

INHERITANCE BIOLOGY

GENETICS



Dr. KAILASH CHOUDHARY

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PREFACE

Why do children resemble their parents? Why does a disorder appear in one generation, skip the next and return in the third? Why do some characters run true in a family while others appear once and never again? These are the questions genetics was invented to answer, and they are as old as agriculture.

Genetics is the study of heredity — of genes, of how they are transmitted, and of everything that follows from the way they work. The characters it accounts for range from the obvious and physical to the whole of health and disease. Like every science it has a vocabulary of its own, and the first of its words is the **gene**: the unit of heredity, and the thing that is actually passed on. The modern subject can be traced to the middle of the nineteenth century and to Gregor Mendel's patient analysis of inheritance in the garden pea. Before Mendel, heredity was largely a matter of speculation; after him it became an experimental science with laws that could be tested by counting.

The first half of the twentieth century built the framework — the chromosome theory, linkage and mapping, mutation, and the one-gene-one-enzyme relationship. The second half supplied the molecular explanation beneath it. The Human Genome Project delivered its draft sequence in 2001 and a complete, gap-free sequence in 2022, and next-generation sequencing has since turned what was once a national undertaking into a routine experiment. The pace of discovery has risen accordingly, and so have the expectations placed on anyone learning the subject. This book sets out that subject as it stands today.

Its fifteen chapters follow a deliberate order. The first four develop Mendelian inheritance and everything that complicates it — dominance relationships, lethal and multiple alleles, gene interaction and epistasis, imprinting, sex linkage, sex-influenced and sex-limited characters, and maternal effect. Chapters 5 and 6 build the genetic and physical map. Chapter 7 leaves the nucleus for mitochondrial and chloroplast inheritance, Chapter 8 turns to human pedigrees and karyotypes, and Chapter 9 to the continuous variation of quantitative characters. Chapter 10 covers bacterial and phage genetics, Chapters 11 to 13 the mutation, rearrangement and recombination of DNA itself, Chapter 14 the behaviour of genes in populations, and Chapter 15 the model organisms in which almost all of it was discovered.

Many books on genetics already exist; fewer of them set out to make a reader want to go on reading. Every topic here therefore begins from the concept rather than from the terminology, and the explanation is kept as plain as the material allows. Each chapter opens with its learning objectives and closes with a Rapid Revision summary. Every figure has been drawn or redrawn for print. **Key Point** panels state what must be remembered, **Do You Know?** panels give the history and the oddities that make the subject worth remembering, and each chapter ends with solved objective problems in the pattern of the national examinations, worked through in full rather than merely answered.

The aim throughout is confidence: that a student appearing for an examination after graduation should meet no question in genetics that this book has not prepared them for. Every effort has been made to keep the text free of error, though I am under no illusion that it is. Comments, corrections and suggestions from teachers, students and every other reader in the life sciences are welcome, and will shape the next edition.

Kailash Choudhary

ACKNOWLEDGEMENT

*Writing **Genetics** — **The Inheritance Biology** has been a long and rewarding journey, and not a solitary one. Every chapter reached its final shape only after a great deal of time, argument and revision, and a great many people gave both.*

My first thanks go to the students of the Institute for Advanced Studies (IFAS). Teaching them is what forced the ideas in this book into their simplest form; their questions decided what needed more explanation, what needed a figure, and what could safely be left out. Whatever clarity this book has, they are the reason for it.

I owe a particular debt to **Er. Radheshyam Choudhary** (Director) and **Dadasaheb Sondge** (COO), IFAS Publications, whose support in more ways than can be listed here is the reason the book exists in its present form.

My special thanks to **Pranshu Dwivedi**, and **Vishal Bhujbal** for their suggestions and for contributions of real value throughout. I am grateful to the reviewers — **Lalji Kannoujiya**, and **Dr. Rakesh Kumawat** — who read the manuscript closely and improved its contents in ways large and small.

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Kailash Choudhary

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CHAPTER

1

Mendelian Genetics

Since prehistoric times, the observation that living things inherit traits from their parents has been used to improve crop plants and animals through selective breeding. But how are characters passed from one generation to the next, and what are the fundamental principles involved? We can now answer these questions thanks to the pioneering work of Gregor Johann Mendel. By studying clearly defined, contrasting traits in the garden pea, counting large progenies and analysing them mathematically, he showed that inheritance is governed by discrete, particulate factors — what we now call genes — that segregate and assort according to simple, predictable rules.

This chapter develops Mendel's two laws from his original pea experiments, links them to the movement of chromosomes during meiosis, and equips you with the quantitative tools that are used to predict and evaluate the outcomes of genetic crosses. These principles form the foundation on which every later topic in inheritance biology is built.

LEARNING OBJECTIVES

- Trace Mendel's work and the rediscovery of his laws.
- Define the core terminology of transmission genetics.
- Explain the monohybrid cross and the law of segregation.
- Relate segregation to chromosome behaviour in meiosis.
- Use the test cross and Punnett square to interpret results.
- Explain the dihybrid cross and independent assortment.
- Apply probability, branch diagrams and the chi-square test.
- Recognise the departures that modify Mendelian ratios and where each is treated.

1.1 Mendel and His Work

Heredity is the transmission of characters from parents to offspring, and **genetics** is the science that explains how this happens — the scientific study of inheritance and variation, of how certain qualities or traits are passed from parents to offspring as a result of differences in the DNA sequence. William Bateson coined the word 'genetics' in 1905, in a letter proposing it for 'the science of heredity and variation', and used it publicly at the Third International Conference on Hybridisation in 1906.

For most of human history, heredity was understood only through the practical art of selective breeding, while its mechanism remained a mystery clouded by the mistaken idea of **blending inheritance**. Gregor Mendel transformed this situation.

1.1.1 Mendel's Work

Mendel was born into a German-speaking family in a village in Northern Moravia (now part of the Czech Republic) on 20 July 1822, and was baptised two days later. During his childhood he worked as a gardener and studied beekeeping. From 1840 to 1843 he studied practical and theoretical philosophy and physics at the Philosophical Institute of the University of Olomouc. His family valued education but had few resources, so he struggled to pay for his schooling.

His professor recommended Mendel to the Augustinian monks at Brunn (now Brno), who valued science, research and education. He became a monk in part because it enabled him to obtain an education without having to pay for it himself.

Figure 1.1 Gregor Johann Mendel (1822–1884), the founder of classical genetics.



After entering the priesthood he was sent to the University of Vienna, where he studied biology, physics and mathematics. He returned to the Brno monastery in 1853 to teach. Alongside teaching he began experiments on plants in a small plot (about 2 hectares) of monastery land. Over seven years (1856–1863) Mendel cultivated and tested some 28,000 plants, the majority of which were common garden peas (*Pisum sativum*).

Mendel selected *Pisum sativum* to establish the fundamental principles of inheritance. He developed the technique of **emasculation** and **bagging** for hybridisation in plants. The pea flower is bisexual; for cross-pollination one plant is treated as the male and another as the female. To designate the female plant, the stamens were removed at a juvenile stage — this is **emasculation** — to prevent self-pollination. The emasculated flowers were covered with bags (**bagging**) to prevent undesirable cross-pollination. Mature pollen grains were then collected from the male plant and dusted over the emasculated flower. Hybrid seeds formed in the female flower, and the plants grown from these seeds constitute the **first filial**, or F1, **generation**.

His experiments led him to formulate three fundamental principles of inheritance — the **concept of dominance**, the **law of segregation** and the **law of independent assortment**. The body of Mendel's experiments and his formulation of the mechanisms of heredity are collectively known as **mendelism**.

Mendel presented his work to the Brunn Society for Natural Science in two lectures, on 8 February and 8 March 1865. His paper, 'Experiments on Plant Hybridization', was published in the society's proceedings the following year.

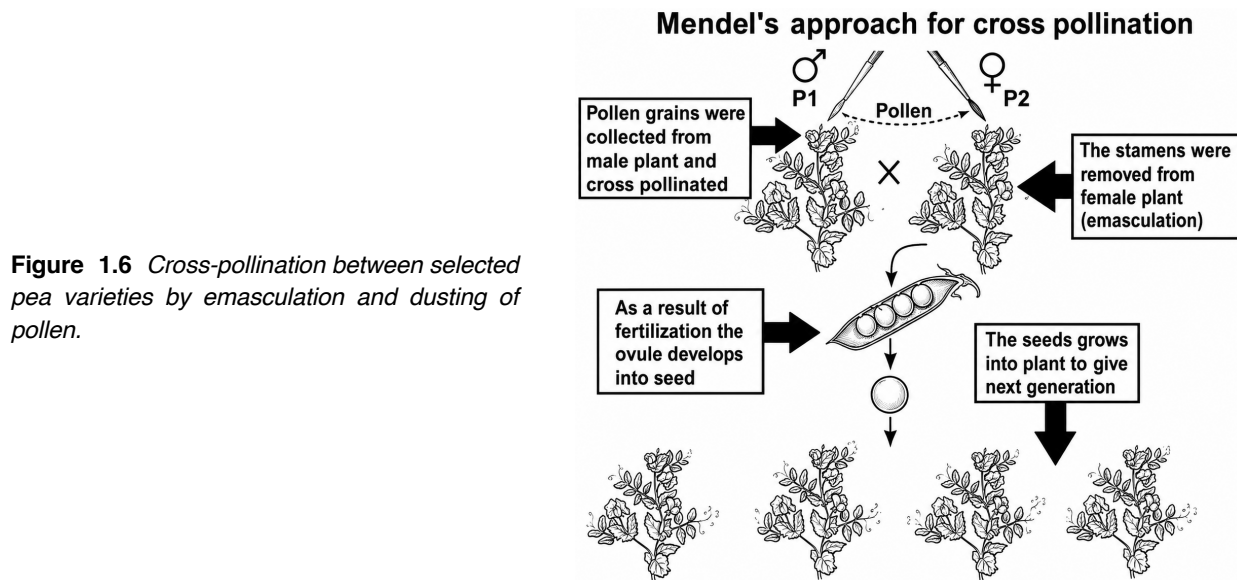


Figure 1.6 Cross-pollination between selected pea varieties by emasculation and dusting of pollen.

In one experiment Mendel crossed a parental (P) plant homozygous for round seeds (RR) with one homozygous for wrinkled seeds (rr) (Figure 1.7), and examined the offspring — the F₁ (first filial) generation. **All** the F₁ progeny had round seeds; only one of the two parental phenotypes appeared.

Mendel repeated the experiment many times and always obtained the same result, and reciprocal crosses gave identical outcomes — all F₁ were round. This contradicted the prevailing belief that hybrids would be intermediate or would show a mixture of round and wrinkled seeds: the wrinkled trait had **disappeared completely** in the F₁.

Mendel did not stop there. He allowed the F₁ plants to self-fertilise, producing the F₂ generation, in which **both** parental traits reappeared. He counted 5474 **round** and 1850 **wrinkled** seeds in the F₂ (Figure 1.7) — a ratio of approximately 3 **round** to 1 **wrinkled**, so that three-quarters of the F₂ seeds were round and one-quarter wrinkled.

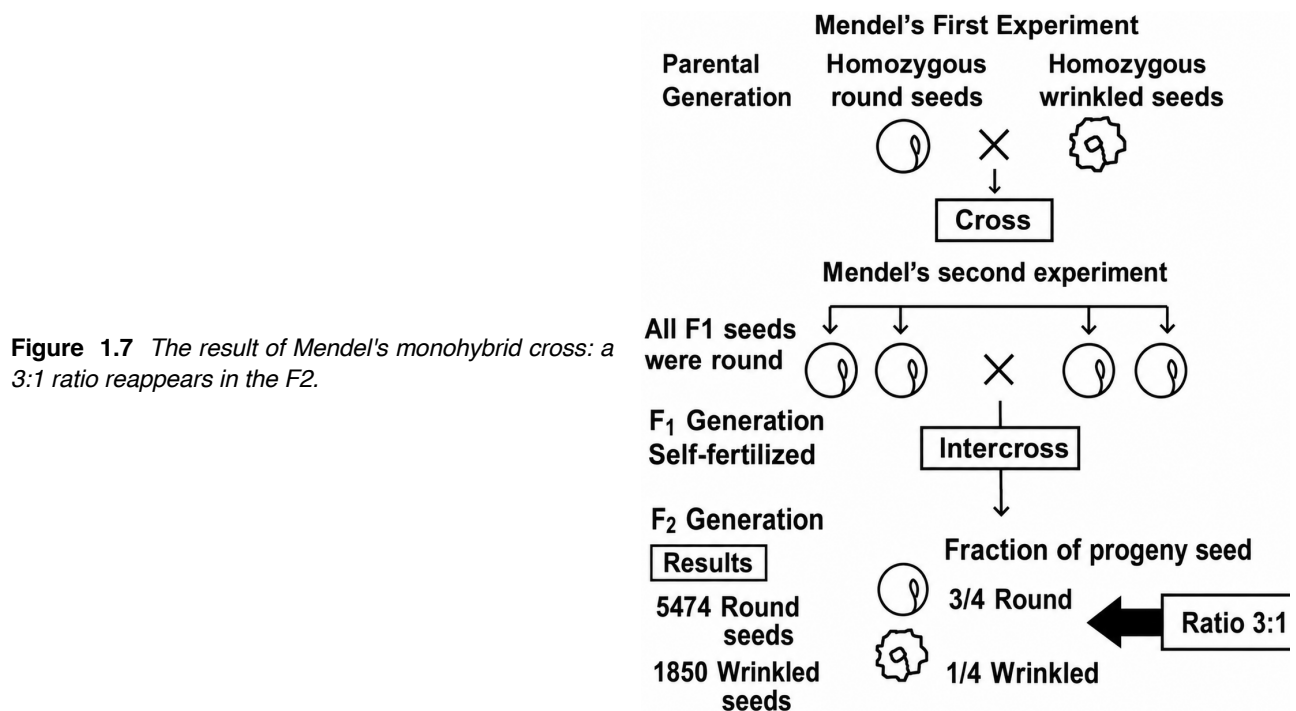


Figure 1.7 The result of Mendel's monohybrid cross: a 3:1 ratio reappears in the F₂.

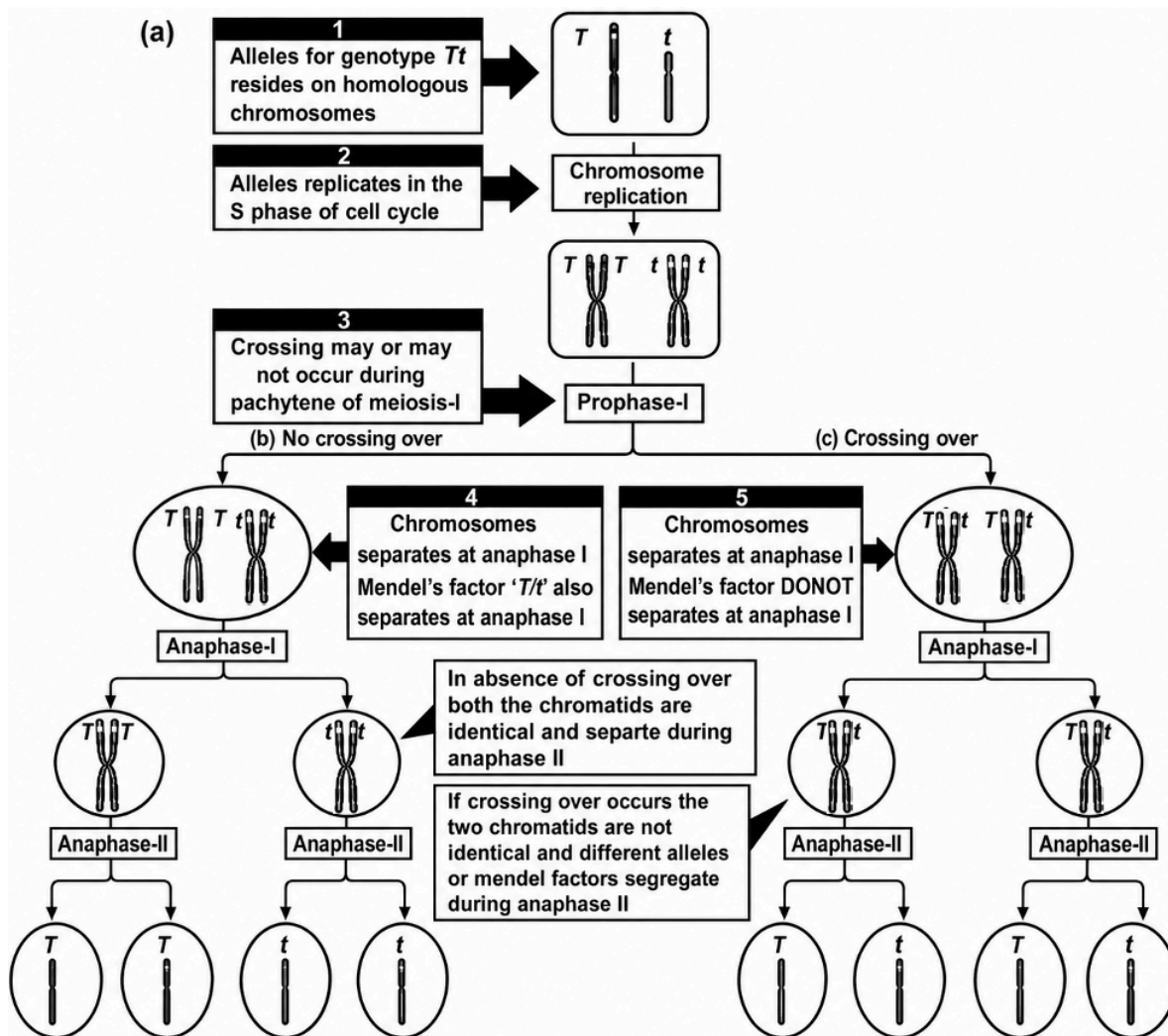


Figure 1.9 The physical basis of heredity: behaviour of homologous chromosomes and alleles during meiosis.

1.5 Interpreting Monohybrid Results — Test Cross and Punnett Square

Mendel devised several ways to predict the outcome of crosses. Crossing tall and dwarf peas, he found tall (T) **dominant** over dwarf (t), and he used the **test cross** to confirm that the dominant F_1 plants were **heterozygous** (Tt).

A test cross is a back cross between an individual of **unknown** genotype and a **homozygous recessive** (tt) partner. To predict the offspring, we first determine the gametes of each parent by the law of segregation (Figure 1.10a): a heterozygous tall plant (Tt) produces $\frac{1}{2}$ T and $\frac{1}{2}$ t gametes, whereas the dwarf (tt) plant produces only t gametes.

The Punnett **square** — devised by Reginald C. Punnett in about 1905 — is a grid that predicts the genotypes of a cross. The gametes of one parent are written along the **top** and those of the other down the **side**; each cell then contains one allele from each gamete, giving the genotype of that class of progeny (Figure 1.10b). For example, a T gamete from the tall plant uniting with a t gamete from the dwarf plant gives Tt , which is tall because T is dominant.

Counting the cells gives the types and ratios of progeny. In Figure 1.10b two cells are Tt (tall) and two are tt (dwarf), a 1:1 **ratio** — confirming that the tested parent was heterozygous.

Here the chain of causation is visible: poor insulation leads to heat loss, which leads to a compensatory rise in metabolism, which draws on resources that would otherwise go into eggs. The frizzle gene is now known to be a deletion in the KRT75 keratin gene of the feather shaft.



Figure 3.6 *The pleiotropic frizzle gene in chickens curls the feathers and alters metabolism, body temperature and fertility.*

Human examples. Marfan syndrome, an autosomal dominant disorder caused by mutation in *FBN1* (encoding fibrillin-1, a component of connective-tissue microfibrils), produces a constellation of effects — tall thin build, joint hypermobility, elongated limbs and digits, dislocation of the lens and a heightened risk of aortic dilatation and dissection. Albinism, from mutation of the tyrosinase gene *TYR*, abolishes melanin and so affects the colour of eyes, hair and skin while also causing involuntary eye movements, sensitivity to light and strabismus, because melanin is needed for the normal wiring of the retina. Phenylketonuria, caused by deficiency of phenylalanine hydroxylase, leads if untreated to intellectual disability, eczema, seizures and lighter pigmentation, the last because the accumulated phenylalanine competitively inhibits tyrosinase. Sickle-cell anaemia, from a single point mutation in *HBB*, is strongly pleiotropic: the altered haemoglobin polymerises when deoxygenated, deforming the red cell, and the consequences run from painful crises and splenic damage to stroke, kidney failure, retinal damage and shortened red-cell survival.

3.5.2 Antagonistic pleiotropy and evolution

A pleiotropic gene may be both **beneficial and harmful** — a situation called **antagonistic pleiotropy** — when it helps early in life but harms later. Because natural selection acts most strongly on traits expressed during the fertile years and only weakly on those expressed afterwards, such trade-offs can persist indefinitely. G. C. Williams proposed in 1957 that this explains **senescence**: genes that raise fitness in the young, reproducing organism may reduce it later, and selection will favour them nonetheless. The tumour-suppressor gene *TP53* is a much-discussed candidate, since the same activity that suppresses cancer in youth also limits the stem-cell divisions that renew tissues in age. The sickle-cell allele met in Chapter 2 is a related, though not identical, case of a trade-off maintained by selection.

Pleiotropy also shapes molecular evolution. The traditional expectation is that the more traits a gene affects, the more **constrained** it is — any mutation is likely to damage at least one function — and therefore the **slower** its rate of sequence evolution. Highly pleiotropic genes such as those of the basic transcription machinery are indeed among the most conserved known. The relationship is not perfectly simple, since a highly connected gene may also have more opportunities to acquire useful new functions, but the broad correlation between pleiotropy and evolutionary conservation is well established.

DO YOU KNOW?

Many cases of epistasis and pleiotropy share a single explanation — the **biochemical pathway**. A gene acting at an **early** step of a pathway is epistatic to genes at later steps, because those later enzymes have nothing left to act on; a gene whose product feeds **many** pathways, like tyrosine metabolism, is pleiotropic. The same logic of 'one pathway, many consequences' underlies both phenomena, seen from opposite

CHAPTER

4

Extra-Mendelian Inheritance

Mendel's laws rest on a hidden assumption: that it does not matter which parent contributes an allele, and that the genotype alone fixes the phenotype. A whole class of phenomena breaks these assumptions — genes whose expression depends on the parent of origin, on the sex of the individual, on the genotype of the mother, or on the environment. These patterns of extra-Mendelian inheritance, and the rules for recognising each of them from a cross or a pedigree, are the subject of this chapter.

LEARNING OBJECTIVES

- Explain genomic imprinting and its role in disease and cancer.
- Distinguish penetrance from expressivity, and define a phenocopy.
- Compare the systems of sex determination and explain dosage compensation.
- Describe X-linked and Y-linked inheritance and how to recognise them.
- Distinguish sex-influenced from sex-limited characteristics.
- Explain genetic maternal effect and contrast it with cytoplasmic inheritance.
- Describe anticipation and its basis in trinucleotide-repeat expansion.

Mendelian inheritance follows the laws of segregation and independent assortment, and a key Mendelian principle is that *the parental origin of a gene does not affect its expression*: reciprocal crosses give identical results. Most autosomal nuclear genes behave in exactly this way, but a substantial minority do not. *Non-Mendelian inheritance* is the general term for any pattern in which traits fail to segregate according to Mendel's laws.

There are two broad reasons why this happens. First, the two sexes do not contribute equally for genes on the sex chromosomes or in the cytoplasm, so reciprocal crosses give **different** results. Second, for a growing list of autosomal genes, expression depends on whether the allele came from the mother or the father — a phenomenon called **genomic imprinting**. This chapter surveys imprinting, penetrance and expressivity, phenocopies, sex determination and dosage compensation, sex-linked, sex-influenced and sex-limited inheritance, genetic maternal effect, and anticipation. Cytoplasmic inheritance, which belongs to the same family of phenomena, is treated separately in Chapter 7.

4.1 Genomic Imprinting

Genomic imprinting refers to autosomal genes whose expression depends on the **sex of the transmitting parent**: a gene inherited from the father may behave differently from the very same gene inherited from the mother. It is an **epigenetic** phenomenon — it changes gene expression in a parent-of-origin-specific manner **without altering the DNA sequence**, and, unlike a mutation, it is **reversible**. Epigenetics is the study of such heritable but reversible marks, through which development and environment shape gene expression.

Imprinting was first demonstrated in transgenic mice: an inserted gene is faithfully transmitted, but its expression depends on the transmitting parent. A gene passed on by a male may be expressed in his offspring yet silenced when his daughter transmits it — **The sex of the parent, not of the offspring, determines expression.** Because an imprinted gene has only one working copy, disease can arise in three ways: by deletion or mutation of the active copy; by **uniparental disomy**, in which both copies of a chromosome come from one parent and none from the other; or by a fault in setting or maintaining the imprint itself.

4.1.1 How imprints are set and read

DNA **methylation** — the addition of methyl groups to cytosines, usually at CpG dinucleotides — is essential to imprinting: mice deficient in DNA methyltransferase activity do not show imprinting at all. The imprint is placed in the **germline**, at a small differentially methylated region often called an **imprinting control region**, and the whole cycle has three steps. The imprint inherited from the previous generation is first **erased** in the primordial germ cells, so that the germ line starts with a clean slate; a new imprint is then **established** according to the sex of the individual carrying it, oocytes receiving the maternal pattern and spermatocytes the paternal one; and the imprint is finally **maintained** through all the divisions of the embryo and adult.

Two further features are worth noting. Imprinted genes are few — at most a few hundred in mammals — and they are usually arranged in **clusters** controlled by a single imprinting centre, so that a whole neighbourhood of genes is regulated together. And although the genome is extensively **demethylated** after fertilisation, in preparation for the totipotency of the early embryo, imprinted regions are specifically **protected** from this wave of erasure and keep their sex-specific marks. The result is that an imprinted gene functions as though the organism were **haploid** at that locus.

Table 4.1 Terminology of imprinting, with worked examples. The word "imprinted" always refers to the copy that is silenced.

Term	Meaning	Expressed copy	Example
Maternally imprinted	The maternal copy is silenced	Paternal	IGF2, SNRPN, MEST
Paternally imprinted	The paternal copy is silenced	Maternal	H19, UBE3A, CDKN1C
Uniparental disomy	Both homologues from one parent	One or none	Prader–Willi, Angelman
Loss of imprinting	The silenced copy becomes active	Both	IGF2 in Wilms' tumour

The terminology in Table 4.1 causes more confusion than any other point in this chapter, because it runs the opposite way to intuition. A **maternally imprinted** gene is one whose **maternal** copy is stamped and switched **off**; the gene is therefore expressed from the **paternal** chromosome. Consider a cross between a female mouse homozygous for allele a of the imprinted growth gene IGF2 and a male homozygous for allele b. Every F1 animal is genotypically ab, but because IGF2 is **maternally imprinted** the maternal a allele is silent and only the **paternal** b allele is transcribed. Reverse the cross and only a is expressed. The genotype is the same in both directions; the expression is not.

4.1.2 Prader–Willi and Angelman syndromes

These two disorders dramatically illustrate imprinting because they arise from **the same deletion** — region q11–13 of chromosome 15 — yet produce opposite syndromes depending on the parent of origin. Prader–Willi syndrome (small hands and feet, short stature, poor sexual development, intellectual disability and an insatiable appetite leading to obesity) results when the deletion is inherited from the **father**. The same 15q11–13 deletion inherited from the **mother** instead causes Angelman syndrome (frequent inappropriate laughter, jerky uncontrolled movements, a large mouth, absent speech and seizures).

CHAPTER

11

Mutation

Mutation is a double-edged sword. It is the ultimate source of all genetic variation — the raw material of evolution and the geneticist's most powerful analytical tool — and yet most mutations are harmful, and they underlie a great part of human disease. This chapter classifies mutations three times over: by their molecular nature, by their effect on the function of the gene product, and by their cause; and then shows how they are detected and how they are used to take a gene apart.

LEARNING OBJECTIVES

- Distinguish somatic from germ-line mutations.
- Classify gene mutations by structure and by their effect on the codon.
- Classify mutations by their effect on function, and predict dominance from that.
- Explain the spontaneous and induced causes of mutation.
- Detect mutations by reversion analysis and the Ames test.
- Describe the one-gene–one-enzyme hypothesis and insertional mutagenesis.

A **mutation** is a **heritable change in the DNA sequence**. Two words in that definition carry weight. **Heritable** excludes a temporary chemical injury that is repaired before the next replication; and **sequence** excludes the epigenetic changes of Chapter 4, which alter expression without altering the sequence at all.

Mutations are the source of all genetic variation — without them no organism could adapt and evolution could not occur — but the great majority are deleterious, simply because a working gene has far more ways of being spoiled than improved. They are also indispensable research tools: much of Mendel's and Morgan's success rested on carefully chosen mutants, and the genetic analysis of almost any process still begins by collecting a good set of them.

11.1 Somatic and Germ-line Mutations

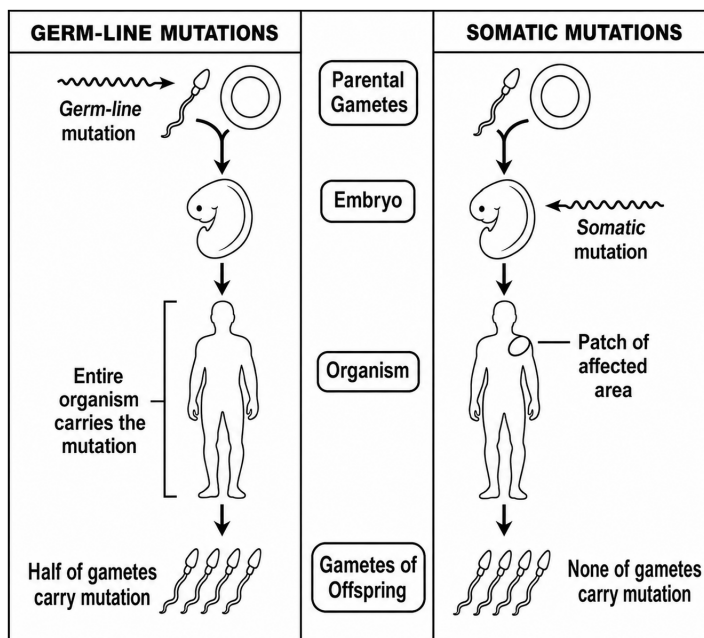
In a multicellular organism, mutations fall into two categories according to the tissue in which they arise (Figure 11.1). A **somatic** mutation occurs in non-reproductive tissue and is passed by **mitosis** to a clone of cells within that individual; the earlier in development it occurs, the larger the resulting clone.

With something like 10^{14} cells in a human body, somatic mutations are extremely numerous, and they matter enormously — cancer is a disease of accumulated somatic mutation — but they die with the individual.

A **germline mutation** arises in a cell of the lineage that gives rise to gametes and can therefore be **transmitted** to offspring, who will carry it in every cell of their bodies.

When geneticists speak of mutation in a multicellular organism they usually mean the germ-line kind, because only those appear in a pedigree. In a single-celled organism the distinction disappears altogether, since every cell division makes a new individual — which is one reason why bacteria and yeast are such convenient material for mutational analysis.

Figure 11.1 The two basic classes of mutation: somatic, passed by mitosis to a clone of cells, and germ-line, which is heritable.



11.2 Types of Gene Mutation

Gene mutations fall into three structural classes: **Base substitutions**, **insertions and deletions**, and **expanding trinucleotide repeats** (Figure 11.2).

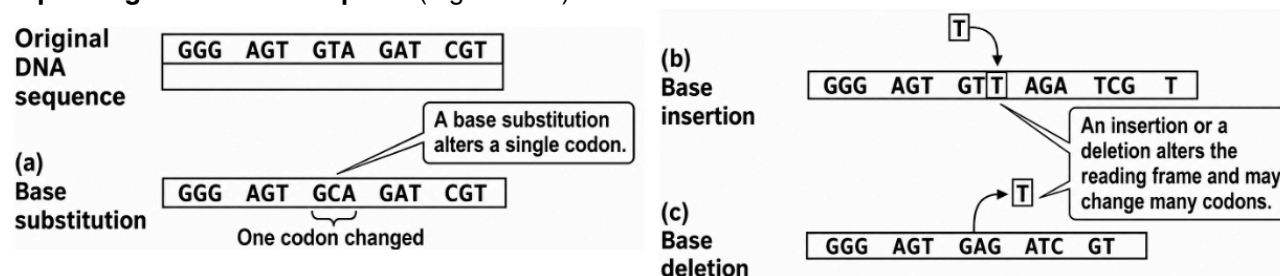


Figure 11.2 The three basic structural types of gene mutation: base substitution, insertion and deletion.

11.2.1 Base substitutions

A base substitution alters a single nucleotide; because the two strands are complementary, it becomes a **base-pair** substitution at the next replication. Substitutions are of two kinds (Figure 11.3). A **transition** replaces a purine by a purine or a pyrimidine by a pyrimidine — that is, A by G, or C by T, or the reverse.

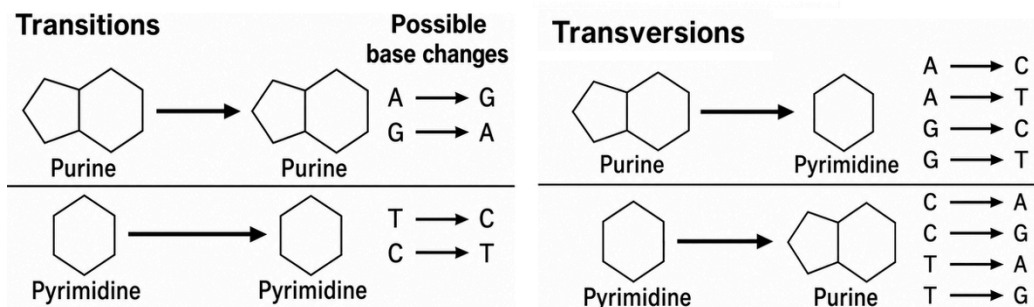


Figure 11.3 Transition — purine to purine or pyrimidine to pyrimidine — against transversion, purine to pyrimidine

A **transversion** replaces a purine by a pyrimidine or the other way about. Chemically the transition is much the easier change, since the replacement base has the same shape and fits the helix without distortion, and transitions are correspondingly commoner. But there are **twice as many** possible transversions as transitions, since each base can be replaced by either of the two of the other class, which is a point examinations return to.

11.2.2 Insertions, deletions and frameshifts

Insertions and deletions add or remove nucleotides, and despite the common assumption that substitutions dominate they are in fact **more frequent**. Their consequence inside a coding sequence depends entirely on arithmetic. An insertion or deletion whose length is **not A multiple of three** shifts the reading frame — a **frameshift** mutation — so that every codon downstream of the change is misread and every amino acid from that point on is wrong, usually until a spurious stop codon is reached. An insertion or deletion of a multiple of three is an in-frame mutation, which adds or removes whole amino acids and leaves the rest of the protein untouched; such mutations are correspondingly much milder.

11.2.3 Expanding trinucleotide repeats

A third class was recognised only in 1991, when the fragile-X syndrome — the commonest inherited cause of intellectual disability — was traced to a run of CAG repeats in the FMR-1 gene that had grown in copy number. A normal allele carries up to about 60 repeats; an affected individual carries hundreds or thousands. Two properties make these **expanding trinucleotide repeats** unlike any other mutation. The copy number **correlates** with severity and with earlier onset; and the longer a repeat becomes the more **unstable** it is, so it tends to expand further at each transmission. Together these give the **anticipation** described in Chapter 4 — a disorder that appears earlier and more severely in each successive generation. Table 11.1 lists the main examples.

Expansion is thought to arise from **strand slippage** during replication, or from unequal crossing over, both of which are made far more likely by the tendency of a single-stranded run of repeats to fold back on itself into a **hairpin** (Figure 11.4). The nascent strand slips, the hairpin holds the loop out of the way, and replication continues past it, so that the new strand ends up longer than the template.

Figure 11.4 The number of trinucleotide repeats can increase by strand slippage during replication, aided by the formation of a hairpin.

