J. M. CONNOR
M. A. FERGUSON-SMITH

ESSENTIAL MEDICAL GENETICS

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J. M. Connor MD BSc MRCP
Wellcome Trust Senior Lecturer, and
Honorary Consultant in Medical Genetics

M. A. Ferguson-Smith FRS FRSE FRCP FRCPath
Professor of Medical Genetics, and
Director of the West of Scotland Regional Genetics Service

University of Glasgow, and
Duncan Guthrie Institute of Medical Genetics
Yorkhill, Glasgow

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Preface

A genetic component is evident in the aetiology of most human diseases. Hence a knowledge of medical genetics is essential for all practitioners of medicine. Only a few years ago such knowledge had to be self-taught but medical genetics is now included in most medical and dental undergraduate curricula. This book was produced to meet the needs of medical and dental undergraduates for an inexpensive yet comprehensive account of basic principles and clinical applications of modern medical genetics. We also hope that it may be of value to postgraduates who qualified prior to the advent of formal medical genetics tuition.

The text is divided into two sections reflecting our preclinical and clinical lecture courses, developed since their inception in 1963. Over these years the growth in knowledge about the mechanisms of heredity in health and disease has been dramatic and increasingly prevention and treatment of genetic diseases is now possible. This is reflected by the development of medical genetics from a purely academic discipline into a clinical speciality. We have chosen human rather than animal examples of disease to illustrate basic principles, and have sought to emphasise practical ways in which these principles can be applied in medical practice, basing what we teach on our everyday experience in the clinics and laboratories which provide the West of Scotland Regional Genetics Service. We thus include what we regard as essential for medical genetics practice and provide, where necessary, references to specialised texts where the reader may find more extensive coverage of areas of particular interest.

Despite the recent rapid advances, there are still many areas of genetics which are ill-understood. We include these recent advances but also take the less usual step for an undergraduate text of indicating the areas which need further research. Thus we hope to discourage the common undergraduate misconception that nothing is left to discover in this or for that matter any other branch of medicine.

JM Connor
MA Ferguson-Smith

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Contents

Chapter 1
Human Genetics in Perspective

Human genetics is the scientific study of variation and heredity in man, whereas medical genetics is concerned with the application of these principles to the practice of medicine. Although man has always been aware that individuals differ and that children tend to resemble their parents, the scientific basis for these observations was only discovered during the past 150 years. The clinical application of this knowledge is even more recent, with most progress confined to the past 25 years.

Mendel's contribution

Prior to Mendel parental characteristics were believed to blend in the offspring. Whilst this was acceptable for continuous traits such as height or intelligence, it was clearly difficult to account for the family patterns of discontinuous traits such as haemophilia or albinism.

Gregor Mendel (1822-1884), an Austrian monk, studied single clearly defined pairs of contrasting characters in the offspring of the garden pea. He reached three main conclusions:

1. *Inheritance is particulate*
Inherited characteristics are determined by pairs of hereditary elements (now called genes).

2. *Each pair of genes segregates* (*Mendel's first law*)
The two members of a single pair of genes (the alleles) pass to different gametes during reproduction.

3. *The gene pairs show independent assortment* (*Mendel's second law*)
Members of different gene pairs assort to gametes independently of one another.

These two fundamental laws may be summarised: alleles segregate, non-alleles assort.

Although Mendel presented and published his work in 1865 the significance of his discoveries was not realised until the early 1900's

when three plant breeders, de Vries, Correns and Tschermak independently rediscovered 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 became known by 1860 and in 1868 Haeckel, noting that the sperm was largely nuclear material, postulated that the nucleus was responsible for heredity. Walther Flemming identified chromosomes within the nucleus in 1877 and in 1903 Sutton and Boveri independently realised that the behaviour of the chromosomes during the production of gametes paralleled the behaviour of Mendel's hereditary units. Thus the chromosomes were discovered to carry the genes. At that time the chromosomes were known to consist of protein and nucleic acid and 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). Griffith in 1928 added heat-killed smooth bacteria to live rough and found that some of the rough pneumococci were transformed to the smooth, virulent type. Avery, McLeod and McCarthy repeated this experiment in 1944 and showed that nucleic acid was the transforming agent. Thus nucleic acid was shown to carry the hereditary information. This stimulated intense interest in the composition of nucleic acids which culminated in Watson and Crick's discovery of the double helical structure for deoxyribonucleic acid (DNA) in 1953.

Human chromosomal disorders

By 1890 it was known that one human chromosome (known as the accessory 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 there were believed to be 48 chromosomes in each somatic cell. 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 man, trisomy 21, was discovered by Lejeune and colleagues. Other abnormalities were found and by 1970, over 20 different human chromosomal disorders were known. The development of chromosomal banding in 1970 increased the ability to resolve small chromosomal aberrations and so by 1980 more than 50

different chromosome abnormalities were known in addition to many normal variants.

Human single gene traits

The knowledge that certain diseases run in families is not new. In the Jewish Talmud from the 5th Century AD the boys in families affected by haemophilia were excused circumcision. However, the mechanism of inheritance and hence the reasons for the observed familial patterns remained obscure until the 20th century.

In 1902 Sir Archibald Garrod (1858-1936), a London physician, presented his studies on alkaptonuria, a rare condition in which patients have arthritis and urine which darkens on standing. He found 3 of 11 sets of parents of affected patients to be blood relatives and, in collaboration with William Bateson (1861-1926), 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 really represented one extreme of human biochemical variation and that other less clinically significant variations were to be expected. In 1908 Ottenburg and Epstein presented evidence that blood groups were also inherited as Mendelian traits and in 1911 E.B. Wilson (1856-1939) assigned the gene for colour-blindness to the X chromosome, and so made the first gene assignment in man.

There followed numerous descriptions of distinct human single gene traits and in recent years these have been accurately catalogued by Professor V.A. McKusick at the Johns Hopkins Hospital, USA (Table 1.1). At the present time more than 3500 human single gene traits are known.

The dominant traits tend to concern structural and carrier proteins whilst the recessives like alkaptonuria are often enzyme defects. Pauling in 1949 suspected an abnormal haemoglobin to be

Table 1.1 Human single gene traits

	1966	1968	1971	1975	1978	1982	1984
Autosomal dominant	269 (+568)	344 (+449)	415 (+528)	583 (+635)	736 (+753)	934 (+893)	996 (+959)
Autosomal recessive	237 (+294)	280 (+349)	365 (+418)	466 (+481)	521 (+596)	588 (+710)	599 (+741)
X-linked	68 (+51)	68 (+55)	86 (+64)	93 (+78)	107 (+98)	115 (+128)	118 (+137)
Total	574 (+913)	692 (+853)	866 (+1010)	1142 (+1194)	1364 (+1447)	1637 (+1731)	1713 (+1837)
Grand total	1487	1545	1876	2336	2811	3368	3550

Numbers in parentheses refer to loci not yet fully identified or confirmed.

the cause of sickle cell anaemia and this was confirmed by Ingram in 1956 who found a DNA point mutation which altered the haemoglobin polypeptide sequence. This was the first demonstration in any organism that a mutation in a structural gene could produce an altered aminoacid sequence. In 1959 only two abnormal haemoglobins were known; now the number exceeds 325. In 1951, C and G Cori demonstrated the first enzyme defect in an autosomal recessive condition, glycogen storage disease. By 1959 five enzyme defects were known but the number now exceeds 200. The polypeptide product is, however, still unknown in about 85% of human single gene disorders.

Progress has also been made in the assignment of genes to individual chromosomes. Assignment of genes to the X chromosome is readily made on the basis of the characteristic pattern of inheritance. The first autosomal gene to be assigned was thymidine kinase to chromosome 17 by chromosome segegation in man-mouse hybrids by Weiss and Green in 1967 followed by the Duffy blood group to chromosome 1 by Roger Donahue in 1968. Other techniques have allowed the confirmed assignment of more than 247 autosomal genes which together with the 118 confirmed X chromosomal assignments represent about 10% of the known human single gene traits.

Multifactorial inheritance

Sir Francis Galton (1822-1911), Darwin's half first cousin, studied continuous human characteristics such as intelligence and physique. These traits 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, R.A. Fisher (1890-1962), 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; expression only occurred when the genetic contribution passed the threshold. Many human characteristics are determined in this fashion and usually factors in the environment interact with the genetic background.

Clinical applications

Genetically determined disease is becoming an increasingly important part of ill-health in the community now that 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.

Table 1.2 Important advances in human genetics

Year	Landmark	Key Figure(s)
1839	Cell theory	Schleiden and Schwann
1859	Theory of evolution	Darwin
1865	Particulate inheritance	Mendel
1877	Chromosomes observed	Flemming
1901	ABO blood groups discovered	Landsteiner
1902	Biochemical variation	Garrod
1903	Chromosomes carry genes	Sutton, Boveri
1908	Inheritance of ABO blood groups	Ottenburg, and Epstein
1910	1st US genetic clinic	Davenport
1911	Linkage in Drosophila	Morgan
1911	1st human gene assignment	Wilson
1927	Mutagenicity of X-rays	Muller
1928	Transfection	Griffith
1940	Concept of polymorphism	Ford
1944	Role of DNA	Avery
1946	Mutagenicity of X-rays	Muller
1946	1st UK genetic clinic	Roberts
1947	Transposable elements	McClintock
1949	Sex chromatin	Barr
1953	DNA structure	Watson and Crick
1956	Aminoacid sequence of HbS	Ingram
1956	46 chromosomes in man	Tjio and Levan
1959	1st chromosomal abn.	Lejeune
1960	Prenatal sexing	Riis and Fuchs
1960	Chromosome analysis on blood	Moorehead
1961	Biochemical screening	Guthrie
1961	X inactivation	Lyon
1961	Genetic code	Nierenberg
1968	1st prenatal chromosomal analysis	Breg and Steel
1968	1st autosomal assignment	Weiss and Green
1970	Prevention of Rhesus isoimmunisation	Clark
1970	Chromosome banding	Caspersson
1972	AFP screening	Brock
1973	HLA disease associations	Terasaki
1978	1st DNA diagnosis	Kan
1979	in vitro fertilization	Edwards and Steptoe
1982	1st product of genetic engineering marketed	

Charles B. Davenport of the Eugenics Record Office in New York State began to give genetic advice as early as 1910. The first British genetic counselling clinic was established in 1946 at Great Ormond Street, London by John Fraser Roberts. Public demand has 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.

In 1961 the Guthrie screening test for phenylketonuria and certain other inborn errors of metabolism was introduced. All newborn babies in Britain are screened with this test as early diagnosis and treatment of these conditions can prevent permanent handicap.

Prenatal diagnosis with the option of selective termination of pregnancy provides important reassurance for couples at high risk of serious genetic disorders. This was first attempted in 1968 and is now possible for all chromosomal disorders, more than seventy single gene disorders and some multifactorial conditions.

In vitro manipulation of DNA or genetic engineering is starting to have a clinical impact. So far this has been in the synthesis of gene products such as insulin, growth hormone and interferon but increasingly DNA analysis will be used for prenatal and presymptomatic diagnosis and, in the future, direct treatment of faulty genes may be possible.

Summary

Thus during the past twenty-five years there has been a rapid growth in understanding of genetics of both health and disease. For affected families this has already had an impact with improved genetic counselling and increasingly the potential for both therapy and prevention. For the future one might expect continued progress not only along these lines but also into prenatal and preconceptional screening and prevention. This should lead to a reduction in the incidence of all genetic diseases which will benefit not only the individual families at risk but also society in general.

Chapter 2
Physical Basis of Heredity

In 1944 chromosomal nucleic acid was shown to be the carrier of genetic information. In the succeeding years this principle was shown to hold true for all living organisms and details of the structure and function of nucleic acids have gradually been determined.

NUCLEIC ACID STRUCTURE

Two main types of nucleic acid are recognised: DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). Each nucleic acid macromolecule consists of a sugar-phosphate backbone with projecting nitrogenous bases (Fig. 2.1). In DNA the sugar is deoxyribose whereas in RNA it is ribose. The bases are of two types, purines and pyrimidines. In DNA there are two purine bases adenine (A) and guanine (G) and two pyrimidines thymine (T) and cytosine (C). In RNA uracil (U) replaces thymine. Each unit of base, sugar and phosphate is called a nucleotide.

A molecule of DNA is composed of two nucleotide chains which are coiled around one another to form a double helix (Fig. 2.2). The two chains run in opposite directions and are held together by hydrogen bonds between A in one chain and T in the other or between G and C (Fig. 2.3). This pairing is very specific although rarely erroneous combinations may occur. Since A:T and G:C pairing is obligatory the parallel strands must be complementary to one another. Thus if one strand reads ATGA the complementary strand must read TACT. Hence the ratio of A to T is 1 to 1 and of G to C is likewise 1 to 1. Wide variation exists in the (A+T)/(G+C) ratio. Higher plants and animals tend to have an excess of (A+T) and in man the ratio is 1.4 to 1.

In man the total length of DNA in the haploid set of chromosomes is 3000 million base pairs or 3 million kilobases since each kilobase (kb) equals 1000 base pairs. If stretched out this would have a length of 1.74 metres. The average gene is perhaps two kilobases in size thus for a scale comparison if the total DNA was

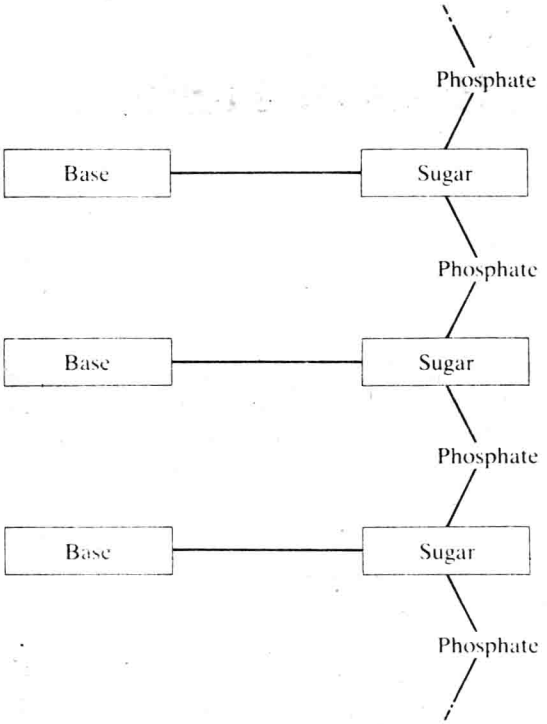

Fig. 2.1 Nucleic acid structure

stretched from Glasgow to London (400 miles) then each gene would occupy about 12 inches.

RNA differs in structure from DNA in several respects:

1. The sugar is ribose rather than deoxyribose
2. Uracil (U) replaces thymine
3. RNA is single stranded
4. Only a single type of DNA is known in man but four types of RNA are found (Table 2.1)

Table 2.1 Types of RNA

Type	Location	Comments
Messenger RNA (mRNA)	nucleus and cytoplasm	variable size, base sequence complementary to transcribed DNA, 1-2% of total RNA
Transfer RNA (tRNA)	cytoplasm	hairpin loop shape, about 40 types, amino acid specific
Ribosomal RNA (rRNA)	ribosomes and nucleoli	about 80% of total cellular RNA
Heterogeneous RNA (HnRNA)	nucleus	high molecular weight, ?mRNA precursor

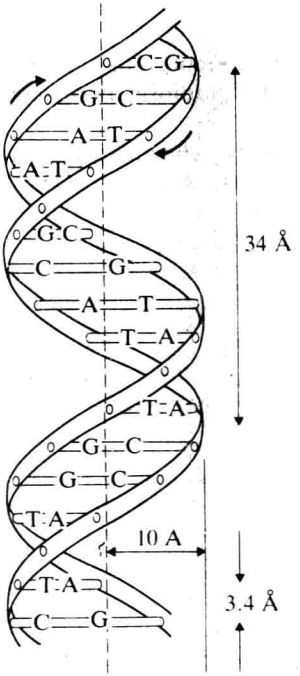

Fig. 2.2 Model of double helix

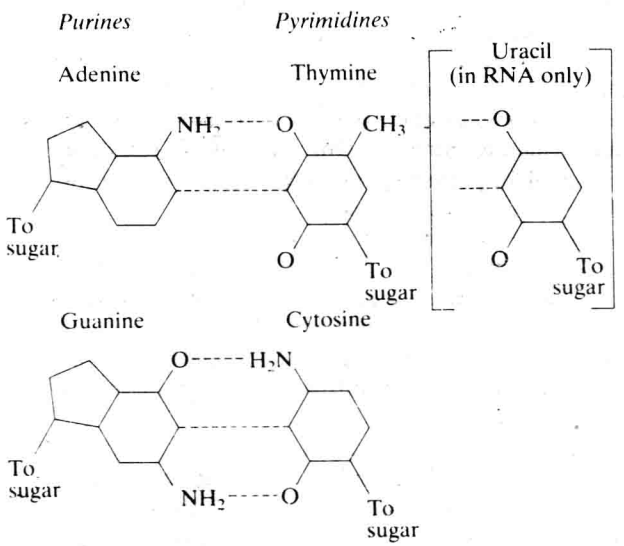

Fig. 2.3 Nucleic acid base pairing

NUCLEIC ACID FUNCTION

Nucleic acids have two major functions: the direction of all protein synthesis and the accurate transmission of this information from one generation to the next.

Proteins, whether structural components, enzymes, carrier molecules, hormones or receptors, are all composed of a series of aminoacids. Twenty aminoacids are known and the sequence of these determines the form and function of the resulting protein. All proteins are encoded in DNA and the unit of DNA which codes for a protein is by definition its gene. Genes vary in size in proportion to their protein products (Table 2.2).

Table 2.2 Examples of genes and their protein products

Protein	Number of aminoacids	Chromosomal location	Approx. gene size (basepairs)
Alpha globin	141	16	39,850
Beta globin	146	11	1,1600
Collagen type I (α1 chain)	1000	17	18,000
Collagen (α2 chain)	1000	7	39,000

Each set of three DNA base pairs or triplet codes for an aminoacid. As each base in the triplet may be any of the four types of nucleotide (A,G,C,T) this results in $(4)^3$ or 64 possible combinations or codons. The codons for each aminoacid are given in Table 2.3. Each codon is shown in terms of the messenger RNA and so the corresponding DNA codon will be complementary.

All aminoacids except methionine and tryptophan are coded for by more than one codon: hence the code is said to be degenerate. Three of the 64 codons designate the termination of a message and these are called chain terminators. One codon AUG (methionine) acts as a start signal for protein synthesis With a few possible exceptions this code is identical in all species.

The first stage in protein synthesis is transcription. The two strands of DNA separate in the area of the gene to be transcribed. One strand functions as a template and messenger RNA (mRNA) is formed with a complementary sequence under the influence of the enzyme RNA polymerase (Fig. 2.4). After some processing and modification the mRNA molecule diffuses to the cytoplasm and the DNA strands reassociate.

The next stage of protein synthesis occurs in the cytoplasm and is called translation. Each mRNA molecule becomes attached to one or more ribosomes. As the ribosome moves along the mRNA from the 5′ (five prime) to the 3′ end each codon is recognised by a matching transfer RNA (tRNA) which contributes its aminoacid to the end of a new growing protein chain.