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Monogenic disorders

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In comparison with chromosomal anomalies or the more common congenital malformations there are special difficulties in establishing the total frequency of monogenic disorders. There are very many conditions, most of which are individually rare. Many of them are not manifest at birth and many present difficulties in diagnosis. There are two possible approaches: collating studies of the frequencies of individual conditions which have been carried out by individual workers with a special interest in the condition using all possible means of ascertainment; or surveillance studies attempting to pick up all monogenic disorders in a particular population. A valuable pioneer study of the second type was that by Stevenson from Northern Ireland (1959). The study, however, was evidently incomplete and several disorders were regarded as monogenic, which would now not be so classified. Nevertheless, the total frequency suggested was of the right order. A current surveillance study is from the British Columbia Register (Trimble and Doughty, 1974). This also, however, is evidently incomplete. In particular relatively common conditions of adult onset are hardly represented and even a common relatively diagnosed autosomal recessive disorder with onset in childhood, cystic fibrosis, is recorded at a frequency of less than half that indicated by *ad hoc* and neonatal screening studies. However, the continuation of such a registry is well worth while and it is likely to become more complete and accurate with time. Therefore, it is necessary to rely largely on studies of the first type attempting to make due allowance for their limitations. A limitation of either type of survey is that birth frequencies in any one country may be atypical. Most of the surveys have come from north-west European populations.

Dominant conditions

Dominant conditions have special importance in radiation genetics. The relation between mutation and birth frequency is relatively direct, the theoretical equilibrium birth frequency being the product of twice the mutation rate and the mean persistence in terms of generations of each mutant gene. Any increase in mutation rate will be reflected at once by an increase in the birth frequency of fresh cases of such dominant conditions born to unaffected parents.

Table 1a summarises data on birth frequencies from *ad hoc* surveys of some of the more common dominant conditions giving frequencies of 0·1 per

Table 1a *Estimates of birth frequencies of some more common dominant conditions in European derived populations per 1000 livebirths*

Nervous system	
Huntington's chorea	0·5 (Shokeir, 1975)
Neurofibromatosis	0·4 (Crowe *et al.*, 1956)
Myotonic dystrophy	0·2 (Grimm, 1975; Klein, 1958)
Intestines	
Multiple polyposis coli	0·1 (Veale, 1965; Reed and Neel, 1958)
Kidney	
Polycystic disease of kidneys	0·8 (Dalgaard, 1957)
Locomotor system	
Diaphysial aclasia	0·5 (Murken, 1963)
Sight	
Dominant forms of blindness	0·1 (Fraser and Friedmann, 1967)
Hearing	
Dominant forms of early childhood onset deafness	0·1 (Stevenson and Cheeseman, 1955; Chung *et al.*, 1958)
Dominant otosclerosis (adult onset)	1·0 (Morrison, 1967)
Circulation	
Monogenic hypercholesterolaemia	2·0 (Heiberg and Berg, 1976)
Teeth	
Dentinogenesis imperfecta	0·1 (Witkop, 1973)
Blood	
Congenital spherocytosis	0·2 (Morton *et al.*, 1962)

Table 1b *Some less common dominants*

Nervous system	
Tuberous sclerosis	0·01 (Borberg, 1951)
Basilar impression	0·03 (Haslam, 1973)
Skeleton	
Thanatophoric dwarfism	0·08 (Harris and Paton, 1971)
Osteogenesis imperfecta	0·04 (Smars, 1961)
Marfan sydrome	0·04 (Lynas, 1958)
Achondroplasia	0·02 (Verschuer, 1962)
Ehlers-Danlos syndrome	0·01 (Beighton, 1970)
Osteopetrosis tarda	0·01 (Salzano, 1961)
Sight	
Retinoblastoma	0·03 (Macklin, 1960)
Face	
Cleft lip and/or palate with mucous pits of lip	0·01 (Cervenka *et al.*, 1967)
Metabolism	
Acute intermittent porphyria	0·01 (Tschudy, 1973)
Variegate porphyria	0·01 (Tschudy, 1973)
Teeth	
Amelogenesis imperfecta	0·02 (Witkop, 1973)

1000 births or more. A birth frequency is the proportion of children born who will at some stage in their lives develop the condition, that is the proportion of children who are born heterozygous for the gene involved. Table 1b summarises findings on some less common dominant conditions with estimated frequencies between 0·1 and 0·01 per 1000 births.

Monogenic hypercholesterolaemia is outstanding in Table 1a. Evidence for such a monogenic entity among the largely multifactorially determined hyperlipidaemias has been increasing over the past 20 years, and recently Brown and Goldstein (1974) have probably identified the specific basic biochemical defect in fibroblast culture, though there may be more than one variant. The combined birth frequency of heterozygotes is not well established, but is perhaps not likely to be less than 1 or more than 4 per 1000. The condition is serious since it is estimated that about a half of heterozygous men have their first coronary by 50 years and about half are dead by 60 years (Slack, 1969). A case has been made for an even more common monogenic form of hyperlipidaemia, with both hypercholesterolaemia and hypertriglyceridaemia (Goldstein *et al.*, 1973), also associated with early onset ischaemic heart disease; but I do not think the case is proven.

Adult onset dominant otosclerosis has a birth frequency of the order of 3·0 per 1000 and the onset is usually below 40 years.

The adult form of polycystic disease of the kidneys had a birth frequency of nearly 1 per 1000 in Dalgaard's Danish survey (1957). It is certainly a relatively common condition in nephrology clinics. Though sometimes benign, the condition usually causes clinical trouble before the 4th decade and may cause death in childhood. The condition has been recognized in twin fetuses aborted at 16 weeks (Blyth and Ockenden, 1971).

There have been numerous prevalence studies of Huntington's chorea. The most complete of these in north-west Europeans tends to give an estimate of 0·05 to 0·1 per 1000 population. With an estimated mean survival after onset of the disease of 15 years, this implies a birth frequency of about 0·5, especially as some cases still remain undiagnosed. The estimate for neurofibromatosis is an old one, but the frequency with which the condition is seen, especially in orthopaedic clinics, indicates that this old estimate may be near the mark.

The other conditions listed largely speak for themselves. Some have regarded multiple exostosis as a trivial condition. However, it may cause embarrassingly short stature, restrict joint mobility, and perhaps 1 in 20 patients develop sarcoma. The birth frequency of dominant otosclerotic deafness has been reduced by two-thirds in Table 1a so as to include only the more severe cases.

The reason for the relatively high frequency of these dominant conditions is probably largely a reflection of their relatively small effect on reproductive fitness. There is no need to postulate an improbably high mutation rate for them, nor to postulate, as some have suggested, that in some circumstances those who possess the gene have an above average reproductive fitness. In the case of monogenic hypercholesterolaemia however it may well be that the much increased risk of early death in men did not apply in a less civilized environment.

The somewhat less common dominants listed in Table 1b also present no special problems. Thanatophoric dwarfism, the most frequent in the table, should not perhaps be included as it is not yet proven that it is a dominant condition. Moreover, unlike the other conditions listed it results in stillbirth or neonatal death. Most estimates of the 'birth frequency' of achondroplasia have been estimates of the birth frequency largely of thanatophoric dwarfism and indeed the paediatric pathologist's concept of the histology of achondroplasia is often that of this condition. Classical achondroplastics seldom die in infancy and so do not provide the pathologist with histological material. Nevertheless, classical achondroplasia is not an uncommon condition, perhaps the most common of the dozen or so forms of surviving short limbed dwarfism apparent at birth.

There are many more well-known dominant conditions. Some of which should perhaps have appeared in Table 1b, if there had been an adequate survey. These include familiar conditions such as cleido-cranial dysostosis, Apert syndrome, Crouzon disease, dominant myotonia congenita, dominant facio-scapula-humeral muscle dystrophy, dominant forms of neurogenic, muscular atrophy, split-hand and foot, von Willebrand's disease, Treacher Collins syndrome, multiple epiphysial dysplasia, and many others. However none of these I think will prove to have frequency which would put them into Table 1a. Any further conditions likely to go into Table 1a are those, like perhaps combined hypercholesterolaemia and hypertriglyceridaemia, if that exists as a monogenic disorder, which have not yet been recognized.

The total frequency of dominant conditions in Table 1a is 6 per 1000, with a third of this caused by monogenic hypercholesterolaemia. The conditions in Table 1b only total 0·3 per 1000. Perhaps 7 per 1000 would be a reasonable figure for all presently known serious dominant conditions. But there may well be others which are not yet recognized. Stevenson's estimate for Northern Ireland was similar, 9·5 per 1000, but Trimble and Doughty's only 0·8 per 1000.

Recessive conditions

Autosomal recessive conditions are of less interest to radiation biologists. The interval between gene mutation and patient may be lengthy, centuries, or even millennia. The full effect of an increase in mutation rate would not be seen for many generations. For example the gene frequency of phenylketonuria in north-west Europe is about 1 in 100. If the mutation rate was, say, 1 in 50 000 this would imply a mean survival time of each mutation of some 500 generations, that is about 12 000 years. This would be shortened, however, if, as is likely, the higher birth frequency in Europe is to some extent the result of founder effect and drift.

Each population appears to have its own pattern of recessive disorders occurring at relatively high frequencies. Birth frequencies of recessive disorders may be much influenced by heterozygote advantage. There is the opportunity for the relatively high frequencies of one or two out of the many hundred individual recessive genes to develop as a result of founder effect and drift in a particular population. The population geneticists do not yet appear to have worked out that frequency of a recessive gene in a particular size of population at which it is no longer reasonable to invoke founder effect and drift and so necessary to invoke heterozygote advantage. The high frequency of tyrosinosis in French Canadians is obviously the result of founder effect, of Tay-Sach's disease in Ashkenazi Jews is acceptable also as the result of founder effect and drift, of phenylketonuria throughout Europe with localized specially high frequencies is perhaps just acceptable. But the apparently consistent high frequency of cystic fibrosis of about 1 in 2000 births over much of Europe is, in my opinion, difficult to visualise as the result of such chance influences and requires a small degree of heterozygote advantage.

Autosomal recessive conditions which appear to have birth frequencies in Britain of about or greater than 0·1 per 1000 births are listed in Table 2. Cystic fibrosis is outstanding for a condition where reproductive fitness is near zero and yet has a high birth frequency. Recent neonatal screening surveys by Stephan's method on albumin in meconium, checked by sweat electrolyte, in Dublin, Cardiff, and in one or two German cities has indicated that the birth frequency may be 1 in 1600 rather than 1 in 2000. The indications are that the relatively high frequency obtains from Ireland across to Russia and perhaps in southern Europe too, but more data are needed. The condition is rare outside Europe and populations derived from Europe. Phenylketonuria is also rare except in Europe and migrants from Europe, but shows distinct variations even within the British Isles, with a cline of increasing frequency as one moves north and west from about 1 in 15 000 in the south east to 1 in 7000 in Ireland and West Scotland. It will be interesting to see how the pattern of frequency develops in Europe as the results of neonatal screening come in. Poland appears to have a high frequency. Finland has such a low frequency that the value of neonatal screening is in doubt. The neurogenic muscle atrophies certainly are common and include 2 and perhaps 3 distinct conditions, distinguishable by age of onset and the rapidity with which paralysis develops. Sickle-cell anaemia is confined to immigrants to Britain from West and Central Africa, but there are sufficient of these to give a figure of 0·1 per 1000 for births in Britain. This would drop rapidly with intermarriage of these migrants with those of other races. The adrenal hypoplasias include 3 varieties, though 2 of these may involve the same enzyme. It has been estimated that recessive congenital deafness perhaps includes at least 5 different forms, though these are not distinguishable clinically. Recessive blindness includes several different forms many of which are distinguishable.

Table 2 *Estimates of birth frequencies of some more common recessive conditions in Britain per 1000 livebirths*

Metabolism	
Cystic fibrosis	0·5 (Hall and Simpkiss, 1968; Wright, 1969; Stephen *et al.*, 1975)
Phenylketonuria classical	0·1 (Carter, 1973)
Nervous system	
Neurogenic muscle atrophies	0·1 (Pearn, 1973; Pearn and Wilson, 1973)
Red blood cells	
Sickle-cell anemia	0·1 (Carter, 1973)
Endocrine glands	
Adrenal hyperplasias	0·1 (Hubble, 1966; Rosenbloom and Smith, 1966)
Hearing	
Severe congenital deafness	0·2 (Stevenson and Cheeseman 1955; Chung *et al.*, 1958)
Sight	
Recessive forms of blindness	0·1 (Fraser and Friedmann, 1967)
Mental retardation severe	
Non-specific recessive forms	0·5 (Carter, personal estimate)

A list of autosomal recessives with frequencies between 0·1 and 0·01 per 1000 would include with their approximate birth frequencies: among the lysozymal enzyme deficiencies—Tay Sach's disease (0·04), mucopolysaccharidosis 1 (0·02), mucopolysaccharidosis 2 (0·01), metachromatic leucodystrophy (0·02); among errors of metabolism affecting carbohydrate metabolism—galactokinase deficiency (0·01) and galactosaemia (0·02); among errors of amino acid metabolism—homocystinuria (0·01), cystinuria (0·06), cystinosis (0·01); among syndromes—Smith-Lemli-Opitz syndrome (0·01).

There are also some hundreds of probably rarer recessive conditions.

The total frequency of conditions listed in Table 2

is 1·7 per 1000 and adding rarer conditions would total about 2·5 per 1000 for presently known recessives. Others will be discovered. Recently for example homozygotes for antitrypsin deficiency, with a birth frequency of about 0·7 per 1000, have been shown to have a high risk of developing severe pulmonary emphysema in early adult life and might have been included in Table 1.

Stevenson's estimate for Northern Ireland was 2·1 per 1000 and Trimble and Doughty's for British Columbia 1·1 per 1000.

X-linked conditions

X-linked conditions are intermediate between dominant and recessive conditions in the information they provide on radiation effects. Where reproductive fitness is zero and there is no selective advantage of the heterozygous woman, and for equal mutation rates in the two sexes, the proportion of males affected is 3 times the mutation rate and of these a third are affected as a result of fresh mutation. Only the latter would be immediately increased by an increase in the mutation rate and it would take several generations for the full effect of a simultaneous increase in female heterozygotes to be reflected in the birth of affected sons.

Table 3 *Estimate of birth frequency in males of more common X-linked conditions in European derived populations per 1000 livebirths*

Locomotor system	
Muscle dystrophy—Duchenne	0·2
Blood clotting	
Haemophilia, classical	0·1
Skin	
Ichthyosis	0·1
Mental retardation	
Non-specific X-linked	0·1
(Estimates mainly from Stevenson and Kerr, 1967)	

Table 3 summarises the findings of *ad hoc* surveys of X-linked conditions with birth frequencies of 0·1 or more per 1000 births. Several surveys are available of Duchenne type X-linked muscular dystrophy giving similar results to the Oxford survey of Stevenson and Kerr (1967). This is also the case with classical haemophilia. Ichthyosis is perhaps not too serious a condition. The relatively high frequency of a non-specific form of X-linked retardation, variously known as the Renpenning or Martin-Bell syndrome has only been recently recognised (Turner *et al.*, 1972). A list for X-linked conditions with birth frequencies between 0·1 and 0·01 per 1000 might include haemophilia B, X-linked deafness, ocular albinism, X-linked nystagmus, the Bruton type of hypogammaglobulinaemia, hypophosphataemic rickets, anidrotic ectodermal dysplasia, X-linked aqueduct stenosis, and X-linked amelogenesis imperfecta. There are many other X-linked conditions some of which also perhaps have a frequency of 0·01 per 1000. These include Aldrich syndrome, Fabry's disease, Borjeson syndrome, choroideremia, nephrogenic diabetes insipidus, chronic granulomatous disease, incontinentia pigmenti, Lowe's syndrome, Menkes syndrome, Type II mucopolysaccharidosis, the Becker type of X-linked muscular dystrophy, Norrie's disease, oral-facial-digital syndrome, Pelizaeus-Merzbacher syndrome, X-linked retinitis pigmentosa, and testicular feminisation syndrome.

There is no indication that heterozygote advantage plays any part in maintaining the frequency of any of these X-linked conditions and as with dominants their frequency probably reflects directly the mutation rate and the reproductive fitness of affected males. Heterozygote advantage against malaria is probably important in the case of G6PD deficiency, but this is uncommon in Britain.

The total frequency of X-linked conditions in Table 3 is about 0·5 per 1000 male births and the total frequency of all X-linked conditions presently known of the order of 0·8 per 1000, that is about 0·4 per 1000 births of both sexes. Both Stevenson's and Trimble and Doughty's estimates were also 0·4.

Conclusion

The total birth frequencies of presently known serious and moderately serious dominant conditions as estimated from *ad hoc* surveys in British and allied populations is about 7·0 for dominants, 2·5 for recessives, and 0·4 for X-linked conditions, i.e. a total of about 10 per 1000 livebirths, which is similar to that obtained by Stevenson (1959) and about 10 times more than that obtained by Trimble and Doughty (1974).

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