Review article

Genes and epilepsy

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Do epilepsy genes exist and, if so, can they be found? The answer is yes certainly to the first question, and yes probably to the second. The evidence supporting these contentions will be examined in this short review.

No-one doubts that neurology textbooks of the third millennium will contain complete accounts of the molecular basis of a host of genetic diseases which affect the nervous system and are inherited in a Mendelian fashion. Huntington's disease, neurofibromatosis, tuberous sclerosis, Freidreich's ataxia, and neuronal ceroid lipofuscinosis have already fallen prey to the power of DNA based linkage analysis. In a field where the most reckless optimism soon seems in retrospect to have been timid caution, it is reasonable to predict that all these genes will be isolated and characterised. The methods are available. The problem is finite. It is merely a matter of time and money.

But what of those diseases in which the genetic contribution, although unequivocal, cannot be confidently ascribed to mutations at a single locus. Among nervous system disorders, psychiatric diseases and the epilepsies come into this category. Can the approaches which have been so spectacularly successful in Mendelian diseases be applied to complex genetic diseases? The epilepsies are merely a particular example of this general problem which has been exercising molecular geneticists for several years in respect of, for example, heart disease and diabetes mellitus. The suggestion that it might be possible to map epilepsy genes was first made several years ago.^{1 2}

It is first necessary to define what is meant by epilepsy. The term itself encompasses as diverse a

group of diseases as does the term anaemia. The evidence for a genetic contribution to specific epilepsy phenotypes will be briefly described with particular reference to the unavoidable uncertainties concerning genetic mechanisms. Strategies for linkage analysis of complex genetic diseases will be considered with particular reference to their application to the epilepsies.

Epilepsy and its causes

Epilepsy is, of course, no more a disease entity than anaemia. The analogy with anaemia is instructive in several ways, but even the most partisan haematologist will admit that the human brain is substantially more complex than the human red cell.

Epilepsy can be simply defined—as recurrent seizures—just as anaemia can be defined as a reduction in haemoglobin concentration. A seizure is a transient disturbance of neuronal synchrony. But dysfunction in this most complex organ not surprisingly generates a vast and overlapping range of clinical entities. Some patients defy categorisation, some may fit into several categories, and some may change their nature with time. No unequivocal diagnostic test exists. The most recent attempt at classification lists a total of 18 different varieties of seizure and 48 distinguishable clinical types of epilepsy.³

The causes of epilepsy range, as do those of anaemia, from the purely environmental (for example, post-traumatic) to the apparently purely genetic (for example, as a component of the phenotype in tuberous sclerosis). Genetic influences on this aspect of brain function may be quite indirect. The genes do not necessarily code for proteins synthesised in the central nervous system: the seizures of hyperphenylalaninaemia owing to mutations in the phenylalanine hydroxylase gene and of hyperammonaemia owing to mutations in the gene for ornithine transcarbamylase would be examples of this. It is not, however, such genes as these which are at issue here. Rather, we seek the equivalent of the genetic haemoglobinopathies.

Unfortunately (or fortunately), one striking contrast between brain cell and red cell lies at this point. Red cell function is dominated by a single protein, albeit encoded by several genes. Brain function depends on anything up to 30 to 40 000 different proteins, a greater complexity of mRNA being expressed within its collective cell types than in any other organ. The list of potential candidate genes is therefore likely to be voluminous, although the actual number of mutated genes which are common in the human gene pool and cause recurrent seizures may be quite small.

Genetics of epilepsy in man

A familial susceptibility to seizures has been recognised since the time of Hippocrates. It is necessary to distinguish first between those conditions in which seizures are merely one component of the phenotype, and those which concern us here, in which recurrent seizures occur as an essentially isolated phenomenon. The former provide unequivocal evidence that genes may influence neuronal synchrony. Genetic studies of the latter provide good evidence for a genetic contribution but inconclusive data on the mechanism of inheritance.

In over 140 Mendelian disorders, epilepsy occurs in a proportion of patients as a component of the phenotype. This group includes diseases ranging from phenylketonuria to tuberous sclerosis. In some, the mutated gene and its product are known, and the pathophysiology at least partially understood: phenylketonuria, again, would be a typical example. The influence on neuronal function is often indirect, the relevant gene as discussed above not necessarily being expressed in the central nervous system. In addition, in many syndromes associated with chromosomal anomalies abnormalities of central nervous system function occur including seizures.

However, these conditions only account for a tiny fraction, perhaps 1%, of all patients with seizures. The epilepsies under consideration here are those in which recurrent seizures are the sole abnormality. Many of these display familial aggregation, but segregation analysis rarely indicates Mendelian inheritance. Indeed, only two 'pure' epilepsy syndromes exist in which there is good evidence for a single gene pattern of inheritance: benign familial neonatal convulsions and progressive myoclonic epilepsy of Unverricht and Lundborg.

The genetics of these human epilepsies has been the subject of numerous studies and has been recently reviewed.⁴ Before briefly considering the results of these studies, it is worth considering the difficulties peculiar to epilepsy which account at least in part for the uncertainties which exist.

Whoever described diabetes as the geneticist's nightmare had evidently not given due consideration to any claims the epilepsies have on this title. Reliable

and accurate clinical information on particular persons is often difficult to obtain. The exact description and circumstances surrounding a seizure may never be available, and subjects may be unaware of seizures occurring in early childhood. Even if the seizures can be accurately defined, particular persons may defy categorisation into particular epilepsy phenotypes. Not only may the particular variety of seizure (of which there are many) change with age but a mixture of different seizure types may occur in the same subject and within a particular pedigree.

The relationship of EEG abnormalities to epilepsy is uncertain. A simplistic view might be that such changes are a sub-clinical indicator of the same pathophysiological state, analogous to a low haemoglobin concentration indicating anaemia in a patient whose pallor had escaped the clinician's eye. But the relationship is clearly more complex, and similar EEG changes may occur in association with apparently quite different seizure types.⁵

Flaws in study design have compounded these inherent difficulties. On occasion there has been a failure to define the types of seizures or epilepsy in relatives as well as probands, and even to define the precise relationship of affected relative to proband. Selection of probands has been susceptible to bias, and inappropriate groups chosen for comparison.

Nevertheless, studies of several epilepsy phenotypes have provided evidence for a genetic component in their aetiology. These include 'grand mal' epilepsy, 'absence' epilepsy, juvenile myoclonic epilepsy of Janz, benign rolandic epilepsy with centrotemporal spikes, and febrile convulsions. In addition, a genetic contribution to the aetiology of several EEG patterns, including generalised spike waves, focal spikes, and the photoconvulsive response, has been identified.^{6,7}

Most commonly, the conclusion has been that the mechanism of inheritance is 'multifactorial', although not infrequently quite different conclusions have emerged from different studies of the same phenotype, or the data have been compatible with more than one mechanism of inheritance. The problem is, of course, that the powers of segregation analysis are limited and the evidence which emerges from such studies often does not allow definitive conclusions to be drawn. Studies relating to the genetics of these epilepsy phenotypes are considered in turn.

BENIGN FAMILIAL NEONATAL CONVULSIONS

This rare syndrome is well documented.⁸ Inheritance is autosomal dominant. Eighty-seven subjects in 14 families have been reported. Short, generalised, clonic convulsions occur with onset between the age of 2 days and 3 months. No aetiology is apparent on intensive investigation and the outcome is favourable with normal psychomotor development. Seizures recur in later life in 14%.

PROGRESSIVE MYOCLONIC EPILEPSY: UNVERRICHT-LUNDBORG TYPE

This subtype of progressive myoclonic epilepsy displays autosomal recessive inheritance,⁹ and represents one of the disease genes enriched in the Finnish population. Onset is between 8 and 13 years with grand mal seizures or myoclonus. Slow and mild mental deterioration occurs, and survival time is variable. Non-specific histological changes are observed in brain, and Lafora bodies are **not** found. Although the nosology of PME has been confused, it is now agreed that this is a distinct entity.

GRAND MAL EPILEPSY: TONIC-CLONIC TYPE

Patients with pure grand mal epilepsy of tonic-clonic type comprise 4 to 10% of all epilepsy patients. A generalised spike and wave pattern is the hallmark on the EEG. The results of family studies depend in part on whether information on EEG in asymptomatic family members has been included.

Eisner *et al*¹⁰ identified 321 probands with generalised tonic-clonic epilepsy. The cumulative risk of epilepsy in sibs by the age of 20 years varied with age of onset in the proband: 7.5% if onset in the proband was before the age of 4 years, 4.3% if between 4 and 15 years of age. Overall seizure rate for first degree relatives was 5.26%, compared with 1.75% in a control population.

Metrakos and Metrakos,¹¹ in their classic studies, investigated probands with either grand mal or absence type epilepsy and generalised spike and wave pattern on the EEG. The risk for seizures among sibs of probands was 12.7%, compared with 4.7% among sibs of controls.

Tsuboi and Endo¹² studied the offspring of 30 patients with tonic-clonic seizures: 4.7% developed seizures, 16.8% developed seizures including febrile convulsions, and 37.3% showed an interictal or asymptomatic 'epileptiform' pattern on EEG.

Twin studies show a major genetic factor in generalised epilepsies including grand mal. The overall concordance rate reported in six major twin studies was 60.2% for monozygotic pairs and 13.2% for dizygotic pairs.¹³

'ABSENCE' EPILEPSY: PURE, CLASSIC, CHILDHOOD ABSENCE OR PETIT MAL

Absence seizures occur in many different epilepsy syndromes. Their classification has recently been reviewed.¹⁴ Classic absence of children with 3 Hz spike-wave complexes accounts for 3 to 4% of all patients with epilepsy.

Mathes¹⁵ studied probands with pure absence and 3 Hz spike and wave discharges. Among 240 sibs, 10% had seizures of some type. Doose *et al*¹⁶ reported that

among sibs of 239 probands with absence seizures 6.7% had seizures (30 of 448). Of 242 sibs in whom EEG information was available, 22.3% had abnormalities including generalised spike and wave or photoconvulsive reactions. In a twin study by Lennox and Lennox,¹⁷ monozygotic twins were shown to have 75% concordance for absence seizures and 84% concordance for the 3 Hz spike-wave trait. There was no concordance for either in 14 pairs of dizygotic twins.

JUVENILE MYOCLONIC EPILEPSY

This syndrome shows a peak age of onset between 13 and 15 years and includes mild sporadic myoclonias, grand mal convulsions on awakening in 95%, and absence episodes in 37% of patients. The accompanying EEG trait consists of 4 to 6 Hz multispike wave complexes and persists into the sixth and seventh decades of life. There is good evidence for a strong genetic component, and some workers have identified this syndrome as particularly suitable for molecular genetic analysis. Tsuboi and Christian¹⁸ studied 319 probands with JME. Of 1618 first degree relatives, 4.1% had 'epilepsy'. Of the 66 relatives, 21 were parents, 14 offspring, and 31 sibs. An additional 50 subjects showed EEG abnormalities, and overall the pedigree studies showed maternal preponderance and suggest a lower threshold in females for seizure activity. A polygenic pattern of inheritance was proposed.

Delgado-Escueta and Enrile-Bacsal¹⁹ found 24 affected sibs or parents with 43 probands with JME. Seizure types included febrile convulsions (3), grand mal tonic-clonic (11), myoclonic (5), and absence seizures (5).

BENIGN CENTROTEMPORAL EPILEPSY

This entity has a mean age of onset of 10 years and includes brief hemifacial seizures that tend to become generalised when they occur nocturnally. The EEG findings include slow, diphasic, high voltage, centrotemporal spikes, activated by sleep. The prognosis is excellent and recovery is the rule.

Bray and Wiser²⁰ studied 40 probands and their families. Centrottemporal spikes were found in 30% of first degree relatives, four of 21 parents and 17 of 52 sibs. They suggested autosomal dominant inheritance with age dependent penetrance.

Heijbel *et al*²¹ studied 19 probands. Of 34 sibs, 15% had seizures and rolandic discharges and 19% had rolandic discharges in isolation. Of 38 parents, 11% had a history of seizures in childhood and 3% had rolandic discharges on EEG. They concluded that an autosomal dominant gene with age dependent penetrance is responsible for the EEG trait.

FEBRILE CONVULSIONS

Studies of febrile convulsion susceptibility have allowed many genetic models to be proposed, including autosomal dominant,²² autosomal recessive,²³ and polygenic or multifactorial²⁴ mechanisms of inheritance. In the most recent comprehensive study, heterogeneity was apparent when families were divided according to frequency of febrile convulsions in the proband. In families of probands with a single febrile convulsion the polygenic model best explained the data, but in families of probands with multiple febrile convulsions, evidence was consistent with a single major locus model with nearly dominant seizure susceptibility.

MATERNAL INFLUENCE

An intriguing, unexplained, and very consistent observation is an apparent maternal influence on seizure susceptibility: offspring of affected women are more likely to have seizures than are those of affected men. This feature of the inheritance of epilepsy has been extensively analysed by Ottman *et al*^{26,27} and cannot be explained by any simple genetic model. Various possible 'spurious' explanations for this phenomenon have been excluded: it does not, for example, arise from differences in the characteristics of the epilepsies between affected mothers and fathers, anticonvulsant use during pregnancy, non-paternity, or better reporting by mothers than by fathers of their children's seizure histories. The most parsimonious explanation for the maternal excess is that there is a maternally transmitted influence on seizure susceptibility. This raises the interesting possibility that mutations in the maternally inherited mitochondrial genome could account at least in part for this effect. An association between mtDNA mutations and human disease is now well documented,²⁸ and includes disorders in which myoclonic seizures may be a component of the phenotype.

Another possible explanation of this pattern of inheritance is the phenomenon of genomic imprinting. A compelling body of evidence has now arisen to suggest that modification of genetic material takes place depending on whether inheritance is maternal or paternal. This new concept runs contrary to the traditional Mendelian assumption that the parent of origin of a particular gene is not relevant, and may explain 'irregular' patterns of inheritance. It now appears from work in the mouse that, in that species, as many as 10 to 20% of genes have modifications depending on the parent of origin. Unequivocal evidence for imprinting effects has been obtained in several human diseases. Pedigree structures expected to arise from this effect can be predicted.²⁹ Formal analysis of epilepsy pedigrees to establish their compatibility with maternal imprinting has not of course been carried out, but it is possible that such a

mechanism may contribute to the observed maternal influence.

Strategies for molecular genetic analysis

The advent of methods for detecting genetic polymorphism by DNA analysis has of course provided powerful new approaches to the study of inherited disease in man. Two general strategies exist by which these techniques can be applied to the epilepsies, as was described in some detail several years ago.

In the first approach, cloned 'candidate' genes in which a mutation might result in the observed phenotype are used to determine whether inheritance of an allele of the candidate gene correlates with the disease. In the second approach, cosegregation of the disease trait with any of a random set of DNA markers is sought in order to identify the map position of the gene. These will be considered in turn.

'Candidate' genes

Selection of 'candidate' genes for a variety of diseases has usually led to the 'candidate' being excluded as the site of the disease gene mutation. Happily, this exclusion can be achieved without a huge expenditure of effort: one recombination between disease locus and 'candidate' locus is sufficient. However, the high failure rate has led to the realisation that this approach is not as powerful as might naively be imagined.

It is not just that 'candidates' are eagerly selected with a mixture of wishful thinking and a desire to avoid the daunting prospect of a random search of the genome. In general, our relative ignorance of pathophysiology, and the rather stringent requirement that candidate genes must have been cloned in order to be used, conspire to reduce the chance of success. Surely, it is argued, the gene coding for insulin must be a 'candidate' gene for diabetes mellitus. But, of course, the complexities of pathophysiology are such that the genetic factors causing diseases are often far removed from the structural genes encoding a particular peptide or protein, however central to the disease state. The globin genes were and are of course a shining but perhaps misleading exception.

The temptation, therefore, to identify 'candidate' genes for epilepsy must undoubtedly be tempered with considerable caution. The vast number of genes expressed in brain together with our considerable ignorance of pathophysiology spells a high chance of disappointment. Nevertheless, a number of genetically determined functions can be identified which, if disturbed, would lead to disordered neuronal synchrony and clinical seizures.

'Candidate' genes for epilepsy must include, for example, those encoding proteins involved in mediating neuronal inhibition, in inactivation of excitatory neurotransmitters, and in ion transport

across excitable membranes. Generalised failure of inhibitory mechanisms or enhancement of excitatory neurotransmission are two hypothetical if rather simplistic explanations for a variety of forms of epilepsy. Neuronal inhibition is clearly a complex function involving numerous proteins including, for example, the receptors for neurotransmitters, such as GABA and the β endorphins and enzymes of their synthetic pathways. Some of the relevant genes are now available.

Of particular interest is the recent explosion of molecular genetic information concerning the GABA_A receptor.^{30, 31} There is good evidence that GABA_A mediated inhibition is of major importance in the mammalian central nervous system,³² and indirect evidence that defects in this functional pathway may be associated with epilepsy. Inhibition of GABA_A synthesis or blockade of GABA_A receptors, for example, result in seizure activity. Neurochemical markers for GABA_A are altered in human temporal lobe epilepsy³³ and in certain animal models, such as the seizure susceptible gerbil.²⁴ In addition, two classes of neuroconvulsant agent, the benzodiazepines and barbiturates, have modulatory receptor sites on the GABA_A receptor-ionophore protein complex.

Molecular biological techniques are showing the many complexities of the GABA_A receptor.³⁵ It is now apparent that there are at least three α , one β , and two γ subunits, that there is different regional distribution and regional expression of the α subunits, and that various subunit combinations give rise to receptors with different properties. Localisation of α subunit genes to autosomes (chromosomes 4 and 5) and the X chromosome has been achieved using *in situ* hybridisation. It is apparent that mutations in one or several of these genes could conceivably generate phenotypes with the sort of localised pathophysiology and complex inheritance patterns observed in some epilepsy syndromes. Work is in progress to identify polymorphisms at these loci.

A similar case can be made for the importance of excessive excitation at amino acid receptor sites in epileptogenesis.³⁶ Excitatory amino acids applied focally or systemically induce seizure activity, and an apparent increase in the number or efficacy of NMDA preferring receptors is seen in various models of epilepsy. The recent cloning of a glutamate receptor channel,³⁷ and steps towards molecular cloning of the uptake system for excitatory amino acids,³⁸ are likely to give rise to 'candidate' genes in this area.

The ionic basis of the control of neuronal membrane potentials clearly suggests that the genes encoding ion channels could potentially influence the signalling capabilities of individual neurones. Mutations exist in *Drosophila* which affect ion currents, cause increased membrane excitability, and result in phenotypes such as Sh (Shaker) and eag (ether-a-go-go), which display cellular physiological dysfunction not dissimilar to

that found in neurones showing epileptic activity.³⁹ Brain genes coding ion channels have now been cloned^{40, 41} and must also be regarded as 'candidate' genes.

Lastly, the mitochondrial genome can be regarded as a collection of candidate epilepsy genes. It is not difficult to envisage how disruption of cellular energy metabolism may initiate seizure activity, and myoclonic seizures are a component of the phenotype in several diseases in which abnormalities of the mitochondrial genome have been documented. Various mechanisms exist which might confine the phenotypic effects of mutations in this genome to the central nervous system.

Of course, the existence of a host of 'candidate' genes, unimagined and uncloned, specifying complex functions such as those concerned with the development of neuronal interconnections can only be surmised. It can be anticipated that the next few years will see no shortage of gene cloning activity in relation to the human central nervous system: some of those genes may turn out to be involved in the epilepsies.

Linkage analysis using 'random' markers

The epilepsies, in common with a number of important diseases, display most of those characteristics which render them unsuitable for linkage analysis.

Subjects with the mutant genotype may fail to manifest the disease (incomplete penetrance) and those of normal genotype may apparently display the mutant phenotype owing to non-genetic causes (phenocopies). Non-allelic genetic heterogeneity may be present: mutations at several different loci may result in apparently identical clinical conditions. Lastly, the disease trait may result from genetic interactions between alleles at several loci, but at least one locus is essential for development of the disease. The extreme situation of polygenic inheritance, in which alleles at numerous loci interact in an additive way to determine susceptibility, is the only complexity which appears to render attempts at linkage analysis impractical on formal mathematical grounds. The epilepsies do, however, have one advantage. They are not rare.

Confronted by these difficulties, how can the chance of success be maximised and the chance of error be minimised?⁴²

When penetrance is incomplete, the genotype of an unaffected descendant of an affected subject is always in doubt. The safest approach, if resources are sufficient, is not to include data on unaffected subjects. The potential problem of misdiagnosing unaffected persons as affected is another risk: any subject for whom the diagnosis is in doubt is best designated 'phenotype unknown' and excluded from the analysis.

There is no certain way of circumventing the potential problem of non-allelic genetic heterogeneity:

a disease may be clinically homogeneous, even though it arises from mutations at different loci, and vice versa. The risk can be reduced but not eliminated, and it should be remembered that linkage will be obscured by quite a modest degree of heterogeneity. The clinical phenotype may be subdivided, in the hope that clinical features will distinguish the different genetic forms. The study may be confined to a single large pedigree, or to a single geographical region with a relatively isolated population.

Lastly, the method of 'simultaneous search' makes use of the availability of a complete RFLP linkage map of the human genome. If after screening RFLPs spanning the entire genome no single genetic interval shows tight linkage, two or more intervals are examined simultaneously for linkage to the disease. A set of loci accounting together for segregation in all the families is more easily recognised than a single locus accounting for segregation in a fraction of them.

The difficulties encountered in mapping loci which interact to produce a trait correspond to those arising from phenocopies and reduced penetrance. If the allele frequency at a component locus is high ($>10\%$) parental homozygosity may occur. An affected child may inherit either chromosome from a homozygous parent, and linkage to the locus will not be apparent in that family. (The risk of parental homozygosity may be reduced by avoiding families with a high proportion of affected sibs.) The genotypes of unaffected children cannot be used as evidence against linkage to a particular locus: the disease causing allele may have been inherited, but without the required alleles at other loci the disease is not expressed. This equates to one locus causing the disease with low penetrance.

It is clear that a number of approaches can be used in the application of linkage analysis to the epilepsies. An important factor is that the data can be analysed and reanalysed under any number of different assumptions, and different mixtures of assumptions concerning mode of inheritance and genetic homogeneity or heterogeneity. The jigsaw piece can be tried in all orientations. Provided the family resources are large, and pedigrees in which the clinical information is potentially unreliable are ruthlessly excluded, reliable information should emerge.

Two further approaches are worth considering. The affected sib pair method of linkage analysis detects departures from independent segregation of disease and marker phenotypes and requires no specification of the mode of inheritance. This method has recently been generalised to the analysis of pedigrees, the so-called affected pedigree member method of linkage analysis.⁴³

Current mapping data in the epilepsies

At present, evidence has been obtained concerning

the map location of two epilepsy syndromes: benign familial neonatal convulsions (BFNC)⁴⁴ and juvenile myoclonic epilepsy.^{45 46}

BFNC is, of course, the most favourable epilepsy syndrome for linkage analysis, with a segregation pattern indicating an autosomal dominant mode of inheritance, and presents none of the difficulties discussed above. In a single, large pedigree two polymorphic DNA marker loci on chromosome 20 were found to be tightly linked to the disease locus, giving maximum lod scores of 3.12 ($\theta=0.003$, for RMR6 detecting *D20S20*) and 2.87 ($\theta=0.039$, for CMM6 detecting *D20S19*). Multipoint analysis of the disease locus and both these loci gave a lod score of 5.64 with no obligate recombinants.

Juvenile myoclonic epilepsy (JME) is far more representative of the problems pertaining to mapping epilepsy syndromes. This is a non-progressive form of generalised epilepsy distinguished by a characteristic age of onset (9 to 20 years) and myoclonic jerks which occur most often on awakening. Grand mal generalised tonic-clonic seizures occur in 95% of patients, and about 30% have absence seizures. In one study, all untreated patients had an interictal EEG trait consisting of bilaterally symmetrical diffuse 4 to 6 Hz multispikes and wave complexes. Ten per cent also had diffuse 3 Hz spike-wave complexes. Family members may show the same EEG abnormalities.

Linkage of JME to the HLA and Bf loci on human chromosome 6 has been found. Thirty-four, mostly nuclear, families were studied. Anyone with any form of generalised epilepsy or a positive generalised EEG trait was regarded as 'affected', and linkage analysis was carried out assuming either dominant or recessive inheritance and a range of penetrance values. Significant positive lod scores (>3.0) were obtained assuming either model at high penetrance values. Non-JME forms of epilepsy were present in four families. When these cases were reclassified as 'unaffected', the lod score increased under the assumption of a fully penetrant recessive. If these results are confirmed they will support hopes that linked loci can be found in epilepsy phenotypes displaying complex inheritance patterns.

Conclusions

The evidence that 'epilepsy genes' exist is strong. Familial segregation of human epilepsies provides good support for a genetic contribution to aetiology in several epilepsy syndromes, and present knowledge of the pathophysiology of seizures indicates that genes control functions related to neuronal synchrony. It is very reasonable to suppose that mutant alleles at specific loci manifested by liability to seizures occur in the human population.

Can these genes now be identified? There is no doubt that the molecular genetic techniques exist to

examine the potential role of any 'cloned' candidate genes in the aetiology of seizures. It can be anticipated that a significant minority of the many thousands of genes expressed in human brain tissue will be cloned in the foreseeable future. Some of them may be the site of the disease mutations.

Mapping the disease loci through linkage to DNA markers on a 'random' basis is a more contentious issue. It is undeniable that the results of segregation analysis of some human epilepsies have been compatible with mechanisms of inheritance which are not at present amenable to linkage analysis. However, the evidence often does not allow other mechanisms to be conclusively excluded, and some of these, such as segregation of a single major locus, may yield to such an approach. It is not therefore possible to know in advance that a random search of the genome will prove futile, any more than it was possible to know in advance whether linkage studies in autosomal recessive disorders such as cystic fibrosis would be confounded by heterogeneity. What is now available is an experimental method for testing alternative hypotheses concerning inheritance; demonstration of linkage does more than map the gene locus.

The experiment is of course a daunting one. It requires the assembly of a very large resource of carefully documented families, genotyping of thousands of subjects at hundreds of loci, and complex computer assisted linkage analysis based on a wide range of different assumptions concerning mechanisms of inheritance and phenotypic classifications. A European collaboration to achieve this is under way.

There is no guarantee of success, but the potential rewards are immense. The major benefits of the 'new genetics' are surely most likely to emerge in such common, non-lethal conditions. Some order may be imposed on a confused and confusing collection of clinical entities, and new, rapid, and accurate diagnostic methods will emerge. DNA analysis may not render EEGs obsolete, but it may one day be just as much a 'routine' investigation in a patient with epilepsy. Finally, there is a real possibility that new pharmacological tools will emerge based on the molecular pathological understanding of these common and disabling diseases.

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