BIO-373

Genetics & Genomics

Mendelian genetics

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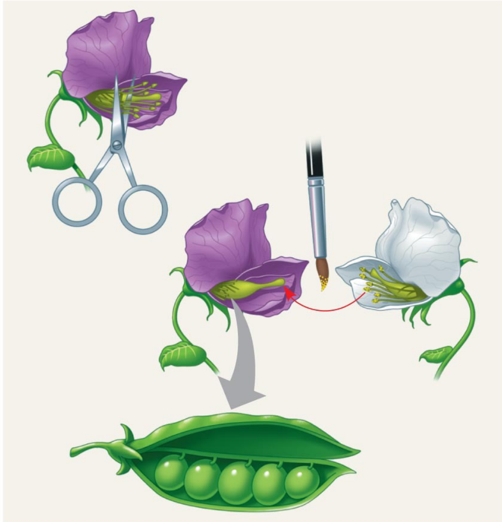
Contents

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 – the one-trait cross

- **Definition:** a cross between two individuals that are heterozygous at one locus (Aa x Aa)
- Involve a single pair of contrasting traits
  - Allele A
  - Allele a
- P_1 generation: parents (true-breeding invidiuals)
  - AA or aa (all homozygous)
- F_1 generation: offspring (P_1 x P_1 = F_1)
  - Aa (all heterozygous)
- F_2 generation: offspring of F_1 (F_1 x F_1 = F_2)

Monohybrid cross – the one-trait cross

- **Assumptions:**
  - Two alleles: one dominant and one recessive
  - Segregation of alleles in meiosis; random fertilisation
  - Locus acts independently of others
  - No selection, mutation, or sampling bias

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 (AA x aa → Aa)
  - Phenotype: all plants have the same phenotype (one of the two possible traits)
  - Genotype: 100% Aa
- F_2 generation (Aa x Aa)
  - Phenotype: 3 dominant : 1 recessive (3/4 vs 1/4)
  - Genotype: 1 AA : 2 Aa : 1 aa
  - The recessive trait "disappears" in F_1 and reappears in ¼ of F_2

Reciprocal cross to proof autosomal inheritance pattern

- Reciprocal cross definition: perform a cross twice and swap which phenotype is used in males and females
- Phenotypes in F_1 and F_2 identical independent which parents were used for cross
- Inheritance is not sex-dependent (ie, autosomal gene)
- Autosomal trait with complete dominance
- When phenotypes of reciprocal crosses don’t match: X/Y-linked gene, mitochondrial inheritance, genomic imprinting

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**

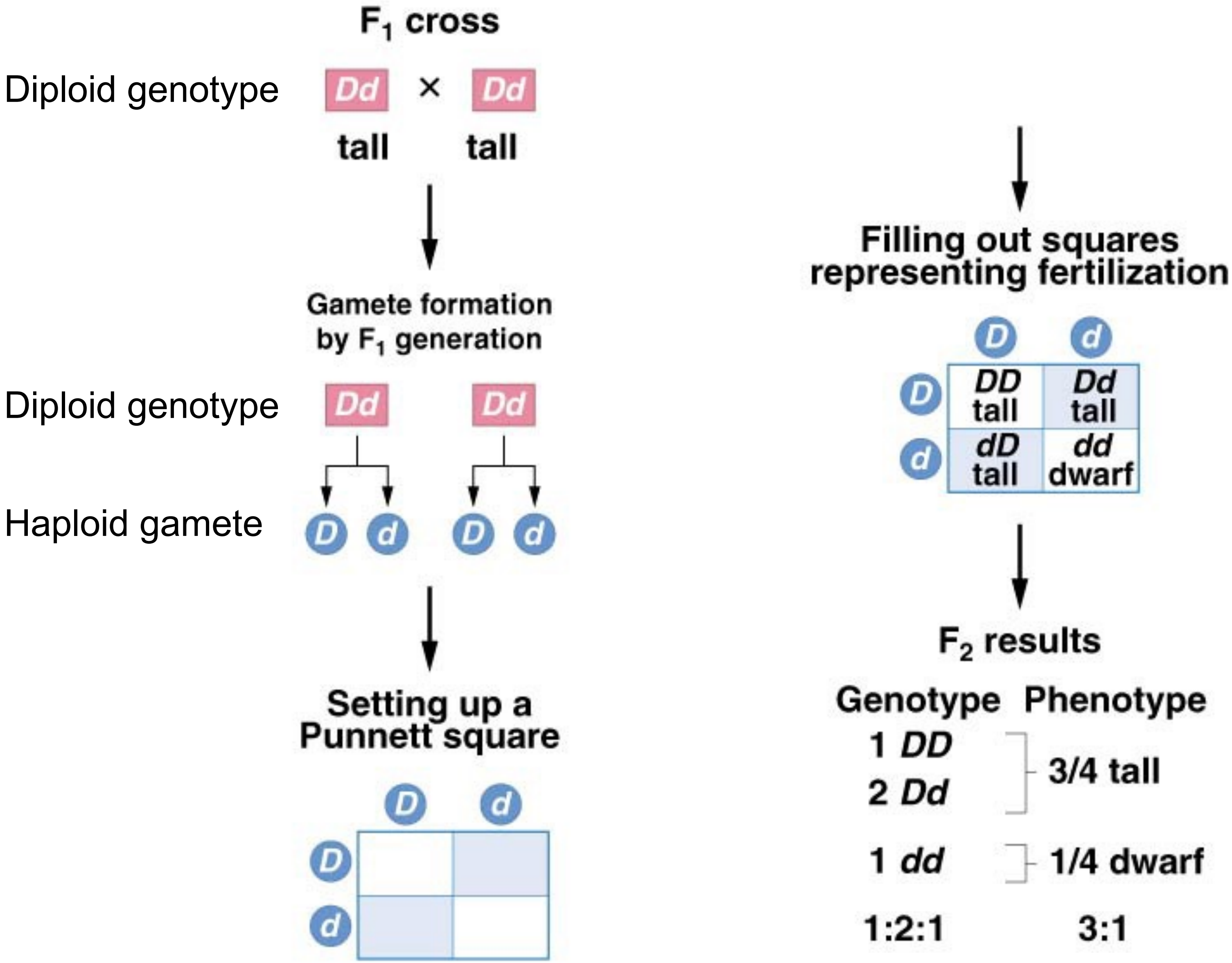
Genetic terminology

- **Gene**
  - A segment of DNA that codes for a specific protein
  - Basic unit of heredity
- **Allele**
  - Different versions of the same gene (locus) on homologous chromosomes (eg, *A* or *a* allele)
- **Genotype**
  - Genetic constitution of an individual
  - Alleles written in pairs (*AA*, *Aa*, or *aa*)
- **Phenotype**
  - The observable characteristic or trait of an individual, and determined by its genotype(s) and influenced by the environment

Punnett square

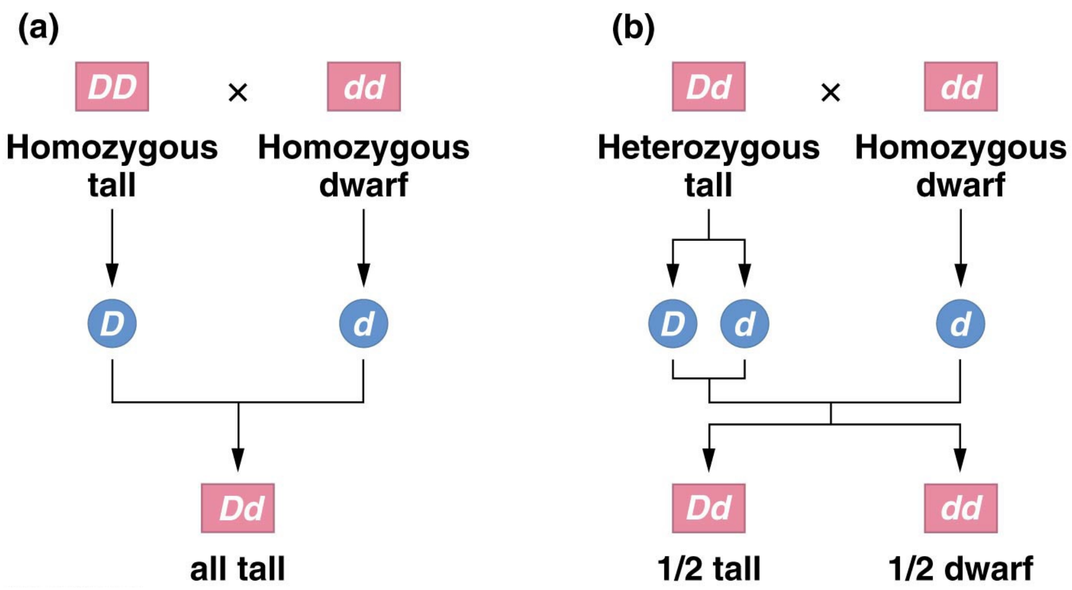
- Devised by R. C. Punnett, founder of the *Journal of Genetics* in 1910
- Genotypes and phenotypes resulting from combining gametes can be visualized
- Displays all possible random fertilization events

F_2 generation



Testcross (or recessive backcross)

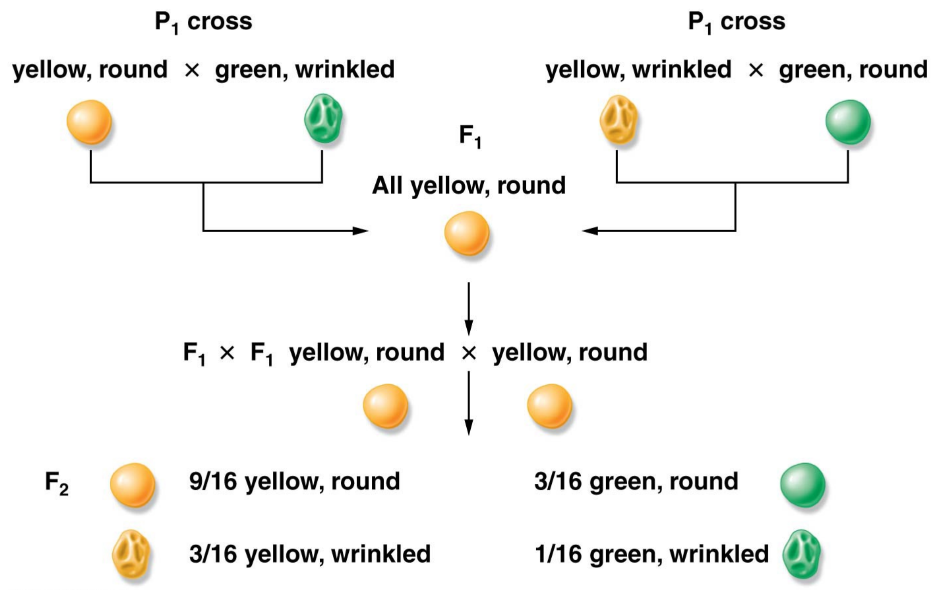
- **Definition:** cross an individual with a dominant phenotype (yet unknown genotype) with a homozygous recessive (tester) to reveal unknown genotype
- Determines if individual with dominant phenotype is homozygous (AA) or heterozygous (Aa)
- Scenario a: Unknown individual is DD → 100% tall offspring
- Scenario b: Unknown individual is Dd → 1 tall : 1 dwarf



2. Dihybrid cross

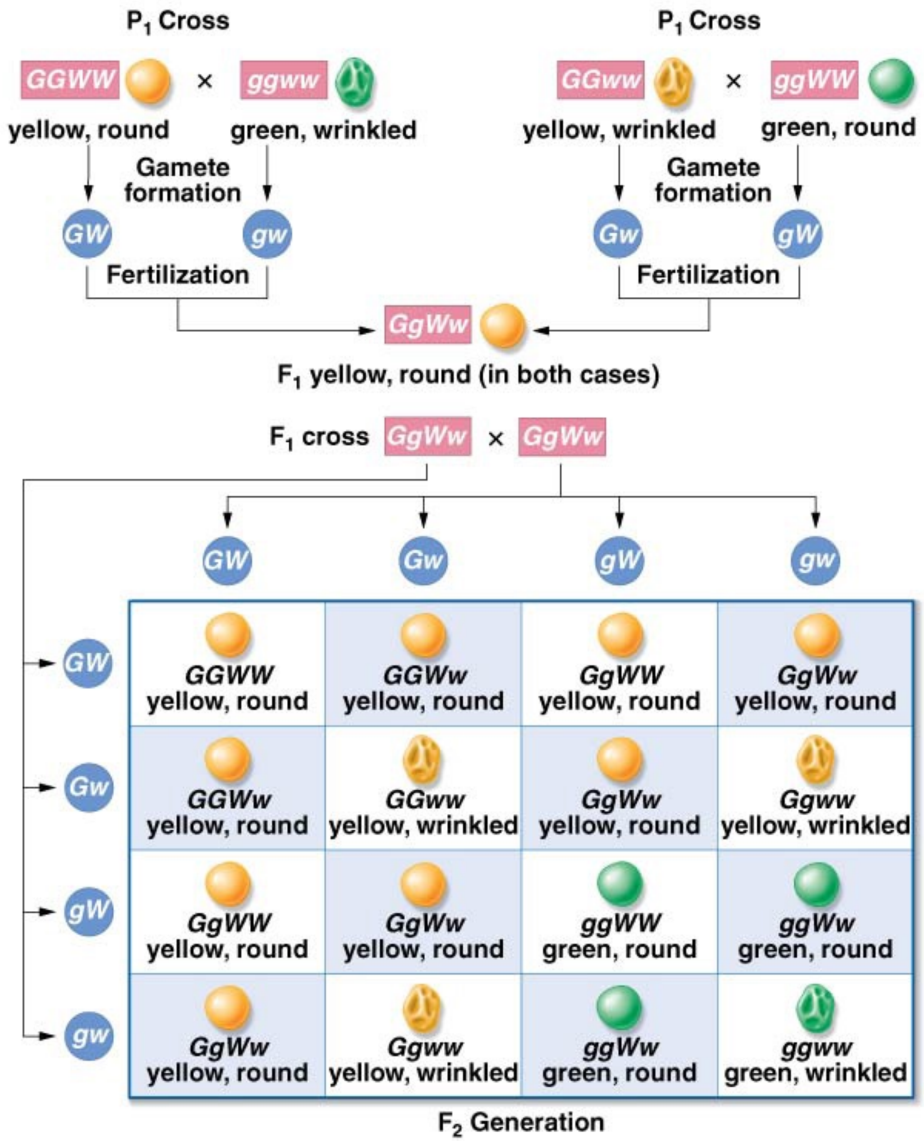
Dihybrid cross

- **Definition:** a genetic cross that follows two genes at once and two pairs of contrasting traits
- Setup: true-breeding parents (AABB x aabb) → F_1 dihybrids (AaBb) → F_1 x F_1 is the dihybrid cross
- Gametes from each dihybrid: AB, Ab, aB, ab (each ¼ probability)
- Assumptions: complete dominance and independent assortment
- Deviation if genes are in linkage (same chromosome)



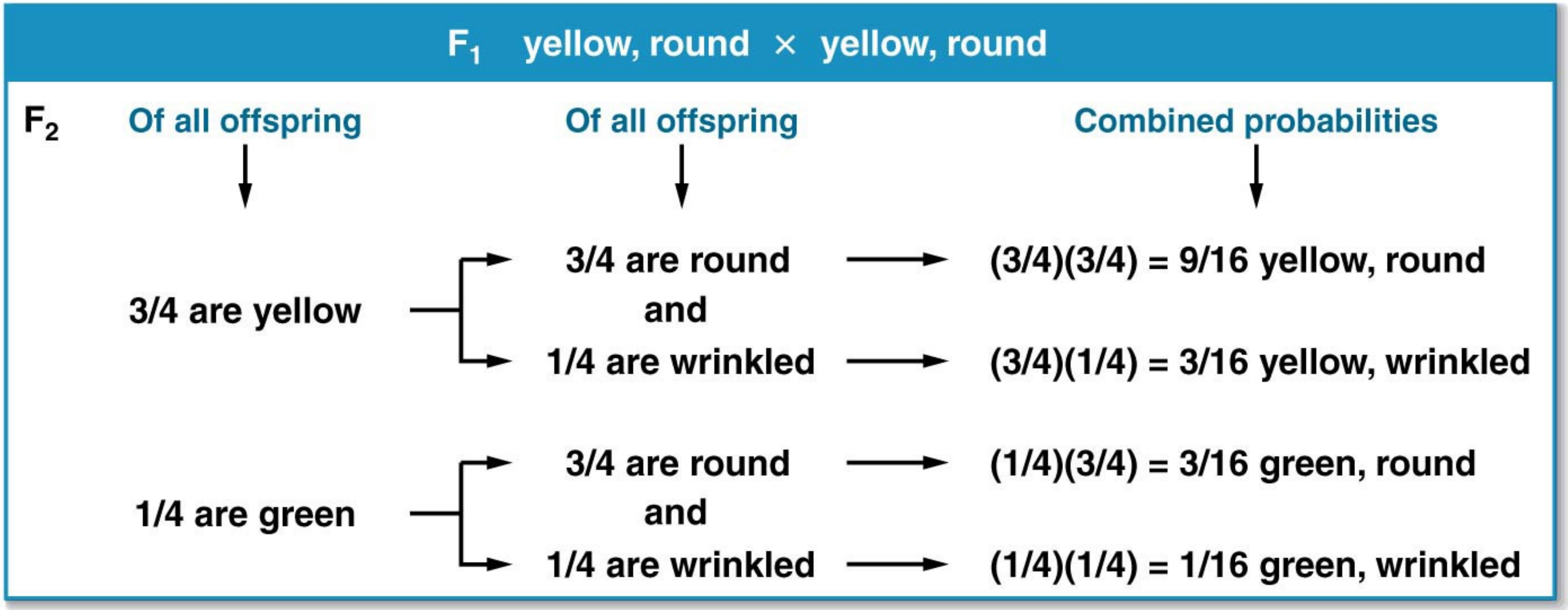
Mendel's 9:3:3:1 dihybrid ratio

- **9:3:3:1 dihybrid ratio** in F_2
  - 9/16 (56%) yellow, round seeds
  - 3/16 (19%) yellow, wrinkled seeds
  - 3/16 (19%) green, round seeds
  - 1/16 (6%) green, wrinkled seeds



Combination of probabilities

- Used to predict frequency of two independent events occurring simultaneously



Mendel’s laws

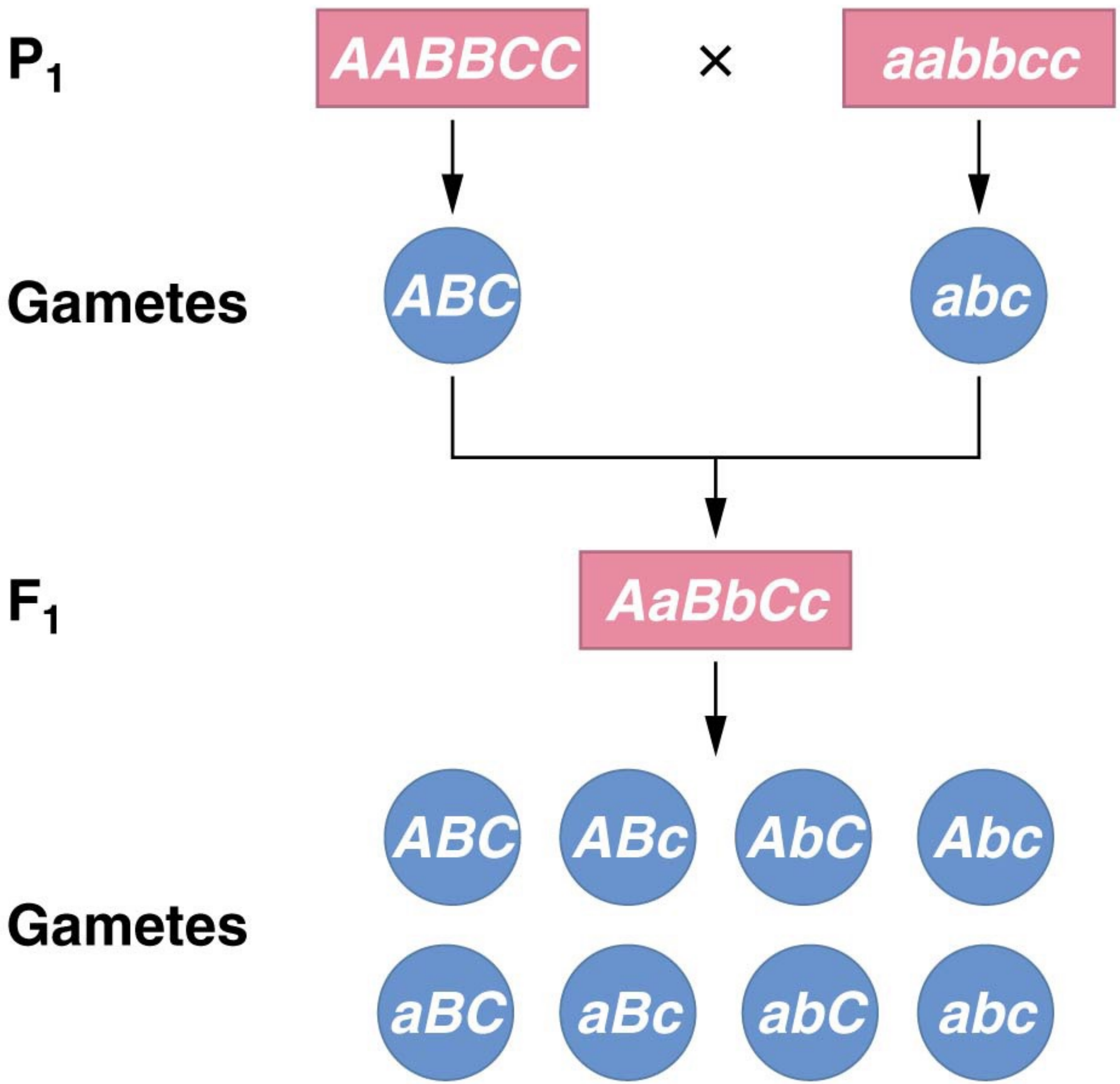
1. **Dominance**
   – In a pair of unit factors, one unit (allele) is dominant, the other recessive
2. **Segregation**
   – Alleles of a gene segregate randomly during gamete formation
3. **Independent assortment**
   – Separate genes assort independently during gamete formation (i.e. genes do not influence each other with regard to the sorting of alleles into gametes)

3. Trihybrid Cross

Trihybrid Cross

- Complete dominance, 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**)
  - Treat each gene as an independent mini-problem, compute outcome probabilities, and multiply along branches to get joint outcomes

Trihybrid gamete formation



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*

Checks that the 8 phenotype groups sum up to 64

Etc…

Crosses between Organisms Heterozygous for Genes Exhibiting Independent Assortment

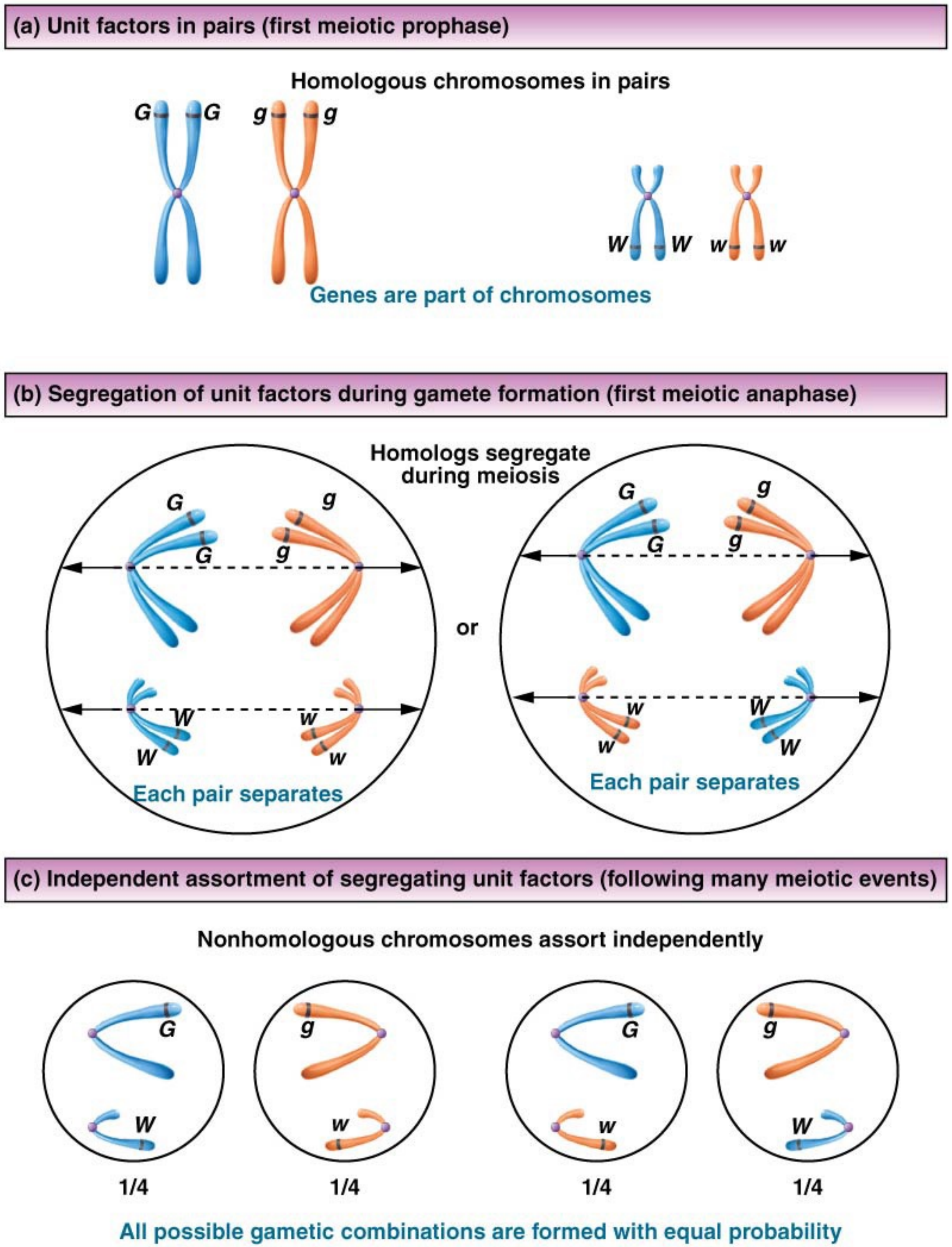
Number of Heterozygous Gene Pairs	Number of Different Types of Gametes Formed	Number of Different Genotypes Produced	Number of Different Phenotypes Produced*
n	2^n	3^n	2^n
1	2	3	2
2	4	9	4
3	8	27	8
4	16	81	16

*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 serves as basis for Mendel’s principles of segregation and independent assortment


(a) Unit factors in pairs (first meiotic prophase)
Homologous chromosomes in pairs
G G g g
W W w w
Genes are part of chromosomes
(b) Segregation of unit factors during gamete formation (first meiotic anaphase)
Homologs segregate during meiosis
G G g g
W W w w
Each pair separates
or
G G g g
w w W W
Each pair separates
(c) Independent assortment of segregating unit factors (following many meiotic events)
Nonhomologous chromosomes assort independently
G W
1/4
g w
1/4
G w
1/4
g W
1/4
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 (eg, ¾ x ¾ x ¼ = 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

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 (completely) 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

Steps in χ^2 calculations for the F_2 generation of a monohybrid and a dihybrid crosses

(a) Monohybrid

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

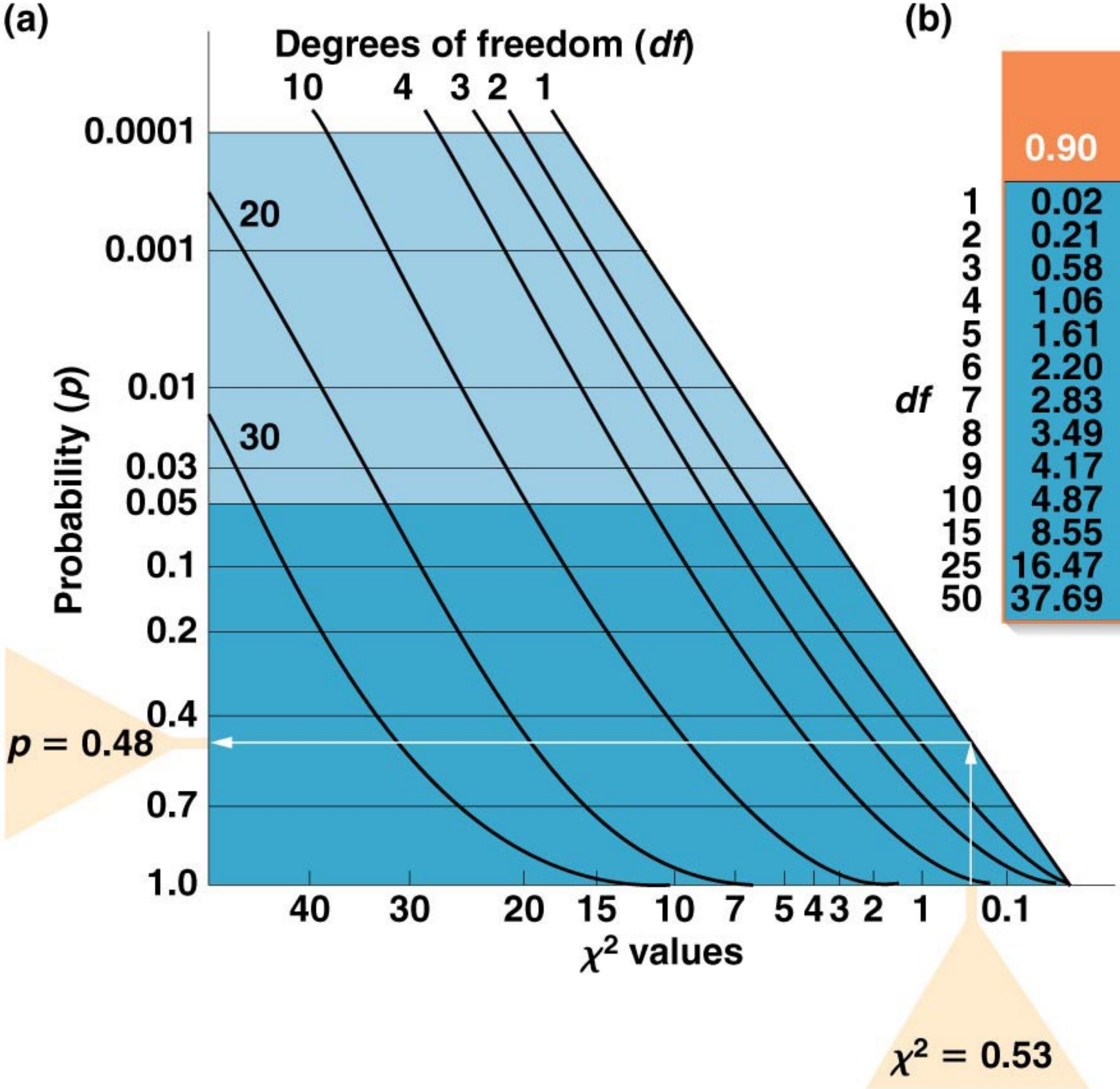
(b) Dihybrid

Cross Expected Ratio	Observed (o)	Expected (e)	Deviation ($o - e$)	Deviation (d^2)	d^2/e
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	56	63	−7	49	0.78
	Total = 1008				$\chi^2 = 4.16$
					$p = 0.26$

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)

df	Probability (p)					
	0.90	0.50	0.20	0.05	0.01	0.001
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

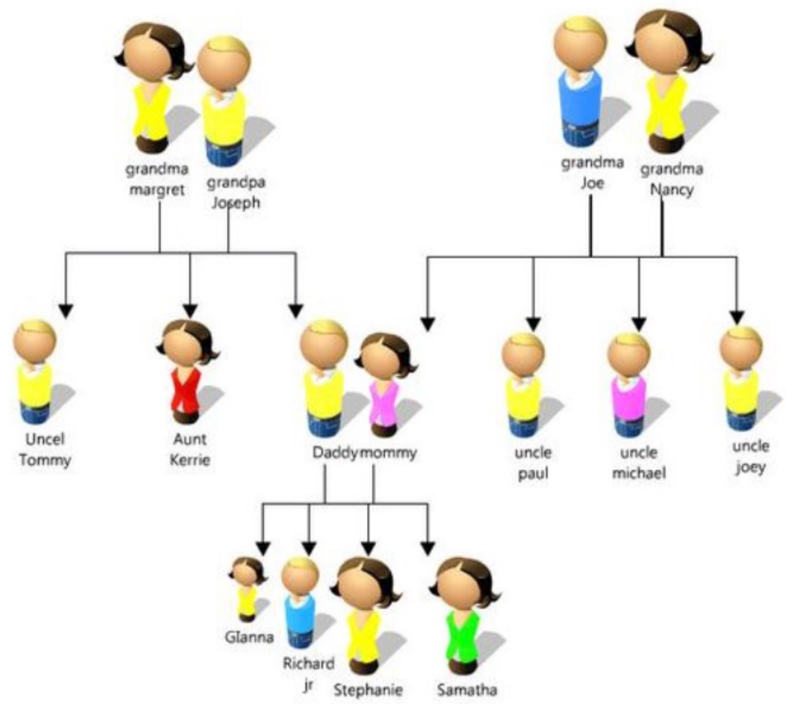
Fails to reject the null hypothesis
Rejects the null hypothesis

6. Pedigrees reveal patterns of inheritance of human traits

Pedigrees (genealogical trees)

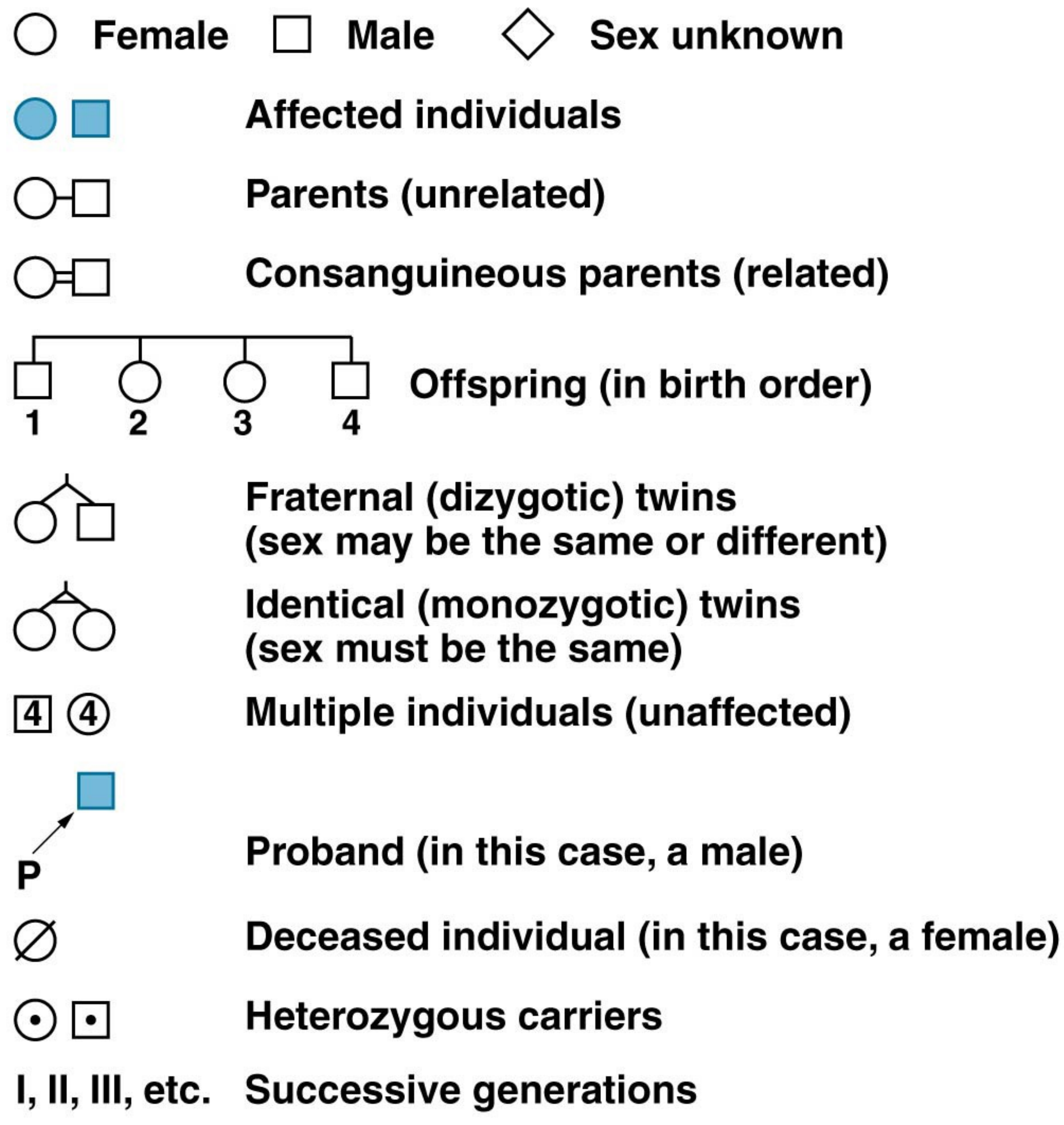
Pedigrees are very useful to understand the transmission mode of genetic diseases

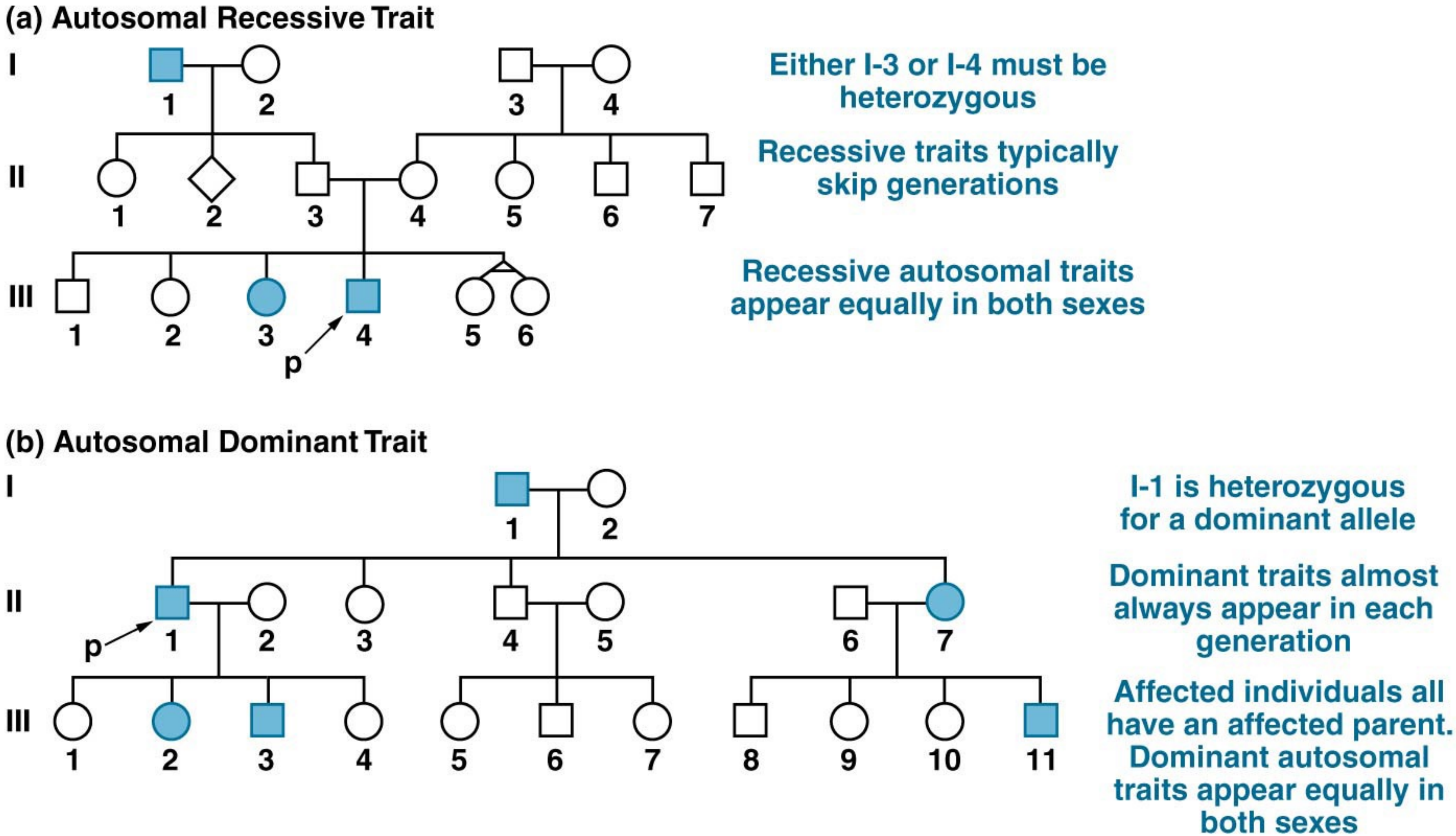
To build them, precise conventions must be followed



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)
1
2
3
4
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)
P
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
I
II
III
1
2
3
4
5
6
7
p
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
II
III
1
2
3
4
5
6
7
8
9
10
11
p
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
- Recurence risk if one kid is affected: 25%

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)

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