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EDITORIAL

Molecular genetics in psychiatric epidemiology: the promise and challenge[1]

Psychiatric epidemiology is becalmed. Since mid-century, there has been substantial progress in finding risk factors for the common mental disorders of anxiety and depression. This has been almost entirely within a social paradigm. Much has been learned about the effects of interpersonal and other social exposures across the lifespan in contributing to these disorders (Brown & Harris, 1978, 1989; Paykel, 1992; Blazer, 1995; Henderson, 1988, 1999). But the range of possibly causal variables has been narrow: demography, socio-economic status, childhood experiences, recent exposure to adversity and the availability of social support. The dominant paradigm has been environmental exposure, examining how experiences that arise outside the individual may have an enduring impact on mental health. The environment in question has been interpersonal or social. Within this paradigm, no new hypotheses of major significance have emerged in recent years.

Epidemiologists have known that the biological domain might be important in aetiology, but for the common mental disorders it has been largely passed over. Properties of the adult brain, whether innate or moulded by environmental exposures, have only rarely been accessible. With the advances in molecular genetics, this is changing (Rutter & Plomin, 1997). For epidemiology, there is now the possibility of bringing molecular genetics into studies of aetiology. Because of the significance of this development, we present a critical assessment of the prospects for population-based research using molecular genetics, the work already reaching publication and the methodological issues that are arising.

LOCATING GENES

Several successful strategies have evolved to locate disease-related genes. Sometimes karyotype analysis has revealed chromosome rearrangements that are direct signposts to the location of a gene, or the biology of a disease might suggest a candidate gene that can be directly examined for mutations. More often, and especially in psychiatric disorders, there is insufficient prior knowledge of candidate genes. The search for their chromosomal location is then based on linkage analysis or methods for the detection of allelic association. These often involve the use of a series of polymorphic markers to screen the entire genome in groups of families or pairs of affected siblings. In its simplest form, linkage analysis aims to identify a chromosome segment that is inherited from the parents by all of the affected and none of the unaffected members in a family. The part of a chromosome that is transmitted with the disease phenotype down each generation is the likely location of a disease-related gene. Further efforts to characterize the gene can then focus on that region. Typically, linkage analysis uses families with a high incidence of disorder over two or more generations, or large cohorts of pairs of siblings, both affected by illness. The dramatic successes of linkage studies in neuropsychiatric disorders, leading for example to the characterization of genes causing Huntington's disease and Alzheimer's disease, have not yet been matched in schizophrenia and the affective disorders. No disease-related mutations in genes have yet been identified for the major psychoses. Nevertheless, linkage studies have identified several chromosomal regions showing suggestive linkage to schizophrenia, bipolar disorder or to both conditions and in some cases results have been replicated in more than one study (Crow & De Lisi, 1998).

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Such limited progress is to be expected in psychiatric illnesses that are considered as 'complex' genetic disorders because they are familial but show no clear pattern of Mendelian inheritance. Complex traits are often common in the population and may be polygenic (two or more genes) or multifactorial (contributions from several genes and environmental risk factors). Linkage analyses are most powerful when applied to single gene disorders but are sensitive to inaccurate definition of the phenotype and to incorrect assumptions about the penetrance and mode of inheritance of the disease. The major psychoses are likely to be aetiologically and genetically heterogeneous, showing various patterns of inheritance in different families and populations. The effects of heterogeneity can be reduced by looking for linkage in isolated populations or in single large kindreds rather than in large assemblies of small families or pairs of affected siblings. Even a highly polygenic disorder may be attributed to the expression of a single or very small number of genes in some individual families. Indeed, some of the strongest evidence for linkage in bipolar disorders and schizophrenia has been found in single multiply affected families when the assumption is made that a single gene is a major contributor to illness (Straub *et al.* 1994; Pekkarinen *et al.* 1995; Barden *et al.* 1996; Blackwood *et al.* 1996; Freimer *et al.* 1996; Ginns *et al.* 1996; Silverman *et al.* 1996; Ewald *et al.* 1998).

Allelic association studies for complex traits

Allelic association (or linkage disequilibrium) studies complement linkage and are another important method to locate genes. A well-known example of allelic association is the increased frequency of specific HLA antigens in several diseases. One likely interpretation would be that immunological mechanisms mediated by HLA are themselves pathogenic. It might also be inferred that HLA is not the responsible gene but is a polymorphic marker lying very close to the disease-related gene. When a disease is transmitted from parent to offspring, the disease-causing gene is inherited along with a segment of the chromosome lying alongside. The pattern of DNA variants (polymorphisms) within that segment will also be transmitted and all descendants who inherit the disease from a founding individual will inherit some of the surrounding haplotype. Markers very close to the gene will show allelic association with the disease in a population that includes the descendants of the disease founder. Since meiotic recombination at each generation steadily erodes the transmitted haplotype, only markers very close to a disease gene continue to show association after many generations. Detecting association is therefore a powerful tool for mapping disease genes over short genetic distances. The simplest design is to compare the frequency of alleles of a polymorphic marker in cases and controls drawn from the same population. Association is particularly suited to the study of candidate genes considered on theoretical grounds to be implicated in a disease process. The ideal situation for detecting association is when the polymorphism itself directly influences the function of a candidate gene. Association studies also have power to detect genes of small effect that contribute only a small proportion to the relative risk of a disorder (see above). In many circumstances, they have much greater power than linkage studies (Risch & Merikangas, 1996; Collier & Sham, 1997; Owen *et al.* 1997).

QUANTITATIVE TRAITS

Complex disorders can be conveniently considered as either qualitative or quantitative traits. Qualitative traits include all clinical diagnoses such as schizophrenia, depression and alcohol dependence that enable individuals in a family or population to be categorized as affected or unaffected. The methods of linkage and association described above can be applied to these dichotomous variables. Quantitative traits include attributes such as the height or blood pressure of a person or the yield of grain in a cereal. These are continuous variables considered to reflect the concerted action of many genes each having only a small effect on the trait (Ostrander & Giniger, 1997). A variety of methods have been developed to map these genes, called quantitative trait loci (QTLs). Different study designs are possible. For example depression can be measured in a population not as a dichotomous diagnosis but as a score on a scale of severity. Comparisons are then be made between the groups with the highest and lowest scores using similar tests for

association as for qualitative traits. As an example, sib pair and twin methods for the detection of quantitative traits were successfully applied in a study of reading disability that mapped a quantitative trait (scores on a reading test) to a locus on chromosome 6 (Cardon *et al.* 1994). The score on a personality questionnaire can be used to define a disease phenotype as quantitative traits that arguably may reveal the underlying pathogenesis (Plomin *et al.* 1994; Cloninger *et al.* 1996; Collier & Sham, 1997).

IMPEDIMENTS TO PROGRESS

In the last few years, the psychiatric genetics literature has become replete with QTL studies searching for a possible association between mental disorders or vulnerability traits on the one hand, and candidate genes related to neurotransmitter function on the other. Some have claimed to have found an association, but none has been conclusively replicated. The present situation is 'a bewildering array of seemingly positive results interlaced with numerous failed replications' (Baron, 1997). A series of papers have commented on the possible reasons (Berrettini, 1997; Nimgaonkar, 1997; Paterson, 1997; Collier & Sham, 1997; Owen *et al.* 1997; Baron, 1998; Greenberg *et al.* 1998). It is because the prospect of incorporating molecular genetics into psychiatric epidemiology is such an attractive one that the methodological impediments identified by these authors now need to be tackled collaboratively by geneticists and epidemiologists. The principal issues are as follows.

Measuring the phenotype

Accurate measurement of the phenotype is an obvious prerequisite. Because international replication is essential in confirming an association for a QTL, the cases of anxiety, depression or substance abuse should meet the diagnostic criteria in international use. In the published reports so far, confirmation of this has been reported only exceptionally. But if the criteria are applied, it is likely that some investigators will use the ICD-10 Diagnostic Criteria for Research (WHO, 1993) while others will use DSM-IV (American Psychiatric Association, 1994). It is known that the two systems produce comparable prevalence rates in community surveys, but they commonly identify different individuals as cases (Henderson *et al.* 1994). Andrews *et al.* (1999) found that the concordance ranged from 83% for a depressive episode to a low of 33% for substance abuse. For population studies using molecular genetics, this is a major impediment to the comparability of findings. One solution is to use only those cases that satisfy both sets of criteria.

In addition to using individuals that lie above the threshold for a diagnosis, there are grounds for also applying continuous measures of symptoms, thereby avoiding the use of imperfect and artificially dichotomous classifications and, at the same time, making more efficient use of statistical information in large community samples. For personality traits, it is rational to focus on those that are known both to be associated with anxiety, depression or substance abuse, and for which a biological basis has been proposed. Again, it is inevitable that different investigators will use different tests, which in turn measure similar but distinct constructs. Examples are neuroticism and extraversion as measured by the Eysenck Personality Questionnaire (Eysenck *et al.* 1985) and the respective traits of harm-avoidance and novelty-seeking in the Tridimensional Personality Questionnaire (Cloninger *et al.* 1991, 1993). Such variation in measures is likely to persist, but investigators need to recognize the advantages of having a standard core of these.

Selecting a candidate gene

To select a candidate gene for QTL studies, it is a distinct advantage to have some theoretical basis for the choice. The principle followed so far is to focus on genes related to the synthesis, breakdown or reuptake of neurotransmitters. The rationale has been that disturbance in the latter is believed to be central in schizophrenia and the affective disorders; and that drugs affecting their metabolism are known to bring about changes in behaviour, mood and cognition. This makes good sense, and some weak associations with such QTLs have been proposed (Williams *et al.* 1997). Chakravarti

(1999) has suggested that attention should be given not only to common variants in the coding sequences of candidate genes, but also in their regulatory regions. Another approach is to identify genes related to behaviour in laboratory animals using selective breeding, then study that same gene in humans. However, in the near future, the Human Genome Project will make available to researchers the sequences of all genes expressed in brain, doubtless many with functions that are entirely novel to neuroscience.

Statistical analysis

If there are about 100000 genes in the human genome with about 20000 related to brain structure and function, there is a low prior probability that a polymorphism in any one gene will be causally related to one of the common mental disorders. Indeed, it is a bold expectation that an association might exist between a trait such as neuroticism and a single polymorphism, and that it is of sufficient strength to be measurable. Yet this expectation lies behind most of the current research activity. Even if a single gene were causally related, its contribution to measurable variation in the phenotype may be too weak to be detected (Brown & Hartwell, 1998). This situation is in marked contrast to the success in identifying single genes of large effect, as in Huntington's disease or cystic fibrosis.

The large number of tests that have to be made greatly increases the chances of a type 1 error. This calls for large sample sizes and a high threshold for claiming that an association may exist. Crowe (1993) showed that even if there were only five genes conferring vulnerability to a psychiatric disorder and 20000 genes were examined, the traditional threshold of $P < 0{\cdot}05$ would bring a false positive rate of 99·5%, or of 80% at $P < 0{\cdot}001$. The P value itself may be suspect as a measure of the strength of an association (Lang *et al*. 1998) because it is confounded by the sample size and by the base-rate for the allele in the controls. In the case–control situation, the odds ratio with confidence intervals may be more appropriate (Nimgaonkar, 1997). Vieland & Hodge (1998) have argued for using the likelihood ratio, closely related to the LOD score used in linkage studies. Where large community samples are being studied, the population attributable risk is a statistic that will give clear expression to the clinical and public health significance of an association.

Epistatic effects

Some genes are influenced by the concurrent action of another gene, a phenomenon called epistasis (Phillips, 1998). Some are activated by another, while some are suppressed, and this activity may change over time, as in neurodevelopmental events. Gene–gene interaction may play a large part in complex disorders such as anxiety, depression or substance abuse. But few studies have looked for epistatic effects arising from one or more genes because this raises formidable statistical problems (Frankel & Schork, 1996). Recent developments in variance-based methods to detect quantitative trait loci for complex traits in outbred populations offer a means to detect the presence of two interacting loci contributing to a phenotype (Almasy & Blangero, 1998; Visscher *et al*. 1999).

Selection of controls for association studies

Genetic variation has been created by mutations in the human genome throughout evolution. Through processes of natural selection and population migration, separate human groups can develop different frequencies of diseases and of alleles at many common polymorphic sites. Association studies are therefore liable to generate misleading evidence in favour of associations when cases and controls are inadvertently drawn from different subpopulations. One elegant solution to avoid the effects of population stratification is the use of family-based controls. This is done by selecting trios, made up of the index individual (case) and both parents. Allelic association with disease is sought by comparing the frequency of the alleles transmitted from parents to offspring (case alleles) with the frequency of the parental alleles that are not transmitted (control alleles). Some writers have proposed that only family-based association studies are sufficiently robust to be reported. But in community-based surveys, there are major practical and financial difficulties in obtaining an extensive psychiatric assessment of many hundreds of index persons,

together with DNA, both from them and two first-degree relatives. Unlike clinical research on families where one or more members have a disorder, the respondents in epidemiological studies have no equivalent motivation to cooperate by recruiting both parents or two siblings, even where these are both living and accessible. For this reason, a design using trios could introduce unacceptable bias in the type of families successfully examined. Furthermore, where gene–environment interaction is being studied, trios bring overmatching for exposures to the social environment in both childhood and adult life. We, therefore, believe that valuable data can be obtained in populations that are known to be reasonably homogeneous in ethnic origin, provided that comparison groups are carefully matched for age and sex and that a number of such studies are conducted in different geographical regions.

EMERGING TECHNOLOGIES: DNA CHIPS AND SNPs

In the next few years, it will become possible to examine the entire human genome for QTLs associated with selected phenotypes using high capacity, highly automated methods based on microchips. Each microchip will contain several thousand DNA samples to be simultaneously analysed (Pease *et al*. 1994; Chee *et al*. 1996). Chip technology is not yet free of errors and is very costly, but it should soon be possible to examine an individual's DNA for several thousand variants in a single assay.

There is a parallel technical development that will make the use of DNA chips even more powerful. Very large numbers of DNA markers, including the abundant single nucleotide polymorphisms (SNPs), are currently being identified as the human genome is sequenced. This is creating a dense map of markers that may revolutionize the genetic analysis of common mental disorders. DNA samples from many thousands of human subjects could then be analysed against thousands of markers (Wang *et al*. 1998). The density of these markers will be important because many human behavioural traits must be of great antiquity in higher primate evolution. Examples are novelty seeking and harm avoidance, in which the preservation of genetic diversity has probably conferred species advantage. Chakravarti (1999) says that if complex disorders are determined by many loci, these alleles are likely to be common, in which case they are also very old, with ages of at least 10000 years. As a consequence, linkage disequilibrium between genes for such traits and equally ancient polymorphisms, including many SNPs, will have diminished over a large number of generations and will not be detectable. Genes that are phylogenetically old are most likely to be detected through polymorphisms that directly affect the function of the gene itself. For this reason, a very dense series of markers will be required for mapping to be successful. But such maps are rapidly being constructed and will make QTL studies increasingly powerful.

THE NEXT GENERATION OF EPIDEMIOLOGICAL STUDIES IN PSYCHIATRY

Epidemiological research directed at the causes of common mental disorders now has a choice. It can obviously continue its search for pathogenic factors within the social environment, despite the lack of new hypotheses in that paradigm. The alternative is to incorporate molecular genetics as well as environmental exposures in the design of population-based studies. For this, two complementary strategies can be considered. The first is to make full use of the traditional case–control study in large clinical series, comparing the frequency of QTLs in persons with and without a disorder, by exposure status. As in all case–control studies, the cases should be rigorously diagnosed using the criteria in international use, they should be incident rather than prevalent, and both they and the controls should be free of possible bias from selection effects in their manner of recruitment from the general population (Berkson, 1946). These requirements have not been fulfilled in the great majority of studies published so far, but there is no reason for this to continue.

The second strategy for incorporating molecular genetics is in large community-based field studies. It is now easy to add DNA samples to the assessment of symptoms and psychosocial variables, either through a blood sample or cheek-swab. This provides an opportunity to look for associations

between candidate genes and phenotypes defined by psychiatric diagnosis or by scores at the extreme ends of continuous measures of symptoms or traits. From the genetics viewpoint, there are two situations where large community samples can be put to good use. In the first, the gene being examined has already been identified as contributing to the onset of clinical disease, but its population attributable risk is unknown in the general population. This was the situation with the apolipoproteinE $\epsilon 4$ allele in Alzheimer's disease when its association with cognitive decline was studied in large community samples (Henderson *et al*. 1995). In the second context, the candidate gene or genes is not yet known to be associated with a particular phenotype. This was the situation in the community study by Jorm *et al*. (1998) on the serotonin transporter gene. Next, there is no reason to restrict genetic analyses to cross-sectional designs, as seems invariably to have been the case so far. A prospective design could be used to test hypotheses predicting higher or lower incidence rates in persons with particular polymorphisms.

With both cross-sectional and prospective longitudinal designs, there is also the opportunity to include environmental exposures, both in the person's childhood and more recent past. Such a prospect of looking for gene–environment interaction holds considerable attraction. The hypothesis is that symptoms are more likely to arise in persons with a particular allele who also have had a certain exposure. A few studies have already looked for interaction between a particular polymorphism and environmental exposures (Macciardi *et al*. 1996; Berman & Noble, 1997; Jorm *et al*. 1998), but it is too early to evaluate these. The reporting of adverse life events has itself been shown to be partly familial and possibly genetic (McGuffin *et al*. 1988; Kendler & Karkowski-Shuman, 1997). It may therefore be possible to relate candidate genes to the reporting of adversity.

At the population level, it is well established that in the face of adversity, the majority of individuals do not become cases of anxiety or depression (Dohrenwend, 1998). Little is known about this reciprocal aspect of pathogenesis, despite its relevance for public health and strategies for prevention. For that reason, the significance of QTLs conferring resistance to anxiety or depression may be even greater than for vulnerability, especially where the impact of noxious social exposures is being included in the analyses.

The possibility of at last being able to introduce biological variables to population-based research is tempered by the methodological difficulties we have outlined. But if geneticists and epidemiologists working together can overcome these, the scientific dividends could be far reaching. If they cannot be overcome, it will leave much of psychiatric epidemiology in the twentieth century.

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