GENETICS · FINAL EXAM

Final Exam Study Guide

The final covers all 14 chapters. Fourteen separate piles of notes would be hard to hold, so this guide pairs the chapters into seven themes, each built on one way of thinking. Transmission turns crosses into fractions. Sex, organelles and maps add the parent's sex and the distance between genes. Microbes and chromosomes zoom from tiny genomes to whole chromosome sets. DNA to protein follows the molecules. Regulation and tools ask how genes are switched and how we read and edit them. Traits and populations bring in statistics. The last theme carries genes into development, cancer and the clinic. Work one theme a day and the whole course fits into a week.

THE SEVEN THEMES AND THE CHAPTERS IN EACH

- Transmission: chapters 1 and 2.
- Sex, organelles and maps: chapters 3 and 4.
- Microbes and chromosomes: chapters 5 and 6.
- DNA to protein: chapters 7 and 8.
- Regulation and tools: chapters 9 and 10.
- Traits and populations: chapters 11 and 12.
- Development, cancer and the clinic: chapters 13 and 14.
- Every theme carries what to know, a formula table, worked examples, the traps and a 10 item self-test.

THEME 1 · CHAPTERS 1 AND 2

Transmission

What to know

Alleles come in pairs and separate into gametes with equal odds (**segregation**, homologs parting in anaphase I). Unlinked genes sort on their own (**independent assortment**, random orientation at

metaphase I). So *Aa* × *Aa* gives 1:2:1 genotypes and 3:1 phenotypes, a dihybrid intercross gives 9:3:3:1 and a dihybrid testcross 1:1:1:1.

Solve each gene alone and multiply. Multiply for "and," add for "or," condition on what you know (an unaffected sibling of a recessive patient is a carrier with chance 2/3), use the binomial for "exactly k of n" and subtract from 1 for "at least one." Chi square, $\Sigma(O - E)^2/E$ with df = classes − 1, asks whether counts fit a ratio.

In pedigrees, unaffected parents with an affected child mean recessive, and affected parents with an unaffected child mean dominant.

Real ratios bend. Incomplete dominance and codominance give 1:2:1. A recessive lethal with a visible heterozygote gives 2:1. Epistasis regroups sixteenths into 9:3:4, 12:3:1, 9:7, 15:1, 13:3 or 9:6:1. Penetrance asks whether a trait shows, and expressivity how strongly. A complementation test tells whether two recessive mutations are in the same gene: a wild type F_1 means different genes.

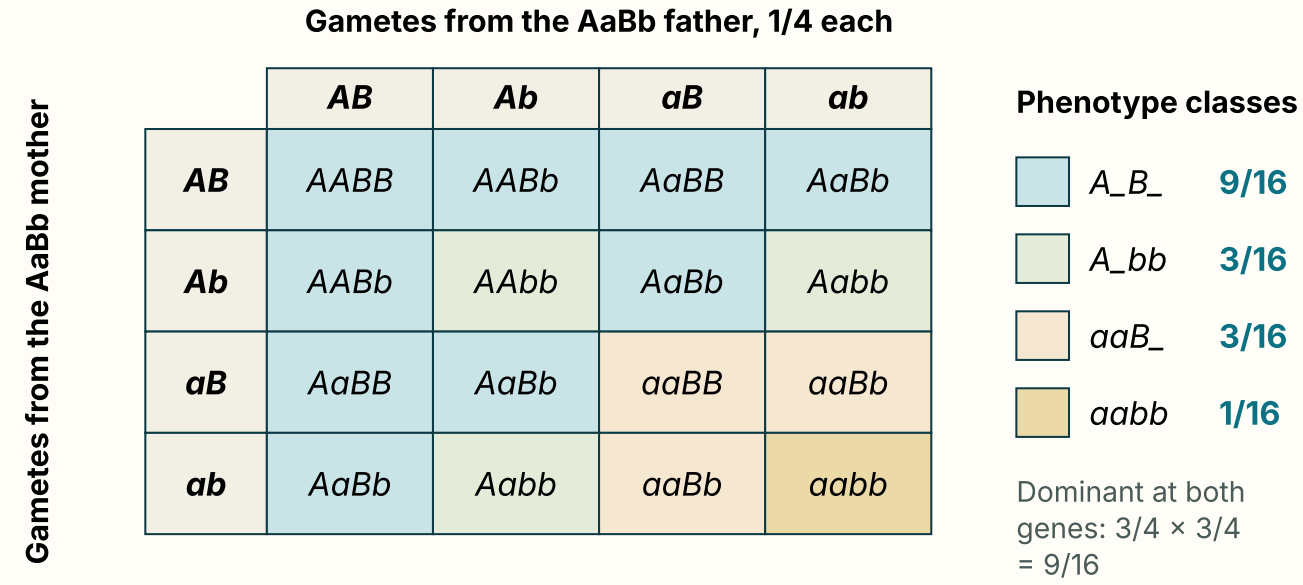
Dominance is a property of the heterozygote and can change with the level of analysis: the sickle cell allele is recessive for disease, incompletely dominant for cell shape and codominant for the proteins. With n alleles in a population there are n(n + 1)/2 genotypes, and ABO mixes dominance with codominance.

Phenotype depends on genotype and environment together. Temperature sensitive tyrosinase colors only the cool points of Siamese cats, diet prevents the harm of PKU, phenocopies mimic genetic traits, and a norm of reaction charts one genotype across environments.

> **How the two chapters connect.** Chapter 2 never breaks Chapter 1. Every odd ratio is still sixteen equally likely Punnett cells, grouped differently or with a class removed. When a ratio looks strange, write out *A_B_*, *A_bb*, *aaB_* and *aabb* first, then ask which classes share a phenotype or fail to survive.

LOCK THESE IN

- 3:1, 1:2:1, 1:1, 9:3:3:1, 1:1:1:1 and 2:1.
- Unaffected sibling of a recessive patient: carrier chance 2/3.
- df = classes − 1; critical 3.841, 5.991, 7.815.
- Epistatic ratios still add to 16. Divide counts by total/16.
- Risk with reduced penetrance = P(inherit) × penetrance.
- Wild type F_1 in a complementation test: different genes.



Sixteen equally likely cells. Count by color: 9 : 3 : 3 : 1. A testcross (AaBb × aabb) gives 1 : 1 : 1 : 1.

A dihybrid cross, cell by cell. Each parent makes four gametes in equal numbers, so the square has sixteen equal cells. Grouping them by phenotype gives 9:3:3:1.

Ratio	*A_B_* 9/16	*A_bb* 3/16	*aaB_* 3/16	*aabb* 1/16	Name
9:3:3:1	9	3	3	1	no merging (baseline)
9:3:4	9	3	3	1	recessive epistasis
12:3:1	9	3	3	1	dominant epistasis
9:7	9	3	3	1	complementary genes
15:1	9	3	3	1	duplicate dominant
13:3	9	3	3	1	dominant and recessive
9:6:1	9	3	3	1	cumulative effect

Same color means the classes look alike, and dashed lines mark classes that merged.
Every row still adds to 16. Divide each count by one sixteenth of the total to spot the ratio.

Epistasis only regroups. The sixteen Punnett cells keep their usual 9, 3, 3 and 1. Masking makes some classes look alike, so the ratio collapses.

Ratios and rules

Item	Rule	Use
Gene counts	2^n gametes; 3^n genotypes; 2^n phenotypes; 4^n cells	n heterozygous genes
Binomial	$[n!/(s!\ t!)]\ p^s q^t$	exactly s of n
Chi square	$\Sigma(O - E)^2/E$	counts, not percents
Multiple alleles	$n(n + 1)/2$ genotypes	ABO, rabbit coat
Modified ratios	9:3:4 recessive; 12:3:1 dominant; 9:7 complementary; 15:1 duplicate	epistasis
Lethal plus gene	twelfths, such as 6:3:2:1	16 − 4 = 12 cells

Terms to define in one line

Term	Meaning
Allele	one form of a gene
Segregation	the two alleles part into different gametes
Independent assortment	unlinked genes sort into gametes on their own
Testcross	cross to a homozygous recessive to reveal gametes
Conditional probability	probability after ruling out known outcomes
Degrees of freedom	classes free to vary; classes minus 1
Codominance	both allele products show in the heterozygote
Epistasis	one gene masks another
Penetrance	percent of carriers who show the trait
Complementation group	mutations that fail to complement; one gene

Worked examples

WORKED EXAMPLE 1 · CHI SQUARE ON A DIHYBRID

A dihybrid F_2 gives 98, 28, 26 and 8 offspring in the four classes. Test 9:3:3:1.

STEP 1 · EXPECTED

Total 160, so 90, 30, 30 and 10.

STEP 2 · TERMS

64/90 = 0.711; 4/30 = 0.133; 16/30 = 0.533; 4/10 = 0.400.

STEP 3 · SUM

χ^2 = **1.78** with df 3.

STEP 4 · DECIDE

1.78 < 7.815, so **fail to reject** 9:3:3:1.

WORKED EXAMPLE 2 · AT LEAST ONE OF FIVE

Two carriers of a recessive condition have five children. What is the chance at least one is affected?

STEP 1 · NONE AFFECTED

$(3/4)^5 = 243/1{,}024$.

STEP 2 · SUBTRACT

$1 - 243/1{,}024 =$ **781/1,024, about 0.76**.

WORKED EXAMPLE 3 · NAMING A MODIFIED RATIO

An F_2 of squash gives 200 white, 40 yellow and 16 green. Which ratio fits?

STEP 1 · ONE SIXTEENTH

$256 \div 16 = 16$.

STEP 2 · DIVIDE

200/16 = 12.5; 40/16 = 2.5; 16/16 = 1.0. That reads as 12:3:1.

STEP 3 · CHI SQUARE

Expected 192, 48, 16: 64/192 + 64/48 + 0 = 0.33 + 1.33 = **1.67**, df 2.

STEP 4 · DECIDE

1.67 < 5.991, so **dominant epistasis** fits.

WORKED EXAMPLE 4 · PENETRANCE AND AN UNAFFECTED CHILD

A dominant condition has 90 percent penetrance. A known heterozygote has an unaffected child with a noncarrier partner. What is the chance the child carries the allele?

STEP 1 · CARRIER AND UNAFFECTED

$1/2 \times 0.10 = 0.05$.

STEP 2 · NONCARRIER

$1/2 \times 1 = 0.50$.

STEP 3 · CONDITION

$0.05 \div 0.55 =$ **1/11, about 9 percent**.

TRAPS PEOPLE FALL INTO

- **Answering 1/2 for an unaffected sibling.** It is 2/3.
- **Using percents or rounded expected values in chi square.** Use raw counts and keep decimals.

- **Confusing epistasis with dominance.** Epistasis is between genes; dominance within one gene.
- **Reading penetrance as severity.** That is expressivity.
- **Calling incomplete dominance blending.** The parental types return unchanged in the F_2.
- **Running a complementation test with dominant mutants.** The F_1 is mutant either way.

Self-test · Theme 1

1. A plant with the dominant phenotype is testcrossed and gives 1 dominant : 1 recessive. What is its genotype?

A Homozygous recessive, *aa*

B Homozygous dominant, *AA*

C It cannot be told

D Heterozygous, *Aa*

D. Heterozygous, *Aa*. A heterozygote sends *A* and *a* gametes equally, and the recessive tester reveals each one.

2. In *AaBbCc* × *AaBbCc*, what fraction of offspring are recessive for all three traits?

A 1/64

B 1/27

C 3/64

D 1/8

A. 1/64. $(1/4)^3 = 1/64$.

3. Two carriers have four children. What is the chance that exactly one is affected?

A 81/256

B 3/16

C 27/64

D 1/4

C. 27/64. $4 \times (1/4)(3/4)^3 = 4 \times 27/256 = 108/256 = 27/64$.

4. A chi square test of a 1:2:1 ratio gives 4.9. What do you conclude at P = 0.05?

A Reject, since any value above 1 fails

B Fail to reject, since 4.9 is below 5.991

C Reject, since 4.9 is above 3.841

D Accept 1:2:1 as proven by the test

B. Fail to reject, since 4.9 is below 5.991. Three classes give df 2 and a critical value of 5.991.

5. Two affected parents have an unaffected child. What is the mode of inheritance?

A Y linked

B Recessive

C Dominant

D Mitochondrial

C. Dominant. Affected parents can have an unaffected child only if each carries a hidden normal allele, so affected must be dominant.

6. What is the blood type ratio among children of $I^Ai \times I^Bi$ parents?

A 1 A : 1 B : 2 AB : 0 O

B 1 A : 1 B : 1 AB : 1 O

C 2 A : 1 B : 1 AB : 0 O

D 3 A : 3 B : 1 AB : 1 O

B. 1 A : 1 B : 1 AB : 1 O. Each parent gives two alleles equally, so all four combinations appear in equal shares.

7. An F_2 shows 9 colored : 3 brown : 4 white. What is this?

A Incomplete dominance

B Duplicate dominant genes

C Dominant epistasis

D Recessive epistasis

D. Recessive epistasis. A homozygous recessive genotype at one gene masks the other, merging 3 + 1 into 4, as in Labrador coats.

8. A dominant allele has 60 percent penetrance. A heterozygote has a child with a noncarrier. What is the chance the child is affected?

A 0.30

B 0.50

C 0.60

D 0.40

A. 0.30. 1/2 × 0.6 = 0.30.

9. Neurofibromatosis type 1 has penetrance near 100 percent but ranges from a few spots to many tumors. What does the range show?

A Codominance of alleles

B A phenocopy in some

C Variable expressivity

D Incomplete penetrance

C. Variable expressivity. Expressivity is how strongly a trait shows in people who have it.

10. Two recessive white flowered lines give purple F_1 plants. What is the most likely F_2 ratio?

A 9 purple : 7 white

B 1 purple : 1 white

C 3 purple : 1 white

D 15 purple : 1 white

A. 9 purple : 7 white. The lines complement, so they carry mutations in two genes acting in series, which gives 9:7.

Read the full chapter: Chapter 1 · Chapter 2

THEME 2 · CHAPTERS 3 AND 4

Sex, organelles and maps

What to know

In mammals SRY on the Y makes a male. In flies the X:A ratio decides. In birds the ZW female is heterogametic. Males are hemizygous for X genes, so X linked recessive traits mostly hit males, never pass father to son, and every daughter of an affected man is a carrier. X linked dominant traits pass from an affected father to all daughters.

Female mammals silence one X with XIST, at random and clonally, so Barr bodies = X − 1. Sex influenced and sex limited traits are autosomal. mtDNA passes from mothers to all children. A maternal effect follows the mother's nuclear genotype and shows ratios a generation late. Imprinting silences one parental copy.

Linked genes travel together. Find the phase first: the two largest testcross classes are the parentals. RF = recombinants ÷ total, 1% = 1 cM, and RF never passes 50%. In a three point cross the gene that differs between a parental and its double crossover class is in the middle, and doubles count in both intervals. c.o.c. = observed/expected doubles and I = 1 − c.o.c.

Haldane and Kosambi correct RF for hidden crossovers. In human families, LOD = $\log_{10}[L(\theta)/L(0.5)]$. Scores add across families, 3 supports linkage and −2 excludes it.

Dosage compensation takes three forms: female mammals silence one X, male flies double their X, and worm hermaphrodites halve both. About 15 percent of human X genes escape inactivation, which is why 45,X and 47,XXY have effects. Skewed inactivation can make a carrier a manifesting heterozygote.

Map units measure crossover frequency, not DNA length. Human 1 cM averages about 1 Mb, but hotspots, centromeres and sex (the female map is about 1.6 times longer) shift it. Gene order on genetic and physical maps agrees.

> **How the two chapters connect.** Both chapters ask one question: when do Mendel's equal, independent shares fail? The sex of a parent, an organelle in the egg, an imprint or a shared chromosome each break the symmetry in a way you can recognize from reciprocal crosses or testcross classes.

LOCK THESE IN

- No father to son passage for X linked traits.
- X linked recessive: males q, females q^2.
- Barr bodies = X − 1.
- Largest classes are parental. Smallest are double crossovers.
- RF from chiasmata = ½ × crossover fraction.
- LOD 3 linked; −2 excluded.

Morgan's cross

white female × red male

Eggs \ Sperm	X^+	Y
X^w	X^+X^w red daughter	X^wY white son
X^w	X^+X^w red daughter	X^wY white son

The reciprocal cross

red female × white male

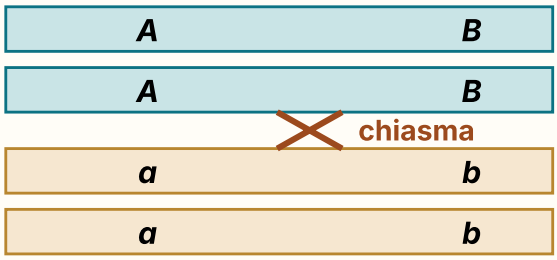
Eggs \ Sperm	X^w	Y
X^+	X^+X^w red daughter	X^+Y red son
X^+	X^+X^w red daughter	X^+Y red son

A son gets his only X from his mother, so sons show the mother's X linked trait.

Reciprocal crosses differ for X linked genes. For autosomal genes they match.

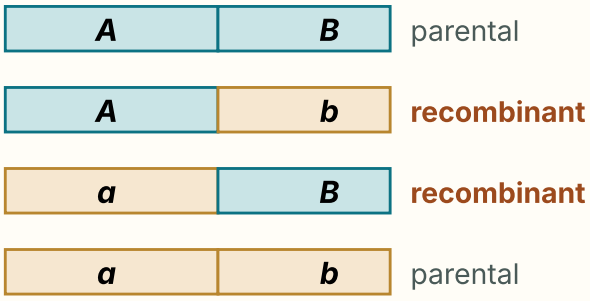
Crisscross inheritance. Fathers pass their X to every daughter and their Y to every son. That is why the two reciprocal crosses give different children.

Prophase I: one crossover between A and B



Two homologs, each two sister chromatids.
The crossover joins one chromatid of each.

The four products



2 of 4 recombinant = 50 percent

Even a crossover in every meiosis gives only half recombinant gametes, so RF tops out at 50 percent.
RF = ½ × fraction of meioses with a crossover in the interval. 1 percent RF = 1 map unit = 1 cM.

Why recombination frequency stops at 50 percent. A crossover involves only two of the four chromatids. Half of the products stay parental no matter what.

Formulas for sex linkage and mapping

Quantity	Formula	Note
Recombination frequency	recombinants ÷ total	1% = 1 cM
Expected DCO	$RF_1 \times RF_2 \times$ total	
Interference	I = 1 − observed/expected	
Haldane	$d = -\frac{1}{2} \ln(1 - 2r)$	no interference
Kosambi	$d = \frac{1}{4} \ln[(1 + 2r)/(1 - 2r)]$	interference
LOD, phase known	$\log_{10}[\theta^{R}(1 - \theta)^{NR} \div 0.5^{R + NR}]$	

Terms to define in one line

Term	Meaning
Heterogametic sex	the sex with two different sex chromosomes
Hemizygous	one copy of an X linked gene, as in males
Crisscross inheritance	sons like mothers, daughters like fathers
Barr body	the condensed, inactive X
Heteroplasmy	mixed normal and mutant organelle genomes
Coupling and repulsion	*AB*/*ab* versus *Ab*/*aB*
Chiasma	visible site of a crossover
Centimorgan	distance giving 1 percent recombination
Interference	one crossover discourages another nearby
LOD score	$\log_{10}$ odds of linkage versus none

Worked examples

WORKED EXAMPLE 1 · PHASE AND DISTANCE FROM A TESTCROSS

A testcross gives 412 *Ab*, 398 *aB*, 96 *AB* and 94 *ab*. Find the phase and the distance.

STEP 1 · PARENTALS

The large classes, *Ab* and *aB*, are parental, so the dihybrid was in **repulsion**.

STEP 2 · RECOMBINANTS

96 + 94 = 190 of 1,000.

STEP 3 · DISTANCE

RF = 0.19, so **19 cM**.

WORKED EXAMPLE 2 · INTERFERENCE

Two adjacent intervals are 12 and 15 cM. Among 2,000 offspring, 22 double crossovers appear. Find c.o.c. and I.

STEP 1 · EXPECTED

$0.12 \times 0.15 \times 2{,}000 = 36$.

STEP 2 · C.O.C.

$22 \div 36 =$ **0.61**.

STEP 3 · INTERFERENCE

$1 - 0.61 =$ **0.39**.

WORKED EXAMPLE 3 · A LOD WITH NO RECOMBINANTS

Eight phase known meioses show no recombinants. Find the LOD at $\theta = 0.05$.

STEP 1 · LIKELIHOODS

$L(0.05) = 0.95^8$. $L(0.5) = 0.5^8$.

STEP 2 · ODDS

$(0.95/0.5)^8 = 1.9^8$.

STEP 3 · LOG

$8 \times \log_{10} 1.9 = 8 \times 0.279 =$ **2.23**, short of 3.

WORKED EXAMPLE 4 · X LINKED FREQUENCIES

An X linked recessive trait affects 6 percent of males. Predict affected and carrier females.

STEP 1 · Q

Males show it at q = 0.06, so p = 0.94.

STEP 2 · AFFECTED FEMALES

q^2 = 0.0036, about **0.36 percent**.

STEP 3 · CARRIER FEMALES

2pq = 2 × 0.94 × 0.06 = **0.113, about 11 percent**.

WORKED EXAMPLE 5 · A TORTOISESHELL CROSS

A tortoiseshell female (X^OX^o) mates with an orange male (X^OY). Predict the kittens, ignoring white.

STEP 1 · DAUGHTERS

They get X^O from the father: 1/2 orange (X^OX^O) and 1/2 tortoiseshell.

STEP 2 · SONS

They get Y: 1/2 orange (X^OY) and 1/2 black (X^oY).

STEP 3 · CHECK

No son is tortoiseshell, because that needs two X chromosomes.

TRAPS PEOPLE FALL INTO

- **Assuming coupling.** Let the data show the phase.
- **Dropping doubles from an interval.** They count in both.
- **Calling sex limited traits X linked.** They are autosomal.
- **Confusing maternal effect with mtDNA inheritance.** Nuclear gene versus organelle genome.
- **Using the sperm to set sex in birds.** The ZW female's egg decides.
- **Treating RF near 50% as proof of separate chromosomes.** Distant syntenic genes look the same.

Self-test · Theme 2

1. A woman whose father had an X linked recessive condition has a son with an unaffected man. What is the chance the son is affected?

A 0

B 1/2

C 1/4

D 1/8

B. 1/2. She is an obligate carrier, having received her father's X. Each son has a 1/2 chance of her mutant X.

2. A fly with XO and two sets of autosomes is what sex?

A A fertile female

B A fertile male

C An intersex fly

D A sterile male

D. A sterile male. X:A = 0.5 makes a male. Without the Y, its sperm fertility genes are missing.

3. How many Barr bodies does a 47,XXX woman have?

A Two

B None

C One

D Three

A. Two. Three X chromosomes minus one active X leaves two inactive.

4. A father has a mitochondrial disorder. What is the risk to his children?

A All of them

B One quarter

C One half

D None at all

D. None at all. Sperm mitochondria are destroyed after fertilization, so mtDNA comes from the mother.

5. A snail is sinistral. What can you say for sure?

A Its offspring will be sinistral

B Its father was *dd*

C Its mother was *dd*

D It is *dd* itself

C. Its mother was *dd*. Coiling follows the mother's genotype. The snail's own genotype sets its offspring's coiling.

6. A chiasma forms between two genes in 24 percent of meioses. What is the map distance?

A 6 cM

B 12 cM

C 48 cM

D 24 cM

B. 12 cM. One crossover makes half the chromatids recombinant: 0.24 × 0.5 = 0.12.

7. In a three point cross the parentals are + *b* + and *a* + *c*, and the doubles are + + + and *a b c*. Which gene is in the middle?

A *c*

B None of them

C *b*

D *a*

C. *b*. Compare + *b* + with + + +. Only *b* differs.

8. Why does RF level off at 50 percent for distant genes?

A Only sister chromatids cross over at long range

B Odd and even numbers of crossovers become equally likely

C Distant genes cannot pair in prophase I at all

D Interference stops all crossovers past 50 cM

B. Odd and even numbers of crossovers become equally likely. An odd number of exchanges gives a recombinant and an even number restores the parental. At long range they balance.

9. Kosambi gives a smaller corrected distance than Haldane for the same r. Why?

A It uses base pairs instead of crossovers as units

B It assumes no interference at all between crossovers

C It applies only when r is above 0.5 in a cross

D It assumes interference already removed some doubles

D. It assumes interference already removed some doubles. Haldane assumes random crossovers. Kosambi allows interference, so it corrects less.

10. Three families give LOD scores of 1.2, 1.1 and 0.9 at θ = 0.1. What is the conclusion?

A. LOD 3.2 supports linkage

B. LOD scores cannot be added

C. LOD 1.07 is inconclusive

D. LOD 1.2 is the best estimate

A. LOD 3.2 supports linkage. Scores from independent families add: 1.2 + 1.1 + 0.9 = 3.2.

Read the full chapter: Chapter 3 · Chapter 4

THEME 3 · CHAPTERS 5 AND 6

Microbes and chromosomes

What to know

Bacteria are haploid, so mutations show at once. Replica plating finds auxotrophs, and the fluctuation test showed that mutations arise before selection. F^+ cells pass F, Hfr cells pass chromosome in order from *oriT*, and F′ cells make partial diploids. Time of entry maps genes on a 100 minute circle.

Transformation takes up free DNA and is blocked by DNase. Generalized transduction packages random 2 minute fragments, and the rarest three factor class marks the middle gene. Specialized transduction moves only genes beside the prophage. Benzer kept complementation (same gene?) apart from recombination (same site?), with RF = 2 × K12 titer ÷ B titer. RNA viruses mutate fast, and retroviruses reverse transcribe and integrate.

A chromosome needs origins, one centromere and two telomeres. Deletions cause pseudodominance, and duplications add dose. A crossover in a paracentric inversion loop gives a dicentric and an acentric, and in a pericentric loop it gives duplication plus deficiency.

Translocation carriers are semisterile from adjacent segregation, and Robertsonian carriers risk translocation Down syndrome.

Nondisjunction in meiosis I makes all four gametes abnormal, and in meiosis II half. Trisomies 21, 18 and 13 survive to birth. *AAaa* autotetraploids give 1:4:1 gametes and 35:1 on selfing. Triploids are nearly sterile. Allopolyploids are fertile new species. t(9;22) makes BCR-ABL1.

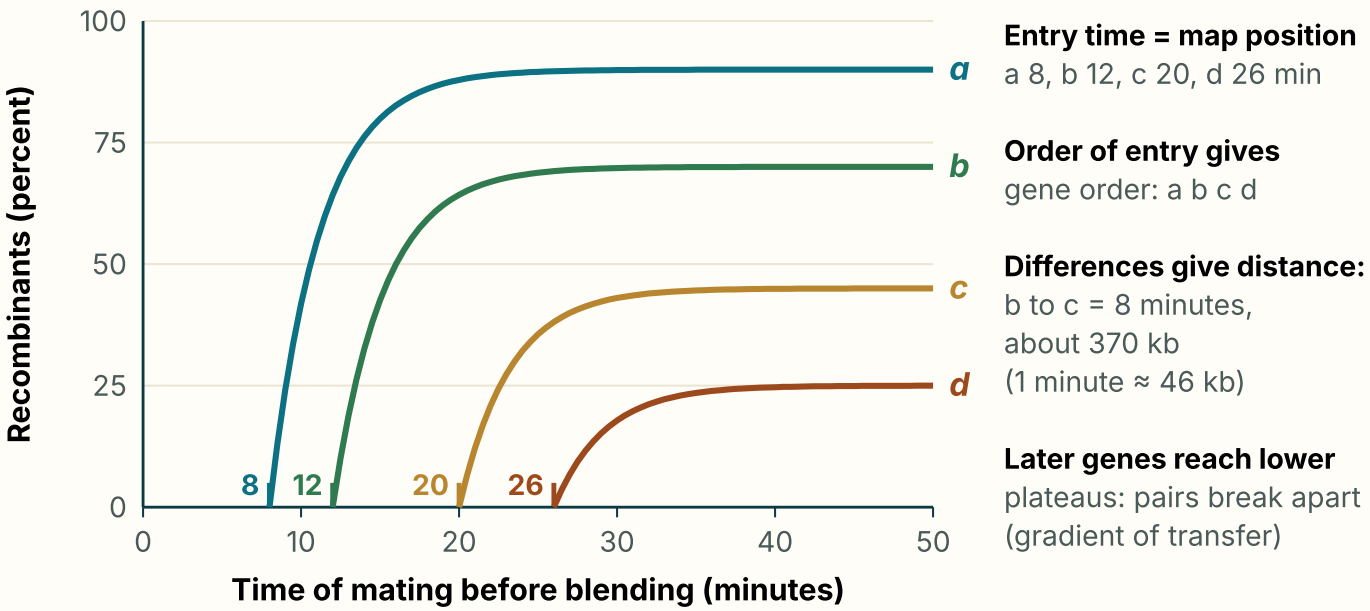
Plasmids replicate on their own: F for fertility, R for resistance, Col for colicins. A single crossover cannot bring donor DNA into a circular chromosome; it takes an even number, and RecA.

G-band notation counts outward from the centromere on p and q. FISH counts and locates targets, and microarrays find gains and losses but not balanced changes. Microdeletions flanked by repeats cause syndromes such as 22q11.2 deletion and Williams syndrome.

> **How the two chapters connect.** Bacteria and phages turned recombination into a mapping tool at the finest scale; chromosome mutations show the same breaks and joins at the coarsest. In both, ask what was gained, lost or moved, and whether the products are balanced.

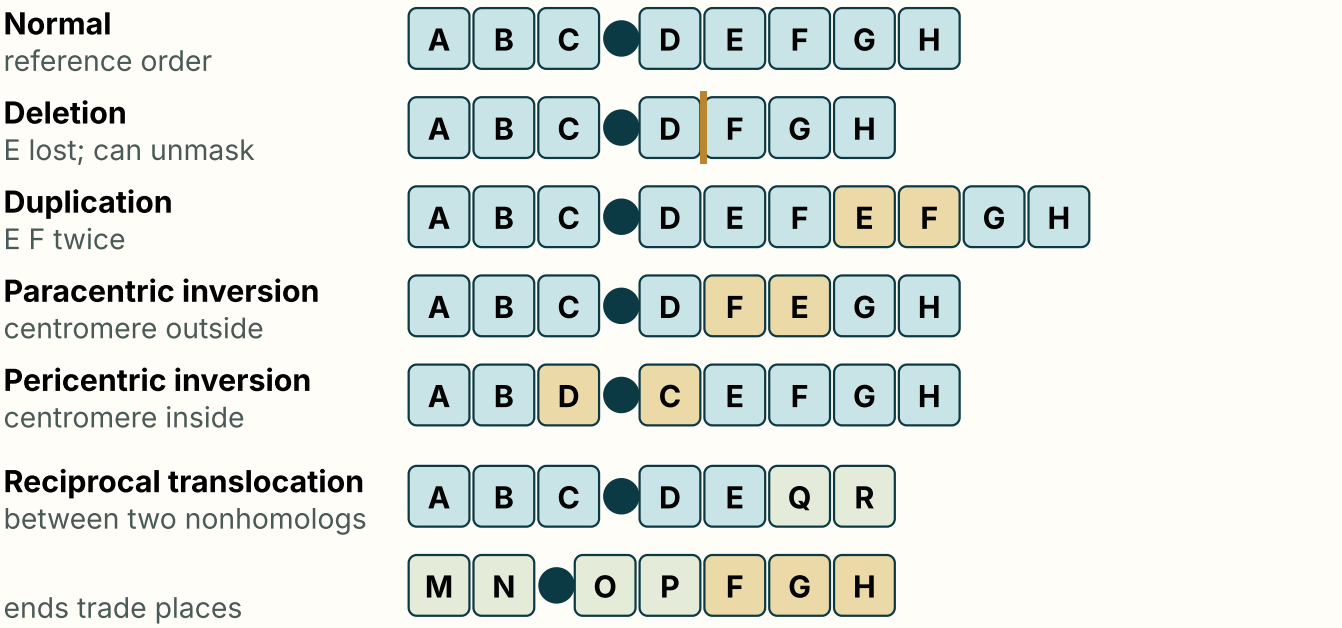
LOCK THESE IN

- DNase blocks transformation only.
- Hfr recipients stay F^-.
- Benzer RF doubles the K12 fraction.
- Paracentric: dicentric + acentric. Pericentric: duplication + deficiency.
- MI nondisjunction: both homologs. MII: two sister copies.
- Triploid balanced gametes = $2 \times (1/2)^x$.



Mapping by interrupted mating. Each gene first appears at its time of entry. Order of entry is gene order, and the gaps between entry times are distances in minutes.

Letters are gene blocks and the dark dot is the centromere. Gold marks the changed part.



Translocation start: A B C • D E F G H and M N • O P Q R. F G H and Q R trade places.
Duplications often arise by unequal crossing over. A deletion can unmask a recessive allele.

Rearrangements, block by block. Ask two questions of any rearrangement: is genetic material lost or gained, and does the changed segment include the centromere?

Formulas for microbes and chromosomes

Quantity	Formula	Note
Mutation rate (P_0)	$m = -\ln P_0$; rate = m/N	zeros avoid jackpots
Wu formula	$C = (1 - d/2)^3$	P1, minutes
Phage titer	plaques ÷ (mL × dilution)	
Arm ratio	q/p	> 3 acrocentric
Unbalanced from inversion	½ × loop crossover fraction	
Tetraploid *AAaa*	gametes 1:4:1; selfed 35:1	

Terms to define in one line

Term	Meaning
Auxotroph	needs a supplied nutrient to grow
Hfr	donor with F integrated into the chromosome
F′	F carrying a piece of chromosome
Cotransduction	two markers carried in one phage head
Prophage	phage genome integrated in the host
Cistron	unit of function defined by complementation
Pseudodominance	recessive allele shows opposite a deletion
Semisterility	about half the gametes abort, as in translocation carriers
Aneuploidy	gain or loss of single chromosomes
Allopolyploid	sets from two different species

Worked examples

WORKED EXAMPLE 1 · TRIPLOID FERTILITY

A triploid has x = 12. What fraction of its gametes are balanced?

STEP 1 · ALL SINGLE

$(1/2)^{12} = 1/4{,}096$.

STEP 2 · ALL DOUBLE

1/4,096.

STEP 3 · ADD

2/4,096 = **1/2,048**, about 0.05 percent.

WORKED EXAMPLE 2 · A ROBERTSONIAN CARRIER

A man carries der(14;21). With a normal egg, which outcomes are viable and what does each look like?

STEP 1 · HIS GAMETES

Six kinds: 14 + 21; der alone; der + 21; 14 alone; der + 14; 21 alone.

STEP 2 · ADD A NORMAL EGG

Normal; balanced carrier; translocation Down syndrome; monosomy 21; trisomy 14; monosomy 14.

STEP 3 · VIABLE

Only the first three survive to birth. The observed Down syndrome risk is lower than one in three, under 5 percent when the father is the carrier.

WORKED EXAMPLE 3 · A MUTATION RATE

Fifty cultures each grow to 2×10^8 cells. Twenty show no resistant colonies. Estimate the rate.

STEP 1 · P_0

20/50 = 0.40.

STEP 2 · M

$-\ln 0.40 = 0.916$ events per culture.

STEP 3 · RATE

$0.916 \div 2 \times 10^8 =$ **4.6×10^{-9} per division**.

WORKED EXAMPLE 4 · WU FORMULA

Two markers are cotransduced by P1 at a frequency of 0.60. Estimate their distance.

STEP 1 · SET UP

$0.60 = (1 - d/2)^3$.

STEP 2 · CUBE ROOT

$0.60^{1/3} = 0.843$, so $d/2 = 0.157$.

STEP 3 · DISTANCE

d = **0.31 minute**, about 14 kb.

TRAPS PEOPLE FALL INTO

- **Calling F^+ cells good chromosome donors.** Hfr cells are.
- **Forgetting Benzer's factor of 2.** The double mutant is invisible.
- **Using microarray for balanced translocations.** No gain or loss to see.
- **Calling all four crossover products in an inversion loop unbalanced.** Only two are.
- **Using the mean colony count for the rate.** Jackpots inflate it. Use the zero class.
- **Thinking Robertsonian carriers are affected.** Only redundant rRNA arms are lost.

Self-test · Theme 3

1. A colony grows on complete medium only, not on minimal plus methionine or minimal plus leucine. What might it need?

A. Both nutrients, or one not yet tested

B. Leucine alone and nothing else at all

C. Nothing, since it is a prototroph

D. Methionine alone and nothing else

A. Both nutrients, or one not yet tested. Neither single supplement rescues it. It may be a double auxotroph, or it may need another nutrient.

2. Interrupted mating shows gene *x* entering at 9 minutes and *y* at 26. How far apart are they?

A 35 minutes

B 26 minutes

C 9 minutes

D 17 minutes

D. 17 minutes. Map distance is the difference in entry times.

3. Which transfer needs no cell contact and resists DNase?

A Transformation

B Transduction

C Replica plating

D Conjugation

B. Transduction. DNA travels inside a phage head, so DNase cannot reach it and no contact is needed.

4. Two rII mutants fail to lyse K12(λ) together but give rare wild type recombinants in B. What does that mean?

A Same gene, same site

B Different genes, same site

C Same gene, different sites

D Different genes, different sites

C. Same gene, different sites. No complementation means one cistron. Recombination to wild type means the sites differ.

5. Which viruses must carry their own polymerase inside the virion?

A All bacteriophages

B Plus strand RNA viruses

C Minus strand RNA viruses

D Double stranded DNA viruses

C. Minus strand RNA viruses. A minus strand genome cannot be translated until a packaged polymerase copies it into mRNA.

6. A chromosome has p = 2.0 µm and q = 4.6 µm. How is it classified?

A Metacentric

B Telocentric

C Acrocentric

D Submetacentric

D. Submetacentric. q/p = 2.3, inside the 1.7 to 3.0 range.

7. What does a crossover inside a pericentric inversion loop produce?

A A dicentric chromatid and an acentric piece

B Chromatids with a duplication and a deficiency

C A Robertsonian fusion of the two arms

D Four balanced chromatids every time

B. Chromatids with a duplication and a deficiency. With the centromere inside the loop, each recombinant has one centromere but unbalanced ends.

8. A trisomy 21 child has two different chromosome 21 homologs from the mother. Where did nondisjunction occur?

A Maternal meiosis I

B Maternal meiosis II

C A mitotic error

D Paternal meiosis I

A. Maternal meiosis I. Two different maternal homologs mean the homologs failed to separate, which is meiosis I.

9. What fraction of offspring of an *AAaa* × *aaaa* testcross show the recessive phenotype?

A 1/4

B 1/6

C 1/2

D 1/36

B. 1/6. Only *aa* gametes from the tetraploid (1/6) give *aaaa* offspring.

10. Which cancer change is a fusion gene?

A BCR-ABL1 from t(9;22)

B *MYC* next to IGH

C *RB1* deletion

D *ERBB2* amplification

A. BCR-ABL1 from t(9;22). t(9;22) joins BCR and ABL1 into one gene. The others are amplification, enhancer moving and deletion.

Read the full chapter: Chapter 5 · Chapter 6

THEME 4 · CHAPTERS 7 AND 8

DNA to protein

What to know

Replication is semiconservative. Polymerases need primers and extend only 3′ ends, so the lagging strand is made as Okazaki fragments. Pol III builds, pol I removes primers and ligase seals. Eukaryotic origins are licensed in G1 and fired once in S. Telomerase extends the G-rich strand with its own RNA template.

Homologous recombination repairs breaks through resection, Rad51 invasion and Holliday junctions, and mismatches in heteroduplex cause gene conversion. Mutations are transitions or transversions and silent, missense, nonsense or frameshift. Each repair pathway has its disease: XP (NER), Lynch (mismatch repair), BRCA (HR).

RNA matches the coding strand with U for T. Bacterial sigma reads −35 and −10 elements. Eukaryotic pol II needs general factors and a phosphorylated CTD. Pre-mRNA is capped, spliced (GU...A...AG, lariat) and polyadenylated.

The code is a nonoverlapping triplet with 61 sense codons and 3 stops. Wobble lets one tRNA read several codons. The ribosome uses A, P and E sites and is a ribozyme. Bacteria start at Shine Dalgarno with fMet, and eukaryotes scan from the cap to a Kozak AUG.

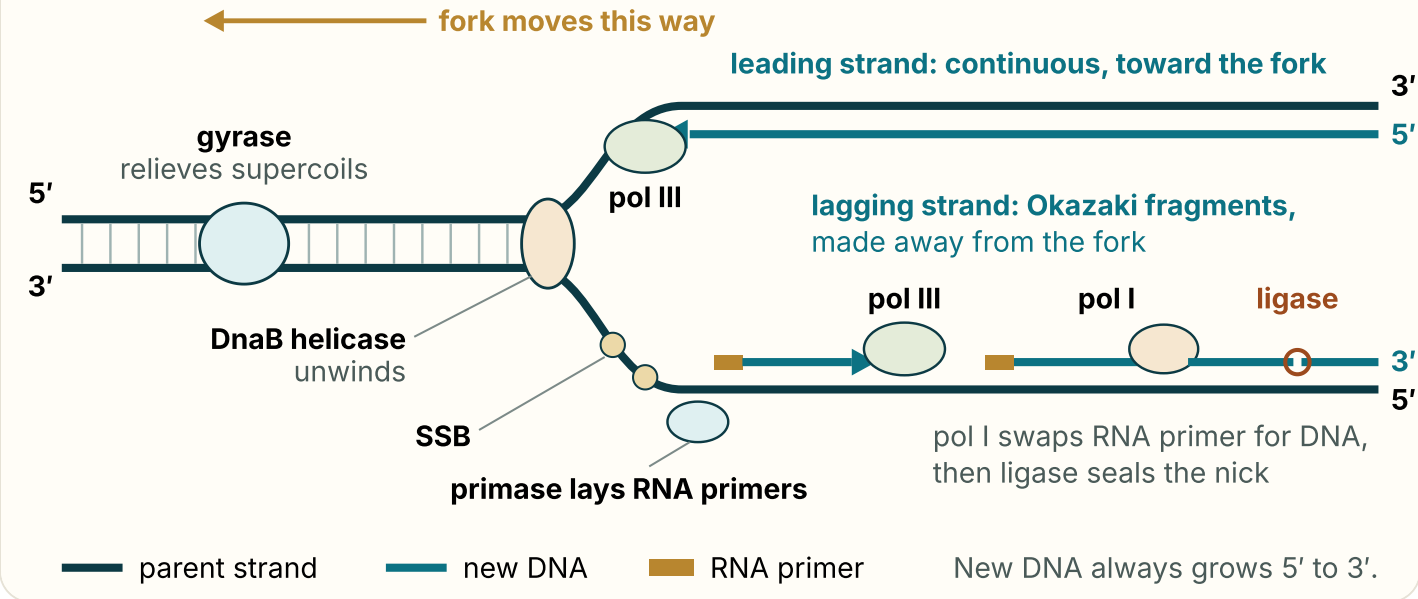
Fidelity has three layers: base selection, proofreading by the 3′ to 5′ exonuclease and mismatch repair. Spontaneous damage includes depurination, deamination (5-methylcytosine to thymine at CpG hot spots) and 8-oxoguanine, which pairs with A.

Eukaryotic mRNAs are protected and checked. The cap and tail aid export and translation, alternative splicing makes isoforms, editing changes coded sequence, and nonsense mediated decay destroys mRNAs with premature stops upstream of an exon junction.

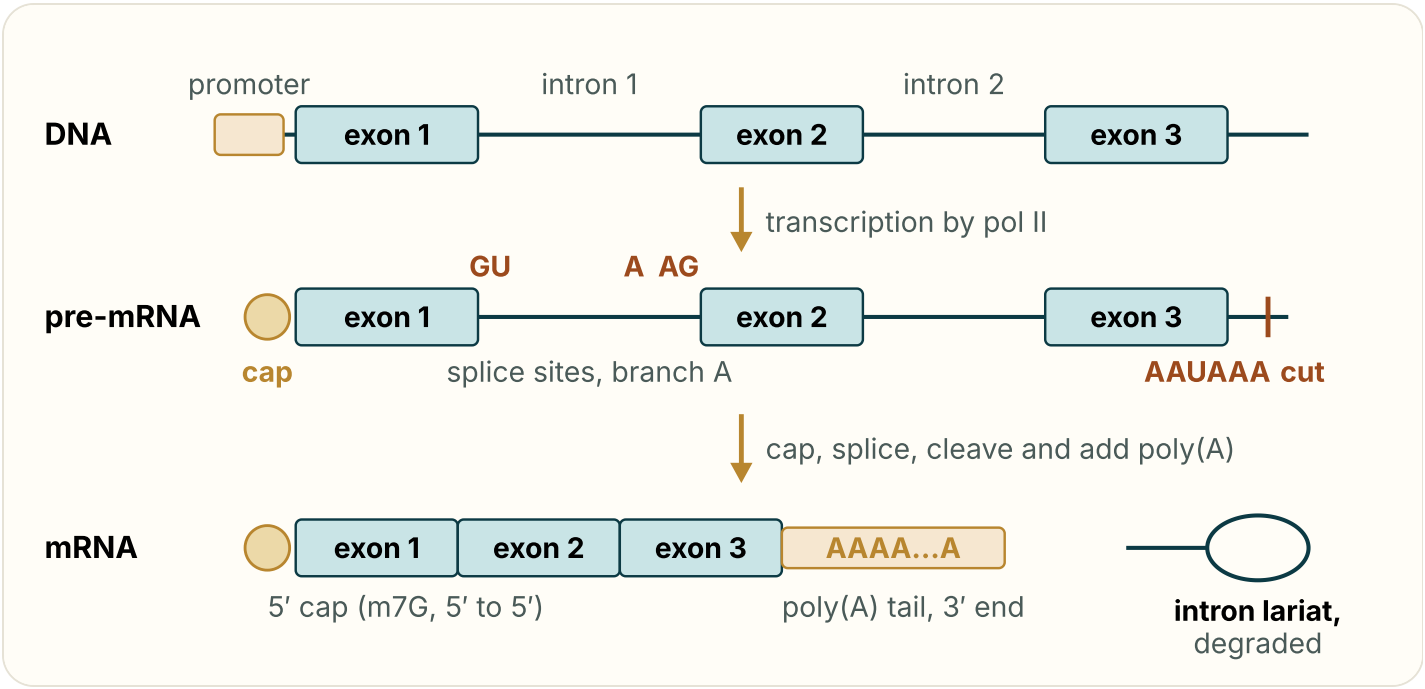
> **How the two chapters connect.** The same rules run through both chapters: polymerases add to 3′ ends, strands are antiparallel, and base pairing carries information. A mutation in Chapter 7 becomes a changed codon, a lost splice site or a premature stop in Chapter 8.

LOCK THESE IN

- Hybrid fraction = $2/2^n$.
- Okazaki fragments come from 3′ only synthesis plus antiparallel strands.
- Transition: purine to purine. Transversion: purine to pyrimidine.
- RNA = coding strand with U.
- Exon skip with length not divisible by 3: frameshift.
- Wobble: G reads C/U; U reads A/G; I reads U/C/A.



One fork, two ways of copying. Polymerase only extends a 3′ end, so one new strand runs toward the fork and the other is stitched together from Okazaki fragments.



From pre-mRNA to mRNA. The cap goes on first, introns leave as lariats, and the tail is added after a cut downstream of AAUAAA. All of it happens while pol II is still working.

Molecular numbers

Quantity	Value or formula	Note
Fork speed	about 1,000 nt/s bacteria; 50 nt/s eukaryotes	
Okazaki length	1,000 to 2,000 nt bacteria; 100 to 200 eukaryotes	
Error rate after all layers	10^{-9} to 10^{-10}	
Germ line rate	1.2×10^{-8}/bp/generation; about 74 per child	
Codons	64 = 61 + 3 stops	AUG start
Protein cost	about 4 high energy bonds per residue	

Terms to define in one line

Term	Meaning
Semiconservative	each daughter keeps one old strand
Okazaki fragment	short primed piece of lagging strand
Telomerase	reverse transcriptase with its own RNA template
Gene conversion	nonreciprocal transfer, as in 6:2 octads
Transversion	purine to pyrimidine or the reverse
Sigma factor	directs bacterial polymerase to promoters
CTD	pol II tail whose phosphorylation recruits processing
Lariat	looped intron freed by splicing
Wobble	flexible pairing at the codon's third base
Peptidyl transferase	rRNA center that makes peptide bonds

Worked examples

WORKED EXAMPLE 1 · REPLICATION TIME

A bacterial chromosome is 5.0 Mb with one origin and forks at 1,000 nt per second. How long does one round take?

STEP 1 · PER FORK

$5.0 \times 10^6 \div 2 = 2.5 \times 10^6$ nt.

STEP 2 · TIME

$2.5 \times 10^6 \div 1{,}000 = 2{,}500$ s, about **42 minutes**.

WORKED EXAMPLE 2 · A ONE BASE DELETION

An mRNA reads 5′-AUG GCA UUC AAA UGA GCU-3′. The A of GCA is deleted. Translate before and after.

STEP 1 · BEFORE

AUG GCA UUC AAA UGA: Met-Ala-Phe-Lys, then stop.

STEP 2 · AFTER

AUG GCU UCA AAU GAG CU...: Met-Ala-Ser-Asn-Glu and onward.

STEP 3 · READ IT

A one base deletion shifts every later codon and reads straight through the old stop. This is a **frameshift**.

WORKED EXAMPLE 3 · A RANDOM COPOLYMER

A random copolymer has U and G in a 3:1 ratio. Predict the amino acid shares.

STEP 1 · CODON ODDS

UUU 27/64; UUG, UGU, GUU 9/64 each; UGG, GUG, GGU 3/64 each; GGG 1/64.

STEP 2 · GROUP

Phe (UUU) 27. Leu (UUG) 9. Cys (UGU) 9. Val (GUU + GUG) 12. Trp (UGG) 3. Gly (GGU + GGG) 4.

STEP 3 · CHECK

27 + 9 + 9 + 12 + 3 + 4 = 64. Phe is **about 42 percent**.

WORKED EXAMPLE 4 · A TELOMERE BUDGET

Telomeres start at 9,000 bp, lose 150 bp per division and trigger senescence at 4,500 bp. How many divisions remain?

STEP 1 · ALLOWED LOSS

9,000 − 4,500 = 4,500 bp.

STEP 2 · DIVISIONS

4,500 ÷ 150 = **30**.

TRAPS PEOPLE FALL INTO

- **Calling the lagging strand 3′ to 5′.** All new strands grow 5′ to 3′.
- **Saying telomerase copies both strands.** Only the G-rich 3′ strand.
- **Copying the template as the RNA.** The RNA matches the coding strand.
- **Pairing anticodon and codon in parallel.** Pair them antiparallel.
- **Calling a damaged base a mutation.** Replication must fix it first.
- **Treating UTRs as introns.** UTRs are parts of exons.

Self-test · Theme 4

1. Fully ^{15}N labeled cells grow three generations in ^{14}N. What fraction of DNA molecules is hybrid?

A 1/8

B 3/4

C 1/2

D 1/4

D. 1/4. 2 hybrid molecules out of $2^3 = 8$.

2. What does the beta clamp give DNA polymerase III?

A Primer removal at each fragment

B Its 3′ to 5′ proofreading

C High processivity on the template

D The ability to start chains

C. High processivity on the template. The ring keeps the polymerase on the DNA so it can add thousands of nucleotides.

3. Most human somatic cells stop dividing after 40 to 60 doublings. Why?

A Telomeres shorten without telomerase

B Mismatch repair runs out of enzyme

C Okazaki fragments grow longer each time

D Origins can be licensed only 60 times

A. Telomeres shorten without telomerase. Short telomeres trigger a damage response and senescence. This is the Hayflick limit.

4. GAG to GTG at codon 6 of beta globin is which kind of change?

A. A frameshift by one base

B. A transition and silent mutation

C. A transition and nonsense mutation

D. A transversion and missense mutation

D. A transversion and missense mutation. A to T swaps a purine for a pyrimidine, and Glu becomes Val.

5. Lynch syndrome comes from defects in which repair pathway?

A. Base excision repair

B. Nucleotide excision repair

C. DNA mismatch repair

D. Homologous recombination

C. DNA mismatch repair. MSH2, MLH1 and partners fix replication errors. Their loss gives microsatellite instability and colorectal cancer.

6. What sequence in a bacterial RNA makes an intrinsic terminator?

A. A C rich rut site bound by Rho

B. A GC rich hairpin then a run of U

C. An AAUAAA signal and a GU element

D. The −10 element TATAAT

B. A GC rich hairpin then a run of U. The hairpin pulls on the polymerase while the weak A:U hybrid lets the RNA go.

7. Which polymerase makes 5S rRNA and tRNAs in eukaryotes?

A DNA primase complex

B RNA polymerase III

C RNA polymerase II

D RNA polymerase I

B. RNA polymerase III. Pol I makes the large rRNAs and pol II makes pre-mRNAs.

8. What is the first step in removing an intron?

A The cap is removed from the RNA

B Exon 1 attacks the 3′ splice site

C The poly(A) tail is trimmed back

D The branch A attacks the 5′ site

D. The branch A attacks the 5′ site. The 2′-OH of the branch A forms the lariat. Exon joining is the second step.

9. Which tRNA anticodon (5′ to 3′) can read both UUA and UUG?

A AAU

B GAA

C UAA

D CAA

C. UAA. The wobble U pairs with A or G at the codon's third base. CAA reads only UUG, and GAA reads UUC and UUU.

10. In bacteria, what brings the first tRNA to the ribosome?

A. IF2 places fMet-tRNA in the P site

B. EF-G moves fMet-tRNA to the E site

C. RF1 places it beside the start codon

D. EF-Tu places fMet-tRNA in the A site

A. IF2 places fMet-tRNA in the P site. The initiator goes straight to the P site with IF2 and GTP. EF-Tu delivers elongation tRNAs.

Read the full chapter: Chapter 7 · Chapter 8

THEME 5 · CHAPTERS 9 AND 10

Regulation and tools

What to know

Cis sites affect only their own molecule, and trans factors diffuse. lac is negative and inducible with a positive CAP-cAMP layer, so it is high only with lactose present and glucose absent. trp is negative and repressible and is tuned by attenuation. In partial diploids, I^- is recessive, I^S dominant and O^c cis dominant.

Eukaryotic activators are modular, and enhancers act at a distance and in either orientation through Mediator. Acetylation and H3K4me3 mark active genes, and H3K27me3 and H3K9me3 silent ones. DNMT1 copies CpG methylation. miRNAs pair through the seed (2 to 8), and siRNAs slice.

Restriction sites appear once per 4^n bp. PCR doubles each cycle, and qPCR fold change = $2^{-\Delta\Delta Ct}$. Sanger read short to long gives the new strand. Coverage C = LN/G, with e^{-C} missed.

Cas9 cuts 3 bp upstream of an NGG PAM. NHEJ leaves indels and HDR copies a donor. About 1.5% of the human genome codes for protein and about half is transposon derived. Orthologs split at speciation and paralogs at duplication, and ω = dN/dS shows selection.

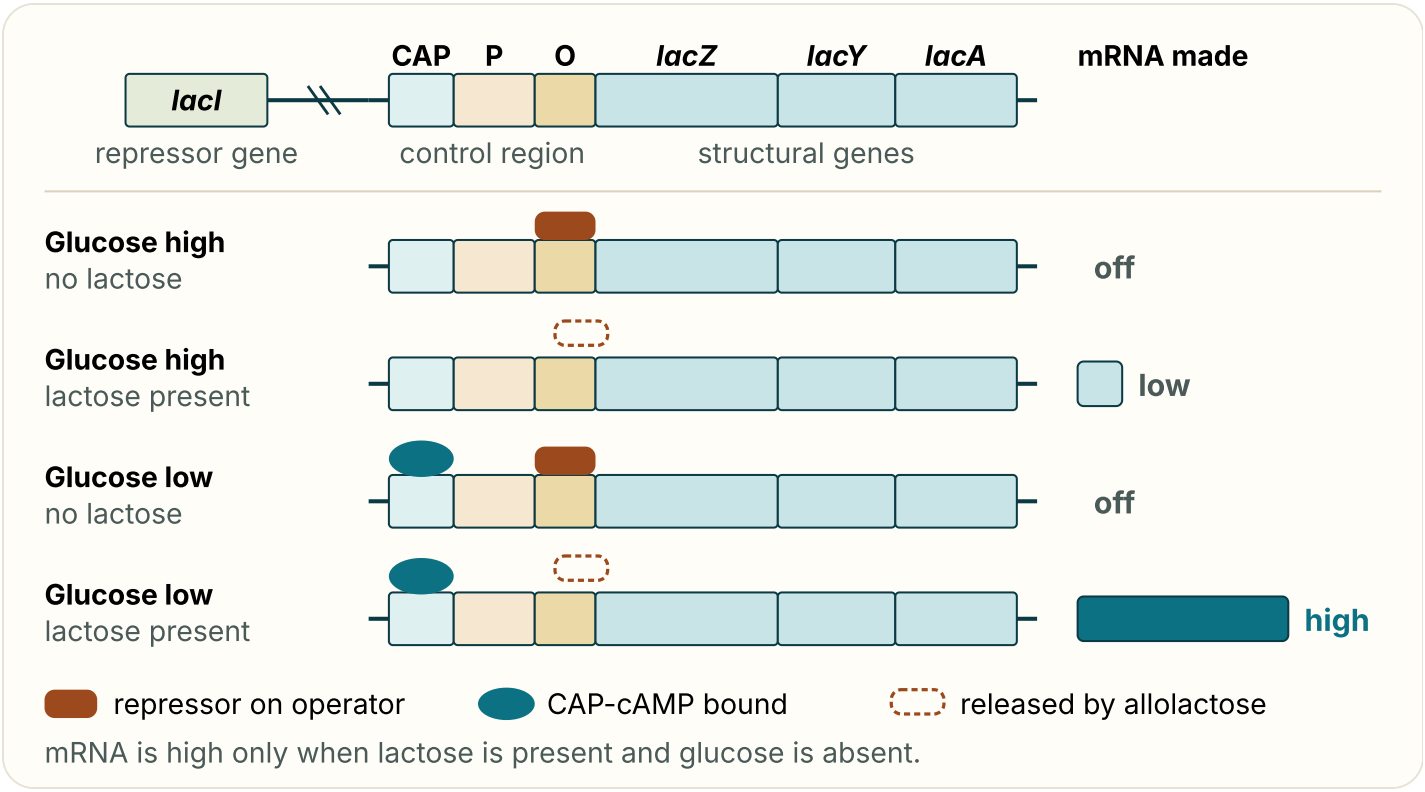
DNA methylation is set by DNMT3A and DNMT3B, copied by DNMT1 at hemimethylated sites and removed by TET enzymes. Bisulfite turns unmethylated C into T while methylated C stays C. Imprinting at *Igf2* and *H19* uses CTCF at a methylated control region.

Base editors change single bases without a double strand break, prime editors write small edits, and dCas9 fusions turn genes down or up. RNA-seq counts must be normalized (counts per million) before comparing samples, and changes are reported as $\log_2$ fold change.

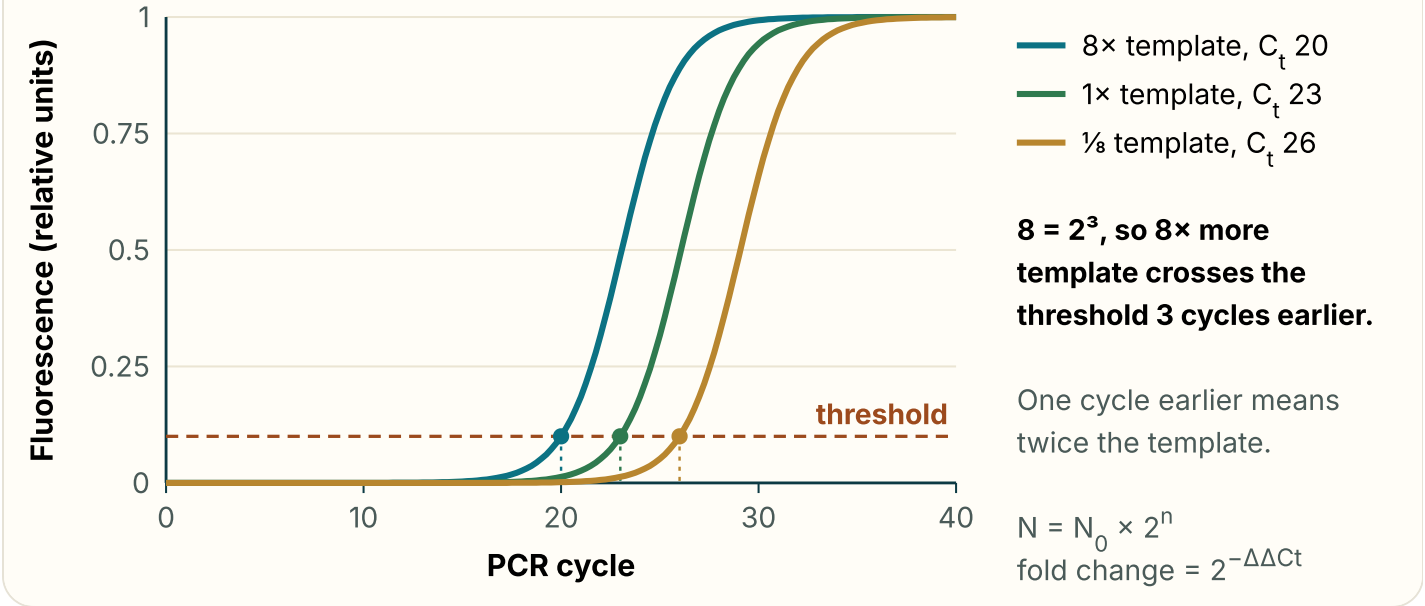
How the two chapters connect. Chapter 9 explains how cells choose which genes to use; Chapter 10 gives you the tools to watch and change those choices. A reporter assay, a bisulfite read, a qPCR fold change and a CRISPR knockout are all ways to test a regulatory idea.

LOCK THESE IN

- Negative or positive: the protein. Inducible or repressible: the signal.
- O^c acts only in cis.
- $N = s/k$; $k = \ln 2/t_{1/2}$.
- qPCR: $2^{-\Delta\Delta Ct}$.
- Coverage LN/G; missed e^{-C}.
- Guide = 20 nt before NGG, never the PAM.



Two switches on one operon. The repressor is the negative switch and CAP-cAMP is the positive one. Transcription is high only when lactose is present and glucose is absent.



Reading C_t in real time PCR. More starting template crosses the threshold sooner. Each doubling moves C_t one cycle earlier, which is why fold change is a power of 2.

Formulas for regulation and tools

Quantity	Formula	Note
Steady state	$N = s \div (\ln 2/t_{1/2})$	97% in 5 half lives
Site frequency	4^n	
PCR	$N_0 \times 2^n$	
qPCR	$2^{-\Delta\Delta Ct}$	normalize first
Coverage	$C = LN/G$; e^{-C} missed	
dN/dS	$\omega < 1$ purifying; > 1 positive	divide by sites

Terms to define in one line

Term	Meaning
Cis-acting	affects only its own DNA molecule
Trans-acting	diffusible product acting anywhere
Attenuation	early termination set by leader translation
Enhancer	distance and orientation independent activator site
Mediator	bridges activators and pol II
Hemimethylated	methylated on the old strand only
Seed region	miRNA nucleotides 2 to 8
PAM	NGG next to the Cas9 target
Coverage	average reads per base
Ortholog	homolog split by speciation

Worked examples

WORKED EXAMPLE 1 · A LAC PARTIAL DIPLOID

Chromosome: $I^- O^c Z^+ Y^-$. F′: $I^+ O^+ Z^- Y^+$. Glucose absent. Predict each enzyme.

STEP 1 · REPRESSOR

The F′ makes working repressor, which reaches every O^+.

STEP 2 · B-GALACTOSIDASE

Its only working gene sits beside O^c, so it is **constitutive**.

STEP 3 · PERMEASE

Its only working gene sits beside O^+ on the F′, so it is **inducible**.

WORKED EXAMPLE 2 · PCR AND COVERAGE

(a) A PCR starts with 2,000 copies. How many after 25 perfect cycles? (b) A 4.6 Mb genome gets 200,000 reads of 150 bases. Find the coverage and the bases missed.

STEP 1 · PCR

$2{,}000 \times 2^{25} = 2{,}000 \times 33{,}554{,}432 =$ **about 6.7×10^{10}**.

STEP 2 · COVERAGE

$150 \times 200{,}000 \div 4{,}600{,}000 =$ **6.5x**.

STEP 3 · MISSED

$e^{-6.52} \times 4.6 \times 10^6 =$ **about 6,800 bases**.

WORKED EXAMPLE 3 · A SECOND QPCR

A target has C_t 25.0 in control and 23.0 in treated cells. The reference is 18.0 and 18.5. Find the fold change.

STEP 1 · ΔC_T

Control 7.0. Treated 4.5.

STEP 2 · $\Delta\Delta C_T$

$4.5 - 7.0 = -2.5$.

STEP 3 · FOLD

$2^{2.5} =$ **5.7 fold up**.

WORKED EXAMPLE 4 · STEADY STATE

An mRNA is made at 15 per minute with a half life of 2 minutes. Find its steady state level.

STEP 1 · K

0.693 ÷ 2 = 0.347 per minute.

STEP 2 · N

15 ÷ 0.347 = **about 43 molecules**.

TRAPS PEOPLE FALL INTO

- **Calling trp positive control.** TrpR is a repressor.
- **Expecting a distant O^+ to rescue O^c.** Operators work in cis only.
- **Reporting raw C_t gaps.** Normalize to a reference gene.
- **Including the PAM in the guide.** The guide is the 20 nt protospacer.
- **Copying the miRNA seed as the target.** Use the reverse complement.
- **Comparing raw RNA-seq counts.** Normalize for depth first.

Self-test · Theme 5

1. An mRNA has a half life of 4 minutes and is made at 10 per minute. What is its steady state level?

A. About 58 molecules
B. About 40 molecules
C. About 29 molecules
D. About 14 molecules

A. About 58 molecules. k = 0.693/4 = 0.173. N = 10/0.173 = 57.7.

2. A strain is I^S/F′ I^+, with O^+ next to every *lacZ*$^+$. How is β-galactosidase made?

A. It is made only with glucose

B. It is constitutive

C. It is uninducible

D. It is inducible

C. It is uninducible. The superrepressor binds every O^+ and never lets go, even with inducer.

3. Tryptophan is scarce and the leader is translated normally. Which leader structure forms?

A. No structure at all

B. The 2:3 antiterminator

C. The 1:2 pairing only

D. The 3:4 terminator

B. The 2:3 antiterminator. The ribosome stalls at the Trp codons on region 1, leaving region 2 free to pair with region 3.

4. Which mark is the classic sign of an active promoter?

A. CpG island methylation

B. H3K9me3

C. H3K27me3

D. H3K4me3

D. H3K4me3. H3K4me3 marks active promoters. The others mark silent chromatin.

5. What does Dicer do in the miRNA pathway?

A. Exports the pre-miRNA through the nuclear pore

B. Cuts the loop off the pre-miRNA in the cytoplasm

C. Slices targets that pair along their full length

D. Crops the pri-miRNA hairpin in the nucleus

B. Cuts the loop off the pre-miRNA in the cytoplasm. Drosha crops in the nucleus, Exportin-5 exports, Dicer cuts the loop and Argonaute holds the guide.

6. About how often does a 6 bp site appear in random DNA?

A. Once every 65,536 bp

B. Once every 256 bp

C. Once every 1,296 bp

D. Once every 4,096 bp

D. Once every 4,096 bp. $4^6 = 4{,}096$.

7. The target gene's $\Delta\Delta C_t$ is −2. What is the fold change?

A. 2 fold down

B. 4 fold down

C. 4 fold up

D. 2 fold up

C. 4 fold up. $2^{-(-2)} = 2^2 = 4$.

8. Sanger fragments, shortest to longest, end in G, A, A, C. What is the template, written 5′ to 3′?

- A GTTC
- B GAAC
- C CAAG
- D CTTG

A. GTTC. The new strand is 5′-GAAC-3′. Its complement, read 3′ to 5′, is CTTG, so the template written 5′ to 3′ is GTTC.

9. Which outcome follows Cas9 cutting with no donor DNA?

- A Silencing with no DNA change
- B Small indels from NHEJ
- C A C to T edit by deamination
- D A precise knock-in from HDR

B. Small indels from NHEJ. Without a template, NHEJ rejoins the ends and often adds or removes a few bases.

10. Human α-globin and β-globin are what kind of homologs?

- A Orthologs
- B Synonyms
- C Paralogs
- D Pseudogenes

C. Paralogs. They arose by a duplication within one lineage. Human and mouse β-globin are orthologs.

Read the full chapter: Chapter 9 · Chapter 10

Traits and populations

What to know

With n additive genes, an F_2 has $2n + 1$ classes and $(1/4)^n$ at each extreme. Variance divides by $n - 1$, and independent variances add. The midparent regression slope is h^2. $H^2 = V_G/V_P$ and $h^2 = V_A/V_P$. Twins give $h^2 \approx 2(r_{MZ} - r_{DZ})$.

$R = h^2S$ and $S = i\sigma_P$. Heritability describes a population in an environment, never a person or a difference between groups. QTL mapping uses LOD scores in crosses. GWAS uses LD and the 5×10^{-8} threshold.

Hardy Weinberg gives p^2, $2pq$ and q^2. For a rare recessive, carriers are about $2q$. The HW chi square has df 1 for two alleles. Inbreeding moves Fpq from heterozygotes into each homozygote, and first cousins give $F = 1/16$.

Migration: $\Delta q = m(q_m - q)$. Drift removes $1/(2N_e)$ of heterozygosity per generation and fixes neutral alleles at their frequency. Selection weights by fitness and divides by $\bar{w}$. Heterozygote advantage gives $\hat{q} = s/(s + t)$. The clock is $K = 2\mu T$.

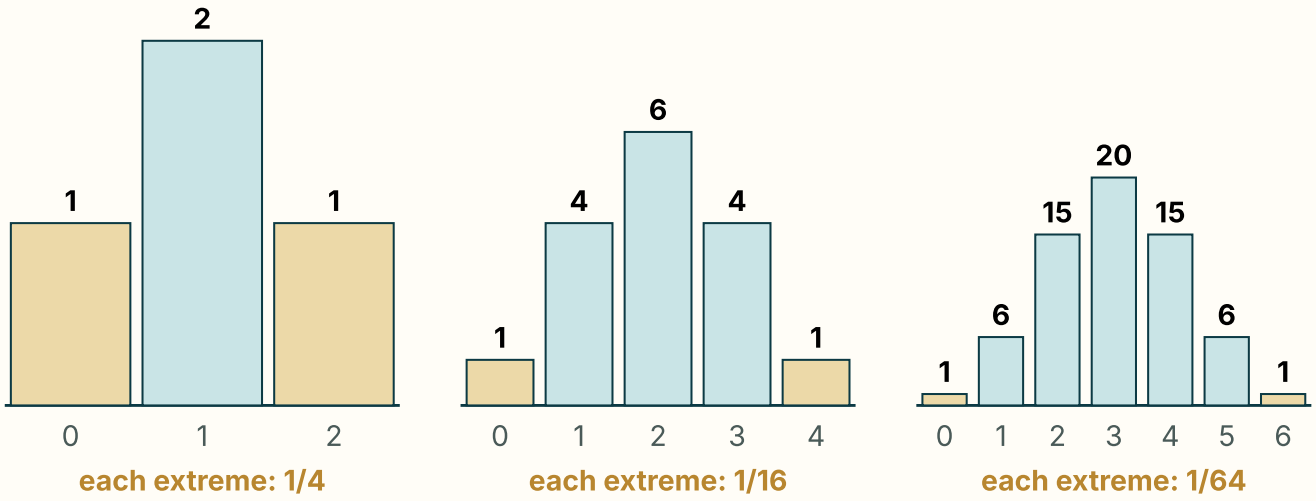
Threshold traits look present or absent but rest on continuous liability. Relatives' risk falls fast with distance and rises with more or more severely affected relatives. GWAS hits are mostly regulatory, highly polygenic and often only neighbors of the causal variant.

Founder effects and bottlenecks are drift in small groups. Selection against a rare recessive is slow because carriers hide it. Mutation selection balance holds harmful recessive alleles near $\sqrt{(u/s)}$. Species form mostly in allopatry, and polyploidy gives fast sympatric speciation in plants.

> **How the two chapters connect.** Quantitative genetics follows variances; population genetics follows allele frequencies. Both rest on the same fact: parents pass alleles, not genotypes, so only additive effects and allele frequencies carry forward.

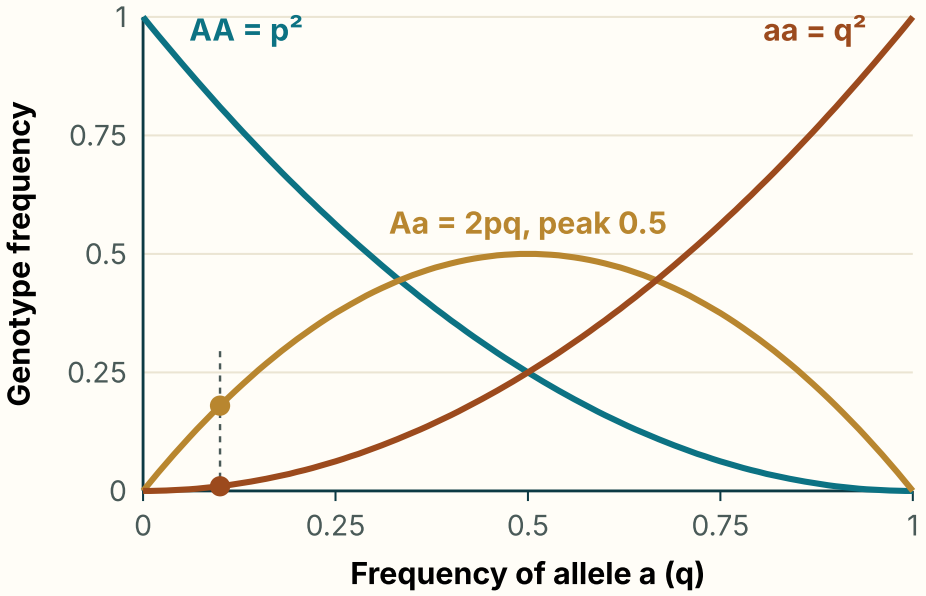
LOCK THESE IN

- $2n + 1$ classes; $(1/4)^n$ extremes.
- $h^2 \le H^2$; $R = h^2S$.
- Carriers $\approx 2q$; HW chi square df 1.
- $F = \Sigma(1/2)^n(1 + F_A)$.
- P(fix neutral) = frequency.
- $\hat{q} = s/(s + t)$; $K = 2\mu T$.



x axis: number of additive (capital) alleles. Bars drawn to scale; the tallest bar, 2/4, is one half. More genes give more, smaller steps. Add environmental noise and the steps blur into a bell curve.

Many genes, small effects. With n additive genes the F_2 has $2n + 1$ classes in binomial proportions, and $(1/4)^n$ match each parent.



At q = 0.1:
affected aa = 0.01
carriers Aa = 0.18
Carriers outnumber affected 18 to 1.

Rare recessive:
q = √(affected)
carriers ≈ 2q

$p + q = 1$
$p^2 + 2pq + q^2 = 1$

Hardy Weinberg at every allele frequency. Heterozygotes can never pass 50 percent. When an allele is rare, almost every copy hides in a carrier.

Formulas for traits and populations

Quantity	Formula	Note
Heritability	$H^2 = V_G/V_P$; $h^2 = V_A/V_P$	
Selection response	$R = h^2S = i\,h^2\sigma_P$	
Hardy Weinberg	$p^2 + 2pq + q^2$	
Inbreeding	$q^2 + Fpq$	raises recessive frequency
Effective size	$4N_mN_f/(N_m + N_f)$	
Balance	$s/(s + t)$; $\sqrt{(u/s)}$; u/s	

Terms to define in one line

Term	Meaning
Meristic trait	counted trait with many classes
Additive variance	the part parents pass on
Narrow sense heritability	V_A/V_P
Realized heritability	R/S from a selection experiment
QTL	region holding genes for a quantitative trait
Linkage disequilibrium	nonrandom association of nearby alleles
Identical by descent	two copies of one ancestral allele
Effective population size	ideal size drifting at the same rate
Heterozygote advantage	Aa fitter than either homozygote
Molecular clock	steady neutral substitutions used to date splits

Worked examples

WORKED EXAMPLE 1 · HETEROZYGOTE ADVANTAGE

Fitnesses are AA 0.8, Aa 1 and aa 0.4. Find the equilibrium frequency of *a*.

STEP 1 · SELECTION COEFFICIENTS

s = 1 − 0.8 = 0.2 against AA. t = 1 − 0.4 = 0.6 against aa.

STEP 2 · EQUILIBRIUM

$\hat{q} = s/(s + t) = 0.2/0.8 =$ **0.25**.

WORKED EXAMPLE 2 · A SELECTION RESPONSE

A trait has mean 200 and phenotypic SD 20. The top 10 percent are kept (i = 1.76) and $h^2 = 0.30$. Predict the next mean.

STEP 1 · S

1.76 × 20 = 35.2.

STEP 2 · R

0.30 × 35.2 = 10.56.

STEP 3 · NEW MEAN

200 + 10.56 = **about 210.6**.

WORKED EXAMPLE 3 · MIGRATION OVER FIVE GENERATIONS

An island has q = 0.10. Each generation 5 percent of breeders come from a mainland with q = 0.50. Find q after five generations.

STEP 1 · FORMULA

$q_t = q_m + (q_0 - q_m)(1 - m)^t$.

STEP 2 · PLUG IN

$0.50 + (-0.40)(0.95)^5 = 0.50 - 0.40 \times 0.774$.

STEP 3 · ANSWER

0.50 − 0.310 = **0.19**, moving toward 0.50 but never past it.

WORKED EXAMPLE 4 · ABO FREQUENCIES

In a population, 36 percent are type O and 45 percent are type A. Find the three allele frequencies and predict types B and AB.

STEP 1 · R

$r = \sqrt{0.36} = 0.6$.

STEP 2 · P

$p^2 + 2(0.6)p = 0.45$ gives p = 0.3.

STEP 3 · Q

q = 1 − 0.6 − 0.3 = 0.1.

STEP 4 · PREDICT

$B = q^2 + 2qr = 0.01 + 0.12 =$ **0.13**. AB = 2pq = **0.06**. Check: 0.36 + 0.45 + 0.13 + 0.06 = 1.00.

TRAPS PEOPLE FALL INTO

- **Treating heritability as personal.** It describes population variation.
- **Using df 2 for HW.** Two alleles give df 1.

- **Thinking inbreeding changes allele frequency.** Only genotype frequencies.
- **Forgetting the 2 in the clock.** Both lineages change.
- **Using the arithmetic mean for N_e.** Use the harmonic mean.
- **Reading a tall Manhattan point as weak.** Taller means smaller P.

Self-test · Theme 6

1. In an F_2, 1/16 of plants match each parent. How many additive genes, and how many classes?

A. 16 genes and 33 classes

B. 4 genes and 9 classes

C. 2 genes and 4 classes

D. 2 genes and 5 classes

D. 2 genes and 5 classes. $(1/4)^2 = 1/16$, and $2n + 1 = 5$.

2. $V_P = 50$, $V_A = 20$, $V_D = 10$ and $V_E = 20$. What are H^2 and h^2?

A. $H^2 = 0.6$ and $h^2 = 0.4$

B. $H^2 = 0.4$ and $h^2 = 0.6$

C. $H^2 = 0.4$ and $h^2 = 0.2$

D. $H^2 = 0.6$ and $h^2 = 0.2$

A. $H^2 = 0.6$ and $h^2 = 0.4$. $V_G = 30$, so $H^2 = 30/50$. $h^2 = 20/50$.

3. MZ twins correlate at 0.60 and DZ twins at 0.40. What is h^2?

A 0.20

B 0.40

C 0.60

D 0.80

B. 0.40. $2(0.60 - 0.40) = 0.40$.

4. A selected group is 8 units above the mean and the offspring are 2 units above. What is the realized heritability?

A 4.00

B 0.16

C 0.40

D 0.25

D. 0.25. R/S = 2/8.

5. On a Manhattan plot, which point is genome wide significant?

A $-\log_{10}P = 8.1$

B $P = 0.001$

C $P = 1 \times 10^{-6}$

D $-\log_{10}P = 6.9$

A. $-\log_{10}P = 8.1$. The bar is 7.3 ($P = 5 \times 10^{-8}$). 8.1 is above it.

6. A recessive trait shows in 1 of 900 people. What is the carrier frequency?

A. About 0.033

B. About 0.130

C. About 0.064

D. About 0.0011

C. About 0.064. q = 1/30 = 0.033. 2pq = 2 × 0.967 × 0.0333 = 0.064.

7. What is F for a child of first cousins once removed?

A. 1/16

B. 1/32

C. 1/8

D. 1/64

B. 1/32. Two common ancestors, each in a loop of six: $2 \times (1/2)^6 = 1/32$.

8. A population has 1,000, then 20, then 1,000 breeders. Which is closest to N_e?

A. About 1,000

B. About 673

C. About 20

D. About 57

D. About 57. Harmonic mean: 3 ÷ (0.001 + 0.05 + 0.001) = 3 ÷ 0.052 = 57.7.

9. A new neutral mutation arises once in a population of 500 diploids. What is its chance of fixation?

A 1/2

B 1/250

C 1/1,000

D 1/500

C. 1/1,000. One copy among 2N = 1,000 copies.

10. What does ω = dN/dS of 2.1 in a viral surface protein suggest?

A Positive selection for amino acid change

B A molecular clock that has stopped

C Strong purifying selection on the protein

D Neutral evolution as in a pseudogene

A. Positive selection for amino acid change. ω above 1 means amino acid changes were favored, as expected for a protein escaping immunity.

Read the full chapter: Chapter 11 · Chapter 12

THEME 7 · CHAPTERS 13 AND 14

Development, cancer and the clinic

What to know

Cells keep a full genome and differ by expression. Maternal effect phenotypes follow the mother. Fly segmentation runs maternal gradients, gap bands, 7 pair rule stripes, 14 segment polarity stripes and then Hox identity. Hox genes are colinear and share the homeobox. The ABC model builds flowers.

CDKs need cyclins. Rb holds E2F until G1 cyclin and CDK complexes phosphorylate it. p53 induces p21 or apoptosis. Oncogenes gain function with one hit, and tumor suppressors lose function with two hits, often through LOH. Cancer is multistep: incidence rises as age^{k-1}.

In families: AD (1/2, male to male), AR (1/4, sibling carrier 2/3), X linked recessive (half of a carrier's sons) and mitochondrial (maternal). q = √incidence, and carriers are about 2q. Multifactorial risks follow the liability threshold model and the Carter effect.

PPV depends on prevalence. Bayes runs prior × conditional = joint, then normalize. Ethics rest on consent, the right not to know, testing children only for childhood benefit, cascade testing, GINA's limits and equity. Testing and reproductive decisions belong to the family.

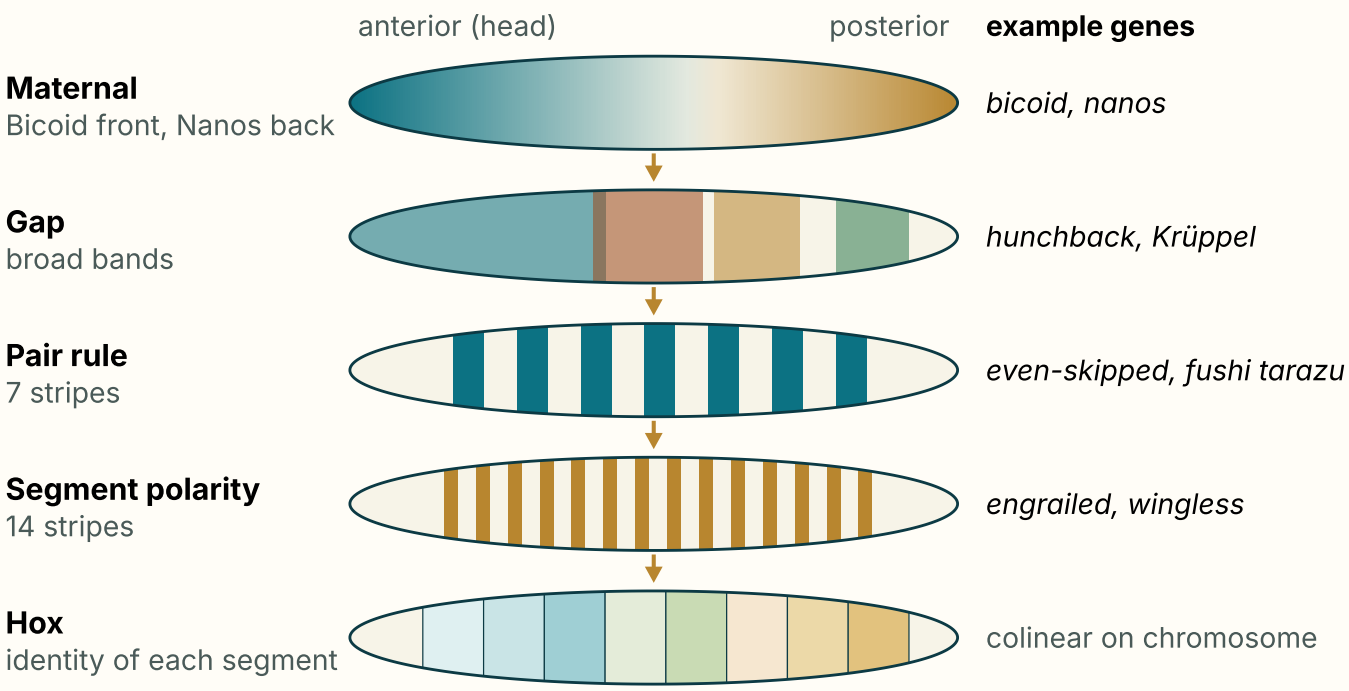
Checkpoints stop the cycle; they do not repair. Chk1 blocks Cdc25 at G2/M, and Mad2 blocks Cdc20 until every kinetochore is attached. The colorectal sequence runs *APC*, *KRAS*, *SMAD4* and *TP53*, and PARP inhibitors exploit synthetic lethality in BRCA deficient tumors.

Match the test to the variant: karyotype for large and balanced changes, microarray for copy number, sequencing for small variants, and special tests for repeats and methylation. A variant of uncertain significance should not guide care. Newborn screening finds treatable conditions such as PKU before harm.

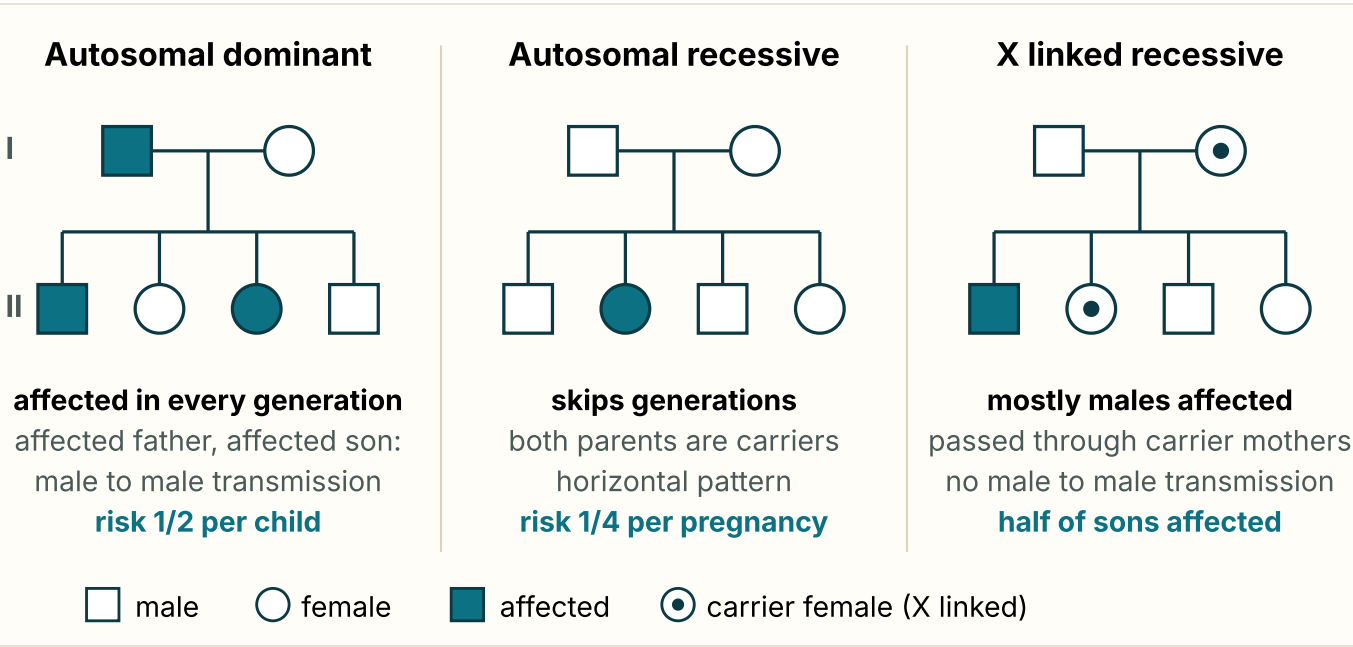
> **How the two chapters connect.** Development and cancer use the same genes: signals, transcription factors, cyclins and checkpoints. The clinic then applies everything from Mendel to Bayes to real families, and every decision about testing belongs to the people being tested.

LOCK THESE IN

- Maternal effect: mother's genotype.
- Oncogene: one hit. Tumor suppressor: two hits.
- Incidence ∝ age^{k-1}.
- Sibling of AR patient: 2/3 carrier.
- PPV = TP/(TP + FP).
- Bayes: prior, conditional, joint, posterior.



Each tier reads the one above. Gradients become bands, bands become 7 stripes, 7 become 14, and Hox genes tell each segment what to be.



Reading a pedigree. Ask three questions: does it skip generations, does it pass father to son, and are mostly males affected?

Formulas for the clinic

Quantity	Formula	Note
Carrier frequency	$2pq \approx 2\sqrt{\text{incidence}}$	
Couple risk	$P_1 \times P_2 \times 1/4$	
PPV	TP ÷ (TP + FP)	falls with prevalence
Odds ratio	(ad) ÷ (bc)	1 = no effect
Edwards	$\sqrt{\text{incidence}}$	first degree
Bayes	joint ÷ sum of joints	

Terms to define in one line

Term	Meaning
Genomic equivalence	differentiated cells keep the full genome
Morphogen	gradient that gives positional information
Homeobox	180 bp sequence for the homeodomain
Restriction point	late G1 commitment to divide
Loss of heterozygosity	loss of the remaining normal allele
Synthetic lethality	losing both of two genes kills the cell
Consultand	the person seeking counseling
Carter effect	higher risk to relatives of the rarer affected sex
Positive predictive value	share of positives that are true
Cascade testing	testing relatives outward from a known variant

Worked examples

WORKED EXAMPLE 1 · PPV AT LOW PREVALENCE

A test has 95 percent sensitivity and 98 percent specificity. Prevalence is 1 in 100. Find the PPV.

STEP 1 · PER 10,000

100 affected, 9,900 unaffected.

STEP 2 · TRUE AND FALSE POSITIVES

TP = 95. FP = 0.02 × 9,900 = 198.

STEP 3 · PPV

95 ÷ 293 = **0.32**, about one in three positives.

WORKED EXAMPLE 2 · BAYES AND AGE

A person at 1/2 prior risk for Huntington disease is unaffected at an age by which 70 percent of carriers show symptoms. What is the updated risk?

STEP 1 · PRIOR

Carrier 1/2; noncarrier 1/2.

STEP 2 · CONDITIONAL

Unaffected: 0.30 if a carrier, 1 if not.

STEP 3 · JOINT

0.15 and 0.50.

STEP 4 · POSTERIOR

0.15 ÷ 0.65 = **3/13, about 23 percent**. Whether to test stays the person's choice.

WORKED EXAMPLE 3 · A NEGATIVE CARRIER SCREEN

A partner from a group with carrier frequency 1/40 tests negative on a screen that detects 80 percent of carriers. What is the residual carrier risk?

STEP 1 · PRIOR

Carrier 1/40 = 0.025; noncarrier 0.975.

STEP 2 · CONDITIONAL

A negative result: 0.20 if a carrier, 1 if not.

STEP 3 · JOINT

0.025 × 0.20 = 0.005; 0.975 × 1 = 0.975.

STEP 4 · POSTERIOR

0.005 ÷ 0.980 = **about 1 in 196**.

WORKED EXAMPLE 4 · ONE UNAFFECTED SON

A woman's mother carries hemophilia A. The woman has one unaffected son. What is her carrier risk, and her next son's risk?

STEP 1 · PRIOR

1/2 and 1/2.

STEP 2 · CONDITIONAL

Unaffected son: 1/2 if a carrier, 1 if not.

STEP 3 · JOINT

1/4 and 1/2.

STEP 4 · POSTERIOR

(1/4) ÷ (3/4) = **1/3**. Next son: 1/3 × 1/2 = **1/6**.

TRAPS PEOPLE FALL INTO

- **Calling tumor suppressor predisposition recessive.** It is inherited as dominant.
- **Using the embryo's genotype for a maternal effect.** Use the mother's.
- **Equating sensitivity with PPV.** PPV moves with prevalence.
- **Ignoring new evidence in risk.** Use Bayes.
- **Testing children for adult onset conditions by default.** Test only for childhood benefit.
- **Assuming GINA covers life insurance.** It does not.

Self-test · Theme 7

1. Which cells can form the placenta as well as the embryo?

A. Multipotent blood stem cells

B. Totipotent cells such as the zygote

C. Pluripotent inner cell mass cells

D. Unipotent progenitor cells

B. Totipotent cells such as the zygote. Only totipotent cells make extraembryonic tissue. Inner cell mass cells are pluripotent.

2. Loss of an *Ultrabithorax* function turns the third thoracic segment into a copy of the second. What does this show?

A. Losing a Hox gene makes a segment more anterior

B. Hox genes set the number of segments only

C. Hox genes act only in the adult fly

D. Losing a Hox gene makes a segment more posterior

A. Losing a Hox gene makes a segment more anterior. The more anterior Hox program takes over, so the fly grows a second pair of wings.

3. An *Arabidopsis* mutant lacks C function. What are its whorls, outside in?

A. Sepal, sepal, carpel, carpel

B. Carpel, stamen, stamen, carpel

C. Sepal, petal, petal, sepal

D. Petal, petal, stamen, stamen

C. Sepal, petal, petal, sepal. Without C, A spreads into whorls 3 and 4. A + B gives petals and A alone sepals.

4. Which protein links mitotic entry to Wee1 removal?

A The p16 inhibitor

B The Rb protein

C Cyclin D with CDK4

D Cdc25 phosphatase

D. Cdc25 phosphatase. Cdc25 removes Wee1's inhibitory phosphate from CDK1, and active CDK1 boosts Cdc25 in return.

5. HPV E6 and E7 cause cancer mainly by doing what?

A Amplifying ERBB2

B Fusing BCR and ABL1

C Disabling p53 and Rb

D Activating KRAS

C. Disabling p53 and Rb. E6 targets p53 for destruction and E7 binds Rb, removing both main brakes.

6. Incidence rises $3^4 = 81$ fold from age 25 to age 75. About how many rate limiting steps?

A 5

B 4

C 81

D 3

A. 5. Age triples, so $3^{k-1} = 81$ gives $k - 1 = 4$ and $k = 5$.

7. A woman's brother has a recessive condition. Her partner's carrier chance is 1/40. What is the risk for their first child?

A 1/80

B 1/240

C 1/160

D 1/320

B. 1/240. Her carrier chance is 2/3. So 2/3 × 1/40 = 1/60, and 1/60 × 1/4 = 1/240.

8. In a case control study, 150 of 500 cases and 100 of 500 controls carry an allele. What is the odds ratio?

A About 1.50

B About 0.58

C About 2.00

D About 1.71

D. About 1.71. (150 × 400) ÷ (350 × 100) = 60,000 ÷ 35,000 = 1.71.

9. A healthy 8 year old has a parent with Huntington disease. What does guidance usually say about predictive testing?

A Test now so the family can plan ahead

B Test only the parent again, not the child

C Defer it until the child can choose as an adult

D Test now, since early treatment prevents it

C. Defer it until the child can choose as an adult. There is no childhood benefit, so testing waits to preserve the child's own future choice.

10. Which result is a secondary finding?

A. A *CFTR* variant found in a child tested for CF

B. A trisomy found on a prenatal karyotype

C. A VUS in the gene that was the test's target

D. A *BRCA2* variant in a seizure workup

D. A *BRCA2* variant in a seizure workup. A secondary finding is medically actionable and unrelated to the reason for testing. People may opt out of receiving them.

Read the full chapter: Chapter 13 · Chapter 14

ONE PAGE

Cram sheet

Every ratio, formula and rule from all 14 chapters on one sheet. Cover the right column and rebuild each row from memory.

Ratios

Situation	Ratio
Monohybrid F_2; testcross	3:1 (1:2:1); 1:1
Dihybrid F_2; testcross	9:3:3:1; 1:1:1:1
Incomplete dominance or codominance	1:2:1
Recessive lethal, visible heterozygote	2:1
Epistasis	9:3:4, 12:3:1, 9:7, 15:1, 13:3, 9:6:1
Morgan cross B F_2	1:1:1:1 (red and white in each sex)
Sex influenced F_2	3:1 in one sex, 1:3 in the other
Autotetraploid *AAaa*	gametes 1:4:1; selfed 35:1; testcross 5:1
Polygenes, n genes	$2n + 1$ classes; $(1/4)^n$ extremes

Probability and statistics

Name	Formula	Note
Product; sum	P(A)P(B); P(A) + P(B)	and; or
Conditional	P(A and B)/P(B)	2/3 rule
Binomial	$[n!/(s!\ t!)]\ p^s q^t$	
Chi square	$\Sigma(O - E)^2/E$; df = classes − 1 (− 1 more per estimated frequency)	3.841, 5.991, 7.815, 9.488
Variance; SD; SE	$\Sigma(x - \bar{x})^2/(n - 1)$; √; s/√n	
Covariance; r; b	cov; $cov/(s_x s_y)$; cov/s_x^2	
Poisson zero class	e^{-mean}	P_0, coverage, two hits
Bayes	prior × conditional = joint; joint/sum = posterior	

Mapping and microbes

Name	Formula	Note
RF	recombinants/total; from chiasmata ½ × fraction	1% = 1 cM; max 50%
Three point	interval = (singles + DCO)/total; outside = sum	
Interference	c.o.c. = obs/exp; I = 1 − c.o.c.	
Haldane; Kosambi	−½ ln(1 − 2r); ¼ ln[(1 + 2r)/(1 − 2r)]	
LOD	$\log_{10}[L(\theta)/L(0.5)]$	≥ 3 linked; ≤ −2 excluded
Conjugation	distance = entry time difference; circle = 100 min	
Wu	$C = (1 - d/2)^3$	
Benzer RF	2 × K12 titer ÷ B titer	
Mutation rate	$m = -\ln P_0$; rate = m/N	

Molecules and tools

Name	Formula or value	Note
Meselson and Stahl	hybrid = $2/2^n$	
Origins needed	length ÷ (2 × speed × S seconds)	
Telomere budget	(start − critical)/loss per division	
Codons	64; 61 sense; 3 stop; 3 frames per strand	
Protein energy	$2n + 1 + 2(n - 1) + 1 \approx 4n$	
Steady state	$N = s/k$; $k = \ln 2/t_{1/2}$	
Site frequency; PCR	4^n; $N_0 \times 2^n$	
qPCR	$2^{-\Delta\Delta Ct}$	
Coverage	$C = LN/G$; e^{-C} missed	
Selection on proteins	$\omega = dN/dS$	< 1 purifying

Traits, populations and the clinic

Name	Formula	Note
Heritability	$H^2 = V_G/V_P$; $h^2 = V_A/V_P$; $2(r_{MZ} - r_{DZ})$	
Selection	$R = h^2S$; $S = i\sigma_P$	
Hardy Weinberg	p^2, $2pq$, q^2; carriers $\approx 2q$	X: males q
Inbreeding	$q^2 + Fpq$; $F = \Sigma(1/2)^n(1 + F_A)$	cousins 1/16
Migration; drift	$m(q_m - q)$; H loss $1/(2N_e)$	
Balance	$s/(s + t)$; $\surd(u/s)$; u/s	
Clock	$K = 2\mu T$	
Age incidence	incidence $\propto t^{k-1}$	
Clinic	PPV = TP/(TP + FP); OR = ad/bc; Edwards $\surd$incidence	

Twelve rules that settle most questions

Topic	The rule
Phenotype or genotype	Pick one and use it for every gene in the product.
Known information	Cut away ruled out outcomes before multiplying.
Pedigrees	Unaffected parents, affected child: recessive. Male to male: not X linked.
Linkage	Largest classes are parental; smallest are doubles.
Cis and trans	Sites act in cis; products act in trans.
Complementation	Wild type F_1: different genes.
Strands	RNA matches the coding strand; pair codon and anticodon antiparallel.
Frames	An indel or skipped exon not divisible by 3 shifts the frame.
Chromosomes	Microarrays miss balanced rearrangements.
Heritability	It describes population variation in one environment.
Cancer	Oncogenes need one hit; tumor suppressors need two.
Counseling	Update risk with Bayes. Decisions belong to the family.

Pedigree and family risk quick table

Situation	Risk
AD heterozygote × unaffected	1/2 of children
Two AR carriers	1/4 affected; unaffected child 2/3 carrier
XR carrier mother × unaffected father	1/2 of sons affected; 1/2 of daughters carriers
XR affected father	all daughters carriers; no affected sons
XD affected father	all daughters affected; no sons
Mitochondrial, affected mother	all children may inherit; variable from heteroplasmy
Imprinted gene, paternal expression	carrier father 1/2 affected; carrier mother 0
First cousin parents	F = 1/16; about 2 to 3 points above background

Enzymes and proteins worth naming

Molecule	Job
Primase; pol III; pol I; ligase	primers; main synthesis; primer removal; sealing
Telomerase (TERT + TERC)	extends G-rich 3′ strand
Rad51 (RecA); BRCA2	strand invasion; loading Rad51
Sigma; Rho	promoter recognition; termination helicase
TBP; TFIIH	TATA binding; DNA opening and CTD serine 5 kinase
Spliceosome (U1, U2, U4, U5, U6)	intron removal by two transesterifications
Aminoacyl tRNA synthetase	charges each tRNA
DNMT1; DNMT3A/B; TET	copies; sets; removes methylation
Drosha; Dicer; Argonaute	crop; cut; silence
Cas9	cuts 3 bp upstream of NGG
Rb; E2F; p53; p21	brake; S phase activator; damage sensor; CDK inhibitor

Which test answers which question

Question	Best test
Extra or missing whole chromosome	karyotype or microarray
Balanced translocation	karyotype or FISH (not microarray)
Small deletion or duplication	chromosomal microarray
Known familial variant	targeted variant test
Unknown cause in a child	microarray, then exome or genome
Repeat expansion	PCR sizing or Southern blot
Imprinting disorder	methylation test
Methylation at each CpG	bisulfite sequencing

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