Acta orthop. scand. *46*, 338–349, 1975

Department of Orthopaedic Surgery, University of Edinburgh, Scotland.

A REVIEW OF GENETICS IN ORTHOPAEDICS

RUTH WYNNE-DAVIES

There has been greatly increased interest in inherited and developmental disorders over the past decade, with a huge volume of literature appearing in a variety of journals. This review of "genetics in orthopaedics" is taken to mean a review of those disorders occurring in orthopaedic practice which have a known genetic basis.

Human genetics is of immense complexity. On only one chromosome there are thousands of genes, and in man there are 46 chromosomes. On only one gene there are many different sites where mutations, or a change in chemical structure, can occur, perhaps with clinically apparent disease resulting—although it is still not clear why these structural changes should occur.

Developmental disorders, in man, whether apparent at birth or only in later years, can result either from adverse genetic or environmental factors, or from a mixture of both. If a genetic abnormality is present it must fall into one of three groups:

i) Chromosome anomalies (groups of genes)
ii) Unifactorial (single gene) disorders with dominant, recessive or X-linked patterns of inheritance
iii) Multifactorial disorders due to multiple genes together with environmental factors.

CHROMOSOME ANOMALIES

Up to a few years ago it was only possible to arrange man's 23 pairs of chromosomes roughly into groups, according to their size and the position of the centromere. However, new fluorescent techniques and radioactive labelling make it possible now to identify individual chromosomes and their specific defects. This means that cytogenetic diagnosis is becoming a great deal more accurate and many "new" syndromes

involving only a part of one chromosome are being described. We should be aware of the possibility of these less extensive defects as well as the chromosome anomalies that have been known for the past 10 years or so, but a detailed knowledge of this subject is not of great practical value to the orthopaedic surgeon. Many foetuses with chromosome anomalies will abort early, and many infants are stillborn or die in the first year of life. Chromosomal defects involve large numbers of genes and the damage to the body is usually widespread with mental defect and general disorganisation of development.

UNIFACTORIAL DISORDERS

Unifactorial disorders are caused by mutation of *single* genes. Most are rare and less influenced by environmental factors than multiple gene disorders. The three patterns of inheritance commonly seen are: autosomal dominant, autosomal recessive and X-linked recessive inheritance. X-linked dominant disorders do occur, but infrequently. A review of the single-gene, unifactorial disorders in orthopaedic practice is largely a review of the generalised skeletal dysplasias and malformation syndromes.

The *generalised skeletal dysplasias* form a subject of great difficulty because of the rarity of the disorders and the absence of detailed family studies identifying the complete range of anomalous development associated with one gene. One has only to think of the various signs and symptoms in osteogenesis imperfecta (bone fragility, blue sclerotics, deafness and so on), some appearing in one member of a family, some in another, to realise the problems of assessment. Genetic counselling, therefore, is often hazardous because of this general ignorance and because of the variable expression, particularly of the dominantly inherited disorders. It is impossible to cover the whole field, so I have chosen four groups of disorders where "new" diagnoses or diagnostic techniques have been established recently.

(i) Short-limbed dwarfism
(ii) Metaphyseal disorders
(iii) Increased bone density
(iv) Storage diseases

Inevitably there is some overlap betwen them, and for details the reader is referred to Carter & Fairbank (1974), Spranger et al. (1974), and Maroteaux (1975).

(i) *Short-limbed dwarfism*

In the past, all short-limbed dwarfs were thought to have achondroplasia. It is now known that there are at least 20 or 30 different conditions, some inherited and some not. True, or *'classical' achondroplasia* is characterized by an enlarged vault of the skull, depressed nasal bridge and narrow interpedicular distance of the lumbar vertebrae, this narrowing of the spinal canal leading perhaps to paraplegia in adult life. The nearest condition to it is *hypochondroplasia,* this being rather less severe and lacking the skull abnormality. Both are of dominant inheritance.

There are several forms of short-limbed dwarfs either stillborn, or dying in early infancy. In *achondrogenesis* and *thanatophoric dwarfism* the limbs are excessively short. In the *short-rib-polydactyly syndromes,* including *asphyxiating thoracic dystrophy,* there are very short ribs accompanied by pre- or post-axial polydactyly. Death usually occurs from respiratory difficulties, the lungs being too large for the narrow thorax.

The inheritance of thanatophoric dwarfism is unknown, but the other lethal forms are of autosomal recessive inheritance; thus there is a high risk of the parents having another similar child.

Other members of the 'short-limbed dwarfism' group are likely to live until maturity, and many of them present difficult orthopaedic problems. The *Ellis van Creveld* syndrome has been known for several years, and is of autosomal recessive inheritance, with particularly short distal limb segments, post-axial polydactyly and often congenital heart disease. *Diastrophic dwarfism* is also recessively inherited, and presents difficulties in treatment due to intractable clubfoot, joint contractures and scoliosis developing in early infancy. Curious associated features are the cystic swellings of the ears in the first few weeks of life, subsequently becoming 'cauliflower' deformities, and the short first metacarpals.

Chondrodysplasia punctata (Conradi disease) probably occurs in two forms, dominant and recessive, though the clinical distinction is not always clear. The recessive form is associated with icthyosis and cataracts and is frequently lethal in the first year of life. The less severe, dominant, form is not really an example of short limbed dwarfism, because the limb shortening is likely to be asymmetrical. Both forms of Conradi's disease show punctate calcification or stippling of epiphyses, but this radiological sign disappears as the child grows.

In *pseudo-achondroplasia* the body proportions look very similar to classical achondroplasia, but the skull is not affected, and the disorder is not apparent until 1 or 2 years of age. Radiography makes the diagnosis clear, because here epiphyses are irregular and small and the vertebrae are affected, being biconvex with a protruding central tongue. The genetics are uncertain; indeed, this is probably a heterogeneous group of disorders, some dominant, some recessive.

Metatrophic dwarfism presents in infancy with short limbs but in later life platyspondyly and a particularly intractable scoliosis contribute to a short-trunk type of dwarfism. As with so many of the short-limbed dwarfs, the thorax is narrow and respiratory difficulties occur. Inheritance is not yet clear.

Kniest disease is the last of the dwarfs with short limbs associated with a generalised skeletal dysplasia to be described. These children have a peculiar face with a depressed nasal bridge, and also a short trunk associated with platyspondyly. About half of them have a cleft palate. A characteristic radiological feature are the very broad femoral necks. Inheritance is probably autosomal dominant (or perhaps X-linked dominant).

There are several forms of dwarfism in which the shortness is produced by structural defects of the limb bones: *Nievergelt syndrome,* and the *ulno-fibular type,* (both of dominant inheritance) and mesomelic dwarfism (recessive inheritance).

(ii) *Metaphyseal disorders*

The rare *metaphyseal dysostosis (Jansen type of dominant inheritance)* with severe dwarfing and hypercalcaemia early in the disease has been known for many years. The *Schmid type of metaphyseal chondrodysplasia* is less severe, affecting mainly the lower limbs and particularly the femoral necks. These individuals are of short stature with normal epiphyses. This disorder, of dominant inheritance, is to be distinguished from the *McKusick type of metaphyseal chondrodysplasia,* of recessive inheritance. Formerly known as the cartilage-hair syndrome, these individuals have rather short limbs, fine, sparse hair and the metaphyses round the knee are particularly affected. In some individuals Hirschsprung disease, chronic neutropenia and lymphopenia occur with impaired cellular immunity. Indeed, there are now two additional forms of metaphyseal chondrodysplasia associated with these features (one with *thymolymphopenia,* and the other with *pan-*

creatic insufficiency and neutropenia, both of recessive inheritance). So, in metaphyseal disorders, look also for white cell and immunity problems.

One further disorder affecting the metaphyses needs mention—the *Kozlowski type of spondylometaphyseal dysplasia*, differentiated from the preceding diseases by spinal involvement, where platyspondyly and scoliosis contribute to a short-trunk type of dwarfism (dominant inheritance).

(iii) *Increased bone density*

Osteopetrosis has been recognized for many years. There is the *congenital or early onset* type, of recessive inheritance, with severe manifestions, progressive anaemia due to encroachment on the marrow space, cranial nerve palsies and so on. The *late-onset* form is often of dominant inheritance and is less severe. More recently other 'dense bone' disorders have been described. In *pyknodysostosis* there is short stature, Wormian bones, dental anomalies, short clavicles and short terminal phalanges as well as bone fragility. Marrow problems do not occur; it is of recessive inheritance. *Dysosteosclerosis* (recessive inheritance) is characterized also by bone fragility, dental anomalies and increased density of all bones; however, it is differentiated from osteopetrosis by platyspondyly, absence of marrow complications and a zone of increased translucency just proximal to the metaphyseal area. In *sclerosteosis* (recessive inheritance) the main features are increased density of the skull, mandible and to a less extent, the long bones. Syndactyly is present, and there is a failure of modelling of the diaphyses.

There are various disorders in which hyperostosis principally of the skull occurs, with or without thickening of long bones (*craniometaphyseal dysplasia, craniodiaphyseal dysplasia,* and *frontometaphyseal dysplasia*).

(iv) *Storage diseases*

The storage diseases are among the inborn errors of metabolism, and we have known of the six mucopolysaccharidoses, including the Hurler and Morquio syndromes, for several years. More recently another group, the mucolipidoses, have been described, sharing clinical features of both the mucopolysaccharidoses and the third 'storage' group—the sphingolipidoses (Table 1).

Table 1. Storage diseases.

	Inheritance	Enzyme	Age of onset	Acid mucopolysaccharide in urine
Mucopolysaccharidoses				
Hurler syndrome (MPS I.H.)	Autosomal recessive	Deficient α-L iduronidase	First few months	Dermatan and heparan sulphate
Scheie syndrome (MPS I.S.)	„	„	Later childhood	„ „ „
Hunter syndrome	X-linked recessive	Low sulphoiduronate sulphatase	6–12 months	„ „ „
Sanfilippo syndrome	Autosomal recessive	Low N-heparan-sulphatase or α-acetyl-glucosaminidase	Early childhood	Heparan sulphate
Morquio syndrome	„	?	2–4 years	Keratan „
Maroteaux-Lamy syndrome	„	?	Early-late childhood	Dermatan „ (some heparan)
Mucolipidoses				
GM_1 gangliosidosis Type I	„	Deficient β-galactosidase	Birth-early infancy	Nil
Mucolipidoses I	„	?	Late infancy	„
II (I cell disease)	„	?	Early infancy	„
III	„	?	Over 2 years	„
Sphingolipidoses				
Gaucher disease (also Nieman Pick disease, metachromatic leucodystrophy, Fabry disease and lactosyl ceramidosis)	„	Reduced glucocerebrosidase	Childhood or adulthood	„

The skeletal findings in all the mucopolysaccharide disorders and the mucolipidoses are similar, and merely indicate that there is some abnormality of mucopolysaccharide or glycoprotein metabolism. Differential diagnosis of these diseases depends upon clinical information such as age of onset, presence or absence of mental retardation, type of inheritance and the type of acid mucopolysaccharide in the urine—this being absent altogether in the mucolipidoses. Radiographic features shared to a greater or lesser extent by the group are a large skull and shallow sella turcica, broad anterior ends of the ribs with thick clavicles and scapulae; oval-shaped vertebrae with an anterior projection inferiorly (though in Morquio disease platyspondyly is present); a wide iliac flare and dysplasia of the femoral heads. Other bones show irregular modelling, and a pointed base of the metacarpals is quite characteristic. Fibroblast cultures grown from these patients show metachromatic granules on staining with toluidine blue, and it is interesting that cultures grown together from different patients in this same group of diseases will correct each other's metachromasia. In the future it will no doubt be possible to identify each disease by identifying each specific enzyme deficiency. At the present time only one has been discovered, the alpha-L iduronidase deficiency in the Hurler syndrome and also (the same enzyme) in the Scheie syndrome, perhaps due to different mutations of the same gene.

MULTIFACTORIAL DISORDERS

These are caused by many genes, polygenes, together with the action of environmental factors. The characteristic of this group, firstly, is that the disorders are quite common in the general population—indeed providing a large part of the orthopaedic surgeons' work: clubfoot, congenital dislocation of the hip, spina bifida and so on. Secondly, the risk of recurrence in a family is low. By "common" one means perhaps 1, 2 or 3 per 1,000 births. The genetic element is not strong and the risk of recurrence is typically only about 2–5 %, very much lower than the risks in the unifactorial disorders. In disorders of unifactorial inheritance even single families may give valuable information, but in multifactorial disorders large, carefully planned family surveys are needed before any pattern of inheritance emerges and figures for genetic counselling can be obtained. It is impossible to give accurate figures for recurrence risks, since each family must be considered separately; unlike the single gene disorders, the risks here are variable. In general terms,

if the parents are normal and have had one child with clubfoot, spina bifida or any member of this group, the probability of a second one being born with the same defect is perhaps 2–5 %. If they have already had two children with the defect, or if one of the parents has the same anomaly, then the figures rise steeply to between 10 and 40 %. We are all familiar with "clubfoot" families, for example. The more there are in a family the more there are likely to be, this being one of the main characteristics of multifactorial inheritance.

The main disorders of orthopaedic importance likely to be of multifactorial inheritance are:

I. VERTEBRAL COLUMN
- Neural tube defects (anencephaly, spina bifida cystica) (Williamson 1965, Carter et al. 1968, Carter & Evans 1973).
- Congenital scoliosis with multiple vertebral defects (Wynne-Davies 1975).
- Idiopathic scoliosis (though some cases may be of dominant inheritance) (Cowell et al. 1972, Riseborough & Wynne-Davies 1973, Wynne-Davies 1973).
- Spondylolisthesis (Wiltse 1962).
- Ankylosing spondylitis (Stecher & Hersch 1955, Blécourt et al. 1961, Emery & Lawrence 1967).

II. HIP JOINT
- Congenital dislocation of the hip (Record & Edwards 1958, Carter & Wilkinson 1964, Wynne-Davies 1970).
- Perthes' disease (Fisher 1972, Gray et al. 1972).
- Slipped upper femoral epiphyses (Rennie 1972).

III. LIMBS
- Talipes equino varus, calcaneo-valgus and metatarsus varus (Wynne-Davies 1965, Ching et al. 1969, Chung et al. 1969).

In most of these disorders there is nothing new to add to well-established data on genetic and environmental factors. There are just two points of particular note:

(i) *The neural tube defects and congenital scoliosis.* It has been known for many years that spina bifida with meningocoele (with or without hydrocephalus) is aetiologically related to anencephaly, because both types of defect occur in the same families. A recent survey from Edinburgh and London by Wynne-Davies (1973 and 1975) has

shown that patients from congenital scoliosis clinics with multiple vertebral defects belong to the same aetiological group, whether or not there is spina bifida occulta or any spinal cord defect. All these families have a much increased risk of a subsequent child being born with any one of these defects—anencephaly, spina bifida cystica or multiple vertebral anomalies only.

The solitary, isolated defects of one hemivertebra or the limited anterior vertebral body defects associated with kyphoscoliosis appear to be sporadic, non-genetic events, carrying no risk to sibs.

(ii) *Ankylosing spondylitis.* There have been many family surveys of this condition over the past 25 years and it is well established that increased numbers of relatives of index patients suffer from the same condition, the likelihood being that multiple genes are involved as well as environmental factors. Recently, Brewerton et al. (1973) reported that a very high proportion (90 %) of patients with ankylosing spondylitis have the HL-A27 antigen. This means that individuals who possess the gene for this antigen have an increased probability of developing the disease, compared with the population who do not have HL-A27. The picture is not yet complete, but at least one gene in the system causing ankylosing spondylitis has now been identified.

THE CONTROL OF GENETIC DISEASE AND ANTE-NATAL DIAGNOSIS

Until fairly recently the only possibility of controlling genetic disease was by giving advice to parents relating to the probability of another child being born with the same defect, leaving to them the decision as to whether or not to have another child. This sort of genetic advice is still important, but the need for accuracy is even greater now that ante-natal diagnosis is becoming possible in a number of disorders and selective abortion in the early stages of pregnancy can be considered. There is no doubt that there will be a reduced number of children born with serious defects in the immediate future, as a result of new techniques for analysing the amniotic fluid and the mothers' serum in early pregnancy. It is possible safely to withdraw some amniotic fluid from about the 15th week of pregnancy, there not being sufficient until this time. The fluid itself is of *maternal* origin (not primarily foetal urine, as has been thought in the past; the proteins in it are nearly all derived from the mother). It is not, therefore, (with one major exception) useful for diagnosing disease in the child. However, the cells floating in the

fluid are of foetal origin (desquamated epithelial cells and so on). These can be examined in order to determine the sex of the foetus, any chromosome anomalies, and (after culture) enzyme defects in certain inborn errors of metabolism. Current practice in antenatal diagnosis is at present confined to four groups of disorders:

(i) *Down's syndrome (trisomy 21, mongolism).* This can be diagnosed in the 14th or 15th week of pregnancy by examing the chromosomes of foetal cells. If trisomy 21 is found, abortion can be offered to the parents. This test is currently in use by many obstetricians for all pregnant women over the age of 35 or 40 years, since the disorder is particularly common amongst older mothers.

(ii) *X-linked recessive disorders.* Diagnosing the sex of a foetus is important in the X-linked recessive disorders. A mother who is a carrier of, for example, haemophilia or Duchenne's muscular dystrophy knows there is a 50 % chance that if she has a son he will have the disease. It may be possible antenatally to detect the affected male, or she could elect to have only daughters (half of whom will also be carriers, but will not themselves be diseased). Conversely, it is also possible that a man with haemophilia could elect to have only sons—who will all be normal as they carry only his Y chromosome, whereas all his daughters would be carriers.

(iii) *Inborn errors of metabolism.* There are a few rare metabolic disorders which can be diagnosed on cultured foetal cells before the 20th week of pregnancy and abortion offered if the foetus is affected. In practice, this is a very small part of antenatal diagnosis work at present, and it is only after one such child has been born to parents each carrying a recessive gene, that the family becomes known as a "high risk". Subsequent pregnancies can then be screened and abortion offered if indicated.

This field, however, has great scope for development and it should ultimately be possible, by screening all pregnancies, to eradicate these recessively inherited enzyme disorders.

(iv) *Neural tube defects.* A major addition to the field of possible antenatal diagnoses are the "open" neural tube defects of anencephaly and spina bifida cystica. Here the cerebro-spinal fluid is leaking into the amniotic fluid and large quantities of a "new" protein—"alpha-fetoprotein"—can easily be identified, as first described by Brock & Sutcliffe (1972). It is possible that this is a sort of foetal albumin, since its level decreases as true albumin increases. Research is currently being directed to identifying this protein in the mother's serum (where

the concentration is about one hundred times less than in amniotic fluid) (Brock et al. 1973). The 'closed' spina bifida lesions and multiple vertebral anomalies belong in the same aetiological group, but cannot be identified pre-natally because there is no leakage of cerebrospinal fluid. However, these families are at risk of having subsequent children with an 'open' lesion, and they may request investigation.

These neural tube and vertebral defects are the commonest of all congenital malformations known to man. The discovery of alpha-fetoprotein and the possibility that we may, in future, be able to diagnose some of these conditions by maternal blood tests, gives a great potential for reducing the numbers of severely deformed children.

SUMMARY

A review of disorders with a known genetic basis which occur in orthopaedic practice is presented. Four groups of skeletal dysplasias are briefly described (short-limbed dwarfism, metaphyseal disorders, disorders of increased bone density and the storage diseases). Amongst the multifactorial defects, the aetiological relationship of congenital scoliosis with multiple vertebral anomalies to the neural tube defects is noted, as well as the high proportion of ankylosing spondylitis patients with HL-A27 antigen. A summary of current practice in antenatal diagnosis is given, including modern methods of detecting open neural tube defects by estimating alpha-fetoprotein.

REFERENCES

Blécourt, J. J. de, Polman, A. & Blécourt-Meindersma, T. de (1961) Hereditary factors in rheumatoid arthritis and ankylosing spondylitis. *Ann. rheum. Dis.* **20**, 215.

Brewerton, D. A., Caffrey, M., Hart, F. D., James, D. C. O., Nicholls, A. & Sturrock, R. D. (1973) Ankylosing spondylitis and HL-A27. *Lancet* **i**, 904.

Brock, D. J. H., Bolton, A. E. & Monaghan, J. M. (1973) Antenatal diagnosis of anencephaly through maternal serum alpha-fetoprotein. *Lancet* **ii**, 923.

Brock, D. J. H. & Sutcliffe, R. G. (1972) Alpha-fetoprotein in the antenatal diagnosis of anencephaly and spina bifida. *Lancet* **ii**, 197.

Carter, C. O., David, P. A. & Laurence, K. M. (1968) A family study of major central nervous system malformations in South Wales. *J. med. Genet.* **5**, 81.

Carter, C. O. & Evans, K. (1973) Spina bifida and anencephalus in Greater London. *J. med. Genet.* **10**, 209.

Carter, C. O. & Fairbank, T. J. (1974) *The genetics of locomotor disorders.* Oxford University Press.

Carter, C. O. & Wilkinson, J. (1964) Persistent joint laxity and congenital dislocation of the hip. *J. Bone Jt Surg.* **46**-B, 40.

Ching, G. H. S., Chung, C. S. & Nemechek, R. W. (1969) Genetic and epidemiological

studies of clubfoot in Hawaii: ascertainment and incidence. *Amer. J. hum. Genet.* **21**, 566.

Chung, C. S., Nemechek, R. W., Larsen, I. J. & Ching, G. H. S. (1969) Genetic and epidemiological studies of clubfoot in Hawaii: general and medical considerations. *Hum. Hered.* **19**, 321.

Cowell, H. R., Hall, N. J. & MacEwen, G. D. (1972) Genetics of idiopathic scoliosis. *Clin. Orth. and rel. res.* **86**, 121.

Emery, A. E. H. & Lawrence, J. S. (1967) Genetics of ankylosing spondylitis. *J. med. Genet.* **4**, 239.

Fisher, R. L. (1972) An epidemiological study of Legg-Perthes disease. *J. Bone Jt Surg.* **54**-A, 769.

Gray, I. M., Lowry, R. B. & Renwick, D. H. G. (1972) Incidence and genetics of Legg-Perthes disease (osteochondritis deformans) in British Columbia: evidence of polygenic determination. *J. med. Genet.* **9**, 197.

Maroteaux, P. (1975) *Les maladies osseuses de l'enfant.* Flammarion, Paris.

Record, R. G. & Edwards, J. H. (1958) Environmental influences related to the aetiology of congenital dislocation of the hip. *Brit. J. Prev. soc. Med.* **12**, 8.

Rennie, A. M. (1972) The inheritance of slipped epiphysis. *J. Bone Jt Surg.* **54**-B, 754.

Riseborough, E. J. & Wynne-Davies, R. (1973) A genetic survey of idiopathic scoliosis in Boston, Massachusetts. *J. Bone Jt Surg.* **55**-A, 974.

Spranger, J. W., Langer, L. O. & Wiedemann, H. R. (1974) *Bone dysplasia: An atlas of constitutional disorders of skeletal development.* Gustav Fischer Verlag, Stuttgart; W. B. Saunders, Philadelphia.

Stecher, R. M. & Hersh, A. H. (1955) Familial occurrence of ankylosing spondylitis. *Brit. J. phys. Med.* **18**, 176.

Williamson, E. M. (1965) Incidence and family aggregation of major congenital malformations of central nervous system. *J. med. Genet.* **2**, 161.

Wiltse, L. L. (1962) The etiology of spondylolisthesis. *J. Bone Jt Surg.* **44**-A, 539.

Wynne-Davies, R. (1965) Family studies and aetiology of clubfoot. *J. med. Genet.* **2**, 227.

Wynne-Davies, R. (1970) A family study of neonatal and late diagnosis congenital dislocation of the hip. *J. med. Genet.* **7**, 315.

Wynne-Davies, R. (1973) Genetic and other factors in the aetiology of scoliosis. Ph.D. Thesis. University of Edinburgh.

Wynne-Davies, R. (1975) Congenital vertebral anomalies: aetiology and relationship to spina bifida cystica. *J. med. Genet.* In press.

Key words: review; genetic; orthopaedic; short-limbed dwarfism; metaphyseal disorders; increased bone density; storage diseases; vertebral anomalies; neural tube defects; alpha-fetoprotein; ante-natal diagnosis; multifactorial inheritance; ankylosing spondylitis; HL-A27

Correspondence to:

Dr. Ruth Wynne-Davies, M.B., F.R.C.S., Ph.D.
Department of Orthopaedic Surgery
University of Edinburgh
12 George Square
Edinburgh EH8 9JZ
Scotland