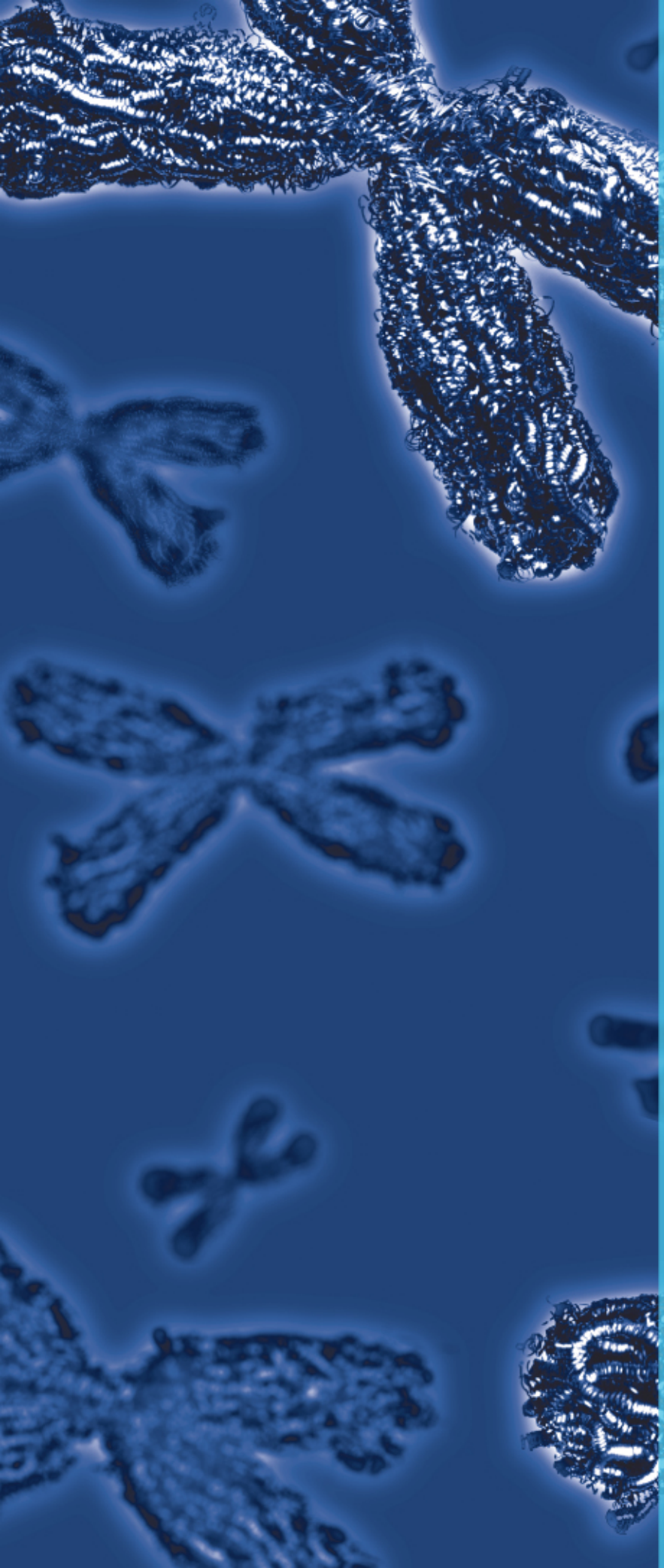

Medical Genetics at a Glance

Third Edition

Dorian J. Pritchard
Bruce R. Korf

WILEY-BLACKWELL

Medical Genetics at a Glance

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Medical Genetics at a Glance

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Preface to the first edition

This book is written primarily for medical students seeking a summary of genetics and its medical applications, but it should be of value also to advanced students in the biosciences, paramedical scientists, established medical doctors and health professionals who need to extend or update their knowledge. It should be of especial value to those preparing for examinations.

Medical genetics is unusual in that, whereas its fundamentals usually form part of first-year medical teaching within basic biology, those aspects that relate to inheritance may be presented as an aspect of reproductive biology. Clinical issues usually form a part of later instruction, extending into the postgraduate years. This book is therefore presented in three sections, which can be taken together as a single course, or separately as components of several courses. Chapters are however intended to be read in essentially the order of presentation, as concepts and specialised vocabulary are developed progressively.

There are many excellent introductory textbooks in our subject, but none, so far as we know, is at the same time so comprehensive and so succinct. We believe the relative depth of treatment of topics appropriately reflects the importance of these matters in current thinking.

Dorian Pritchard
Bruce Korf

Preface to the third edition

The first two editions have been quite successful, having been translated into Chinese, Japanese, Greek, Serbo-Croat, Korean, Italian and Russian. In keeping with this international readership, we stress clinical issues of particular relevance to the major ethnic groups, with information on relative disease allele frequencies in diverse populations. The second edition was awarded First Prize in the Medicine category of the 2008 British Medical Association Medical Book Competition Awards. In this third edition we aim to exceed previous standards.

Editions one and two presented information across all subject areas in order of the developing complexity of the whole field, so that a reader's vocabulary, knowledge and understanding could progress on a broad front. That approach was popular with student reviewers, but their teachers commented on difficulty in accessing specific subject areas. The structure of this third edition has therefore been completely revised into subject-based sections, of which there are fourteen.

Three former introductory chapters have been combined and all other chapters revised and updated. In addition we have written seventeen new chapters and five new case studies, with illustrations to accompany the latter. New features include a comprehensively illustrated treatment of cardiac developmental pathology, a radically revised outline of cancer, a much extended review of biochemical genetics and outline descriptions of some of the most recent genomic diagnostic techniques.

Dorian Pritchard
Bruce Korf

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We thank the staff of Wiley for their encouragement and tactful guidance throughout the production of the series and Jane Fallows and Graeme Chambers for their tasteful presentation of the artwork.

Dorian Pritchard
Bruce Korf

List of abbreviations

A: adenine; blood group A.
α_1-AT: α_1-antitrypsin.
AB: blood group AB.
***abl*:** the Abelson proto-oncogene, normally on 9q, that participates in the Philadelphia derivative chromosome.
ACE: angiotensin-1 converting enzyme.
ACo-D: autosomal dominant.
AD: autosomal dominant.
ADA: adenosine deaminase.
ADH: alcohol dehydrogenase.
AE: acrodermatitis enteropathica.
AER: ridge of ectoderm along the apex of the limb bud.
AFP: α-fetoprotein.
AIP: acute intermittent porphyria.
AIRE: autoimmune regulator protein.
ALD: adrenoleukodystrophy.
ALDH: acetaldehyde dehydrogenase.
APC: antigen presenting cell.
APKD: adult polycystic kidney disease.
APP: amyloid-β precursor protein.
APS: autoimmune polyendocrinopathy syndrome.
AR: autosomal recessive.
ARMS: amplification refractory mutation system.
AS: Angelman syndrome; ankylosing spondylitis.
ASD: atrial septal defect.
ASO: allele-specific oligonucleotide.
ATP: adenosine triphosphate.
AVC: atrioventricular canal.
AZF: azoospermic factor.
B: blood group B.
BAC: bacterial artificial chromosome.
BCAA: branched chain amino acid.
BCL: bilateral cleft lip.
***BCR*:** the breakpoint cluster region, normally on 22q that participates in the Philadelphia chromosome.
BLS: bare lymphocyte syndrome.
BMD: Becker muscular dystrophy.
BMI: body mass index.
BMP-4: bone morphogenetic protein 4.
bp: base pair.
***BRCA1*, *BRCA2*:** breast cancer susceptibility genes 1 and 2.
C: cytosine; haploid number of single-strand chromosomes; number of concordant twin pairs; complement.
2C: diploid number of single-strand chromosomes.
CAD: coronary artery disease.
CAH: congenital adrenal hyperplasia.
CAM: cell adhesion molecule.
CATCH 22: cardiac defects, abnormal facies, thymic hypoplasia, cleft palate and hypocalcemia caused by microdeletion at 22q11.2: an example of a medical acronym that can cause distress and should be avoided, now referred to as 'Chromosome 22q11.2 deletion syndrome'.
CBAVD: congenital bilateral absence of the vas deferens.
CCD: charge-coupled device.
cDNA: DNA copy of a specific mRNA.
CF: cystic fibrosis.
***CFTR*:** cystic fibrosis transmembrane conductance regulator; the cystic fibrosis gene.
CGD: chronic granulomatous disease.
CGH: comparative genome hybridization.
CGS: contiguous gene syndrome.
CHARGE: coloboma, heart defects, choanal atresia, retarded growth, genital abnormalities and abnormal ears.
CHD: congenital heart disease.
CL ± P: cleft lip with or without cleft palate.
CML: chronic myelogenous leukaemia.
CMV: *Cytomegalovirus.*
CNS: central nervous system.
CNV: copy number variation.
Co-D: codominant.
CpG: cytosine-(phosphate)-guanine (within one DNA strand).
CRASH: corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraparesis and hydrocephalus due to mutation in the L1 CAM cell adhesion molecule, a second example of a medical acronym that can cause distress and should be avoided.
CSF: cerebrospinal fluid.
CT scan: computerized technique that uses X-rays to obtain cross-sectional images of tissues.
CVS: chorionic villus sampling.
CX26: connexin 26.
CYP: cytochrome P450.
D: number of discordant twin pairs.
DA: ductus arteriosus.
ddA (/T/C/G)TP: dideoxynucleotide A (T,C,G).
del: chromosome deletion.
***der*:** derivative chromosome.
DHPR: dihydropteridine reductase.
DMD: Duchenne muscular dystrophy.
DMPK: dystrophia myotonica protein kinase.
DNA: deoxyribonucleic acid.
dNTP: deoxyribonucleotide.
DOCK: dedicator of cytokinesis.
DOPA: dihydroxyphenylalanine.
***dup*:** duplicated segment of a chromosome.
DZ: dizygotic, arising from two zygotes.
ECM: extracellular matrix.
EDD: expected date of arrival.
EF: elongation factor.
ELSI: the Ethical, Legal and Social Implications Program of the Human Genome Project.
ER: endoplasmic reticulum.
EVAS: enlarged vestibular aqueduct syndrome.
EXT: multiple hereditary exostosis.
F: Wright's inbreeding coefficient.

FAD: flavin adenine dinucleotide.
FAP(C): familial adenomatous polyposis (coli).
FCH: familial combined hyperlipidaemia.
Fe: iron.
FGF: fibroblast growth factor.
FGFR: fibroblast growth factor receptor.
FH: familial hypercholesterolaemia.
FISH: fluorescence *in-situ* hybridization.
***FMR*:** a gene at Xq27.3 containing a CGG repeat, expansion of which causes fragile-X disease.
fra: fragile site.
FRAX: fragile-X syndrome.
FSH: follicle-stimulating hormone.
G: guanine.
G0, G1, G2: phases of the mitotic cycle.
G6PD: glucose-6-phosphate dehydrogenase.
Gal 1 PUT: galactose-1-phosphate uridyltransferase.
GALC: galactocerebrosidase.
GALT: galactose-1-phosphate uridyltransferase.
GCDHD: glutaryl-CoA dehydrogenase deficiency.
GF: growth factor.
GFR: growth factor receptor.
GI: gastrointestinal.
GlcNAc: *N*-acetylglucosamine.
GLI3: a zinc finger transcription controlling protein.
GM: ganglioside.
GSD: glycogen storage disorder.
GVH: graft versus host.
HA: homogentisic acid.
HAO: hereditary angioneurotic oedema.
HbA: normal allele for β-globin.
HbS: sickle cell allele of β-globin.
***HFE*:** High Fe: the haemochromatosis gene.
HFI: hereditary fructose intolerance.
HGPRT/HPRT: hypoxanthine-guanine phosphoribosyl transferase.
HIV: human immunodeficiency virus.
HMGCoA: hydroxymethylglutaryl coenzyme A.
HMSN: hereditary motor and sensory neuropathy, Charcot–Marie–Tooth disease.
HNF: hepatic nuclear factor.
HNPCC: hereditary non-polyposis colon cancer.
hnRNA: heterogeneous nuclear RNA.
***HoxA–D*:** Homeobox genes A–D.
***i*:** isochromosome.
ICSI: intracytoplasmic sperm injection.
IDDM: insulin-dependent diabetes mellitus, a term now replaced by T2D or T2DM, q.v.
Ig: immunoglobulin.
Ig-CAM: immunoglobulin cell adhesion molecule.
IMC: invasion metastasis cascade.
***ins*:** inserted segment in a chromosome.
***inv*:** inverted segment of a chromosome.
IP: incontinentia pigmenti.
IQ: intelligent quotient.
IRT: immunoreactive trypsin.
IVC: inferior vena cava.
kb: kilobase (1000 bases).
λ_S: lambda-s, relative risk for a sib.
LA: left atrium.
LAD: leucocyte adhesion deficiency.
LCHAD: long-chain hydroxyacyl coenzyme A deficiency.
LDLR: low-density lipoprotein receptor.
***LEFTA/B*:** human equivalent of the gene Lefty-1/2.
LHON: Leber hereditary optic neuropathy.
LINES: Long interspersed nuclear elements.
LMP: last menstrual period.
LNS: Lesch–Nyhan syndrome.
lod: 'Log of the odds'; the logarithm ($\log_{10}$) of the ratio of the probability that a certain combination of phenotypes arose as a result of genetic linkage (of a specified degree) to the probability that it arose merely by chance.
LSD: lipid storage disorder.
LV: left ventricle.
M: monosomy; mitotic phase of the cell cycle.
M1, M2: first, second divisions of meiosis.
MAPH: multiplex amplifiable probe hybridization.
Mb: megabase (1 000 000 bases).
MBP: mannan-binding protein.
MCAD: medium-chain acyl-coenzyme A deficiency.
MD: myotonic dystrophy.
MELAS: mitochondrial encephalopathy, lactic acidosis and stroke-like episodes.
MEN: multiple endocrine neoplasia.
MERRF: myoclonic epilepsy with ragged red fibres.
MHC: major histocompatibility complex.
miRNA: microRNA.
MIS: Müllerian inhibiting substance.
MND: Menkes disease.
MPS: mucopolysaccharidosis.
MRI: magnetic resonance imaging.
mRNA: messenger RNA.
MS: mass spectrometry; multiple sclerosis.
MS/MS: tandem mass spectrometry.
MTC: medullary thyroid carcinoma.
mtDNA: mitochondrial DNA.
MZ: monozygotic, derived from one zygote.
N: haploid number of chromosomal DNA double-helices; in humans, 23.
NAD: nicotinamide adenine dinucleotide.
NARP: neurodegeneration, ataxia and retinitis pigmentosa.
NF1, NF2: neurofibromatosis types 1 and 2.
NFκB: nuclear factor kappa B.
NHC protein: non-histone chromosomal protein.
NIDDM: non-insulin-dependent diabetes mellitus.
NOR: nucleolar organizer region.
***NSD-1*:** nuclear SET domain 1; the gene at 5q35 responsible for Sotos syndrome.
NTD: neural tube defect.
O: blood group O.
OCA: oculocutaneous albinism.
OHD: 21-hydroxylase deficiency.
p: chromosomal short arm: symbol for allele frequency.
P: degree of penetrance.

p53: mitosis suppressor protein product of the gene, *TP53*.
PA: phenylalanine.
PAH: phenylalanine hydroxylase.
PCR: polymerase chain reaction.
PDS: Pendred syndrome.
PFGE: pulsed-field gel electrophoresis.
PGD: preimplantation genetic diagnosis.
Phe508del: deletion of the codon for phenylalanine at position 508 in the *CFTR* gene.
PKU: phenylketonuria.
PNP: purine nucleoside phosphorylase.
Pol II: RNA polymerase II.
P-WS: Prader–Willi syndrome.
q: chromosomal long arm; symbol for allele frequency.
***r*:** ring chromosome.
RA: right atrium.
rad: an absorbed dose of 100 ergs of radiation per gram of tissue.
***ret*:** a proto-oncogene that becomes rearranged during transfection, initiating tumorigenesis.
RFLP: restriction fragment length polymorphism.
Rh: Rhesus.
RISC: RNA- induced silencing complex.
RNA: ribonucleic acid.
RNAi: RNA interference.
RNA-seq: array sequencing of RNA.
rob: Robertsonian translocation; centric fusion.
rRNA: ribosomal RNA.
S: Svedberg unit; DNA synthetic phase of the cell cycle.
SCID: severe combined immunodeficiency disease.
***Shh*:** sonic hedgehog, a gene concerned with body patterning.
SINES: short interspersed nuclear elements.
siRNA: small interfering RNA.
SLE: systemic lupus erythematosus.
SLO: Smith–Lemli–Opitz syndrome.
SMA: spinal muscular atrophy.
SNP: single nucleotide polymorphism.
snRNA: small nuclear RNA.
snRNP: small nuclear ribonucleo-protein; protein–RNA complex important in recognition of intron/exon boundaries, intron excision or exon splicing, etc.
***SRY*:** Y-linked male sex determining gene.
SSCP: single-strand conformation polymorphism; study of DNA polymorphism by electrophoresis of DNA denatured into single strands.
STAT: signal transducer and activator of transcription.
STC: signal transduction cascade.
STR: short tandem repeat.
SVAS: supravalvular aortic stenosis.
SVC: superior vena cava.
t: reciprocal translocation.
T: thymine; trisomy.
T1D/T1DM: type 1 diabetes mellitus.
T2D/T2DM: type 2 diabetes mellitus.
TA: truncus arteriosus.
TAP: transporter associated with antigen presentation.
Taq: *Thermus aquaticus*.
TCR: T-cell receptor.
***ter*:** terminal, close to the chromosome telomere.
TFM: testicular feminization, or androgen insensitivity syndrome.
TLR: toll-like receptor.
TNF: tumour necrosis factor.
TORCH: *Toxoplasma*, other, *Rubella*, *Cytomegalovirus* and *Herpes*.
***TP53*:** the gene coding for protein p53.
tRNA: transfer RNA.
ts: tumour suppressor.
TSC: tuberous sclerosis.
U: uracil.
UCL: unilateral cleft lip.
UDP: uridine diphosphate.
VACTERL: as for VATER with cardiac and limb defects also.
VATER: vertebral defects, anal atresia, tracheo-oesophageal fistula and renal defects.
VCFS: velocardiofacial syndrome.
VNTR: variable number tandem repeat; usually applied to minisatellites.
VSD: ventricular septal defect.
WAGR: Wilms tumour, aniridia, genitourinary anomalies and (mental) retardation.
WES: whole exome sequencing.
WGS: whole genome sequencing.
XD: X-linked dominant.
XLA: X-linked agammaglobulinaemia.
XP: xeroderma pigmentosum.
XR: X-linked recessive.
YAC: yeast artificial chromosome.
ZIC3: a zinc finger transcription controlling protein.
ZPA: zone of proliferating activity.
φ: phi; coefficient of kinship.

1 The place of genetics in medicine

Figure 1.1 **Genetic disorders in children as causes of death in Britain and among those admitted to hospital in North America**

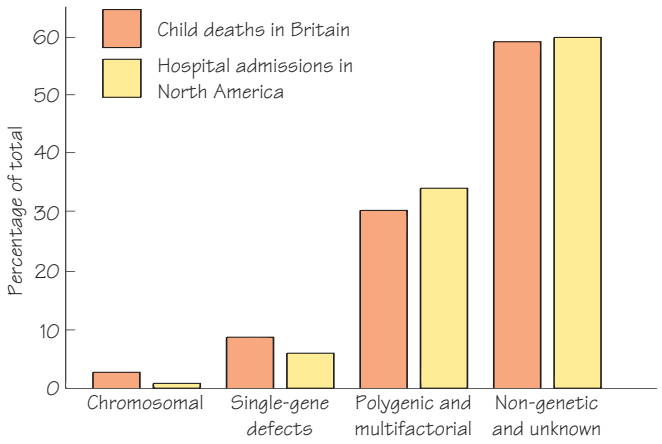
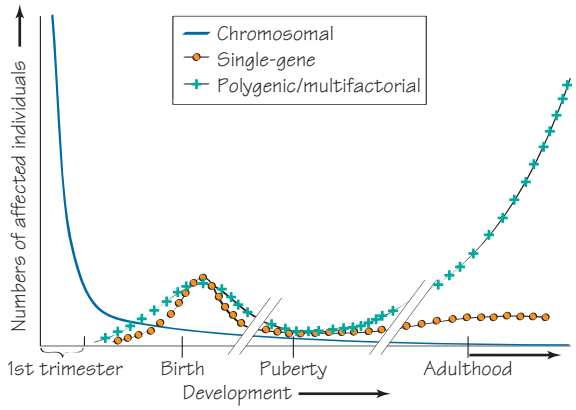


Figure 1.2 **Expression of the major categories of genetic disease in relation to development**



Source: Gelehrter, T.D, Collins, F.S. and Ginsburg, D. (1998) *Principles of Medical Genetics*, 2nd edn. LWW.

The case for genetics

In recent years medicine has been in a state of transformation, created by the convergence of two major aspects of technological advance. The first is the explosion in information technology and the second, the rapidly expanding science of genetics. The likely outcome is that within the foreseeable future we will see the establishment of a new kind of medicine, **individualized medicine**, tailored uniquely to the personal needs of each patient. Some diseases, such as hypertension, have many causes for which a variety of treatments may be possible. Identification of a specific cause allows clinicians to give personal guidance on the avoidance of adverse stimuli and enable precise targeting of the disease with personally appropriate medications.

One survey of over a million consecutive births showed that at least one in 20 people under the age of 25 develops a serious disease with a major genetic component. Studies of the causes of death of more than 1200 British children suggest that about 40% died as a result of a genetic condition, while genetic factors are important in 50% of the admissions to paediatric hospitals in North America. Through variation in immune responsiveness and other host defences, genetic factors even play a role in infectious diseases.

Genetics underpins and potentially overlaps all other clinical topics, but is especially relevant to reproduction, paediatrics, epidemiology, therapeutics, internal medicine and nursing. It offers unprecedented opportunities for prevention and avoidance of disease because genetic disorders can often be predicted long before the onset of symptoms. This is known as **predictive** or **presymptomatic genetics**. Currently healthy families can be screened for persons with a particular **genotype** that might cause later trouble for them or their children.

'**Gene therapy**' is the ambitious goal of correcting errors associated with inherited deficiencies by introduction of 'normal' versions of genes into their cells. Progress along those lines has been slower than anticipated, but has now moved powerfully into related areas. Some individuals are hypersensitive to standard doses of commonly prescribed drugs, while others respond poorly. **Pharmacogenetics** is the study of differential responses to unusual biochemicals and the insights it provides guide physicians in the correct prescription of doses.

Genes in development

Genes do not just cause disease, they define normality and every feature of our bodies receives input from them. Typically every one of our cells contains a pair of each of our 20 000–25 000 genes and these are controlled and expressed in molecular terms ***at the level of the cell***. During embryonic development the cells in different parts of the body become exposed to different influences and acquire divergent properties as they begin to express different combinations of the genes they each contain. Some of these genes define structural components, but most define the amino acid sequences of enzymes that catalyse biochemical processes.

Genes are in fact coded messages written within enormously long molecules of **DNA** distributed between 23 pairs of **chromosomes**. The means by which the information contained in the DNA is interpreted is so central to our understanding that the phrase: *'DNA makes RNA makes protein'*; or more correctly: ***'DNA makes heterogeneous nuclear RNA, which makes messenger RNA, which makes polypeptide, which makes protein';*** has become accepted as the **'central dogma'** of molecular biology.

During the production of the gametes the 23 pairs of chromosomes are divided into 23 single sets per ovum or sperm, the normal number being restored in the **zygote** by fertilization. The zygote proliferates to become a hollow ball that implants in the maternal uterus. Prenatal development then ensues until birth, normally at around 38 weeks, but all the body organs are present in miniature by 6–8 weeks. Thereafter embryogenesis mainly involves growth and differentiation of cell types. At puberty development of the organs of reproduction is re-stimulated and the individual attains physical maturity. The period of 38 weeks is popularly considered to be 9 months, traditionally inter-

preted as three '**trimesters**'. The term '**mid-trimester**' refers to the period covering the 4th, 5th and 6th months of gestation.

Genotype and phenotype

Genotype is the word geneticists use for the genetic endowment a person has inherited. **Phenotype** is our word for the anatomical, physiological and psychological complex we recognize as an individual. People have diverse phenotypes partly because they inherited different genotypes, but an equally important factor is what we can loosely describe as 'environment'. A valuable concept is summarized in the equation:

Phenotype = Genotype × Environment × Time

It is very important to remember that practically every aspect of phenotype has both genetic and environmental components. Diagnosis of high liability toward 'genetic disease' is therefore not necessarily an irrevocable condemnation to ill health. In some cases optimal health can be maintained by avoidance of genotype-specific environmental hazards.

Genetics in medicine

The foundation of the science of genetics is a set of principles of heredity, discovered in the mid-19th century by an Augustinian monk called Gregor Mendel. These give rise to characteristic patterns of inheritance of variant versions of genes, called **alleles**, depending on whether the unusual allele is dominant or recessive to the common, or 'wild type' one. Any one gene may be represented in the population by many different alleles, only some of which may cause disease. Recognition of the pattern of inheritance of a disease allele is central to prediction of the risk of a couple producing an affected child. Their initial contact with the clinician therefore usually involves construction of a 'family tree' or **pedigree diagram**.

For many reasons genes are expressed differently in the sexes, but from the genetic point of view the most important relates to possession by males of only a single X-chromosome. Most sex-related inherited disease involves expression in males of recessive alleles carried on the X-chromosome.

Genetic diseases can be classed in three major categories: **monogenic, chromosomal** and **multifactorial**. Most monogenic defects reveal their presence after birth and are responsible for 6–9% of early **morbidity** and mortality. At the beginning of the 20th century, Sir Archibald Garrod coined the term '**inborn errors of metabolism**' to describe inherited disorders of physiology. Although individually most are rare, the 350 known inborn errors of metabolism account for 10% of all known single-gene disorders.

Because chromosomes on average carry about 1000 genes, too many or too few chromosomes cause gross abnormalities, most of which are incompatible with survival. Chromosomal defects can create major physiological disruption and most are incompatible with even prenatal survival. These are responsible for more than 50% of deaths in the first trimester of pregnancy and about 2.5% of childhood deaths.

'Multifactorial traits' are due to the combined action of several genes as well as environmental factors. These are of immense importance as they include most of the **common disorders of adult life**. They account for about 30% of childhood illness and in middle-to-late adult life play a major role in the common illnesses from which most of us will die.

The application of genetics

If genes reside side-by-side on the same chromosome they are '**genetically linked**'. If one is a disease gene, but cannot easily be detected, whereas its neighbour can, then alleles of the latter can be used as markers for the disease allele. This allows prenatal assessment, informing decisions about pregnancy, selection of embryos fertilized *in vitro* and presymptomatic diagnosis.

Genetically based disease varies between ethnic groups, but the term '**polymorphism**' refers to genetic variants like blood groups that occur commonly in the population, with no major health connotations. The concept of polymorphism is especially important in blood transfusion and organ transplantation.

Mutation of DNA involves a variety of changes which can be caused for example by exposure to X-rays. Repair mechanisms correct some kinds of change, but new alleles are sometimes created in the **germ cells**, which can be passed on to offspring. Damage that occurs to the DNA of somatic cells can result in **cancer**, when a cell starts to proliferate out of control. Some families have an inherited tendency toward cancer and must be given special care.

A healthy immune system eliminates possibly many thousands of potential cancer cells every day, in addition to disposing of infectious organisms. Maturation of the immune system is associated with unique rearrangements of genetic material, the study of which comes under the heading of **immunogenetics**.

The study of chromosomes is known as **cytogenetics**. This provides a broad overview of a patient's genome and depends on microscopic examination of cells. By contrast **molecular genetic** tests are each specifically for just one or a few disease alleles. The molecular approach received an enormous boost around the turn of the millennium by the detailed mapping of the human genome.

The modern application of genetics to human health is therefore complex. Because it focuses on reproduction it can impinge on deeply held ethical, religious and social convictions, which are often culture variant. At all times therefore, clinicians dealing with genetic matters must be acutely aware of the real possibility of causing personal offence and take steps to avoid that outcome.

2 Pedigree drawing

Figure 2.1 **Recommended symbols for use in pedigree diagrams**

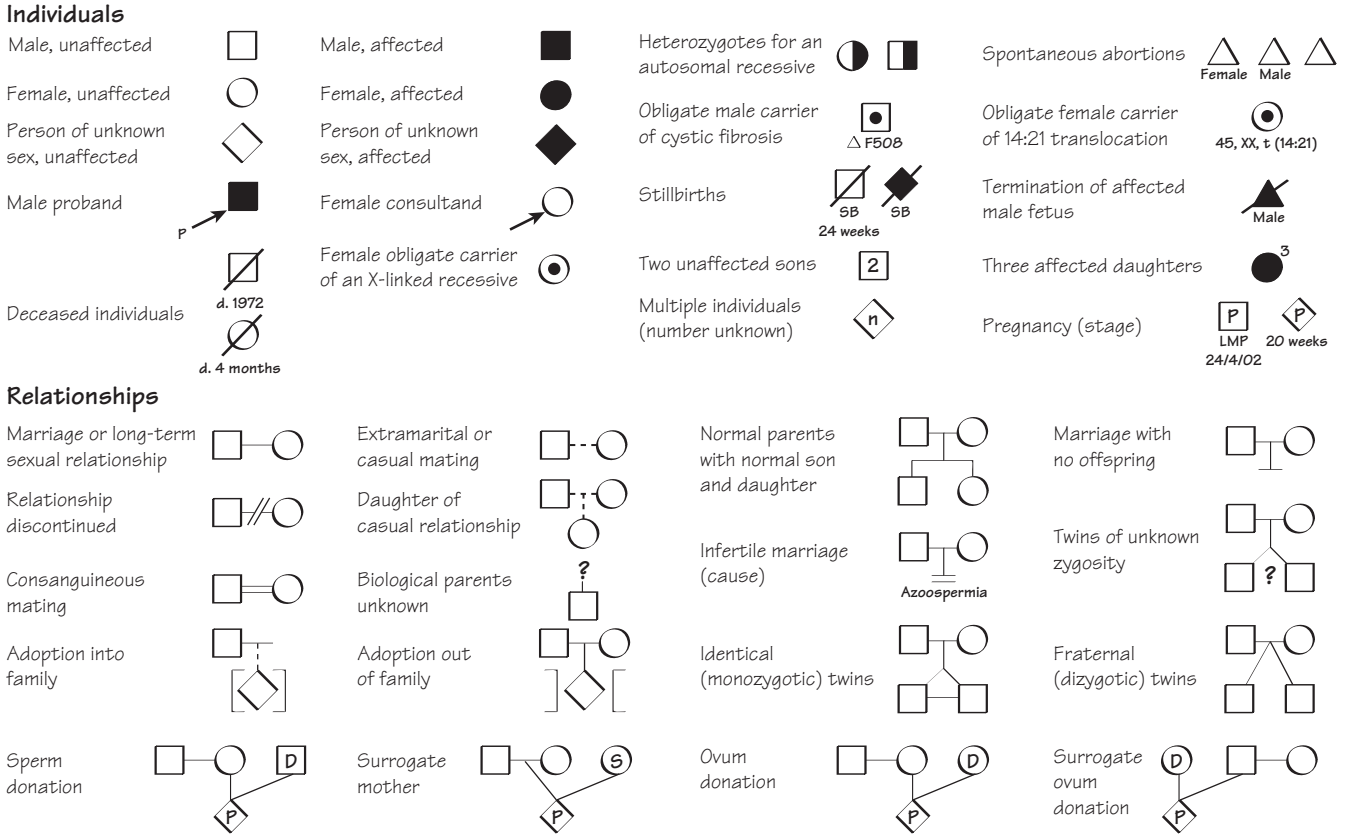


Figure 2.2 **Sample pedigree**

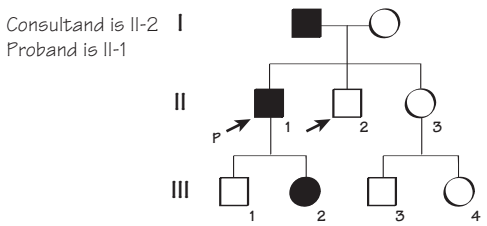


Figure 2.3 **A pedigree showing an affected female homozygous for an AD condition who nevertheless had two productive marriages**

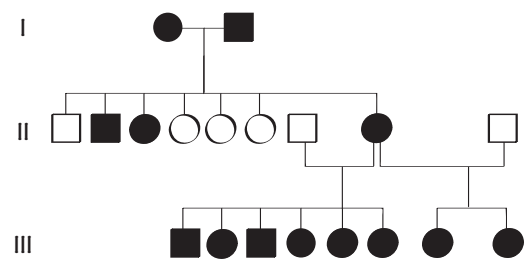
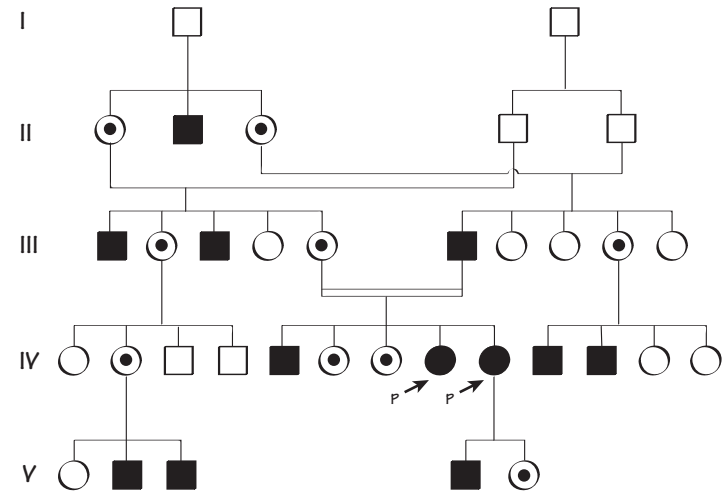


Figure 2.4 **A pedigree for haemophilia showing parents who are double first cousins. The probands are affected sisters**



Overview

The collection of information about a family is the first and most important step taken by doctors, nurses or genetic counsellors when providing genetic counselling. A clear and unambiguous **pedigree diagram**, or '**family tree**', provides a permanent record of the most pertinent information and is the best aid to clear thinking about family relationships.

Information is usually collected initially from the **consultand**, that is the person requesting genetic advice. If other family members need to be approached it is wise to advise them in advance of the information required. Information should be collected from both sides of the family.

The affected individual who caused the consultand(s) to seek advice is called the **propositus** (male), **proposita** (female), **proband** or **index case**. This is frequently a child or more distant relative, or the consultand may also be the proband. A standard medical history is required for the proband and all other affected family members.

The medical history

In compiling a medical history it is normal practice to carry out a **systems review** broadly along the following lines:

- **cardiovascular system**: enquire about congenital heart disease, hypertension, hyperlipidaemia, blood vessel disease, arrhythmia, heart attacks and strokes;
- **respiratory system**: asthma, bronchitis, emphysema, recurrent lung infection;
- **gastrointestinal tract**: diarrhoea, chronic constipation, polyps, atresia, fistulas and cancer;
- **genitourinary system**: ambiguous genitalia and kidney function;
- **musculoskeletal system**: muscle wasting, physical weakness;
- **neurological conditions**: developmental milestones, hearing, vision, motor coordination, fits.

Rules for pedigree diagrams

Some sample pedigrees are shown (see also Chapters 4–12). Females are symbolized by circles, males by squares, persons of unknown sex by diamonds. Affected individuals are represented by solid symbols, those unaffected, by open symbols. Marriages or matings are indicated by horizontal lines linking male and female symbols, with the male partner preferably to the left. Offspring are shown beneath the parental symbols, in birth order from left to right, linked to the mating line by a vertical, and numbered (1, 2, 3, etc.), from left to right in Arabic numerals. The generations are indicated in Roman numerals (I, II, III, etc.), from top to bottom on the left, with the earliest generation labelled I.

The proband is indicated by an arrow with the letter P, the consultand by an arrow alone. (N.B. earlier practice was to indicate the proband by an arrow without the P).

Only conventional symbols should be used, but it is admissible (and recommended) to annotate diagrams with more complex information. If there are details that could cause embarrassment (e.g. illegitimacy or extramarital paternity) these should be recorded as supplementary notes.

Include the contact address and telephone number of the consultand on supplementary notes. Add the same details for each additional individual that needs to be contacted.

The compiler of the family tree should record the date it was compiled and append his/her name or initials.

The practical approach

1 Start your drawing in the middle of the page.
2 Aim to collect details on three (or more) generations.
3 Ask specifically about:
  (a) consanguinity of partners;
  (b) miscarriages;
  (c) terminated pregnancies;
  (d) stillbirths;
  (e) neonatal and infant deaths;
  (f) handicapped or malformed children;
  (g) multiple partnerships;
  (h) deceased relatives.
4 Be aware of potentially sensitive issues such as adoption and wrongly ascribed paternity.
5 To simplify the diagram unrelated marriage partners may be omitted, but a note should be made whether their phenotype is normal or unknown.
6 Sibs of similar phenotype may be represented as one symbol, with a number to indicate how many are in that category.

The details below should be inserted beside each symbol, whether that individual is alive or dead. Personal details of normal individuals should also be specified. The ethnic background of the family should be recorded if different from that of the main population.

Details for each individual:
1 full name (including maiden name);
2 date of birth;
3 date and cause of death;
4 any specific medical diagnosis.

Use of pedigrees

A good family pedigree reveals the mode of inheritance of the disease and can be used to predict the genetic risk in several instances (see Chapter 13). These include:
1 the current pregnancy;
2 the risk for future offspring of those parents (**recurrence risk**);
3 the risk of disease among offspring of close relatives;
4 the probability of adult disease, in cases of diseases of late onset.

3 Mendel's laws

Figure 3.1 Matings between different homozygotes

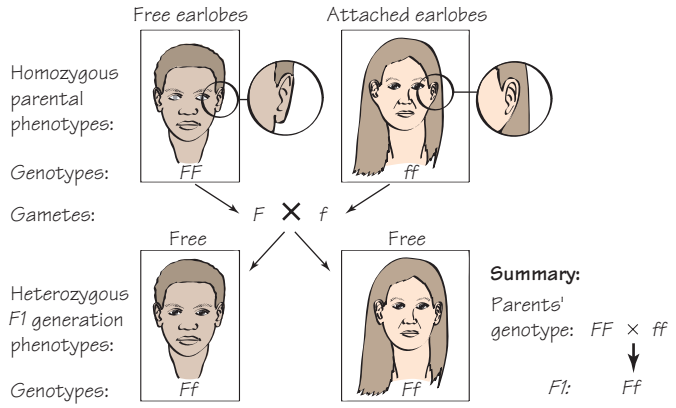


Figure 3.2 Matings between (F1) heterozygotes

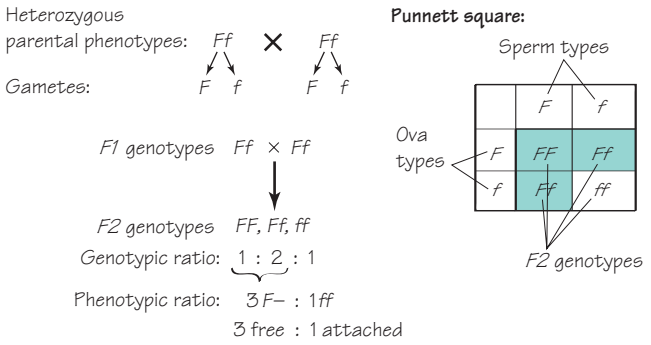


Figure 3.3 Mating of a double heterozygote with a recessive homozygote

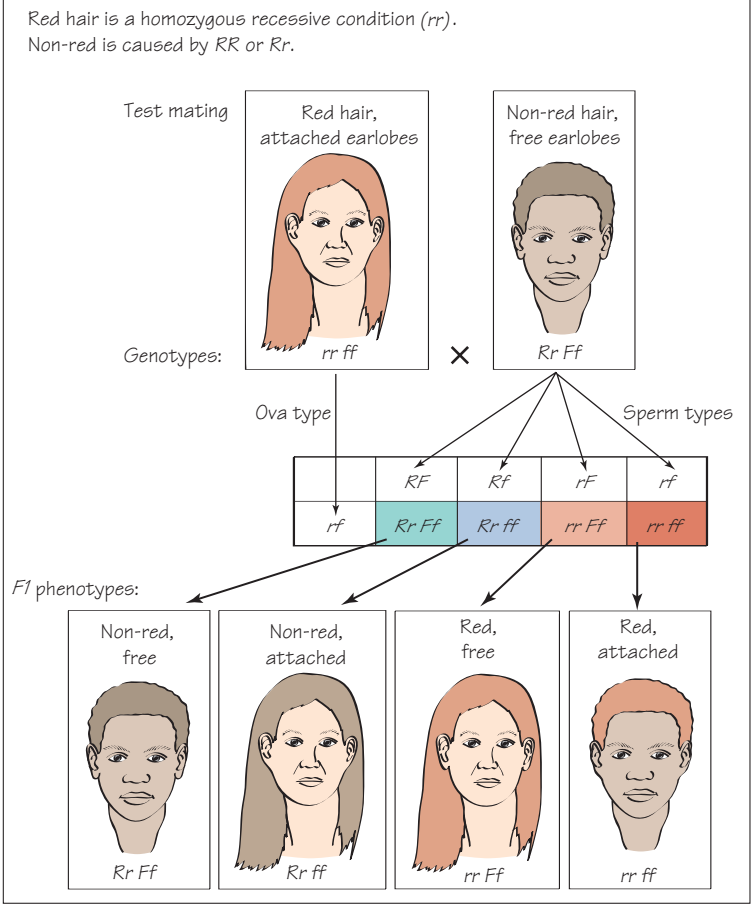


Figure 3.4 Mating of a double heterozygote with a dominant homozygote

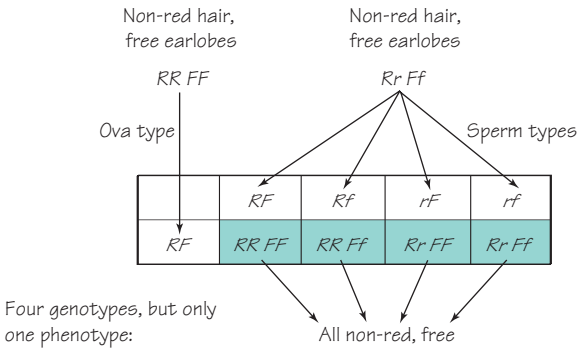
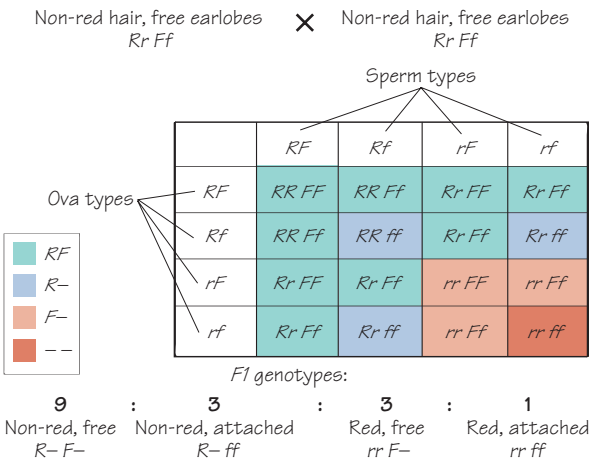


Figure 3.5 Matings between double heterozygotes



Overview

Gregor Mendel's laws of inheritance were derived from experiments with plants, but they form the cornerstone of the whole science of genetics. Previously, heredity was considered in terms of the transmission and mixing of 'essences', as suggested by Hippocrates over 2000 years before. But, unlike fluid essences that should blend in the offspring in all proportions, Mendel showed that the instructions for contrasting characters segregate and recombine in simple mathematical proportions. He therefore suggested that the hereditary factors are particulate.

Mendel postulated four new principles concerning **unit inheritance**, **dominance**, **segregation** and **independent assortment** that apply to most genes of all diploid organisms.

The principle of unit inheritance

Hereditary characters are determined by indivisible units of information (which we now call genes). An allele is one version of a gene.

The principle of dominance

Alleles occur in pairs in each individual, but the effects of one allele may be masked by those of a dominant partner allele.

The principle of segregation

During formation of the gametes the members of each pair of alleles separate, so that each gamete carries only one allele of each pair. Allele pairs are restored at fertilization.

Example

The earlobes of some people have an elongated attachment to the neck while others are free, a distinction we can consider for the purposes of this explanation to be determined by two alleles of the same gene, ***f*** for **attached**, ***F*** for **free**. (Note: In reality some individuals have earlobes of intermediate form and in some families the genetic basis is more complex.)

Consider a man carrying two copies of *F* (i.e. *FF*), with free earlobes, married to a woman with attached earlobes and two copies of *f* (i.e. *ff*). Both can produce only one kind of gamete, *F* for the man, *f* for the woman. All their children will have one copy of each allele, i.e. are *Ff*, and it is found that all such children have free earlobes because *F is dominant to f.* The children constitute the **first filial generation** or **F1 generation** (irrespective of the symbol for the gene under consideration). Individuals with identical alleles are **homozygotes**; those with different alleles are **heterozygotes**.

The **second filial**, or **F2, generation** is composed of the grandchildren of the original couple, resulting from mating of their offspring with partners of the same genotype in this respect. In each case both parents are heterozygotes, so both produce *F* and *f* gametes in equal numbers. This creates three genotypes in the F2: *FF, Ff* (identical to *fF*) and *ff,* **in the ratio: 1 : 2 : 1**.

Due to the dominance of *F* over *f*, dominant homozygotes are phenotypically the same as heterozygotes, so there are three offspring with free earlobes to each one with attached. ***The phenotypic ratio 3 : 1 is characteristic of the offspring of two heterozygotes.***

The principle of independent assortment

Different genes control different phenotypic characters and the alleles of different genes re-assort independently of one another.

Example

Auburn and 'red' hair occur naturally only in individuals who are homozygous for a recessive allele ***r***. Non-red is dominant, with the symbol ***R***. All red-haired people are therefore *rr*, while non-red are either *RR* or *Rr*.

Consider the mating between an individual with red hair and attached earlobes (*rrff*) and a partner who is heterozygous at both genetic loci (*RrFf*). The recessive homozygote can produce only one kind of gamete, of genotype *rf*, but the double heterozygote can produce gametes of four genotypes: *RF, Rf, rF* and *rf*. Offspring of four genotypes are produced: *RrFf, Rrff, rrFf* and *rrff* and ***these are in the ratio 1 : 1 : 1 : 1.***

These offspring also have phenotypes that are all different: non-red with free earlobes, non-red with attached, red with free, and red with attached, respectively.

The test-mating

The mating described above, in which one partner is a double recessive homozygote (*rrff*), constitutes a **test-mating**, as his or her recessive alleles allow expression of all the alleles of their partner.

The value of such a test is revealed by comparison with matings in which the recessive partner is replaced by a double dominant homozygote (*RRFF*). The new partner can produce only one kind of gamete, of genotype *RF,* and four genotypically different offspring are produced, again in equal proportions: *RRFF, RRFf, RrFF* and *RrFf*. However, due to dominance all have non-red hair and free earlobes, so the genotype of the heterozygous parent remains obscure.

Matings between double heterozygotes

The triumphant mathematical proof of Mendel laws was provided by matings between pairs of double heterozygotes. Each can produce four kinds of gametes: *RF, Rf, rF* and *rf*, which combined at random produce nine different genotypic combinations. ***Due to dominance there are four phenotypes, in the ratio 9 : 3 : 3 : 1*** (total = 16). This allows us to predict the odds of producing:

1 a child with non-red hair and free earlobes (*R-F-*), as 9/16;
2 a child with non-red hair and attached earlobes (*R-ff*), as 3/16;
3 a child with red hair and free earlobes (*rrF-*), as 3/16; and
4 a child with red hair and attached earlobes (*rrff*), as 1/16.

Biological support for Mendel's laws

When published in 1866 Mendel's deductions were ignored, but in 1900 they were re-discovered and rapidly found acceptance. This was in part because the chromosomes had by then been described and the postulated behaviour of Mendel's factors coincided with the observed properties and behaviour of the chromosomes: (i) both occur in homologous pairs; (ii) at meiosis both separate, but reunite at fertilization; and (iii) the homologues of both segregate and recombine independently of one another. This coincidence is because the genes are components of the chromosomes.

Exceptions to Mendel's laws

Several patterns of inheritance deviate from those described by Gregor Mendel for which a variety of explanations has been suggested.

1. Sex-related effects

The genetic specification of sexual differentiation is described in Chapter 43. In brief, male embryos carry one short chromosome designated Y and a much longer chromosome designated X, so the male

karyotype can be summarized as XY. The Y carries a small number of genes concerned with development and maturation of masculine features and also sections homologous with parts of the X. The normal female karyotype is XX, females having two X chromosomes and no Y.

A copy of the father's Y chromosome is transmitted to every son, while a copy of his X chromosome is passed to every daughter. Y-linked traits (of which there are very few) are therefore confined to males, but X-linked can show a criss-cross pattern from fathers to daughters, mothers to sons down the generations.

The most significant aspect of sex-related inheritance concerns X-linked recessive alleles, of which there are many. Those which have no counterpart on the Y are more commonly expressed in hemizygous males than in homozygous females.

2. Mitochondrial inheritance

The units of inheritance such as Mendel described are carried on the **autosomes** (non-sex chromosomes), which exist in homologous pairs. These exchange genetic material by 'crossing over' with their partners and segregate at meiosis (see Chapter 18). In addition there are multiple copies of a much smaller genome in virtually every cell of the human body, which resides in the tiny subcellular organelles called mitochondria (see Chapter 12).

The mode of inheritance of mitochondria derives from the mechanism of fertilization. Sperm are very small, light in weight and fast moving. They carry little else but a nucleus, a structure that assists penetration of the ovum and a tail powered by a battery of mitochondria. The latter are however shed before the sperm nucleus enters the ovum and so make no contribution to the mitochondrial population of the zygote. By contrast the ovum is massive and loaded with nutrients and many copies of the subcellular organelles of somatic body cells (see Chapter 14). All the genes carried in the mitochondrial genome are therefore passed on only by females, and equally to offspring of both sexes. Mitochondrial inheritance is therefore entirely from mothers, to offspring of both sexes.

3. Genetic linkage

Mendel did not know where the hereditary information resides. He was certainly unaware of the importance of chromosomes in that regard and the traits he described showed independent assortment with one another. 'Genetic linkage' refers to the observed tendency for combinations of alleles of different genes to be inherited as a group, because they reside close together on the same chromosome (see Chapter 31).

4. Polygenic conditions

Many aspects of phenotype cannot be segregated simply into positive and negative categories, but instead show a continuous range of variation. Examples are height and intelligence. The conventional explanation is that they are controlled by the joint action of many genes. In addition, environmental factors modify phenotypes, further blurring genetically based distinctions (see Chapters 50 and 51).

5. Overdominance, codominance, variable expressivity and incomplete penetrance

Mendel's concept of dominance is that expression of a dominant allele obliterates that of a recessive and that heterozygotes are phenotypically indistinguishable from dominant homozygotes, but this is not always the case. In achondroplasia, a form of short-limbed dwarfism, homozygotes for the dominant achondroplasia allele are so severely affected that they die *in utero*. This phenomenon is called **overdominance**. The consequence is that the live offspring of heterozygous achondroplastic partners occur in the ratio of two affected not three, to each unaffected recessive homozygote (see Chapter 5).

Codominance refers to the expression of *both* antigens in a heterozygote. A familiar example is the presence of both A and B antigenic determinants on the surfaces of red blood cells of AB blood group heterozygotes (see Chapter 29).

The expression of many genes is modified by alleles of other genes as well as by environmental factors. Many genetic conditions therefore show **variable expressivity**, confusing the concept of simple dominance.

In some cases an apparently dominant allele may appear to skip a generation because its expression in one carrier has been negated by other factors. Such alleles are said to show **incomplete penetrance** (see Chapter 9).

6. Genomic imprinting

A striking exception to Mendel's description is mutant alleles that confer markedly different phenotypes in relation to the parental origin of the mutant gene. For example, when a site on the long arm of the maternally derived chromosome 15 has been deleted it gives rise to Angelman syndrome in the offspring. Children with this condition show jerky movements and are severely mentally handicapped. When the equivalent site is deleted from the paternally derived chromosome 15, the child is affected in a very different way. These children have Prader–Willi syndrome**,** characterized by features that include compulsive consumption of food, obesity and a lesser degree of mental handicap. The explanation is in terms of differential 'imprinting' of the part of chromosome 15 concerned (see Chapter 27). Several hundred human genes receive 'imprinting'.

7. Dynamic mutation

Around 20 human genetic diseases develop with increasing severity in consecutive generations, or make their appearance in progressively younger patients. A term that relates to both features is '**dynamic mutation**', which involves progressive expansion of three-base repeats in the DNA associated with certain genes (see Chapter 28).

8. Meiotic drive

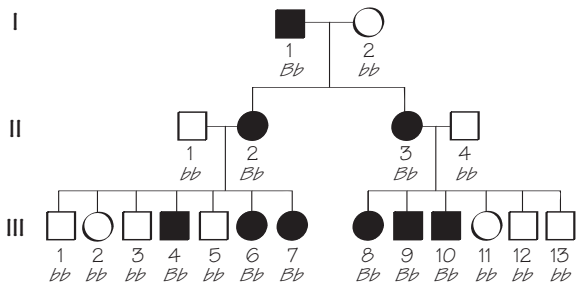
Heterozygotes produce two kinds of gametes, carrying alternative alleles at that locus and the proportions of the offspring described by Mendel indicate equal transmission of those alternatives. Rarely one allele is transmitted at greater frequency than the other, a phenomenon called **meiotic drive**. There is some evidence this may occur with myotonic dystrophy (see Chapter 28).

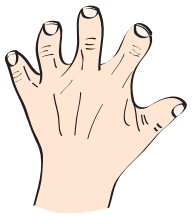
Conclusion

Despite being derived from simple experiments with garden plants and the existence of numerous exceptions, Mendel's laws remain the central concept in our understanding of familial patterns of inheritance in our own species, and in those of most other 'higher' organisms. Examples of simple dominant and recessive conditions of great medical significance are familial hypercholesterolaemia (Chapters 5 and 6) and cystic fibrosis (Chapter 6).

4 Principles of autosomal dominant inheritance and pharmacogenetics

Figure 4.1 **Part of original pedigree for brachydactyly**





A brachydactylous hand

(See Chapter 2 for meaning of symbols)

Figure 4.2 **Estimation of risk for offspring, autosomal dominant inheritance**

Overview

In principle, dominant alleles are expressed when present as single copies (c.f. recessive, Chapter 6), but '**incompletely penetrant**' alleles can remain unexpressed in some circumstances (see Chapter 9). Some alleles that are especially important in medicine are revealed only when people are exposed to unusual chemicals. Some such '**pharmacogenetic traits**' are inherited as dominants, others in other ways (see below).

Rules for autosomal dominant inheritance

The following are the basic rules for simple **autosomal dominant (AD) inheritance**. These rules apply only to conditions of complete penetrance and where no novel mutation has arisen.

1 ***Both males and females express the allele and can transmit it equally to sons and daughters.***

2 ***Every affected person has an affected parent*** ('vertical' pattern of expression in the pedigree). Direct transmission through three generations is practically diagnostic of a dominant.

3 In affected families, ***the ratio of affected to unaffected children is almost always 1 : 1***.

4 ***If both parents are unaffected, all the children are unaffected.***

Example

The first condition in humans for which the mode of inheritance was elucidated was **brachydactyly**, characterized by abnormally short phalanges.

In Mendelian symbols, dominant allele ***B*** causes brachydactyly and every affected individual is either a homozygote (*BB*) or a heterozygote (*Bb*). In practice most are heterozygotes, because ***brachydactyly is a rare trait*** (i.e. <1/5000 births), ***as are almost all dominant disease alleles.*** Unrelated marriage partners are therefore usually recessive homozygotes (*bb*) and the mating can be represented:

Bb × *bb*
↓
Bb,bb
1 : 1

Dominant disease alleles are kept at low frequency since their carriers are less fit than normal homozygotes.

Matings between heterozygotes are the only kind that can produce homozygous offspring:

Bb × *Bb*
↓
BB, *Bb, bb*
1 : 2 : 1; i.e. 3 affected : 1 unaffected.

Dominant disease allele homozygotes are extremely rare and with many disease alleles homozygosity is lethal or causes a more pronounced or severe phenotype.

Matings between heterozygotes may involve inbreeding (see Chapter 5), or occur when patients have met as a consequence of their disability (e.g. at a clinic for the disorder).

All offspring of affected homozygotes are affected:

BB × *bb*
↓
Bb

Unaffected members of affected families are normal homozygotes, so do not transmit the condition: *bb* × *bb* → *bb.*

Estimation of risk

In simply inherited AD conditions where the diagnosis is secure, estimation of risk for the offspring of a family member can be based simply on the predictions of Mendel's laws. For example:

1 For the offspring of a heterozygote and a normal homozygote (*Bb* × *bb* → 1 *Bb*; 1 *bb*),
risk of *B*– = 1/2, or 50%.

2 For the offspring of two heterozygotes (*Bb* × *Bb* → 1 *BB*; 2 *Bb*; 1 *bb*),
risk of *B*– = 3/4, or 75%.

3 For the offspring of a dominant homozygote with a normal partner (*BB* × *bb* → *Bb*),
risk of *B*– = 1, or 100%.

Medical Genetics at a Glance, Third Edition. Dorian J. Pritchard and Bruce R. Korf.

Table 4.1 Some important autosomal dominant inherited diseases in order of approximate frequency in Caucasians.

Condition	Frequency	Map loc.	Gene product
Dominant otosclerosis	1/300–4000	16p	
Familial hypercholesterolaemia (>900 alleles)	1/500	19p	*LDL receptor*
Dentinogenesis imperfecta	1/1000		
Adult polycystic kidney disease	1/1000	16p, etc.	*Polycystin*
Multiple exostosis	1/2000	8q, 11p	
Hereditary motor and sensory neuropathy Type I due to duplication of PMP22 gene. Slow nerve condition, exaggerated foot arch, clawing of toes.	1/3000	17p	
Neurofibromatosis Type I 80% are new mutations. Café-au-lait patches, dermal fibromas, macrocephaly, scoliosis, learning difficulties. Serious complications can be caused by compression by internal fibromas. (see Chapters 9, 57)	1/3000–1/5000	17q	*Neurofibromin t.s.*
Hereditary spherocytosis Red blood cells appear spherical leading to haemolytic anaemia.	1/5000	8p	*ankrin -1*
Osteogenesis imperfecta Highly variable, with multiple fractures and lens deformity. There are recessive forms also. Type I: blue sclerae and deafness; Type II: lethal perinatally; Type III: severe progressive deformation; Type IV: mild bone breakage, short stature, dental abnormalities.	1/5000–1/10 000	17q 7q	*Collagen – COL 1A1* *Collagen – COL 1A2*
Myotonic dystrophy Progressive muscle weakness with inability to relax muscle tone normally, cataracts, cardiac conduction defects, hypogonadism. Caused by CAG triplet expansion. (see Chapter 28)	1/9000	19p 3q	*DM kinase* *zinc finger protein*
Ehlers–Danlos syndrome Numerous types and highly variable, genetic heterogeneity suspected; skin fragility and elasticity, joint hypermobility. Type IV has high risk of early death due to vascular rupture.	1/10 000	2q, etc	*Collagen Type IV:COL 3A1*
Marfan syndrome (several hundred alleles)	1/10 000		
Achondroplasia	1/10 000–1/50 000		
Dominant blindness	1/10 000		
Dominant congenital deafness	1/10 000		
Familial adenomatous polyposis coli (see Chapter 55)	1/10 000	5q	*APC t.s.*
Tuberous sclerosis Type I Type II Highly variable, cortical brain tubers, 'ash leaf spots' and raised lesions on skin, lung lesions, severe mental handicap, epilepsy. (see Chapter 51)	1/15 000	9q 16p	*Hamartin t.s.* *Tuberin t.s.*
Adult-onset cerebellar ataxia Progressive cerebellar ataxia often associated with ophthalmoplegia and dementia.	1/20 000	6p, etc.	*Ataxin* (Spinal CA, Type I)
Huntington disease (see Chapters 28)	1/20 000	4p	*Huntingtin*
Neurofibromatosis Type II Bilateral acoustic neuromas and early cataracts. (see Chapter 56)	1/50 000	22q	*schwannomin (merlin)t.s.*
Von Hippel Lindau syndrome (see Chapter 56)	1/50 000		
Facio-scapulo-humeral dystrophy Progressive limb girdle and facial weakness particularly of the shoulder muscles.	1/50 000	4q	

Calculations involving dominant conditions can, however, be problematical as we usually do not know whether an affected offspring is homozygous or heterozygous (see Chapter 13).

Estimation of mutation rate

The frequency of dominant diseases in families with no prior cases can be used to estimate the natural frequency of new point mutations (see Chapter 26). This varies widely between genes, but averages about one mutational event in any specific gene per 500 000 zygotes. Almost all point mutations arise in sperm, each containing, at the latest estimates, 20–25 000 genes (see Chapter 19). There are therefore perhaps 25 000 mutations per 500 000 sperm, so we can expect around 5% of viable sperm (and babies) to carry a new genetic mutation. However, only a minority of these occurs within genes that produce clinically significant effects, or would behave as dominant traits.

Pharmacogenetics

Pharmacogenetic traits are inherited in a variety of ways (**AD, AR, X-linked R, ACo-D**, etc., see Abbreviations and Chapter 29).

Debrisoquine hydroxylase deficiency (AR)

Genes of the **cytochrome P450** group are of particular importance in drug deactivation (see Chapter 29). One such is **debrisoquine hydroxylase**, involved in the metabolism of the antihypertensive ***debrisoquine*** and other drugs. Five to 10% of Europeans show serious adverse reactions to debrisoquine.

Porphyria variegata (AD)

Skin lesions, abdominal pain, paralysis, dementia and psychosis are brought on by sulphonamides, barbiturates, etc., in about one in 500 South Africans. Death can result from concentration of haem in the liver, following induction of haem-containing Cytochrome P450 proteins.

G6PD deficiency (X-linked R) (see Chapter 11)

G6PD deficiency causes sensitivity notably to ***primaquine*** (used for treatment of malaria), ***phenacetin***, ***sulphonamides*** and **fava beans** (broad beans), hence the name '**favism**' for the haemolytic crisis that occurs when they are eaten by male hemizygotes.

N-acetyl transferase deficiency (AR)

In Western populations, 50% of individuals are homozygous for a recessive allele that confers a dangerously slow rate of elimination of certain drugs, notably ***isoniazid*** prescribed against tuberculosis. The Japanese are predominantly rapid inactivators.

Pseudocholinesterase deficiency (AR)

One European in 3000 and 1.5% of Inuit (Eskimo) are homozygous for an enzyme deficiency that causes lethal paralysis of the diaphragm when given ***succinylcholine*** as a muscle relaxant during surgery.

Halothane sensitivity, malignant hyperthermia (genetically heterogeneous)

One in 10 000 patients can die in high fever when given the anaesthetic ***halothane***, especially in combination with succinylcholine.

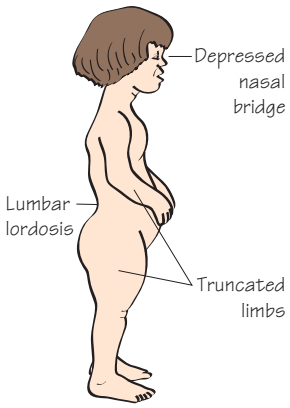
Thiopurine methyltransferase deficiency (ACo-D)

Certain drugs prescribed for leukaemia and suppression of the immune response cause serious side-effects in about 0.3% of the population with deficiency of ***thiopurine methyltransferase.***

5 Autosomal dominant inheritance, clinical examples

Figure 5.1 Achondroplasia

(a) A girl with achondroplasia (Ac ac) showing small stature



(b) Risk of transmission of achondroplasia in a marriage between two achondroplasics

Ac ac × *Ac ac*

~~*Ac Ac*~~	:	*Ac ac*	:	*ac ac*
Lethal	:	2 affected	:	1 unaffected

Gametes →	*Ac*	*ac*
Ac	~~*Ac Ac*~~	*Ac ac*
ac	*Ac ac*	*ac ac*

Ac Ac is lethal before or soon after birth

Risk for liveborn offspring: 2/3 = 67%

Figure 5.2 Disorders of fibroblast growth factor receptors

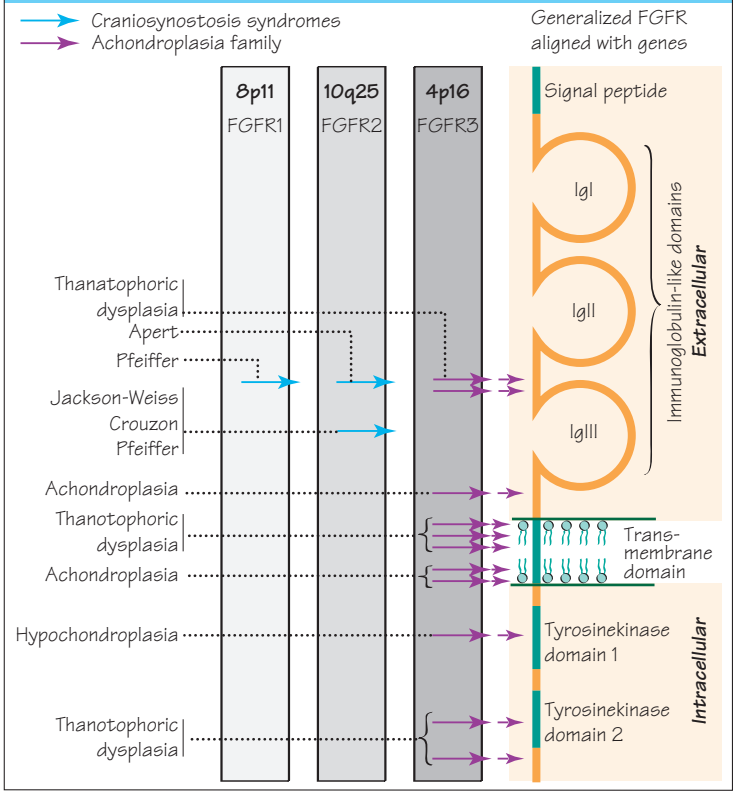
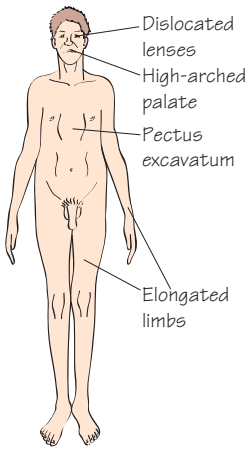
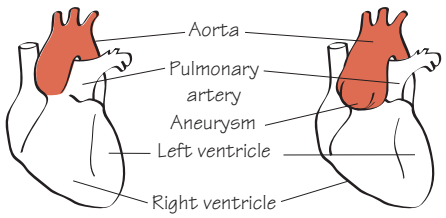


Figure 5.3 Marfan syndrome

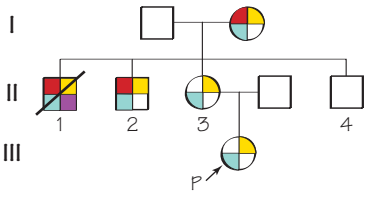
(a) Adult heterozygote showing tall stature



(b) Heart defect



(c) Family pedigree showing variable expression



Unconventional symbols

Cardiac defects	Sudden death
Dislocated lenses	Elongated limbs

Figure 5.4 Receptor-mediated endocytosis and biosynthesis of cholesterol, showing sites of action of mutations of classes I–IV that cause hypercholesterolaemia