

BIO-373
Genetics & Genomics

Mendelian genetics

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Contents

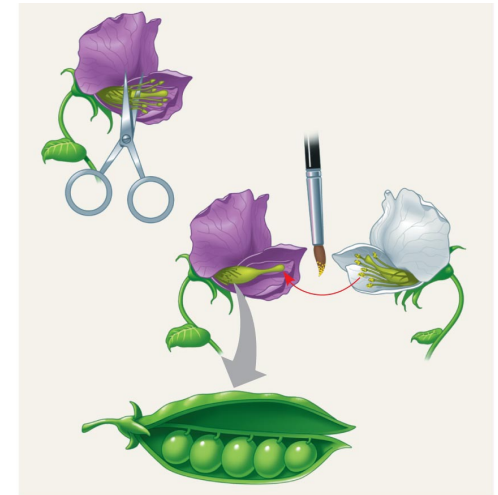
- 1 Mendel's experimental approach and monohybrid cross
 - 2 Dihybrid cross
 - 3 Trihybrid cross
 - 4 The role of chromosomes
 - 5 Probabilities and χ^2 analysis
 - 6 Pedigrees
-

1. Mendel's experimental approach and monohybrid cross

Mendel's experimental approach

- **Mendel's model organism: peas**

- easy to grow
- Relatively fast growth
- controlled mating: self-fertilization or cross-fertilization
- 7 observable characteristics with two distinct forms (binary variation)



Monohybrid cross

- **Involve a single pair of contrasting traits**
 - P_1 generation: parents (“true breeding”)
 - F_1 generation: offspring ($P_1 \times P_1 = F_1$)
 - F_2 generation: offspring of F_1 ($F_1 \times F_1 = F_2$)
-

Character	Contrasting traits		F ₁ results	F ₂ results	F ₂ ratio
Seed shape	round/wrinkled		all round	5474 round 1850 wrinkled	2.96:1
Seed color	yellow/green		all yellow	6022 yellow 2001 green	3.01:1
Pod shape	full/constricted		all full	882 full 299 constricted	2.95:1
Pod color	green/yellow		all green	428 green 152 yellow	2.82:1
Flower color	violet/white		all violet	705 violet 224 white	3.15:1
Flower position	axial/terminal		all axial	651 axial 207 terminal	3.14:1
Stem height	tall/dwarf		all tall	787 tall 277 dwarf	2.84:1

Constraining traits

- F_1 generation monohybrid cross
 - All plants have the same phenotype (one of the two possible traits)
 - F_2 generation
 - 3/4 of plants exhibit the same trait as the F_1 generation
 - 1/4 exhibit the contrasting trait that disappeared in the F_1 generation
 - **3:1 ratio**
-

Reciprocal cross

- Not sex dependent
 - F_1 and F_2 patterns of inheritance similar regardless of P_1 source
 - Dwarf plant pollinates tall plant
 - Tall plant pollinates dwarf plant
 - Results for F_1 and F_2 are the same
-

Particulate unit factors

- Mendel called the basic units of heredity, which determine the traits expressed by an organism, **“particulate unit factors”**
 - They are passed unchanged from generation to generation
 - They exist in pairs: a variable trait is controlled by a pair of “unit factors”, which we now call **alleles**
-

Genetic terminology

- **Gene**
 - Unit of inheritance
 - **Allele**
 - Alternative form of a single gene
 - **Genotype**
 - Genetic makeup of individual
 - Alleles written in pairs (*DD*, *Dd*, or *dd*)
 - **Phenotype**
 - Physical expression of a trait
-

Punnett square

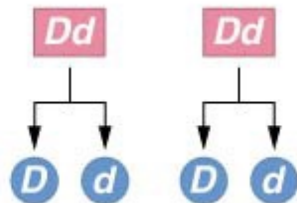
- Devised by R. C. Punnett, founder of the *Journal of Genetics* in 1910
 - Genotypes and phenotypes resulting from combining gametes can be visualized
 - Displays all possible random fertilization events
-

F₂ generation

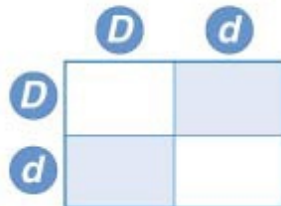
F₁ cross

Dd × **Dd**
tall tall

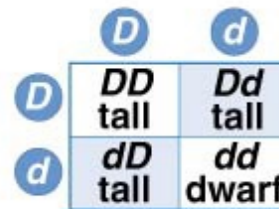
Gamete formation
by F₁ generation



Setting up a
Punnett square



Filling out squares
representing fertilization

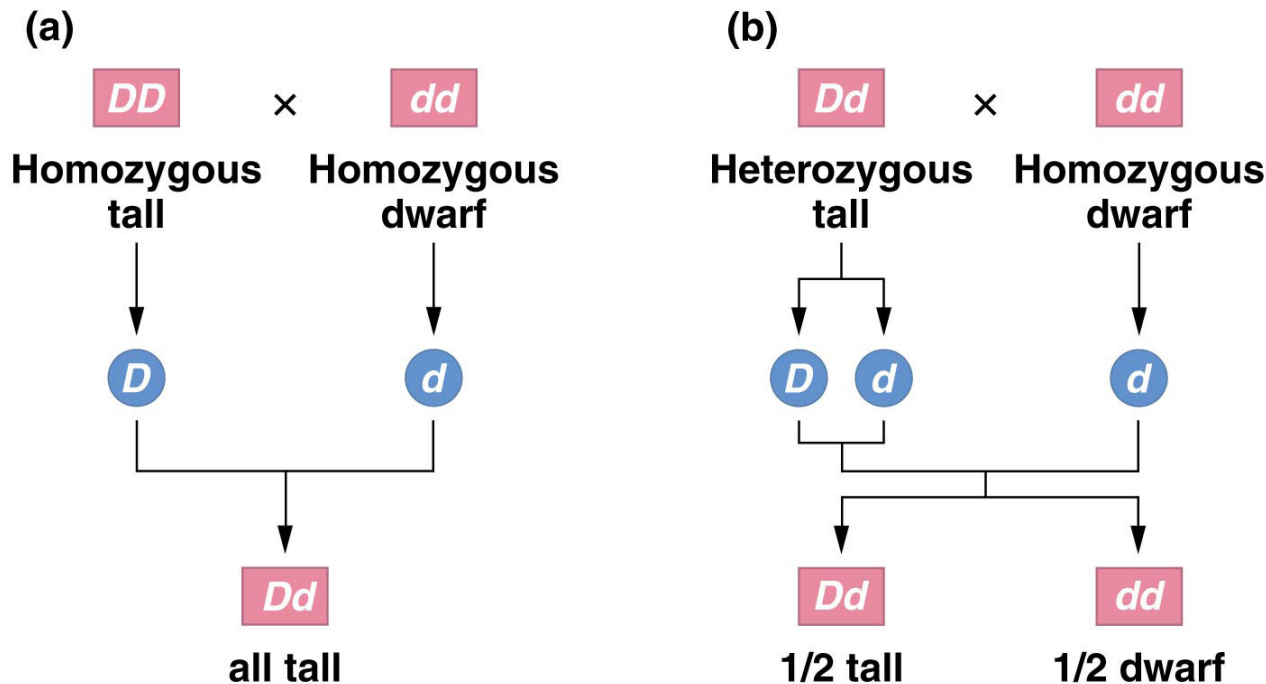


F₂ results

Genotype	Phenotype
1 DD	3/4 tall
2 Dd	
1 dd	1/4 dwarf
1:2:1	3:1

Testcross

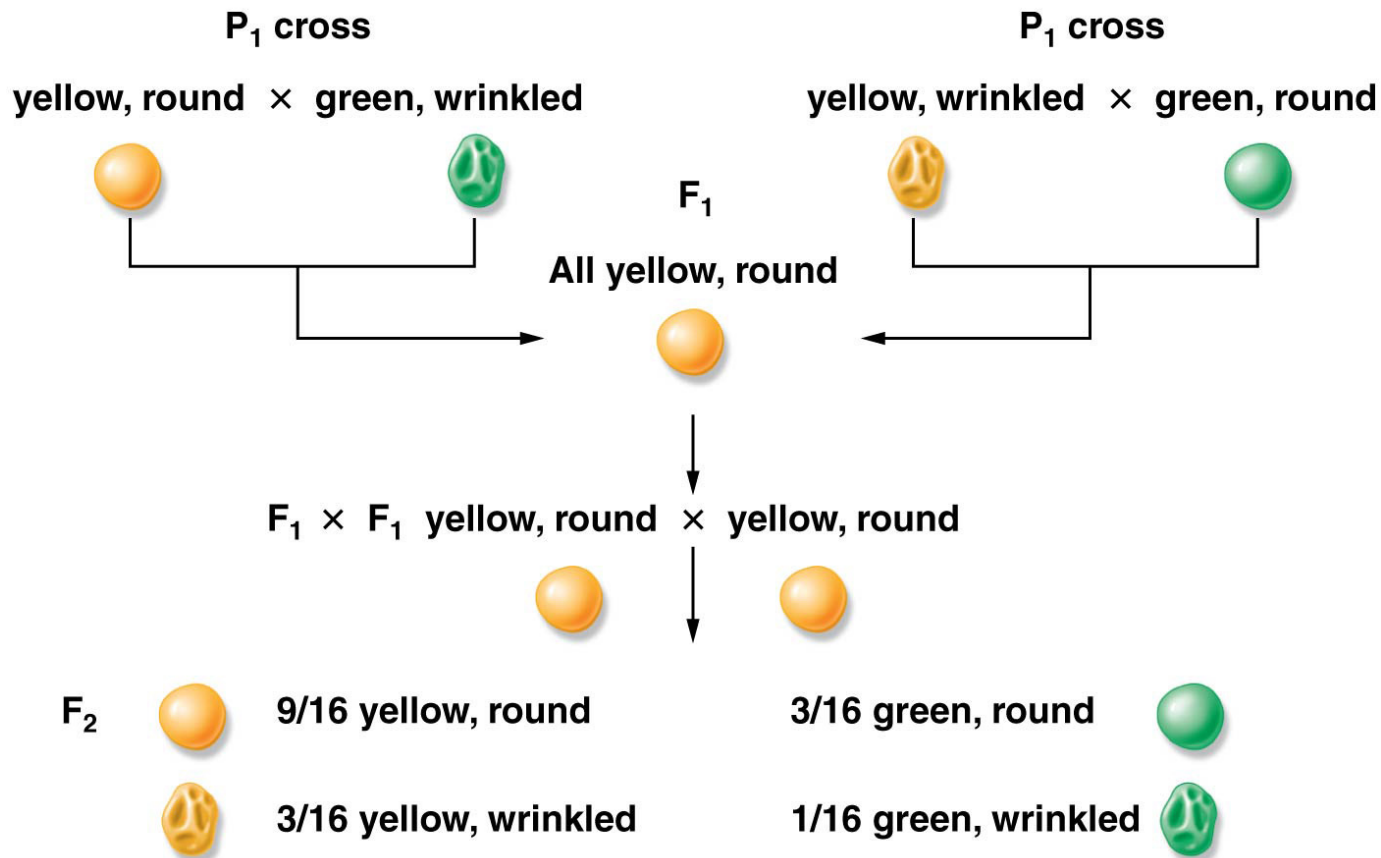
- Determines if individual with dominant phenotype is homozygous or heterozygous for that trait
- Cross between dominant phenotype and homozygous recessive



2. Dihybrid cross

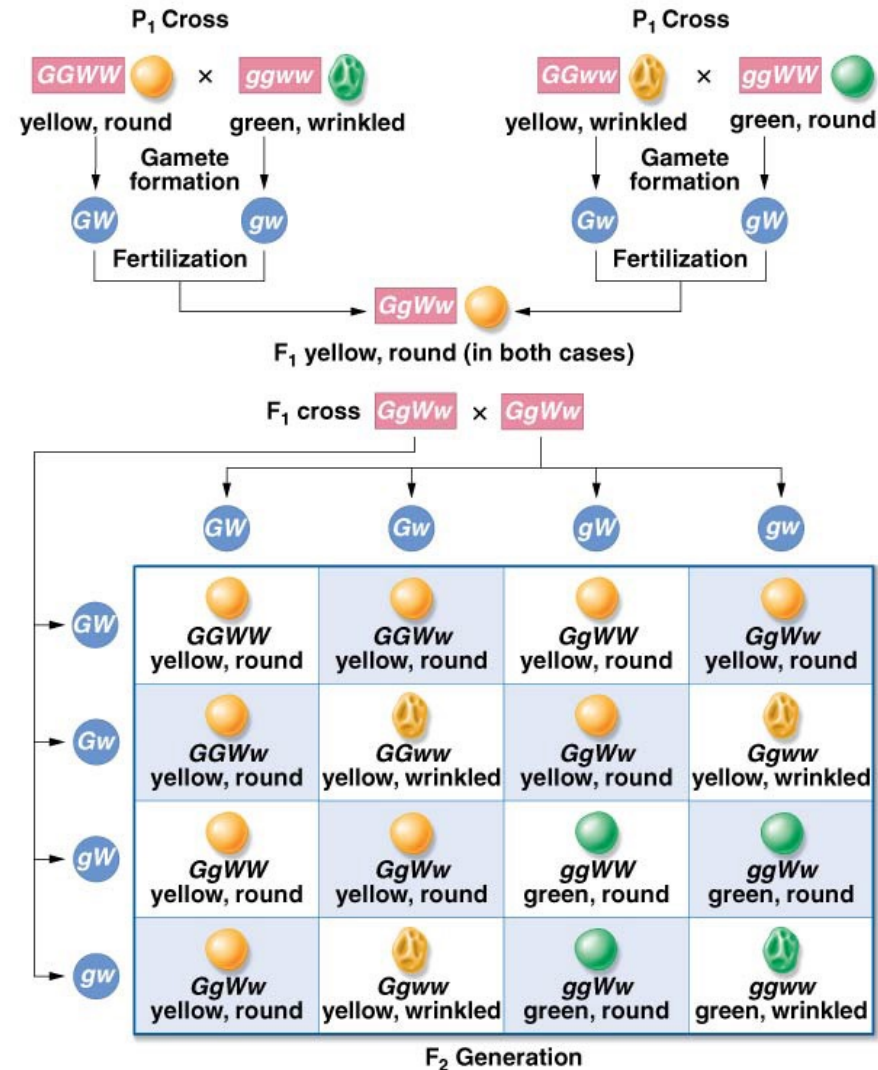
Dihybrid Cross

- Two pairs of contrasting traits
- Generates a unique F_2 generation



Mendel's 9:3:3:1 dihybrid ratio

- $F_1 \times F_1$ fertilization event
- Each zygote can receive one of four combinations
- Results in a **9:3:3:1 dihybrid ratio** in F_2
 - 9/16 yellow, round seeds
 - 3/16 yellow, wrinkled seeds
 - 3/16 green, round seeds
 - 1/16 green, wrinkled seeds



Combination of probabilities

- Used to predict frequency of two independent events occurring simultaneously

F ₁ yellow, round × yellow, round				
F ₂	Of all offspring		Of all offspring	Combined probabilities
	↓		↓	↓
3/4 are yellow	→	3/4 are round	→	$(3/4)(3/4) = 9/16$ yellow, round
		and		
	→	1/4 are wrinkled	→	$(3/4)(1/4) = 3/16$ yellow, wrinkled
1/4 are green	→	3/4 are round	→	$(1/4)(3/4) = 3/16$ green, round
		and		
	→	1/4 are wrinkled	→	$(1/4)(1/4) = 1/16$ green, wrinkled

Mendel's laws

1. Dominance

- In a pair of unit factors, one unit (allele) is dominant, the other recessive

2. Segregation

- Alleles of a gene segregate randomly during gamete formation

3. Independent assortment

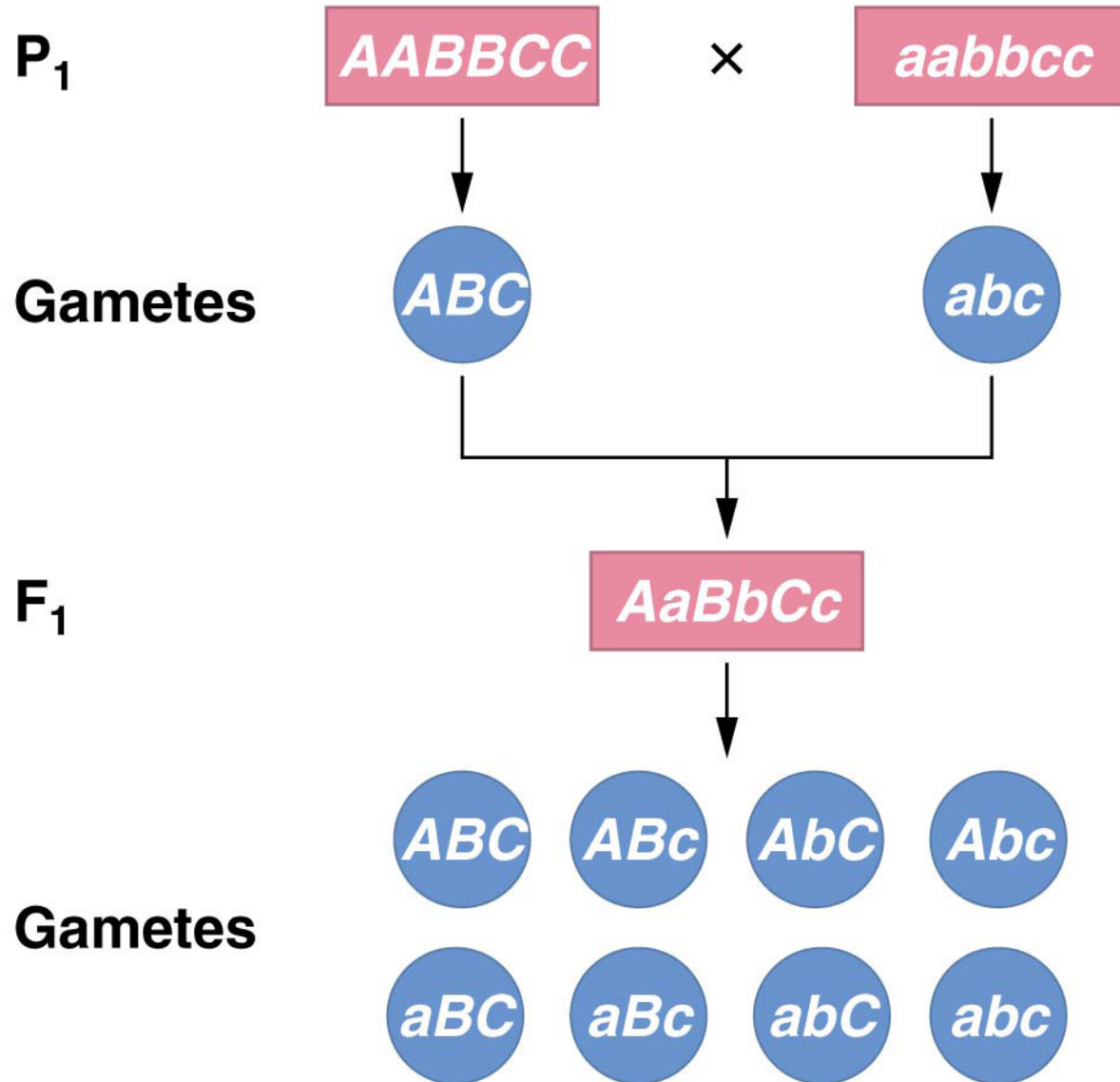
- Separate genes assort independently during gamete formation (i.e. genes do not influence each other with regard to the sorting of alleles into gametes)
-

3. Trihybrid Cross

Trihybrid Cross

- Segregation and independent assortment applied to three pairs of constraining traits
 - Punnett square with 64 boxes
 - Easier to use the **forked-line method (branch diagram)**
-

Trihybrid gamete formation



Generation of F₂ trihybrid phenotypes

<i>A or a</i>	<i>B or b</i>	<i>C or c</i>	Combined proportion	
$\frac{3}{4} A$	$\frac{3}{4} B$	$\frac{3}{4} C$	$(\frac{3}{4})(\frac{3}{4})(\frac{3}{4})$	$ABC = \frac{27}{64} ABC$
		$\frac{1}{4} c$	$(\frac{3}{4})(\frac{3}{4})(\frac{1}{4})$	$ABc = \frac{9}{64} ABc$
	$\frac{1}{4} b$	$\frac{3}{4} C$	$(\frac{3}{4})(\frac{1}{4})(\frac{3}{4})$	$AbC = \frac{9}{64} AbC$
		$\frac{1}{4} c$	$(\frac{3}{4})(\frac{1}{4})(\frac{1}{4})$	$Abc = \frac{3}{64} Abc$
$\frac{1}{4} a$	$\frac{3}{4} B$	$\frac{3}{4} C$	$(\frac{1}{4})(\frac{3}{4})(\frac{3}{4})$	$aBC = \frac{9}{64} aBC$
		$\frac{1}{4} c$	$(\frac{1}{4})(\frac{3}{4})(\frac{1}{4})$	$aBc = \frac{3}{64} aBc$
	$\frac{1}{4} b$	$\frac{3}{4} C$	$(\frac{1}{4})(\frac{1}{4})(\frac{3}{4})$	$abC = \frac{3}{64} abC$
		$\frac{1}{4} c$	$(\frac{1}{4})(\frac{1}{4})(\frac{1}{4})$	$abc = \frac{1}{64} abc$

Etc...

**Crosses between Organisms Heterozygous for Genes
Exhibiting Independent Assortment**

Number of Heterozygous Gene Pairs	Number of Different Types of Gametes Formed	Number of Different Genotypes Produced	Number of Different Phenotypes Produced*
n	2^n	3^n	2^n
1	2	3	2
2	4	9	4
3	8	27	8
4	16	81	16

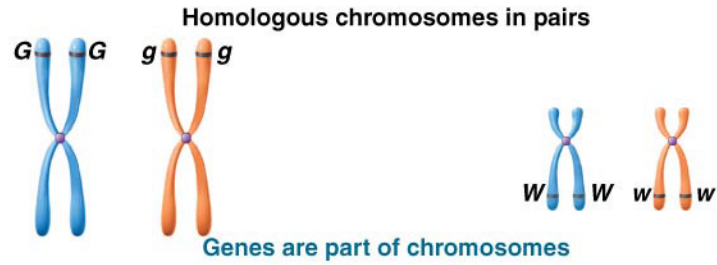
*The fourth column assumes a simple dominant-recessive relationship in each gene pair.

4. Chromosomes as substrates of segregation and independent assortment

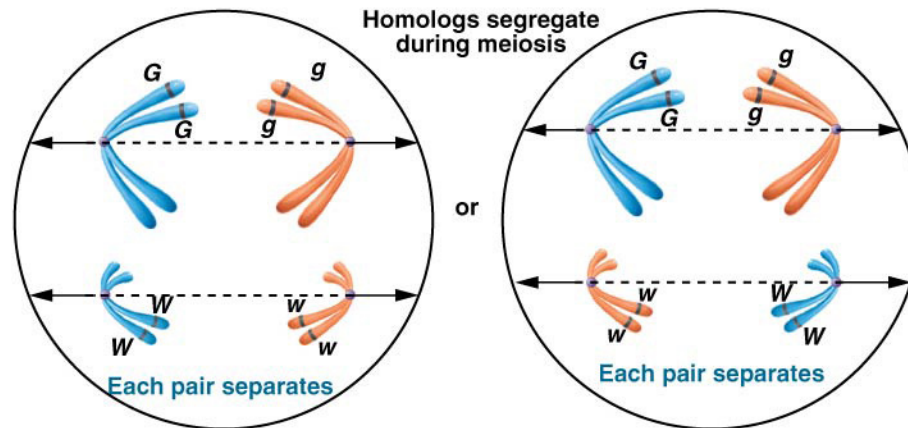
Chromosomal theory of inheritance

- Genetic material in living organisms contained in chromosomes
 - Separation of chromosomes during meiosis served as basis for Mendel's principles of segregation and independent assortment
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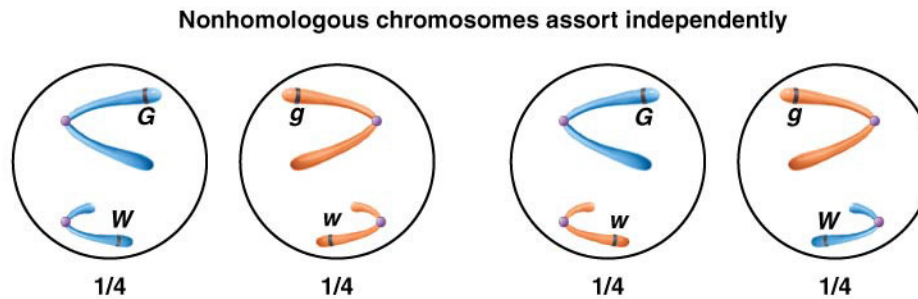
(a) Unit factors in pairs (first meiotic prophase)



(b) Segregation of unit factors during gamete formation (first meiotic anaphase)



(c) Independent assortment of segregating unit factors (following many meiotic events)



All possible gametic combinations are formed with equal probability

Homologous chromosomes

- **Criteria for classifying two chromosomes as homologous pairs**
 - Both are same size and exhibit identical centromere locations
 - Excludes X and Y chromosomes in mammals
 - Form pairs or synapse during stages of meiosis
 - Contain identical linear order of gene loci
-

5. Probabilities and χ^2 analysis

Genetic ratios as probabilities

- Laws of probability help to explain genetic events
 - **Product law:** *the probability of two or more events occurring simultaneously is equal to the product of their individual probabilities*
 - ➔ we used it before in the branch diagram to calculate the phenotype distribution in F_2 , e.g. $\frac{3}{4} \times \frac{3}{4} \times \frac{1}{4} = 9/64$)
 - **Sum law:** *the probability of obtaining any single outcome, where that outcome can be achieved by two or more events, is equal to the sum of the individual probabilities of all such events*
 - ➔ binomial theorem, which has various applications in genetics, including analysis of polygenic traits and of population equilibrium
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Genetic ratios as probabilities

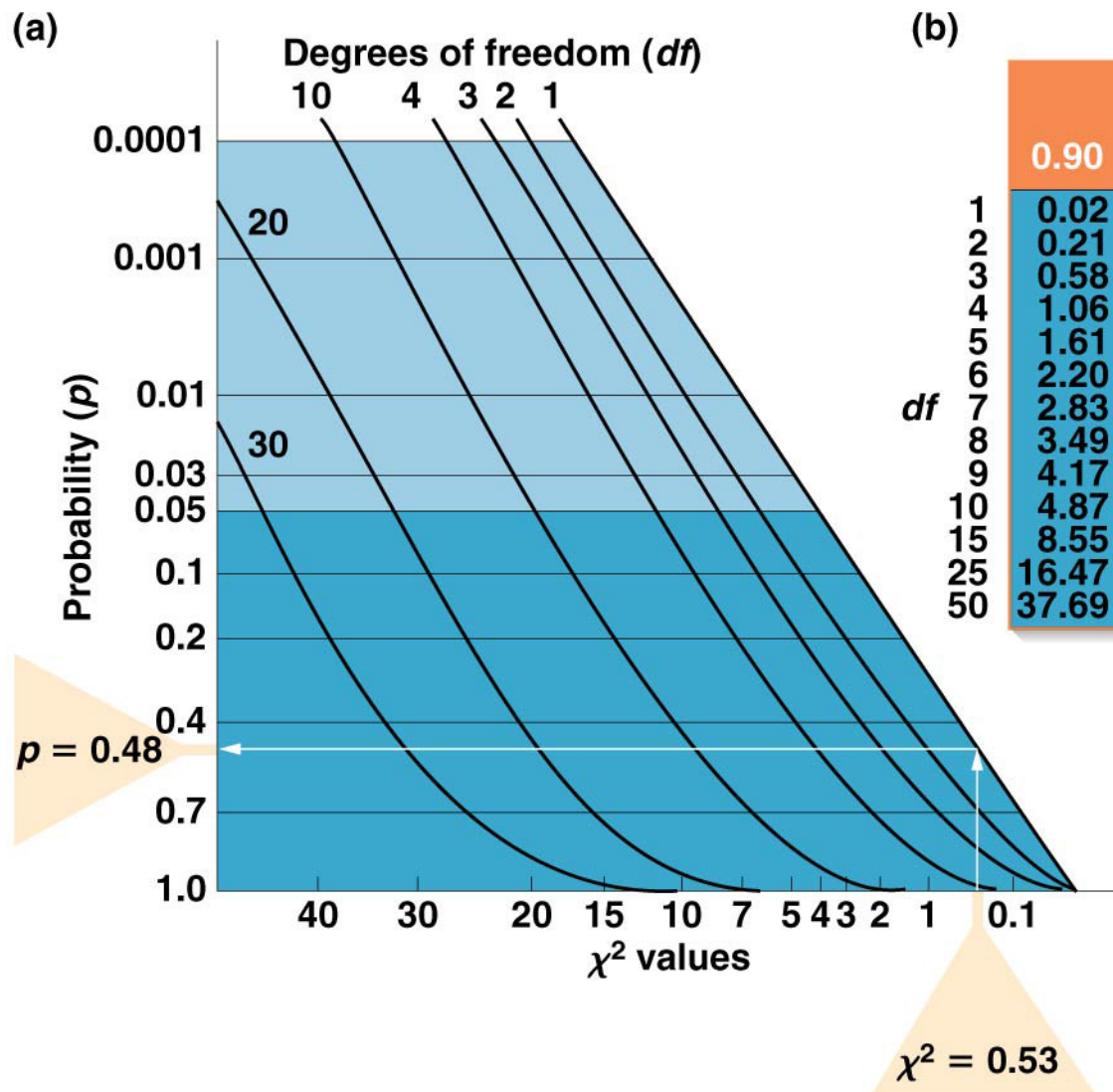
- Mendel's 3:1 monohybrid and 9:3:3:1 dihybrid ratios are predictions based on the following assumptions:
 - (1) Each allele is dominant or recessive
 - (2) Segregation
 - (3) Independent assortment
 - (4) Random fertilization
 - (3) and (4) are influenced by chance events and therefore are subject to random fluctuation
-

Chi-square analysis

- A χ^2 analysis evaluates the influence of chance on the distribution of genetic data
 - Analysis of **observed vs. expected** deviations
 - **Goodness of fit** of null hypothesis (i.e. how well the data fit the null hypothesis)
 - Null hypothesis:
 - Assumes data will fit given ratio
 - Assumes there is no real difference between measured values and predicted values
-

Degrees of freedom (*df*) and p-value

- Equal to $n - 1$
 - n = number of different categories into which data points may fall (different outcomes)
 - 3:1 ratio: $n = 2$ $df = 1$
 - 9:3:3:1 ratio: $n = 4$ $df = 3$
 - When number of degrees of freedom is determined, the χ^2 value can be interpreted in terms of a corresponding probability value (*p-value*)
-



(b)

	Probability (p)					
	0.90	0.50	0.20	0.05	0.01	0.001
df 1	0.02	0.46	1.64	3.84	6.64	10.83
2	0.21	1.39	3.22	5.99	9.21	13.82
3	0.58	2.37	4.64	7.82	11.35	16.27
4	1.06	3.36	5.99	9.49	13.28	18.47
5	1.61	4.35	7.29	11.07	15.09	20.52
6	2.20	5.35	8.56	12.59	16.81	22.46
7	2.83	6.35	9.80	14.07	18.48	24.32
8	3.49	7.34	11.03	15.51	20.09	26.13
9	4.17	8.34	12.24	16.92	21.67	27.88
10	4.87	9.34	13.44	18.31	23.21	29.59
15	8.55	14.34	19.31	25.00	30.58	37.30
25	16.47	24.34	30.68	37.65	44.31	52.62
50	37.69	49.34	58.16	67.51	76.15	86.60

χ^2 values

Fails to reject the null hypothesis
 Rejects the null hypothesis

Steps in χ^2 calculations for the F₂ generation of a monohybrid and a dihybrid crosses

(a) Monohybrid

Cross Expected Ratio	Observed (<i>o</i>)	Expected (<i>e</i>)	Deviation (<i>o</i> - <i>e</i>)	Deviation (<i>d</i> ²)	<i>d</i> ² / <i>e</i>
3/4	740	3/4(1000) = 750	740-750 = -10	(-10) ² = 100	100/750 = 0.13
1/4	<u>260</u>	1/4(1000) = 250	260-250 = +10	(+10) ² = 100	100/250 = <u>0.40</u>
	Total = 1000				$\chi^2 = 0.53$
					<i>p</i> = 0.48

(b) Dihybrid

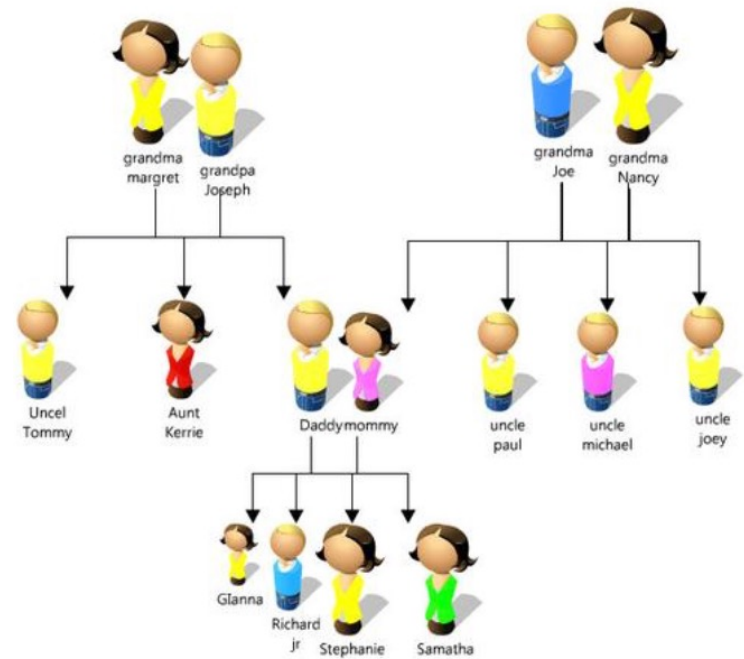
Cross Expected Ratio	Observed (<i>o</i>)	Expected (<i>e</i>)	Deviation (<i>o</i> - <i>e</i>)	Deviation (<i>d</i> ²)	<i>d</i> ² / <i>e</i>
9/16	587	567	+20	400	0.71
3/16	197	189	+8	64	0.34
3/16	168	189	-21	441	2.33
1/16	<u>56</u>	63	-7	49	<u>0.78</u>
	Total = 1008				$\chi^2 = 4.16$
					<i>p</i> = 0.26

6. Pedigrees reveal patterns of inheritance of human traits

Pedigrees (genealogical trees)

Pedigrees are very useful to understand the transmission mode of genetic diseases

To build them, precise conventions must be followed



Pedigree

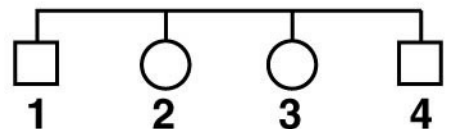
- **Family tree with respect to given trait**
 - **Pedigree conventions**
 - Circle = female / Square = male
 - Diamond = unknown sex
 - Parents connected by single horizontal line
 - Offspring stem off vertical line from parent
 - Double line = related parents, such as two cousins (“consanguineous”)
 - Twins = diagonal lines stemming from vertical line connected to the sibship line
-

○ Female □ Male ◇ Sex unknown

● ■ Affected individuals

○—□ Parents (unrelated)

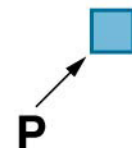
○=□ Consanguineous parents (related)

 Offspring (in birth order)

 Fraternal (dizygotic) twins
(sex may be the same or different)

 Identical (monozygotic) twins
(sex must be the same)

④ ④ Multiple individuals (unaffected)

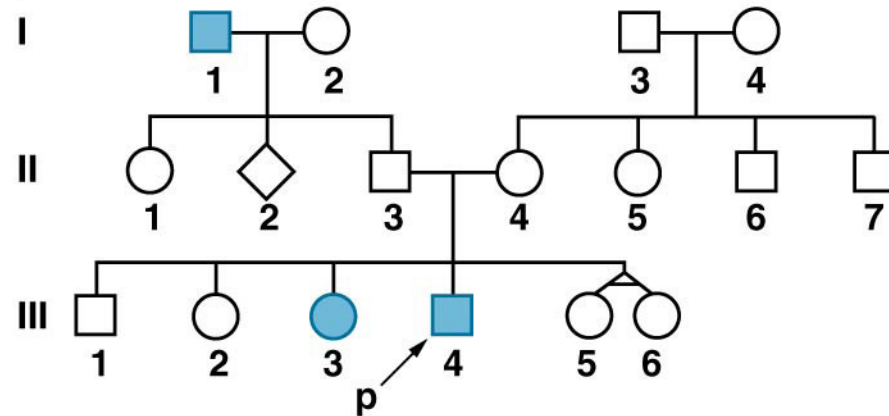
 Proband (in this case, a male)

⊘ Deceased individual (in this case, a female)

◉ ◑ Heterozygous carriers

I, II, III, etc. Successive generations

(a) Autosomal Recessive Trait

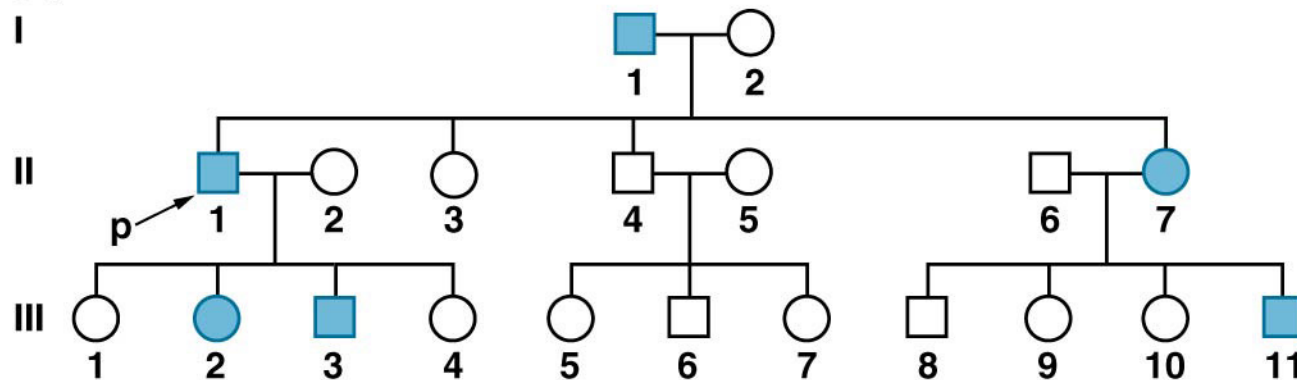


Either I-3 or I-4 must be heterozygous

Recessive traits typically skip generations

Recessive autosomal traits appear equally in both sexes

(b) Autosomal Dominant Trait



I-1 is heterozygous for a dominant allele

Dominant traits almost always appear in each generation

Affected individuals all have an affected parent.
Dominant autosomal traits appear equally in both sexes

Dominant transmission

- Affected individuals in several generations
 - Male/female ratio = 1
 - Every affected individual has one affected parent, except in case of *de novo* mutation
 - Risk for each child of an affected parent : 50%
 - Unaffected individual doesn't transmit
 - Inbreeding doesn't increase risk
-

Recessive transmission

- Not visible in all generations
 - Male/female ratio = 1
 - Inbreeding increases risk
 - Parents of an affected kid are heterozygous
 - Recurrence risk if one kid is affected: 25%
-

Recessive Traits

Albinism

Alkaptonuria

Ataxia telangiectasia

Color blindness

Cystic fibrosis

Duchenne muscular
dystrophy

Galactosemia

Hemophilia

Lesch-Nyhan syndrome

Phenylketonuria

Sickle-cell anemia

Tay-Sachs disease

Dominant Traits

Achondroplasia

Brachydactyly

Congenital stationary
night blindness

Ehler-Danlos syndrome

Hypotrichosis

Huntington disease

Hypercholesterolemia

Marfan syndrome

Myotonic dystrophy

Neurofibromatosis

Phenylthiocarbamide tasting

Porphyria (some forms)

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