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EDITORIAL

Can linkage and marker association resolve the genetic aetiology of psychiatric disorders? Review and argument[1]

Recent advances in DNA technology have accelerated the process of locating genes on the human chromosome map or genome, have increased the scope and precision of the information available for genetic counselling, and have revitalized the outlook for research into human genetics as a whole. As the mapping of the human chromosomes proceeds apace using simple markers – blood groups, protein polymorphisms, visible chromosome variants, and more recently restriction fragment length polymorphisms, known as RFLPs (Botstein *et al.* 1980; Weatherall, 1982), it makes sense to use statistical methods to detect disease susceptibility loci. Established methods for investigating the complex genetics of conditions such as psychiatric disorders involve statistical analysis of pedigree data and come under the broad headings of 'segregation analysis' and 'path analysis'. Unfortunately, the progress achieved by their use in conditions such as schizophrenia has been frustratingly small. Can the new marker technology provide a remedy for disappointment and lead to a breakthrough for schizophrenia in the way that it has for Huntington's disease (Gusella *et al.* 1983)?

A major obstacle is that the aetiology of schizophrenia is considerably more complex than that of Huntington's disease which, long prior to the linkage discovery, was known to have a simple mendelian basis, in which penetrance (i.e. the probability of being affected, given a particular genotype) is age-related. Thus, linkage analysis established the position of a Huntington's disease locus on chromosome 4, not the mode of inheritance. It would be difficult to dispute that there is a substantial genetic contribution to the manifestation of schizophrenia (Gottesman & Shields, 1982), but it seems unlikely that a single mendelian locus (even with reduced penetrance) could wholly account for its transmission (O'Rourke *et al.* 1982; Tsuang *et al.* 1982). It is possible that further refinement of diagnostic categories could yield genetic subtypes of disorder, some of which are controlled by simple loci but, so far, attempts to do this have not met with success (Gottesman & Shields, 1982; McGuffin *et al.* 1983).

A hope for the near future is that new simple genetic markers will enable us to distinguish subtypes of schizophrenia for which there are major loci but which have not yet been clinically differentiated. Two ways in which the study of marker polymorphisms can play a part in elucidating the aetiology of psychiatric conditions is through genetic *linkage* with disease susceptibility loci and through marker *association* with disorder. Recent attention has focused on the potential use of RFLPs as linkage markers, but some doubts have been expressed. For example, Cloninger and colleagues (1983) hold that, in the case of conditions like schizophrenia, 'the RFLP technique is not the panacea some have touted it to be', and imply that linkage analysis cannot be used to establish and characterize the involvement of a simple major locus in conditions whose genetic aetiology is poorly understood. This is an issue of current concern for the allocation of resources to research in view of the costs of DNA technology.

LINKAGE AND ASSOCIATION: THEIR INTER-RELATEDNESS

Classical neurofibromatosis is due to a mutant allele (or alleles) whose *penetrance* is virtually 100%, i.e. it is possible to identify an adult carrying the mutant allele by a combination of characteristic signs and symptoms. The clinical expressivity, however, is extremely variable, some

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cases presenting only with *café au lait* spots (Riccardi, 1981). We have not yet found any analogous simply-inherited indicants of 'sub-clinical' schizophrenia and so, for the present, definition of the main trait in linkage and association studies must rely upon the overt clinical manifestations of the syndrome.

Despite an absence of convincing evidence at the phenotypic level (*BMJ*, 1976; Farmer *et al.* 1984), schizophrenic disorders may yet be genetically heterogenous. We must therefore consider the implications of transmission due to several 'susceptibility' loci for the disorder, each of which could be located anywhere on the human genome and could exhibit any form of interaction in their effects on manifest disease. It is quite possible that there are some alleles at some loci which invariably lead to manifest schizophrenia, and some which completely protect from disorder, but such completely penetrant genes could account for only a minority of cases. Most susceptibility loci would be expected to show reduced penetrance for the disorder when considered individually; i.e. some statistical association with disease would be apparent when persons are categorized solely according to their disease status and their genotype at the particular locus under consideration, irrespective of their genotype at other loci that may have an effect on the disorder.

The type of association which is due to the transcription products of a segment of DNA facilitating or protecting against the manifestation of disorder is a genotype-specific or allele-specific phenomenon which, with certain provisos, ought to be detectable in any sample of persons drawn from the population. It is to be distinguished from genetic linkage, which is the result of mechanical forces tending to convey alleles of quite separate genetic systems together in the same gamete and hence to the next generation because of their propinquity on the same chromosome. The observed effects of the two genetic systems tend to be inherited as a pair, but are functionally quite independent, so that different phenotypes are found in each other's company in different pedigrees.

More has been made of the distinction between association and linkage than of their interrelatedness. Very tight linkage can preserve chance associations over so many generations that they may be observed in the whole population. It can also magnify and preserve the effect of selection acting jointly on two linked loci, when the selection pressure is too small to be detectable (Edwards, 1980). These phenomena have been termed gametic or allelic association or linkage disequilibrium. The association of two characters in loose linkage, however, can be observed in sibships but decays rapidly over the generations.

Thus, having argued the case for susceptibility loci scattered around the genome, each having a direct facilitating (or inhibitory) effect on the disorder, or on a sub-category of the disorder, we know that each is flanked on either side by a region where any products of the DNA will show an induced association with the disorder due to tight linkage. Flanking this region again on each side are regions where linkage might be detectable in pedigrees, but would be too loose to preserve associations in distant relatives.

Having selected a 'gene probe' at random, it is *a priori* more likely to be linked with a susceptibility locus for the disease than to play a genuine causal role and, again, more likely to be loosely linked rather than to be in allelic association with the susceptibility locus. This does not imply that what is known as 'linkage analysis' is a better strategy than 'association analysis' for the detection of useful probes.

'MODEL-FREE' LINKAGE ANALYSIS

There are well-established methods for linkage analysis (Maynard-Smith *et al.* 1961), and computer programs are available (Ott, 1974) which require information about the mode of inheritance of the disease as input. If we do not have any clear model for the mode of inheritance we have to ask whether it is possible to adapt current methods, or to use some other approach which allows us to manage without a model.

The earliest methods of linkage analysis used data from sets of brothers and sisters (Penrose, 1935). The first human linkage, between the Lutheran blood group and the secretor locus, was established by this method of sib-pair analysis (Mohr, 1951). Methods were then developed that were able to

use data from families consisting of grandparents, parents and children (Morton, 1955). Later, methods that could use whole pedigrees were developed (Elston & Stewart, 1971; Ott, 1974). It became apparent that, for a given number of tested persons, more information about linkage could be extracted if they were members of one large pedigree (and if their relationships of kinship were utilized in the analysis), than if the same number of subjects came from several small pedigrees. The sibling method therefore fell into disuse among research workers whose main interest was in locating simple markers on chromosomes. The general approach continued to be used by those whose main concern was in disease epidemiology; these workers continued to elaborate the method because it was not clear how to apply the more efficient (model dependent) methods to disease phenotypes.

Sibship methods have been thought by some to offer a model-free approach. A further claimed advantage is that, since the subjects are of similar age, age-correction for age-related conditions is not required. However, recent work has shown that it is impossible to differentiate linkage from association effects in sibship data, since too many unknown parameters must be estimated with only restricted information (Hodge, 1981). It is therefore unrealistic to expect to find a 'model-free' method of linkage analysis. The original sib-pair method and its successors can only demonstrate that some *unspecified* effect is in operation if 'significance' is obtained.

USE OF SIBSHIP DATA

If sibships cannot be used to estimate linkage parameters, can they be used to detect the presence linkage? Unless linkage is very tight, its observed effects in pedigrees are relatively weak. Only a specific type of family (containing a parent heterozygous at both the marker and disease loci) is likely to yield information (Thompson *et al.* 1978). Reduced penetrance in one of the genetic systems adds 'noise' to the linkage relationship and means that more pedigree data are required to demonstrate the linkage. Lange *et al.* (1976) show that linkage can be detected between a quantitative trait and a marker if the phenotype distributions for the trait are fairly well separated. In the case of two distributions, one for the 'disease' allele and one for the common genotype, which have equal standard deviations, there needs to be a distance of about 3 standard deviations between their means. From normal tables this amounts to an overlap of about only 7%. Conditions where this is the case would be expected to show unequivocal evidence of a simple major locus controlling the trait when subjected to segregation analysis (Morton & Maclean, 1974).

Classification by dichotomy is inherently less powerful than using a quantitative trait (Lange *et al.* 1976). The expected information yielded from a set of pedigrees falls off markedly when the disease locus has reduced penetrance (McGuffin, 1984). Thus, for example, the relative sample size required to detect linkage at a recombination fraction of 0·01 is 76 times greater for a trait where the manifestation rate is 50% than for a trait where the rate is 100%, and for a trait with 'penetrance' equal to 10% the relative sample size must be more than 2000 times greater. In attempting to fit single locus models, various workers have estimated the penetrance of a supposed schizophrenia susceptibility gene at between 8% and 20% (Slater, 1958; Elston & Campbell, 1970; Tsuang *et al.* 1982).

The lod score method is further limited by the small effects produced by moderate to loose linkage. It may prove impractical to try to detect *by any method* moderately loose linkage with a disease susceptibility locus with incomplete penetrance. However, marker–disease *association*, whether or not caused by very tight linkage, does produce perturbations in the joint disease–marker distribution in sibships, even when the genetic factors involved in the disease are obscure (Suarez *et al.* 1982).

A set of sibships would therefore provide a useful dataset for screening an array of markers to find whether any marker showed any interaction with the presence of disorder. The use of sibship data is a method of controlling for stratification in the population that is unknown to the research worker. Suitable statistical techniques would be a log-linear model for dichotomized disease status or an analysis of variance model if some indicator of disease liability can be measured on a continuous scale. In either case, the analysis should reflect the clustered nature of the sample (Cohen, 1976). One would attempt to obtain large sibships for this purpose and one must use markers that

segregate within the sibship (Smith, 1979). A related approach suitable for a highly polymorphic marker is to observe the identity-by-descent (IBD) distribution of marker haplotypes among affected and unaffected sibs of the index case. If the disease allele has low penetrance, then most of the information is given by the marker haplotypes of affected sibs. Marker testing of one or both parents is generally required (Green & Woodrow, 1977).

THE NEED FOR INTEGRATED MARKER–DISEASE ANALYSIS

A. Analysis of pedigrees

If we accept the need for a model we must start out with one that is sufficiently complex to bear some relationship to reality. Only then will an examination of bodies of data indicate whether the model can be simplified. Edwards (1969) distinguishes between *structural parameters* relating to mechanism (for example, the linkage recombination fraction, often denoted by θ) and *summarizing indices* (for example, penetrance parameters which are dependent on techniques of measurement, or definition of the phenotype). Our model must contain both types of parameter.

It has become apparent in recent years that many of the proposed models for statistical tests for linkage and for disease association fail to incorporate the richness of possible mechanisms by which the products of a segment of DNA can show some association with a disease phenotype. For example, nearly all disease association models assume zero recombination between a marker and a disease susceptibility locus when such a locus may not in fact exist as a separate entity (Sturt, 1984). The lod score method and sibship 'linkage' methods, if applied to a disease whose expression is directly affected by the marker alleles, have both been shown to produce misleading results (Clerget-Darpoux & Bonaiti-Pellie, 1980; Hodge, 1981; Hodge & Spence, 1981). Similarly, erroneous conclusions result if gametic disequilibrium is ignored (Clerget-Darpoux, 1982). The only value of applying a simple method of linkage analysis when a population association is known between the marker and a disease phenotype is to establish that the association is not due to stratification.

Research workers using probes in an effort to elucidate the genetic aetiology of a disorder would count evidence of either linkage or association as a success and as a basis for further research. Some proposed research strategies are based on using simple markers, such as RFLPs, to scan a considerable length of chromosome. In this way, workers hope to find a loose linkage, and then to 'home in' on the disease locus via neighbouring fragment polymorphisms. It should be noted that a 'significant result' from the (mis-)application of linkage analysis does not imply single-locus control of the disease. It merely implies a susceptibility locus in the vicinity of the marker. It may be that one has chanced upon very close linkage with a locus that is a minor contributory factor or even that the transcribed products of the marker DNA actually play a part in the disease process. If this were the case, techniques of 'chromosome walking' would not find a locus that is a major determinant of the disorder. It therefore becomes important to discriminate between these possibilities.

Further problems arise in the interpretation of any positive linkage results obtained for schizophrenia (or disease phenotypes with a similar family pattern). One would embark on a linkage analysis with the hypothesis that the disorder is caused by a factor with mendelian transmission in a minority of cases. Only those families where this is the case could possibly be informative for linkage. Thus results cannot be generalized to schizophrenia as a whole. It is a dubious exercise, having originally collected pedigrees for their 'mendelian appearance', to argue for mendelian control on the basis of a positive linkage result. It would be a better strategy to ascertain pedigrees systematically – for example, through a consecutive series of probands. Then, if linkage is established, one can make some statement about the subgroup of schizophrenia to which it applies.

B. Analysis of population samples

Until recently, linkage analysis and analysis for association have involved quite different approaches to data collection as well as to analysis. Analysis for association was thought to require a sample of unrelated individuals and used well known general methods for the analysis of categorical data

(e.g. see Bishop *et al.* 1975). It was generally accepted that the sample of unrelated individuals should be 'homogenous', and this was generally interpreted as a requirement for all to be of the same ethnic group. If the sample was, unknown to the research worker, drawn from a number of subgroups having different marker allele frequencies and disease frequencies, then this could either mask a genuine association or seem to indicate an association that was actually spurious (Sturt, 1984). It is therefore important to control for such stratification effects when carrying out and evaluating association studies and, where necessary, to use appropriate methods of analysis to overcome them (Bishop *et al.* 1975).

However, an ethnically homogenous sample is not, in fact, a set of unrelated people, even though their common ancestors may be remote. A sample of apparently unrelated persons from a large, ancient, geographically isolated population (excluding people of known recent immigrant descent) is likely to be as homogenous as is possible with respect to the kinship of its members to each other. For this type of sample it is possible to make a (crude) estimate of the total number of opportunities for recombination in the ancestral lines of currently sampled genes (Thompson, 1978). In this way, one is regarding the series as a sample from the latest generation of one huge pedigree. Olaisen and colleagues (1983) obtained a sample of this type and have devised an approach to the analysis of linkage that actually capitalizes on its relationship with allelic association. The order and distances between sub-units of the HLA complex were inferred from the frequencies of whole segments of chromosome strands in the population. For tight linkage groups this approach is much more efficient than pedigree linkage analysis.

When dealing with marker-disease data in a population sample, it is possible to determine which marker has the strongest association with the disease (Thomson, 1981), but it is not possible to determine from population data how many loci are involved. Whether the data consist of a population sample or of related persons, crossing over cannot be easily differentiated from reduced penetrance at the disease susceptibility locus. Where a disease does not have a clear mendelian basis, both effects must be allowed for.

REQUIREMENTS FOR STATISTICAL METHODOLOGY

It is of great practical importance to maximize the statistical power of the methodology, both at the stage of planning data collection and at the time of analysis. Statistical efficiency is the reciprocal of required sample size, and this has obvious implications for overall cost and time to publication. Efficiency must be a priority which is second only to the requirement of correctness and appropriateness of the statistical method, and should certainly take precedence over considerations of ease of calculation and familiarity.

It makes sense to choose a method which uses all the data that have been collected, whether or not they consist of complete pedigrees of a specified type. Because of the large difference in the information content of different pedigree structures, Thompson *et al.* (1978) recommend that analysis of data should proceed in parallel with the marker data collection process, so that expected linkage scores can be used to decide which family members should be studied next. The resulting complex pedigree structure of the data means that likelihood methods are required.

INTEGRATED ANALYSIS: SOME RECENT ADVANCES

The discovery and subsequent confirmation of an association of specific histocompatibility (HLA) antigens with hereditary haemochromatosis offered the promise of resolution of the mode of inheritance of this disease. Kravitz *et al.* (1979) studied a single large pedigree where most members were typed for serum transferrin saturation and HLA A and B. Analysis of the data proceeded within the framework of a two-locus model; the first locus was the HLA complex; and the second disease locus was attributed a bi-allelic simple mendelian model with a normally distributed phenotype for each genotype. When the whole pedigree was analysed without the HLA data, two distinct local maxima were observed on the likelihood surface, corresponding approximately to a recessive and

an additive mode of inheritance for the posited haemochromatosis locus. Further analysis, including the HLA types and allowing for linkage between the two loci, yielded a high positive lod score for the recessive submodel and an estimate of $\theta = 0$. Conversely, at the other local maximum (corresponding to additive inheritance) there was no evidence for linkage.

The previously known association between the trait and HLA implied either the existence of a susceptibility locus in linkage disequilibrium with the HLA complex or a direct effect of some HLA haplotypes or haplotype combinations on the condition. Hence, in this case, performing a linkage analysis with the linkage parameter allowed to be zero or a small positive value, and allowing this analysis to confirm one of the local maxima, is perfectly valid. What this analysis does *not* do is to establish the existence of a haemochromatosis susceptibility locus as a separate entity from the HLA complex. The authors reject direct effects of HLA alleles as an explanation for the observed association on the grounds that 'one would have to resort to the notion of low penetrance' (Kravitz *et al.* 1978). However, the existence of further subdivision of known HLA A alleles or of an unlinked disease locus interacting with particular HLA alleles for expression of haemochromatosis are explanations that should be considered. The question is still open.

Ott & Falk (1982) have demonstrated how to extend a linkage model to allow for allele-specific effects on the manifestations of the disease in the analysis of pedigree data. Essentially, they have shown how to incorporate both linkage and direct association into one model and how to perform a likelihood analysis of pedigree data within this framework. The method allows the use of an existing computer program for maximum likelihood pedigree linkage analysis (Ott, 1974), provided that the data are entered in a particular way. The authors re-analysed a published pedigree with 'strong evidence' for linkage between Lp serum lipoprotein and the polymorphic enzyme esterase D (ESD), resulting in a considerable drop of the lod score for linkage when the possibility of the phenotype of the ESD locus having a direct effect on the Lp phenotype was allowed for. In this pedigree each effect, linkage and association, is strong when the other is assumed absent and each is marginal when the other is allowed for. Analyses of disease–marker relations by this method will show the extent to which it is possible to disentangle these effects when both occur simultaneously. This would be a suitable method of analysis for the haemochromatosis data (above) or any other full pedigree data for disease phenotypes with mendelian markers.

THE FUTURE?

In linkage analysis one needs to infer the fate of alleles of the two systems over two or more successive meioses. It is gametes, rather than individuals, that are recombinant or non-recombinant. A sibship consisting of the offspring of an individual is the closest one can get at present to inspecting an individual's gametes. The pedigree of choice has a tested grandparent whose genotype is 'informative', i.e. gives the origin of each allele of the doubly heterozygous parent of a large sibship. If it becomes possible to test for genetic markers in a single cell, then human recombination will become as easy to observe as recombination in bacteria, since all one would require would be 'informative' parents whose doubly heterozygous son was prepared to supply specimens of semen. This would only be of use for biochemical variants. For the present, however, pedigrees are required to estimate linkage recombination fractions.

Because of the relative weakness of the effects of moderate to loose linkage, and because reduced penetrance at a disease locus severely limits the power of a simple marker to 'scan' for such a disease locus, we hold out little hope for finding linkages between random polymorphisms and disorders like schizophrenia. We have only been able to find one reference (Smith *et al.* 1983) to a linkage between a simple marker and a disease that does not have a known mendelian basis that has been established *in the absence of a previously known population association* between the disease and the marker. On the other hand, rare diseases with a mendelian aetiology are being located: for example, an allele involved in classical neurofibromatosis is now thought to be on chromosome 19 (Westerveld & Naylor, 1984).

Marker polymorphisms that are very tightly linked to a susceptibility locus show most promise

of being of value in the resolution of major gene effects in the aetiology of schizophrenia. Putative associations between psychiatric disorders and markers such as HLA (McGuffin *et al.* 1981; Goldin & Gershon, 1983) may suggest starting points for research. Another approach is to start with a probe for a gene which is hypothesized to be of pathophysiological importance in the aetiology of major psychoses – for example, genes coding for proteins involved in neurotransmission (Gurling *et al.* 1984).

One would like to know, while in the planning stage of this type of research, which approach to data collection would provide the most sensitive method of detecting any type of marker–disease interaction. There may be no general solution to this problem; indeed, the best strategy may depend on the actual values of unknown parameters (recombination fractions, penetrance vectors) requiring the research team to revise the strategy continually in the light of results to date. Both pedigree data and series of 'unrelated' persons should be studied. In the analysis of both types of data, one should not reduce the number of parameters in a model to make it more tractable if this makes it implausible on theoretical grounds. On the other hand, crude methods of analysis are not entirely worthless. If applied carefully, they can produce suggestive leads and even provide preliminary estimates of parameters for likelihood methods.

We feel that advances in gene mapping in general, and in DNA technology in particular, will eventually advance our understanding of the genetic aetiology of psychiatric disorders. However, the complexity of the causal pathway from DNA to disorder will not yield to simple solutions and will require the use of statistical methods which are no less complex and sophisticated than current path-analytic or segregation techniques.

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