New Studies in Biology

Human Genetics and Medicine

Third Edition

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First published in Great Britain 1970 by
Edward Arnold (Publishers) Ltd, 41 Bedford Square, London WC1B 3DQ

Edward Arnold (Australia) Pty Ltd, 80 Waverley Road, Caulfield East,
Victoria 3145, Australia

Edward Arnold, 3 East Read Street, Baltimore, Maryland 21202, U.S.A.

Reprinted with additions 1972
Reprinted with additions 1974
Second edition 1977
Reprinted 1980
Third edition 1987

British Library Cataloguing in Publication Data

Clark, *Sir* Cyril A.
Human genetics and medicine.—3rd ed.—
(New studies in biology)
1. Medical genetics
I. Title II Series
616'.042 RB155

ISBN 0-7131-2944-1

Text set in 10/11pt Plantin Compugraphic
by Colset Private Limited, Singapore
Printed and bound in Great Britain by Whitstable Litho, Whitstable, Kent

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Dominant and Recessive Inheritance

1.1 Dominant inheritance: Huntington's chorea as an example of a rare disorder

Huntington's chorea (HC) is an inherited disease characterized by involuntary muscular movement and progressive mental deterioration. The age of onset is usually about 35 years so that the majority of those affected can produce a family before they are aware of their plight. The disease is transmitted by an autosomal dominant gene (Fig. 1.1), so both sexes are equally affected and, moreover, because penetrance (see glossary) is complete the disorder never skips a generation. It is rare – one estimate in this country is five cases per 100 000 of the population – and so affected individuals are highly likely to be heterozygotes (see below for explanation of this point). The mutant gene at the HC locus is probably on chromosome 4 and it is now possible in certain families to tell which individuals are at risk (see Chapter 12).

The disease, introduced into North America by two Suffolk immigrants in 1630, derives its name from the US doctor who first described it in 1872. Fraser Roberts (1973) writes 'the boy George Huntington, driving through a wooded lane in Long Island while accompanying his father on professional rounds, suddenly came upon two women, mother and daughter, both tall, thin, almost cadaverous; both bowing, twisting, grimacing, so that he stared in wonderment, almost in fear. The memory was as vivid more than fifty years later, long

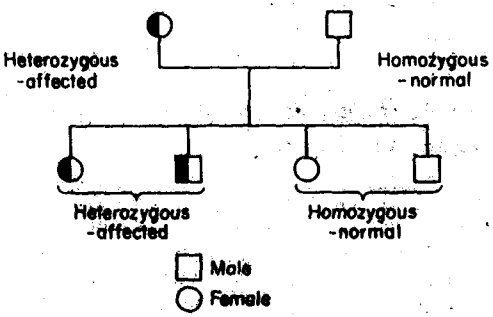

Fig. 1.1 Pedigree of Huntington's chorea (HC).

after he had translated into fact the youthful resolve, born that day, to make chorea the subject of his first contribution to medical science: a resolve which led him into many a home where the bearers of the gene waited with stern Calvinistic stoicism for the dreadful fate that Providence had meted out to them.'

Affected individuals will almost invariably be heterozygous for the condition because their parents will have married normal partners. Though theoretically an affected × affected mating *could* take place and produce a homozygote, this would probably be lethal, and the gene is so rare that it is most unlikely to occur. By contrast, where a trait is common, such as the various ABO blood types, it is readily possible to have the homozygote, e.g. blood group OO or AA.

1.2 The problem of controls in assessing the mutation rate in HC

A matter of considerable interest is the reason for the persistence of the disease. 'Recurrent mutation' is the obvious answer, but another explanation is that, since heightened sexual desire (increased libido) is one of the early symptoms, affected individuals will have more children than their unaffected siblings (brothers and sisters) and this in fact has been found to be so. The mutation rate, therefore, could be extremely low (or even non-existent) since, on the assumption that unaffected sibs behave as normal individuals, the biological fitness (see glossary) is higher than unity in the patients. However, to use the unaffected sibs may not be the right comparison because, since they are aware of the inherited nature of their disease, they may marry late or limit their families. In fact, where the fitness of HC individuals is compared with *normal* people it is well below unity (0.81) and if these are the right controls (as seems likely) then a higher mutation rate must be invoked. It might be thought that this is only of theoretical importance but in an age of radiation hazards *any* information about mutation rates is of great importance, and HC shows how difficult it is to assess it – a value for biological fitness being necessary for the calculation.

The situation in HC should be compared with that of duodenal ulcer (see p. 16) and it will be clear that it is perfectly legitimate to draw opposite conclusions about the best type of control in the two diseases.

1.3 Dominant inheritance: Dupuytren's contracture as an example of a common disorder

Few doctors have ever seen a case of HC whereas Dupuytren's disease is very common and therefore of more general interest. Figure 1.2 shows the contracture in the hands (the feet may also be affected) which is the result of the formation of an abnormal type of connective tissue (collagen). The condition is inherited as an autosomal dominant: non-familial cases are also reported but this is probably because insufficient care has been taken in examining the rela-

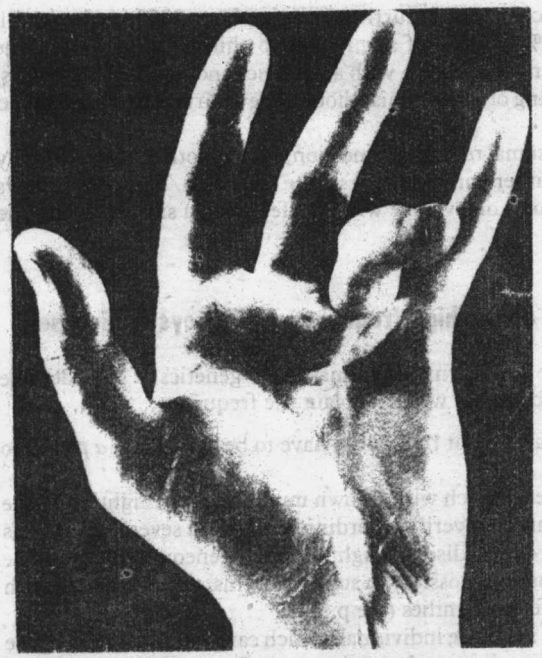

Fig. 1.2 Dupuytren's contracture. (From Hueston and Tubiana (1974), *Dupuytren's Disease*, Churchill Livingstone.)

tives. The condition may be very mild in young adults, is usually much less marked in women but all cases worsen with age and it has been stated that 25% of male old age pensioners have the condition. It is not surprising, therefore, that a host of associations has been found, e.g. with diabetes mellitus, alcoholism and epilepsy. An interesting piece of research would be to find out what the homozygotes look like and with such a common condition this could easily be done. The gene in double dose may simply result in a worse form of the disorder or possibly produce some other abnormality.

1.4 Recessive inheritance: (a) fibrocystic disease (FCD)

This disease, mainly affecting Europeans, is a generalized disorder of mucus secreting glands, particularly those in the pancreas, the intestines and the lungs. The mucus is more viscid than normal and, as a result, dried up secretions block the glands and their ducts so that they atrophy and become replaced by scar tissue. However, the cells in the pancreas which secrete insulin are not affected so diabetes does not occur. Another feature is that the sweat contains a higher concentration of sodium chloride than normal i.e. above 60 mmol/litre in infants or 100 to 110 mmol/litre in adults.

The disease is fairly common, occurring once in about 2000 births, and it accounts for between 1% and 2% of admissions to children's hospitals. The outlook for a sufferer is not good even with antibiotics and pancreatic extracts, many of the children dying of pneumonia, though a few survive to adult life and may have offspring.

The disease is an autosomal recessive condition, so that both sexes are equally affected and as a rule neither parent manifests the condition. Figure 1.3 shows that one in four individuals on average will be affected in a sibship where the disease occurs.

Possible explanations of the high frequency of fibrocystic disease

The fact that the disease is often met with makes the genetics of considerable interest and any of the following would explain the frequency:

(*a*) A high mutation rate – but this would have to be so high as, *a priori*, to be unlikely.

(*b*) Several different genes, each with its own mutation rate, might cause the condition which could vary in severity according to which of several alleles was responsible. In other words, the disease might be heterogeneous (as is often the case with other conditions) and possibly in support of this, the association with HLA types varies in different families (see p. 53).

(*c*) The heterozygotes, i.e. those individuals which carry one dose of the gene and which form 5% of the entire population (see p. 31 for the way in which this figure is calculated), might have an advantage, that is be biologically fitter, than the normal homozygotes. Thus the disease might constitute a polymorphic system (see p. 22) though what the advantage of the heterozygotes may be or may have been is unknown. Danks *et al.* (1965) investigated the family size of parents of children with fibrocystic disease, and they *did* find when investigating 144 of these grandparental couples, matching three different control groups with each grandparental pair, that there was a tendency for the grandparents of children with fibrocystic disease to have larger families.

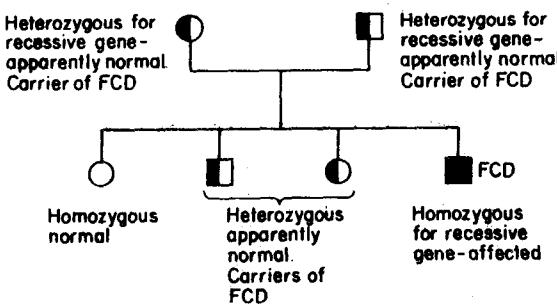

Fig. 1.3 Mating between two individuals heterozygous for the gene controlling FCD. Pedigree of fibrocystic disease (FCD).

Why grandparents? Parents of known fibrocystic disease patients might well limit their families, but in the generations before, heterozygotes would have been likely to marry normal people, and it is these who produced the bigger families than the controls.

The authors of the paper, however, put forward their results with great reservation, since the magnitude of the heterozygous advantage apparently shown is very much greater than would be needed to maintain the gene at a steady frequency in the community.

1.5 Detection of heterozygotes in fibrocystic disease

This still remains a problem, and the two following approaches have been made.

The sodium content of the sweat

It was thought at one time that the sodium content of the sweat in the heterozygotes might be helpful in identification. It is true that on average these have a somewhat higher value than do normal people yet the range is very great and there is much overlap. Furthermore, allowance is often not made for age. The sodium content of the sweat rises as one gets older and therefore comparison must be made between patients of similar age groups. Figure 1.4 demonstrates this point, where it will be seen that there is practically no difference in the sodium content of the sweat between parents of affected individuals, i.e. known heterozygotes, and that of normal controls *of the same age group*.

Linkage analysis

Since the basic gene effect remains unidentified the only available method for searching for its position is linkage analysis by exclusion mapping, using polymorphic DNA probes that have been mapped to a known chromosome region (see Chapter 12). In this way, using only samples from affected individuals and obligate heterozygotes a number of chromosome regions have been found *not* to be linked to fibrocystic disease. More recently (October, 1985), there have been advances indicating that chromosome 7 is involved and a new marker has been found, but not very close to the cystic fibrosis gene (see Chapter 12). The whole point of this genetic engineering exercise is to identify carriers of the gene or affected fetuses *in utero*.

1.6 Recessive inheritance: (b) phenylketonuria (PKO) (incidence 1 in 15 000 births)

The features are mental retardation, restlessness and anxiety, the muscles are hypertonic ('stiff') and there is often eczema and epilepsy. Affected children

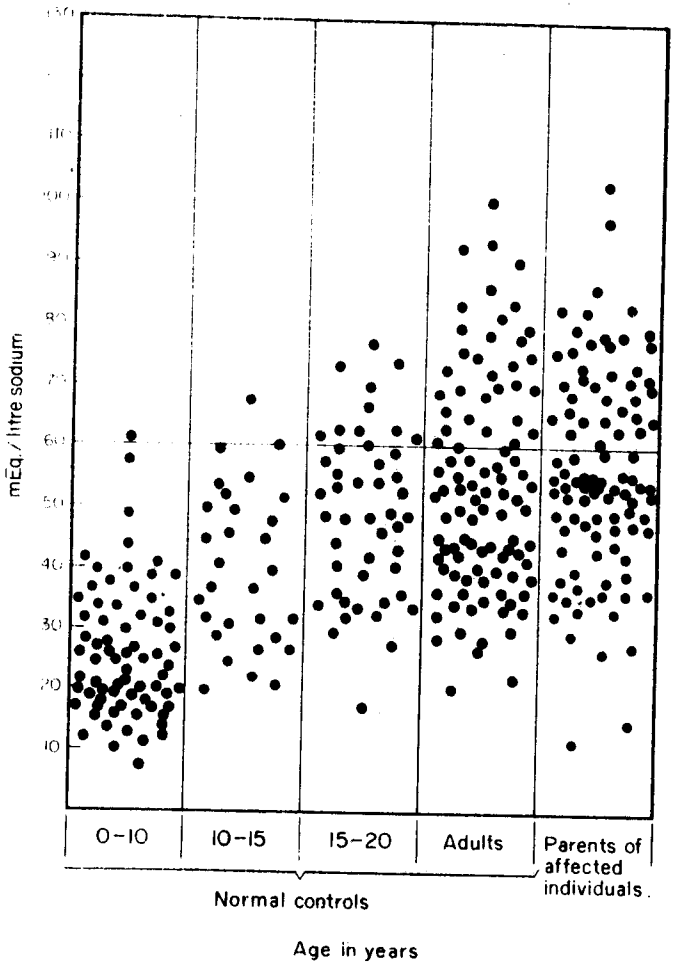

Fig. 1.4 Sodium content of sweat in relation to age. (Redrawn with permission from Anderson and Freeman (1960) 'Sweat Test' results in normal persons of different ages compared with families with fibrocystic disease. *Archives of Disease in Childhood*, **35**, 581–7.)

frequently have blue eyes and fair hair. The biochemical lesion is lack of a specific enzyme, phenylalanine hydroxylase, which normally converts phenylalanine into tyrosine. Everyone lacks the enzyme for about 2 days after birth but in phenylketonurics the synthesis never begins. Thus, 'the earlier the better' may not always be best for screening tests. Lack of tyrosine leads to diminution in melanin production, hence the characteristic fair hair of the patients. The diagnosis is made by a bacteriological inhibition test (the Guthrie test) performed on blood from a heel prick. The principle of the test is that the

growth of *Bacillus subtilis* is inhibited by a chemical which in its turn is overcome by phenylalanine, thus allowing the growth of the bacillus i.e. if the bacillus grows the child has the disease.

A low phenylalanine diet often prevents symptoms developing but there are difficulties in deciding for how long the diet should be continued.

Mild cases may occur and phenylketonuric women bear children. A counsellor might be tempted to say that the risk of these children being affected is very small since it would only happen if the affected woman married a carrier. However, a woman with mild PKU may produce mentally retarded children because her phenylalanine has crossed the placenta, and although the affected children are not true PKUs this does not help them. Treated PKU women will increasingly pose the problem of whether dieting should be resumed during pregnancy.

There are still other problems. *The* feature of PKU is brain damage, but the primary enzyme defect lies in the liver and kidneys. Recently there have come to light variant forms of PKU; the result of defects in the metabolism of a co-factor of the missing enzyme, and a study of patients with these variants may perhaps teach us something about substances which are essential to normal brain development.

The antenatal diagnosis of PKU is in the process of being improved by the use of restriction fragment length polymorphisms and this principle is explained in Chapter 12.

2

Sex (X)-Linked Inheritance

2.1 Haemophilia as an example of sex-linked recessive inheritance

Haemophilia is a world-wide anomaly of blood coagulation (clotting) inherited as a sex-linked recessive, and is the disease which created such havoc in the royal families of Europe when introduced into them by the daughters and descendants of Queen Victoria (see Fig. 2.1). Haemorrhage, usually following injury but sometimes spontaneous, is the essential symptom. The bleeding is of the nature of a persistent, slow oozing which is out of all proportion to the extent of the injury; this can last for weeks and may lead to profound anaemia. Orthopaedic problems often occur due to recurrent haemarthroses (bleeding into the joints) but this can be greatly improved by aspiration.

The disease usually appears in early childhood or even in infancy, and it is due to the deficiency of one of the clotting factors of the blood (factor VIII, anti-haemophiliac globulin, or AHG) and is known as 'haemophilia A'. Its severity is very variable, yet within a given family it remains constant and this makes it likely that there are a number of alleles of the haemophilia gene. Also, there is a whole group of conditions which are the result of a deficiency of other blood clotting factors. The best known of these, Christmas disease (or 'haemophilia B') which was called after the patient in whom it was first described, is also a sex-linked recessive, and is due to deficiency of the Christmas factor (factor IX), which is distinct from AHG. A mixture of two equal parts of blood, one from a patient with haemophilia A and the other from a patient with Christmas disease clots normally, whereas separate samples show delayed clotting.

Another disorder of bleeding where the level of AHG is diminished is Von Willebrand's disease but this, unlike haemophilia, is inherited as an autosomal dominant. The disease is of considerable interest. Although factor VIII is again involved it is in a different way, there being defective synthesis of that part of the molecule which is concerned with the immunological factors needed for normal platelet function. The bleeding, therefore, is due to a different cause. The treatment is the same.

Returning to haemophilia it must be remembered that haemophiliacs may develop entirely unrelated diseases, and the writer has seen a fatal case of intestinal haemorrhage which was thought to be due to the haemophilia but was in fact secondary to a duodenal ulcer. In this connection, it is important to realize

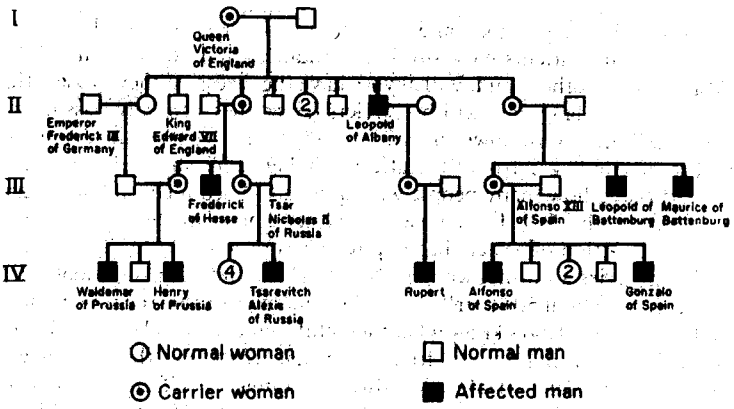

Fig. 2.1 Sex-linked recessive inheritance. Pedigree of haemophilia in the royal families of Europe. All affected individuals trace ancestry to Queen Victoria of England, who undoubtedly was a carrier. Her father was normal, nothing suggests that her mother was a carrier, and therefore Queen Victoria seems to have received a new mutant allele from one of her parents.

It will be realized that many individuals in later generations are not included – among them our own royal family, who are quite free, being descended from an unaffected male. All Queen Victoria's children are entered in the pedigree. (By courtesy of Professor Curt Stern (1960) *Principles of Human Genetics*, Freeman.)

that haemophiliacs withstand operations quite well if they are suitably prepared with blood or (fresh) AHG beforehand.

The gene controlling haemophilia is situated on the X chromosome, and this is almost always what is meant by 'sex linkage' since Y linkage has very rarely been reported in Man, and several claims to its occurrence have not been substantiated on further investigation. It will be realized that since a woman is XX and a man is XY, an X-linked gene can be passed to either sex, whereas one on the Y could only go from father to son. (When a gene can only *express* itself in one sex it is said to be sex-limited or sex-controlled. This situation is described on page 12, and is quite different from sex-linkage.) Most, though not all, sex-linked genes in Man are recessive. Just as with the autosomes, crossing-over (see Chapter 8) can take place between one X and the other, but crossing-over between X and Y has only very rarely been reported, since there is a part of the X chromosome which does not pair with the Y.

It will readily be understood that since haemophilia is controlled by a sex-linked recessive gene, female carriers of the gene will never be affected unless they are homozygotes. This is because females have two X chromosomes and the normal gene on their second X will prevent the haemophilia gene from expressing itself – they will however pass on equal numbers of normal and abnormal X chromosomes to their offspring of both sexes, so that the offspring of carrier females will consist of half normal and half affected sons and of half normal and half carrier daughters. Owing to the rarity of the gene, females are

most unlikely to be homozygotes and hence haemophiliacs, but cases have been reported and some patients have survived childbirth and borne haemophilic sons. Males, on the other hand, will always have the disease if they possess the gene, and all their daughters will be carriers (since they can only pass on an affected X). All their sons, however, will be completely free from the disease as they will receive only a Y from their affected father. This should be apparent but it is surprising how many people with quite advanced medical knowledge do not appreciate this fact. I often used to ask candidates in medical examinations what proportion of a male haemophiliac's sons will develop the disease provided he marries a normal woman. Nearly all candidates pause, look very wise and then say 'about 50%, sir'! It must be remembered that the *men* in these affected families can always know what their children will be. The normal ones in them will have all normal children by normal wives (and they will never develop the disease later in life as it always manifests itself early), whereas haemophiliac men, if they live long enough to have any children at all, will have all normal sons and all carrier daughters. It is those women who have, say, a haemophiliac brother, and who may have inherited the gene from a carrier mother who are in doubt, and it is sad that they cannot know for certain whether or not they are carriers, though about 85% (see p. 34 for explanation) of these heterozygote carriers can be detected by assessing the degree of factor VIII reduction in their plasma.

Factor VIII is very much in the news at the present time because it can be engineered and therefore should be free of the virus that causes AIDS. However the clinical as opposed to the *in vitro* efficiency of the product is still unknown.

A side issue of the synthesis of the factor VIII molecule is that part of it resembles in its amino acid sequences the molecule of the quite unrelated protein ceruloplasmin which bonds copper atoms and its function in human plasma may be to convert ferrous (Fe^{2+}) into ferric (Fe^{3+}) ions. Perhaps evolution may have hit on a way of using a pre-existing molecular structure (ceruloplasmin) as a method of helping blood to clot rather than carrying out its normal function of banishing Fe^{2+} ions.

Before leaving haemophilia it is perhaps appropriate to give a résumé of how blood coagulation works. The end result must be a plug to stop the bleeding, but the steps involved in this are numerous – constriction of blood vessels, aggregation of platelets to damaged surfaces, and finally the formation of fibrin clots. These are all regulated by enzymes which function as a cascade, each releasing an active factor from an inert precursor and all are under genetic control. Therefore at each step there may be abnormalities and most of these mutants and variants have been recognized from a study of patients, haemophilia, as will be appreciated, being the classic example. But lack of 'contact factors' may also inhibit coagulation, for example a defect in factor XI which produces a bleeding disease found particularly in Ashkenazi Jews. Factor XIII the last in the line is responsible for the stabilization of fibrin and its deficiency (controlled by an autosomal recessive gene) may lead to a faulty clot with the result that bleeding occurs from the umbilical stump a week or so after birth.

2.2 The fragile X

X-linkage is also important in mental retardation because it has recently been shown that there is an inherited form due to a chromosomal abnormality – the fragile X syndrome – so called because in squash preparations (in which the cultured material is 'squashed' between glass slides) the X chromosome readily fractures at a particular site (Turner *et al.*, 1978). The affected boys have a tendency to big ears, a protruding chin, large hands and feet and large testes.

The syndrome is of extreme current interest because it still contains many uncertainties. Thus, occasionally, carrier females are themselves mildly mentally retarded, and more importantly, there is an increasing number of reports of transmission through males who appear perfectly normal. Such males have heterozygous daughters who are never mentally retarded and have either no fragile sites or very few indeed. By contrast, in the subsequent generation a third of the female heterozygotes are mentally subnormal, with an average of 29% fragile sites. This information suggests that there is a premutation which generates the definitive mutation only when transmitted by a female. It is proposed that initially there is a mutation that causes no ill effect *per se* but generates a significant genetic imbalance when involved in a recombination event (in a woman) with the other X chromosome. This hypothesis (Pembrey *et al.*, 1985) explains many of the puzzling aspects of the syndrome, but a great deal more work needs to be done, particularly as the subject is related to the question of therapeutic abortion of carrier women who are pregnant with male fetuses.

2.3 Duchenne muscular dystrophy

This is an appalling disease of young boys which almost always ends fatally before the age of twenty years. It starts with a waddling gait and then increasing difficulty in climbing stairs. The thigh muscles are wasted but there is pseudohypertrophy of the calf muscles. By about the age of ten, patients have to use a wheelchair and in their early teens they usually realize that they are going to die – they are *mentally perfectly normal* – whereas earlier they have just regarded themselves as the semi-invalid of the family.

Since affected boys hardly ever reproduce (Harper, 1981), the disease is transmitted almost entirely by healthy carrier females. Serum creatinine kinase is the standard test and is usually raised in carriers, but there are many pitfalls. It is also sometimes of help to test for muscle weakness in potential carriers. Very recently (1985) using a gene probing technique (see Chapter 12) much more accurate prenatal diagnosis and carrier detection became possible.

The rules for simple mendelian inheritance may be modified by information in particular families. For example, a woman who has had two affected sons *must* be a carrier. Her daughter *may* or *may not be* but if she had four normal sons the risk for a subsequent pregnancy would be much reduced.

There is a much milder form of the disease, Becker muscular dystrophy, also sex-linked, which has different clinical features and a later onset. Patients often

reproduce; all their daughters will be carriers and all their sons normal (see Fig. 2.2 for positions on the X chromosome).

2.4 The mapping of the X chromosome

Crossing-over (see glossary) will be discussed in Chapters 4 and 8, as will the method of calculating the cross-over value, which indicates how far apart the genes are likely to be on the chromosome (p. 41).

Quite a number of genes are known to be situated on the X chromosome (some concerned with disease but many not), the best known among them being those controlling colour vision, two types of muscular dystrophy, the skin disease of ichthyosis, the two forms of haemophilia already mentioned, G6PD deficiency (see p. 71) and the very important Xg blood group system. The last two conditions are detectable in the heterozygote, and the frequency of the Xg heterozygote in the European female population (i.e. the frequency of women having the gene controlling the Xg^a blood group antigen on one X chromosome but not on the other) is as high as 46%. Many families, therefore, which segregate for one of the rare sex-linked conditions mentioned above will also segregate for Xg, and one does not have to search for families segregating for two rare traits. It thus becomes possible to find the relationship of the rare mutant gene to the Xg locus, and thence to one another. The distances are measured in cross-over units, or map units, one map unit being equal to 1% of crossing-over. Thus if 5% of the offspring of informative matings (see p. 41) are of the 'recombinant' type – that is, they are the result of crossing-over – then the two gene loci are said to be about 5 map units apart. Work is in constant progress so that the map is often altered, but Fig. 2.2 is reasonably up to date.

2.5 Sex limitation or sex control

It was mentioned earlier that genes are said to be sex-controlled or sex-limited when they can express themselves only in one sex, and this is quite different from sex-linkage. An instance is described here for comparison. Frontal baldness only shows itself in males except on the rare occasions where a female receives the gene in double dose. The fact that an affected male can transmit the condition to his son shows that the gene responsible cannot be on his X chromosome, and the fact that he can transmit it to his daughter shows that it cannot be on the Y. Thus the gene is on an autosome but can only express itself in the male gene complex – why this is so is unknown.

2.6 Expressivity of genes

What has been written in the first two chapters is simply standard genetics but we need to know more than whether a gene is dominant, recessive or sex-linked. Of equal interest is why genes only express themselves in the appropriate organ and here there are new discoveries.