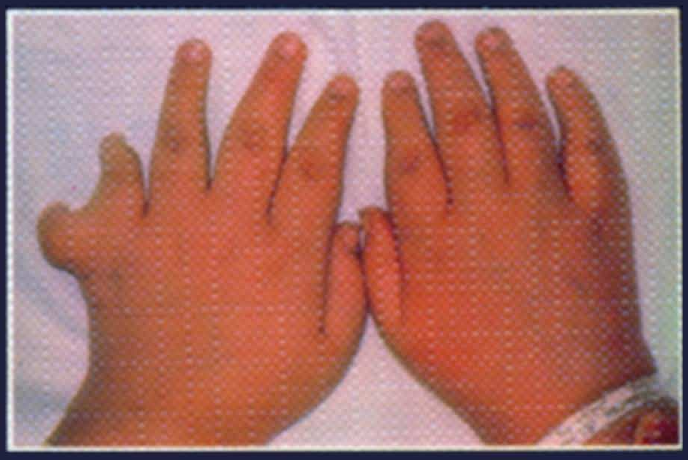
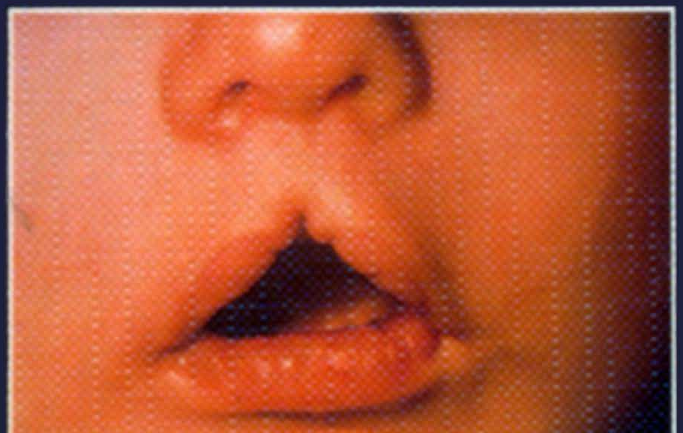
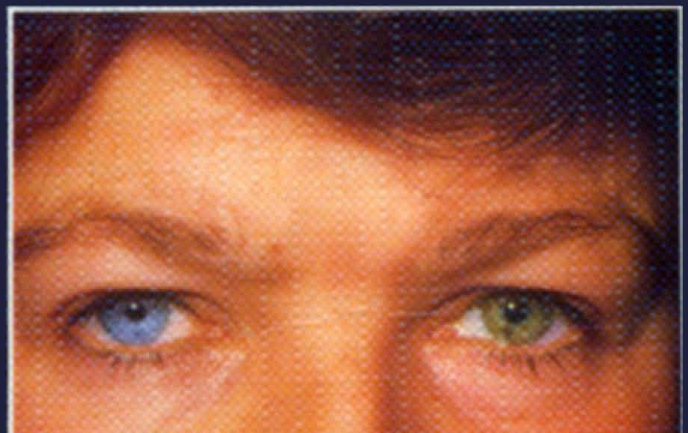
A Colour Atlas of
CLINICAL GENETICS

Michael Baraitser & Robin Winter







A Colour Atlas of Clinical Genetics

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Preface

Genetically determined conditions are individually rare but collectively they contribute significantly to the 2–3% of children born with malformations. If those conditions with a later age of onset are added to the total, it is not surprising that there are between 2000 and 3000 conditions listed by McKusick in his catalogue of *Mendelian Inheritance in Man* (see References). Unfortunately, the diagnosis of these conditions can be difficult. X-rays and blood tests are not always helpful and many of the syndromes can only be identified by pattern recognition. It is for this reason that pictures have become indispensable for the clinician and it is hoped that an Atlas will aid the diagnostic process by making typical representations available.

In the present work, verbal descriptions are brief and the reader is referred to other works for further details. Systems are dealt with individually but the section on syndromes defies precise grouping and the reader is encouraged to page through the section in order to search out the appropriate diagnostic category that his patient might have.

1 Introduction

Clinical genetics

Patients with genetic disorders can be encountered in every speciality of medicine; in their management, the clinical geneticist has a specific role which involves diagnosis, risk estimation and interpretation of laboratory results, and counselling.

a. The diagnostic role

Although a broad diagnosis may be made by a specialist, the clinical geneticist will appreciate the possibility of heterogeneity within a particular disease entity. It is important to recognize that the combination of signs and symptoms which make up a syndrome can have different causes. For example, motor neurone disease is usually sporadic (i.e. only one family member is affected), but in about 10% of cases there is a positive family history and inheritance may be autosomal dominant: retinitis pigmentosa can be caused by autosomal recessive, dominant or X-linked genes; diabetes is aetiologically heterogeneous – some types having a stronger genetic component than others. The different modes of inheritance might be distinguished by an assessment of factors such as age of onset, severity, and duration of the disease. If there are no specific pointers in an individual case, then the relative probability of a particular causative factor could be calculated.

The variability of genetic disorders within families must also be taken into account. Gene carriers may show minimal signs of a disorder, which nevertheless have important consequences for the risk to offspring, and extended family studies may be necessary in order to identify individuals at risk.

In certain groups of disorders the clinical geneticist has a primary diagnostic function. Syndromes caused by chromosomal abnormalities can often be diagnosed clinically; non-chromosomal malformation syndromes must be recognized when a family is sent for genetic counselling. Because of referrals for chromosomal analysis and genetic counselling, experience is gained of a great variety of syndromes, and this is reflected by the

b. Risk estimation and interpretation of laboratory results

The estimation of risks is fairly straightforward when one is dealing with a simple Mendelian situation, such as a mating between two known carriers of an autosomal recessive disorder or a mating when one partner is affected with an autosomal dominant disorder, however complications can arise in certain situations. For example, if a male is the only member of a family affected with an X-linked recessive disorder, then his mother might be a carrier of the abnormal gene; alternatively he could have received the abnormal gene as a new mutation, and in this case his mother would not be a carrier and would have a very low risk of having further affected sons. Estimation of precise risks that a woman is a carrier in this situation would depend upon the combination of various items of data, such as the number and relationship of normal males in the pedigree, and the results of any carrier detection tests (for example, the estimation of serum creatine phosphokinase in Duchenne muscular dystrophy). The methods of estimation are covered in many standard works on clinical genetics (see References). In other situations, the chances of an individual carrying an abnormal gene can be estimated by studying the joint inheritance of a *linked* marker gene in the family (see page 13). This approach has been used to estimate the chance of carrying the gene for dystrophia myotonica, both in individuals at risk and for fetuses prenatally, using linkage to the secretor locus for the ABO blood group substances.

Some risks cannot be based on Mendelian theory and must be obtained from large surveys of couples who have had a child with a particular abnormality. These *empirical* risks are used in counselling common malformations such as neural tube defects, dislocated hip or cleft lip and palate, where the causation is thought to be multifactorial.

c. Counselling

The essential prerequisites for good genetic counselling are an accurate diagnosis of affected family members (including an assessment of the

other family members. These processes rely on the diagnostic and analytical skills of the clinical geneticist. Having decided on the specific risks, the geneticist must then communicate them to the patient, and this entails a different range of skills. It is important to determine the nature of the patient's enquiry. If parents have had an abnormal child they may wish to know the risks to future children. Alternatively they may come purely to discuss prognosis in the affected child or they may be concerned about their normal children and their future offspring. Occasionally considerable blame and guilt is expressed, either because individuals feel they are personally responsible for passing on an abnormal gene, or because parents feel that avoidable factors during a pregnancy gave rise to an abnormal child. These anxieties and guilt feelings should be discussed and as far as possible relieved.

Risks should be presented and put in perspective. There are many different ways of expressing risk. In racing circles odds are often used. These are the ratio of the probabilities of two distinct events. For example the odds for an abnormal child as against a normal child might be 1:3 (1 to 3). Risks for a particular event can be derived from odds. For example odds of an event A as against B of 1:3 represent a risk of A of 1 in (1 + 3) = 4. Risks can also be represented in percentage terms (e.g. 1 in 4 = 25%) or as absolute probabilities (i.e. 1 in 4 equals a probability of 0.25). In the authors' experience risks are best expressed as proportions (e.g. 1 in 2, 1 in 50, etc.), but it is important that patients get the risks the right way round. It is always worth emphasizing that a 1 in 20 risk of an abnormal child means that 19 times out of 20 one would expect a child *not* to be affected. The genetic counsellor rarely tells a patient directly what to do as a consequence of specific risks, although he does explain all the options. Nevertheless risks can be put in perspective and looked at in the light of the severity of the genetic condition. Everyone takes a 1 in 50 risk of having a child with a serious problem each time they reproduce. In the light of this, figure genetic risks of 1 in 50 are usually acceptable. In general terms, risks greater than 1 in 10 are high and less than 1 in 20 are considered low. Between 1 in 10 and 1 in 20 is an intermediate zone and risks in this area must be discussed in detail, in relation to the severity of the disease.

If parents want further children and risks are high, then several different strategies must be discussed. Depending on the circumstances these might include prenatal diagnosis (where available for the disorder in question), artificial insemination (donor) or adoption.

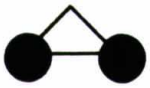
It is not the place of an Atlas of this nature to cover in detail the intricacies of risk estimation and counselling. A brief résumé of some basic genetic facts is given, but the bulk of the book is devoted to the clinical manifestations of genetic syndromes with particular emphasis on heterogeneity and syndrome identification.

2 Pedigree symbols

= Unaffected male.

= Affected female.

= Dizygotic twins.

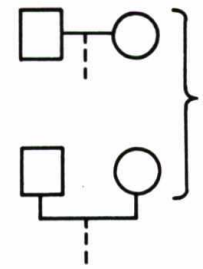


= Monozygotic twins.

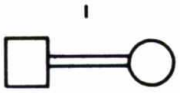
= Abortion.

= Propositus (i.e. the affected individual who brought the family to the attention of the geneticist).

= Deceased.



= Mating.



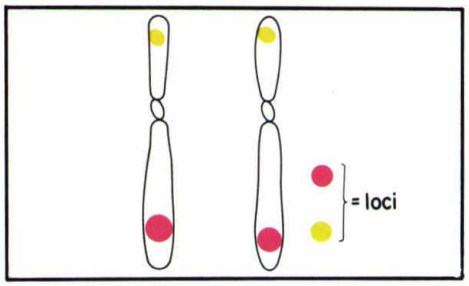
= Consanguineous mating.

= Heterozygote.

3 Mendelian inheritance

Genes and chromosomes

1



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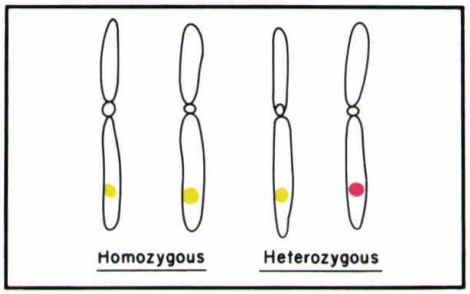
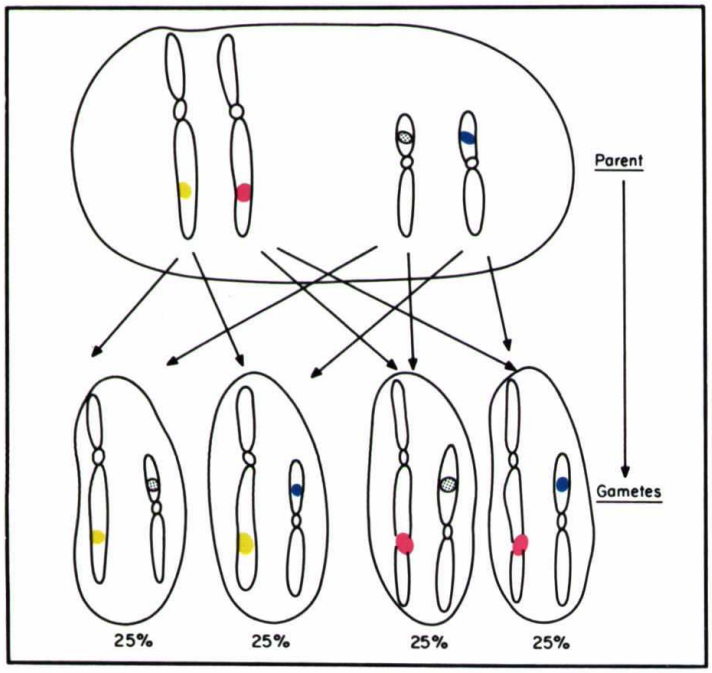


1 Genes are carried on chromosomes. Because chromosomes are paired, everybody carries two copies of each gene (with the exception of genes carried on the sex chromosomes in males). Each gene is located at a specific point on a chromosome known as a locus.

The diagram shows a pair of chromosomes (*'homologues'*) on which are situated two loci. At each locus there are two genes, one on each chromosome.

2 Genes at the same locus are known as *alleles*. If the two alleles at a locus are identical, the individual is said to be *homozygous* at that locus. If the two alleles are non-identical, then the individual is said to be *heterozygous*.

3



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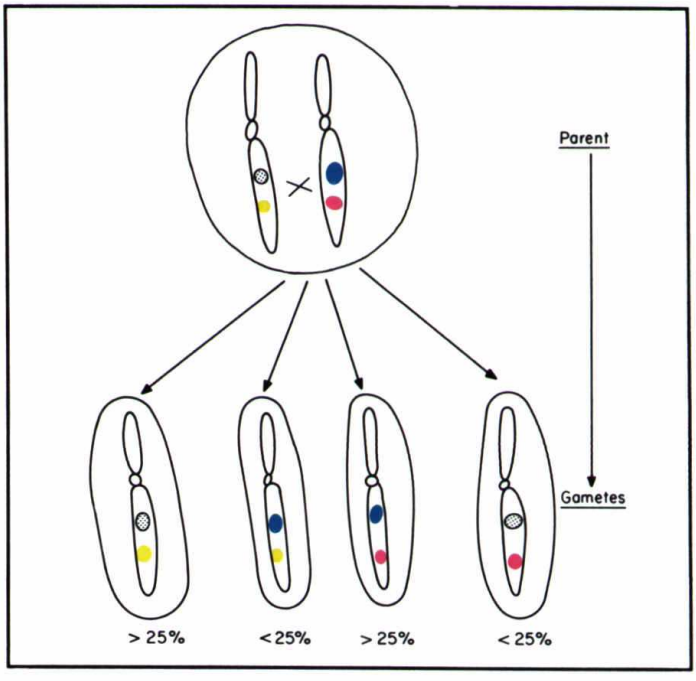


3 At meiosis the chromosome number is halved, with each member of a chromosome pair passing to a different gamete. The chance of an offspring inheriting a specific allele is therefore 1 in 2 (50%). This process is known as *segregation*. If genes are carried at loci on different chromosomes, then the inheritance of an allele at one locus is independent of the inheritance of an allele at the other locus. This is known as independent assortment.

4 When genes are carried on the same chromosome, there can only be independent assortment if a cross-over occurs between the loci at meiosis. The closer the loci are together the more unlikely this will occur. Two loci that are close together on a chromosome are said to be *linked*. Alleles at linked loci do not segregate independently. This means that pairs of alleles ('haplotypes') at linked loci on the same chromosome in a parent are more likely

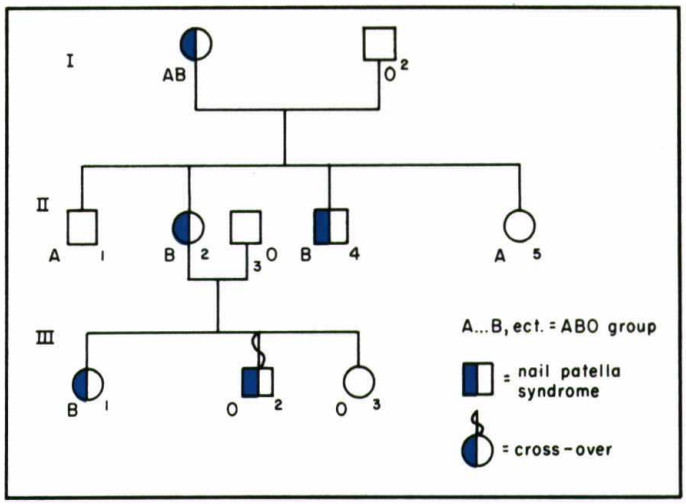
5 If two loci are linked, it does *not* mean that alleles at one locus are more likely to be carried on the same chromosomes as alleles at the other locus, if one selects individuals at random from the population.

For example, the locus for the nail patella syndrome is linked to the ABO blood group locus (the nail patella syndrome is an autosomal dominant disorder). This does not mean that someone in the population with a particular blood group (e.g. AB) is more or less likely to have the nail patella syndrome. Nevertheless, in a particular family, the nail patella allele will tend to segregate with a particular ABO blood group allele.

The pedigree suggests that the nail patella allele is carried on the same chromosome as the blood group B allele in I_1; this can be inferred by looking at her children. Children of I_1 who inherit the B blood group allele also inherit the nail patella syndrome. II_2, however, has a child who is blood group O, but who has the nail patella syndrome. This means that a cross-over must have occurred between the two loci at meiosis during the formation of the ovum that gave rise to III_2.

If two characters do tend to be found together in members of the population, then this is known as *association*. Association of characters does not necessarily mean that they are caused by linked genes (although this can sometimes be the cause, if two loci are very closely linked). An example of association is the increased tendency of individuals with blood group O to develop duodenal ulcers. At present this phenomenon is not thought to be caused by a gene linked to the ABO blood group locus.

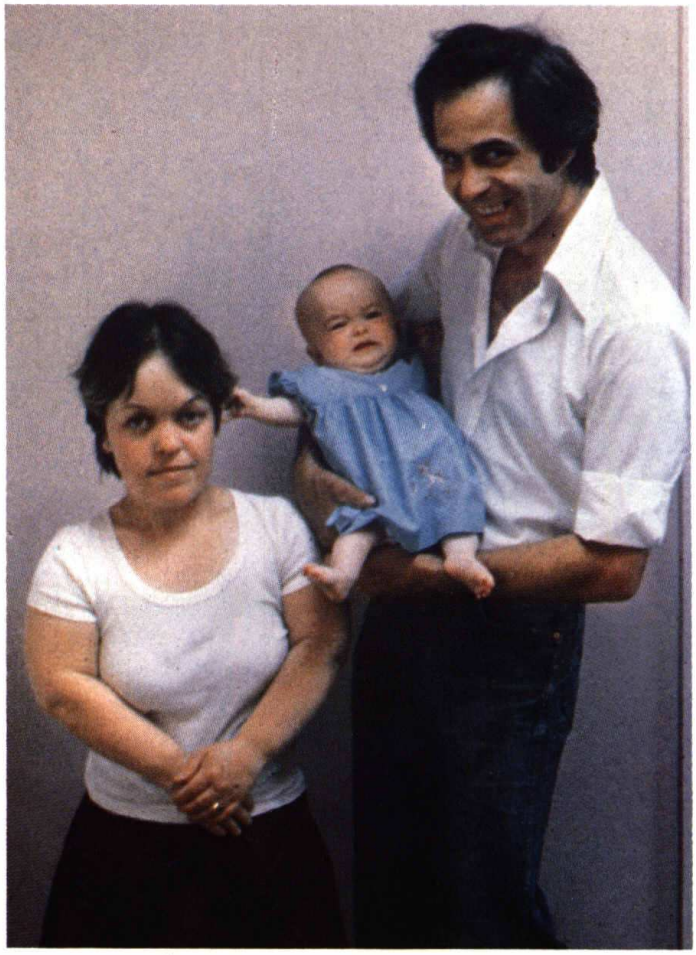
5



4 Types of pedigree

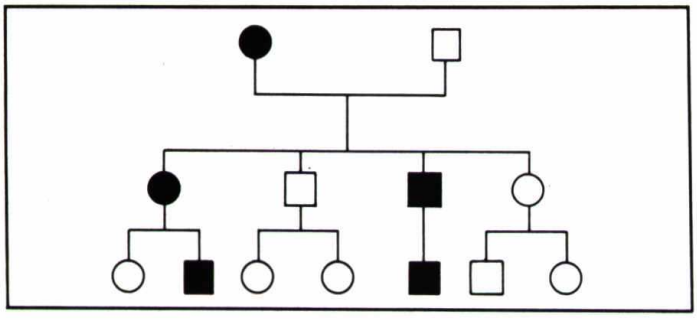
Autosomal dominant with complete penetrance

6



6 Achondroplasia in mother and daughter with normal father. This illustrates autosomal dominant inheritance.

7



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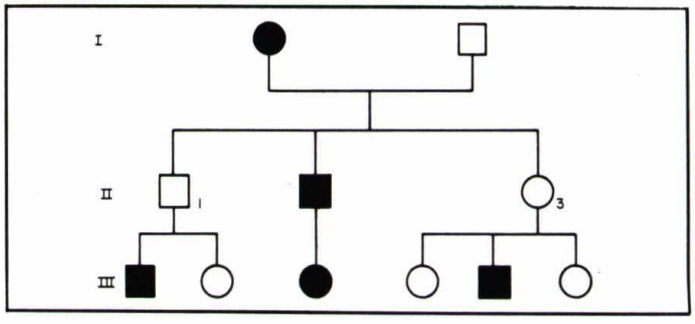

7 Note:
(a) Both males and females are affected.
(b) Affected individuals can pass the condition on to children of either sex; on average 1 in 2 children are affected.
(c) If an individual is not affected, then his

Autosomal dominant inheritance with incomplete penetrance

8 Note that the segregation pattern is the same as complete penetrance, with the exception that some