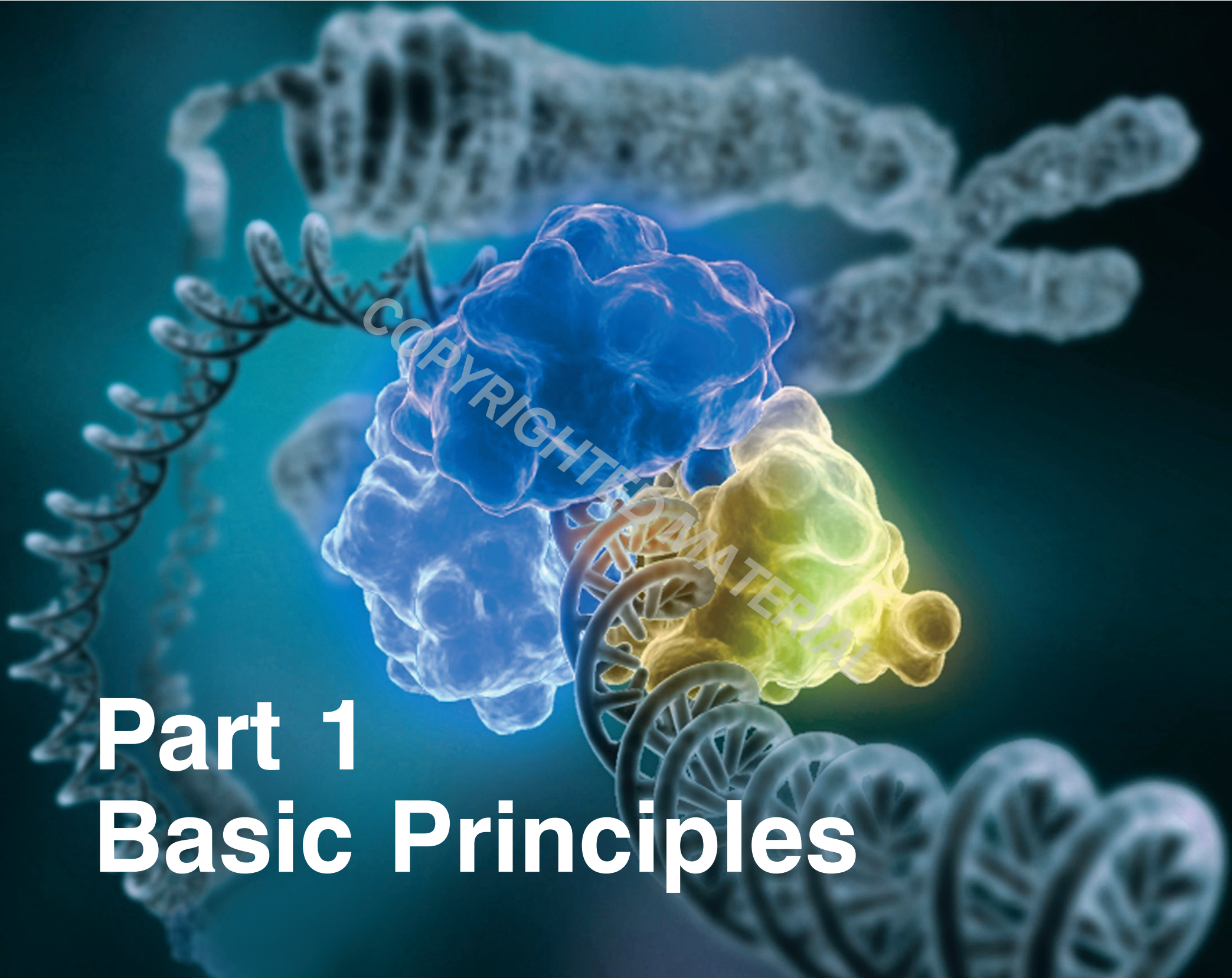
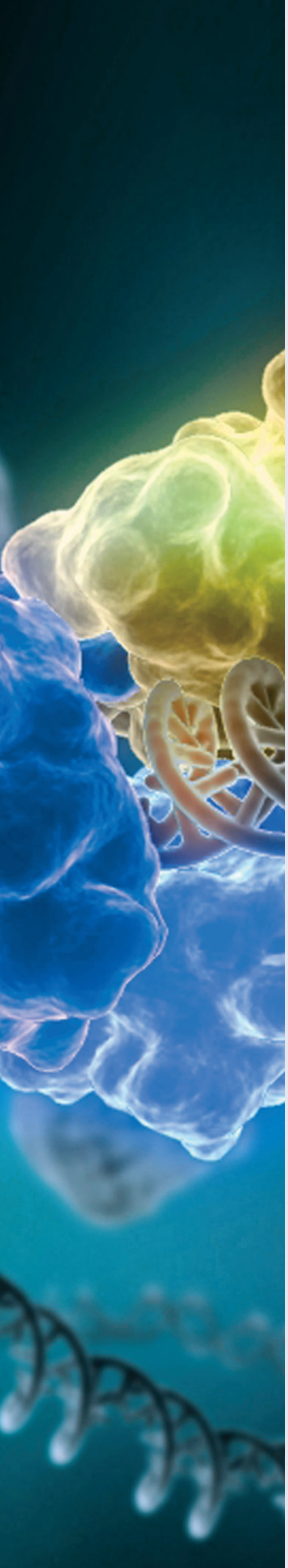


Part 1
Basic Principles



CHAPTER 1

Medical genetics in perspective

Key Topics

Introduction

Medical genetics is the science of human biological variation as it relates to health and disease. Although people have long been aware that individuals differ, that children tend to resemble their parents and that certain diseases tend to run in families, the scientific basis for these observations was only discovered during the past 140 years. The clinical applications of this knowledge are even more recent, with most progress confined to the past 50 years (see Table 1.1). In particular, the rapid sequencing of the entire human genome, completed in 2003, has greatly accelerated the process of gene mapping for genetic conditions and a vast quantity of valuable and continuously updated information has become readily accessible via the internet (as described in detail in Part 3 and on this book's accompanying website at www.wiley.com/go/tobias).

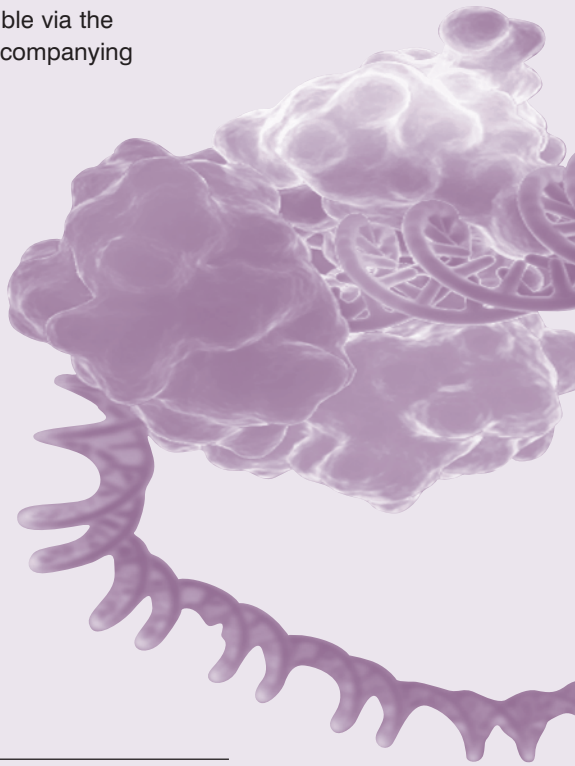


Table 1.1 Some important landmarks in the development of medical genetics

Year	Landmark	Key figure(s)
1839	Cell theory	Schleiden and Schwann
1859	Theory of evolution	Darwin
1865	Particulate inheritance	Mendel
1882	Chromosomes observed	Flemming
1902	Biochemical variation	Garrod
1903	Chromosomes carry genes	Sutton, Boveri
1910	First US genetic clinic	Davenport
1911	First human gene assignment	Wilson
1944	Role of DNA	Avery
1953	DNA structure	Watson, Crick, Franklin and Wilkins
1956	Amino acid sequence of sickle haemoglobin (HbS)	Ingram
1956	46 chromosomes in humans	Tjio and Levan
1959	First human chromosomal abnormality	Lejeune
1960	Prenatal sexing	Riis and Fuchs
1960	Chromosome analysis on blood	Moorhead
1961	Biochemical screening	Guthrie
1961	X chromosome inactivation	Lyon
1961	Genetic code	Nirenberg
1964	Antenatal ultrasound	Donald
1966	First prenatal chromosomal analysis	Breg and Steel
1966	First print edition of Mendelian Inheritance in Man (MIM)	McKusick
1967	First autosomal assignment	Weiss and Green
1970	Prevention of Rhesus isoimmunisation	Clarke
1970	Chromosome banding	Caspersson and Zech
1975	DNA sequencing	Sanger, Maxam and Gilbert
1976	First DNA diagnosis	Kan
1977	First human gene cloned	Shine
1977	Somatostatin made by genetic engineering	Itakura
1979	*In vitro* fertilisation	Edwards and Steptoe
1979	Insulin produced by genetic engineering	Goeddel
1982	First genetic engineering product marketed (Humulin)	Many contributors
1985	DNA fingerprinting	Jeffreys
1986	Polymerase chain reaction (PCR)	Mullis
1987	Linkage map of human chromosomes developed	Many contributors
1987	Online Mendelian Inheritance in Man (OMIM) first available	McKusick
1990	First treatment by supplementation gene therapy	Rosenberg, Anderson, Blaese
1990	First version of London Dysmorphology Database	Baraitser and Winter
1990	First clinical use of preimplantation genetic diagnosis (PGD)	Handyside, Winston and others
1991	First version of London Neurogenetics Database	Baraitser and Winter
1993	First physical map of the human genome	Many contributors

Table 1.1 *continued*

Year	Landmark	Key figure(s)
2000	First draft of the human genome sequence	Many contributors
2003	Completion of human genome sequencing (99.999%)	HGSC and Celera
2006	Preimplantation genetic haplotyping (PGH) announced	Renwick, Abbs and others
2007	Human genome SNP map (3.1 million SNPs) reported	International HapMap Consortium
2007	Completion of DNA sequencing of personal genomes	Watson and Venter
2008	Launch of project to sequence the genomes of over 1000 individuals from 20 different populations worldwide	International 1000 Genomes Project
2010	Publication of catalogue of human genetic variation (believed to be 95% complete)	International 1000 Genomes Project

HGSC: Human Genome Sequencing Consortium; OMIM: Online Mendelian Inheritance in Man; SNP: single nucleotide polymorphism.

Scientific basis of medical genetics

Mendel's contribution

Prior to Mendel, parental characteristics were believed to blend in the offspring. While this was acceptable for continuous traits such as height or skin pigmentation, it was clearly difficult to account for the family patterns of discontinuous traits such as haemophilia or albinism. Mendel studied clearly defined pairs of contrasting characters in the offspring of the garden pea (*Pisum sativum*). These peas were, for example, either round or wrinkled and were either yellow or green. Pure-bred strains for each of these characteristics were available but when cross-bred (the first filial or F_1 progeny) were all round or yellow. If F_1 progeny were bred then each characteristic was re-observed in a ratio of approximately 3 round to 1 wrinkled or 3 yellow to 1 green (in the second filial or F_2 progeny). Mendel concluded that inheritance of these characteristics must be particulate with pairs of hereditary elements (now called genes). In these two examples, one characteristic (or trait) was dominant to the other (i.e. all the F_1 showed it). The fact that both characteristics were observed in the F_2 progeny entailed *segregation of each pair of genes with one member to one gamete and one to another gamete* (Mendel's first law).

Figures 1.1 and 1.2 illustrate these experiments with upper-case letters used for the dominant characteristic and lower-case letters used for the masked (or recessive) characteristic. If both members of the pair of genes are identical, this is termed homozygous (for the dominant or recessive trait), whereas a heterozygote has one gene of each type.

In his next series of experiments Mendel crossed pure-bred strains with two characteristics, e.g. pure-bred round/yellow with pure-bred wrinkled/green. The F_1 generation showed only the two dominant characteristics – in this case round/yellow. The F_2 showed four combinations: the original two, namely round/yellow and wrinkled/green, in a ratio of approximately 9:1 and two new combinations – wrinkled/yellow and round/green in a ratio of approximately 3:3 (Fig. 1.3).

In these experiments, there was thus no tendency for the genes arising from one parent to stay together in the offspring. In other words, *members of different gene pairs assort to gametes independently of one another* (Mendel's second law).

Although Mendel presented and published his work in 1865, after cultivating and studying around 28,000 pea plants, the significance of his discoveries was not realised until the early 1900s when three plant breeders, De Vries, Correns and Tschermak, confirmed his findings.

Chromosomal basis of inheritance

In 1839, Schleiden and Schwann established the concept of cells as the fundamental living units. Hereditary transmission through the sperm and egg was known by 1860, and in 1868, Haeckel, noting that the sperm was largely nuclear material, postulated that the nucleus was responsible for heredity. Flemming identified chromosomes within the nucleus in 1882, and in 1903 Sutton and Boveri independently realised that the behaviour of chromosomes during the production of gametes paralleled the behaviour of Mendel's hereditary elements. Thus, the chromosomes were discovered to carry the genes. However, at that time, although the chromosomes were known to consist of protein and nucleic acid, it was not clear which component was the hereditary material.

Chemical basis of inheritance

Pneumococci are of two genetically distinct strains: rough or non-encapsulated (non-virulent) and smooth or encapsulated (virulent). In 1928, Griffith added heat-killed smooth bacteria to live rough bacteria and found that some of the rough pneumococci were transformed to the smooth, virulent type. Avery, MacLeod and McCarty repeated this experiment in 1944 and showed that nucleic acid was the transforming agent. Thus, nucleic acid was shown to carry hereditary information. This stimulated intense interest in the composition of nucleic acids,

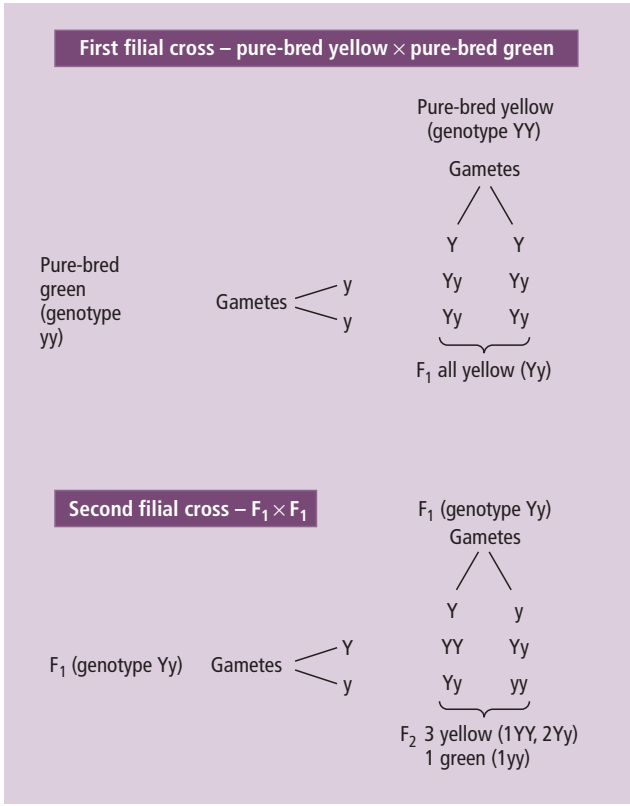


Fig. 1.1 Example of Mendel's breeding experiments for a single trait (yellow or green peas).

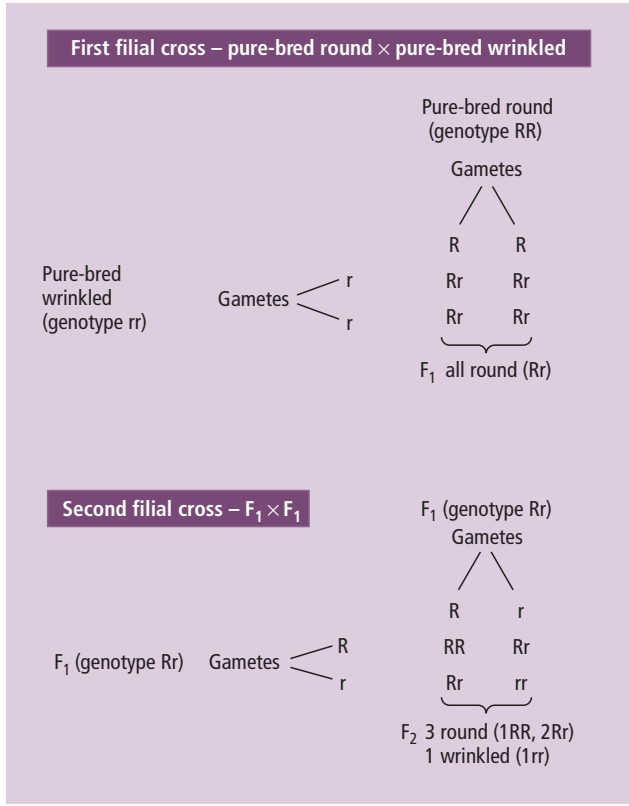
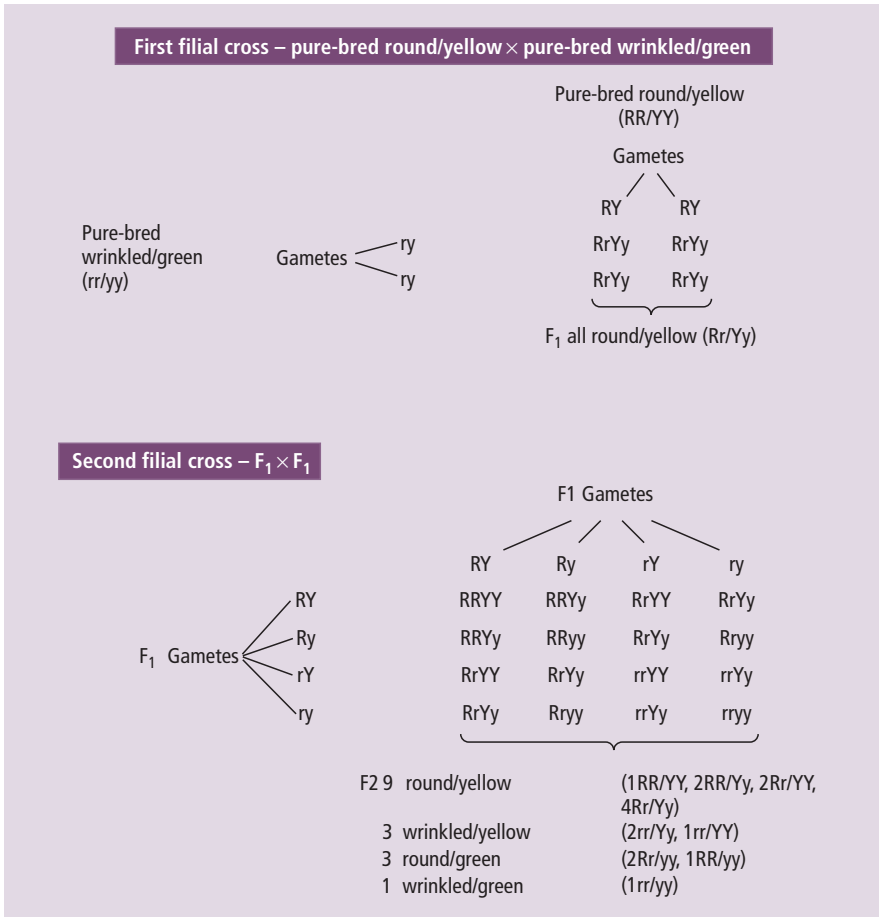


Fig. 1.2 Example of Mendel's breeding experiments for a single trait (round or wrinkled peas).

Fig. 1.3 Example of Mendel's breeding experiments for two traits (yellow or green and round or wrinkled peas).



which culminated in the discovery, by Watson, Crick, Franklin and Wilkins, of the double-helical structure for deoxyribonucleic acid (DNA) in 1953.

Chromosomal disorders

By 1890, it was known that one human chromosome (the X chromosome) did not always have a partner, and in 1905 Wilson and Stevens extended this observation by establishing the pattern of human sex chromosomes. At this time, it was believed that there were 47 chromosomes, including one X chromosome, in each male somatic cell and 48 chromosomes, including two X chromosomes, in each female cell. In 1923, the small Y chromosome was identified, and both sexes were thought to have 48 chromosomes. Tjio and Levan refuted this in 1956 when they showed the normal human chromosome number to be 46. In 1959, the first chromosomal disease in humans, trisomy 21, was discovered by Lejeune and colleagues, and by 1970, over 20 different human chromosomal disorders were known. The development of chromosomal banding in 1970 markedly increased the ability to resolve small chromosomal aberrations, and so by 1990 more than 600 different chromosome abnormalities had been described, in addition to many normal variants. This number has increased further with the development of improved techniques including various fluorescence *in situ* hybridisation (FISH) methods and comparative genomic hybridisation (CGH). In fact, the increased resolution of the more recently developed techniques such as array CGH (see Chapter 7), has led to greater difficulties in differentiating between the increasingly numerous normal and abnormal chromosomal variants. This, in turn, has necessitated the development of international databases of such submicroscopic variants such as DECIPHER (Fig. 1.4), based at the Sanger Institute (http://decipher.sanger.ac.uk/), and the Database of Genomic Variants at Toronto (http://projects.tcag.ca/variation).

Mitochondrial disorders

Mitochondria have their own chromosomes and these are passed on from a mother to all of her children but not from the father. These chromosomes are different in several respects from their nuclear counterparts. For instance, they contain only 37 genes, a high and variable number of DNA copies per cell, very little non-coding DNA and no introns (see Chapter 5). Mutations in genes on these mitochondrial chromosomes can cause disease and this was first shown in 1988 for a maternally inherited type of blindness (Leber optic neuropathy). Since then, it has been shown that many different mitochondrial mutations, including point mutations, deletions and duplications, alone or in combination, can result in a variety of different disorders. Moreover, the relationship between genotype and phenotype is not straightforward, in part due to heteroplasmy, the tendency for a mitochondrial mutation to be present in only a proportion of the cell's mitochondrial genome copies (see Chapter 10).

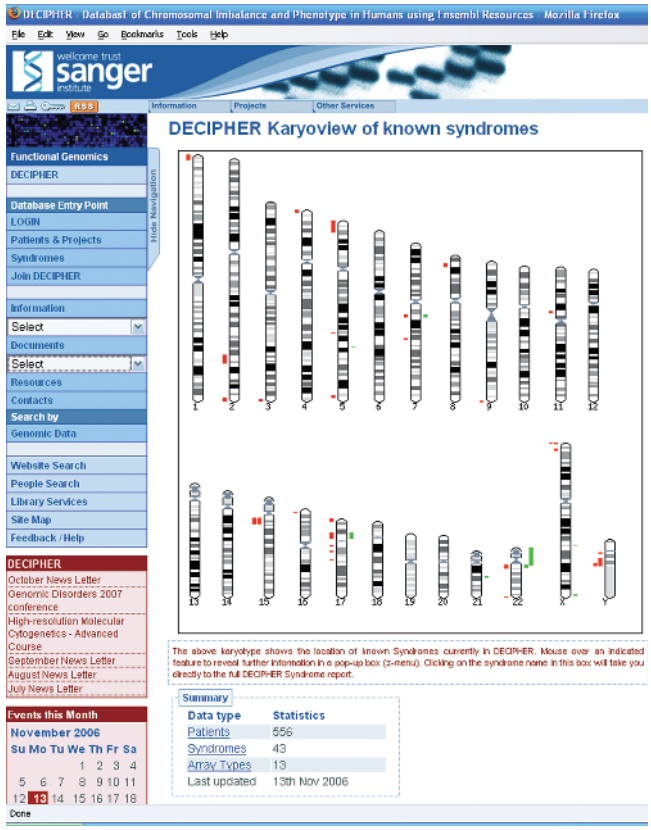


Fig. 1.4 Diagram displayed on the DECIPHER website (at http://decipher.sanger.ac.uk/syndromes) indicating chromosomal loci associated with known clinical syndromes. Reproduced with permission from the Wellcome Trust Sanger Institute. Flicek et al. (2010) Nucleic Acids Res 38 (Database issue):D557–62.

Single-gene disorders

In 1902, Garrod presented his studies on alkaptonuria, a rare condition in which patients have urine that darkens on standing and arthritis. He found three of 11 sets of parents of affected patients to be blood relatives and, in collaboration with Bateson, proposed that this was a Mendelian recessive trait with affected persons homozygous for the underactive gene. This was the first disease to be interpreted as a single-gene trait. Garrod also conceived the idea that patients with alkaptonuria and other inborn errors of metabolism really represented one extreme of human biochemical variation and that other less clinically significant variations were to be expected.

There followed numerous descriptions of distinct human single-gene traits and at the present time more than 7,000 human single-gene traits are known (Table 1.2). In 1949, Pauling suspected an abnormal haemoglobin to be the cause of sickle-cell anaemia, and this was confirmed by Ingram in 1956, who found an altered haemoglobin polypeptide sequence. This was the first demonstration in any organism that a mutation in a structural gene could produce an altered amino acid sequence. In 1959, only two abnormal haemoglobins were known; now the number exceeds 450. In 1948, Gibson

Table 1.2 Human genes and single-gene traits (see McKusick, 2007, and the OMIM database)

	1966	1975	1986	1994	2010
Autosomal dominant	837	1,218	2,201	4,458	19,007 (6,469)
Autosomal recessive	531	947	1,420	1,730	autosomal*
X-linked	119	171	286	412	1,131 (515)
Y-linked	–	–	–	19	59 (11)
Mitochondrial	–	–	–	59	65 (30)
Total	1,487	2,336	3,907	6,678	20,262 (7,025)

*The distinction between autosomal dominant and autosomal recessive traits was not maintained in the Mendelian Inheritance in Man (MIM) catalogue after May 1994 for several reasons. These included: the distinction being only relative (with, for instance, a deficiency state in an otherwise 'autosomal recessive' condition being detectable in a heterozygote with a sufficiently sensitive detection system); and for several conditions, the occurrence of both autosomal dominant and recessive forms that result from the same gene, depending on which specific mutations are present. Figures correct on 22 November 2010. In parenthesis are the total numbers of OMIM entries that have phenotypic information.

demonstrated the first enzyme defect in an autosomal recessive condition (NADH-dependent methaemoglobin reductase in methaemoglobinaemia). The specific biochemical abnormalities in over 400 inborn errors of metabolism have now been determined, but the polypeptide product is still unknown in many human single-gene disorders. Study of these rare, and not so rare, single-gene disorders has provided valuable insights into normal physiological mechanisms; for example, our knowledge of the normal metabolic pathways has been derived largely from the study of inborn errors of metabolism.

Huge progress has been made in the assignment of genes to individual chromosomes, in mapping the genes' precise locations and, more recently, in identifying their entire nucleotide sequences. The first human gene assignment was made by Wilson, who identified the X-linked trait for colour blindness in 1911 and assigned the gene to the X chromosome. Other X-linked traits rapidly followed, while the first autosomal gene to be assigned was thymidine kinase to chromosome 17 in 1967. By 1987, a complete linkage map of all human chromosomes had been developed and this was followed in 1993 by the first physical map. These were essential steps towards the final goal of the Human Genome Project. The Human Genome Project, initiated in 1990, aimed to map and sequence all human genes by the year 2005. Rapid technological advances, particularly the development of high-throughput automated fluorescence-based DNA sequencing (see Chapter 4), in addition to competition between the publicly funded (International Human Gene Sequencing Consortium) and private company (Celera) schemes, led to the early completion of the human genome sequence in 2003 (see Chapter 2). This sequence information, together with an enormous body of associated data, has been made publicly available via internet databases. The information available includes associations with human diseases, gene mapping data, cross-species comparisons, expression patterns and predicted protein features (Fig. 1.5). These and other valuable databases are described in Part 3, and a user's guide is provided online (at www.wiley.com/go/tobias).

Multifactorial (part-genetic) disorders

Galton studied continuous human characteristics such as intelligence and physique, which did not seem to conform to Mendel's laws of inheritance, and an intense debate ensued, with the supporters of Mendel on the one hand and those of Galton on the other. Finally, a statistician, Fisher, reconciled the two sides by showing that such inheritance could be explained by multiple pairs of genes, each with a small but additive effect. Discontinuous traits with multifactorial inheritance, such as congenital malformations, were explained by introducing the concept of a threshold effect for the disorder: manifestation only occurred when the combined genetic and environmental liability passed the threshold. Many human characteristics are determined in this fashion. Usually factors in the environment interact with the genetic background.

Although the genetic contribution to multifactorial disorders is now well accepted, the number and nature of the genes involved and their mechanisms of interaction between each other and environmental factors are largely unknown. This is the current focus of a great deal of research and progress has been made in identifying the genetic contribution for several of these conditions including insulin-dependent diabetes mellitus, rheumatoid arthritis, dementia due to Alzheimer's disease, premature vascular disease, schizophrenia, Parkinson disease, atopic dermatitis and asthma.

Somatic cell genetic (cumulative genetic) disorders

All cancers result from the accumulation of genetic mutations. Usually these mutations only occur after conception and are thus confined to certain somatic cells, but in a small but clinically important proportion, an initial key mutation is inherited. Boveri first advanced the idea that chromosomal changes caused cancer, and early support for this idea came from the demonstration in 1973 of a specific chromosomal translocation (the Philadelphia chromosome) in a type of leukaemia. Subsequently, a large number of both specific and non-specific chromosomal changes have been found in a wide variety of cancers. In turn,

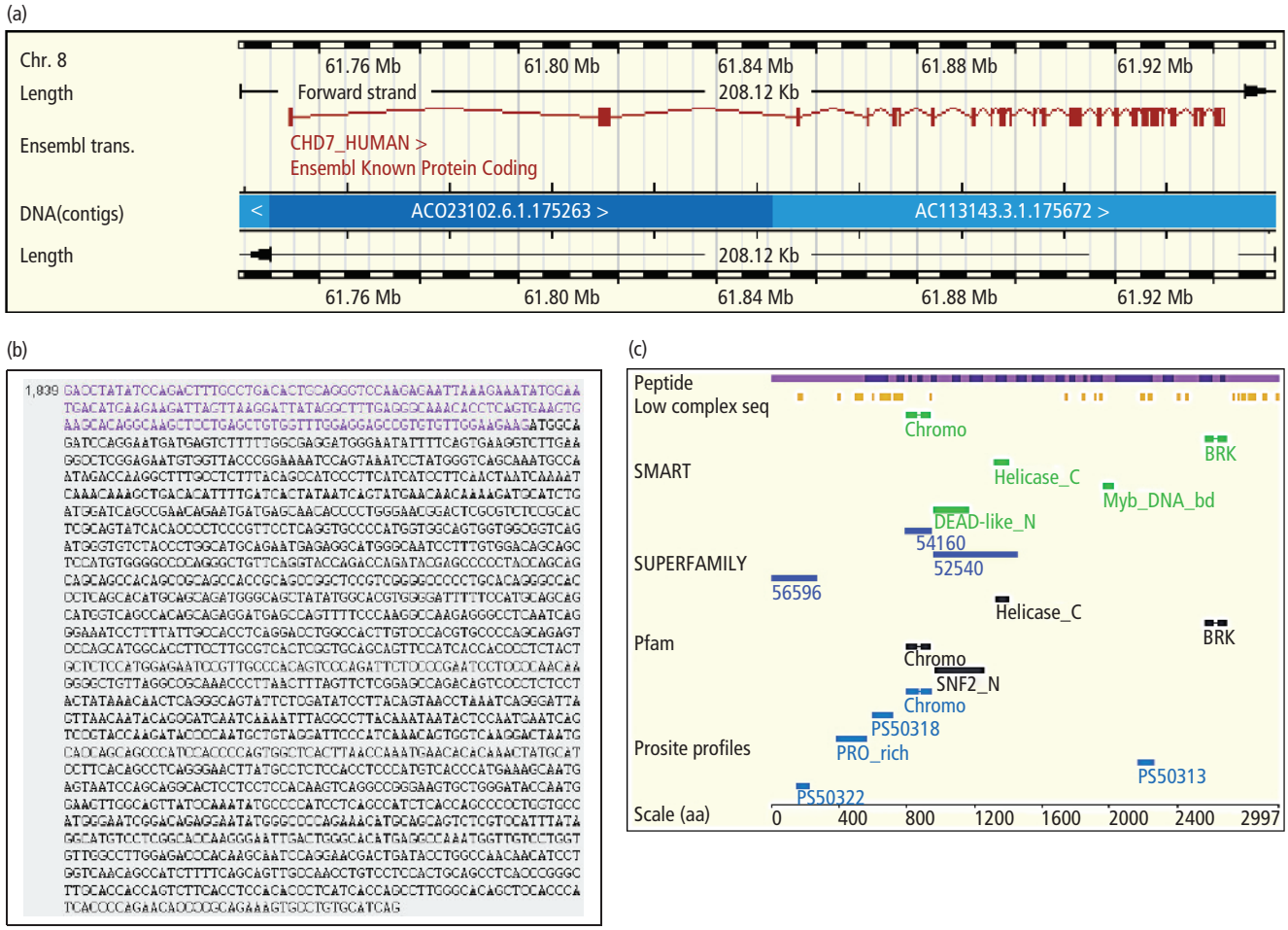


Fig. 1.5 (a) Transcript structure of the 38-exon CHARGE association gene, *CHD7*, on human chromosome 8. (b) DNA sequence of the first coding exon (containing the start codon). The DNA sequence displayed in purple is the untranslated region of this exon, immediately preceding the ATG start codon. (c) Protein features of CHD7, as predicted by the different computer programs (e.g. SMART) shown on the left. Reproduced with permission from the Ensembl database at the Wellcome Trust Sanger Institute. Flicek et al. (2010) Ensembl's 10th year. Nucleic Acids Res 38 (Database issue):D557–62. See Chapter 19.

these changes were clues to specific genes that were key determinants of progression to cancer. Many of these genes have now been cloned and this has resulted in an improved understanding of the molecular basis of cancer and provided the clinician with a means of detection of presymptomatic carriers of cancer-predisposing genes. In addition, it is now recognised that changes in the DNA sequence occurring within somatic cells play an important role in ageing and in certain mosaic disorders such as McCune–Albright syndrome, which results from post-zygotic somatic activating mutations in the *GNAS1* gene. They also may be responsible for the exacerbation of symptoms with age in some inherited disorders such as myotonic dystrophy, in which there is somatic expansion of the inherited mutation (see Chapter 16), and mitochondrial disorders (see Chapter 10).

Clinical applications of medical genetics

Genetically determined disease has become an increasingly important part of ill health in the community now that most infections can be controlled and now that modern medical and nursing care can save many affected infants who previously would have succumbed shortly after birth. This has led to an increased demand for informed genetic counselling and for screening tests both for carrier detection and to identify pregnancies at risk.

Genetic assessment and management

Davenport began to give genetic advice as early as 1910 in the USA, and the first British genetic counselling clinic was established in 1946 at Great Ormond Street, London. Public demand has since caused a proliferation of genetic counselling centres so that there are now more than 40 in the UK and more than 450 in the USA. The scope for genetic counselling has, in fact, in recent years expanded dramatically with the increasingly available data on human genetic disorders (e.g. their mechanism of inheritance in addition to their associated genes and markers) and the increasing availability of mutation analysis. Clinical geneticists play an increasingly important role

in the clinical assessment and genetic testing of patients with genetic conditions and their at-risk relatives. Furthermore, geneticists are now much more involved in the management of patient follow-up, often coordinating several other specialties and initiating patient participation in multicentre clinical studies. These include trials of clinical screening methods and of new therapeutic strategies.

In addition to an accurate assessment of the risks in a family, the clinical geneticist also needs to discuss reproductive options. Important advances in this respect have been made with regard to prenatal diagnosis with the option of selective termination, and this has been a major factor in increasing the demand for genetic counselling. Prenatal diagnosis and now, in certain cases, preimplantation diagnosis (see below), offer reassurance for couples at high risk of serious genetic disorders and allow many couples, who were previously deterred by the risk, the possibility of having healthy children.

Genetic amniocentesis was first attempted in 1966 and the first prenatally detected chromosome abnormality was trisomy 21 in 1969. Chromosome analysis following amniocentesis is now a routine component of obstetric care, and over 200 different types of abnormality have been detected. Amniocentesis or earlier chorionic villus sampling can also be used to detect biochemical alterations in inborn errors of metabolism. This was first used in 1968 for a pregnancy at risk of Lesch–Nyhan syndrome and has since been used for successful prenatal diagnosis in over 150 inborn errors of metabolism. Prenatal diagnosis can also be performed by DNA analysis of fetal samples. This approach was first used in 1976 for a pregnancy at risk of α-thalassaemia and has now been used in over 200 single-gene disorders, and for many of these, including cystic fibrosis, the fragile X syndrome and Duchenne muscular dystrophy, it has become the main method of prenatal diagnosis.

Preimplantation diagnosis (PGD), first used clinically (for sex determination) in 1990, is a more recently established technique that permits the testing of embryos at a very early stage following *in vitro* fertilisation (IVF), prior to implantation in the uterus. In this procedure, a single cell or blastomere is removed by suction, apparently harmlessly, from the embryo. This is usually carried out at the five- to ten-cell stage, at approximately 3 days post-fertilisation. Using the polymerase chain reaction (PCR) or FISH, it is then possible to determine the fetal sex in cases of sex-linked disease or to detect a specific mutation or chromosomal abnormality (also see Chapter 12).

A more recent extension of the PGD technology is the technique known as preimplantation genetic haplotyping (PGH), which was announced in 2006 (see Renwick *et al.*, 2006 in Further reading). In this technique, as in PGD, a cell is extracted from an embryo following IVF. In PGH, however, the DNA undergoes testing for a set of DNA markers closely linked to the disease gene without requiring the prior identification of the precise causative mutation. This can be performed by carrying out simultaneous or multiplex PCRs of several DNA markers, using fluorescence to detect and differentiate the products. The possible future possibilities and likely limitations of PGD are discussed in an interesting opinion article published very recently in *Nature* (see Handyside, 2010).

The prenatal tests that detect chromosomal, biochemical or DNA alterations cannot, however, detect many of the major congenital malformations. The alternative approach of fetal visualisation has been necessary for these. High-resolution ultrasound scanning was first used to make a diagnosis of fetal abnormality (anencephaly) in 1972 and since then over 400 different types of abnormality have been detected. The clinical benefits of the more recently developed three-dimensional ultrasound techniques over standard two-dimensional ultrasound fetal imaging are not yet clear and three-dimensional ultrasound is not currently in routine clinical use during pregnancy in the UK.

Treatment and prevention of genetic disease

A great deal of research has been undertaken into the possibility of effective treatment of genetic diseases. In 1990, the first attempts at human supplementation gene therapy for a single-gene disorder (adenosine deaminase deficiency) were performed. Since then, different gene therapy methods have been devised, depending on the nature of the mutation, and several hundred gene therapy trials are now underway. Unfortunately, the development of a safe, effective, non-immunogenic, well-regulated system that permits the efficient delivery of the therapeutic DNA to sufficient numbers of target cells continues to present a significant challenge.

Although cures for genetic diseases continue to remain elusive, there are now many genetic conditions for which a precise diagnosis leads to significant benefits in terms of clinical management. In some conditions, for example, the almost complete prevention or reversal of the phenotypic effects of a genotype is achievable. This is the case, for instance, with regular venesection for haemochromatosis, with dietary treatment of phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency and with modern enzyme replacement therapy for Gaucher's disease and Fabry's disease. In other cases, appropriate surveillance for clinical complications to permit their early treatment can be instituted. For example, as described in more detail in Chapter 13, screening can permit the early removal of pre-cancerous neoplastic lesions in hereditary cancer syndromes such as familial adenomatous polyposis (FAP), MYH polyposis, hereditary non-polyposis colorectal cancer (HNPCC) and familial breast cancer. In addition, in many other familial conditions, a genetic diagnosis facilitates the detection and early treatment of other complications such as diabetes and heart block in myotonic dystrophy; scoliosis, optic glioma and hypertension in neurofibromatosis type 1 (NF1); and aortic dilatation in Marfan syndrome. Moreover, as mentioned above, following their genetic diagnosis, patients are increasingly enrolled by clinical geneticists in large multicentre trials of new clinical screening and therapeutic methods. Such trials currently include, for instance, biochemical and ultrasound ovarian

screening for women at high risk of developing ovarian cancer and the Mirena intra-uterine device for women with mismatch repair gene mutations who are at risk of endometrial cancer.

The majority of couples are not aware that they are at risk of having offspring with a genetic condition until they have an affected child. This has led to an increased emphasis on prenatal screening, for example by fetal ultrasound examination and by measurement of maternal serum α-fetoprotein and other analytes to detect pregnancies at increased risk of neural tube defects and chromosomal abnormalities. For example, the efficiency of prenatal screening has increased to a point where approximately 85–90% of cases of fetal Down syndrome can be detected by 10–13 weeks' gestation for a false positive rate of 3.5%. Maternal age alone is no longer a suitable indication for prenatal diagnosis and far fewer amniocenteses are now required (see Chapter 17). Neonatal screening was introduced in 1961 for PKU and other conditions where early diagnosis and therapy will permit normal development, such as congenital hypothyroidism. More recently, neonatal screening for cystic fibrosis has been introduced, and it is likely that in the future there will be continued development of population screening, as well as prenatal, neonatal and preconceptional screening, which should lead to a reduced frequency of several genetic diseases.

SUMMARY

- The scientific basis of medical genetics began to be elucidated in 1865 when Mendel published his laws of segregation and independent assortment. These were confirmed around 40 years later.
- Chromosomes were identified in 1882, the hereditary information was shown in 1944 to consist of nucleic acid and the double-helical structure of DNA was discovered in 1953.
- The first single-gene trait, alkaptonuria, was identified in 1902 as a Mendelian recessive condition. Numerous other genes associated with Mendelian traits have been discovered since.
- Extremely rapid advances have been made in gene mapping and automated sequencing, facilitating the early completion of the human genome sequence in 2003.
- Prenatal diagnosis and screening are important adjuncts to genetic counselling as they allow couples at risk of fetal abnormality the confidence to plan for future healthy children.
- PGD is an IVF-based technique that can permit the detection of genetic abnormalities in certain cases, before implantation of an embryo.
- An enormous quantity of human molecular genetic information is now freely available on the internet. Ways of accessing this information are presented in Chapter 19 and online at (www.wiley.com/go/tobias).

FURTHER READING

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Handyside A (2010) Let parents decide. *Nature* **464**:978–9.

McKusick VA (2007) Mendelian Inheritance in Man and its online version, OMIM. *Am J Hum Genet* **80**:588–604.

Ogilvie CM, Braude PR, Scriven PN (2005) Preimplantation genetic diagnosis – an overview. *J Histochem Cytochem* **53**:255–60.

Renwick PJ, Trussler J, Ostad-Saffari E, Fassihi H, Black C, Braude P, Ogilvie CM, Abbs S (2006) Proof of principle and first cases using preimplantation genetic haplotyping – a paradigm shift for embryo diagnosis. *Reprod Biomed Online* **13**:110–9.

WEBSITES

European Society for Human Reproduction and Embryology (ESHRE):
http://www.eshre.com

Human Fertilisation and Embryology Authority (HFEA):
http://www.hfea.gov.uk

OMIM (Online Mendelian Inheritance in Man):
http://www.ncbi.nlm.nih.gov/omim/

Preimplantation Genetics Diagnosis International Society (PGDIS), which is monitoring PGD activity worldwide:
http://www.pgdis.org/

Self-assessment

1. Which of the following is not a typical feature of mitochondrial inheritance?
A. Maternal transmission
B. Heteroplasmy
C. More introns in mitochondrial genes than in nuclear genes
D. The presence of fewer than 40 genes in the mitochondrial genome
E. Lack of a straightforward genotype–phenotype relationship

2. In preimplantation genetic diagnosis (PGD), which of the following does not take place?
A. *In vitro* fertilisation
B. Testing of each of the cells of the embryo for the specific mutation
C. Fetal sex determination of embryos in sex-linked disease
D. The use of the polymerase chain reaction (PCR) to detect a specific mutation or haplotype
E. The use of fluorescence *in situ* hybridisation (FISH) to detect an unbalanced chromosome abnormality

3. Which one of the following conditions is not usually regarded as multifactorial?
A. Rheumatoid arthritis
B. Insulin-dependent diabetes mellitus
C. McCune–Albright syndrome
D. Asthma
E. Parkinson disease

4. Which of the following is not useful in connection with the following genetic conditions?
A. Venesection for iron overload in haemochromatosis
B. Regular blood pressure check in neurofibromatosis type 1 (NF1)
C. Neonatal screening for hypothyroidism and phenylketonuria (PKU)
D. Dietary treatment for PKU
E. Enzyme replacement therapy for familial adenomatous polyposis (FAP)

5. Which of the following pairings between individuals and a genetics landmark is incorrect?
A. Mendel and the independent assortment of different gene pairs to gametes
B. Flemming and the identification of chromosomes within the nucleus
C. The discovery of the helical structure of DNA and Watson, Crick, Franklin and Wilkins
D. The first identification of a chromosomal abnormality and Jeffreys
E. PCR and Mullis