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Зміст
Multifactorial inheritance

The concept of multifactorial inheritance implies that a disease is caused by the interaction of several adverse genetic and environmental factors. The liability of a population to a particular disease follows a normal distribution curve, most people showing only moderate susceptibility and remaining unaffected. Only when a certain threshold of liability is exceeded is the disorder manifest. Relatives of an affected person will show a shift in liability, with a greater proportion of them being beyond the threshold. Familial clustering of a particular disorder may therefore occur. Genetic susceptibility to common disorders is likely to be due to sequence variation in a number of genes, each of which has a small effect, unlike the pathogenic mutations seen in mendelian disorders. These variations will also be seen in the general population and it is only in combination with other genetic variations that disease susceptibility becomes manifest. Unravelling the molecular genetics of the complex multifactorial diseases is much more difficult than for single gene disorders. Nevertheless, this is an important task as these diseases account for the great majority of morbidity and mortality in developed countries. Approaches to multifactorial disorders include the identification of disease associations in the general population, linkage analysis in affected families, and the study of animal models. Identification of genes causing the familial cases of diseases that are usually sporadic, such as Alzheimer disease and motor neurone disease, may give insights into the pathogenesis of the more common sporadic forms of the disease. In the future, understanding genetic susceptibility may enable screening for, and prevention of, common diseases as well as identifying people likely to respond to particular drug regimes. Several common disorders thought to follow polygenic inheritance (such as diabetes, hypertension, congenital heart disease and Hirschsprung disease) have been found in some individuals and families to be due to single gene defects. In Hirschprung disease (aganglionic megacolon) family data on recurrence risks support the concept of sex-modified polygenic inheritance, although autosomal dominant inheritance with reduced penetrance has been suggested in some families with several affected members. Mutations in the ret proto-oncogene on chromosome 10q11.2 or in the endothelin-B receptor gene on chromosome 13q22 have been detected in both familial and sporadic cases, indicating that a proportion of cases are due to a single gene defect.

Risk of recurrence

The risk of recurrence for a multifactorial disorder within a family is generally low and mainly affects first degree relatives. In many conditions family studies have reported the rate with which relatives of the index case have been affected. This allows empirical values for risk of recurrence to be calculated, which can be used in genetic counselling. Risks are mainly increased for first degree relatives. Second degree relatives have a slight increase in risk only and third degree relatives usually have the same risk as the general population. The severity of the disorder and the number of affected individuals in the family also affect recurrence risk. The recurrence risk for bilateral cleft lip and palate is higher than the recurrence risk for cleft lip alone, and the recurrence risk for neural tube defect is 4% after one affected child, but 12% after two. Some conditions are more common in one sex than the other. In these disorders the risk of recurrence is higher if the disorder has affected the less frequently affected sex. As with the other examples, the greater genetic susceptibility in the index case confers a higher risk to relatives. A rational approach to preventing multifactorial disease is to modify known environmental triggers in genetically susceptible subjects. Folic acid supplementation in pregnancies at increased risk of neural tube defects and modifying diet and smoking habits in coronary heart disease are examples of effective intervention, but this approach is not currently possible for many disorders.

Heritability

The heritability of a variable trait or disorder reflects the proportion of the variation that is due to genetic factors. The level of this genetic contribution to the aetiology of a disorder can be calculated from the disease incidence in the general population and that in relatives of an affected person. Disorders with a greater genetic contribution have higher heritability, and hence, higher risks of recurrence.

Box 12.1 Factors increasing risk to relatives in multifactorial disorders

- High heritability of disorder
- Close relationship to index case
- Multiple affected family members
- Severe disease in index case
- Index case being of sex not usually affected

Twins

Twins share a common intrauterine environment, but though monozygous twins are genetically identical with respect to their inherited nuclear DNA, dizygous twins are no more alike than any other pair
of siblings, sharing, on average, half their genes. This provides the basis for studying twins to determine the genetic contribution in various disorders, by comparing the rates of concordance or discordance for a particular trait between pairs of monozygous and dizygous twins. The rate of concordance in monozygous twins is high for disorders in which genetic predisposition plays a major part in the aetiology of the disease. The phenotypic variability of genetic traits can be studied in monozygous twins, and the effect of a shared intrauterine environment may be studied in dizygous twins. Twins may be derived from a single egg (monozygous, identical) or two separate eggs (dizygous, fraternal). Examination of the placenta and membranes may help to distinguish between monozygous and dizygous twins but is not completely reliable. Monozygosity, resulting in twins of the same sex who look alike, can be confirmed by investigating inherited characteristics such as blood group markers or DNA polymorphisms (fingerprinting).

**Box 12.2 Twinning**

**Dizygous twins**
- May be familial
- More common in black people than white Europeans

**Monozygous twins**
- Seldom familial
- Occur in 0.4% of all pregnancies
- Associated with twice the risk of congenital malformations

as singleton or dizygous twin pregnancies

**Diabetes**

A genetic predisposition is well recognised in both type I insulin dependent diabetes (IDDM) and type II non-insulin dependent diabetes (NIDDM). Maturity onset diabetes of the young (MODY) is a specific form of non-insulin dependent diabetes that follows autosomal dominant inheritance and has been shown to be due to mutations in a number of different genes. Clinical diabetes or impaired glucose tolerance also occurs in several genetic syndromes, for example, haemochromatosis, Friedreich ataxia, and Wolfram syndrome (diabetes mellitus, optic atrophy, diabetes insipidus and deafness). Only rarely is diabetes caused by the secretion of an abnormal insulin molecule. IDDM affects about 3 per 1000 of the population in the UK and is a T cell dependent autoimmune disease. Genetic predisposition is important, but only 30% of monozygous twins are concordant for the disease and this indicates that environmental factors (such as triggering viral infections) are also involved. About 60% of the genetic susceptibility to IDDM is likely to be due to genes in the HLA region. The overall risk to siblings is about 6%. This figure rises to 16% for HLA identical siblings and falls to 1% if they have no shared haplotype. An association with DR3 and DR4 class II antigens is well documented, with 95% of insulin dependent diabetics having one or both antigens, compared to 50–60% of the normal population. As most people with DR3 or DR4 class II antigens do not develop diabetes, these antigens are unlikely to be the primary susceptibility determinants. Better definition of susceptible genotypes is becoming possible as subgroups of DR3 and DR4 serotypes are defined by molecular analysis.

For example, low risk HLA haplotypes that confer protection always have aspartic acid at position 57 of the DQB1 allele. High risk haplotypes have a different amino acid at this position and homozygosity for non-aspartic acid residues is found much more often in diabetics than in non-diabetics. The second locus identified for IDDM was found to be close to the insulin gene on chromosome 11. Susceptibility is dependent on the length of a 14bp minisatellite repeat unit. Short repeats (26–63 repeat units) confer susceptibility, perhaps by influencing the expression of the insulin gene in the developing thymus. Subsequent mapping studies have identified a number of other possible IDDM susceptibility loci throughout the genome, whose modes of action are not yet known. NIDDM is due to relative insulin deficiency and insulin resistance. There is a strong genetic predisposition although other factors such as obesity are important. Concordance in monozygotic twins is 40–100% and the risk to siblings may approach 40% by the age of 80. Although the biochemical mechanisms underlying NIDDM are becoming better understood, the genetic causes remains obscure. In rare cases, insulin receptor gene mutations, mitochondrial DNA mutations or mild mutations in some of the MODY genes are thought to confer susceptibility to NIDDM.

**Coronary heart disease**

Environmental factors play a very important role in the aetiology of coronary heart disease, and many risk factors have been identified, including high dietary fat intake, impaired glucose tolerance, raised blood pressure, obesity, smoking, lack of exercise and stress. A positive family history is also important. The risk to first degree relatives is increased to six times above that of the general population, indicating a considerable underlying genetic predisposition. Lipids play a key role and coronary heart disease is associated with high LDL cholesterol, high ApoB (the major protein fraction of LDL), low HDL cholesterol and elevated Lp(a) lipoprotein levels. High circulating Lp(a) lipoprotein
concentration has been suggested to have a population attributable risk of 28% for myocardial infarction in men aged under 60. Other risk factors may include low activity of paraoxonase and increased levels of homocysteine and plasma fibrinogen. Lipoprotein abnormalities that increase the risk of heart disease may be secondary to dietary factors, but often follow multifactorial inheritance. About 60% of the variability of plasma cholesterol is genetic in origin, influenced by allelic variation in many genes including those for ApoE, ApoB, ApoA1 and hepatic lipase that individually have a small effect. Familial hypercholesterolaemia (type II hyperlipoproteinaemia), on the other hand, is dominantly inherited and may account for 10-20% of all early coronary heart disease. One in 500 of the general population is estimated to be heterozygous for the mutant LDLR gene. The risk of coronary heart disease increases with age in heterozygous subjects, who may also have xanthomas. Severe disease, often presenting in childhood, is seen in homozygous subjects. Familial aggregations of early coronary heart disease also occur in people without any detectable abnormality in lipid metabolism. Risks to other relatives will be high, and known environmental triggers should be avoided. Future molecular genetic studies may lead to more precise identification of subjects at high risk as potential candidate genes are identified.

Schizophrenia and affective psychoses

A strong familial tendency is found in both schizophrenia and affective disorders. The importance of genetic rather than environmental factors has been shown by reports of a high incidence of schizophrenia in children of affected parents and concordance in monozygotic twins, even when they are adopted and reared apart from their natural relatives. The same is true of manic depression. Empirical values for lifetime risk of recurrence are available for counselling, and the burden of the disorders needs to be taken into account. Both polygenic and single major gene models have been proposed to explain genetic susceptibility. A search for linked biochemical or molecular markers in large families with many affected members has so far failed to identify any major susceptibility genes.

Congenital malformations

Syndromes of multiple congenital abnormalities often have mendelian, chromosomal or teratogenic causes, many of which can be identified by modern cytogenetic and DNA techniques. Some malformations are non-genetic, such as the amputations caused by amniotic bands after early rupture of the amnion. Most isolated congenital malformations, however, follow multifactorial inheritance and the risk of recurrence depends on the specific malformation, its severity and the number of affected people in the family. Decisions to have further children will be influenced by the fact that the risk of recurrence is generally low and that surgery for many isolated congenital malformations is successful. Prenatal ultrasonography may identify abnormalities requiring emergency neonatal surgery or severe malformations that have a poor prognosis, but it usually gives reassurance about the normality of a subsequent pregnancy.

Mental retardation or learning disability

Intelligence is a polygenic trait. Mild learning disability (intelligence quotient 50-70) represents the lower end of the normal distribution of intelligence and has a prevalence of about 3%. The intelligence quotient of offspring is likely to lie around the mid-parental mean. One or both parents of a child with mild learning disability often have similar disability themselves and may have other learning-disabled children. Intelligent parents who have one child with mild learning disability are less likely to have another similarly affected child. By contrast, the parents of a child with moderate or severe learning disability (intelligence quotient < 50) are usually of normal intelligence. A specific cause is more likely when the retardation is severe and may include chromosomal abnormalities and genetic disorders. The risk of recurrence depends on the diagnosis but in severe non-specific retardation is about 3% for siblings. A higher recurrence risk is observed after the birth of an affected male because some of these cases represent X linked disorders. Recurrence risks are also higher (about 15%) if the parents are consanguineous, because of the increased likelihood of an autosomal recessive aetiology. The recurrence risk for any couple increases to 25% after the birth of two affected children.