The genetics of deafness

'It is certain that whatever diagnostic refinements are employed, it will remain impossible to assign an exact cause of hearing loss in a substantial proportion of deaf persons'. These prophetic words were penned by Dr George Fraser at the conclusion of his survey into the causes of profound childhood deafness in over 3500 patients in 1976.[1] Despite the startling scientific advances which the intervening years have heralded, Dr Fraser's assertion still holds true today. Nowhere is this more pertinent than in a discussion on hereditary deafness because, if an aetiology for deafness cannot be identified, it is impossible to calculate an exact prevalence figure for hereditary deafness. Yet deafness is a common congenital problem with an incidence in the European population of approximately 0·9 per 1000 live births.[2] At least half of the congenital deafness load in a community has been calculated to be due to genetic causes,[3] thus making genetically determined deafness a significant contributor to morbidity in our population.

The spectrum encompassed by hereditary deafness is broad and ranges from simple deafness without other clinical abnormalities (that is, non-syndromic deafness) to genetically determined syndromes wherein deafness is but a feature among a group of clinically recognisable signs that together comprise a syndrome. About 30% of all genetically determined deafness is said to occur in syndromic form. The remaining 70% occurs as non-syndromic forms of deafness and it is to these children that Dr Fraser's comments especially apply, for it is frequently not possible to distinguish deaf children of genetic aetiology from deaf children of environmental aetiology in the absence of other helpful clinical stigmata.

Genetic counselling for deafness

Many of the syndromes that include deafness among their features are inherited in a mendelian manner thus facilitating accurate genetic counselling to affected individuals as to offspring risks, provided the syndrome has been recognised. Among the more familiar such syndromes are Waardenburg's syndrome and Branchio-Oto-Renal syndrome, both of which are inherited as autosomal dominant conditions, and Usher's syndrome, which is inherited in an autosomal recessive fashion. By contrast, genetic counselling in non-syndromic deafness is a much more complex matter. It has been estimated that autosomal recessive forms predominate accounting for 70–85% of genetic non-syndromic deafness.[3] [4] Genes acting in an autosomal dominant manner account for 12–25%[3] of such cases and sex linked genes account for approximately 3%.[1] Although it may be possible to recognise the autosomal dominant and sex linked types on the basis of the inheritance pattern involving other affected family members and counsel accordingly, these individuals will comprise a minority of the genetically deaf population. The vast majority of such cases are due to autosomal recessive genes and the nature of recessive inheritance is, that in a given family, it usually appears in one generation only and, unless there are many affected siblings in that generation, there is no way of knowing whether the deafness in an individual case is genetically or environmentally determined. In these difficult situations the geneticist is forced to rely on empirical risk figures, derived from population surveys of the occurrence of deafness among children of deaf couples, hearing couples, and couples in whom one partner was deaf and the other partner hearing, some such surveys dating from the last century.[5]

A further complication for the geneticist is introduced by the high frequency of marriage between individuals both of whom are deaf. This may lead to a complex genetic situation in which there may be multiple possible causes of deafness in a given pedigree. The combinations of deafness causing genes thus generated can lead to widely varying risks from one deaf couple to the next, risks that may have to be revised after a deaf child is born.

For many monogenic disorders gene tracking or mutation detection by DNA analysis has become an aid to diagnosis and genetic counselling. It is not surprising though that the dramatic advances in identifying gene loci responsible for single gene disorders such as cystic fibrosis[6] have yet to make an impact on non-syndromic forms of deafness. The main obstacle that has retarded the impact of molecular genetics on genetic deafness has been the problem of genetic heterogeneity.

Genetic heterogeneity

Although between 70–85% of non-syndromic genetic deafness is thought to be due to autosomal recessive inheritance,[3] [4] it is known that all autosomal recessive deafness cannot be explained on the basis of mutations at a single gene locus. This conclusion is based on the observation that couples with known autosomal recessive deafness of non-syndromic type usually have children who are all normally hearing.[1] This implies that the deafness in the parents is recessive in origin but involving different gene loci. Estimates vary as to how many mutant loci are capable of causing autosomal recessive deafness. The lowest figure proposed is that of Chung and Brown who suggested that there might be five such loci, based on their observations of the frequency of deaf offspring born to deaf parents.[7] Earlier estimates placed the number of such loci somewhere between 12[4] and 45.[8] As observed by Fraser, there is no means by which these phenotypically similar but genetically distinct forms of deafness can be distinguished.[1] Herein lies the nub of the problem for the genetic counsellor and the explanation for the continuing reliance on empirical risk data. Genetic heterogeneity is not confined to autosomal recessive forms of hereditary deafness for it is thought that a number of different loci may be capable of causing autosomal dominant deafness[4] and there is recent linkage evidence to suggest that not all forms of the rare sex linked deafness involve the same gene locus.[9]

Progress in mapping genes for deafness

In the family linkage strategy, DNA is collected from pedigrees who, indisputably, share the same clinical condition. This DNA is probed using DNA probes of known genetic location with a view to 'mapping' the location of the disease causing gene. In essence one is looking for DNA probes that faithfully coinherit with the disease within the family. When applied to clinical disorders due to a single mutant locus this is a very powerful technique. Its value in genetic deafness is limited by genetic heterogeneity but it has been central to the progress made so far in localising deafness causing genes. In very recent times the genes which cause Waardenburg's syndrome type I[10] and Usher's syndrome type II[11] have been 'mapped' to the long arms of chromosomes 2 and 1 respectively. Now that the responsible genes have been roughly localised, they will in due course be cloned and their protein products become available for

comparison with the normal. In this manner we can hope better to understand the pathogenesis of these two forms of genetic deafness in the foreseeable future. Syndromes such as these, which have a clear clinical definition, will continue to be 'mapped' using the linkage approach.

This method will not prove so useful in non-syndromic deafness, however, where families sharing similar inheritance of deafness may not necessarily share the same causative gene. None of the autosomal genes for non-syndromic deafness have yet been cloned but there has been some progress in mapping the X chromosomal genes which may cause non-syndromic deafness. Linkage studies in two separate families had indicated that a locus for deafness could be 'mapped' to the q13–q21 region of the long arm of the X chromosome.[12][13] A further more extensive study, involving several pedigrees has now confirmed this locus.[9] Not all the pedigrees with sex linked deafness can be attributed to this locus, however, and it seems very likely that, even for the very rare sex linked deafness, at least two possible loci may exist.[9]

As the molecular genetics of collagen genes begins to be unravelled an association with deafness is emerging, although the precise nature of that association is at present unclear. What is certain is that a progressive, sensorineural deafness is a common feature of the Stickler-Marshall syndrome.[14] Genetic linkage between the type II procollagen gene (COL2A1) on chromosome 12 and Stickler-Marshall syndrome has been documented in some families with this condition,[15][16] which suggests that mutations in the COL2A1 gene may be responsible for the clinical manifestations of Stickler-Marshall syndrome in the families concerned. Secondly, it is clear that osteogenesis imperfecta type 1 may be linked to either type I collagen subunit gene COL1A1 or COL1A2.[17] However all pedigrees in whom deafness is a feature are linked to the COL1A1 gene on chromosome 17.[18] These data suggest that deafness may result from mutations affecting certain subunits of both types I and II collagen genes but the precise reasons for this observation require further study.

Future progress

For further progress to be made, it is apparent that alternatives to the family linkage approach will have to be employed to surmount the problems posed by genetic heterogeneity. One such strategy would be the study and isolation of genes responsible for non-syndromic deafness in the mouse.[19] By capitalising on the considerable DNA sequence homology between mouse and human genomes, these genes could then be used to search the human genome for genes responsible for deafness. Identification and cloning of such genes with subsequent study of their protein products and the interactions thereof would bring us many new insights into the embryological and pathogenic mechanisms responsible for the complex group of conditions we currently label as non-syndromic deafness. The practical benefits which would accrue from identification of genes capable of causing deafness would be accurate carrier detection tests, more refined genetic counselling with less reliance on empirical risk data and early diagnosis of deafness in at risk individuals based on DNA analysis rather than on less reliable techniques.

Notwithstanding the complexities outlined here, many deaf people and their doctors continue to seek genetic counselling. It is a tribute to generations of past geneticists that their studies are still so pertinent to the modern practice of medical genetics in relation to deafness and a constant reminder of the enormity of the challenges which await solutions in this field.

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