Background genetics

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GENES carry information to direct the synthesis of specific proteins. We cannot directly observe the *genotype*, the sum total of the genes carried by an individual, but can only infer knowledge about the genotype from examination of the individual's appearance (his *phenotype*), and the phenotypes of persons genetically related to him. The phenotype is the result of the many complex interactions between the genes and gene products, and between them and the succession of environments experienced from conception onwards. But any phenotypic trait studied may lie anywhere in the range from a molecular to a gross morphological or behavioural characteristic, i.e. from an enzyme to a complex character.

Genes are located in linear order on chromosomes in the nuclei of cells, and each chromosome occurs twice (with the exception of the sex-chromosomes) in all somatic cells. At each *gene locus* there will be two copies of the gene. Where these copies are different they are known as alternative *alleles* of the gene and the individual is said to be *heterozygous* at this locus.

Gene differences are identified by particular patterns of segregation of alternative phenotypes in pedigrees. Consideration of a number of hypothetical pedigrees will make this clear. Pedigree A (Fig. 1)

illustrates the phenotypes of the children and grandchildren from a marriage between a man showing a particular phenotypic effect and an unaffected or normal woman. It is evident that wherever the trait appears in a sibship at least one parent is also affected, and there is a trail of affected individuals running through the pedigree. In all sibships from marriages between an affected and an unaffected individual the ratio of affected to normal sibs is 1:1. This segregation is consistent with the possibility that each affected individual has one normal and one altered allele at some gene locus. During gamete production a reduction division occurs in the gonad cells so that only one of each pair of chromosomes is incorporated into each gamete. Each affected person would then produce gametes of two types carrying one or other allele of the gene. Normal people would be *homozygous* for the normal allele and produce only one type of gamete with respect to this locus. Random combination of gametes from these parents can give only two genotypes in equal numbers. If an individual with one or two copies of the altered allele shows the phenotypic effect, this allele is said to show *dominance* over the normal one.

Pedigree B (Fig. 2) presents a different picture. The trait does not appear in the offspring of the first or second generations so that the basis of the

FIG. 1. Pedigree A. Open squares, normal males; open circles, normal females; closed squares, affected males; closed circles, affected females.

FIG. 2. Pedigree B. Open squares, normal males; open circles, normal females; closed squares, affected males; closed circles, affected females.

phenotype cannot be a mutant gene of dominant effect, but must be recessive. A *recessive* effect is expressed only if the individual is homozygous and carries two copies of the particular allele. The couple that constitute the first cousin marriage in pedigree B (x and y) must have received one copy each of the allele from their parents who must also have been heterozygous for this gene. In a marriage between two individuals both heterozygous for a particular locus each person can form two types of gamete (carrying one or other allele). When these gametes

combine at random they generate the ratio 1:2:1 for the three genotypic classes (the one homozygote, the heterozygote and the other homozygote). When the trait is recessive the heterozygote and the homozygote without the allele in question appear identical, giving an overall ratio of three normal to one affected. The appearance of the one affected daughter in the sibship of five from the first cousin marriage approximates closely to this expectation.

The frequency of any particular mutant trait in a population is rare so that the heterozygotes are not very common either (see later). Any increase in the incidence of marriages between genetically related people above that expected by chance (i.e. inbreeding) is more likely to bring together heterozygotes (like x and y) who have received the same allele, identical by descent from a common ancestor.

One important exception to these two basic patterns of inheritance of traits is that relating to genes carried on the X-chromosome. Since females have two X-chromosomes and males only one X which they receive from their mother, recessive X-linked traits will always be manifest in males carrying the mutant allele.

Pedigree C (Fig. 3) shows a characteristic pattern of inheritance of a sex-linked trait. It is recessive since it is not seen in the second generation at all. It reappears in families of second generation females but not from second generation males, and then in only 50% of the male progeny (two out of four). Affected females would be very rare since they would necessarily have to be products of a marriage between a heterozygous (or *carrier*) female and an affected male. Only one Y-linked trait is known in man but such traits would show a patrilineal pattern of inheritance as well as expression restricted to males, and would be very easy to recognize.

FIG. 3. Pedigree C. Open squares, normal males; open circles, normal females; closed squares, affected males; closed circles, affected females.

Though these examples have shown how various patterns of incidence can be interpreted in terms of basic Mendelism yet the real situations may be rather more complicated. The phenomenon of dominance shows that genetic identity cannot be deduced solely from phenotypic identity. This is made more evident in the following example. Marriages do occur between deaf-mutes both of which have family history of this defect, that is they show evidence for a genetic basis for the defect. Occasionally all the children of such a marriage are normal. The genetic basis of the defect must have been different in the two families, and due to genes with recessive effect. The normal children are evidence that each defective gene is complemented by the correct copy from the other parent. A further possible confusion in identifying genotypes from phenotypes stems from the fact that some genetic effects can be mimicked by environmental agents (*phenocopies*).

The same genotype will not necessarily produce the same phenotype under all environmental conditions. Consider a gene segregating which has a dominant effect (cf. Fig. 1). If this gene is not expressed phenotypically in all individuals carrying it (it is not completely *penetrant*) then the genetic prognosis of a simple dominant effect becomes less easy. Many gene mutations with recessive or dominant effects do not have 100% *penetrance* and pedigree analysis becomes correspondingly more difficult.

In assembling evidence for a new recessive gene effect one other point must be remembered. As discussed earlier (pedigree B) the affected individuals appear in sibships from unaffected parents, both putative heterozygotes. Summing the phenotypes in these isolated sibships identified by at least one affected member will not give the best estimate of the segregation ratio since sibships born to similar parents but without affected members will not be included. There are recognized methods of correcting for this bias.

So far consideration has been limited to differences due to single gene differences. These are certainly the most tractable to study, but most characters are affected by, and the results of, differences at several gene loci as well as environmental effects, all of which in summation affect the liability to a particular condition. If a single spina bifida child is born to parents the incidence of the trait in subsequent sibs is empirically observed to be about 4%. If two affected children are produced the observed frequency of a subsequent affected sib rises to 10%. The basic rules of inheritance state that there is random combination of gametes so that the probabilities of forming particular genotypes are fixed. The observations above are not in contradiction with this. The sibships with two affected children will

include those in which more genes affecting the condition are segregating and in which therefore the genetic expectation of a further affected individual is higher.

Part of the environment of any gene is the rest of the genotype, so that penetrance of a gene may be affected by particular alleles present at other gene loci. We may call the other loci modifier loci or the total basis of the effect may be termed polygenic or multifactorial, the difference in terminology merely reflecting whether attention is focused on any one particular locus or not.

When the number of possible phenotypes for a character is large or more arbitrary in definition and the direct relationship with gene differences is less clear, for example with metrical characters, the concept of heritability is used to describe the genetic situation. This is a measure of the proportion of the total variability in a character in a population that is the result of segregating gene differences. It can also be viewed as a predictor in the sense that if the heritability is high, phenotypes will accurately reflect their genotypes, and can be used to estimate their progeny phenotypes.

A third basic approach to genetic variation in human populations is through twin studies. Monozygotic twins are genetically identical, whereas dizygotic twins are the result of two independent fertilization events. A comparison of the degree of phenotypic similarity (concordance) within monozygotic and dizygotic twin-pairs should indicate the contribution of genetic differences to the character though the figures are sometimes at variance with experience from pedigree analysis.

When the genotypes at segregating loci have been identified in a population the question arises as to whether they are varying with time. Changes in genetic composition are measured by following changes in allele frequency over generations at the locus in question. Shortly after the rediscovery of Mendel's work early this century it was realized that gene and genotypic frequencies remain constant from generation to generation, in the absence of selection, mutation, migration and non-random mating. If the frequency of allele A at the locus with two alleles is represented by p and that of allele a by q then the frequencies of the three possible genotypes AA, Aa, and aa are given by p^2 , $2pq$ and q^2 respectively. This is known as the Hardy-Weinberg rule. If the limiting conditions listed above do not hold, departures from these expectations may occur. Random fluctuations in number in small populations can also lead to changes in gene frequency, but here we will consider only the effects of selection against particular phenotypes.

If selection tends to remove the recessive a/a or the dominant A/A_a, an equilibrium will eventually be

reached at the point when mutation is introducing new copies of the allele at the same rate as they are being removed by selection. In the situation where the genotype a/a has a very deleterious phenotype one might ask whether the frequency of a could be reduced by encouraging a/a individuals to restrain from reproduction. Removal of a/a individuals from the breeding pool reduces slightly the frequency of allele a . The frequency of homozygotes a/a (q^2) falls as the square of this value (q) so that as q decreases an increasingly larger proportion of a alleles will be present in heterozygotes where they cannot be identified and removed. It has been calculated that it would take 500 generations during which time all sufferers from fibrocystic disease of the pancreas (the commonest autosomal recessive effect) would have to abstain from reproduction to reduce the frequency of sufferers from its present value of one in 2000 births to one in 4000 births. The important conclusion is that selection against a recessive follows a law of diminishing returns and would never be complete because of recurrent mutation.

The alternative mode of selection is the situation where the heterozygote is favoured over either homozygote. One of the few well-documented cases is that of sickle cell anaemia. The heterozygote Hb^A/Hb^S has better resistance to malarial infection than either homozygote. The price paid for this resistance is the homozygote class Hb^S/Hb^S who are severe anaemics. As long as malaria was present selection against anaemic homozygotes did not reduce the frequency of Hb^S , though in the absence of malaria now in many areas selection has reverted to simple selection against the recessive.

The basics of genetics have been discussed in this paper in terms of genes of drastic effect. It is important not to confuse the genetic fitness of an individual with the more common concept of fitness or health. However extreme a phenotype is, if it survives to reproductive age and contributes on average equally to the next generation, selection is not operating against it even though in social and medical terms the individual is far from fit. This applies in particular to deleterious phenotypes

which have a late onset of expression after reproductive maturity is reached. If there is selection against a genotype the severity of selection determines how long any mutation producing that phenotype stays in the population. If a dominant mutation confers a survival 99/100 of the other genotypes it persists a long time on the average before being eliminated, whereas if its survival is only 1/100 of other genotypes it will not persist for many generations. The balance sheet in genetic terms is the same, the occurrence of a mutation and its gradual elimination, but in medical, social and human terms the cost may not be the same for the two cases.

Genotypes with drastic phenotypic effects constitute a decided minority of the population. This raises the question as to whether natural selection is operating at all on most of the population. In Western Europe and North America most people survive to reproductive age and are fertile. We have little knowledge about the frequency of very early intra-uterine death. Natural abortions and implantation failures may go unnoticed but in all these classes some losses may be attributable to genetic causes. This makes the area of maternal/foetal incompatibility an important area of study. Finally it should be realized that of the many components of selection the one that assumes increasing importance, because it still shows variation, is family size. If an individual has a large family he leaves behind more copies of his genes, and in genetic terms is more fit. Many of the subtleties of selection in human populations then hinge on the relation between family size and the phenotypic characters we are interested in.

Further introductory reading

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