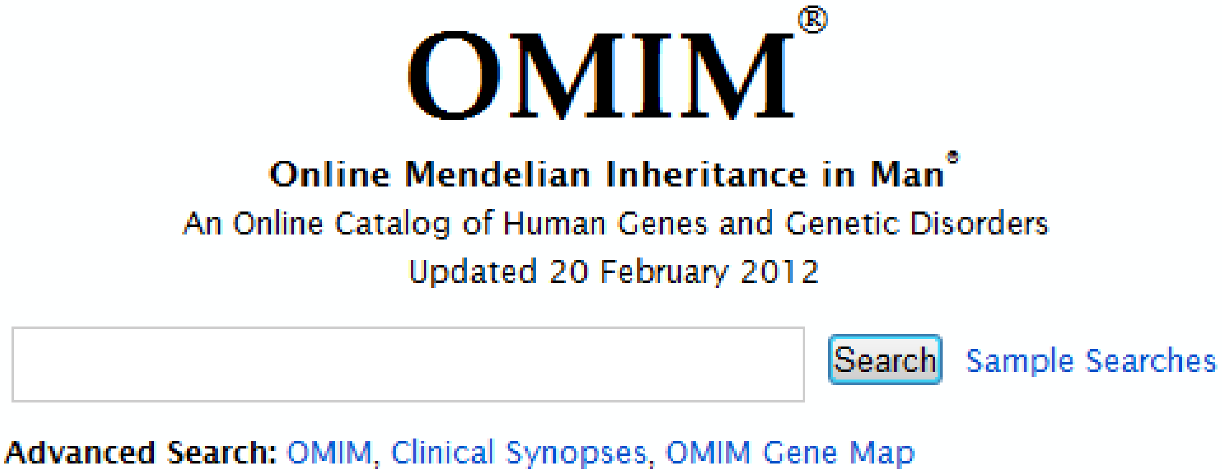
Polydactyly



多指/趾症（显性）

OMIM (Online Mendelian Inheritance in Man)

http://www.omim.org/



OMIM®

Online Mendelian Inheritance in Man®

An Online Catalog of Human Genes and Genetic Disorders

Updated 20 February 2012

Advanced Search: OMIM, Clinical Synopses, OMIM Gene Map

McKUSICK-NATHANS Institute of Genetic Medicine

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Section II:

Extensions to Mendelism

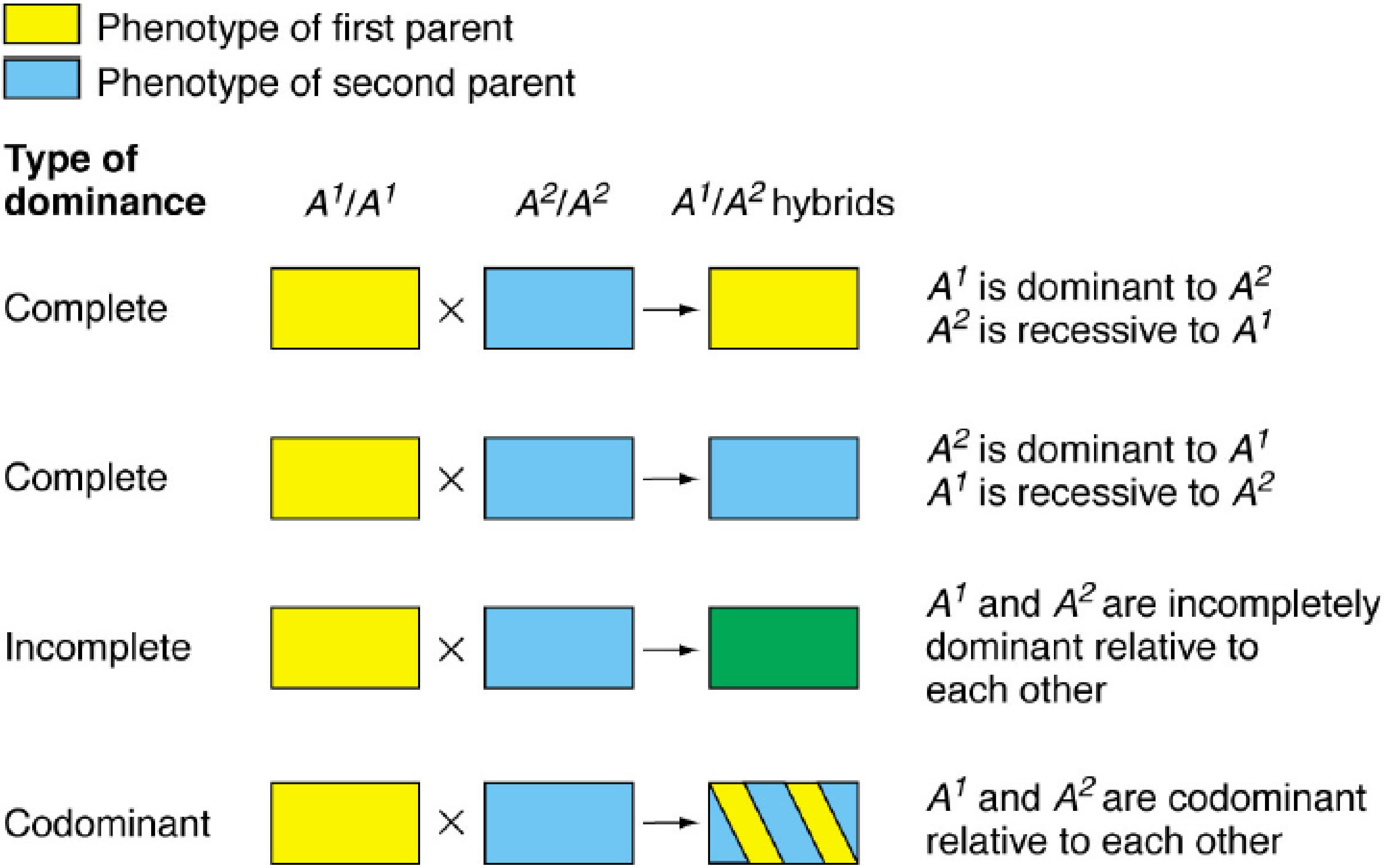
1. Single-gene Inheritance

Dominance is not always complete

◇ Complete dominance（完全显性）

◇ Incomplete dominance（不完全显性）

◇ Codominance（共显性）



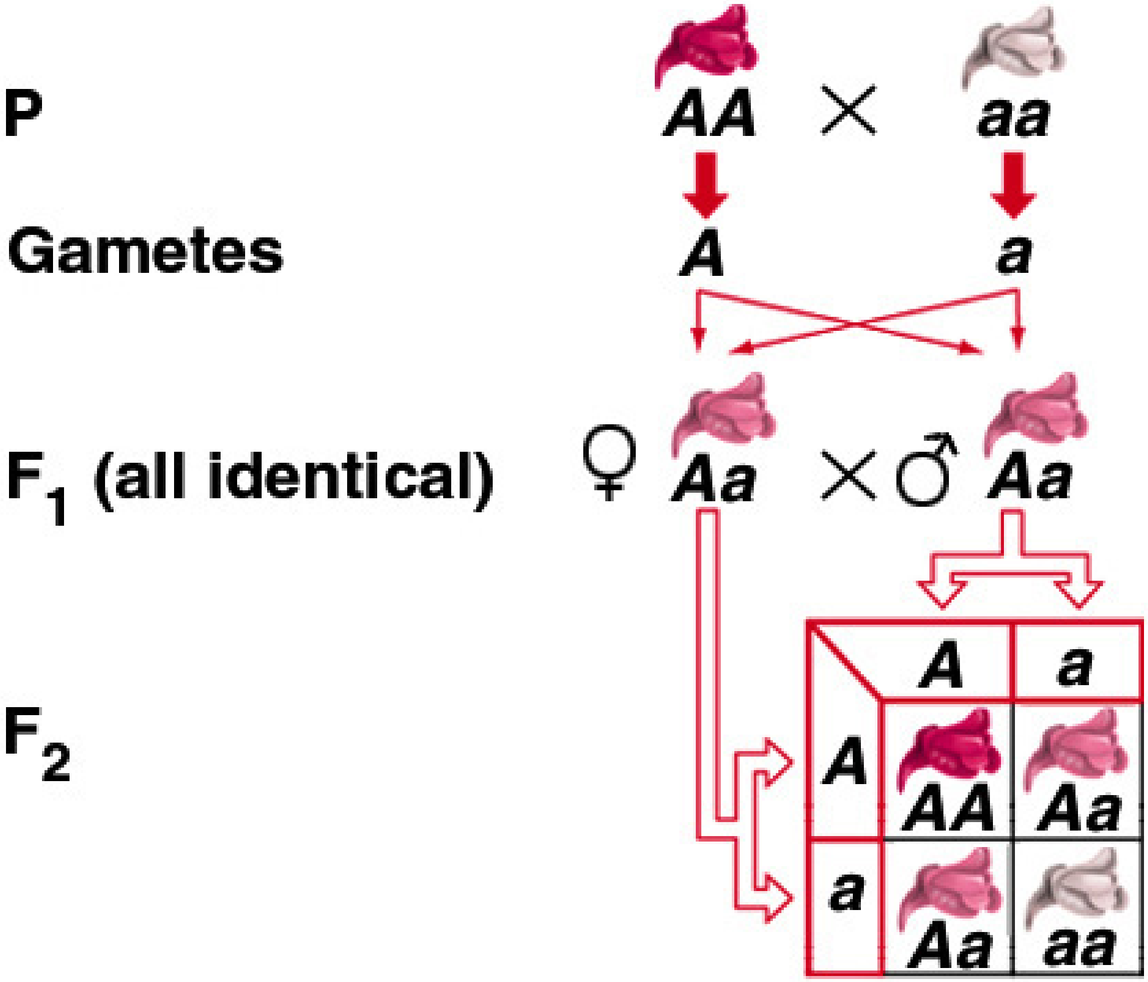
🟨 Phenotype of first parent

🟦 Phenotype of second parent

Type of dominance	A^1/A^1		A^2/A^2		A^1/A^2 hybrids	
Complete	🟨	×	🟦	→	🟨	A^1 is dominant to A^2 A^2 is recessive to A^1
Complete	🟨	×	🟦	→	🟦	A^2 is dominant to A^1 A^1 is recessive to A^2
Incomplete	🟨	×	🟦	→	🟩	A^1 and A^2 are incompletely dominant relative to each other
Codominant	🟨	×	🟦	→	▨	A^1 and A^2 are codominant relative to each other

Incomplete dominance

Antirrhinum majus (snapdragons)



P *AA* × *aa*

Gametes *A* *a*

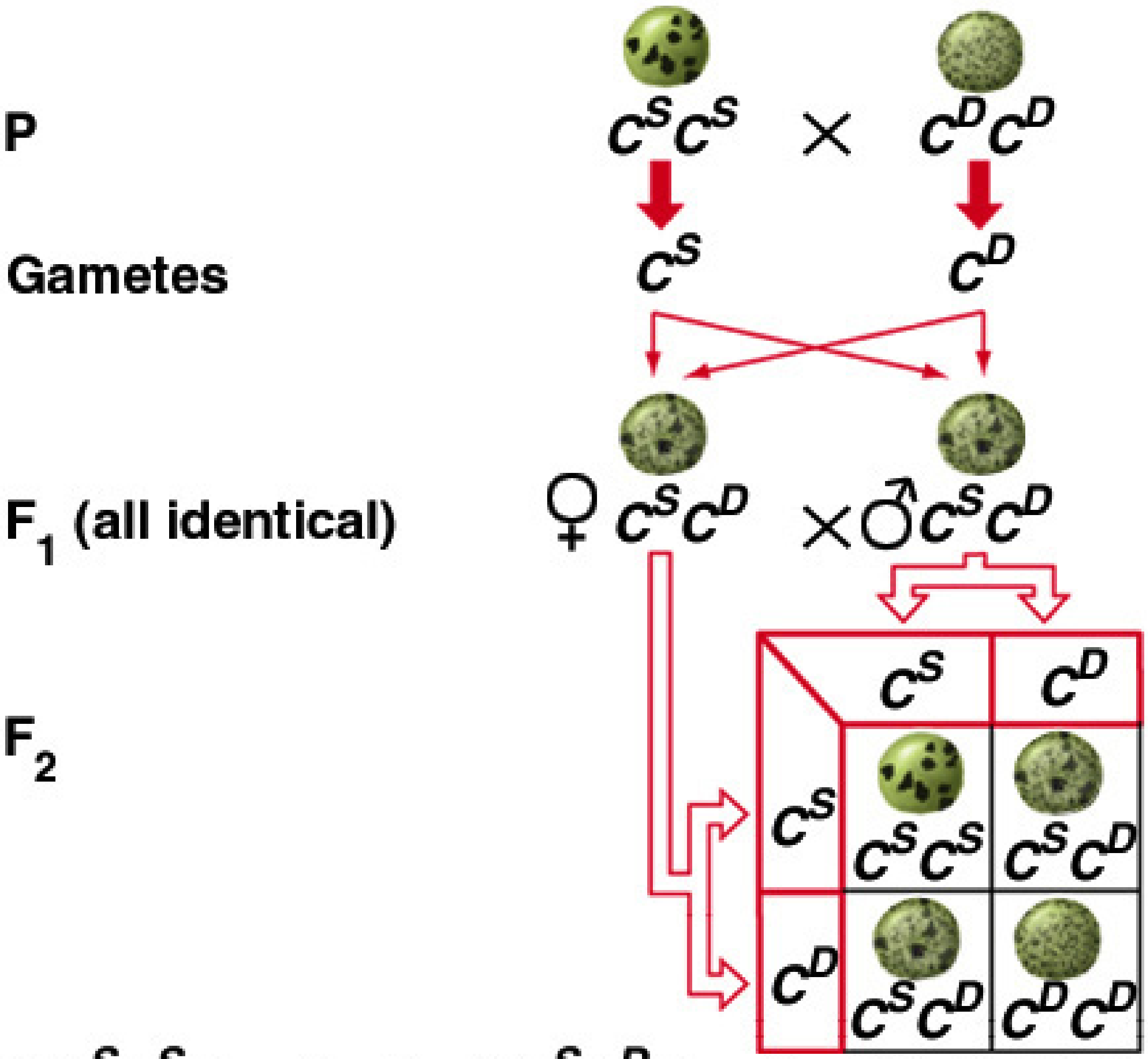
F_1 (all identical) ♀ *Aa* × ♂ *Aa*

F_2

	A	*a*
A	*AA*	*Aa*
a	*Aa*	*aa*

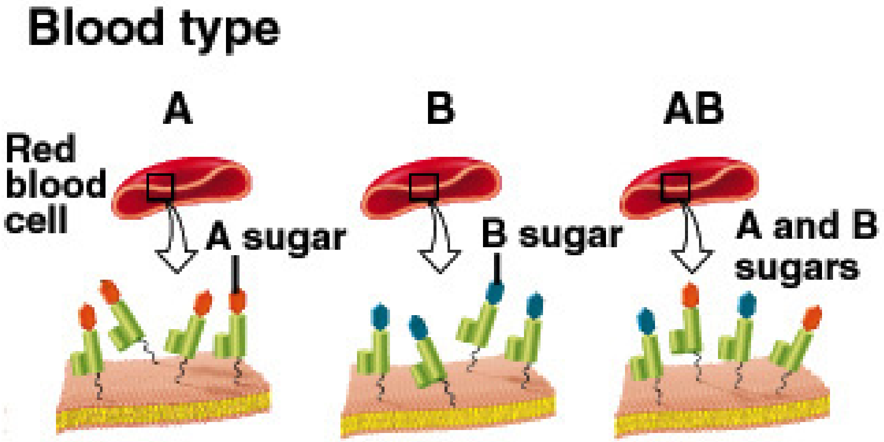
1 *AA* (red) : 2 *Aa* (pink) : 1 *aa* (white)

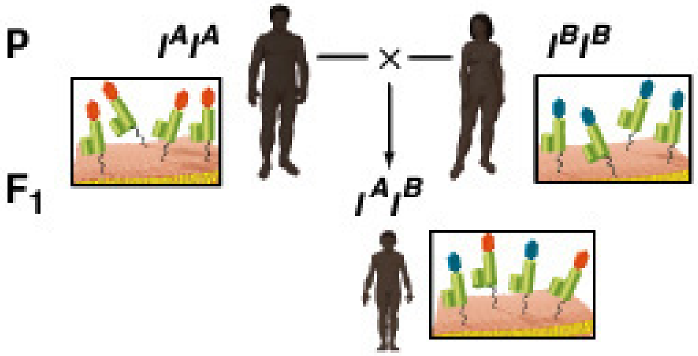
Codominance



1 C^SC^S (spotted) : 2 C^SC^D (spotted/dotted) : 1 C^DC^D (dotted)

ABO blood types





Genotypes	Corresponding Phenotypes: Type(s) of Molecule on Cell
I^AI^A I^Ai	A
I^BI^B I^Bi	B
I^AI^B	AB
ii	O

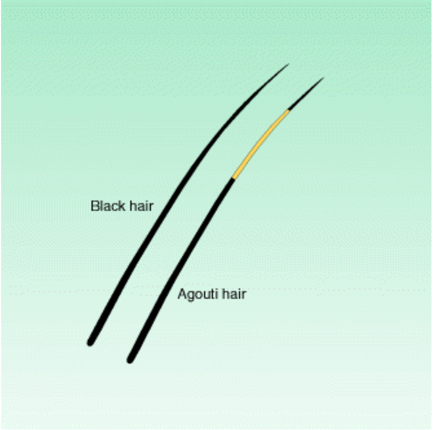
A gene may have more than two alleles

Mutiple alleles（复等位基因）

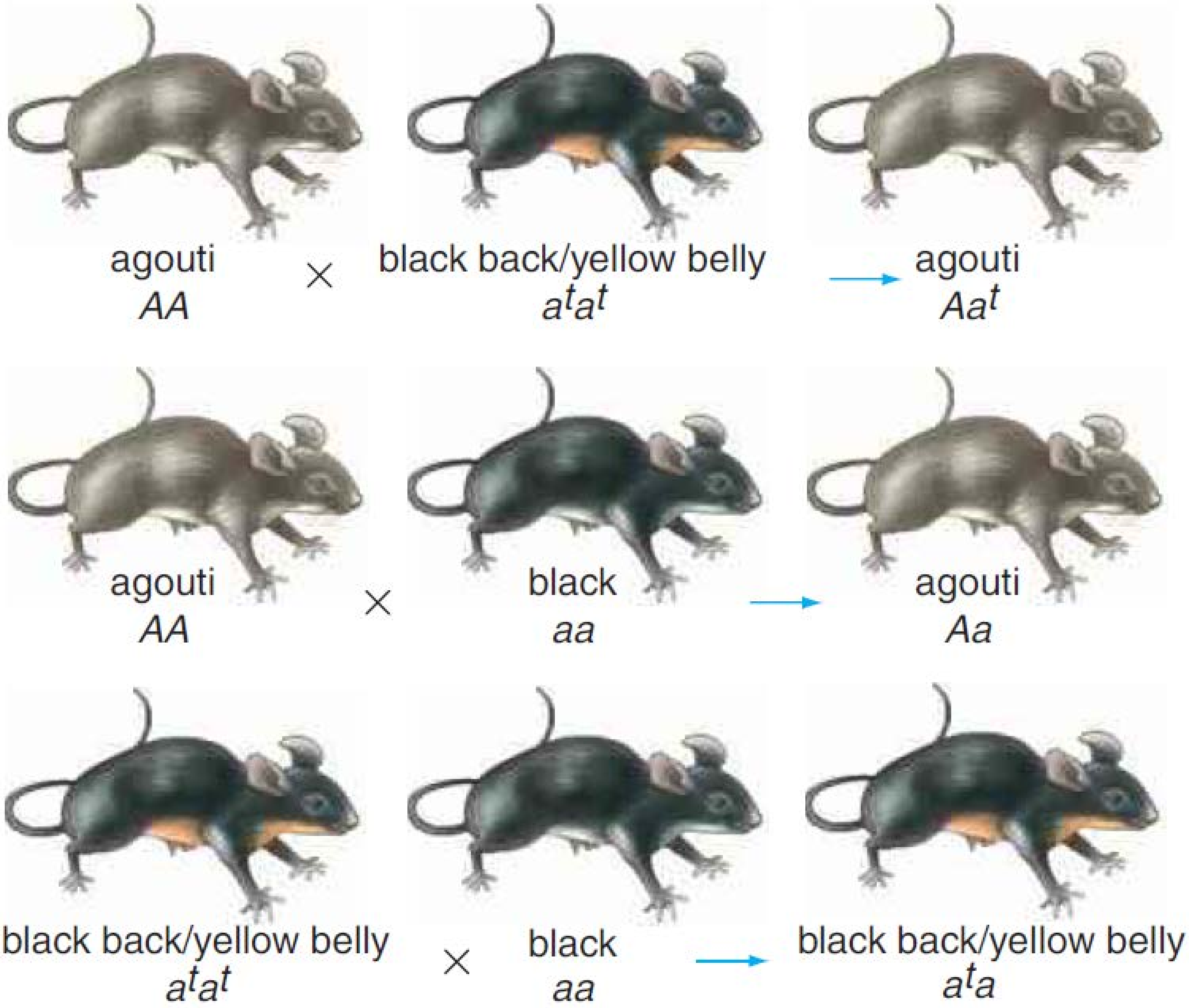
A condition in which a particular gene occurs in three or more allelic forms in a population of organisms

ABO blood types: I^A , I^B , i

Researchers have identified in the laboratory 14 distinguishable mutant alleles for the *agouti* gene.



(b) **Genotype**	**Phenotype**
$A\_$	agouti
a^ta^t	black/yellow
aa	black



agouti AA × black back/yellow belly a^ta^t → agouti Aa^t

agouti AA × black aa → agouti Aa

black back/yellow belly a^ta^t × black aa → black back/yellow belly a^ta

Dominance series: $A > a^t > a$

Mutations are the source of new alleles

- An allele whose frequency in a population is greater than 1% is by definition a **wild-type** allele
- An allele with frequency of less than 1% is considered a **mutant** allele
- A gene with only one common, wild-type allele is **monomorphic**

One gene may contribute to several visible characteristics

- **Pleiotropy** (基因多效性)

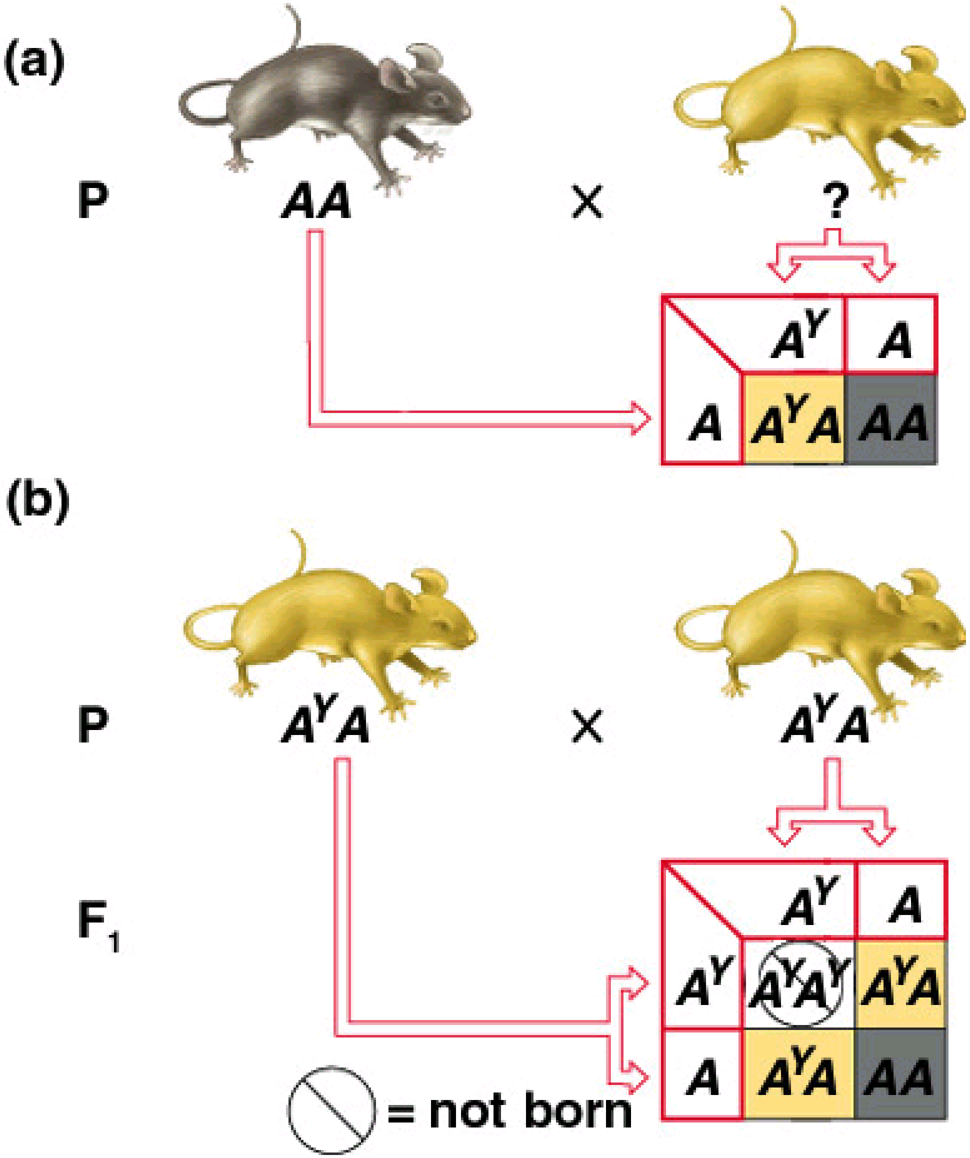
  Aboriginal Maiori People Of New Zealand

  Respiratory problem and sterile

  Cilia (纤毛) and flagella (鞭毛)

- Some alleles may cause **lethality**

Recessive lethal alleles

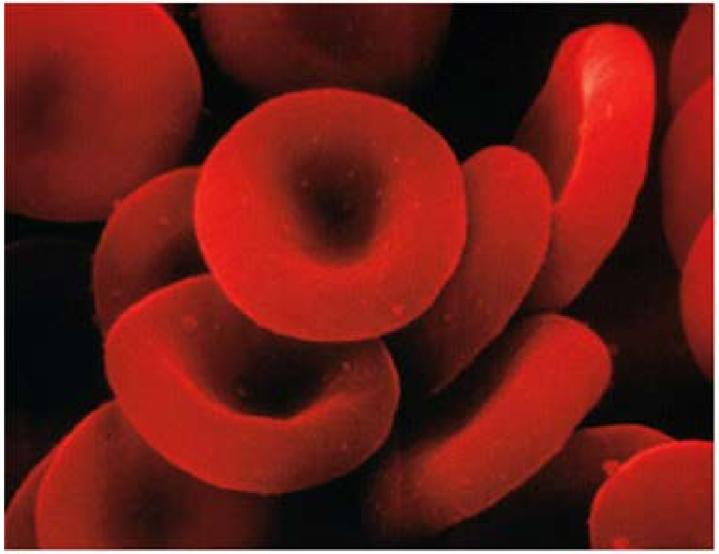


A^Y: A recessive lethal allele that also produces a dominant coat color phenotype

The molecular basis of the Agouti gene → **Reading**

A comprehensive example:

- Sickle-cell syndrome 镰刀型贫血病

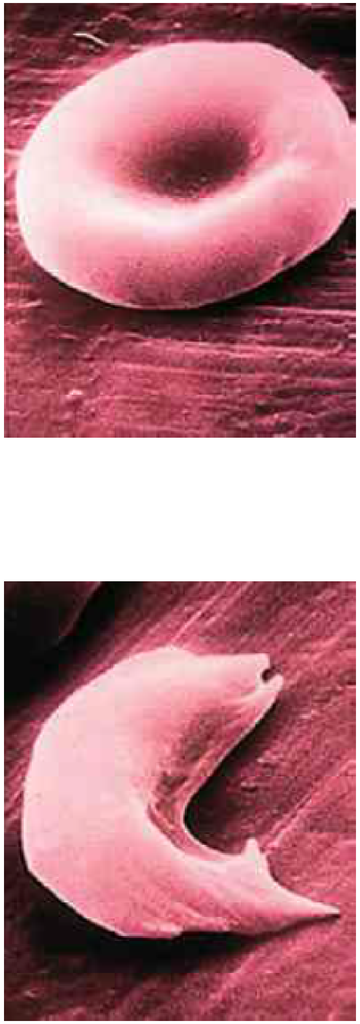


(a)

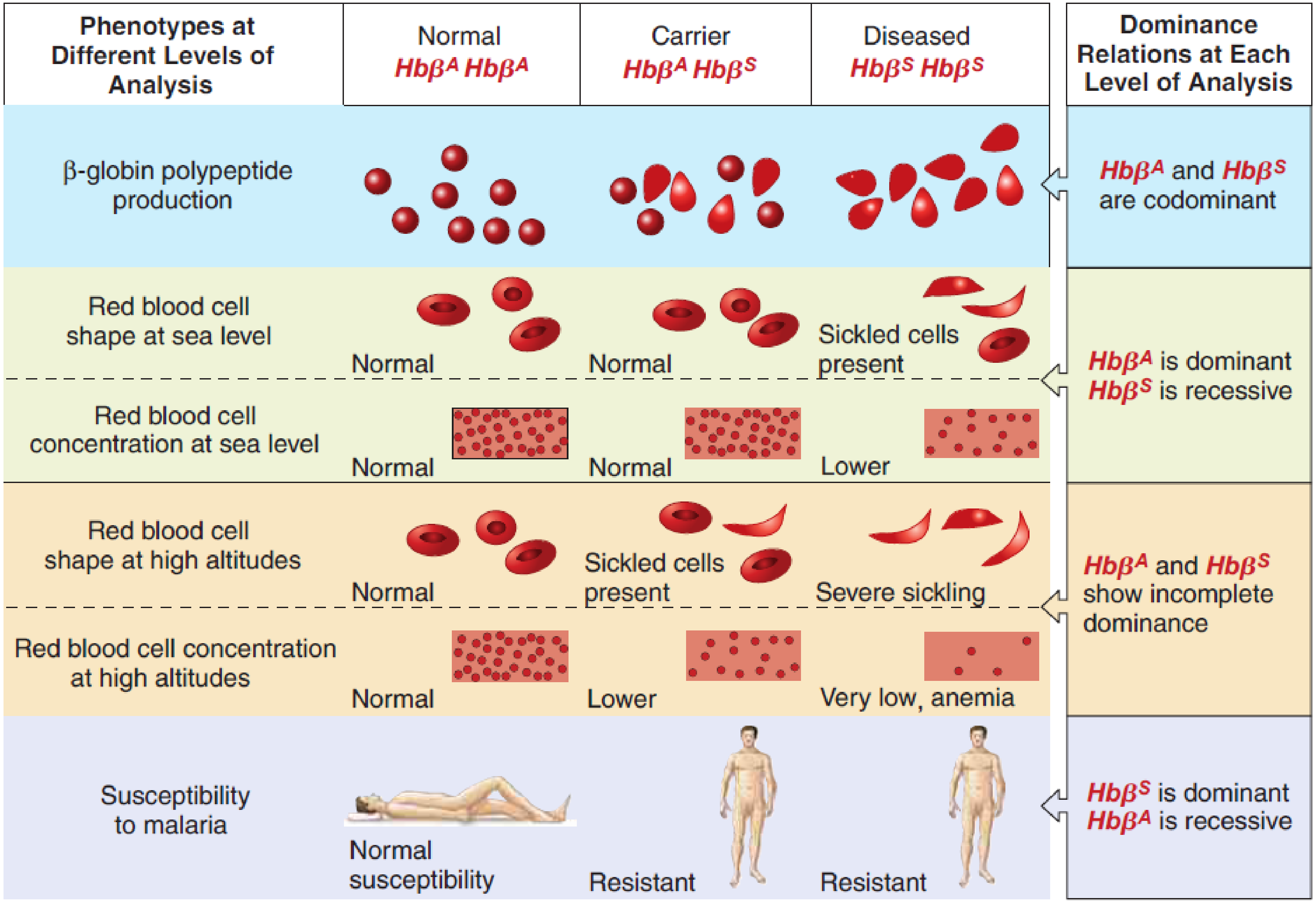
(b)

- Hemoglobin:
  - α-globin (Hbα)
  - β-globin (Hbβ)
    - $Hb\beta^{A}$: Wild-type
    - 400 mutant alleles, $Hb\beta^{S}$ (Glu 6 Val)

Pleiotropy of sickle-cell anemia



(a)



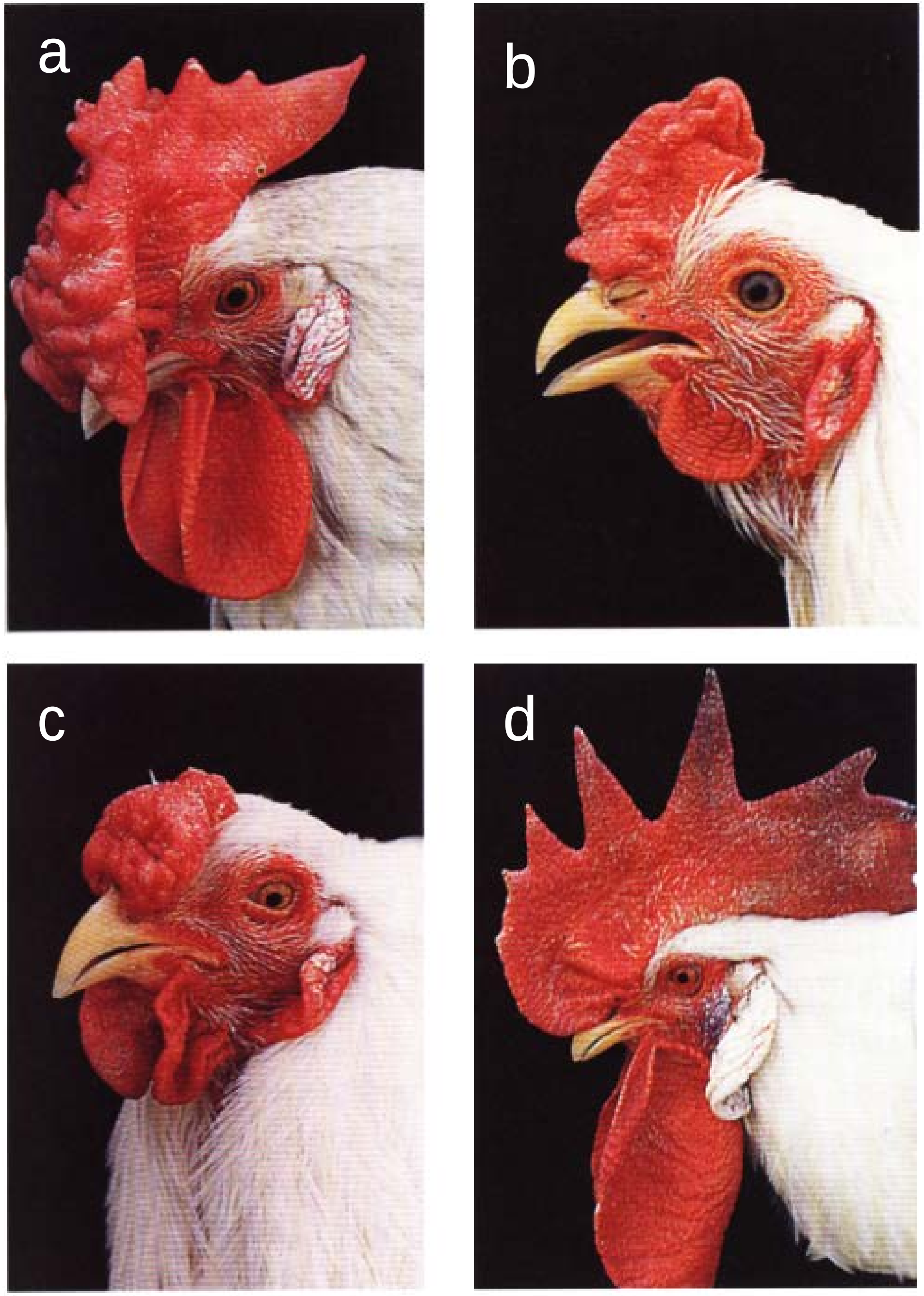
Phenotypes at Different Levels of Analysis	Normal $Hb\beta^A\ Hb\beta^A$	Carrier $Hb\beta^A\ Hb\beta^S$	Diseased $Hb\beta^S\ Hb\beta^S$	Dominance Relations at Each Level of Analysis
β-globin polypeptide production				$Hb\beta^A$ and $Hb\beta^S$ are codominant
Red blood cell shape at sea level	Normal	Normal	Sickled cells present	$Hb\beta^A$ is dominant $Hb\beta^S$ is recessive
Red blood cell concentration at sea level	Normal	Normal	Lower	
Red blood cell shape at high altitudes	Normal	Sickled cells present	Severe sickling	$Hb\beta^A$ and $Hb\beta^S$ show incomplete dominance
Red blood cell concentration at high altitudes	Normal	Lower	Very low, anemia	
Susceptibility to malaria	Normal susceptibility	Resistant	Resistant	$Hb\beta^S$ is dominant $Hb\beta^A$ is recessive

(b)

2. Multifactorial Inheritance

Two or more genes can interact to determine **one trait**

- **Gene interactions (基因互作)**

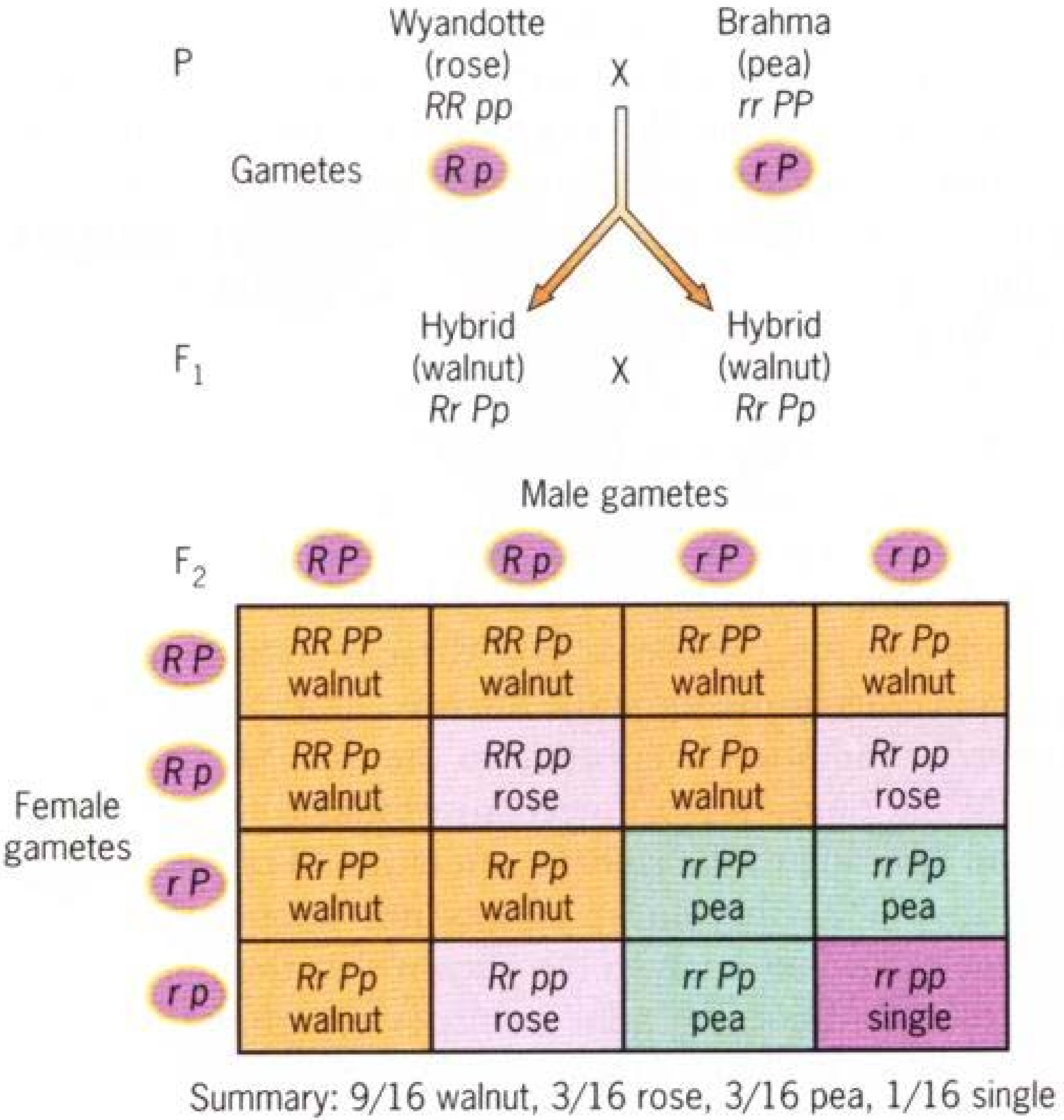


a. Rose, Wyandottes

b. Pea, Brahmas

c. Walnut, hybrid from cross between rose and pea combs

d. Single, Leghorns



P
Wyandotte (rose) *RR pp* X Brahma (pea) *rr PP*

Gametes *R p* *r P*

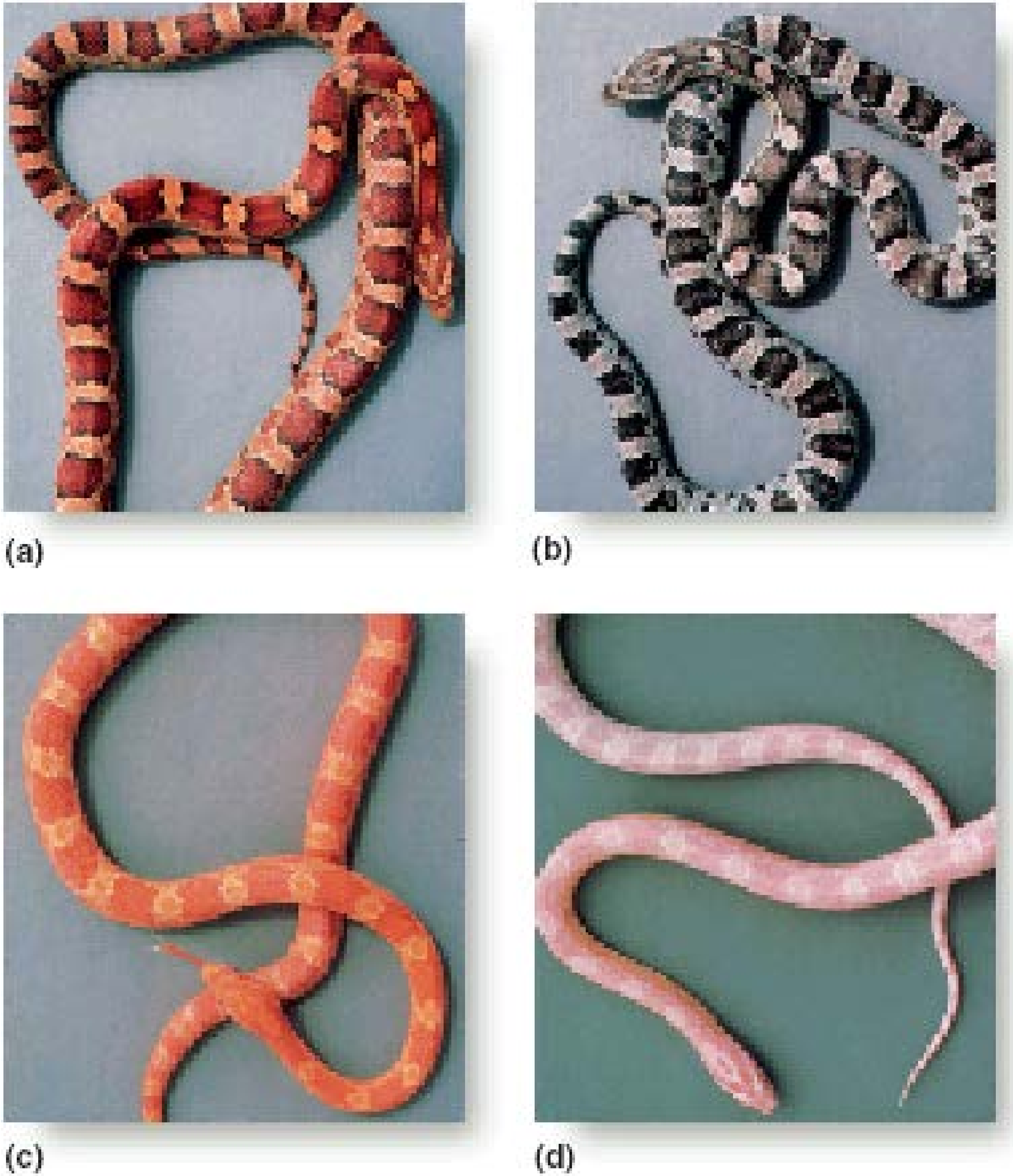
F$_1$
Hybrid (walnut) *Rr Pp* X Hybrid (walnut) *Rr Pp*

F$_2$

Male gametes

Female gametes	*R P*	*R p*	*r P*	*r p*
R P	*RR PP* walnut	*RR Pp* walnut	*Rr PP* walnut	*Rr Pp* walnut
R p	*RR Pp* walnut	*RR pp* rose	*Rr Pp* walnut	*Rr pp* rose
r P	*Rr PP* walnut	*Rr Pp* walnut	*rr PP* pea	*rr Pp* pea
r p	*Rr Pp* walnut	*Rr pp* rose	*rr Pp* pea	*rr pp* single

Summary: 9/16 walnut, 3/16 rose, 3/16 pea, 1/16 single


(a)
(b)
(c)
(d)

P ooBB × OObb

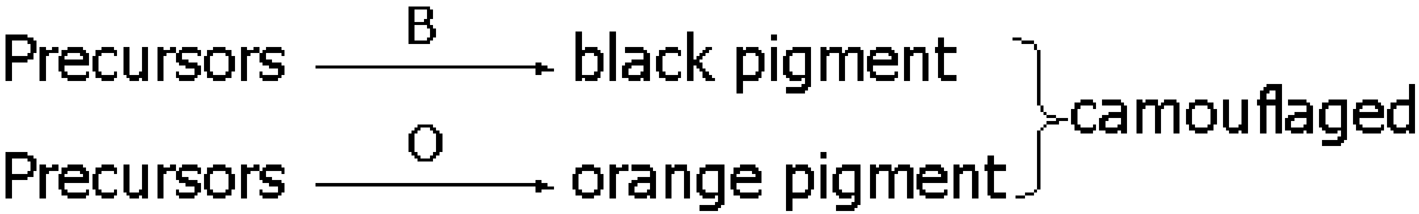
(black) (orange)

↓

F1 OoBb (camouflaged)

↓

F2	O_B_	O_bb	ooB_	oobb
	(camouflaged)	(orange)	(black)	(white)
	9	3	3	1



Precursors $\xrightarrow{B}$ black pigment

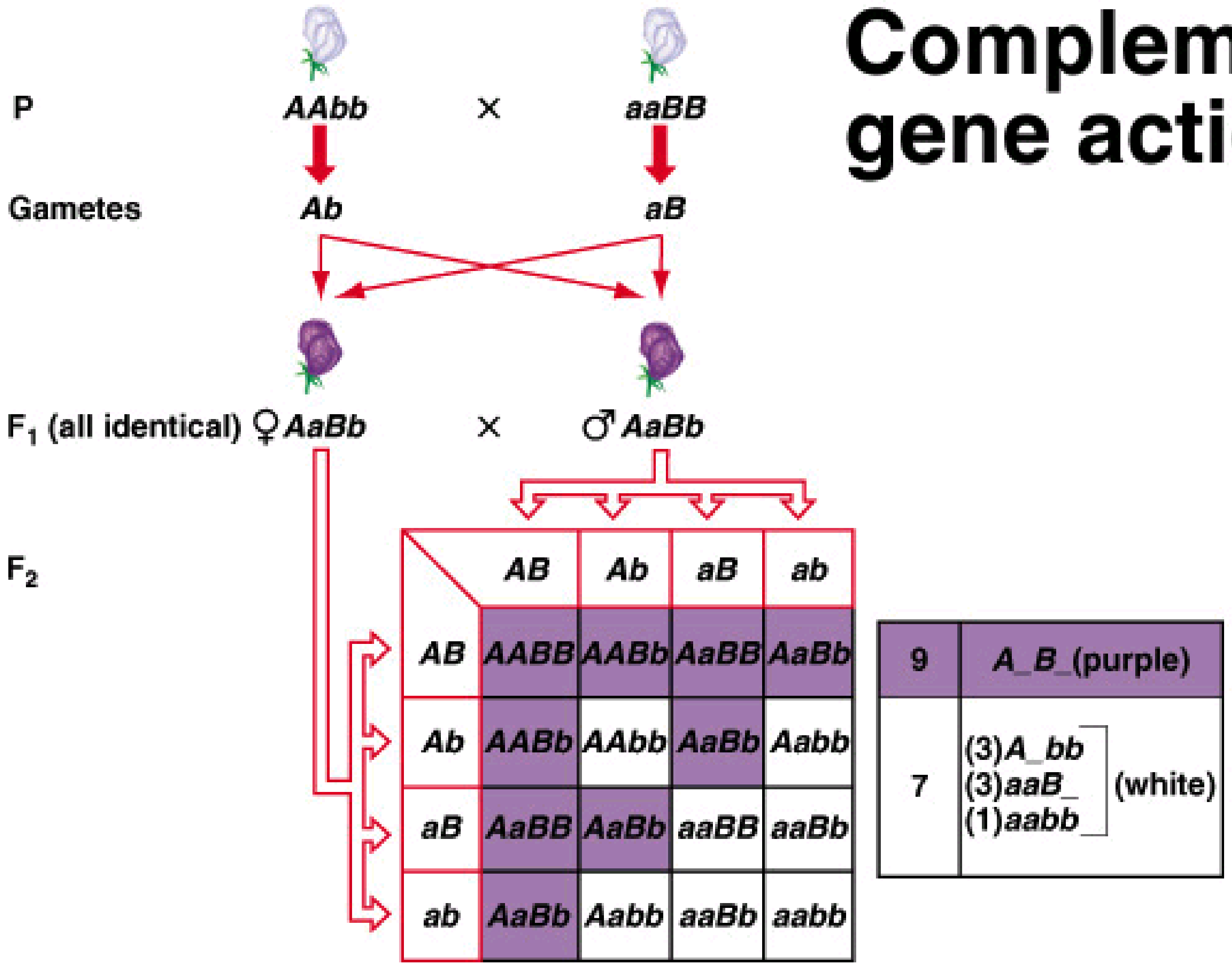
Precursors $\xrightarrow{O}$ orange pigment

} camouflaged

- **Complementary gene**

  （互补基因）

Complementary gene action



P *AAbb* × *aaBB*

Gametes *Ab* *aB*

F₁ (all identical) ♀ *AaBb* × ♂ *AaBb*

F₂

	AB	*Ab*	*aB*	*ab*
AB	*AABB*	*AABb*	*AaBB*	*AaBb*
Ab	*AABb*	*AAbb*	*AaBb*	*Aabb*
aB	*AaBB*	*AaBb*	*aaBB*	*aaBb*
ab	*AaBb*	*Aabb*	*aaBb*	*aabb*

9	*A_B_* (purple)
7	(3)*A_bb* (3)*aaB_* (1)*aabb* (white)

Colorless precursor 1 → Allele *A* / Pigment change catalyzed → Colorless precursor 2 → Allele *B* / Pigment change completed → Purple pigment

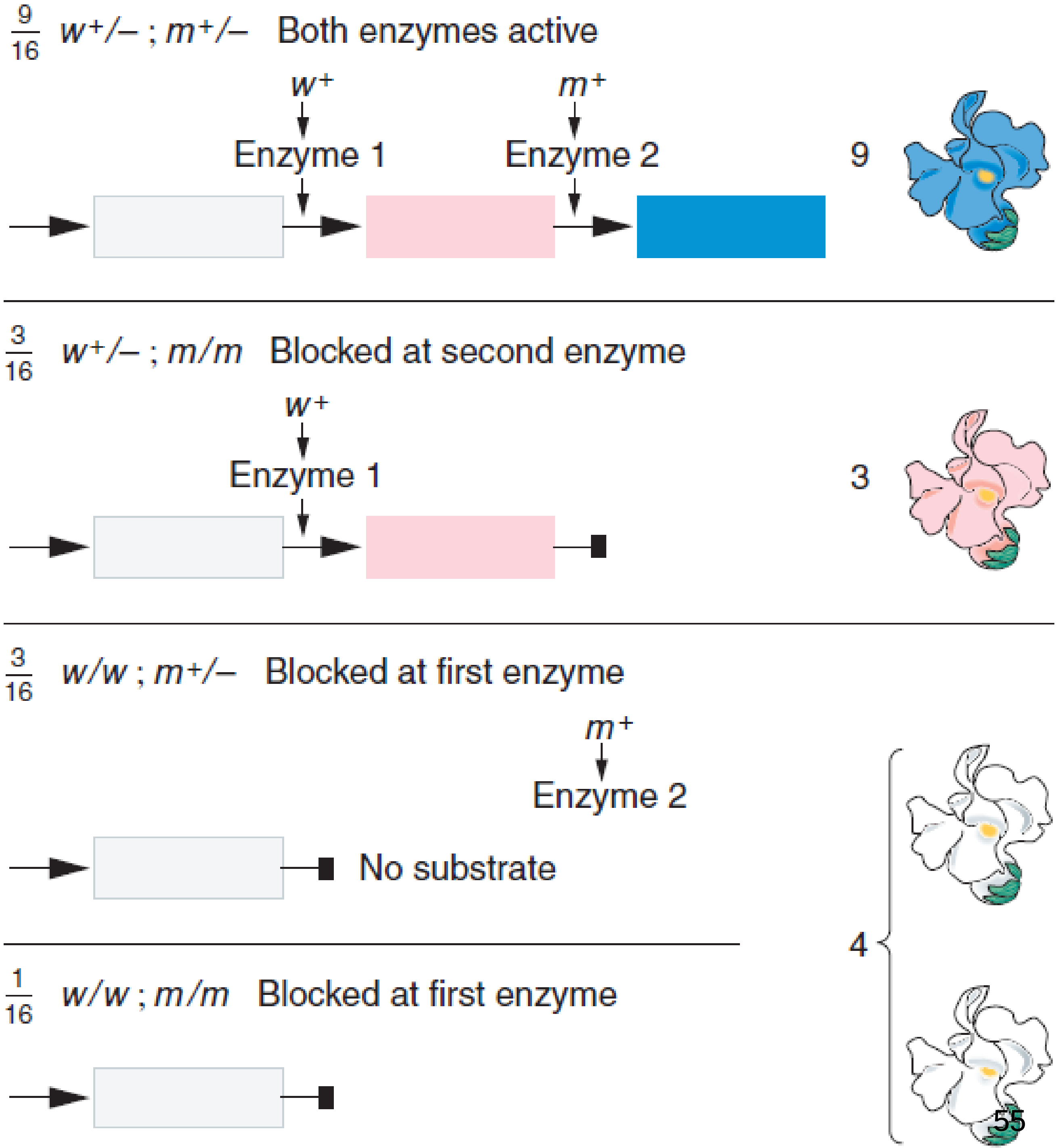
- **Epistasis** （上位）

A gene interaction in which the effects of an allele at one gene hide the effects of alleles at another gene

recessive epistasis

dominant epistasis

Recessive epistasis



$\frac{9}{16}$ $w^+/-$; $m^+/-$ Both enzymes active

w^+ → Enzyme 1 → m^+ → Enzyme 2 → 9

$\frac{3}{16}$ $w^+/-$; m/m Blocked at second enzyme

w^+ → Enzyme 1 → 3

$\frac{3}{16}$ w/w ; $m^+/-$ Blocked at first enzyme

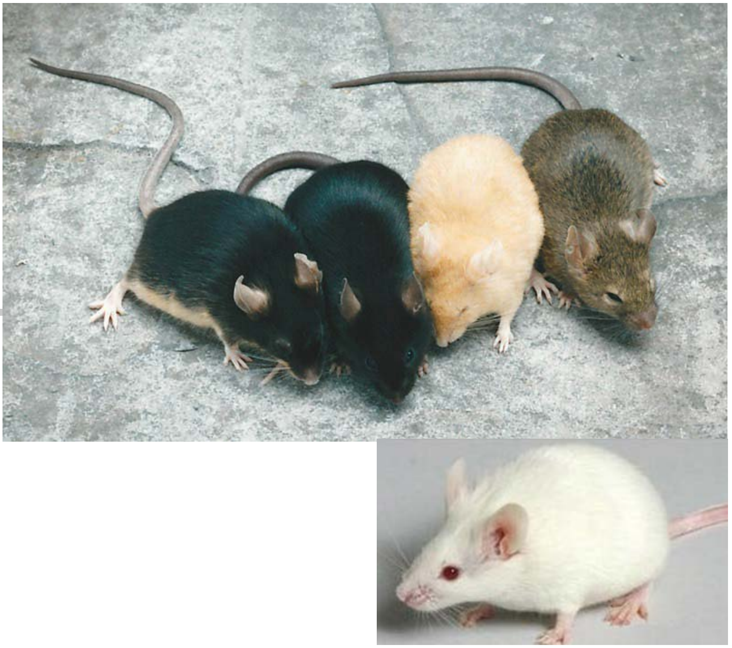
m^+ → Enzyme 2

No substrate

$\frac{1}{16}$ w/w ; m/m Blocked at first enzyme

4

小鼠毛色的遗传



Agouti复等位基因座：

A^Y	**yellow**
A	**agouti**
a^t	**black/yellow**
a	**black**

B_A_	**agouti**
B_aa	**black**
bbA_	**white**
bbaa	**white**

另一个**B**基因控制黑色素形成

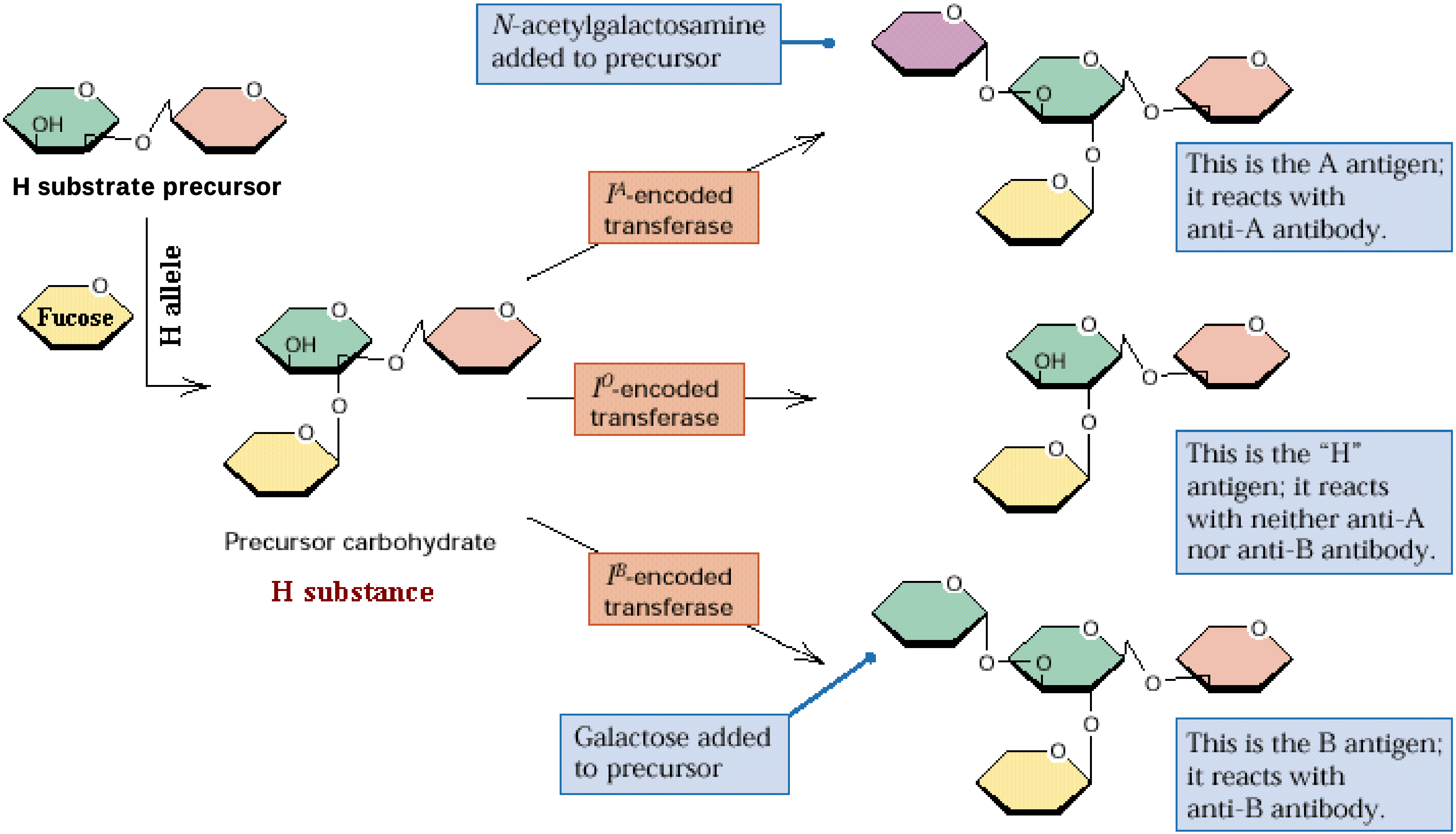
ABO blood types

O phenotype × O phenotype

$\downarrow$

O, A, B

?



H substrate precursor

H allele

Precursor carbohydrate

H substance

N-acetylgalactosamine added to precursor

I^A-encoded transferase

This is the A antigen; it reacts with anti-A antibody.

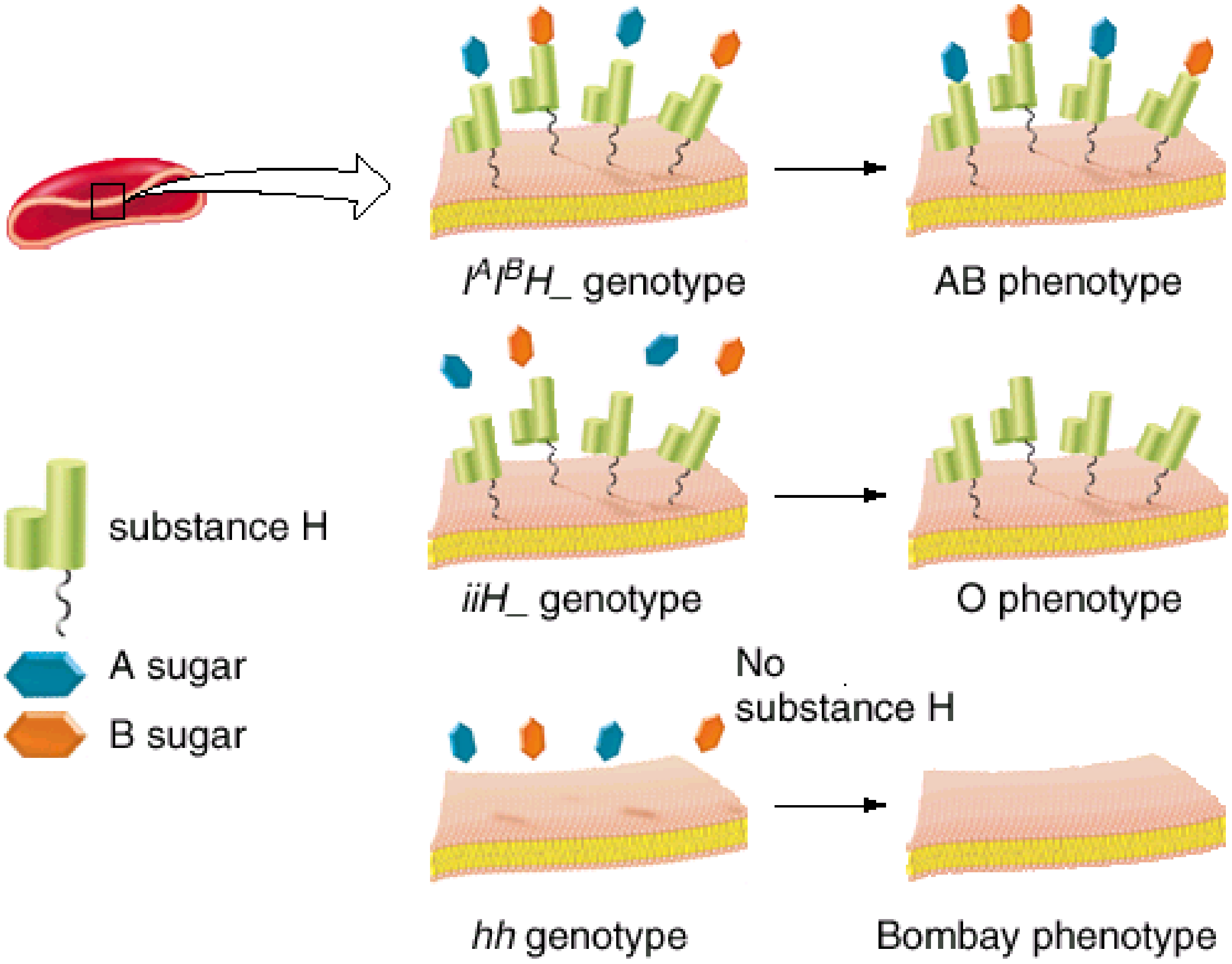
I^O-encoded transferase

This is the "H" antigen; it reacts with neither anti-A nor anti-B antibody.

I^B-encoded transferase

Galactose added to precursor

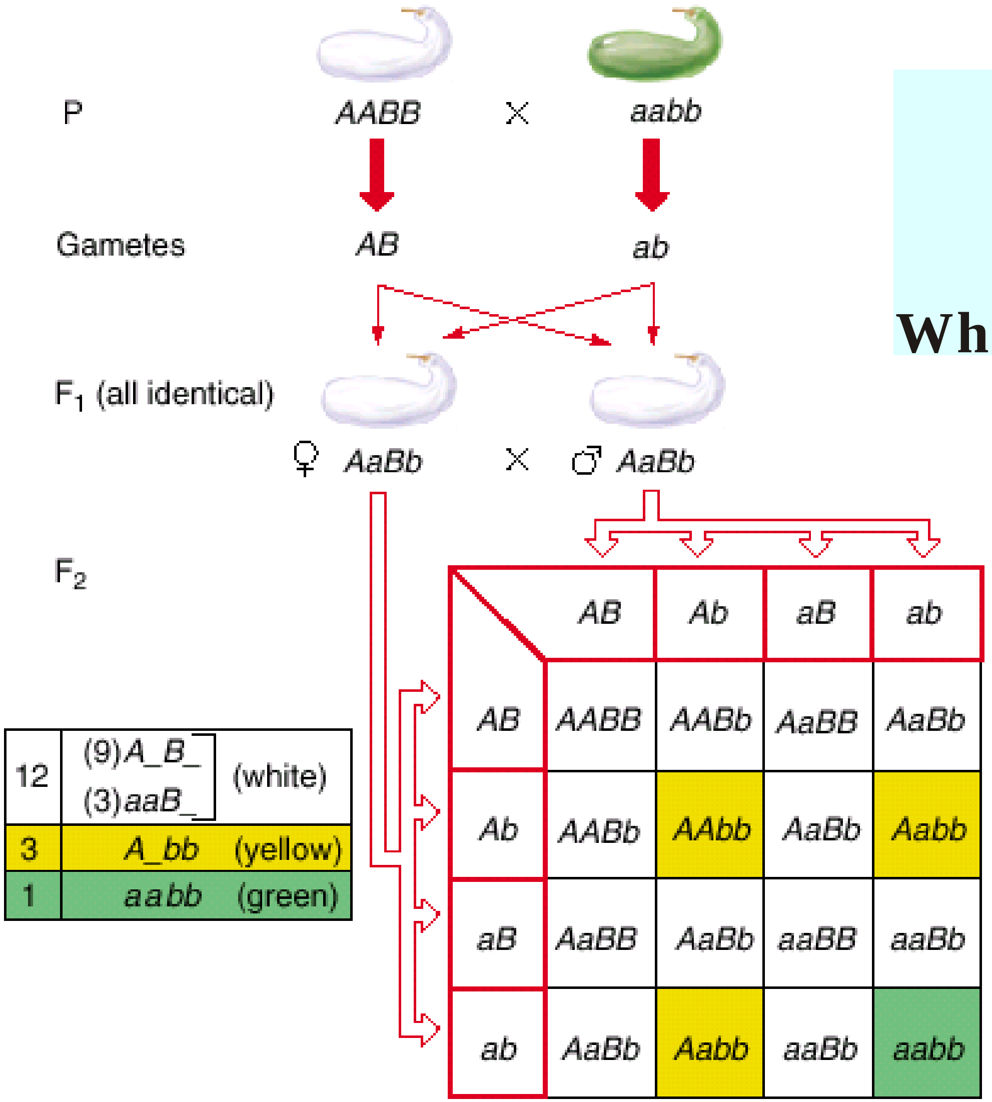
This is the B antigen; it reacts with anti-B antibody.



I^AI^Ahh × $iiHH$ → I^AiHh

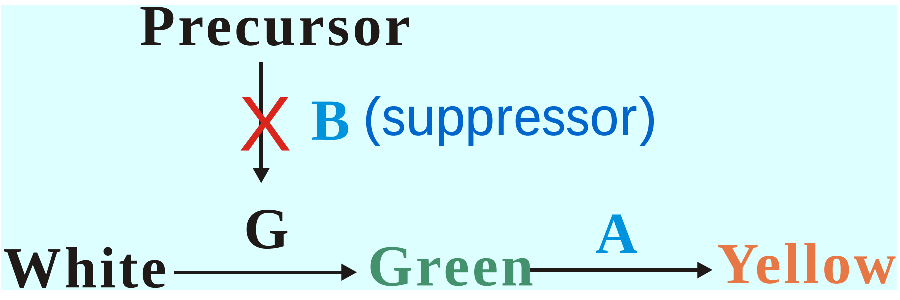
O O A

Dominant epistasis



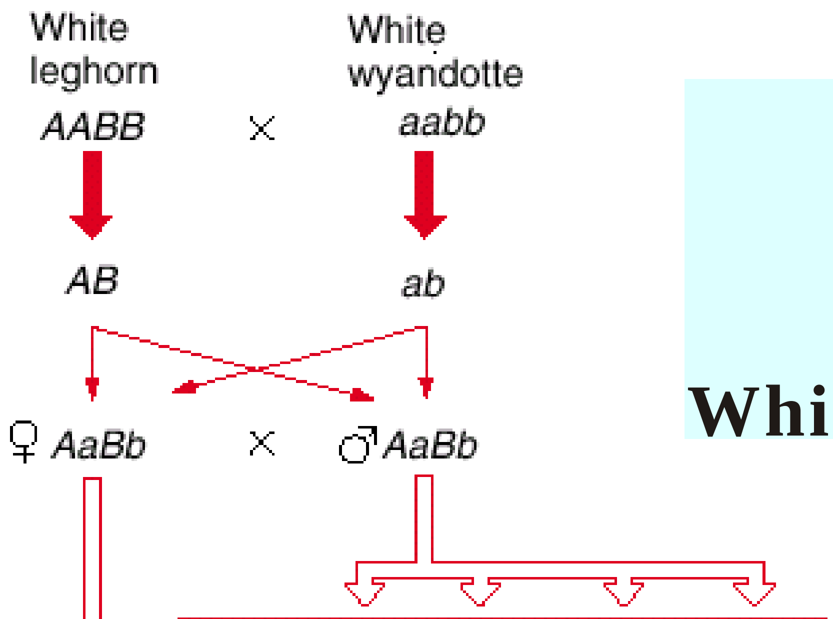
	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

12	(9)A_B_ (3)aaB_	(white)
3	A_bb	(yellow)
1	aabb	(green)



$$\begin{tikzcd} & \text{Precursor} \arrow[d, "\times\ \text{B (suppressor)}"] & \\ \text{White} \arrow[r, "G"] & \text{Green} \arrow[r, "A"] & \text{Yellow} \end{tikzcd}$$

A_: yellow
aa: green



P — White leghorn *AABB* × White wyandotte *aabb*

Gametes — *AB* — *ab*

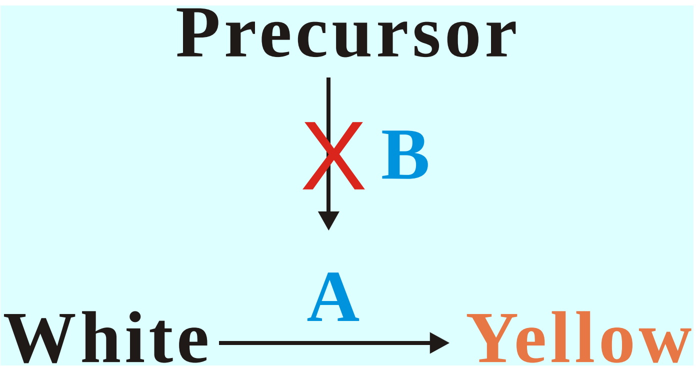
F_1 (all white) — ♀ *AaBb* × ♂ *AaBb*

F_2

	AB	*Ab*	*aB*	*ab*
AB	*AABB*	*AABb*	*AaBB*	*AaBb*
Ab	*AABb*	*AAbb*	*AaBb*	*Aabb*
aB	*AaBB*	*AaBb*	*aaBB*	*aaBb*
ab	*AaBb*	*Aabb*	*aaBb*	*aabb*

13	(9) *A_B_* (3) *aaB_* (1) *aabb*	(white)
3	*A_bb* (colored)	

Feather color



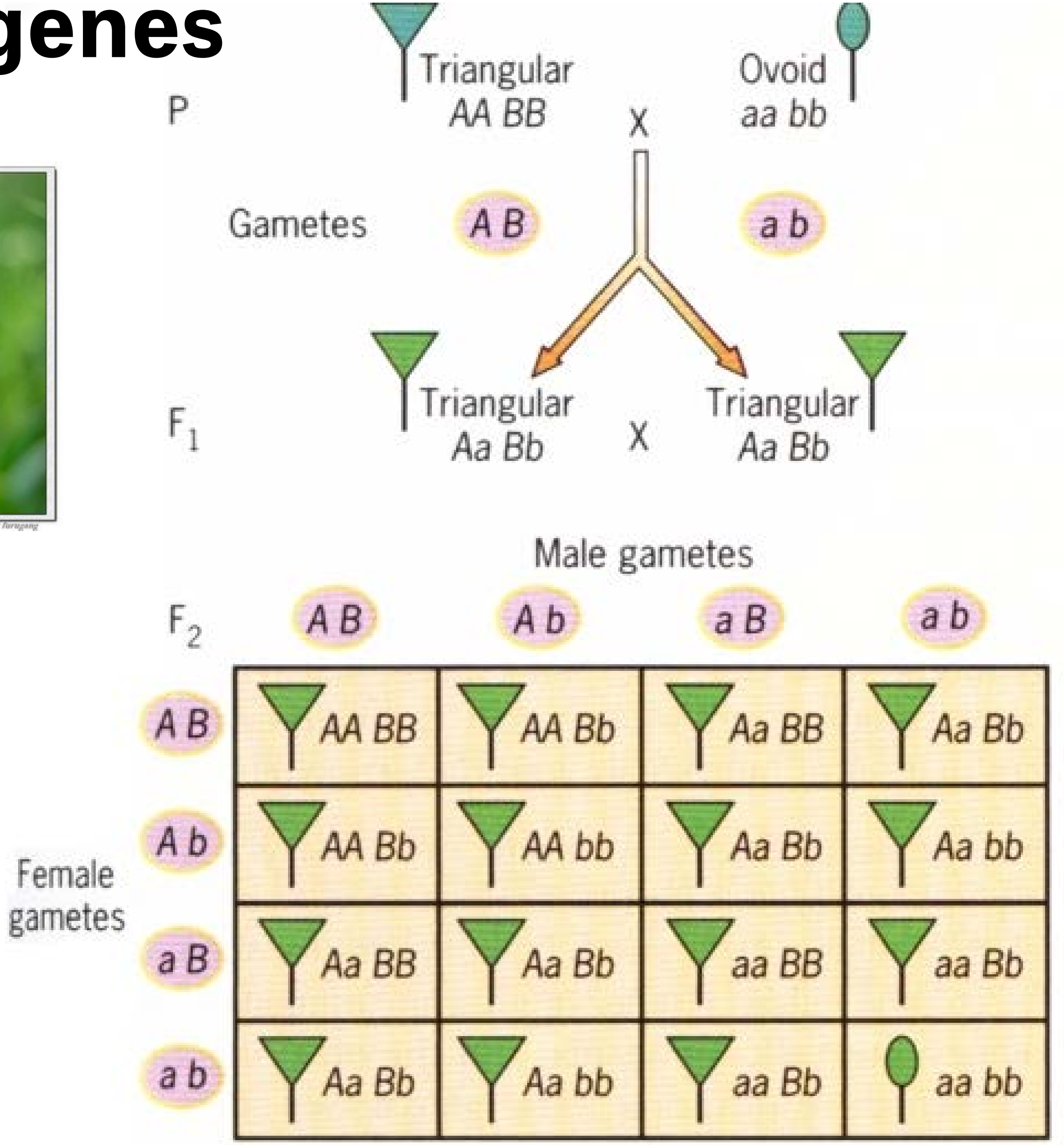
Precursor

X B

A

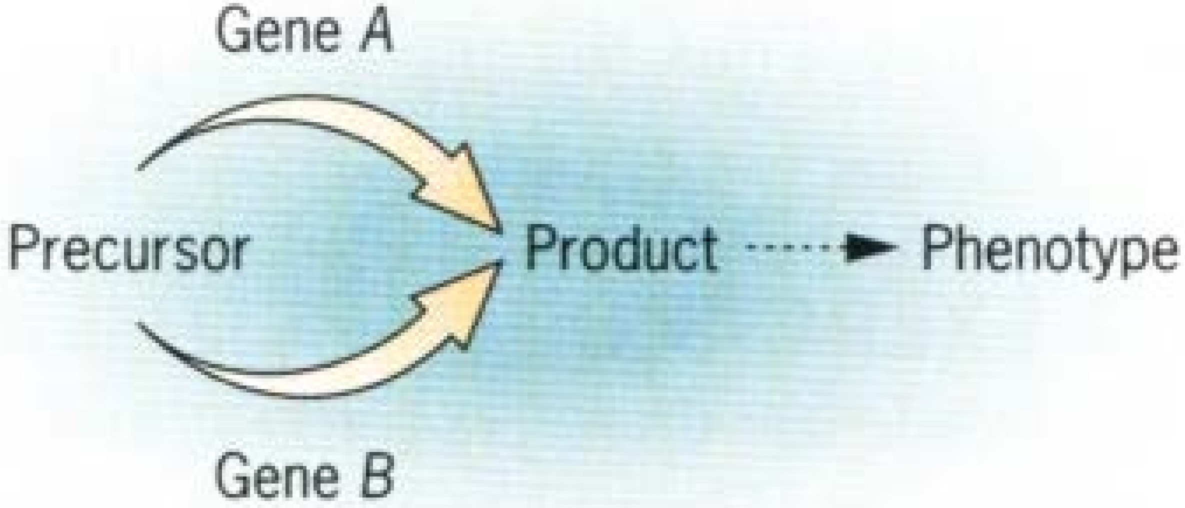
White → Yellow

Duplicate genes

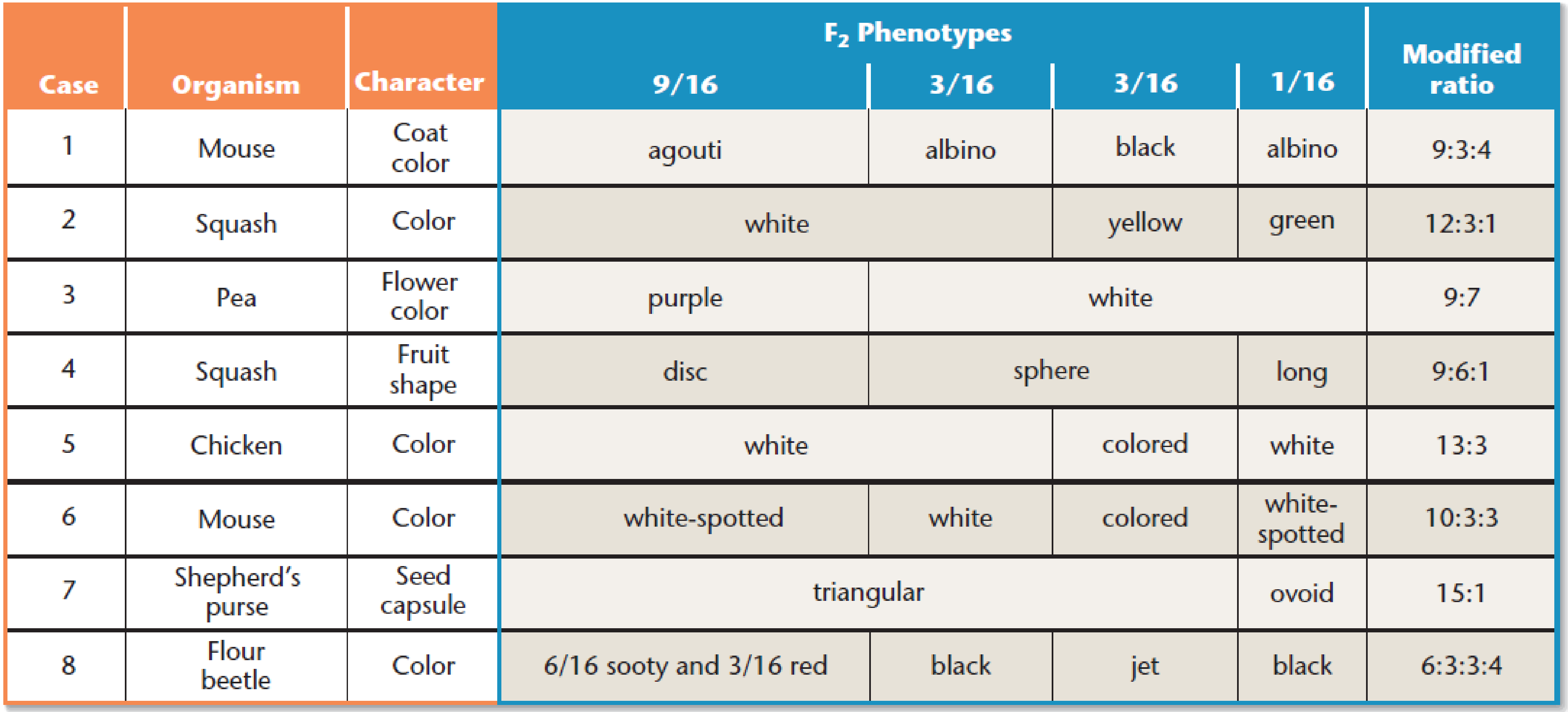


	A B	A b	a B	a b
A B	AA BB	AA Bb	Aa BB	Aa Bb
A b	AA Bb	AA bb	Aa Bb	Aa bb
a B	Aa BB	Aa Bb	aa BB	aa Bb
a b	Aa Bb	Aa bb	aa Bb	aa bb

Summary: 15/16 triangular, 1/16 ovoid



Genotype			
A– *B*–	+	+	triangular
aa *B*–	+	+	triangular
A– *bb*	+	+	triangular
aa *bb*	+	–	ovoid



Case	Organism	Character	F_2 Phenotypes				Modified ratio
			9/16	3/16	3/16	1/16	
1	Mouse	Coat color	agouti	albino	black	albino	9:3:4
2	Squash	Color	white		yellow	green	12:3:1
3	Pea	Flower color	purple	white			9:7
4	Squash	Fruit shape	disc	sphere		long	9:6:1
5	Chicken	Color	white		colored	white	13:3
6	Mouse	Color	white-spotted	white	colored	white-spotted	10:3:3
7	Shepherd's purse	Seed capsule	triangular			ovoid	15:1
8	Flour beetle	Color	6/16 sooty and 3/16 red	black	jet	black	6:3:3:4

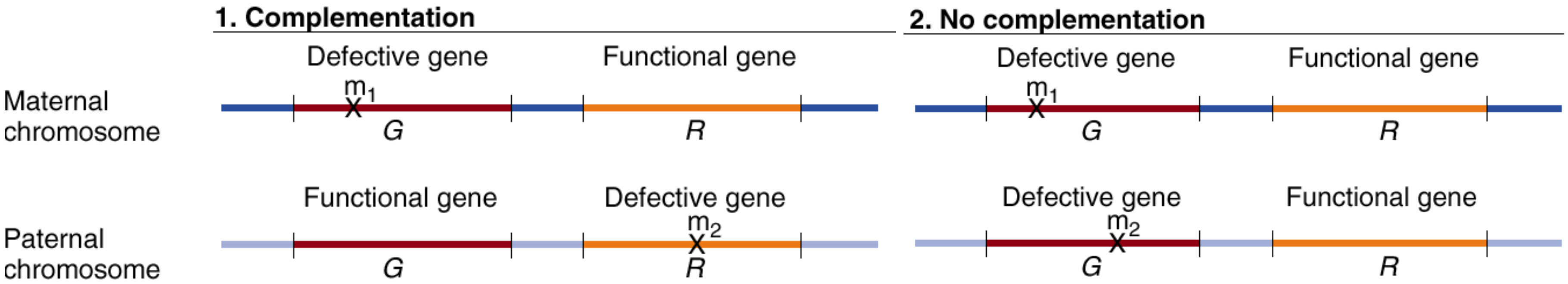
The key point of two genes inheritance is the modification to 9:3:3:1 ratio

Are two mutations that yield similar phenotypes present in the same gene or in two different genes?

Heterogeneous trait: A mutation at any one of a number of genes can give rise to the same phenotype

- Deafness in humans: 50 genes

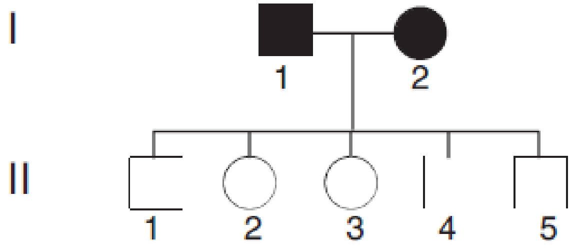
Complementation test can determine if two **recessive** mutations causing a similar phenotype are alleles of the same gene

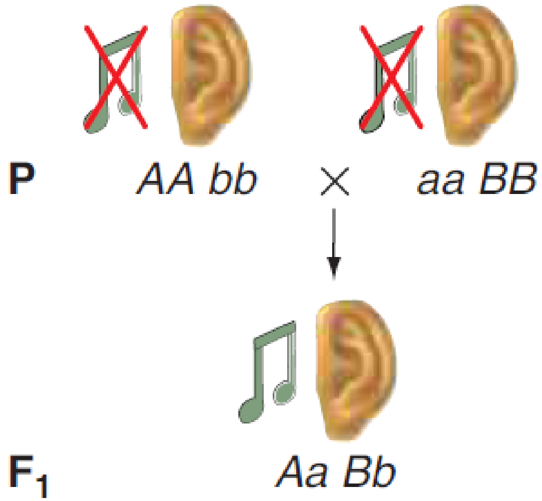


Conclusion: m_1 and m_2 are in different genes.
m_1/m_2 has wildtype phenotype because one chromosome supplies gene *G* function while the other supplies gene *R* function.

Conclusion: m_1 and m_2 are in the same gene.
m_1/m_2 has mutant phenotype because organism has no gene *G* function.

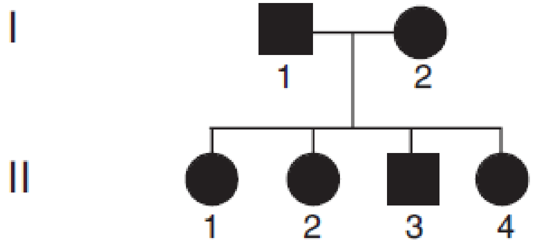
(a) Complementation: mutations in two different genes

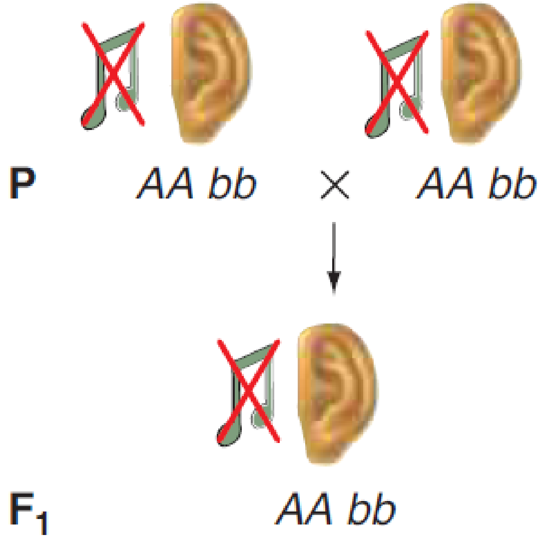




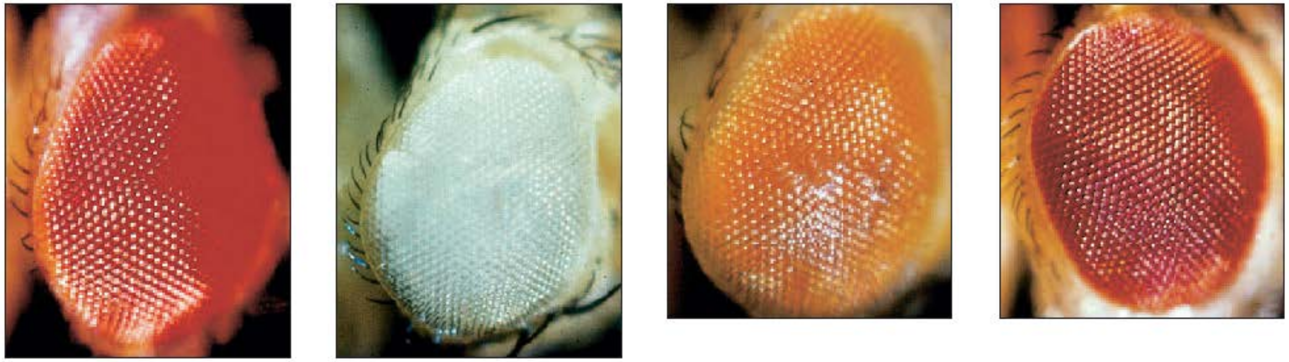
Genetic mechanism of complementation

(b) Noncomplementation: mutations in the same gene





Genetic mechanism of noncomplementation

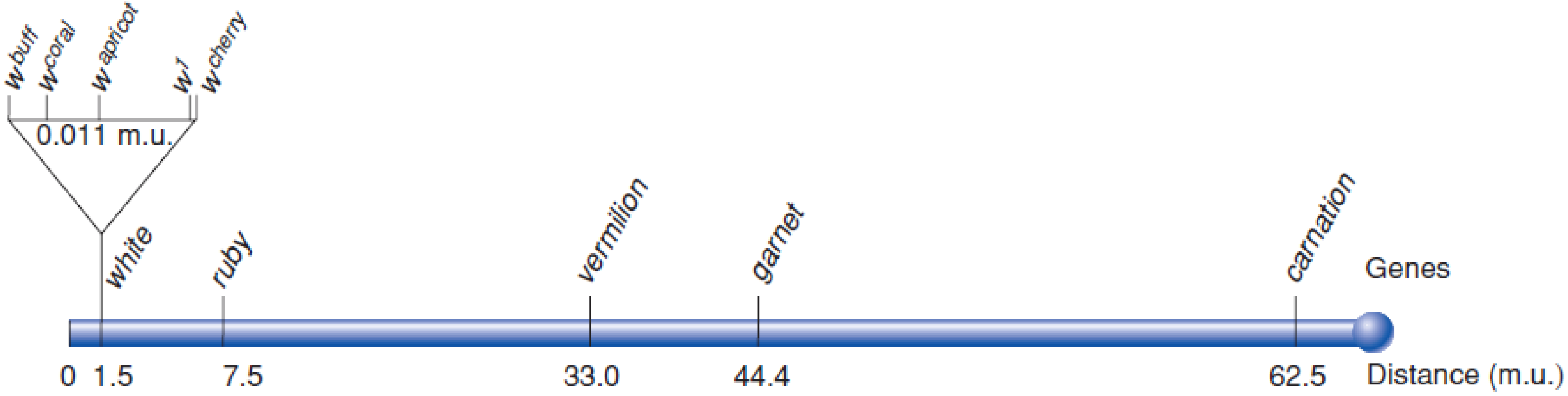


Drosophila eye color mutations

(b) A complementation table: X-linked eye color mutations in *Drosophila*

Mutation	white	garnet	ruby	vermilion	cherry	coral	apricot	buff	carnation
white	−	+	+	+	−	−	−	−	+
garnet		−	+	+	+	+	+	+	+
ruby			−	+	+	+	+	+	+
vermilion				−	+	+	+	+	+
cherry					−	−	−	−	+
coral						−	−	−	+
apricot							−	−	+
buff								−	+
carnation									−

(c) Genetic map: X-linked eye color mutations in *Drosophila*



The figures and tables are cited from:

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